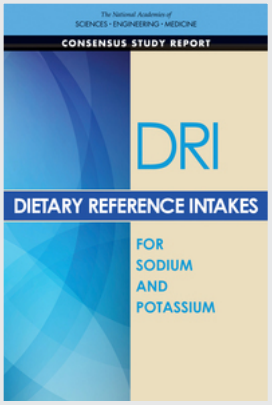

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DIETARY REFERENCE INTAKES
FOR SODIUM AND POTASSIUM

Committee to Review the Dietary Reference Intakes for
Sodium and Potassium

Virginia A. Stallings, Meghan Harrison, and Maria Oria, *Editors*

Food and Nutrition Board

Health and Medicine Division

A Consensus Study Report of

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **EILEEN T. KENNEDY,** Tufts University, and **CATHERINE E. WOTEKI,** Iowa State University. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Preface

As essential nutrients, sodium and potassium contribute to the fundamental physiology of human health. In the clinical setting, these are frequently measured blood electrolytes. Yet, blood electrolyte concentrations are rarely influenced by typical dietary intake in healthy individuals, as the kidney and hormone systems carefully regulate blood values. However, the sodium and potassium intake story is more dynamic in the public health setting. Evidence suggests that sodium and potassium intakes influence current and longer-term population health in children and adults mostly through complex and not fully understood mechanisms between dietary intake and blood pressure and cardiovascular health status. Based on a 2017 report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 50 percent of men and 44 percent of women ages 45–54 years have clinically significant hypertension, and the prevalence increases with age. This information—such high prevalence of hypertension beginning early in adult life—was a surprise to me. Cardiovascular disease, including diagnoses of cardiovascular disease risk factors such as prehypertension, hypertension, and abnormal blood lipids, is common, and a majority of adults in the United States has more than one cardiovascular disease risk factor. The public health importance of the relationships of sodium and potassium intakes and health is clear. Congress asked the Centers for Disease Control and Prevention (CDC) to undertake a review of the Dietary Reference Intakes (DRIs) for sodium. Given the interrelationship between sodium and potassium, it was determined that assessing both together would be prudent. CDC, together with

the Food and Drug Administration, Health Canada, the National Institutes of Health, the Public Health Agency of Canada, and the U.S. Department of Agriculture, sponsored this study. The National Academy of Sciences' W.K. Kellogg Foundation Fund and the National Academy of Medicine's Kellogg Health of the Public Fund provided additional financial support.

The committee was charged to review the available evidence and to update the current DRIs for sodium and potassium. In 2005, the evidence supported an Adequate Intake (AI) for both nutrients, and a Tolerable Upper Intake Level (UL) only for sodium. In addition, we were asked to consider adding, if relevant, sodium and potassium intake values to reduce the risk of chronic disease endpoints. Committee deliberations were guided by three sources: *Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcomes and Related Risk Factors*, an Agency for Healthcare Research and Quality (AHRQ) systematic review of the evidence commissioned to be used by this committee; *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease*; and the DRI organizing framework. The 2011 *Dietary Reference Intakes for Calcium and Vitamin D* also served as a resource, as it was the most recent DRI report that considered the evidence of dietary intake and chronic disease indicators to make recommendations.

In addition to these reports, the committee gained insight from expert testimony, additional comprehensive literature searches as needed to ascertain the state of the science on specific questions, and committee expertise and deliberation. Our committee members represented key disciplines and skill sets needed for this work; they not only dedicated significant time and effort, but also created a collaborative environment of learning, lively debate, and commitment to a thorough review prior to making decisions. Implementing the new DRI concept of dietary intake recommendations of reduce the risk of chronic disease was a responsibility the committee embraced. This report provides the first DRI based on chronic disease recommendations and documents both the evidence and the deliberative process to inform future DRI committees considering chronic disease recommendations.

Research into cardiovascular disease, hypertension, and diet has been among the priority areas for decades, yet numerous knowledge gaps persist. Additional research is essential to inform the next review of how sodium and potassium dietary intakes affect health across the DRI life stages. High-quality evidence to guide dietary recommendations to support the health of the youngest children, oldest adults, and pregnant and lactating women in the United States and Canada is also sparse.

Understanding the food and beverage sources of dietary sodium and potassium was not examined in detail, nor were the complex interactions of nonprocessed and processed food availability, cultural and personal taste

preference, and behavioral components of food choice. However, some common misconceptions came to light. Most of the salt in our modern diet pattern comes from commercially prepared food and beverage components and products, not from salt added by consumers cooking at home or from salt added by the consumer at the time of consumption. When considering sodium sources for the population over 2 years of age, most common sodium sources are breads, pizza, and cured meats and poultry. For children specifically, cheese is the top food category source of sodium, followed by cured meats and poultry, and then mixed dishes including pizza. For the desired public health benefit of reduced sodium intake to be achieved, more attention must be paid by industry to reducing sodium in the food supply and by consumers who have the needed sodium content information and an understanding of how to make health-inspired food choices. Dietary potassium intake is related to specific vegetable or fruit intakes—and then remember that as a population, our vegetable and fruit intake rarely meets the recommended servings per day. When you consider all ages, higher dietary sources of potassium are from milk, white potatoes, and fruit. Coffee is the top source of potassium in people in the 51 years of age and older group in the United States.

The committee thoroughly considered the totality of evidence available and used processes now established for DRI review and revisions. Our DRI report provides a sodium intake level as an AI, and with sodium, the report establishes the first Chronic Disease Risk Reduction Intake (CDRR) level. Our report provides a potassium intake level as an AI, and the committee determined there was insufficient evidence to establish a CDRR for potassium. In addition, using the evolving toxicological risk assessment approach, the committee found there was insufficient evidence of risk of excess sodium or potassium intake within the healthy populations to establish a UL for either nutrient.

Many other people contributed to this report. Two consultants, Mei Chung and Paul Whelton, provided their advice and guidance to the committee. Emily Callahan provided editorial assistance with the report. The National Academies Research Center, particularly Jorge Mendoza-Torres, provided support and assistance with the design and execution of the committee's scoping literature searches. The committee was also assisted by Jennifer Garner, who was an intern with the Food and Nutrition Board in Spring 2018. The committee would also like to thank both CDC and Health Canada for providing intake distribution tables and other information requested by the committee.

Lastly, as chair, I express my sincere appreciation to each committee member and to each member of our National Academies staff, including Meghan Harrison and Maria Oria, for their extraordinary commitment to the project and to our shared goal to complete this complex task in a way

that serves the public's health and health care in general. We worked well together to prepare a report that will contribute to actively improving the health of children and adults.

Virginia A. Stallings, *Chair*
Committee to Review the
Dietary Reference Intakes
for Sodium and Potassium

Contents

Summary

Potassium and sodium are physiologically essential nutrients. Their functions are closely intertwined, and each has important roles in maintaining physiological homeostasis. Both nutrients have also been implicated in chronic disease risk, particularly cardiovascular disease, mainly through their effects on blood pressure. Additionally, a possible association of sodium intake with other adverse health outcomes has been suggested at low levels of intake. The unique nature of potassium and sodium—that is, the coexistence of their essentiality with a relationship to adverse health effects, including chronic disease risk—necessitated a new approach to the review of intake recommendations for these nutrients within the Dietary Reference Intakes (DRIs) context.

The DRIs are a set of quantitative reference values for the apparently healthy population, developed jointly for the United States and Canada. The DRIs are derived through an iterative process that was developed in response to recognition of the need for a safe and adequate range of intake for nutrients and other food substances, beyond meeting essential requirements to prevent deficiency diseases. Although the DRI model envisioned use of evidence for chronic disease risk, the model proved to be challenging and insufficient for that purpose. The relationships between diet and chronic disease risk are complex and are dependent on a variety of factors, both nutritional and nonnutritional, such as an individual's baseline risk for the chronic disease, environmental factors, and nutrient–diet or nutrient–nutrient interactions, exposure time, and other lifestyle factors. The intake–response relationships between nutrient intakes and chronic

disease risk are often more complex than the relationships observed for adequacy and toxicity effects.

The evolution of both the DRIs and the definition of nutritional health to include more than the essential nutrients led to the reexamination of the DRI model for ways to consider inclusion of chronic disease in the process. A 2017 National Academies of Sciences, Engineering, and Medicine (the National Academies) report, *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*), provides guidance and recommendations for expanding the DRI model to include a new category of reference values specific to chronic disease risk reduction. This study represents efforts to apply those recommendations to the process of deriving DRIs for potassium and sodium.

THE COMMITTEE'S TASK AND APPROACH

The inextricable link between potassium and sodium, in both biology and study designs, makes their concurrent DRI review both scientifically justified and efficient. An ad hoc committee of the National Academies was asked to review current evidence and update, as appropriate, the DRIs for potassium and sodium that were established in the 2005 report *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*). The committee's Statement of Task is presented in Box S-1.[1]

BOX S-1
Statement of Task

An ad hoc committee will undertake a study to assess current relevant data and update, as appropriate, the Dietary Reference Intakes (DRIs) for sodium and potassium intake. The review will include consideration of indicators of deficiency, inadequacy, and toxicities, as well as relevant chronic disease endpoints. The study will incorporate the Agency for Healthcare Research and Quality systematic evidence review of sodium and potassium on chronic disease endpoints, as appropriate, and the Health and Medicine Division report on guiding principles for inclusion of chronic disease endpoints, along with the DRI organizing framework. Indicators for adequacy and excess will be selected based on the strength and quality of the evidence and the demonstrated public health significance, taking into consideration sources of uncertainty in the evidence. Estimates of dietary intake of sodium and potassium will be compatible with optimal health throughout the lifespan and may decrease risk of chronic disease where data indicate they play a role.

[1]The Statement of Task was abbreviated for this Summary. The complete Statement of Task is presented in Chapter 1, Box 1-1.

The committee was asked to incorporate the DRI organizing framework, which provides a structured process for establishing DRIs and consists of the following steps:

1. Review the evidence on indicators and select the indicator(s) that will inform the DRIs.[2]
2. Assess the intake–response relationships of the selected indicator(s) and establish DRI values.
3. Compare current population intake levels to DRI values to characterize risk.
4. Discuss public health implications and special considerations.

In addition to the DRI organizing framework, the committee was asked to apply the guidance from the *Guiding Principles Report*, which allows for evidence on chronic disease risk to be used to derive DRI values separate from the other DRI categories for adequacy and toxicity. With the existing DRI categories, which focused on essentiality and toxicity that can affect all individuals, the general assumption is that failure to derive a reference value is often not a viable public health option. In contrast, reference values for the DRI based on chronic disease are generally intended to be established only when the body of the evidence is sufficient to do so. In particular, the *Guiding Principles Report* recommended at least a moderate strength of evidence for both the causal and intake–response relationships between nutrient and chronic disease risk.[3] In the context of this DRI review of potassium and sodium, the committee has called the specific category of DRIs based on chronic disease reference value the Chronic Disease Risk Reduction Intake (CDRR).[4]

The committee was provided with a systematic review prepared for this study, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*), which served as a primary source of evidence. The *AHRQ Systematic Review* included risk-of-bias and strength-of-evidence assessments, along with meta-analyses of randomized controlled

[2]In context of the DRIs, an indicator broadly refers to clinical endpoints, surrogate markers, biomarkers, and chronic disease risk factors.

[3]For consistency throughout this report and in alignment with the terminology used in the *AHRQ Systematic Review*, the committee uses the term *strength of the evidence* instead of *quality of the evidence* or *certainty of the evidence* when describing the grading of the evidence used to derive DRIs based on chronic disease.

[4]Throughout the report, *DRIs based on chronic disease* is used when broadly describing the category. The committee uses CDRR to describe the specific category of values established. This aligns with the committee's use of the phrases *DRIs for adequacy*, which broadly refers to the Estimated Average Requirement, Recommended Dietary Allowance, and Adequate Intake, and *DRIs for toxicity*, which refers to the Tolerable Upper Intake Level.

trial results.[5] As a user of the *AHRQ Systematic Review*, the committee assessed its methodological quality and identified two domains that could be strengthened: exploring unexplained heterogeneity in meta-analyses and providing clear explanations of the process for grading the strength of the evidence. To interpret the evidence, the committee addressed these domains by conducting heterogeneity analyses and explaining in detail its grading of the evidence for assessments central to its decision making.[6]

The committee also undertook information-gathering activities that included hosting a workshop and public comment session, requesting information from the public and stakeholders, performing scoping searches to identify potential indicators, and conducting supplemental literature searches on selected indicators not included in the *AHRQ Systematic Review*.

The committee's findings, conclusions, and resulting DRIs for potassium and sodium are presented in the following sections, organized by the steps in the DRI framework outlined above.

DIETARY REFERENCE INTAKES FOR POTASSIUM

Step 1: Review and Selection of Indicators

Indicators to Establish Potassium DRIs for Adequacy

The committee's review of the evidence on potential indicators to inform the potassium DRIs for adequacy revealed the following:

- There is no sensitive biomarker that can be used to characterize the distribution of potassium requirements in the apparently healthy population.
- Limitations in the design of potassium balance studies—particularly the small sample size and incomplete measurement of intake and losses—precluded the committee from using such data to estimate median potassium requirements and the distribution of potassium requirements in the apparently healthy population.

[5]A meta-analysis is a statistical analysis that combines the results of multiple scientific studies. Its interpretation is complicated by heterogeneity among the studies. Observed differences in the intervention effect between the studies could result from clinical diversity (the participants, interventions, and outcomes studied) and/or methodological diversity (differences in study design and risk of bias).

[6]For DRIs based on chronic disease, the committee used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the strength of the evidence as high, moderate, low, or insufficient depending on the level of confidence in the effect estimate related to potassium or sodium intake.

The committee concludes that none of the reviewed indicators for potassium requirements offer sufficient evidence to establish Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) values. Given the lack of evidence of potassium deficiency in the population, median intakes observed in an apparently healthy group of people are appropriate for establishing the potassium Adequate Intake (AI) values.

Indicators to Establish Potassium DRIs for Toxicity

The committee's review of the evidence on potential indicators to inform the potassium DRIs for toxicity revealed the following:

- Case reports provided evidence that very large doses of potassium supplements can result in cardiac abnormalities and death. The doses of potassium in these case studies are generally imprecise and have been confounded by comorbidities and medication use.
- Potassium supplementation may slightly increase blood concentrations of potassium, although among adults with normal kidney function, there is no evidence that it results in hyperkalemia (serum potassium concentration > 5.5 mmol/L).
- No consistent patterns of reported adverse events were identified across the potassium supplementation trials included in the *AHRQ Systematic Review* and in the committee's supplemental literature search.

The committee concludes that there is insufficient evidence of potassium toxicity risk within the apparently healthy population to establish a potassium Tolerable Upper Intake Level (UL).

Indicators to Establish Potassium DRIs Based on Chronic Disease

The committee's review of the evidence on potential indicators to inform the potassium DRIs based on chronic disease revealed the following:

- The independent effect of potassium intake on all-cause mortality, cardiovascular disease, coronary heart disease, myocardial infarction, stroke, and chronic kidney disease has not been assessed in randomized controlled trials. Evidence from prospective cohort studies tended to be rated as having moderate or high risk of bias, and there was potential confounding of results attributable to dietary potassium's strong correlation with other nutrients in the diet. These limitations precluded the determination of causal

relationships and led to grading of low or insufficient strength of evidence for these indicators.

- The results of potassium supplementation trials on bone mineral density may differ by conjugate anion in the supplement (e.g., citrate, bicarbonate, or chloride), and therefore do not necessarily reflect the independent effect of potassium.
- There is insufficient evidence of an effect of potassium intake on kidney stones, and there is low strength of evidence that higher potassium intake may be associated with lower risk of kidney stones.
- There is insufficient evidence of a causal relationship between potassium intake and incident diabetes, glycemic control, and insulin sensitivity.
- There is moderate strength of evidence that potassium supplementation significantly reduces systolic and diastolic blood pressure. The effect was stronger among studies that included adults with hypertension. Still, considerable heterogeneity existed across trials and the committee was unable to determine its source. An intake–response relationship with dose of supplemental potassium could not be established.

The committee concludes that, although there is moderate strength of evidence for a causal relationship between potassium supplementation and reductions in blood pressure, heterogeneity across studies, lack of evidence for an intake–response relationship, and lack of supporting evidence for benefit of potassium on cardiovascular disease prevents the committee from establishing a potassium Chronic Disease Risk Reduction Intake (CDRR).

Step 2: Establishing Potassium Dietary Reference Intake Values

Data from the Canadian Community Health Survey–Nutrition 2015 (CCHS Nutrition 2015) and the National Health and Nutrition Examination Survey 2009–2014 were used to derive the potassium AIs. The committee sought to use intake data from apparently healthy survey participants, particularly those whose usual potassium intake would not be affected by illness, use of medications, or medical nutrition management. For adults, this consisted of normotensive males and females without a self-reported history of cardiovascular disease. The highest median potassium intake across the two surveys was selected as the AI for each of the DRI age and sex groups in children and adolescents, for adult females, and for adult males. The potassium AIs for infants were derived from estimates of potassium intakes in breastfed infants. The updated potas-

sium DRIs consist only of AIs for all age, sex, and life-stage groups (see Table S-1). There was insufficient evidence to establish EARs, RDAs, ULs, or CDRRs for potassium. A summary of the updated potassium DRIs is presented in Box S-2.

TABLE S-1 Potassium Dietary Reference Intakes by Age, Sex, and Life-Stage Group

Life-Stage Group	AI (mg/d)	UL	CDRR
Infants			
0–6 months	400	ND[b]	ND[c]
7–12 months	860[a]	ND[b]	ND[c]
Children			
1–3 years	2,000[a]	ND[b]	ND[c]
4–8 years	2,300[a]	ND[b]	ND[c]
Males			
9–13 years	2,500[a]	ND[b]	ND[c]
14–18 years	3,000[a]	ND[b]	ND[c]
19–30 years	3,400[a]	ND[b]	ND[c]
31–50 years	3,400[a]	ND[b]	ND[c]
51–70 years	3,400[a]	ND[b]	ND[c]
> 70 years	3,400[a]	ND[b]	ND[c]
Females			
9–13 years	2,300[a]	ND[b]	ND[c]
14–18 years	2,300[a]	ND[b]	ND[c]
19–30 years	2,600[a]	ND[b]	ND[c]
31–50 years	2,600[a]	ND[b]	ND[c]
51–70 years	2,600[a]	ND[b]	ND[c]
> 70 years	2,600[a]	ND[b]	ND[c]
Pregnancy			
14–18 years	2,600[a]	ND[b]	ND[c]
19–30 years	2,900[a]	ND[b]	ND[c]
31–50 years	2,900[a]	ND[b]	ND[c]
Lactation			
14–18 years	2,500[a]	ND[b]	ND[c]
19–30 years	2,800[a]	ND[b]	ND[c]
31–50 years	2,800[a]	ND[b]	ND[c]

NOTE: AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; ND = not determined; UL = Tolerable Upper Intake Level.

[a]Updated DRI value, as compared to the *2005 DRI Report*.

[b]Not determined owing to lack of a toxicological indicator specific to excessive potassium intake.

[c]Not determined owing to insufficient strength of evidence for causality and intake–response.

BOX S-2
Summary of the Updated Potassium Dietary Reference Intakes

- As was the case in the *2005 DRI Report*, there remains insufficient evidence to establish Estimated Average Requirements, Recommended Dietary Allowances, or Tolerable Upper Intake Levels for potassium.
- In the absence of a specific indicator of potassium adequacy or deficiency, Adequate Intakes (AIs) were derived using two nationally representative surveys. The highest median potassium intake across the two surveys was selected for each DRI group in children and adolescents, for adult females, and for adult males. For adults, the data that informed the potassium AIs were from normotensive males and females without a self-reported history of cardiovascular disease. For infants, the AIs were derived from estimates of potassium intakes in breastfed infants.
- Despite moderate strength of evidence that potassium supplementation reduces blood pressure, particularly among adults with hypertension, a potassium Chronic Disease Risk Reduction Intake cannot be established because of heterogeneity across studies, lack of an intake–response relationship, and low or insufficient strength of evidence for related chronic disease endpoints.

Steps 3 and 4: Characterization of Risk and Implications for Public Health

A comparison of the updated potassium AI values to distributions of potassium intakes in the United States and Canada revealed slight differences across population groups reviewed. For instance, in the United States, non-Hispanic blacks tended to have lower potassium intakes than their non-Hispanic white and Hispanic counterparts. Because it is unknown how the AI value relates to actual requirements, interpretation of intakes below the AI in terms of inadequacy cannot be made.

The committee cautions against misinterpretation of the revised potassium DRIs. The potassium AIs, although based on evidence from normotensive adult males and females, are intended to be applicable to the broader apparently healthy population. The previous potassium AI for adults was based on evidence from potassium supplementation trials that investigated chronic disease–related health outcomes. In the expanded DRI model, chronic disease risk reduction is characterized under a separate DRI category. The lack of a potassium CDRR does not necessarily indicate that there is a lack of an effect of potassium intake. Rather, the moderate strength of evidence for a blood pressure lowering effect of potassium supplementation, coupled with both a lack of an intake–response relationship and a lack of evidence of an effect on chronic disease endpoints, highlights

the need for further exploration of the effect of different doses and forms of potassium. Similarly, the absence of a potassium UL does not mean there is no risk from excessive intake either overall or for segments of the population. Caution against high intake through supplemental potassium is warranted for certain population groups, particularly those with or at high risk for compromised kidney function.

DIETARY REFERENCE INTAKES FOR SODIUM

Step 1: Review and Selection of Indicators

Indicators to Establish Sodium DRIs for Adequacy

The committee's review of the evidence on potential indicators to inform the sodium DRIs for adequacy revealed the following:

- There is no sensitive biomarker that can be used to characterize the distribution of sodium requirements in the apparently healthy population.
- Sodium balance studies generally had small sample sizes and incomplete measurement of losses, which limits generalizability and accuracy. Furthermore, intra-individual variability and emerging evidence of infradian rhythms (i.e., lasting more than 24 hours) augment the uncertainty related to the duration needed to reach a steady state; recent evidence on potential skin and muscle sequestration may also affect the interpretation of data from balance studies.
- There is a limited and inconsistent body of evidence on the potential harms of low sodium intake. The inconsistency appears to be caused, in part, by methodological approaches used in observational studies.

The committee concludes that none of the reviewed indicators of sodium requirements offer sufficient evidence to establish Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) values. Adequate Intakes (AIs) are therefore established. Median population intakes are not suitable for establishing sodium AIs because they exceed the sodium Chronic Disease Risk Reduction Intake (CDRR) values. The committee concluded that the lowest levels of sodium intake evaluated in randomized trials and evidence from the best-designed balance study conducted among adults were congruent and are appropriate values on which to establish the sodium AIs.

Indicators to Establish Sodium DRIs for Toxicity

The committee's review of the evidence on potential indicators to inform the sodium DRIs for toxicity revealed the following:

- Very high, acute intakes of sodium have resulted in hypernatremia (serum sodium concentration > 145 mmol/L) and death, but such intakes generally occur only under extreme circumstances.
- There is evidence to suggest that adverse effects could result when sodium is consumed in a concentrated form, but the evidence does not currently allow for quantification of a UL based on a specific toxicological effect.
- Some trials have reported headaches to be less prevalent during the lower-sodium period or in the lower-sodium group of participants, as compared to those in the higher-sodium interventions. Current evidence does not characterize the type, severity, duration, and frequency of headaches reported.

The committee concludes that there is insufficient evidence of sodium toxicity risk within the apparently healthy population to establish a sodium Tolerable Upper Intake Level (UL).

Indicators to Establish DRIs Based on Chronic Disease

The committee's review of the evidence on potential indicators to inform the sodium DRIs based on chronic disease revealed the following:

- Few trials have assessed the effect of sodium intake reductions on the following indicators: cardiovascular mortality, myocardial infarction, left ventricular mass, stroke, osteoporosis, or kidney disease. The strength of evidence for causal relationships between sodium intake and these indicators was rated as low or insufficient.
- There is a moderate strength of evidence for a causal relationship between reductions in sodium intake and all-cause mortality. There are, however, more specific chronic disease endpoints with moderate or high strength of evidence.
- There is a moderate strength of evidence for a causal relationship between reductions in sodium intake and any cardiovascular event.[7] Likewise, there was moderate strength of evidence from

[7]In contrast to meta-analyses examining a single cardiovascular event as an outcome (e.g., a meta-analysis of cardiovascular mortality data), this meta-analysis combines data on cardiovascular events together (e.g., mortality, stroke, heart failure).

randomized controlled trials to suggest that reducing sodium intake reduces hypertension incidence.

- There is a high strength of evidence from randomized controlled trials that reducing sodium intake reduces systolic and diastolic blood pressure. Much of the observed heterogeneity among trials examining systolic blood pressure could be explained by the net reduction in sodium (intake–response) and the baseline systolic blood pressure level. Among trials examining diastolic blood pressure, heterogeneity was mainly related to the difference in the size, rather than in the direction, of the effect. The effect of sodium reduction was greater among adults with hypertension, but it was also evident among nonhypertensive adults.

The committee concludes there is moderate to high strength of evidence for both a causal relationship and an intake–response relationship between sodium and several interrelated chronic disease indicators: cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure. Evidence from these indicators can be synthesized to inform the development of a sodium Chronic Disease Risk Reduction Intake (CDRR).

Step 2: Establishing Sodium Dietary Reference Intake Values

Establishing the Sodium AIs

To establish the sodium AIs, the committee reviewed the range of sodium intakes that have been assessed in sodium reduction trials included in the *AHRQ Systematic Review*. In a controlled feeding trial, the lowest levels of sodium intake ranged from 949 to 2,452 mg/d (41 to 107 mmol/d). The low sodium intake group or period in eight additional sodium reduction trials was below 1,800 mg/d (78 mmol/d). Across the trials, no deficiency symptoms were reported. Furthermore, there was insufficient evidence that low sodium intakes are associated with other potential harmful health effects. Taking these two types of evidence, together with evidence from the best-designed balance study, in which approximately neutral balance was achieved with daily heat stress[8] at sodium intake of 1,525 mg/d (66 mmol/d), the committee established the sodium AIs for adults 19 years of age and older at 1,500 mg/d (65 mmol/d). The adult AI was extrapolated to children and adolescents 1–18 years of age based on sedentary Estimated Energy Requirements. The sodium AIs for infants were derived from estimates of sodium intakes in breastfed infants.

[8]This text was revised since the prepublication release.

Establishing the Sodium CDRRs

The sodium CDRR for adults is based on a synthesis of evidence from sodium-reduction trials and outcomes of incident cardiovascular disease, incident hypertension, systolic blood pressure, and diastolic blood pressure. The sodium CDRR is the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. Further reductions in sodium intake below the CDRR have demonstrated a lowering effect on blood pressure, but the effect on chronic disease risk could not be characterized.

Although there was insufficient evidence to establish a CDRR based on trials conducted in children and adolescents, there is evidence of blood pressure and cardiovascular disease risk tracking from early childhood into adulthood. Despite uncertainties about the long-term chronic disease benefits of reduced sodium intake beginning in childhood, the committee considered the risk of not setting a CDRR for children and adolescents to outweigh the risk of establishing a CDRR. In the absence of indicators for adverse effects, the adult CDRR is extrapolated to children and adolescents 1–18 years of age based on sedentary Estimated Energy Requirements.

Summary of the Sodium DRIs

The committee updated the sodium AIs across the DRI age, sex, and life-stage groups and introduced CDRRs for individuals 1 year of age and older (see Table S-2). There is insufficient evidence to establish EARs, RDAs, or ULs for sodium. A summary of the updated sodium DRIs is presented in Box S-3.

Steps 3 and 4: Characterization of Risk and Implications for Public Health

The vast majority of the U.S. and Canadian populations consume sodium above both the AI and CDRR values. There is no concern regarding sodium inadequacy in the population. Intakes above the CDRR, however, increase the risk of chronic disease in the population. Although larger effects of sodium reduction on blood pressure have been observed in adults with hypertension as compared with normotensive adults, the benefits of sodium intake reduction related to the CDRR are applicable to both. The evidence was insufficient to further define the applicable population (e.g., by age, weight status, race/ethnicity, comorbidities). As such, the committee notes that there are population groups with higher prevalence and risk for hypertension and cardiovascular disease. These include, but are not limited to, older individuals and certain race/ethnicity groups, particularly

TABLE S-2 Sodium Dietary Reference Intakes by Age, Sex, and Life-Stage Group

Life-Stage Group	AI (mg/d)	UL	CDRR
Infants			
0–6 months	110[a]	ND[b]	ND[c]
7–12 months	370	ND[b]	ND[c]
Children			
1–3 years	800[a]	ND[b]	Reduce intakes if above 1,200 mg/day[d]
4–8 years	1,000[a]	ND[b]	Reduce intakes if above 1,500 mg/day[d]
Males			
9–13 years	1,200[a]	ND[b]	Reduce intakes if above 1,800 mg/day[d]
14–18 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day[d]
19–30 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day
31–50 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day
51–70 years	1,500[a]	ND[b]	Reduce intakes if above 2,300 mg/day
> 70 years	1,500[a]	ND[b]	Reduce intakes if above 2,300 mg/day
Females			
9–13 years	1,200[a]	ND[b]	Reduce intakes if above 1,800 mg/day[d]
14–18 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day[d]
19–30 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day
31–50 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day
51–70 years	1,500[a]	ND[b]	Reduce intakes if above 2,300 mg/day
> 70 years	1,500[a]	ND[b]	Reduce intakes if above 2,300 mg/day
Pregnancy			
14–18 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day[d]
19–30 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day
31–50 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day
Lactation			
14–18 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day[d]
19–30 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day
31–50 years	1,500	ND[b]	Reduce intakes if above 2,300 mg/day

NOTE: AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; ND = not determined; UL = Tolerable Upper Intake Level.

[a]Updated DRI value, as compared to the *2005 DRI Report*.

[b]Not determined owing to lack of a toxicological indicator specific to excessive sodium intake.

[c]Not determined owing to insufficient strength of evidence for causality and intake–response.

[d]Extrapolated from the adult CDRR based on sedentary Estimated Energy Requirements.

BOX S-3
Summary of the Updated Sodium Dietary Reference Intakes

- As was the case in the *2005 DRI Report*, there remains insufficient evidence to establish Estimated Average Requirements or Recommended Dietary Allowances for sodium.
- The Adequate Intake (AI) for adults 19 years of age and older is based on the lowest levels of sodium intakes evaluated in randomized controlled trials for which there was no evidence of deficiency, evidence from the best-designed balance study, and insufficient evidence of harmful effects from observational studies. Sodium AIs for children and adolescents were extrapolated based on sedentary Estimated Energy Requirements. For infants, the AIs were derived from estimates of sodium intakes in breastfed infants.
- There is insufficient evidence of toxicological risk from high levels of sodium intake, separate from chronic disease risk. As such, no sodium Tolerable Upper Intake Level is established.
- There is sufficient evidence for the causal and intake–response relationships between sodium intake and chronic disease risk; therefore, the committee has established a sodium Chronic Disease Risk Reduction Intake (CDRR). The sodium CDRR integrates evidence of the beneficial effect of the reduction of sodium intake on cardiovascular disease risk, hypertension risk, systolic blood pressure, and diastolic blood pressure.

For sodium, the CDRR is the intake above which intake reduction is expected to reduce chronic disease risk within an apparently healthy population.

non-Hispanic blacks. Reducing intake toward the CDRR level will likely be particularly beneficial for these groups. Although there is evidence that further reductions in sodium intake below the CDRR can lower systolic and diastolic blood pressure, the effect on chronic disease risk cannot be characterized at this time.

The committee cautions against misinterpretation of the revision to the sodium DRIs. The sodium AI for adults 19–50 years of age that was established in *2005 DRI Report* is reaffirmed. There remains limited evidence on sodium intakes below 1,500 mg/d (65 mmol/d), which prevented the committee from considering further reductions in the sodium AI. With the expansion of the DRI model, the UL now represents an intake above which toxicological risk increases. The risk that was formerly characterized in the sodium UL established in the *2005 DRI Report* is now captured in the CDRR. The sodium CDRR, however, extends beyond the approach and evidence that informed the sodium UL in the *2005 DRI Report*. The sodium CDRR is derived from evidence of risk of incident cardiovascular disease and incident hypertension, and reductions in systolic and diastolic blood pressure. It also

incorporates different methodologies, including use of a systematic review, committee-conducted meta-analyses, and grading of the evidence.

RESEARCH NEEDS AND FUTURE DIRECTIONS

The expansion of the DRI model afforded the committee the opportunity to specify the lowest level of sodium intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction in the population. This expansion also created challenges for the committee to define the potassium AIs and the sodium UL, which previously drew on evidence related to chronic disease endpoints. The refinement of the DRI categories brought to light the dearth of evidence on potassium and sodium requirements outside of the chronic disease context. Characterizing the toxicological effects of excessive potassium and sodium intake levels also posed challenges, as human studies are not designed to examine toxic effects because of ethical considerations.

Future potassium and sodium DRIs would benefit from additional research that identifies requirements for both nutrients and better characterizes negative health effects from high intake levels, to the extent that safety can be assessed. Future updates to the sodium CDRR would benefit from research that provides additional insight into population groups that have different responses to sodium intake. With the vast majority of the U.S. and Canadian populations consuming sodium at levels above the CDRR, opportunities exist to find novel solutions to reduce population sodium intakes, including technical innovations to decrease sodium in the food supply. Regarding potassium, the evidence on the relationships with chronic disease endpoints was of insufficient strength to establish a CDRR. Future trials that assess the long-term effects of different doses and forms of potassium are needed to characterize the intake–response relationship with blood pressure and chronic disease outcomes. Methodologically rigorous randomized controlled trials that study the effect of sodium on chronic disease endpoints are also still needed. Furthermore, additional research is needed on the interrelationship between potassium and sodium intakes.

Finally, as the first to implement the guidance in the *Guiding Principles Report*, the committee identified opportunities for improvement. These opportunities are related to defining applicable populations when prevalence of chronic disease is high, integrating a systematic review of the evidence into the DRI process, adapting the guidance and recommendations for establishing DRIs based on the expanded model, and providing additional guidance on the expanded DRI model as experience is gained over time.

Part I

Part I of this report presents background information about the study and a description of the methodological considerations reviewed by the committee in its approach to establish Dietary Reference Intakes (DRIs) for potassium and sodium. This part of the report consists of three chapters.

Chapter 1 provides context for the study. The chapter includes an introduction to the DRIs, the DRI organizing framework, and the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks*. The chapter also presents the Statement of Task for this study and a brief overview of the committee's approach to its task.

Chapter 2 presents an overview of how the committee applied guidance from the 2017 National Academies of Sciences, Engineering, and Medicine report *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* to its derivation of DRIs based on chronic disease.

Chapter 3 presents the methodological considerations related to assessing the evidence on potassium and sodium intake. The chapter discusses the application of the evidence to the decisions that informed the committee's approach to establishing DRIs for potassium and sodium.

1

Introduction

The Dietary Reference Intakes (DRIs) are a set of quantitative reference values developed jointly for the United States and Canada. They are derived through an iterative process that has evolved to account for advancements in their supporting data and evidence, changes in population-based public health concerns, and a widening range of adaptation to various applications and uses. The DRIs recognize the need for adequate intakes of essential nutrients in order to prevent deficiency diseases, and they have been broadened to recognize the need for safe intakes of nutrients and other food substances, as well as the role of nutrients and other food substances in reducing the risk of chronic disease.

The DRIs were built on the concepts that defined their precursor, the Recommended Dietary Allowances (RDAs). The RDAs were conceived as recommended nutrient intake levels "judged on the basis of available scientific evidence to meet the known nutritional needs of practically all healthy persons in the United States" (IOM, 1994, p. 4). These recommended nutrient intakes provided "standards to serve as a goal for good nutrition and as a 'yardstick' by which to measure progress toward that goal" (NRC, 1941, p. 1). When the RDAs were developed, nutritional deficiency diseases were prevalent across the population. As the public health burden of these conditions diminished with improvements in dietary intake, concerns about the risk of diet-related chronic disease began to emerge. The growing evidence of, and attention to, the relationship between diet and risk of chronic disease (HHS, 1988; NRC, 1989) prompted members of the Food and Nutrition Board to consider whether the RDAs should be revised to

better integrate the concept of a health-promoting diet while retaining their foundational concepts (IOM, 1994).

The model that emerged, the DRIs, included reference values to ensure intake adequacy (Estimated Average Requirement [EAR] and RDA) and an upper bound of a safe and adequate intake range (Tolerable Upper Intake Level [UL]). As the DRIs were further developed, the Adequate Intake (AI), Acceptable Macronutrient Distribution Range (AMDR), and Estimated Energy Requirement (EER) were incorporated into the model.

Although it envisioned consideration of evidence for chronic disease risk (IOM, 1994), the DRI model proved to be challenging and insufficient for that purpose (IOM, 2008). For example, whereas threshold models were useful for setting DRIs for adequacy and toxicity, these models did not work well for informing DRI decisions about the role of nutrient intake in reducing chronic disease risk. The relationships of nutrient intakes to adequacy are based on experimental evidence for a deficiency, and for some nutrients there are relationships with toxicity outcomes. This manifests in a curvilinear relationship (between inadequacy on the lower end and toxicity on the upper end) that makes it possible to identify a "cut point" or threshold effect for defining the DRIs. Conversely, relationships between diet and chronic disease risk are dependent on a variety of factors, both nutritional and nonnutritional. These factors involve lengthy exposure times and include an individual's baseline risk for the chronic disease, environmental factors, nutrient–diet or nutrient–nutrient interactions, and lifestyle factors other than diet. The intake–response relationships between nutrient intakes and chronic disease risk often differ from the threshold relationships observed for adequacy and toxicity effects.

With the evolution of both the DRI model and the definition of nutritional health to include not only essential nutrients but also other nutritional substances in foods, the DRI Steering Committee of the U.S. and Canadian governments recognized the need to reexamine the DRI model to consider inclusion of chronic disease endpoints in the process. It asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to undertake the task. The resulting report, *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (hereafter referred to as the *Guiding Principles Report*), provides guidance and recommendations for expanding the DRI model to include a new category of values specific to chronic disease risk reduction (NASEM, 2017).

This study represents the first effort to apply the recommendations from the *Guiding Principles Report* to the process of deriving DRIs for sodium and potassium. Potassium and sodium are physiologically essential nutrients. Their functions are closely intertwined, and each has important roles in maintaining physiological homeostasis. Both nutrients have also been implicated in chronic disease risk, particularly cardiovascular disease,

mainly through their effects on blood pressure. Additionally, a possible association of sodium intake with adverse outcomes has been suggested at low levels of intake. For purposes of reviewing intake recommendations for these nutrients, the coexistence of their physiological essentiality with their relationships to adverse health effects, including chronic disease risk, called for an expanded DRI model. Guidance on expanding the DRI model is offered in the *Guiding Principles Report*.

STUDY OVERVIEW AND STATEMENT OF TASK

In 2013, the DRI Steering Committee implemented a new process by which nutrients and other food substances would be nominated for DRI review (HHS, 2018). The intent of this process was for DRI updates to be determined by the emergence of new and significant evidence with public health relevance, rather than being determined by the amount of time that had elapsed since the last DRI review. Twenty-six submissions nominating 16 different nutrients were received. The federal agencies that make up the DRI Steering Committee prioritized the list of nominated nutrients, and selected omega-3 fatty acids, potassium and sodium, magnesium, and vitamin E for further consideration.

Preparation for new DRI reviews included efforts to determine how evidence on chronic disease could be used in deriving DRI values. Recognizing that a DRI based on chronic disease would not necessarily fit the existing DRI framework, the DRI Steering Committee organized a multidisciplinary working group in 2014 to identify and offer solutions to the challenges that DRI committees would likely encounter. The working group released its report in 2017, *Options for Basing Dietary Reference Intakes (DRIs) on Chronic Disease: Report from a Joint U.S.-/Canadian-Sponsored Working Group* (*Options Report*) (Yetley et al., 2017). As noted above, a National Academies consensus committee was charged with reviewing the *Options Report* and providing guiding principles for developing DRIs based on chronic disease. The resulting report, the *Guiding Principles Report* (NASEM, 2017), provides guidance and recommendations for expanding the DRI model to include a new category of values specific to chronic disease risk reduction; the intent was for future DRI committees to incorporate this guidance into the existing DRI process.

Since the DRIs for sodium were established in 2005, two Institute of Medicine reports were published with widely varying conclusions about the implications for optimal intake levels of sodium and strategies for reduction in intake (IOM, 2010, 2013). These reports, along with additional emerging evidence, reignited the debate about optimal levels of sodium intake. In response, Congress requested that the Centers for Disease Control and Prevention (CDC) undertake a review of the DRIs for sodium.

The inextricable link between potassium and sodium, in both physiology and study designs, make their concurrent review for purposes of the DRIs both scientifically justified and efficient. CDC, together with the Food and Drug Administration, Health Canada, the National Institutes of Health, the Public Health Agency of Canada, and the U.S. Department of Agriculture, asked the National Academies to undertake a review of the DRIs for sodium and potassium.

As set forth in the Statement of Task (see Box 1-1), the committee was asked to review current evidence and update, as appropriate, the DRIs for sodium and potassium that were established in the 2005 report, *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (hereafter referred to as the *2005 DRI Report*) (IOM, 2005). In its review of the evidence, the committee was asked to apply the guidance provided in the *Guiding Principles Report* (NASEM, 2017), which allows for a new category of DRIs to be established when there is sufficient strength of evidence for the relationship between intake and chronic disease risk.[1] To fulfill its task, the committee was provided with an Agency for Healthcare Research and Quality (AHRQ) systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (hereafter referred to as the *AHRQ Systematic Review*) (Newberry et al., 2018).

The committee was tasked with reviewing and assessing the evidence on potassium and sodium adequacy and toxicity, as well as each nutrient's relationship with chronic disease risk, to derive the quantitative reference intake values, as appropriate. Translating the DRIs into food-based guidance is an important application, but it is beyond the scope of this study. Thus, the committee focused its evidence review on the independent effects of potassium and sodium intake. To guide its review of the evidence and its derivation of DRIs for potassium and sodium, the committee followed the previously existing DRI model, where applicable, and integrated guidance from the *Guiding Principles Report*. The *Guiding Principles Report* expands the model to include a new DRI category that characterizes the relationship between intake and chronic disease risk. This new DRI category, described in detail in Chapter 2 as it applies to potassium and sodium, does not replace the prior DRI model and leaves the other DRI categories largely intact. The following sections provide a brief overview of key concepts of the DRI model that existed before the *Guiding Principles Report*

[1]For consistency throughout this report and in alignment with the terminology used in the *AHRQ Systematic Review*, the committee uses the term *strength of the evidence* instead of *quality of the evidence* or *certainty of the evidence* when describing the grading of the evidence used to derive DRIs based on chronic disease. A description of the guidance provided in the *Guiding Principles Report* (NASEM, 2017) on using the strength of the evidence and the committee's application of that guidance in its review of the evidence on potassium and sodium is provided in Chapter 2.

BOX 1-1
Statement of Task

An ad hoc committee will undertake a study to assess current relevant data and update, as appropriate, the Dietary Reference Intakes (DRIs) for sodium and potassium intake. The review will include consideration of indicators of deficiency, inadequacy, and toxicities, as well as relevant chronic disease endpoints. The study will incorporate the Agency for Healthcare Research and Quality (AHRQ) systematic evidence review of sodium and potassium on chronic disease endpoints, as appropriate, and the Health and Medicine Division report on guiding principles for inclusion of chronic disease endpoints along with the DRI organizing framework. Indicators for adequacy and excess will be selected based on the strength and quality of the evidence and the demonstrated public health significance, taking into consideration sources of uncertainty in the evidence. Estimates of dietary intake of sodium and potassium will be compatible with optimal health throughout the lifespan and may decrease risk of chronic disease where data indicate they play a role.

Specifically, in carrying out its work, the committee will

1. Review evidence on indicators of inadequacy and potential effects of low sodium and potassium intakes and on indicators of excess intake relevant to the general U.S. and Canadian populations, including for those subgroups whose needs for or sensitivity to the nutrient may be affected by blood pressure, increased age, or factors related to race/ethnicity, and by particular conditions which are widespread in the population such as obesity, hypertension, diabetes, or chronic kidney disease.
2. Consider systematic evidence-based reviews including those made available by the sponsors and carefully document the approach used by the committee to select reviews and conduct any of its own literature reviews of original studies and systematic reviews, including, but not limited to, databases, search criteria, inclusion and exclusion criteria for studies, study quality assessment criteria, and relevance to the task at hand, consistent with generally accepted procedures used by systematic reviews. Summary tables of studies based on relevant indicators used to assess the DRI shall include, but not be limited to, the study design; setting; participant age, gender, or life-stage group; sample size; intervention or exposure; methods used to determine nutrient intake levels and outcome measures; and a description of the statistical analysis used by investigators.
3. As specified in the organizing framework, review and describe, as appropriate, dietary sources (e.g., foods, beverages, supplements, antacids, and water).
4. Update indicators on which to base the DRIs and update the DRI values, as appropriate, for each age, gender, and life-stage group, using the risk assessment approach as described in the DRI organizing framework and drawing on the DRI guiding principles for inclusion of chronic disease endpoints.
5. Identify research gaps to address the uncertainties identified in the process of deriving the reference values and evaluating their public health implications.

and provide a summary of two reports central to the committee's task—the *2005 DRI Report* and the *AHRQ Systematic Review*.

The DRI Organizing Framework

The DRI organizing framework provides a structured process for establishing DRIs (see Box 1-2). Based on a risk assessment framework, the DRI organizing framework outlines four steps for the scientific assess-

BOX 1-2
Dietary Reference Intakes Organizing Framework

Excerpted from the *Dietary Reference Intakes for Calcium and Vitamin D*

Step 1: Indicator Review and Selection

An initial starting point for this report—as for all deliberations based on risk assessment—is the identification and review of the potential indicators to be used. Based on this review, the indicators to be used in developing Dietary Reference Intakes (DRIs) are selected. As described within the DRI framework, this step of indicator identification is outlined as follows:

- **Literature reviews and interpretation.** Subject-appropriate and well-done systematic evidence-based reviews, as well as other relevant scientific reports and findings, serve as a basis for deliberations and development of findings and recommendations for the nutrient under study. De novo literature reviews carried out as part of the study are well documented and include, but are not limited to, information on search criteria, inclusion/exclusion criteria, study quality criteria, summary tables, and study relevance to the task at hand, consistent with generally accepted methodology used in the systematic review process.
- **Identification of indicators to assess adequacy and excess intake.** Based on results from literature reviews and information-gathering activities, the evidence is examined for potential indicators related to adequacy for requirements and the effects of excess intakes of the substance of interest. Chronic disease outcomes are taken into account. The approach includes a full consideration of all relevant indicators, identified for each age, gender, and life-stage group for the nutrients under study, as data allow.
- **Selection of indicators to assess adequacy and excess intake.** Consistent with the general approach, indicators are selected based on the strength and quality of the evidence and their demonstrated public health significance, taking into consideration sources of uncertainty in the evidence. They are in consideration of the state of the science and public health ramifications within the context of the current science. The strengths and weaknesses of the evidence for the identified indicators of adequacy and adverse effects are documented.

ment conducted by DRI committees and provides an objective and flexible scheme for transparent decision making. Although it predates the *Guiding Principles Report*, and therefore describes the approach in the context of identifying adequate and excessive intakes, the DRI framework generally applies to the expanded DRI model as well.

Step 2: Intake–Response Assessment and Specification of Reference Values

The intake–response (more commonly referred to as dose–response) relationships for the selected indicators of adequacy and excess are specified to the extent the available data allow. If the available information is insufficient, then appropriate statistical modeling techniques or other appropriate approaches that allow for the construction of intake–response curves from a variety of data sources are used. In some instances, most notably for the derivation of UL relative to excess intake, it is necessary to make use of specified levels or thresholds in the absence of the ability to describe a dose–response relationship, specifically a no observed effect level or a lowest observed effect level. Further, the levels of intake determined for adequacy and excess are adjusted as required, appropriate, and feasible by uncertainty factors, variance in requirements, nutrient interactions, bioavailability and bioequivalence, and scaling or extrapolation.

Step 3: Intake Assessment

Consistent with risk assessment approaches, after the reference value is established, based on the information derived from scientific studies, an assessment of the current intake of the nutrient of interest is carried out in preparation for the discussion of implications and special concerns. That is, the known intake is examined in light of the reference value established. Where information is available, an assessment of biochemical and clinical measures of nutritional status for all age, gender, and life-stage groups can be a useful adjunct.

Step 4: Discussion of Implications and Special Concerns

Characterization of the implications and special concerns is a hallmark of the organizing framework. For DRI purposes, it includes an integrated discussion of the public health implications of the DRIs and how the reference values may need to be adjusted for special vulnerable groups within the normal population. As appropriate, discussions on the certainty/uncertainty associated with the reference values are included as well as ramifications of the committee's work that the committee has identified as relevant to its risk assessment tasks.

SOURCE: IOM, 2011.

Indicators for Developing DRIs

A critical step in the DRI organizing framework is identifying and selecting indicators of adequate and excessive intakes. In this context, an indicator broadly refers to clinical endpoints, biomarkers, surrogate markers, and chronic disease risk factors. As quantitative reference intake values, the DRIs are intended to be derived using evidence based on indicators that are "feasible, valid, reproducible, sensitive, and specific" (WHO, 2006, p. 24). The scientific literature includes evaluation of relationships between potassium and sodium intakes and a variety of indicators (see Appendix D), but not all indicators are relevant for establishing a DRI. Final selection of an indicator is guided by consideration of the strength of the evidence and its public health significance.

Dietary Reference Intake Categories

The DRIs include several categories of reference values that serve different purposes and convey different information. The DRI categories described below are those that are relevant to the committee's task of reviewing DRIs for potassium and sodium that existed in the DRI model prior to the *Guiding Principles Report*. Other reference values not relevant to this task—the EER and the AMDR—have been detailed elsewhere (IOM, 2006). Chapter 2 provides additional context and information regarding the new DRI category based on chronic disease.

Estimated Average Requirement The EAR is "the average daily nutrient intake level that is estimated to meet the nutrient needs of half of the healthy individuals in a life-stage or gender group" (IOM, 2006, p. 10). Because nutrient needs in a population are variable, the EAR is based on the statistical concept of distribution and is an estimate of the *median* requirement for a nutrient (see Figure 1-1). As such, the EAR is expected to exceed the needs of half of the population and fall below the needs of the other half. The EAR is used in the planning and assessment of adequate dietary intake of groups.

Recommended Dietary Allowance The RDA is "an estimate of the daily average dietary intake that meets the nutrient needs of nearly all (97–98 percent) healthy members of a particular life-stage and gender group" (IOM, 2006, p. 10). As shown in Figure 1-1, an RDA is generally established as the intake level that is two standard deviations above the EAR. An RDA cannot be established without an EAR. Because an RDA exceeds the nutrient requirements for nearly all individuals in the group, it is not intended to be used for assessing or planning intakes for groups; instead,

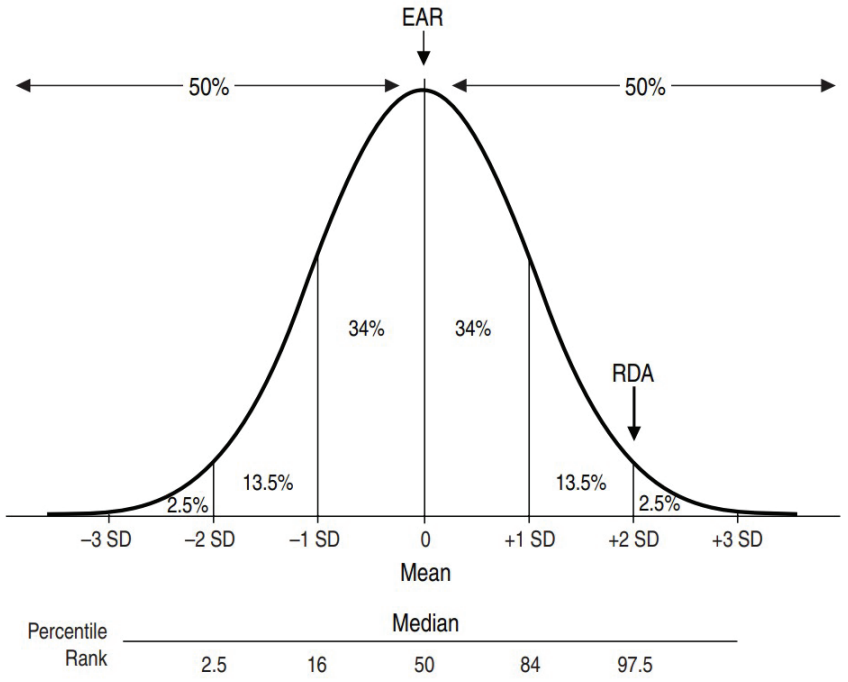

FIGURE 1-1 Normal requirement distribution of hypothetical nutrient showing percentile rank and placement of the EAR and the RDA on the distribution.
NOTE: EAR = Estimated Average Requirement; RDA = Recommended Dietary Allowance; SD = standard deviation.
SOURCE: IOM, 2006.

the RDA has been used for individuals. A usual intake at or above the RDA is characterized as having low probability of being inadequate; the probability of inadequacy increases as intakes fall further away from the RDA (IOM, 2006).

Adequate Intake The AI is "a recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people who are assumed to be maintaining an adequate nutritional state" (IOM, 2006, p. 11). An AI is established when there is insufficient evidence to establish an EAR and an RDA and is expected to meet or exceed the needs of nearly all members of a given sex and life-stage group. Because it cannot characterize risk of inadequacy, an AI is limited in its applications.

Tolerable Upper Intake Level The UL is "the highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular group" (IOM, 2006, p. 11). The potential for risk increases as intake increases above the UL. The absence of a UL for a nutrient likely reflects a lack of evidence rather than a lack of adverse effects, and therefore does not necessarily mean that excessive intakes pose no risks. As discussed in Chapter 2, the *Guiding Principles Report* recommended that in the expanded DRI model, the UL should characterize *toxicological* risk.

Life-Stage Groups

The DRIs are expressed as reference values for groups defined by age, sex, and life stage (e.g., infants, 0–6 months old; males, 14–18 years old; lactating women, 31–50 years old). The DRI age, sex, and life-stage groups allow for the variation in nutrient recommendations to be reflected within a given DRI category (e.g., the AI for an infant can be set lower than the AI for an adult for a given nutrient, as appropriate). The defining characteristics and rationale for such divisions have been detailed in previous reports (IOM, 2006). In context of the expanded DRI model, one of the recommendations in the *Guiding Principles Report* is that extrapolation of DRIs based on chronic disease is appropriate "only to populations that are similar to studied populations in the underlying factors related to the chronic disease of interest" (NASEM, 2017, p. 214).

Applicable Population

The DRIs are intended to provide recommendations for an apparently healthy population, defined as individuals who do not have medical diagnoses or conditions or require medications, medical nutrition therapy, or dietary management with medical foods. Such conditions or diagnoses include but are not limited to malabsorption, malnutrition, or disability requiring decreased energy intakes. Furthermore, the DRIs for adequacy (i.e., EARs and RDAs or AIs) are intended to reflect intakes that meet the needs of apparently healthy age, sex, and life-stage groups.

The *Guiding Principles Report* acknowledged that an apparently healthy population may include individuals with chronic conditions such as obesity, diabetes, or hypertension (whether under medical management or not), but also highlighted the need for DRI committees to characterize which subpopulations are included or excluded in terms of health status for each DRI (NASEM, 2017).

The *2005 DRI Report*

In the *2005 DRI Report*, there was insufficient intake–response data to establish EARs and RDAs for potassium. The potassium AI, established at 4,700 mg/d (120 mmol/d) for adults 19 years of age and older, was "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" (IOM, 2005, p. 235). The selected intake level was further supported by blood pressure evidence in nonhypertensive individuals and epidemiological studies on the relationship between potassium intake and bone loss. The potassium AI for adults was extrapolated to the other DRI age, sex, and life-stage groups. No potassium UL was established, as generally healthy individuals with normal kidney function excrete excess potassium. Individuals with impaired kidney function caused by a medical condition or some medications were identified as groups that should not exceed the potassium AI.

Like potassium, insufficient data on sodium requirements prevented the derivation of EARs and RDAs. The sodium AI, 1,500 mg/d (65 mmol/d) for adults 19–50 years of age, was described as ensuring adequate intake of other important nutrients and covering sodium losses from sweat from physical activity or high temperatures in unacclimatized individuals. The sodium AI was also described as being above the intake level that some studies had reported to have a detrimental effect on blood lipids and insulin resistance. The sodium AI for adults was extrapolated to other DRI age, sex, and life-stage groups. The relationship between sodium intake and blood pressure informed the sodium UL, which was established as 2,300 mg/d (100 mmol/d) for adults 19 years of age and older and extrapolated to other DRI age, sex, and life-stage groups.

The *AHRQ Systematic Review*

Provision of a systematic review to the DRI committee is a recent addition to the process. Only one previous DRI committee—the Committee to Review Dietary Reference Intakes for Vitamin D and Calcium (IOM, 2011)—was provided with systematic reviews to inform its work. AHRQ was responsible for the systematic reviews that informed the 2011 DRI review of calcium and vitamin D, as well as the systematic review that informs this study.

The *AHRQ Systematic Review* sought to answer 8 key questions and 22 subquestions (Newberry et al., 2018) (see Box 1-3). Sodium and potassium each had two key questions designed to explore *effects* of intake on

BOX 1-3
Key Questions Excerpted from the *AHRQ Systematic Review*

Below are the key questions and subquestions that the *AHRQ Systematic Review* sought to answer. These questions were developed prior to the convening of this Dietary Reference Intake committee.

Sodium

1. Among adults and children of all age groups (including both sexes and pregnant and lactating women), what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on blood pressure at the time of the study and in later life?
   a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?
   b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).
   c. Among subpopulations defined by hypertension, diabetes, and obesity health status.

2. Among adults and children, what is the association between dietary sodium intake and blood pressure?
   a. Among subpopulations defined by sex, race/ethnicity, and age (children, adolescents, young adults, older adults, elderly).
   b. Among subpopulations defined by hypertension, diabetes, and obesity health status.

3. Among adults, what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on cardiovascular disease and kidney disease morbidity and mortality and on total mortality?
   a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?
   b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).
   c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

4. Among adults, what is the association between dietary sodium intake and cardiovascular disease, coronary heart disease, stroke and kidney disease morbidity and mortality and between dietary sodium intake and total mortality?
   a. Do other minerals (e.g., potassium, calcium, magnesium) modify the association with sodium?
   b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).

c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

Potassium

5. Among children and adults what is the effect of interventions to increase potassium intake on blood pressure and kidney stone formation?
   a. Do other minerals (e.g., sodium, calcium, magnesium) modify the effect of potassium?
   b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).
   c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

6. Among children and adults, what is the association between potassium intake and blood pressure and kidney stone formation?
   a. Among subpopulations defined by sex, race/ethnicity, and age (children, adolescents, young adults, older adults, elderly).
   b. Among subpopulations defined by hypertension, diabetes, and obesity health status.

7. Among adults, what is the effect of interventions aimed at increasing potassium intake on cardiovascular disease, and kidney disease morbidity and mortality, and total mortality?
   a. Do other minerals modify the effect of potassium (e.g., sodium, calcium, magnesium)?
   b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).
   c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

8. Among adults, what is the association between dietary potassium intake and cardiovascular disease, coronary heart disease, stroke, and kidney disease morbidity and mortality, and between dietary potassium and total mortality?
   a. Do other minerals (e.g., sodium, calcium, magnesium) modify the association with potassium?
   b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).
   c. Among subpopulations defined by hypertension, diabetes, and obesity health status.

SOURCE: Newberry et al., 2018.

select indicators and outcomes, based on evidence from randomized controlled trials; each nutrient also had two key questions designed to explore *associations* between intake and selected indicators and outcomes, based on evidence from observational studies. The *AHRQ Systematic Review* provided detailed syntheses of the available evidence, including meta-analyses of trial data when sufficient evidence was available.[2] The *AHRQ Systematic Review* contains several appendixes that provide in-depth methodological details, including the search strategy, evidence tables, quality assessment, summary of the strength of evidence, and sensitivity analyses.

DESIGN AND APPROACH TO THE STUDY

An ad hoc committee of 14 experts was appointed to respond to the charge set forth in the Statement of Task (see Box 1-1). Committee member expertise included human nutrition across the lifespan, intake assessment methodology, biostatistics, epidemiology, systematic review methodology, cardiovascular disease, hypertension, renal disease, health policy, and risk assessment. Two consultants also provided assistance to the committee in literature search methodologies and sodium and potassium physiology.

The committee undertook several activities to inform its work. It hosted three public sessions over the course of the study, one of which included an opportunity for stakeholders to provide public comment directly to the committee (for public session agendas, see Appendix B). The committee also requested public input to help identify published material that would not be found through a peer-review literature search (e.g., academic, business, government, and industry reports). This request was posted on the study website and also circulated via its electronic mailing list. The call for public input was in addition to the study's feedback mechanism through which stakeholders or interested members of the public could submit comments or materials to the committee throughout the study.

The *AHRQ Systematic Review* (Newberry et al., 2018), provided to the committee by the sponsors, was the primary source of evidence for the relationship between each of the nutrients and chronic disease outcomes, as well as evidence on population subgroups that may be disparately affected by potassium and sodium intake. Prior to using the *AHRQ Systematic Review*, the committee assessed its quality and methodology (see Appendix C) and

[2]A meta-analysis is a statistical analysis that combines the results of multiple scientific studies. Its interpretation is complicated by the presence of heterogeneity among the studies. Observed differences in the intervention effect between the studies could be attributable to variability in clinical diversity (the participants, interventions, and outcomes studied) and/or methodological diversity (differences in study design and risk of bias).

identified two aspects that could be strengthened: the need to explore unexplained heterogeneity in meta-analyses and the need for clear explanations of the process used to grade the strength of the evidence. The committee refined these aspects for key analyses central to its decision making, as further described in Chapters 6 and 10.

To be comprehensive in its review of indicators that could potentially inform a potassium or sodium DRI, the committee also conducted a series of literature scoping searches (see Appendix D). The scoping searches informed the committee's selection of additional indicators that were not included in the *AHRQ Systematic Review* but merited further consideration. Supplemental literature searches were performed for select indicators (see Appendix E).

The Statement of Task directed the committee to provide summary tables of studies used to assess the DRIs (see Box 1-1, numbered item 2). The *AHRQ Systematic Review* provided extensive documentation and tables summarizing all included studies, which the committee used in its review of the evidence. Thus, it would be duplicative for the committee to provide summary tables for every indicator it reviewed. Accordingly, the committee interpreted this component of its charge as including summary tables only for studies that were part of its supplemental literature search.

The committee took similar approaches to reviewing the evidence on potassium and sodium in support of the DRIs for adequacy, for toxicity, and based on chronic disease. However, each nutrient differed in collection of data, had different strengths of evidence, and had different challenges, meriting separate considerations. Throughout this report, the committee offers its synthesis and interpretation of the evidence. For decisions that relied on expert judgment, the committee describes the alternatives it considered and explains why these decisions were made.

ORGANIZATION OF THIS REPORT

This report is divided into four parts. Part I (Chapters 1–3) provides background information about the DRIs, the milestones in DRI history that led to this committee's work, and the sources of evidence the committee used to fulfill its task. Because this is the first DRI committee to apply the guidance in the *Guiding Principles Report* to derive DRIs based on chronic disease, Chapter 2 includes a description of how the guidance was applied and a detailed discussion of concepts related to this new DRI category in the context of the committee's review on potassium and sodium. Chapter 3 discusses methodological considerations related to assessing evidence on potassium and sodium intake and their implications for establishing the DRIs for these nutrients. Part II (Chapters 4–7) provides the committee's evaluation of the evidence and its determination of DRIs for potassium.

Chapter 4 presents the potassium DRIs for adequacy, Chapter 5 presents the potassium DRIs for toxicity, and Chapter 6 summarizes evidence on the relationship between potassium intake and chronic disease risk and explains the committee's determination regarding potassium DRIs based on chronic disease. Chapter 7 compares the potassium DRIs established in this report with current intake levels in the U.S. and Canadian populations, characterizes risk, and describes public health implications and special considerations of the potassium DRI values. Part III (Chapters 8–11) provides the committee's evaluation of the evidence and its derivation of the DRIs for sodium, following the same structure as Part II. Chapter 8 presents the sodium DRIs for adequacy, Chapter 9 presents the sodium DRIs for toxicity, Chapter 10 presents the sodium DRIs based on chronic disease, and Chapter 11 compares the sodium DRIs established in this report with current intake levels in the U.S. and Canadian populations, characterizes risk, and describes public health implications and special considerations of the sodium DRI values. Part IV (Chapter 12) outlines knowledge gaps and research needs to advance understanding of the role of potassium and sodium intake on health and chronic disease, and offers the committee's suggestions for enhancing the DRI process.

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2

Applying the *Guiding Principles Report*

This chapter describes how the committee applied the recommendations from the *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) (NASEM, 2017a) to its review of the Dietary Reference Intakes (DRIs) for potassium and sodium. The committee's interpretation of the *Guiding Principles Report* described in this chapter sets the stage for the evidence review, methodological details, and rationale presented for DRIs based on chronic disease for potassium and sodium (see Chapters 6 and 10, respectively).[1] This chapter also describes the committee's approach to the new DRI category in context of the DRIs for adequacy and toxicity for potassium and sodium.

BACKGROUND

Historically, undernutrition and nutritional deficiencies were prevalent in the population, contributing to high rates of diet-related disease. Although the standardization of food fortification and enrichment along with dietary guidance to the public contributed to reducing the prevalence of nutrition deficiencies, there was a subsequent rise in the prevalence of obesity and related chronic diseases. As the public health burden in the

[1]Throughout this report, *DRIs based on chronic disease* is used when broadly describing the category, such as when referring to the guidance in the *Guiding Principles Report* (NASEM, 2017a). This aligns with the committee's use of the phrases *DRIs for adequacy*, which broadly refers to the Estimated Average Requirement, Recommended Dietary Allowance, and Adequate Intake, and *DRIs for toxicity*, which refers to the Tolerable Upper Intake Level.

United States and Canada shifted toward risk of chronic disease, nutrition science has increasingly focused on the effect of dietary determinants, including nutrients and other food components, as potential modifiers of chronic disease risk.

The public health significance of chronic disease warrants concerted efforts to understand the relationships between diet and chronic disease risk, but such efforts must navigate methodological challenges. Understanding dietary determinants of chronic disease often requires different kinds of conceptual approaches and evidence than are needed for the evaluation of nutrient deficiencies and toxicities. Dietary intake patterns are multidimensional, dynamic, and change over the course of a lifespan. Chronic diseases are complex, multifaceted, and develop over time. These complexities make identifying the relationship between nutrient intake and chronic disease difficult, especially when longitudinal data are limited or unavailable. Additionally, the extended time between exposure and outcome often precludes the use of randomized controlled trials to establish a causal relationship.

Since its inception, the DRIs were intended to consider chronic disease risk (IOM, 1994), but available evidence on chronic disease outcomes was typically too limited to inform the derivation of specific reference values. Furthermore, the DRI process lacked a mechanism for evaluating the evidence for causal and intake–response relationships between nutrient intake and chronic disease risk—two components of the DRI organizing framework (see Chapter 1, Box 1-2). As described in Chapter 1, efforts to overcome these challenges ultimately led to the *Guiding Principles Report* (NASEM, 2017a), which expanded the DRI model to include a new DRI category based on chronic disease.

THE COMMITTEE'S INTERPRETATION OF THE *GUIDING PRINCIPLES REPORT*

The *Guiding Principles Report* provides recommendations on methodological approaches to establishing DRIs based on chronic disease (see Box 2-1). Pursuant to its task (see Chapter 1, Box 1-1), the committee applied those recommendations in context of the available evidence on potassium and sodium. The following sections not only summarize the committee's interpretation of recommendations in the *Guiding Principles Report* that were central to its approach to the new DRI category, but they also describe a few instances in which the committee considered it important and necessary to adapt some of the guidance. The committee notes that adaptations made for potassium and sodium do not invalidate potential applications of the concepts articulated in the *Guiding Principles Report* to future DRI reviews.

BOX 2-1
Recommendations Excerpted from the *Guiding Principles Report*

The recommendations listed below reflect the consensus of a separate National Academies committee, as presented in the *Guiding Principles Report* (NASEM, 2017a).

Recommendation 1: Until better intake assessment methodologies are developed and applied widely, Dietary Reference Intake (DRI) committees should strive to ensure that random and systematic errors and biases of nutrient or other food substance exposure assessment methodologies are considered in their evidence review. In the long term, research agendas should include accelerated efforts to improve nutrient or other food substance exposure assessments for application in studies of chronic disease risk.

Recommendation 2: The ideal outcome used to establish chronic disease DRIs should be the chronic disease of interest, as defined by accepted diagnostic criteria, including composite endpoints, when applicable. Surrogate markers could be considered with the goal of using the findings as supporting information of results based on the chronic disease of interest. To be considered, surrogate markers should meet the qualification criteria for their purpose. Qualification of surrogate markers must be specific to each nutrient or other food substance, although some surrogates will be applicable to more than one causal pathway.

Recommendation 3: The committee recommends that DRI committees use Grading of Recommendations Assessment, Development and Evaluation (GRADE) in assessing the certainty of the evidence related to the causal association between nutrient or other food substances and chronic diseases. Using GRADE, the committee recommends that a decision to proceed with development of chronic disease DRIs be based on at least moderate certainty that a causal relationship exists and on the existence of an intake–response relationship.

Recommendation 4: The committee recommends the use of a single outcome indicator on the causal pathway. However, when a single food substance reduces the risk of more than one chronic disease, reference values could be developed for each chronic disease. The committee, however, does not recommend the use of "multiple indicators of a chronic disease" or "multiple indicators for multiple diseases" unless there is sufficient experience with the use of algorithms or other strong evidence suggesting that multiple indicators point to risk of a chronic disease, due to potential lack of reliability or consistency in the results.

Recommendation 5: The committee recommends extrapolation of intake–response data for chronic disease DRIs only to populations that are similar to studied populations in the underlying factors related to the chronic disease of interest.

continued

BOX 2-1 Continued

Recommendation 6: The committee recommends that DRIs for chronic disease risk take the form of a range, rather than a single number. Intake–response relationships should be defined as different ranges of the intake–response relationship where risk is at minimum, is decreasing, and/or is increasing (i.e., slope = 0, negative, or positive). When a nutrient or other food substance reduces the risk of more than one chronic disease, DRIs could be developed for each chronic disease, even if the confidence levels for each chronic disease are different. The magnitude of risk slope considered necessary to set a DRI should be decided based on clearly articulated public health goals, such as those previously identified by other authorities (e.g., Healthy People 2020). The committee does not recommend, however, developing a family of DRIs for any one nutrient or other food substance for different risk reduction targets for the same chronic disease.

Recommendation 7: The committee recommends retaining Tolerable Upper Intake Levels (ULs) based on traditional toxicity endpoints. In addition, if increased intake of a substance has been shown to increase the risk of a chronic disease, such a relationship should be characterized as the range where a decreased intake is beneficial. If the increase in risk only occurs at intakes greater than the traditional UL, no chronic disease Dietary Reference Intake would be required, because avoiding intakes greater than the UL will avoid the chronic disease risk.

Recommendation 8: The committee recommends that to develop a chronic disease DRI, the level of certainty in the intake–response relationship should generally be the same as the level of certainty for a determination of causality, that is, at least "moderate," using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). However, in some cases, for example when a food substance increases chronic disease risk, the level of certainty considered acceptable might be lower. In all cases, a thorough description of the scientific uncertainties is essential in describing quantitative intake–response relationships. Requiring at least "moderate" certainty extends to cases where relationships between intake and a surrogate marker and between the same surrogate marker and the chronic disease are characterized separately, in a piecemeal (i.e., two-stage) approach.

Recommendation 9: The committee recommends that, if possible, health risk/benefit analyses be conducted and the method to characterize and decide on the balance be made explicit and transparent. Such a decision needs to consider the certainty of evidence for harms and benefits of changing intake and be based on clearly articulated public health goals. If DRI committees do not perform such risk/benefit analyses, it is still necessary to describe the disease outcomes and their severities, the magnitudes of risk increases and decreases over various ranges of intakes, and other factors that would allow users to make informed decisions.

Recommendation 10: Because of the need for close coordination and exchange of ideas when setting DRIs based on indicators of adequacy, toxicity, and chronic disease, one single National Academies of Sciences, Engineering, and Medicine parent committee should develop DRIs for the prevention of nutrient deficiencies and toxicities and for reducing the risk of chronic disease. Due to the need for different expertise and different methodological considerations, two subcommittees could be established at the discretion of the parent committee, for reviewing evidence on (1) adequacy and toxicity and (2) chronic disease, respectively.

Recommendation 11: When sufficient evidence exists to develop chronic disease DRIs for one or more nutrient or other food substances that are interrelated in their causal relationships with one or more chronic diseases, a committee should be convened to review the evidence of their association with all selected diseases. Using a chronic disease as the starting point for the review is not recommended because balancing health risks and benefits for multiple nutrient or other food substances that are related to a single chronic disease endpoint will be a challenge in cases where the same nutrient or other food substances might be associated with more than one chronic disease.

SOURCE: NASEM, 2017a.

Nomenclature and Conceptual Underpinnings

Guidance from the Guiding Principles Report

Nutrient deficiency diseases from inadequate intake and adverse effects from excess intake are well established for many essential nutrients. These relationships are based on the concept of a threshold effect. Intake of an essential nutrient below a certain threshold inevitably leads to deficiencies. For some nutrients, intakes above a certain upper threshold increase risk for adverse effects. As described above, the relationship between intake of a nutrient and risk of chronic disease is more complex; it is unlikely that there is a threshold intake level for which zero risk of chronic disease exists. The *Guiding Principles Report* presented a conceptual diagram of potential intake–response relationships that show variable types of relationships including curvilinear, linear, or U-shaped curves (see Figure 2-1). The different possible intake–response relationships set chronic disease risk apart from the threshold concepts of adequacy and toxicity.

The *Guiding Principles Report* described possible complications in translating the evidence for a chronic disease intake–response relationship into a reference value. For instance, such relationships are often continuous, and benefits of increasing or decreasing intakes could exist across a broad

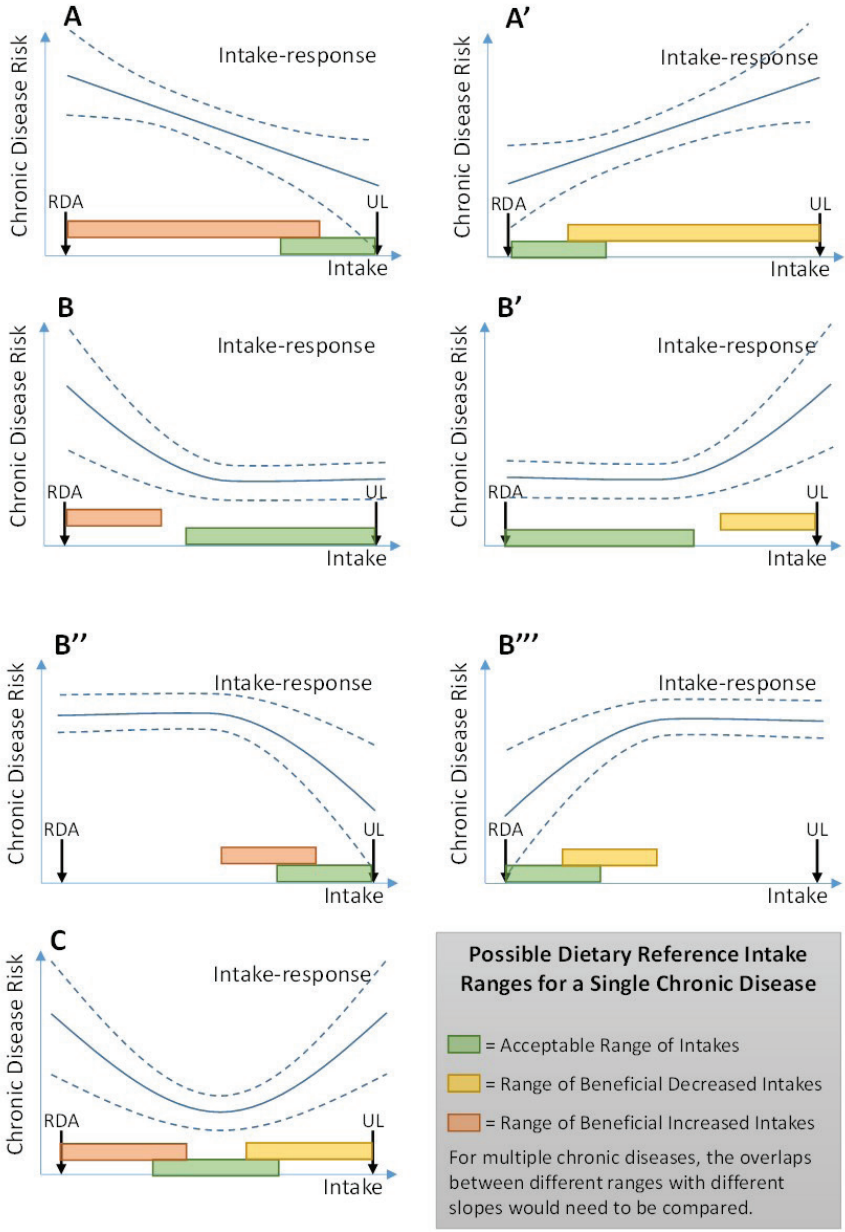

FIGURE 2-1 Possible DRI ranges for a single chronic disease, depending on the shape of the intake–response relationship, as presented in the *Guiding Principles Report*.

FIGURE 2-1 Continued
NOTES: These relationships, and their confidence intervals, are "idealized" and meant for illustration, and are likely to be more complicated (e.g., less smoothly changing) in practice. The different scenarios are qualitatively the same whether absolute or relative risk is considered. However, to estimate the significance of the effect on the population of the different choices of ranges, absolute risks are also needed. Panels A and A′ represent strictly monotonically changing intake–response relationships; panels B, B′, B″, and B‴ represent different "J-shaped" relationships, where there is a plateau at one end of the intake range. Panel C represents a "U-shaped" relationship, where there is an intake level that minimizes risk. RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level; solid line = best estimate of intake–response; dashed lines = confidence intervals of intake–response.
SOURCE: NASEM, 2017a.

range of intakes. Another potential challenge is that individuals within a population may have different baseline risks for chronic disease, owing to factors other than dietary intake (e.g., genetics, other environmental exposures). Such considerations were anticipated to hinder DRI committees' ability to identify a single value to characterize the complexities of the intake–response relationship. The *Guiding Principles Report* therefore described three possible ways to define a DRI based on chronic disease (see Table 2-1).

Committee's Application of the Guiding Principles Report

Although the scope of its work was limited to potassium and sodium, the committee was mindful that its application of the *Guiding Principles Report* might have implications for future DRI reviews, particularly in assessing nonessential nutrients and food substances. One such consideration was the nomenclature the committee used for the new DRI category. In an effort to promote consistency with future DRI reviews, the committee sought to use terminology that would be broadly applicable, yet sufficiently descriptive. The committee acknowledges, however, that the nomenclature used in this report may be reevaluated in future DRI reviews.

The committee considered the use of distinct terms to describe the different types of intake–response relationships that could exist within a new DRI category based on chronic disease (see Figure 2-1 and Table 2-1). However, introducing multiple names and acronyms may be confusing for DRI users. For example, unique terminology for each intake–response relationship has the potential to subdivide the new DRI category in a way that may make it difficult for users to understand the relationship between the DRI values and chronic disease risk. By contrast, a single DRI category that allows flexibility in characterizing the different types

TABLE 2-1 Three Possible DRIs Based on Chronic Disease, as Identified in the *Guiding Principles Report*

Possible DRI for Single Chronic Disease Relationship[a]	Description	Region of Intake–Response
Acceptable Range of Intakes	Range of usual intakes of a food substance without increased risk of chronic disease	Region where slope is flat, outside of which there is increased risk of chronic disease, deficiency, or toxicity
Range of Beneficial Increased Intakes	Range of usual intakes of a food substance where increasing intake can reduce risk of chronic disease	Region where slope is negative, outside of which slope is non-negative, or there is increased risk of deficiency or toxicity
Range of Beneficial Decreased Intakes	Range of usual intakes of a food substance where decreasing intake can reduce risk of chronic disease	Region where slope is positive, outside of which slope is non-negative, or there is increased risk of deficiency or toxicity

[a]In each case, defining the region of the intake–response relationship corresponding to the DRI requires judgment as to what "slope" is small or large enough, and at what confidence level to consider flat, negative, or positive.
SOURCE: Adapted from NASEM, 2017a.

of intake–response relationships for chronic diseases risk would provide greater simplicity and conceptual unity. The committee determined that, in the context of this DRI review, the three terms and descriptions presented in the *Guiding Principles Report* (see Figure 2-1 and Table 2-1) should be consolidated into a single DRI category called the Chronic Disease Risk Reduction Intake (CDRR).

The committee considered several options for the new DRI category before selecting the CDRR. Because the DRIs comprise a set of different reference value categories, labeling the new category itself the *chronic disease DRIs* or *DRI based on chronic disease* had the potential of dividing the DRIs into "the adequacy and toxicity DRIs" and "the chronic disease DRIs." Such a distinction would appear to counter the *Guiding Principles Report* recommendation that a single DRI committee be convened to establish the adequacy, toxicity, and chronic disease reference values for a specific nutrient (see Box 2-1, *Guiding Principles Report* Recommendation 10). Accordingly, the committee considered it important to use nomenclature that positioned the new category as one of several DRI categories. The committee also considered how to align the nomenclature with the naming convention used for the other DRI categories, which include descriptions such as "level," "requirement," and others. Although the *Guiding Princi-*

ples Report conceptualized this new category to be expressed as a range, the committee's experience suggested that there may be circumstances in which a range may not be a sufficiently clear, effective, or appropriate expression of the CDRR. One option considered was using "target" or "goal," but such descriptions had the potential to convey a threshold between risk and no risk for chronic disease. Ultimately, the committee determined that "intake" was sufficiently descriptive and would likely be broadly adaptable to different scenarios. The omission of the "I" in the acronym for this category is for simplicity, similar to the abbreviation of UL (for Tolerable Upper Intake Level).

Although its approach to reviewing the evidence to establish DRIs based on chronic disease and deriving the sodium CDRRs was conceptually aligned with the *Guiding Principles Report*, the committee further considered issues of implementation and clarity of communication in the expression of values. The sodium CDRR values established in this report were informed by the shape and strength of evidence[2] for the intake–response relationship over the studied range of intakes. Defining the upper end of the range for sodium posed challenges. Had the committee established the sodium CDRR as a range and required moderate strength of evidence for an intake–response relationship to do so, the upper bound would be a sodium intake level that is exceeded by a portion of the population (see Chapter 11, Tables 11-4 and 11-6). Such a range would be subject to possible misinterpretation. First, it could be incorrectly viewed as a desirable range of intakes (akin to the concept of the Acceptable Macronutrient Distribution Range), rather than a range of intakes over which reductions in sodium intake are expected to reduce chronic disease risk. Second, it could be incorrectly interpreted as suggesting that high intakes are not associated with chronic disease risks, whereas intakes above this range are likely to pose a continuing risk. The committee was further challenged by the lack of evidence suitable for deriving a sodium UL based on *toxicological* adverse effects. As shown in Figure 2-1, the *Guiding Principles Report* had conceptualized the UL as intake level above which the CDRR would not need to be characterized, because the potential for toxicological risk would be increasing. Without a UL for sodium, this principle could not be applied. This situation fit the scenario anticipated by the *Guiding Principles Report* in which a lower strength of evidence of the intake–response relationship could be used to support a DRI based on chronic disease (see Box 2-1, *Guiding Principles Report* Recommendation 8). Thus, the committee extrapolated

[2]For consistency throughout this report and in alignment with the terminology used in the *AHRQ Systematic Review*, the committee uses the term *strength of the evidence* instead of *quality of the evidence* or *certainty of the evidence* when describing the grading of the evidence used to derive DRIs based on chronic disease.

the intake–response relationship for sodium and chronic disease risk above the intake range where the strength of evidence was at least moderate. As detailed in Chapter 10, the committee expressed the sodium CDRR as the lowest intake level of intake for which there was sufficient evidence to characterize chronic disease risk reduction (see Box 2-2).

Strength of the Evidence

Guidance from the Guiding Principles Report

One of the general assumptions underpinning the DRI model is that available data are often insufficient to draw conclusions, and scientific judgment and transparent documentation must be used when assessing scientific uncertainties (Taylor, 2008). Another general assumption is that failure to derive a reference value is often not a viable public health option (Taylor, 2008). In the case of essential nutrients, there is an obligation for a DRI committee to determine DRIs for adequacy (i.e., Estimated Average Requirements [EARs] and Recommended Dietary Allowances [RDAs], or Adequate Intakes [AIs] when an EAR and an RDA cannot be derived). Accordingly, a DRI committee uses the best available evidence to do so. Similarly, if there is evidence of adverse effects from high levels of intake, a DRI committee uses its expert judgment and best available evidence to determine a level of intake after which risk increases to establish a UL. In contrast, the *Guiding Principles Report* described the new DRI category as being established only when the body of evidence on the relationship between a nutrient and chronic disease risk is sufficient and when an intake–response relationship can be characterized. The conceptual distinction between these DRI categories is summarized in Table 2-2.

BOX 2-2
Chronic Disease Risk Reduction Intake for Sodium

Context: The sodium Chronic Disease Risk Reduction Intake (CDRR) is the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. The concept of a range is embedded in the expression of the sodium CDRR in that for intakes above the CDRR, reduction in sodium intake is expected to reduce chronic disease risk.

For sodium, the CDRR is the intake above which intake reduction is expected to reduce chronic disease risk within an apparently healthy population.

TABLE 2-2 Conceptual Distinction Between DRIs for Adequacy and Toxicity and DRIs Based on Chronic Disease

DRIs for Adequacy and Toxicity	DRIs Based on Chronic Disease
Needed because deficiencies (of essential nutrients) and toxicities:	Are not warranted unless sufficient evidence exists because:
• Will affect everyone, if intake is inadequate or excessive • Are caused by a single nutrient • Are prevented by nutritional interventions	• Risk to acquire chronic diseases varies by individual • Chronic diseases are often related to many risk factors (e.g., genetic, environmental) • Nutritional interventions will only partly ameliorate the risk of chronic disease

SOURCE: Adapted from NASEM, 2017b.

Recognizing the potential for misinterpretation from the results of individual studies, various tools have been developed to assess the strength of scientific evidence that examines a specific health-related question. These tools support a more objective and transparent process, although expert interpretation and judgment are still needed. To determine the strength of the body of evidence for a relationship between intake and chronic disease risk, the *Guiding Principles Report* (NASEM, 2017a) recommended using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE, which was developed in the health care context (see Figure 2-2), rates a body of evidence by assessing five domains that may reduce the strength of the evidence and three domains that may increase the strength (see Box 2-3). This assessment leads to one of four ratings—high, moderate, low, or very low—to describe the certainty in how close the estimated effect is to the true effect (Balshem et al., 2011). The *Guiding Principles Report* recommended a GRADE rating of at least moderate strength for both the causal relationship and the intake–response relationship for the DRI based on chronic disease to be established, although it was also noted that "when a food substance increases chronic disease risk, the level of certainty considered acceptable might be lower" (NASEM, 2017a, p. 220).

Committee's Application of the Guiding Principles Report

The DRI organizing framework guides DRI committees to establish reference values based on the strength of the evidence. The DRI organizing framework provides flexibility to accommodate different evidentiary scenarios that DRI committees may encounter and allows committees to factor in public health ramifications. To that end, the processes for assessing the

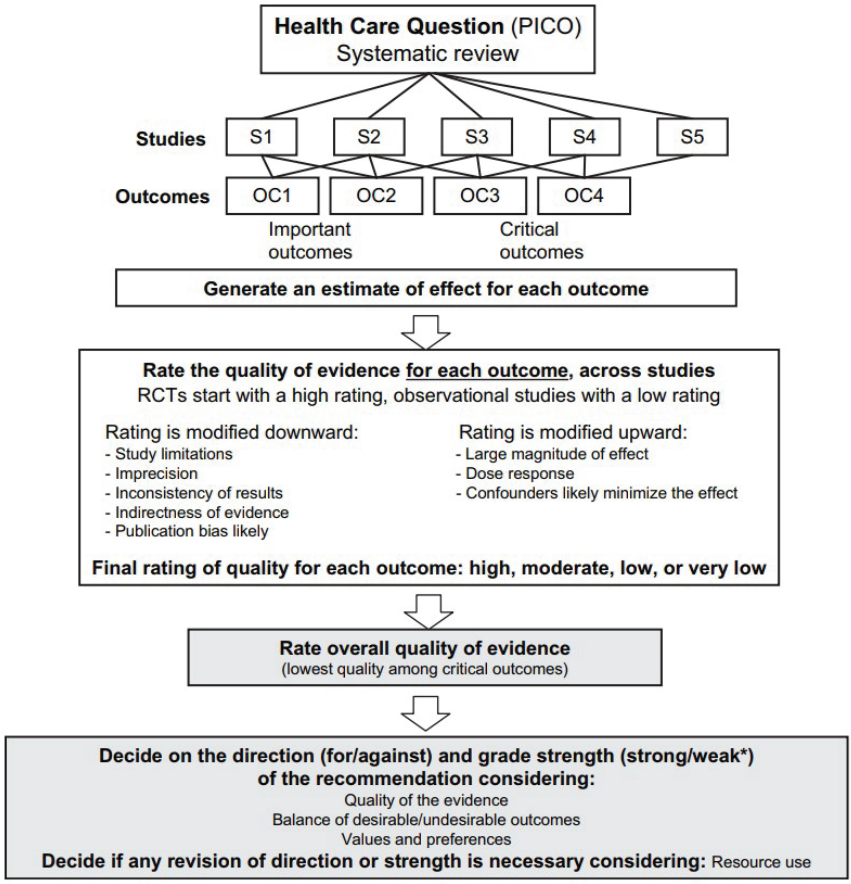

FIGURE 2-2 Schematic view of GRADE's process for developing recommendations. NOTE: GRADE = Grading of Recommendations Assessment, Development and Evaluation; OC = outcomes; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; S = studies.

*Also labeled "conditional" or "discretionary."

SOURCE: Reprinted from Guyatt et al., 2011a, with permission from Elsevier.

strength of evidence and integrating such an assessment into the decision-making process for the DRIs for adequacy and the DRIs for toxicity are not yet standardized. Recommendations in the *Guiding Principles Report* introduce a more formal strength-of-evidence assessment to the DRI process, specifically for informing decision making related to DRIs based on chronic disease. The fundamental conceptual differences outlined in Table 2-2 call for a more standardized approach to assessing and applying strength of

BOX 2-3
Grading of Recommendations Assessment, Development and Evaluation (GRADE) System—Domains Used to Rate the Strength of the Evidence

Domains That May Reduce the Strength of Evidence*

- **Risk of bias** is systematic error attributable to limitations in the study design or execution.
- **Imprecision** is random error that occurs when studies have a small sample size and the number of events is also small.
- **Inconsistency** is unexplained heterogeneity or variability of study results.
- **Indirectness** occurs when a study does not compare the interventions of interest, apply the intervention to the population of interest, or measure the outcomes that are important to patients.
- **Publication bias** is a systematic underestimation or overestimation of the underlying beneficial or harmful effect caused by the selective publication of studies.

Domains That May Increase the Strength of Evidence

- Large magnitude of effect, with consideration for both the magnitude and precision of the estimate.
- Intake–response gradient.
- Plausible residual confounding, which under certain circumstances can increase confidence in an estimate.

*These definitions are direct quotes from NASEM, 2017a (p. 9), which are adapted from Schunemann et al., 2013.

evidence to the derivation of DRIs based on chronic disease compared to the other DRI categories.

In its application of the *Guiding Principles Report* guidance, the committee explored the body of evidence provided in the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018). Although the tool that was used in the *AHRQ Systematic Review* was not GRADE, it is conceptually similar (Berkman et al., 2013). One of the noted differences is terminology. For example, the *AHRQ Systematic Review* referred to the assessment of the body of evidence as "strength of the evidence," whereas GRADE refers to "quality (or certainty) of the evidence." Furthermore, where GRADE uses the ratings of high, moderate, low, and very low, the *AHRQ Systematic Review* used high, moderate, low, and insufficient. Given that the two

approaches are similar, the committee elected to use the *AHRQ Systematic Review* terminology throughout this report.

To effectively use the strength of evidence ratings in the *AHRQ Systematic Review*, the committee first evaluated the methodological approaches taken (see Appendix C). From this evaluation, the committee identified two components of the strength-of-evidence assessment that merited further consideration: risk of bias and inconsistency. Risk of bias was considered an important domain requiring further investigation because of its use in determining the validity of individual study results. The domain of inconsistency assesses the comparability of results in a body of evidence. The committee found that the *AHRQ Systematic Review* did not thoroughly investigate and explain causes of heterogeneity in the results when high levels of inconsistency were found; in some cases, such an investigation was needed to interpret the results of meta-analyses. Accordingly, the committee also investigated the domain of inconsistency. These additional analyses informed and clarified the committee's approach.

Risk of bias Before the strength of a body of evidence can be determined, the individual studies are assessed. The quality of an individual study can vary depending on its specific design features and conduct. To account for this in rating the strength of evidence, consideration is given to risk of bias (see Box 2-4).

The *AHRQ Systematic Review* assessed risk of bias for all studies meeting the inclusion criteria. The committee reviewed the risk-of-bias criteria for both randomized controlled trials and observational studies (for the risk-of-bias criteria, see Appendix C, Annex C-1). One of the risk-of-bias domains was considered by the committee to be of particular importance—methods of potassium and sodium intake assessment. The method used to assess potassium and sodium intake can affect the strength of diet–indicator relationships, the strength of intake–response relationships, and the estimation of usual intake distribution for a population (see Chapter 3). The committee reviewed this and the other domains and concurred with the tools that the *AHRQ Systematic Review* used to assess risk of bias.

The committee also considered the inclusion of observational studies in determining the strength of the evidence for the relationship between potassium or sodium intake and each indicator selected for establishing a CDRR. According to GRADE (Guyatt et al., 2011b), although evidence that relies only on observational studies can be upgraded in rating, such evidence is generally classified as low strength of evidence because observational studies have an inherently weaker design for evaluating evidence on causal effects. Only when there is a large effect size, an intake–response relationship is observed, or plausible residual confounding increases confidence in the estimates can the strength of evidence be upgraded. In addition, in the

BOX 2-4
Risk of Bias (Validity of a Study)

In the design of a study, two types of validity are considered: external (or generalizability) and internal (or comparability). The latter is concerned with the truth of the result of the study, and the risk of a systematic deviation from the truth is termed risk of bias. Flaws in the design, conduct, and reporting of a study can lead to the under- or overestimation of effect of an intervention. This is distinct from the precision of the study results, which is concerned with the extent to which the study result is free from random error.

In evaluating the risk of bias, key components of the design related to internal validity must be assessed. For randomized controlled trials, this includes the sequence generation for allocation of participants to interventions, concealment of the allocation, blinding of participants, personnel, and outcome assessors to the allocation of the intervention, incomplete outcome data or attrition of participants from the study, and selective reporting of outcomes (Higgins and Green, 2011). For observational studies, domains through which bias might be introduced include confounding or residual confounding, selection and rate of participation or dropout of participant subgroups, measurement of interventions (systematic over- or underreporting), departures from intended interventions (secular trends over time), missing data, measurement of outcomes, and selection of the reported result (Sterne et al., 2016).

Tools for assessing the risk of bias are applied to the studies included in a systematic review, and the studies are then classified according to the level of their risk of bias, such as high, moderate, or low. Sensitivity analysis can then be conducted by considering, for example, the meta-analysis including only studies rated as having low risk of bias.

case of sodium, the majority of the observational studies were rated as high risk of bias, mainly because of the biases in the sodium intake ascertainment methods used in observational study designs (for strengths and weaknesses of these methods, see Chapter 3). For these reasons, the committee primarily relied on randomized controlled trials to inform its decision making regarding establishing DRIs based on chronic disease for potassium and sodium. The committee considered observational studies rated as having low risk of bias to supplement the decisions from randomized control trials, particularly when randomized controlled trial data were few or unavailable.

Inconsistency Meta-analyses use statistical methods to compare results from different studies, as a means to identify a consistent pattern across studies. Heterogeneity across the studies in a meta-analysis can arise for a variety of reasons, including variability in the participant characteristics, interventions, and outcomes evaluated; there can also be trial-level variability in study

BOX 2-5
Identifying and Explaining Sources of Heterogeneity in Meta-Analyses

A meta-analysis of studies identified through a systematic review employs statistical methods with a focus on comparing and contrasting study results with the goal of identifying consistent patterns or sources of disagreements among these results. When there are important inconsistencies in the results (direction, magnitude, significance) that cannot be explained, the strength of evidence (i.e., confidence in the estimate of effect) for that outcome decreases (e.g., from high to moderate). Interpretation of a meta-analysis, therefore, is complicated by the presence of this heterogeneity among the studies because the observed differences in the intervention effect among the studies could be attributable to the true intervention effect or to variability in the population, interventions, and outcomes being studied (clinical diversity), and/or study design and risk of bias (methodological diversity). Heterogeneity "manifests itself in the observed intervention effects being more different from each other than one would expect due to random error (chance) alone" (Higgins and Green, 2011, p. 9.27). To properly interpret the results of a meta-analysis, heterogeneity must be assessed and factored into interpretation of the findings.

Heterogeneity is actually expected and potential sources can be identified from the formulation of the population, intervention, comparison, and outcome (PICO) statements. For example, the condition(s) of interest in the population are predefined but may still differ from one study to another. Similarly, the characteristics of the participants of interest likely differ among studies. In addition, specific aspects of the intervention may differ (e.g., type of supplement, diet) and different co-interventions may be permitted among studies, which can affect the results. In addition, different surrogate measures and composite outcomes are often considered. The types of study design, the methodological quality of the studies, and the duration of the study might be sources of heterogeneity.

As a first step in assessing the heterogeneity of the outcome of interest, the results of the comparisons for the interventions are displayed in a forest plot of each treatment comparison and reviewed for patterns and/or outliers. To help determine the extent of heterogeneity for the outcome of interest, statistical measures for heterogeneity, such as I^2, are considered. As noted by Higgins et al. (2003, p. 558):

> $I^2 = 100\% \times (Q - \text{df})/Q$ where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of I^2 are put equal to zero so

design and risk of bias. As described in Box 2-5, unexplained heterogeneity can affect the interpretation of results in meta-analyses. As such, the strength-of-evidence domain of inconsistency, which characterizes heterogeneity, can play an important role in synthesizing and interpreting a body of evidence.

that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.

Different thresholds for identifying the extent of heterogeneity have been proposed. For example:

- $I^2 \leq 0.25$ heterogeneity is not an issue
- $0.25 < I^2 < 0.50$ heterogeneity exists but is not an issue
- $0.50 \leq I^2 < 0.75$ heterogeneity exists and its causes should be explained
- $0.75 \leq I^2$ the causes of heterogeneity must be explained

One method for attempting to explain the cause of heterogeneity is influence analysis. For each pair of treatments, a study is removed and a meta-analysis of the remaining studies performed. This is repeated for each study that is part of the direct evidence. The results of the meta-analyses (such as the point and confidence interval estimates, and I^2) are then assessed to identify the studies having the greatest effect on heterogeneity.

Conceptually similar, cross validation can be performed to help explain the cause of heterogeneity. This method evaluates heterogeneity by removing a study considered to be an outlier and deriving a predictive distribution from the remaining studies. To determine whether heterogeneity exists, the observed treatment effect for the outlier study is compared to the predicted treatment effect for this study based on the predictive distribution. After identifying studies substantively contributing to heterogeneity, the characteristics (as per the PICO statement) and methodological quality of these studies are assessed. Comparing these characteristics and quality indicators with the main body of studies in the evidence base may help identify source(s) of the heterogeneity. Once identified, there are two approaches for determining whether a subgroup effect interacts with the treatment effect:

1. Perform a *subgroup analysis*, which consists of a separate analysis at each level of the subgroup.
2. Perform a *meta-regression analysis*, which contains a common between-trial heterogeneity estimate and an interaction term β with the treatment effect.

Assessment of heterogeneity is an essential aspect of synthesizing results from the studies in a systematic review. Such an assessment can be informative in identifying characteristics of the population that yield different results, which in turn can lead to a better understanding of the efficacy of the intervention under study.

The *AHRQ Systematic Review* performed meta-analyses for key questions and subquestions when randomized controlled trials were available, but it did not explore the potential sources of heterogeneity. Recognizing the importance of explaining the inconsistencies in order to have confi-

dence in the meta-analyses results, the committee carried out subgroup analyses and meta-regression analyses in instances in which heterogeneity was judged to be high. Details of the committee's analyses to explore unexplained heterogeneity are described in Chapters 6 and 10.

Use of strength-of-evidence rating Pursuant to the guidance provided in the *Guiding Principles Report*, the committee determined that it would establish a DRI based on chronic disease if there was at least moderate strength of evidence for both a causal and an intake–response relationship between potassium or sodium intake and chronic disease risk. In this approach, situations can arise in which there is moderate or high strength of evidence of a causal relationship between intake of a nutrient and a chronic disease indicator, but insufficient or low strength of evidence of an intake–response relationship. Pursuant to the guidance in the *Guiding Principles Report*, a DRI based on chronic disease would generally not be established in this case because of limitations in the evidence. The lack of a DRI based on chronic disease, however, does not necessarily mean that no benefit exists; rather, there is a lack of evidence of sufficient strength to characterize the intake–response relationship and thereby establish a DRI based on chronic disease.

The committee primarily used the strength-of-evidence grades provided in the *AHRQ Systematic Review* for causal relationships. In select instances in which the committee explored unexplained heterogeneity, the strength-of-evidence grading was reassessed. The *AHRQ Systematic Review* did not conduct intake–response analyses. Accordingly, for chronic disease indicators with moderate strength of evidence selected to inform the derivation of the CDRRs, the committee sought to characterize the intake–response relationship; details of the committee's additional analyses are provided in Chapters 6 and 10.

Qualified Surrogate Markers

Guidance from the Guiding Principles Report

A surrogate marker is "a biomarker that is intended to substitute for a clinical endpoint" (Biomarkers Definitions Working Group, 2001, p. 91) by accurately predicting the effect of a measured intervention on an unmeasured clinical outcome. Surrogate markers are particularly useful when evaluating the effect of interventions on chronic disease relationships for which a long duration and large sample sizes are needed to evaluate chronic disease outcomes but are not feasible.

The *Guiding Principles Report* recommended that if evidence on the relationship between intake and a qualified surrogate marker is to be used

in establishing the DRI based on chronic disease, it ideally would be used as supporting evidence (NASEM, 2017a) (see Box 2-1, *Guiding Principles Report* Recommendation 2). Qualifying a surrogate marker involves "assessment of available evidence on associations between the biomarker and disease states, including data showing effects of interventions on both the biomarker and clinical outcomes" (IOM, 2010, p. 2). The *Guiding Principles Report* further recommended that "qualification of surrogate markers must be specific to each nutrient or other food substance, although some surrogates will be applicable to more than one causal pathway" (NASEM, 2017a, p. 8). This suggests that, for a DRI committee to use a qualified surrogate marker for the purposes of informing a DRI based on chronic disease, fit for purpose needs to be demonstrated. This type of evaluation stemmed from the recognition that caution is needed when generalizing surrogate marker qualification status from one context to another (IOM, 2010; Yetley et al., 2017).

Committee's Application of the Guiding Principles Report

A 2010 Institute of Medicine report developed a conceptual framework for qualifying surrogate markers for specific uses (IOM, 2010). The two key components of the qualification framework are (1) an objective and rigorous evaluation of the available evidence, and (2) a scientific judgment that the potential surrogate marker is fit for the purpose for which it is intended (e.g., for setting DRIs for the apparently healthy population within a dietary context).

The guidance described in the *Guiding Principles Report* (NASEM, 2017a) and the framework for surrogate markers (IOM, 2010) provided a conceptual foundation that the committee used in reviewing the evidence in support of establishing DRIs based on chronic disease for potassium and sodium. For the committee to consider whether a biomarker was a qualified surrogate marker and use it as supporting evidence to establish CDRRs, a moderate strength of evidence for both a causal relationship and an intake–response relationship between potassium or sodium intake and the biomarker was deemed necessary.

In its application of this guidance, the committee encountered two different scenarios for blood pressure. The details of the evidence and the committee's decision making are presented in Chapters 6 and 10, but because the two scenarios exemplify the concepts related to the use of qualified surrogate markers and fit for purpose, a brief description of the difference is provided here. For potassium, there was evidence of a significant reduction in both systolic and diastolic blood pressure with potassium supplementation. However, an intake–response relationship could not be discerned. Furthermore, there was insufficient evidence of an effect of potassium intake

on cardiovascular disease outcomes. This lack of evidence prevented the committee from considering blood pressure a qualified surrogate marker for cardiovascular disease in the context of potassium intake and from using the evidence to support the derivation of potassium CDRR values. In contrast, the evidence on blood pressure in the context of sodium intake was more robust, and the committee was able to consider blood pressure as a qualitied surrogate marker for hypertension and cardiovascular disease (details of this assessment are provided in Chapter 10, Annex 10-2).

Balancing Benefits and Harms

Guidance from the Guiding Principles Report

The *Guiding Principles Report* states, "deficiency, toxicity, and multiple chronic diseases need to be considered when balancing benefits and harms" (NASEM, 2017a, p. 227). For example, when making decisions about establishing an adequate intake level, the committee may need to evaluate evidence as to whether nutrient intakes below the AI might increase the risk of a chronic disease. That is, DRI committees need to consider whether the benefits associated with the AI might be adversely affected by harms associated with a chronic disease at or below this intake level. Conversely, DRI committees would need to consider a similar evaluation as to whether intakes above a UL might confer benefits that needed to be balanced against the harms associated with intakes at this level.

Committee's Application of the Guiding Principles Report

The information gathered by the committee contained evidence on different indicators related to potassium and sodium intakes that might result in benefits and harms. In deriving the DRIs for adequacy and toxicity, the committee made an effort to consider all types of benefits and harms, including potential chronic disease effects, and to be transparent about its rationale for the decisions made for each DRI category for both nutrients.

THE CHRONIC DISEASE RISK REDUCTION INTAKE IN CONTEXT OF THE OTHER DRI CATEGORIES

In its review of the evidence and application of the guidance in the *Guiding Principles Report*, the committee considered the conceptual interrelationships among the DRI categories. The following sections briefly summarize how the committee applied its collective expert judgment to make the distinction between the CDRR and the other DRI categories for potassium and sodium. It was beyond its scope to determine how future

DRI committees can systematically make such decisions moving forward. The committee acknowledges the challenges that the CDRR might present for DRI users as they attempt to interpret it in the context of the DRI model that existed prior to the *Guiding Principles Report*. The need for additional guidance on the expanded DRI model, for both DRI committees and DRI users, is described as a future direction in Chapter 12.

The CDRR and the DRIs for Adequacy

The committee interpreted the CDRR as distinct from the DRIs for adequacy (i.e., EAR and RDA, or AI). In its approach, the committee attempted to make a delineation between the evidence it reviewed for establishing the DRIs for adequacy (which ultimately remained AIs for both potassium and sodium) and the evidence it reviewed for establishing the CDRRs.

AIs are established when evidence is insufficient to establish EARs and RDAs. The AI is "a recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people who are assumed to be maintaining an adequate nutritional state" (IOM, 2006, p. 11). An adequate nutritional state is defined in various ways, including normal growth, maintenance of normal plasma levels of nutrients, and other features of general health (IOM, 2006). Before DRIs based on chronic disease were included in the DRI model, evidence on chronic disease–related indicators had been considered, and in some cases used to inform the derivation of an AI. The AI for total fiber, for instance, was established based on evidence of its relationship to coronary heart disease (IOM, 2002/2005).

The expanded DRI model allows for a more nuanced characterization of the relationship between nutrient intake and chronic disease risk reduction. Although an important step forward, the expansion of the DRI model created challenges, particularly once the committee determined there was insufficient evidence to establish EARs and RDAs for potassium and sodium. For instance, in the *2005 DRI Report*, the "adequate nutritional state" for potassium encompassed indicators that the committee considered in context for establishing a CDRR. The approach taken to the evidence in support of establishing the potassium DRIs for adequacy is therefore markedly different than that taken in the *2005 DRI Report*.

Despite the conceptual delineation, the review of the evidence indicators was context specific. For instance, the committee reviewed evidence of potential harmful health effects of a range of sodium intakes that was likely to extend below an AI. The range of potential harmful health effects included indicators related to chronic disease. In this context, the evidence was reviewed to ensure that the selected AI values did not potentially lead

to detrimental effects. This use is different than using such evidence as an indicator to establish the sodium CDRRs.

In the case of sodium, failure to identify chronic disease risk reduction at intakes below the CDRR reflects a lack of evidence rather than a lack of effect. This distinction is important from a practical perspective. In the past, the range of intakes between the RDA or AI and the UL has often been characterized as "safe and adequate." The committee cautions against interpreting the gap between the sodium AI and CDRR in such a manner, because intake levels below the sodium CDRR do not reflect a known absence of chronic disease risk. Moreover, as discussed in Chapter 10, there is evidence of benefits with respect to blood pressure with reducing intakes below the CDRR, but the evidence alone was not of sufficient strength to support chronic disease risk reduction.

The CDRR and the UL

The UL is "the highest average daily nutrient intake level likely to pose no risk of adverse health effects for nearly all people in a particular group" (IOM, 2006, p. 11). The *Guiding Principles Report* recommended that the UL be retained in the expanded DRI model, but that it characterize *toxicological* risk (NASEM, 2017a). This recommendation narrows what would qualify as an adverse effect for a UL.

In the expanded DRI model, consideration of both a UL and the CDRR is necessary because the meanings of both are different and valuable. The UL connotes an intake level after which toxicological risk increases with increasing intakes. For sodium, the CDRR reflects the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. According to the *Guiding Principles Report,* if increases in chronic disease risk only occur at intakes greater than the UL, then no CDRR would be necessary.

SUMMARY

The *Guiding Principles Report* served as a foundation as the committee considered the evidence to support DRIs based on chronic disease for potassium and sodium. As the first to implement an expanded DRI model, the committee recognized opportunities to adapt some of the guidance—particularly related to nomenclature—to ensure concepts were clearly and concisely conveyed. The committee followed the guidance on using strength-of-evidence grading in its decision making regarding the potassium and sodium CDRRs. To do so, it relied on evidence in the *AHRQ Systematic Review*. The committee concurred with the risk-of-bias tool that was used in the *AHRQ Systematic Review* and expanded the strength-of-

evidence assessment to explore unexplained heterogeneity. To satisfy the criteria for establishing a CDRR—moderate strength of evidence for both a causal and an intake–response relationship—the committee also conducted intake–response analyses for selected indicators. The committee assessed whether select biomarkers with at least moderate strength of evidence for a causal and an intake–response relationship could serve as a qualified surrogate marker and be used as evidence to support the derivation of a CDRR, in the context of potassium and sodium intake. The committee also considered benefits and harms in its derivation of the potassium and sodium DRIs. The committee interpreted the *Guiding Principles Report* as creating a new DRI category, termed in this report the Chronic Disease Risk Reduction Intake (CDRR), which is distinct from the AI and UL. In moving from the previous DRI model to an expanded model, the committee needed to consider conceptual interrelationships among the DRI categories.

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3

Methodological Considerations

The Dietary Reference Intakes (DRIs) are derived from evidence on relationships between nutrient intake and indicators, which can include clinical endpoints, surrogate markers, biomarkers, and risk factors for a chronic disease. A number of complex methodological considerations are integral to the critical evaluation and interpretation of studies that examine these relationships. This chapter summarizes the committee's review and interpretation of four methodological considerations related to deriving the DRIs for potassium and sodium: relevant biological roles of potassium and sodium, methods for estimating potassium and sodium intake, interactions of potassium and sodium, and evidence on subpopulations.

RELEVANT BIOLOGICAL ROLES OF POTASSIUM AND SODIUM

The first step of the DRI organizing framework is to review evidence on all potentially relevant indicators of adequacy, toxicity, and chronic disease risk in order to identify the indicators that inform the derivation of the DRI values. Final selection of indicators is guided by the strength of the evidence and their public health significance. The scientific literature includes evaluation of relationships between potassium or sodium intakes and a variety of indicators, but not all indicators are necessarily relevant or have a sufficiently robust evidence base on which to establish a DRI. The committee considered the biological plausibility of relationships between potassium and sodium and selected health outcomes and surrogate markers to determine a final list of indicators that could potentially be relevant for establishing DRI values. A brief discussion of the interrelated physiological

roles and regulation of these two nutrients provides context for the selection of indicators for the potassium and sodium DRIs.

Potassium

Approximately 98 percent of total body potassium is found within cells (Russo et al., 2005). Maintenance of this gradient across the cell membrane is important for vital processes, including establishment of the cellular membrane potential, contraction of muscles, control of cardiac conduction, and transmission of nerve signals within and between cells (Kowey, 2002). Potassium also plays a role in regulating water balance and acid–base balance in the blood and tissues (Kowey, 2002).

The imbalance between intracellular and extracellular potassium concentrations is central to how potassium functions in the body, and is therefore tightly regulated through homeostatic mechanisms. Serum potassium concentration is maintained within a narrow range, normally 3.5 to 5.0 mmol/L, over a wide range of potassium intakes. For example, average usual potassium intake among both U.S. and Canadian adults is approximately 2,700 mg/d (69 mmol/d),[1] whereas reported intake among isolated populations is as high as 5,943 mg/d (152 mmol/d) (Oliver et al., 1975); these differences in potassium intake do not typically result in serum potassium concentrations outside of the normal reference range.

The kidney plays a principle role in regulating potassium homeostasis and extracellular potassium concentrations. Potassium is filtered by the glomerulus; bulk potassium reabsorption occurs in the proximal convoluted tubule and, to a lesser degree, in the ascending limb of Henle's loop. Fine regulation of potassium balance occurs in the collecting duct and is regulated by serum potassium concentrations, aldosterone, and acid–base status (Gumz et al., 2015). The gastrointestinal tract also participates in potassium homeostasis, where adaptive changes in the colon can promote potassium secretion via potassium channels for elimination in feces (Batlle et al., 2015). It is likely that additional factors influence potassium homeostasis and communication between the intestines and kidneys.

Mineralocorticoids, principally aldosterone, are important regulators of potassium homeostasis. High serum potassium concentrations activate aldosterone release, and low serum potassium concentrations suppress it. Aldosterone is activated by angiotensin II via activation of the renin-angiotensin-aldosterone system (RAAS) (Lumbers, 1999). Aldosterone promotes potassium excretion, sodium reabsorption, and hydrogen ion

[1]Estimates of mean usual potassium intake for U.S. and Canadian adults 19 years of age and older is 2,721 and 2,697 mg/d, respectively (for details regarding intake distribution evidence sources, see Appendix G).

excretion, resulting in alkalosis. These actions lead to extracellular fluid expansion, increased blood pressure, and decreased serum potassium to within normal ranges. The effects of endogenous hormones and medications also contribute to this homeostatic regulation. Stimulation of the insulin receptor promotes movement of potassium from the extracellular to the intracellular space (McDonough and Youn, 2017). Similar effects are observed with medications that stimulate adrenergic receptors and by increasing systemic pH.

Inadequate potassium intake upregulates the sodium hydrogen exchange 3 (NHE3) protein in the proximal tubule, causing excessive sodium retention, expansion of the extracellular fluid volume, and hypertension. The NHE3 protein is a critical part of the apparatus regulating bulk sodium reabsorption in the proximal tubule, where approximately 60 percent of filtered sodium is reabsorbed. In animal models, potassium depletion promotes adaptive increases in NHE3 activity and sodium transport (Soleimani et al., 1990). Potassium depletion activates the sodium chloride cotransporter in the distal convoluted tubule (Terker et al., 2015); this transporter is inhibited by thiazide-type diuretics. Increased potassium intake acutely increases urinary sodium excretion until a new steady state is reached. When this is achieved, sodium excretion is approximately equivalent to intake. In general, sodium intake does not affect potassium excretion, but net losses of potassium have been documented at very high levels of sodium intake (6,900 mg/d [300 mmol/d]) (Weinberger et al., 1982).

Potassium concentrations may have direct effects on the arterial wall. High potassium concentrations hyperpolarize endothelial cells, causing endothelium-dependent vasodilation, whereas experimental potassium depletion inhibits endothelium-dependent vasodilation (Amberg et al., 2003; Haddy et al., 2006). Low extracellular potassium concentrations have been implicated in stimulating hypertrophy of vascular smooth muscle cells found in the tunica media of the arterial wall (McCabe and Young, 1994). High potassium intake may have favorable and independent cardiovascular effects because of the inhibition of vascular smooth muscle cell proliferation, arterial thrombosis, platelet aggregation, and cytochrome C release (Young et al., 1995).

Potassium status has been linked to other systems of the body. For instance, potassium deficiency may contribute to alterations in glycemic control. Early research indicated that potassium depletion inhibits insulin secretion, whereas potassium infusion has the opposite effect (Dluhy et al., 1972; Rowe et al., 1980). Potassium intake has also been related to urinary calcium excretion. A prominent theory posits a mechanism related to the acid–base balance; diets high in noncarbonic acid–producing foods (e.g., animal protein, cereal grains) and low in potassium-rich foods that provide bicarbonate precursors (e.g., fruits and vegetables) may lead to

diet-induced, low-grade acidosis. Prolonged exposure to such a diet may involve osteoclast mechanisms and the use of skeletal alkaline calcium salts to buffer the acidic pH. The resulting hypercalciuria could potentially have a negative effect on bone health. Additionally, hypercalciuria is a primary risk factor for the formation of calcium-containing kidney stones (Corbetta et al., 2005; Curhan and Taylor, 2008).

Sodium

Approximately 95 percent of the body's total sodium content is extracellular (IOM, 2005). Sodium, along with chloride, has an important role in the maintenance of extracellular volume and plasma osmolality. Sodium is also a critical determinant of cellular membrane potentials and the active transport of molecules across cell membranes.

Approximately 98 percent of consumed sodium is absorbed across a wide range of dietary intakes. It was thought that in a steady state, daily urinary sodium excretion was roughly equal to the amount consumed, but emerging evidence suggests that sodium storage pools may exist in the skin and muscle (Wang et al., 2017). In animal models, high sodium intake results in increased sodium content in skin, thought to be caused by the dysregulation of skin lymphatic expansion. Studies with ^{23}Na-MRI have shown that skin sodium content is related to the blood pressure levels in patients with resistant hypertension (Kopp et al., 2013).[2] Furthermore, recent data suggest that urinary sodium excretion does not mirror sodium intake on a day-to-day basis (Kopp et al., 2013; Lerchl et al., 2015; Rakova et al., 2013; Weaver et al., 2016). If corroborated, these findings suggest that urinary sodium excretion does not necessarily reflect short-term dietary intake.

Sodium balance is influenced by the RAAS, the sympathetic nervous system, the kallikrein-kinin system, atrial natriuretic peptide, mechanisms that regulate renal and medullary blood flow, and intrarenal mechanisms (IOM, 2005). Stimulation of the RAAS occurs with low sodium intake, low blood pressure, or low blood volume. Angiotensin is a strong vasoconstrictor that regulates the proximal tubule of the nephron, promoting sodium retention and stimulating the release of aldosterone from the adrenal cortex. In the distal tubule of the nephron, renal reabsorption of sodium is promoted by aldosterone via a mineralocorticoid receptor-mediated exchange for hydrogen and potassium ions. Likewise, the sympathetic nervous system is activated by short-term, severe sodium restriction

[2]Resistant hypertension is described as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic (Calhoun et al., 2008).

and is suppressed by high sodium intake. Intrarenal mechanisms that are hypothesized to regulate the sympathetic nervous system and renal circulation include locally released prostaglandins, angiotensin, kinins, and endothelial relaxing factor. Meta-analyses have concluded that sodium reduction interventions lead to increases in renin and aldosterone concentrations, but changes in noradrenaline and adrenaline concentrations were not consistently observed (Aburto et al., 2013b; Graudal et al., 2017; He et al., 2013).

Given its relationship with blood pressure, excessive sodium intake is thought to be one mechanism that contributes to the development of hypertension and, eventually, subclinical and clinical cardiovascular disease. Increased left ventricular mass is considered to be a structural adaptation of the heart as a compensatory mechanism in response to high blood pressure and wall stress. Factors that are associated with blood pressure, such as potassium and sodium intake, are also associated with elevated left ventricular mass (Rodriguez et al., 2011). High sodium intake may be associated with elevated left ventricular mass and cardiovascular disease, independent of its association with blood pressure (Jin et al., 2009; Mills et al., 2016).

Increasing sodium intake has been shown to increase urinary calcium excretion (Breslau et al., 1982; Lin et al., 2003). Evidence on the effect of a hypernatremic environment on mouse and human osteoclastogenesis suggests that there may be a cell-mediated effect promoting bone resorption as well as urinary calcium excretion (Wu et al., 2017). This relationship may have implications for bone health.

Implications for the Committee's Review of the Evidence

Potassium and sodium's physiological functions appear to be primarily mediated through blood pressure, which has a strong relationship with cardiovascular disease. Accordingly, the committee focused the indicator review on relationships between potassium and sodium intakes and blood pressure and cardiovascular disease outcomes. Given links between both nutrients and urinary calcium excretion, reviewing evidence on relationships with bone health (particularly bone mineral density and the chronic disease endpoint of osteoporosis) was also warranted. The committee also considered evidence on the relationships between potassium and sodium intake and kidney disease to be potentially informative. Finally, the committee viewed the relationship between potassium and glycemic control as one of possible interest.

METHODS FOR ESTIMATING POTASSIUM AND SODIUM INTAKE

The accuracy of nutrient intake assessments affects multiple steps in the DRI organizing framework. After the committee selects indicators that reflect a causal relationship between intakes and the outcome of interest (first step of the DRI organizing framework), it assesses the evidence on intake–response relationships for each indicator (second step of the DRI organizing framework). The committee then compares the established DRI values with current population intake levels (third step of the DRI organizing framework), which provides context for the public health implications of the selected reference values. The DRI values refer to average daily nutrient intake over time. Thus, the accurate assessment of usual dietary intake—the long-run average daily nutrient intake—is applicable to multiple steps in deriving DRI values.

The accuracy of potassium and sodium intake estimates is critical, as it can affect the strength of diet–indicator relationships, the strength of intake–response relationships, the accuracy of quantitative estimates of the intake–response relationship, and accuracy of the estimation of usual intake distribution for a population. All measures of potassium and sodium intake are subject to random and systematic measurement errors. Specifically, random measurement error leads to estimates of diet–health relationships that are weaker than what actually exists, diminishes the statistical power to detect these relationships, and overestimates the prevalence of low and high population or group intakes. When systematic errors occur, means, distributions, and effect sizes may not be correctly estimated, and the direction of the effect of the error on estimated relationships is not always predictable.

Carefully designed and conducted controlled feeding studies, particularly those that chemically analyze the diets to obtain quantitative compositional information on the nutrient of interest, can clarify the association between potassium and sodium intake and excretion and help validate other instruments that measure intake. However, controlled feeding studies are often challenging to conduct, particularly for extended periods of time, so researchers typically use other methods to assess nutrient intake. The following sections review the strengths and limitations (including potential measurement errors) of commonly used methods to assess potassium and sodium intake.

Urinary Measures

24-Hour Urine

Potassium and sodium intake can be estimated by measuring their excretion in the urine over a 24-hour period. A strength of this approach is

that it is an objective measure without reliance on food composition databases or self-reported dietary intake. Collecting complete urine specimens can be challenging; inaccuracies can occur unless collection is monitored and subject to quality-control methods, such as exclusion of participants who self-report incomplete collection or who are outliers for measures that indicate inaccurate collection (e.g., based on urinary volume, specific gravity, collection duration, para-aminobenzoic acid, creatinine index). Because it can affect the accuracy, it is important to distinguish between 24-hour urine specimens that use quality-control methods and other collection methods that lack these controls.

Sodium excretion varies day to day within individuals, reflecting random error depending on the day or days a specimen is collected (Cogswell et al., 2015; Dyer et al., 1994). Even with random day-to-day variation in excretion, in the absence of systematic error, unbiased (though imprecise) estimates of average usual intakes can be obtained because each measurement of sodium taken on a day reflects true intake plus some random error. A more accurate estimate of the true average intake can be obtained by collecting at least two measurements and by using a statistical model. To estimate attributes of the usual intake distribution of sodium other than the mean (e.g., variability, percentiles), the use of statistical methods to adjust for measurement error is necessary. If no statistical adjustments are applied, a large number of samples (10 or more for each individual), collected on both weekdays and weekends, may be needed to obtain an accurate estimate of the distribution of usual sodium intake in the group that has the correct variance (Dyer et al., 1997; Liu and Stamler, 1984; Luft et al., 1982). Potassium appears to have a greater reliability index than sodium, indicating that fewer replicates may be needed (Sun et al., 2017; Tasevska et al., 2006).

Both potassium and sodium excretion may have infradian rhythms (i.e., lasting longer than 1 day) rather than circadian rhythms (Rakova et al., 2013). Sampling during infradian rhythms is expected to be random across participants and to reflect random error in sampling and unbiased estimates across a population (Freedman et al., 2015). For these reasons, measures of 24-hour urinary potassium and sodium are generally accepted to be recovery biomarkers, meaning that on average they accurately reflect usual dietary intakes and are not subject to systematic bias from personal characteristics.

Because not all consumed potassium and sodium is absorbed and excreted via urine, assumptions are made regarding their absorptive bioavailability. Assumptions vary among studies for the percent of potassium or sodium absorbed that is available for excretion in urine, which affects the estimated distribution of usual intake using these methods. Approximately 77 percent of consumed potassium is excreted in urine, which sug-

gests approximately 77 percent of dietary potassium is absorbed (Aburto et al., 2013a; Tasevska et al., 2006). If the proportion recovered in urine is consistent across population subgroups, inflating biomarker estimates for incomplete recovery is mathematically simple, and the inflated value could be considered an unbiased estimate of intake. However, some evidence suggests that potassium excretion may differ systematically across subgroups or by other dietary intakes (Turban et al., 2013; Weaver et al., 2016). These types of differences would be expected to result in systematic bias (unless statistical adjustment is performed for all known factors that can lead to differences) and would not support the use of potassium as a recovery biomarker; more research is needed to determine if there are systematic biases in 24-hour urinary potassium measurements.

Compared to potassium, a greater proportion of consumed sodium is recovered in the urine. A meta-analysis of data from 35 trials estimated that 92.8 percent of sodium ([95% confidence interval {CI}: 90.7, 95.0], I^2 = 95.1 percent) is excreted in urine (Lucko et al., 2018). Although cautious interpretation of these results is needed because there is a large amount of unexplained heterogeneity, the meta-analysis provides support for using 24-hour urine collections to estimate average sodium intake and recommends multiple 24-hour urine samples to determine an individual's usual sodium intake (Lucko et al., 2018). Therefore, multiple 24-hour urine samples carefully collected with quality-control methods are currently considered to be the best method for assessing long-term intakes of sodium and potassium. Obtaining multiple urines or using statistical methods may adjust for random error from within-person variation in these measures.

Overnight Urine

The challenges of collecting complete 24-hour urine specimens lead some investigators to collect urinary excretion during an overnight period of 8 hours. In one analysis, intra- and interindividual variation in sodium excretion was greater for 8-hour, first-void collections than for 24-hour collections (Ji et al., 2012). There is also potential for systematic error because of greater excretion of sodium overnight than during the day for some individuals, which may differ by factors such as age, sex, or hypertension status (Dyer et al., 1987). Strong correlations between 24-hour and 8-hour sodium excretions have been reported (He et al., 1993; Liu et al., 1979, 1986, 1987), but a more recent systematic review concluded that such correlations vary widely, leaving the validity of this method unclear (Ji et al., 2012).

Spot Urine

Some investigators estimate 24-hour potassium or sodium excretion based on a single ("spot") urine collection. This is the least burdensome urinary measure for participants, but is subject to greater bias owing to the temporal variability in urine tonicity and nutrient excretion between and within individuals (Ji et al., 2012). Factors that may influence variation in sodium concentration in the spot sample includes meal timing and composition, fluid intake, diuretic use, and intense exercise (Mann and Gerber, 2010). Bias can also arise because of the customary approach of indexing spot urine sodium to urine creatinine, which is influenced by urine tonicity and muscle mass, which, in turn, is influenced by age, sex, body weight, and race/ethnicity (Ix et al., 2011). Among healthy individuals, sodium excretion appears to be at its maximum during midday (Cogswell et al., 2015). Accuracy of spot urine estimates may be improved if individual intakes are near the population mean (Mill et al., 2015) or with the collection of multiple spot urines to estimate usual intake (Wang et al., 2015).

Various equations exist to estimate 24-hour potassium or sodium excretion from spot urine samples, including Tanaka, INTERSALT, Kawasaki, Mage, Nerbass, Arithmetic, PAHO, and Danish (Brown et al., 2013; Ji et al., 2014; Kawasaki et al., 1993; Mage et al., 2008; Nerbass et al., 2014; Tanaka et al., 2002; Toft et al., 2014; WHO/PAHO, 2010). Correlations between spot urine samples and measured 24-hour urine excretion are often poor (i.e., < 0.4), exhibit various biases, and vary in reliability by sex and race/ethnicity (Allen et al., 2017; Cogswell et al., 2013; Ji et al., 2014; Mercado et al., 2018). A systematic review comparing spot urine estimates to 24-hour excretion of sodium found correlations to range widely (from 0.17 to 0.86) depending on the timing and number of spot urine samples (Ji et al., 2012).

A single spot urine sample is unlikely to be useful in estimating long-term intake and exposure, particularly at the individual level, given the variation in excretion within and among days as well as the documented issues of measurement bias. Recent evidence suggests that spot urine collections overestimate excretion when intake is low and underestimate excretion when intake is high (He et al., 2018; Huang et al., 2016; Mente et al., 2014), in both healthy individuals and patients with kidney disease (Dougher et al., 2016). These systematic biases may explain, in part, why studies evaluating 24-hour urine sodium tend to have linear relationships with health outcomes (e.g., cardiovascular disease, mortality), whereas those using spot specimens often observe J- or U-shaped relationships (He et al., 2018; Olde Engberink et al., 2017). Although a single spot urine may not provide an unbiased estimate of intake–health relationships, it may be possible to obtain reliable estimates of sodium and potassium to character-

ize usual intake distributions for a population, using excretion obtained from a single or multiple spot urines and using a subset of participants with multiple spot urines as a calibration sample for measurement error adjustment (Wang et al., 2015).

Self-Reported Dietary Intake Assessments

All self-reported dietary assessment methods rely on food composition databases to estimate intake. This method is problematic for sodium, as only about 14 percent of sodium consumed is naturally occurring in unprocessed foods (Harnack et al., 2017). The majority of sodium consumed comes from foods prepared outside the home. To accurately measure sodium intake, consideration must be given to the variability in sodium content across specific brands of foods, limited information for restaurant-prepared food, and the precision and currency of food composition databases to estimate intakes, as well as systemic underreporting of total intake. Furthermore, self-reported dietary assessment methods do not always capture sodium added during cooking or at table, which is estimated to account for 6 and 5 percent of intake, respectively (Harnack et al., 2017). Low reliability among record coders or assumptions made about recipes can also introduce errors.

Every instrument for collecting self-reported dietary intake exhibits misreporting of energy, most commonly in the direction of underreporting for both children and adults. Underreporting of energy appears to be most pronounced among adults when intake is assessed using food frequency questionnaires, compared with energy estimates from doubly labeled water (Freedman et al., 2014).[3] Two major causes of energy underreporting are underestimation of portion size and omission of foods relatively high in energy and low in nutrient density (Millen et al., 2009). The issue of energy underreporting may be more pronounced for respondents who are overweight or obese (Freisling et al., 2012; Lissner et al., 2007). Given that sodium and energy intake are highly correlated (USDA/ARS/FSRG, 2010), it is likely that underreporting of energy results in underreporting of sodium.

24-Hour Dietary Recall

Dietary intake can be estimated through 24-hour dietary recalls in which respondents report all foods and beverages consumed throughout 1 day. This method does not rely on respondent literacy (if interviewer

[3]Doubly labeled water is a technique that can be used to assess energy expenditure under free-living conditions. Individuals consume a dose of water labeled with stable isotopes ($^2H_2{}^{18}O$) and the disappearance rate of the isotopes can be used to calculate energy expenditure.

administered) and it is a relatively low burden for the respondent. The data collected reflect cultural or regional food choices and dietary patterns. Given its retrospective nature, respondents may be less influenced to change their behavior due to observation (i.e., owing to the Hawthorne effect), although the advanced scheduling of the recall may mitigate this benefit. Twenty-four-hour dietary recalls capture details of diet but are short-term instruments, collecting only 1 day of intake; assessment of long-term, or usual, intake is typically of greater interest. This limitation can be reduced by using multiple 24-hour dietary recalls, particularly collected on both weekdays and weekends, and estimating usual intakes using statistical methods (Nusser et al., 1996; Tooze et al., 2006).

Twenty-four-hour dietary recalls attempt to capture usual daily intake, which is subject to both within- and between-person variability. An analysis that evaluated differences in the estimates of the distributions of usual potassium intake (e.g., estimating the prevalence of the population below a cutoff value) using two 24-hour recalls compared with two 24-hour urinary measures found prevalence estimates varied by 7 to 40 percent, with the largest differences in the middle of the distribution (Crispim et al., 2011). Coefficients of variation tend to be greater for sodium than for potassium (Hamdan et al., 2014). Thus, if the mean of 24-hour dietary recalls for an individual is used to estimate usual intake, more replicate recalls would be necessary for the measurement of sodium intake than for potassium intake, preferably including both weekend and weekday data. However, with 2 or more days of data and collection of recalls from both weekend days and weekdays on at least a subset of the population, methods to adjust for measurement errors can be used to estimate the distribution of usual intake of sodium and potassium in populations (Nusser et al., 1996; Thompson et al., 1986; Tooze et al., 2006).

Validation studies have compared 24-hour dietary recall results for potassium and sodium with those of other methods for estimating intake, including urinary biomarkers (Cogswell et al., 2018; Crispim et al., 2011; Freedman et al., 2015; Mossavar-Rahmani et al., 2017; Trijsburg et al., 2015). The level of adjustment for loss appears to be an important consideration when interpreting the results. For example, 24-hour dietary recalls were compared with 24-hour urine excretions for sodium and potassium in an analysis that pooled data from five U.S. studies (Freedman et al., 2015). When urinary potassium was adjusted for 20 percent loss, no bias was identified for men and a –4 percent bias (i.e., underreporting) was identified for women for the 24-hour dietary recall; no significant effects of personal characteristics on reporting bias were identified. When urinary sodium was adjusted for 14 percent loss, bias for sodium was –4 percent for men and –13 percent for women for the 24-hour dietary recall; underreporting of sodium was positively correlated with higher body mass index. In a study

of healthy, weight-stable participants 30–69 years of age, the ratio of mean sodium intake estimated from 24-hour dietary recalls to 24-hour urinary excretions was at least 0.90 at the population level (across sex, age, and weight categories), assuming 86 percent of consumed sodium was excreted in the urine (Rhodes et al., 2013); the ratio was highest among those with a body mass index less than 25 kg/m^2. Taken together, these studies illustrate that, in general, bias for estimating mean potassium intake from 24-hour recall is generally small; bias for sodium intake is slightly greater and may be related to body mass index. Bias in estimating sodium intake, but not potassium intake, has been noted to improve with energy adjustment (+5 to +8 percent) (Freedman et al., 2015).

Estimates of potassium and sodium intake obtained from 24-hour dietary recalls have also been compared to estimates from 24-hour urinary excretions using data from the National Health and Nutrition Examination Survey (NHANES). In 2014, 24-hour urinary samples were collected from a subsample of nonpregnant adult NHANES participants, 20–69 years of age, in addition to other measures including 24-hour dietary recalls. For both the urinary sample and the dietary recall, a replicate measurement was collected from a subset of selected participants. The collection of replicate measurements allowed for usual intake distributions of potassium and sodium to be estimated by applying the National Cancer Institute method, which removes the effect of within-person variability, and by estimating standard errors using the balanced repeated replication method and 24-hour urine sample weights.

The committee was provided with distributions of usual potassium and sodium intake based on the 24-hour urinary samples and 24-hour dietary recall data from the NHANES 2014 subsample (n = 779).[4] Figures 3-1 and 3-2 summarize the estimated usual intake distributions for potassium and sodium, respectively, obtained by three measures of daily nutrient intake: 24-hour dietary recalls, 24-hour urinary excretion, and 24-hour urine excretion adjusted for rate of recovery. The relative error associated with the mean, median, and other quantiles of the distribution of potassium and sodium intakes are approximately at or below 7 and 12 percent, respectively, indicating that intake measured using 24-hour recalls resulted in relatively high accuracy. Potassium intake was estimated to be 20 percent higher by 24-hour dietary recall compared with unadjusted 24-hour urinary potassium excretion; adjusting the mean for 20 percent loss of potassium would result in a bias of –4 percent. A separate analysis of the NHANES 2014 data found no significant difference between mean intake

[4]Distribution tables are available by request from the National Academies of Sciences, Engineering, and Medicine's Public Access Records Office. For more information, email PARO@nas.edu.

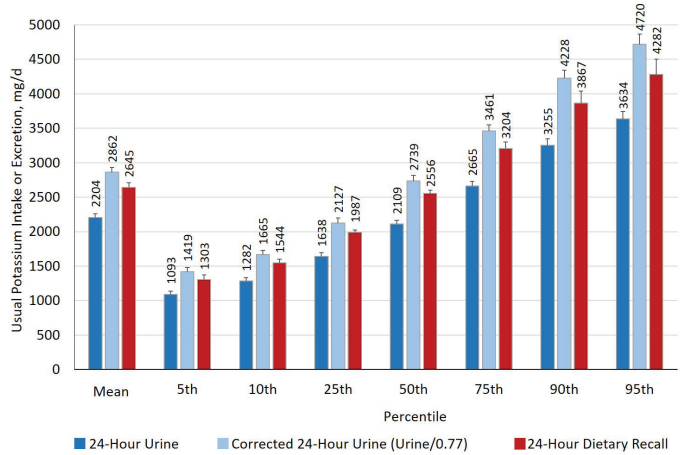

FIGURE 3-1 Mean and quantiles of the estimated usual potassium intake or excretion distributions among 20- to 69-year-olds of both sexes (*N* = 779).
NOTES: The dark blue bars represent amounts of potassium excreted in 24-hour urine samples. The light blue bars represent excretion after correction for percent recovered. The red bars represent potassium intake measured using 24-hour dietary recalls. In all cases, usual intake estimates are adjusted for within-person variability using the National Cancer Institute method.
SOURCE: NHANES, 2014 (unpublished).

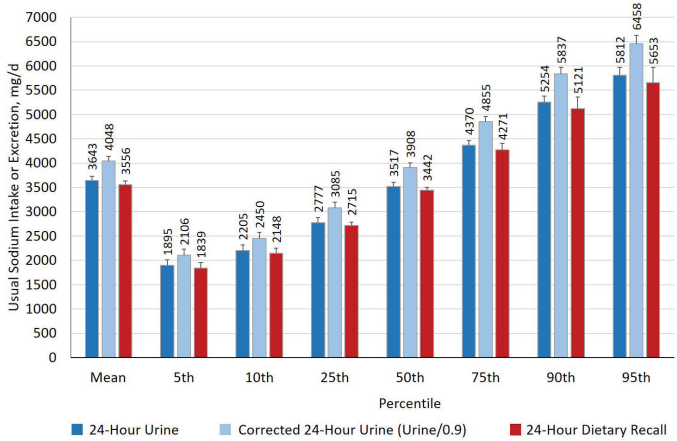

FIGURE 3-2 Mean and quantiles of the estimated usual sodium intake or excretion distributions among 20- to 69-year-olds of both sexes (*N* = 779).
NOTES: The dark blue bars represent amounts of sodium excreted in 24-hour urine samples. The light blue bars represent excretion after correction for percent recovered. The red bars represent sodium intake measured using 24-hour dietary recalls. In all cases, usual intake estimates are adjusted for within-person variability using the National Cancer Institute method.
SOURCE: NHANES, 2014 (unpublished).

of sodium estimated by 24-hour dietary recall and 24-hour urine excretion not adjusted for recovery (Cogswell et al., 2018). These analyses illustrate in a sample of nonpregnant adults representative of the U.S. population that it is appropriate to use 24-hour dietary recalls to describe the usual intake distributions of potassium and sodium for comparing established population intake levels, as prescribed in the third step of the DRI organizing framework.

Measurement error in potassium and sodium intake generally attenuates the diet–health relationship. This effect can be assessed as an attenuation factor (the slope of the regression of truth on self-report), which ranges from 0 to 1. Attenuation factors of at least 0.4 are preferred to distinguish a relationship from a null (Freedman et al., 2015). Attenuation factors for potassium and sodium are higher when more days of 24-hour dietary recall are collected. For potassium, the attenuation factors for 1, 2, and 3 days of 24-hour dietary recalls were estimated to be 0.30, 0.42, and 0.49, respectively, for males and 0.35, 0.47, and 0.51, respectively, for females (Freedman et al., 2015). For sodium, the attenuation factors for 1, 2, and 3 days of 24-hour dietary recalls were estimated to be 0.24, 0.30, and 0.33, respectively, for males and 0.14, 0.22, and 0.32, respectively, for females. Attenuation factors also increased after adjustment for energy (Freedman et al., 2015).

Although the true biological effect of a nutrient is generally attenuated in the presence of measurement error, the test of the null hypothesis of the relationship is usually valid. However, measurement error can also lead to loss of statistical power to detect the diet–health relationship compared to use of true intake. Correlation of a measure with truth can be used to describe the loss of statistical power, with the effective sample size being equal to the actual sample size times the squared correlation (Kaaks et al., 1995). Correlations in the range of 0.52 to 0.59 for two or three 24-hour dietary recalls for potassium, and 0.28 to 0.42 for sodium have been estimated (Freedman et al., 2015). Others have estimated positive correlations between dietary recall results and urinary potassium and sodium excretion (Crispim et al., 2011; Ferrari et al., 2009; Mercado et al., 2015). Correlations of this magnitude indicate that studies in the order of 2.1 to 12.7 times larger would be needed to detect the relationship found with an error-prone 24-hour dietary recall compared with true intake.

To obtain a measurement-error corrected estimate of the relationship between diet and health outcomes, an alternate approach is to use regression calibration to obtain the estimated true value of an individual's usual intake, and then to use this estimate in the diet–health regression model (Rosner et al., 1989). For potassium and sodium, calibration equations can be estimated assuming that the 24-hour urinary biomarkers exhibit only random error, and allowing 24-hour dietary recalls to be calibrated to true

intakes (Freedman et al., 2015; Huang et al., 2014; Mossavar-Rahmani et al., 2017). Although this method will produce deattenuated estimates of diet–health relationships, it cannot restore loss of statistical power.

Although 24-hour dietary recalls are subject to bias for both potassium and sodium, differences in the recovery estimates for the amount of the nutrients excreted in urine vary across studies. This makes it difficult to precisely quantify the degree of bias in estimating the distributions of intakes using 24-hour recalls for potassium and sodium. However, the analysis presented in Figures 3-1 and 3-2 indicates that the estimates of the usual intake distributions measured using 24-hour recalls resulted in relatively high accuracy, which supports the use of recall estimates based on 24-hour dietary recalls for comparison with current population levels (third step of the DRI organizing framework). To assess diet–health relationships, the degree of attenuation expected using 24-hour recalls is large enough that measurement-error correction methods would be beneficial to obtain unbiased estimates of the association, and power would be diminished compared to true intake or the use of multiple 24-hour urine samples.

Food Record

Food records are detailed, respondent-provided descriptions of the types and amounts of foods, beverages, and supplements consumed over a specified period of time. Like 24-hour dietary recalls, food records can be used to obtain detailed information on dietary intake, and they can capture cultural and regional differences in dietary patterns across participants. Participant burden is high and may require both respondent and staff training to promote record quality and ensure appropriate coding of reported foods. Another limitation is underestimation resulting from intentional or unintentional unreported foods and beverages. Food records are infrequently used and studied compared with 24-hour dietary recalls and food frequency questionnaires, which may be attributable, in part, to respondent and investigator burden.

Compared with 24-hour urinary excretions in adults, food records have underestimated mean sodium intake by 2 to 8 percent and varied from mean potassium intake by –4 to +3 percent (Lassale et al., 2015). In an analysis using a comparison to 12-hour overnight urine, mean sodium was 25 percent lower and mean potassium was 28 percent higher on food records (Pereira et al., 2016). Intake estimates from food records were correlated with 24-hour urinary excretions in the range of 0.48 to 0.62 for potassium and 0.17 to 0.48 for sodium (Lassale et al., 2015; McKeown et al., 2001); compared to 12-hour urinary excretions, food record estimates had correlations of 0.30 for potassium and 0.19 for sodium (Pereira et al., 2016). Limited data on children suggest overestimation of potassium on

food records with moderate to strong correlations with urinary potassium excretion (r = 0.58 to 0.78) (Krupp et al., 2012; Lietz et al., 2002).

Food Frequency Questionnaire

Food frequency questionnaires contain a finite list of foods and beverages, or groups of foods and beverages, often paired with an indicator of serving size. Respondents report the frequency with which they consume the foods and beverages over a given reference period (e.g., per month, per year). Respondents may also be asked to estimate the portion size typically consumed. This method benefits from low respondent burden, it is typically self-administered, and it attempts to capture usual, long-term intake through a single assessment. Food frequency questionnaires have some notable limitations. Compared with 24-hour dietary recalls and food records, which capture specific days of intake, food frequency questionnaires ask users to estimate their usual intake over a long period of time, which can be challenging and can potentially lead to systematic bias, particularly for foods influenced by seasonal availability. The focus on broad food categories instead of specific food products is likely to be particularly problematic for sodium, given the wide variation in sodium content that has been observed in some products within food categories.

On average, potassium intakes are underestimated on food frequency questionnaires by 5 to 8 percent in adults, compared with 24-hour urinary biomarkers using a measurement error model (Freedman et al., 2015; Trijsburg et al., 2015). One study reported a 96 percent overestimate of potassium when food frequency questionnaire data were compared with 12-hour urinary excretion (Pereira et al., 2016). Correlation coefficients of potassium between food frequency questionnaires and urinary excretion in adults are low, ranging from 0.26 to 0.29 (McKeown et al., 2001; Pereira et al., 2016). In British schoolchildren 11–13 years of age, potassium was overestimated by more than 100 percent when food frequency questionnaire data were compared with 24-hour urinary excretion; the two measures were not significantly correlated (r = –0.04) (Lietz et al., 2002).

Sodium intake estimated from food frequency questionnaires compared with urinary measures is generally reported to be underestimated by 4–42 percent (Freedman et al., 2015; Kelly et al., 2015; Li et al., 2014; Pereira et al., 2016; Trijsburg et al., 2015), although overestimation has also been reported (Murakami et al., 2012). Bias in reporting has been associated with race, education, and gender (Freedman et al., 2015). Adjustment for energy intake may improve the underreporting bias in sodium intake (Freedman et al., 2015). Correlation coefficients tend to be low between food frequency questionnaire data and urinary sodium excretion, rang-

ing from negligible to 0.37 (McKeown et al., 2001; McLean et al., 2017; Pereira et al., 2016; Sasaki et al., 2003).

Studies assessing the reproducibility of food frequency questionnaires—whether via assessment of kappa coefficients, Pearson correlation, or intraclass correlation—have reported satisfactory reliability across multiple assessments (Barrett and Gibson, 2010; Collins et al., 2015; Ferreira-Sae et al., 2009; McKeown et al., 2001; Mirmiran et al., 2010; Shiraishi et al., 2017). A wide variety of food frequency questionnaires exist, and some are designed for a specific population or dietary pattern or to capture intake of certain nutrients (Apovian et al., 2010; Cheng et al., 2008; Collins et al., 2015; Hamdan et al., 2014).

Food frequency questionnaires are limited in their ability to estimate absolute intake (Carithers et al., 2009; Fayet et al., 2011; Lietz et al., 2002). The evidence suggests that 24-hour dietary recalls are more accurate than food frequency questionnaires for estimating the absolute intakes of both potassium and sodium intake (Ferrari et al., 2009; Freedman et al., 2015; Trijsburg et al., 2015), particularly when 24-hour dietary recalls are administered by phone interview compared with a self-administered Web-based platform (Trijsburg et al., 2015). A systematic review commissioned by the International Consortium for Quality Research on Dietary Sodium/Salt concluded that food frequency questionnaires should not be used to assess absolute sodium intake (McLean et al., 2017).

Implications for the Committee's Review of the Evidence

The various methods for assessing potassium and sodium intake are limited in their comparability and accuracy. Evidence from individual studies examining the relationship between potassium and sodium—particularly absolute intakes—and health outcomes must be interpreted in context of the method used to estimate intake.

The most accurate method to measure usual sodium intake is multiple 24-hour urine collections that use quality control measures. Although a smaller proportion of consumed potassium is excreted in urine, multiple 24-hour urine collections appear to be an accurate measurement approach for assessing usual potassium intake. Self-reported dietary assessment methods, particularly multiple 24-hour recalls, may also provide reasonably accurate measurements of usual potassium intake. Adjustment for measurement error using statistical methods is important, particularly when estimating the distribution of usual sodium or potassium intakes or assessing diet–health relationships.

To operationalize these key methodological considerations, the committee used the approach taken in the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on*

Chronic Disease Outcomes and Risks (*AHRQ Systematic Review*), which embedded intake ascertainment as one of the domains in the risk-of-bias tool (Newberry et al., 2018). For both sodium and potassium, randomized controlled trials that collected at least one 24-hour urinary analysis with reported quality control measures were rated as having low risk of bias for the intake ascertainment domain.[5] For potassium, observational studies that collected multiple days (more than 4, preferably nonconsecutive) of 24-hour urine samples with reported quality control measures or multiple (more than 4, nonconsecutive) 24-hour dietary recalls or food records were considered at low risk of bias for the intake ascertainment domain. For sodium, observational studies that collected multiple days (more than 4 on average, preferably nonconsecutive) of 24-hour urine samples with reported quality control measures were considered at low risk of bias for that domain. Other methods for assessing potassium and sodium intake had higher risk-of-bias ratings for this domain. Annex C-1 in Appendix C presents the full list of the risk-of-bias domains and criteria used in the *AHRQ Systematic Review*.

INTERACTIONS OF POTASSIUM AND SODIUM

Determinants of dietary intake are multidimensional, which refers to "the numerous attributes of dietary intake and the inherent complexities of interdependence and synergy" (Reedy et al., 2018). The multidimensionality of dietary intake can make for a tenuous determination of an association between a single nutrient and health outcome. Approaches to capturing, analyzing, and synthesizing data that characterize these complex interactions are relatively nascent, and efforts are under way to overcome these methodological challenges (Reedy et al., 2018). Nevertheless, the best data available must be used to interpret evidence of the relationship between individual nutrient intake and indicators of health and chronic disease.

One aspect of this complexity is the interactions of nutrients with other food components. Although studying individual nutrients provides fundamental information about underlying biological mechanisms, individual nutrients have complex relationships with other dietary constituents. With respect to deriving DRIs, there are four possible scenarios of interactions to consider:

[5]For potassium other methodologies rated as having low risk of bias for the intake ascertainment domain included "chemical analysis of diet or food diary with intervention/exposure adherence measure, or composition of potassium supplement with intervention/exposure adherence measure" (Newberry et al., 2018, p. E-4).

1. Modulation of the nutrient's effect by another nutrient;
2. Competition of nutrients at the physiological level (i.e., absorption or transport);
3. Substitutions and changes in other dietary components through modulating dietary intake of one nutrient; and
4. Dependency of intake of one nutrient on energy intake (NASEM, 2017).

Consideration of these interactions has implications for the committee's approach to each step of the DRI organizing framework. In the first step, metabolic interactions between nutrients may affect the nature of the relationship observed, and collinearity between nutrients may limit the ability to attribute a relationship to a single nutrient. Similar considerations relate to assessing the intake–response relationship. In the last two steps of the DRI organizing framework, risk can be characterized in context of the interactions and special considerations related to such relationships are explained. To inform its review of the evidence, the committee considered potassium and sodium's interactions with each other, with other nutrients, and with energy intake.

Interactions with Each Other

Measures of potassium and sodium are affected by measurement error, and these are often correlated, which can have a profound effect on observational associations (Cook et al., 1998; Day et al., 2001; Espeland et al., 2001). Although a negative correlation in the diet may be anticipated because high potassium typically represents a good-quality diet and high sodium can reflect a poor-quality diet, the measures are usually positively correlated. This may be partially attributable to dependence on the reported kilocalories consumed or to the collection quality of urine specimens. Despite the positive correlation, the effect of including both nutrients in models for blood pressure or cardiovascular disease can strengthen the association (Cook et al., 1998, 2009). For example, including negatively correlated predictors with positive effect sizes, or positively correlated predictors with opposite effect sizes, can be beneficial in predictive models (Demler et al., 2013). Short-term measurements that include substantial measurement error, however, can distort the underlying relationship with an outcome in observational data (Espeland et al., 2001). Randomized trials specifically designed to intervene on one or both of these measures, however, may offer additional insight.

Some studies have reported that consumption of potassium-containing salts increase urinary sodium excretion and that blood pressure is more highly correlated with the sodium-to-potassium ratio than to intake of

either electrolyte alone (Khaw and Barrett-Connor, 1988). The *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) discussed this evidence but concluded that the data were insufficient to establish a recommendation based on the sodium-to-potassium ratio (IOM, 2005).

There is continued interest in the relationship between the sodium-to-potassium ratio and health outcomes, and in the potential use of this ratio as a practical way to derive dietary advice (Chmielewski and Carmody, 2017; Filippini et al., 2017; Iwahori et al., 2017). The *AHRQ Systematic Review* included key questions that explored whether potassium modulates sodium's relationships with health outcomes (see Chapter 1, Box 1-3). Two randomized controlled trials were identified that assessed whether potassium modified the effect of sodium on cardiovascular disease and total mortality. One study compared the effect of counseling to achieve a low-sodium, high-potassium diet to the effect of counseling to achieve a low-sodium diet (HPTRG, 1990). There was no added effect on blood pressure when the counseling included increased potassium intake versus sodium reduction alone. Another study examined the effects of potassium-enriched salt on cardiovascular disease mortality (Chang et al., 2006). The potassium-enriched salt was 49 percent sodium chloride, 49 percent potassium chloride, and 2 percent other additives. After 31 months, the group consuming the potassium-enriched salt had a significant reduction in cardiovascular disease mortality (age-adjusted hazard ratio = 0.59 [95% CI: 0.37, 0.95]). However, this was compared to usual intake and there was no sodium-reduction-only comparison group. In a 10–15-year posttrial follow-up to Trials of Hypertension Prevention I and II, a higher sodium-to-potassium ratio measured by 24-hour urine collections showed a stronger association with increased risk of cardiovascular disease than either sodium or potassium alone (Cook et al., 2009).

The majority of evidence identified in the *AHRQ Systematic Review* on potassium intake modulating the effect of sodium intake assessed blood pressure. Various types of interventions have been used to explore this question (e.g., increasing dietary potassium intake with foods or different potassium salt substitutes), under the assumption that the effect size of sodium-to-potassium ratio on blood pressure is stronger than that of sodium or potassium alone.

Five studies were identified that compared the effects of a low-sodium diet with and without potassium enrichment (Chalmers et al., 1986; Charlton et al., 2008; Grimm et al., 1988, 1990; HPTRG, 1990; Langford et al., 1991; Nowson and Morgan, 1988). The *AHRQ Systematic Review* concluded that, based on a low strength of evidence, there is no significant moderating effect of potassium intake on the effects of sodium intake on systolic or diastolic blood pressure. The random-effects meta-analysis showed an overall mean difference for systolic blood pressure of –0.56 mm Hg

[95% CI: –2.94, 1.81]. Changes in sodium-to-potassium ratios in these studies were achieved by changing the diet or by dietary counseling alone. Changing the diet to increase potassium intake requires changes that likely increase the consumption of nutrient-rich foods that will increase intakes of other nutrients while also possibly resulting in lower sodium intakes, thus contributing to an improvement in blood pressure. With these types of interventions, it is not possible to discern the independent contribution of the sodium-to-potassium ratio on changes in blood pressure, because multiple, often undefined, dietary changes (e.g., other food components, concomitant dietary compensations) are simultaneously occurring.

The *AHRQ Systematic Review* included 13 randomized controlled trials that explored the effect of potassium-containing salt substitutes (Barros et al., 2015; Charlton et al., 2008; CSSSCG, 2007; Geleijnse et al., 1994; Gilleran et al., 1996; Li et al., 2016; Little et al., 2004; Mu et al., 2009; Sarkkinen et al., 2011; Suppa et al., 1988; Zhao et al., 2014; Zhou et al., 2009, 2016). In these interventions, the sodium-to-potassium ratio was expected to decrease by replacing some of the regular salt (sodium chloride) with a potassium-containing salt substitute (such as potassium chloride or potassium citrate). From this body of evidence, the *AHRQ Systematic Review* concluded that there is a moderate strength of evidence that the use of potassium-containing salt substitutes lowers systolic blood pressure and diastolic blood pressure. The random-effects meta-analysis estimated a mean difference of –5.58 mm Hg ([95% CI: –7.08, –4.09], I^2 = 74 percent) for systolic blood pressure and –2.88 mm Hg ([95% CI: –3.93, –1.83], I^2 = 78 percent) for diastolic blood pressure. The committee has reservations about the interpretation of these results because the meta-analysis included studies that increased potassium intake with interventions that also increased magnesium and/or calcium intake (Charlton et al., 2008; CSSSCG, 2007; Geleijnse et al., 1994; Mu et al., 2009; Sarkkinen et al., 2011; Zhou et al., 2009, 2016), and these minerals might also affect blood pressure and confound the independent effect of potassium. One study of individuals with type 2 diabetes (Gilleran et al., 1996) and one study of individuals who were randomized to receive health education (Li et al., 2016) were also included in the meta-analysis. The implications of these particular designs in the results of the meta-analysis are unknown.

Studies exploring the modulating effects of potassium have been published since the release of the *AHRQ Systematic Review*. Some of these studies used salt substitutes that include magnesium and calcium (Hu et al., 2018; Yang et al., 2018) and therefore have the same limitations described above. One study allowed for the independent moderating effects of potassium to be evaluated. Janda et al. (2018) explored the effect of adding Kardisal (60 percent sodium chloride, 40 percent

potassium chloride) to the Dietary Approaches to Stop Hypertension (DASH) diet for 3 months in 60 adolescents with prehypertension.[6] In the group consuming the potassium-containing salt substitute (n = 26), systolic blood pressure decreased significantly from 138 to 129 mm Hg, whereas diastolic blood pressure also decreased, but the reduction was not statistically significant. In the group consuming the DASH diet (n = 25) the systolic blood pressure decreased significantly from 135 to 132 mm Hg, and the diastolic blood pressure decreased significantly from 85 to 79 mm Hg.[7] The authors concluded that the use of a low-sodium salt did not decrease blood pressure beyond the DASH diet alone. A systematic review and meta-analysis on the relationship between potassium intake and blood pressure reported that potassium supplementation had a stronger lowering effect on blood pressure in trials with a higher achieved sodium-to-potassium ratio (≥ 1) than in trials in which the achieved ratio was less than 1, but the authors noted uncertainties in the data (Filippini et al., 2017). One issue not addressed is whether a potassium supplement within the context of high habitual sodium intakes would have a significant effect on blood pressure.

Interactions with Other Nutrients and Energy

Potassium and sodium are each correlated with other dietary components. For example, an analysis of day-one 24-hour dietary recall data from NHANES 2005–2006 participants 2 years of age and older found energy to be strongly correlated with both potassium intake (r = 0.72) and sodium intake (r = 0.80) (USDA/ARS/FSRG, 2010). The relationship between sodium and energy intake has also been demonstrated in the intake distributions of the U.S. and Canadian populations. In both countries, males consumed more sodium than females; the greater sodium intake among males was largely attributed to higher energy intake, as intake of sodium per kilocalorie consumed did not significantly differ between the sexes.[8] In the DASH-Sodium trial, a feeding trial that examined the effect of sodium intake on blood pressure, individuals were provided diets at low, intermediate, and high sodium levels based on their energy intake. An analysis of the trial data showed that the blood pressure response to sodium intake varied with energy intake (Murtaugh et al., 2018).

[6]The DASH diet is rich in potassium, magnesium, and calcium.

[7]Different final diastolic blood pressure values for this group were reported in the publication. This value was drawn from the narrative text description of the results.

[8]For additional information regarding sources of evidence for potassium and sodium intake distributions, see Appendix G.

Potassium intake is correlated with intake of other nutrients (Adebamowo et al., 2015; Hermann et al., 1992; Larsson et al., 2011). For instance, based on 24-hour dietary recalls collected at baseline and follow-up during a dietary intervention study, Nowson and Morgan (1988) reported that dietary potassium intake was strongly correlated with magnesium intake ($r = 0.82$). The *AHRQ Systematic Review* found insufficient evidence to assess the moderating effects of calcium or magnesium on the effects of potassium or sodium intake with any of the indicators reviewed (i.e., systolic and diastolic blood pressure, cardiovascular disease morbidity and mortality, and kidney disease). The *AHRQ Systematic Review* found no trials that met its inclusion criteria that assessed the modifying effects of calcium or magnesium on the effect of sodium on any of the indicators reviewed. Two trials assessed the modifying effects of calcium or magnesium on the effect of potassium on blood pressure. Rahimi et al. (2007) randomized participants into a control arm, a high-potassium diet, a high-calcium diet, or a high-potassium and high-calcium diet, and reported significant declines in systolic blood pressure for each of the intervention groups as compared to the control group. A crossover study of potassium plus magnesium supplementation did not reduce systolic or diastolic blood pressure more than potassium supplementation alone (Patki et al., 1990). With only these two trials, the *AHRQ Systematic Review* characterized the strength of evidence of a moderating effect as insufficient.

Implications for the Committee's Review of the Evidence

The multidimensional and dynamic nature of dietary intake presents challenges in assessing the relationship between a single nutrient and a health outcome. Potassium and sodium are not consumed in isolation and intakes vary over time. Although there are approaches and methodologies that partly address some of these inherent issues, there are gaps in the evidence on sodium and potassium's interactions with each other, their interactions with other food components, and their contributions to health.

Evidence on the modulating effect of potassium (or other minerals) on the blood pressure effects of sodium intake is insufficient at this time, as is the evidence that high sodium intakes might be mitigated by increasing potassium intakes (through food or supplements). Based on its synthesis of the evidence provided in the *AHRQ Systematic Review*, the committee did not derive DRI values based on the sodium-to-potassium ratio. The committee was concerned that establishing a DRI value as a sodium-to-potassium ratio might lead to the misimpression that altering the ratio with the use of a potassium supplement will result in a beneficial health outcome, on option that has not yet been explored. Furthermore, the committee excluded from consideration studies in which salt

substitutes included other minerals because there is insufficient evidence on if and how other minerals might modulate the effects of sodium or potassium.

Sodium and energy intakes are closely linked, and the sodium-to-energy ratio may be an informative measure (Murtaugh et al., 2018). Despite this relationship, most studies do not administer, report, or analyze intakes on an energy-adjusted basis. Given this limitation of the evidence, the committee deemed it not appropriate to adjust a large number of study results based on either assumed or group mean energy intakes. In addition, the consideration of populations with energy intakes greater than the estimated energy requirements would be a challenge, especially in light of the high prevalence of overweight and obesity in the North American populations. At present, only the macronutrients (which themselves contribute to energy intake) and fiber have DRI values indexed to energy intake (IOM, 2002/2005). The committee was concerned that not only is there insufficient evidence to establish a DRI value as a sodium-to-energy ratio, there are also potential public health ramifications for doing so.

To account for the complexities of dietary intake in the review of the evidence, the committee assessed how studies accounted for factors such as interactions and confounders in their design (e.g., participant inclusion/exclusion criteria, frequency and timing of intake assessment) and analyses (e.g., statistical adjustments, type of dietary exposure used).

EVIDENCE ON SUBPOPULATIONS

The DRI age, sex, and life-stage groups allow for the nutrient reference values to vary, as applicable. With the introduction of DRIs based on chronic disease, opportunity exists to further specify the applicable population group or groups. The *AHRQ Systematic Review* included subquestions to determine if characteristics such as sex, age, race/ethnicity, or comorbidity affected the relationship between sodium or potassium intake and chronic disease outcomes and risk. With the exception of hypertension status, there was largely insufficient evidence to determine if there was an effect modification.

One characteristic that played a substantial role in establishing the potassium AIs in the *2005 DRI Report* was salt sensitivity. The *AHRQ Systematic Review* did not assess the evidence by salt sensitivity status. To that end, the committee considered the extent to which this characteristic could inform a DRI value.

Salt Sensitivity

Salt sensitivity is a continuous variable, and arbitrary criteria have been developed for diagnostic purposes.[9] Salt sensitivity has been defined as

> the extent of blood pressure change in response to a change in salt intake. 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. (IOM, 2005, p. 8)

Many phenotypic characteristics have been observed and used to explain salt sensitivity, including diminished urinary endothelin (which is negatively correlated with a salt load independent of blood pressure status), a deficit in nitric oxide (which increases in response to salt loading), impaired responses to a salt load by the sympathetic nervous system, differences in atrial natriuretic peptides (which increase in response to dietary salt supplementation), and hyperinsulinemia. Salt sensitivity has been identified as a potential risk factor for cardiovascular disease. Hence, this trait would have importance in public health advice and the clinical management of blood pressure (salt-sensitive versus salt-resistant individuals).

Characterizing salt sensitivity remains challenging. The existing criteria have varying ranges of high and low sodium intake levels, durations, and sequences of approach. There continues to be a lack of reproducibility of the acute blood pressure responses to sodium challenges that are indicative of salt sensitivity. For data to be comparable among studies, standard protocols need to be used consistently, and other challenges that impede the identification of salt-sensitive individuals must be addressed.

An alternative approach to identify salt-sensitive individuals is the identification of a valid biomarker. Twenty-four-hour pulse rates and nocturnal dipping of arterial blood pressure have been investigated as biomarkers of salt sensitivity. A promising yet insufficiently explored approach includes identifying urinary biomarkers related to proximal tubular cells or renal exomes that reflect salt sensitivity.[10] No such biomarker has been identified to date.

Another innovative approach is to identify individuals with genetic variants associated with salt sensitivity. Several gene or gene products related to salt sensitivity have been identified in animals, including those that affect the RAAS, the sympathetic nervous system, the endothelin system,

[9]There are various definitions of salt sensitivity. Definitions include a change in blood pressure of 5–10 mm Hg in response to a change in salt intake, or an increase in mean arterial pressure of at least 4 mm Hg with an increase in salt intake.

[10]Exomes are small vesicles that contain mRNA, proteins, and other cell components. The characteristics of those components might be associated with salt sensitivity.

natriuretic peptides, oxidative stress, angiogenesis factors, and inflammation. However, interpretation of animal studies and their implications for humans is complex. In humans, evidence of heritability of salt sensitivity comes from family studies. Although genomewide linkage studies have identified many variants related to blood pressure sensitivity, sample sizes are insufficient to identify significant genetic variants. A recent publication suggests a single nucleotide polymorphism as a promising biomarker (Zhang et al., 2018).

Implications for the Committee's Review of the Evidence

Challenges in characterizing salt sensitivity limit its use for establishing potassium and sodium DRI values at this time. One consideration is the generalizability of the evidence. The DRI values have broad applications across different domains, and the importance and applicability of subgroup differences are considered when establishing DRI values. Depending on the evidence, effect modification may be central to selecting an indicator and establishing the DRI value (the first two steps of the DRI organizing framework) or may be most appropriately handled when characterizing special considerations and vulnerable population groups (fourth step of the DRI organizing framework). The *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) recommended, "extrapolation of intake–response data for chronic disease DRIs only to populations that are similar to studied populations in the underlying factors related to the chronic disease of interest" (NASEM, 2017, p. 214). As such, consideration of differential effects has even greater prominence in the DRI process. Throughout its evidence review, the committee notes where there is evidence of effect modification by a population characteristic.

SUMMARY

In preparation for its review of the evidence, the committee examined a range of methodological considerations that are central to evaluating and interpreting studies assessing the relationship between potassium and sodium intake and indicators. Box 3-1 provides a summary of the implications for the evidence that is reviewed in this report.

BOX 3-1
Methodological Considerations and Implications for the Committee's Review of the Evidence on Potassium and Sodium

Relevant Biological Roles of Potassium and Sodium

- Both sodium and potassium are fundamentally linked to the function of the cardiovascular system. Blood pressure and cardiovascular disease are potentially informative indicators to review and consider.
- Bone health, kidney disease, and glycemic control are also potentially informative indicators.

Methods for Estimating Potassium and Sodium Intake

- The most accurate measure of sodium or potassium intake for the purposes of informing a Dietary Reference Intake (DRI) value is multiple 24-hour urine collections that use quality control measures. Dietary intake assessed through multiple 24-hour dietary recalls appears to be appropriate for assessing usual potassium intake as well.
- The committee agrees with the risk-of-bias tool developed for the *AHRQ Systematic Review*, in which consideration of the methodology for ascertaining potassium and sodium intake is embedded as a key component of the overall risk-of-bias assessment for each study.

Interactions of Potassium and Sodium

- The evidence is currently insufficient to establish DRIs based on the sodium-to-potassium ratio.
- The majority of the studies do not report sodium or potassium intakes on an energy-adjusted basis and therefore the evidence is insufficient to establish the DRIs indexed to energy.
- Interpretation of the independent effects of each nutrient need to be considered in light of potential interactions between nutrients.

Evidence on Subpopulations

- Understanding if and how nutrient intakes disparately affect population subgroups continues to be a key consideration when establishing the DRIs and is an essential component of the new DRI category based on chronic disease.
- Challenges in characterizing salt sensitivity limit its use in establishing potassium and sodium DRI values at this time.

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Part II

Part II of this report presents the evidence the committee reviewed to derive the Dietary Reference Intake (DRI) values for potassium. Based on the committee's review of the evidence on indicators of adequacy, toxicity, and chronic disease as they relate to potassium, the committee provides its recommendations. This part of the report consists of four chapters:

Chapter 4 follows steps 1 and 2 of the DRI organizing framework, provides the committee's review of the evidence on indicators of potassium adequacy, and presents the committee's rationale for revising the previously established Adequate Intake values.

Chapter 5 follows steps 1 and 2 of the DRI organizing framework, provides the committee's review of the evidence on indicators of potassium toxicity, and presents this committee's rationale for not establishing a potassium Tolerable Upper Intake Level under the expanded DRI model.

Chapter 6 follows steps 1 and 2 of the DRI organizing framework, provides the committee's review of the evidence on the relationship between potassium intake and chronic disease risk, and provides the committee's rationale for not establishing a potassium DRI based on chronic disease.

Chapter 7 follows steps 3 and 4 of the DRI organizing framework by characterizing risk in the U.S. and Canadian populations and describing special considerations and public health implications, as they relate to the revised potassium DRI values.

4

Potassium: Dietary Reference Intakes for Adequacy

Potassium is a physiologically essential nutrient. Accordingly, the Dietary Reference Intakes (DRIs) for adequacy serve as an important reference value with a variety of applications. The extent to which an indicator of potassium adequacy has been identified and characterized in the apparently healthy population is at the crux of the committee's decision regarding which DRI for adequacy to establish and at what levels. For an Estimated Average Requirement (EAR) to be established, evidence of a causal relationship between intake of the nutrient and the indicator of adequacy, as well as evidence of an intake–response relationship, are needed to determine the distribution of requirement for adequacy in the population. As described in Chapter 1, once an EAR is determined, a Recommended Dietary Allowance (RDA) can be established. When there is insufficient evidence to establish an EAR and an RDA, a DRI for adequacy is still indispensable, as it provides a benchmark for dietary planning and assessment; in such cases, an Adequate Intake (AI) is established using other data-driven approaches and indicators.

Guided by the DRI organizing framework (see Chapter 1, Box 1-2) and the considerations under the expanded DRI model (see Chapter 2), this chapter describes the committee's review of indicators to inform the potassium DRIs for adequacy and presents its approach and determination of updated reference values for the DRI age, sex, and life-stage groups. The committee's decision was informed by its evaluation of evidence on potassium intake requirements in apparently healthy individuals. The Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ*

Systematic Review) (Newberry et al., 2018), served as a primary source of evidence for the committee's work. However, as described in Chapter 2, the committee sought to differentiate the evidence reviewed for the DRIs for adequacy from the evidence reviewed for the DRI based on chronic disease. None of the indicators included in the *AHRQ Systematic Review* (blood pressure, cardiovascular disease, coronary heart disease, kidney disease, kidney stone formation, mortality, and stroke) were considered sufficiently informative to determine potassium adequacy. Instead, the committee used evidence gathered from its supplemental literature searches and other information-gathering activities. This chapter presents the committee's rationale and conclusions regarding the suitability of these indicators to inform the potassium DRI for adequacy. For context, the committee's findings are preceded by a brief summary of the approach taken to establish the potassium AIs in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005).

POTASSIUM ADEQUATE INTAKE LEVELS ESTABLISHED IN THE *2005 DRI REPORT*

The 2005 report that established the DRIs for potassium served as a starting point for the committee's review of the evidence (IOM, 2005). The approach taken in the *2005 DRI Report* predated the guidance and recommendations offered in the 2017 National Academies of Sciences, Engineering, and Medicine report *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) (NASEM, 2017). Accordingly, potassium adequacy was conceptualized at that time as the following:

> In generally healthy people, frank hypokalemia is not a necessary or usual expression of a subtle dietary potassium deficiency … 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. (IOM, 2005, pp. 192, 194)

The potassium AI for adults in the *2005 DRI Report* was established based on evidence of an intake level that blunted a salt-sensitive rise in blood pressure among normotensive African American men and reduced the recurrence of kidney stone formation (IOM, 2005). The potassium AI was further supported by evidence of potassium intake being positively associated with bone mineral density and evidence of blood pressure–lowering effects among nonhypertensive individuals.

REVIEW OF POTENTIAL INDICATORS OF POTASSIUM ADEQUACY

As part of its task, the committee was asked to update, as appropriate, the potassium AIs established in the *2005 DRI Report*. Owing to the expanded DRI model, the conceptual approach for the potassium DRIs for adequacy in this report is different from that taken in the *2005 DRI Report* described above. For instance, the committee reviewed evidence on the relationship between potassium intake and both blood pressure and kidney stone formation in the context of establishing potassium Chronic Disease Risk Reduction Intakes (CDRRs) (see Chapter 6). Furthermore, as discussed in Chapter 3, the challenges of identifying and characterizing salt sensitivity limit the committee's ability to use it as a defining characteristic to inform the potassium and sodium DRIs.

To explore which additional indicators could potentially be used to characterize the distribution of potassium intake requirements within the apparently healthy population, the committee first considered aspects of potassium physiology, including adaptations of blood potassium concentration to various conditions and hypokalemia.[1] In generally healthy individuals with normal kidney function, serum potassium concentrations are typically kept between 3.5 and 5.0 mmol/L. Homeostatic mechanisms that help to maintain this narrow range include shifting potassium between intracellular and extracellular fluid (internal balance) and retaining or excreting potassium, primarily through the urine (external balance). Dysregulation in either the internal or external balance mechanism can lead to hypokalemia, but each has different implications for total body potassium content. Intracellular shifts maintain total body potassium, whereas excessive potassium losses can decrease total body potassium.

Given the underlying mechanisms that regulate potassium homeostasis, hypokalemia can be caused by inadequate intake, excessive losses, or transcellular shifts. Potassium depletion studies have demonstrated that, among otherwise healthy adults, consuming 0–390 mg/d (0–10 mmol/d) can lead to hypokalemia (Hernandez et al., 1987; Huth et al., 1959; Jones et al., 1982; Kaess et al., 1971; Krishna et al., 1989; Squires and Huth, 1959). These levels of intake, however, are particularly extreme and have been studied over relatively short periods of time. Furthermore, given the external balance mechanisms, potassium can be conserved when intakes are low. As such, inadequate potassium intake is rarely the primary cause of hypokalemia. Instead, hypokalemia is often caused by abnormal losses (e.g., due to renal losses, gastrointestinal losses) and certain medications that promote transcellular shifts (Viera and Wouk, 2015). Clinically, altera-

[1]Generally defined as serum potassium concentrations ≤ 3.5 mmol/L.

tions in blood potassium concentrations outside of the normal range are widely recognized to be detrimental to health and to increase risk of death (Hughes-Austin et al., 2017; Kardalas et al., 2018). For the purposes of determining potassium intake requirements, however, blood potassium concentrations and hypokalemia are not reliable indicators of usual potassium intake or status in the apparently healthy population.

From its information-gathering activities and literature scoping searches (see Appendix D), the committee was unable to identify a sensitive or specific biomarker of potassium status that could be used to determine the distribution of potassium requirements in the population. In the absence of such an indicator of potassium adequacy, the committee reviewed the evidence from balance studies.

Balance Studies

Balance studies measuring total intake and losses have been used in the past to assess adequacy based on the concept that neutral balance reflects homeostasis for the nutrient in adults. Such a neutral balance can be, and has been for some nutrients, interpreted as meeting the physiological requirement and, thus, informative to specify a DRI for adequacy (NASEM, 2018). For example, the EAR for calcium in adults was specified on the basis of calcium balance (IOM, 2011). Applying this rationale to potassium would mean that for an adult to be in neutral balance, intake would be equal to the sum of all potassium losses (sweat, urine, fecal, and other). Individuals with intakes less than losses would be considered in negative balance, indicating deficient intakes. Individuals with intakes greater than losses would be considered in positive balance. In states of growth, positive balance might be necessary to support tissue accretion and, thus, be adequate; in adults, positive balance might indicate intakes above those meeting physiological requirements. To have confidence in such balance studies, intake of potassium and losses by all routes need to be rigorously determined for a sufficient duration of time in controlled feeding studies to ensure that homeostasis has been achieved. In addition, rigorous balance studies must minimize confounding factors that could affect the interpretation of balance, such as bioavailability, physical activity, and high ambient temperature.

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* provided an overview of topics related to potassium balance and considered the effects of heat and physical activity on potassium losses. Urinary potassium excretion was noted to increase at higher doses of potassium intake (Hene et al., 1986). Although potassium excretion was largely unaffected by sodium intake, sodium intakes above

6,900 mg/d (300 mmol/d) have been found to result in net potassium loss (Luft et al., 1982). Fecal potassium excretion reportedly ranged from approximately 112–850 mg/d (3–22 mmol/d) among individuals with potassium intakes of 2,600–2,900 mg/d (66–74 mmol/d) (Holbrook et al., 1984). Increased wheat fiber consumption increased fecal potassium losses (336–1,114 mg/d [9–29 mmol/d]) (Cummings et al., 1976). Serum potassium concentrations were at the lower end of the normal range among nonhypertensive adults maintaining potassium balance while consuming at least 1,564 mg/d (40 mmol/d) potassium (Sebastian et al., 1971).

The concentration of potassium lost in sweat, when sweat losses were minimal, has been found to range from 90–626 mg/L (2–16 mmol/L) (Consolazio et al., 1963). Changes in potassium concentrations in sweat were also assessed in relation to heat exposure and physical activity. Among seven healthy males, sweat potassium concentration was higher during exposure to 40°C (104°F) than during a running exercise (555 ± 180 versus 442 ± 121 mg/L [14 ± 5 versus 11 ± 3 mmol/L]) (Fukumoto et al., 1988). In a study of 12 unacclimatized men performing 6 hours of intermittent treadmill activity in 40°C (104°F) heat, potassium losses from sweat were estimated to be approximately 1,200 mg/d (32 mmol/d) (Armstrong et al., 1985). Among heat acclimatized individuals exposed to heat stress (40°C [104°F]), potassium loss from sweat was estimated to be approximately 2,300 mg/d (60 mmol/d) (Malhotra et al., 1976). An evaluation of three men who were exposed to high temperatures (38°C [100°F]) for 7.5 hours per day for 16 days found that sweat potassium concentrations decreased from 3,100 mg/d (79 mmol/d) on day 2 to 516 mg/d (13 mmol/d) by day 11 (Consolazio et al., 1963). A crossover study assessed potassium losses during a 4-day exercise regimen among eight men while they consumed two different levels of potassium intake (980 versus 3,100 mg/d [25 versus 80 mmol/d]) (Costill et al., 1982). The amount of potassium lost in sweat was reduced during the lower potassium diet phase (426 versus 481 mg/d [11 versus 12 mmol/d]). The *2005 DRI Report* noted that heat exposure and physical activity can increase potassium losses through sweat.

Evidence from the Committee's Supplemental Literature Searches

Studies of potassium balance in normotensive individuals are limited in number, rigor of design, and sample size (see Table 4-1). With the exception of a study in female adolescents described below (Palacios et al., 2010), no studies were identified in which rigorous and complete balance directly measured potassium content of foods consumed and all losses (urinary, fecal using appropriate fecal markers, and whole body sweat). Without the rigorous and direct determination of potassium intake through chemical analysis of the food consumed and the complete assessment of all potas-

TABLE 4-1 Potassium Balance Studies Summarized by Completeness of Assessment of Intake and Losses[a]

Study	Population
Complete Balance—Rigorous Assessment of Intake and All Losses	
Palacios et al., 2010	30 black and 20 white American adolescent females, 11–15 years of age
Incomplete Balance—Limitation on Loss Assessment[e]	
Kodama et al., 2005	109 Japanese males and females, 18–28 years of age[f]
Holbrook et al., 1984	12 healthy American adult males and 16 healthy American females, 20–53 years of age
Consolazio et al., 1963	3 healthy, young American adult males, ages not reported
Costill et al., 1982	8 American males in daily running training program, 20–41 years of age

Potassium Intake (mg/d)			
Negative Balance	Neutral Balance	Positive Balance	Noted Design and Limitations
2,186[b]		2,186[c]	• Controlled potassium intake for 20 days with either high sodium (4,000 mg/d) or low sodium (1,300 mg/d) intakes[d] • Potassium intakes rigorously measured • Urinary, fecal, and sweat potassium losses measured
	2,034[g]		• Series of 11 mineral balance studies of 5–12 days duration with a 2–4-day adaptation period • Potassium intake directly measured • Urinary and fecal potassium losses measured; only arm sweat losses during physical activity measured
		3,300[b] 2,400[i]	• Potassium content of self-selected diet assessed for a period of 1 week, four times over the course of 1 year, chemically analyzed for duplicate samples of all food and beverages consumed • Urinary and fecal potassium losses measured; no sweat losses were determined
		2,493	• Balance determined after a preliminary 8 days at 24°C (75°F) during four 4-day periods at 38°C (100°F), with controlled potassium intake • Dietary potassium intake and urinary and fecal potassium losses were chemically determined, but 24-hour whole body sweat was not measured; some sweat measurements from underarms collected during 38°C (100°F) periods. Balance did not include sweat losses given limitation of its measurement
975		3,120	• Two 4-day diet sequences • Dietary potassium intake was chemically assessed • Urinary potassium excretion measured; sweat potassium from physical activity only • No difference in sweat potassium in 90-minute heat-stress physical activity

continued

TABLE 4-1 Continued

Study	Population
Squires and Huth, 1959	11 American males, ages not reported
Incomplete Balance—Limitation on Both Intake Assessment and Losses[j]	
Hene et al., 1986	6 Dutch males, 24 ± 2 years of age
Tasevska et al., 2006	13 British adults, 23–66 years of age
Kirkendall et al., 1976	8 American males, 24–47 years of age

NOTE: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1.

[a]Only studies reporting balance using crossover or sequential designs in the same participants at studied intakes for a minimum of 3 days are included. Studies using parallel arm randomized controlled trial designs were not included because intra-individual variability might confound results. Studies of hypertensive participants not included.

[b]For white adolescent females consuming a low-sodium diet.

[c]For black adolescent females consuming a low-sodium diet and for both black and white adolescent females consuming a high-sodium diet.

[d]Sodium intakes in Palacios et al. (2010) were reported in the units of mmol/L/d; daily intakes of sodium were drawn from a separate publication on the same protocol (Palacios et al., 2004).

[e]Incomplete balance studies were limited by lack of direct assessment of one or more sources of potassium loss, typically either fecal or whole body sweat or both.

Potassium Intake (mg/d)			
Negative Balance	Neutral Balance	Positive Balance	Noted Design and Limitations
< 39 546–624 975–1,053			• Series of 14 balance studies, only 2–3 per balance study consisting of 3–8-day control period followed by 6–21-day depletion period • Diets were chemically analyzed • Urine and stool samples with marker were analyzed; no sweat losses were determined
		3,120 8,580	• Controlled potassium intake with and without supplementary potassium • Assessed 5 and 6 days after initiating diet only period; assessed 15 and 16 days after initiating diet and supplement period • Dietary intake does not appear to be chemically analyzed for potassium • Only urinary potassium excretion measured
		4,743	• Controlled intake during a 30-day period • Dietary potassium chemically analyzed, except for contributions of coffee and tea[k] • Urine and stool samples with marker were analyzed; no sweat losses were determined
		3,912	• Controlled intakes during a 12-week period, consisting of 4 weeks each of three different levels of sodium intake (230, 4,828, and 9,426 mg/d); potassium intake held constant • Dietary intake not reported to be chemically analyzed for potassium • Urinary excretion measured and fecal losses assessed in three participants; no sweat losses were determined

[f]From a series of 11 balance studies.

[g]Reported to be 39.2 mg/kg body weight; estimated total based on mean body weight (Nishimuta et al., 2012).

[h]Average potassium intake of male participants (n = 12), based on analysis of 1 week's worth of food and beverage samples collected four times over the course of 1 year.

[i]Average potassium intake of female participants (n = 16), based on analysis of 1 week's worth of food and beverage samples collected four times over the course of 1 year.

[j]Incomplete balance studies were limited by lack of direct assessment of potassium content in foods consumed and by lack of assessment of one or more sources of potassium losses as noted for each study.

[k]Coffee and tea consumed ad libitum; contributions to total potassium intake estimated. Total potassium likely underestimated.

sium losses through urine, feces, and sweat, a "true" balance cannot be determined. Especially when sample sizes are small, as they need to be in this type of expensive and meticulous metabolic study, balance may be misclassified by failing to either measure true intake or true loss. Several studies were limited by a lack of rigorous assessment of potassium intake or total losses or both.

A rigorously designed balance study was conducted in adolescent females with controlled potassium intakes (2,186 mg/d [56 mmol/d]) at a high and a low sodium intake level (4,000 and 1,300 mg/d [172 and 57 mmol/d], respectively) for 20 days each (Palacios et al., 2004, 2010). A small positive cumulative daily potassium retention in both white and black adolescents was found during high sodium intakes, but only in black adolescents during low sodium intakes. On low sodium intakes, a small negative cumulative daily potassium retention was reported in white adolescents. Average potassium balance for the entire 20-day experimental period was not reported, which makes it difficult to compare the results from this study to the other studies included in Table 4-1. Nonetheless, the committee interpreted these results as likely demonstrating slight positive potassium balance in adolescents, which may be affected by sodium intakes in white adolescents.

Committee's Synthesis of the Evidence

Current balance studies have limitations and do not offer sufficient evidence for estimating average potassium needs or the distribution of physiological requirements in the apparently healthy population. The body of evidence is potentially confounded and not suitable for use for assessing the adequacy requirements for potassium. Recognizing these limitations, the committee noted that neutral balance was reported with intakes of approximately 2,000 mg/d (51 mmol/d) in one study (Kodama et al., 2005). Negative balance was reported with potassium intakes of less than 39–1,053 mg/d (1–27 mmol/d); negative balance was also found at higher potassium intakes, and appears to vary by factors such as exposure to heat, physical activity, and race/ethnicity.

DIETARY REFERENCE INTAKES OF POTASSIUM ADEQUACY

The committee's review of the evidence on potential indicators to inform the potassium DRIs for adequacy revealed the following:

- There is no sensitive biomarker that can be used to characterize the distribution of potassium requirements in the apparently healthy population.

- Limitations in the design of the balance studies—particularly small sample size and incomplete measurement of intake and losses—precluded the committee from using such data to estimate median requirements and the distribution of requirements in the apparently healthy population.

The committee concludes that none of the reviewed indicators for potassium requirements offer sufficient evidence to establish Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) values. Given the lack of evidence of potassium deficiency in the population, median intakes observed in an apparently healthy group of people are appropriate for establishing the potassium Adequate Intake (AI) values.

The AI is "a recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people who are assumed to be maintaining an adequate nutritional state" (IOM, 2006, p. 11). The concept *apparently healthy people* (*or populations*) underpins the DRI. Most commonly, the concept refers to the population to which the DRIs apply (see Chapter 1). In the context of setting an AI, however, the term is used to describe the group or groups of individuals whose data were used to derive the AI values. The apparently healthy group used to inform the AI values may be a subset of the apparently healthy population at large.

To derive the potassium AI values, the committee sought to identify a group of apparently healthy individuals whose usual potassium intake would not be affected by illness, medications use, or medical nutrition management. Antihypertensive medications are known to affect blood potassium concentrations, which may in turn affect potassium intake. Some classes of medication, such as angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and potassium-sparing diuretics can increase blood potassium concentrations, which could lead to diet modification to reduce potassium intake. Conversely, loop and thiazide diuretics can cause low blood potassium concentrations, which may lead to prescription of potassium supplements and an increase in dietary intake of potassium. Therefore, individuals on hypertensive medications would not necessarily reflect the nutritional status of potassium in a group of apparently healthy people, and would not be an appropriate population group to use to derive the potassium AIs. Furthermore, although the evidence was not sufficiently strong to use blood pressure as an indicator for establishing a potassium CDRR (see Chapter 6), there is evidence of a relationship between potassium intake (based on supplement trials) and

blood pressure, particularly among adults with hypertension.[2] It is not possible to establish cause-and-effect relationships using a cross-sectional data source such as a national survey to estimate both nutrient intake and disease status. Therefore, it is possible that differences in potassium intakes by hypertension or cardiovascular disease status could reflect either direct or reverse causality; in the latter case, difference in intake would reflect a response to the disease, and not reflect an intake by an apparently healthy group of people.

The committee had available for its consideration the usual potassium intake distribution tables from two nationally representative surveys: the Canadian Community Health Survey–Nutrition 2015 (CCHS Nutrition 2015) and the National Health and Nutrition Examination Survey (NHANES) 2009–2014. The methodological approaches for collecting and analyzing the 24-hour dietary recalls were similar between the two surveys (CDC/NCHS, 2018; Statistics Canada, 2017; also see Appendix G); as such, their simultaneous consideration was deemed appropriate. As described below, the committee defined the "group of apparently healthy people" used to derive the potassium AI values for adults as normotensive males and females without a self-reported history of cardiovascular disease.

The committee considered three options for using the median intake data across the two different nationally representative surveys: (1) use the lowest median intake estimate within an age and sex group, (2) use a midpoint between the median intake estimates from the two surveys, or (3) use the highest median intake estimate within an age and sex group between the two surveys. Using the lowest of the median intakes to establish the potassium AI values was determined to be not appropriate, because of uncertainties of the effect of lower intakes on the population with higher median intake. Although using a midpoint of the two estimates would increase the AI values, averaging medians is not appropriate and still suffered from the issue of being below the higher median population intake. Accordingly, the committee considered the highest median intake across the two surveys, mathematically rounded, the most appropriate basis for establishing the potassium AI values. The committee applied this general approach across the DRI age, sex, and life-stage groups for individuals 1 year of age and older. For infants 0–12 months of age, potassium intake of breastfed infants was estimated to derive the potassium AI values. The sections that follow present additional details on the committee's derivation of potassium AI values for each of the DRI age, sex, and life-stage groups.

[2]This text was revised since the prepublication release.

Infants 0–12 Months of Age

Details of the committee's approach to estimating the concentration of potassium in breast milk and the contributions of complementary foods to total potassium intake are provided in Appendix F. To establish the potassium AIs for infants 0–6 and 7–12 months of age, the committee estimated the potassium concentration in mature breast milk. Different concentrations are used for the two infant age groups in the estimates below, as the potassium content of breast milk changes over the course of the first year. To establish the potassium AI for infants 7–12 months of age, potassium intake from complementary foods was estimated and added to the estimated potassium intake from breast milk.

The potassium AI for infants 0–6 months of age is based on estimated potassium intakes from breast milk alone. The mean potassium concentration of breast milk for this age group was estimated to be 515 mg/L (13 mmol/L). Assuming an average breast milk consumption of 780 mL/d, the potassium AI for infants 0–6 months is established at 400 mg/d (10 mmol/d).

The potassium AI for infants 7–12 months of age is based on estimated potassium intakes from breast milk and complementary foods. The mean potassium concentration in breast milk for this age group was estimated to be 435 mg/L (11 mmol/L). Assuming an average breast milk consumption of 600 mL/d, approximately 260 mg/d (7 mmol/d) potassium is consumed from breast milk. Potassium intake from complementary foods was estimated to be 600 mg/d (15 mmol/d). The potassium AI for infants 7–12 months is therefore established at 860 mg/d (22 mmol/d). A summary of the infant potassium AI values is presented in Table 4-2.

Children and Adolescents 1–18 Years of Age

Despite having a general approach to establishing the potassium AIs (selecting the highest of the median usual potassium intakes across the two nationally representative surveys), the committee had two additional

TABLE 4-2 Potassium Adequate Intakes, Infants 0–12 Months of Age

DRI Age, Sex, and Life-Stage Group	Potassium Adequate Intake, mg/d
Infants	
0–6 months	400
7–12 months	860

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. DRI = Dietary Reference Intake; mg/d = milligrams per day.

options to consider in its derivation of potassium AIs for children and adolescents 1–18 years of age, outlined below:

- *Stratification by sex:* The potassium AIs for adolescents 9–13 and 14–18 years of age could either be stratified by sex or be a single value for both males and females in each age range. Both CCHS Nutrition 2015 and NHANES 2009–2014 showed differences in potassium intake by sex in these age groups. As the committee's premise for establishing the potassium AIs is that there is a lack of evidence for potassium deficiency in the population, the different median intakes are assumed to be adequate for each sex. To that end, the committee elected to stratify the AIs for the two older children's age groups by sex. For children 1–3 and 4–8 years of age, DRIs are not typically stratified by sex. Data from CCHS Nutrition 2015, however, provided sex-stratified estimates of usual potassium intake for these two age categories. Rather than attempting to combine the male and female data from CCHS Nutrition 2015, the committee applied its general approach to select for each of these two age groups a single AI based on the available data (i.e., the highest median usual potassium intake among Canadian males, Canadian females, and U.S. males and females, per age group).
- *Use of normotensive data:* The NHANES 2009–2014 intake distribution tables stratified by hypertension status included the estimates for children and adolescents 8 years of age, 9–13 years of age, and 14–18 years of age. CCHS Nutrition 2015 did not assess blood pressure status for children (Statistics Canada, 2017). The committee had the option to use the normotensive-only data from NHANES 2009–2014, particularly for the two older children's age groups. As the majority of children in these age groups were normotensive, the median usual potassium intakes from the normotensive-only data were nearly identical to the estimate for children of all blood pressure statuses; use of normotensive-only data would not have affected the selected potassium AIs for these DRI age, sex, and life-stage groups. NHANES 2009–2014 estimates presented in this section reflect the estimates of all blood pressure statuses.

Figure 4-1 presents the median potassium intakes among U.S. and Canadian children and adolescents 1–18 years of age; for context, the figure shows the potassium AIs that were established in the *2005 DRI Report*. Median intakes were higher in the Canadian estimates, as compared to the U.S. estimates. As noted above, methods for collecting

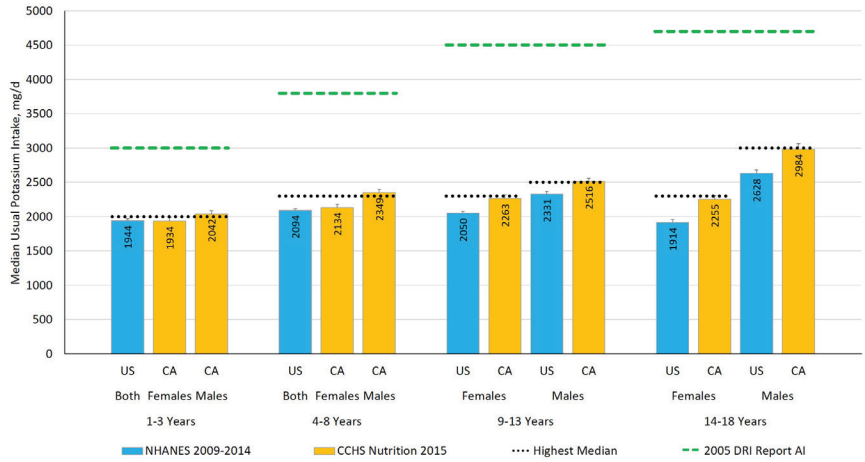

FIGURE 4-1 Median usual potassium intake of U.S. and Canadian children and adolescents 1–18 years of age.
NOTES: The figure presents groups as provided in the data source. The green dashed lines are the potassium AIs that were established in the *2005 DRI Report*. The black dotted line is the highest median potassium intake across two nationally representative surveys for each DRI age, sex, and life-stage group, mathematically rounded, which was used to establish the potassium AI values in this report. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. AI = Adequate Intake; CA = Canada; CCHS Nutrition 2015 = Canadian Community Health Survey–Nutrition 2015; NHANES = National Health and Nutrition Examination Survey; US = United States.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

24-hour dietary recalls, nutrient databases, and statistical methods used to estimate intakes were similar between the two analyses, and therefore would not be expected to explain these differences (for details of methodology, see Appendix G). The highest median intake for each DRI age, sex, and life-stage group, mathematically rounded, was used to establish the potassium AI values. The potassium AIs for children and adolescents 1–18 years of age are presented in Table 4-3.

Adults 19 Years of Age and Older

The committee defined the "group of apparently healthy people" used to derive the potassium AIs for adults as normotensive males and

TABLE 4-3 Potassium Adequate Intakes, Children and Adolescents 1–18 Years of Age

DRI Age, Sex, and Life-Stage Group	Potassium Adequate Intake, mg/d
Children	
1–3 years	2,000
4–8 years	2,300
Males	
9–13 years	2,500
14–18 years	3,000
Females	
9–13 years	2,300
14–18 years	2,300

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. DRI = Dietary Reference Intake; mg/d = milligrams per day.

females 19 years of age and older, without a self-reported history of cardiovascular disease. CCHS Nutrition 2015 and NHANES 2009–2014 differed in their approaches to identifying and categorizing hypertension status and cardiovascular disease. CCHS Nutrition 2015 asked participants if a health professional had ever told them they had high blood pressure or had heart disease (Statistics Canada, 2017). The CCHS Nutrition 2015 data presented in this section reflect survey participants who reported that they did not have high blood pressure and that they did not have heart disease. NHANES 2009–2014 data, in contrast, identified normotensive adults based on the mean of up to three consecutive blood pressure measurements or use of hypertensive medications, using the 2017 American College of Cardiology and the American Heart Association guidelines for adults (Whelton et al., 2018). Questions also included whether a doctor or other health professional had ever told the participant they had a stroke or heart attack (myocardial infarction). The NHANES 2009–2014 data presented in this section reflect normotensive survey participants who reported that they did not have cardiovascular disease. The differences in the approach to categorizing hypertension status across the two surveys is a noted limitation; however, the alternative was to use usual median intake from the entire adult population, which would include individuals with hypertension and cardiovascular disease. Thus, the committee determined that, despite the methodological limitations of classifying blood pressure status, normotensive data were more likely to reflect a group of apparently healthy people than data from all survey participants.

The committee had two additional options to consider in its derivation of potassium AIs for adults 19 years of age and older, as outlined below:

- *Stratification by sex:* The potassium AIs for adults could either stratify by sex or be applicable to both males and females in age and life-stage group. The survey data showed sex differences in median usual potassium intakes. As the committee's premise for establishing the potassium AIs is that there is a lack of evidence for potassium deficiency in the population, the different median intakes are assumed to be adequate for each sex. To that end, the committee elected to stratify the adult potassium AIs by sex.
- *Stratification by age group:* The DRI groups allow for age group–specific potassium AIs. Given the uncertainties associated with an AI, particularly as it relates to the requirements, the committee was concerned that different values for each age group would convey greater precision and certainty in the evidence than what is currently available. As such, the committee did not stratify the potassium AIs by adult age group.

Figure 4-2 presents the median usual potassium intakes among normotensive U.S. and Canadian adults; for context, the figure shows the potassium AIs that were established in the *2005 DRI Report*. The updated potassium AIs for adults were established using the highest median intake across the two nationally representative surveys among the adults, mathematically rounded, stratified by sex. The AIs for adults 19 years of age and older are presented in Table 4-4.

Pregnancy

Very few estimates of body potassium stores during pregnancy are available. Evidence suggests that nearly all potassium accretion occurs during the final trimester of pregnancy (Butte et al., 2003; Forsum et al., 1988); potassium accretion during this time has been estimated to be 120 mg/d (3 mmol/d) (EFSA, 2016). Potassium balance and deposition may be affected by changes in hormones during pregnancy (Ehrlich and Lindheimer, 1972). Accretion rates and total potassium content in mature fetuses and full-term neonates progressively increase throughout pregnancy (EFSA, 2016).

Despite increases in mineralocorticoid activity and filtered potassium load that occur, healthy women do not normally develop hypokalemia during pregnancy (EFSA, 2016). Physiological changes that occur during pregnancy are associated with renal reabsorption of potassium. Urinary potassium excretion is maintained by adaptive mechanisms that adjust to

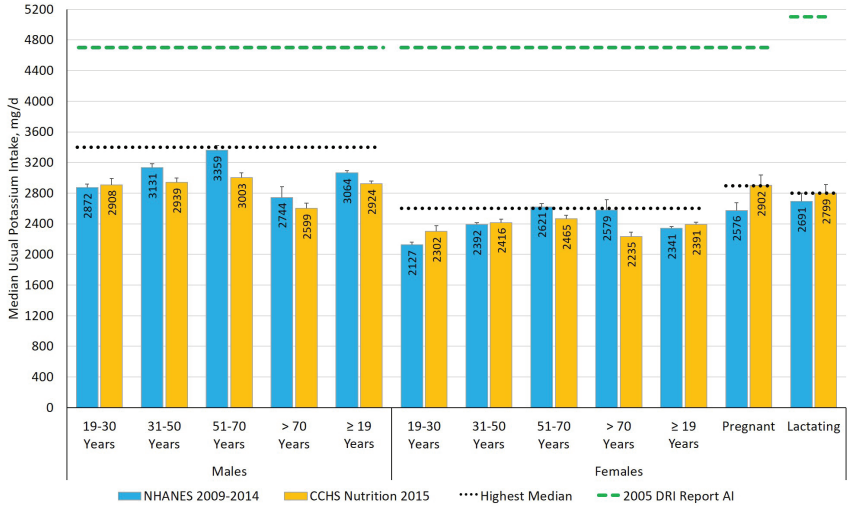

FIGURE 4-2 Median usual potassium intake of U.S. and Canadian normotensive adults 19 years of age and older.
NOTES: The green dashed lines are the potassium AIs that were established in the *2005 DRI Report*. The black dotted line is the highest median potassium intake across two nationally representative surveys for adult males, females, or life-stage group, mathematically rounded, which was used to establish the potassium AI values in this report. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. AI = Adequate Intake; CCHS Nutrition 2015 = Canadian Community Health Survey–Nutrition 2015; DRI = Dietary Reference Intake; NHANES = National Health and Nutrition Examination Survey.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

the increases in filtered potassium load and aldosterone-mediated retention of sodium (Brown et al., 1986; Cheung and Lafayette, 2013; Ehrlich and Lindheimer, 1972). The antikaliuretic effect of progesterone may contribute to the maintenance of potassium homeostasis in pregnant women (Lindheimer et al., 1987).

In the absence of evidence on differing requirements in pregnancy, the highest median usual potassium intake among pregnant females in the two nationally representative surveys is presumed to be adequate. For pregnant adolescent females, 14–18 years of age, the committee considered two options. One option would be to use the same potassium AI value for all pregnant females including those 14–18 years of age. The strength of this approach is that the potassium AI would be based on available intake data

TABLE 4-4 Potassium Adequate Intakes, Adults 19 Years of Age and Older

DRI Age, Sex, and Life-Stage Group	Potassium Adequate Intake, mg/d
Males	
19–30 years	3,400
31–50 years	3,400
51–70 years	3,400
> 70 years	3,400
Females	
19–30 years	2,600
31–50 years	2,600
51–70 years	2,600
> 70 years	2,600

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. DRI = Dietary Reference Intake; mg/d = milligrams per day.

from pregnant females. However, the committee was concerned about the lack of representation of adolescent females among pregnant survey participants. Furthermore, if this approach were to be taken, the potassium AIs for pregnant adolescents would be 600 mg/d (15 mmol/d) more than for nonpregnant female adolescents of the same age (2,300 versus 2,900 mg/d [59 versus 74 mmol/d]). The second option would assume the pregnant survey participants were primarily adult females. The difference between the pregnant and nonpregnant adult female potassium AIs (300 mg/d [8 mmol/d]) could be added to the nonpregnant female adolescent potassium AI (2,300 mg/d [59 mmol/d]) to derive the pregnant adolescent potassium AI. The committee was concerned that different values for the pregnancy age groups would convey greater precision and certainty in the evidence than what is currently available. However, with no clear evidence that a 600 mg/d (15 mmol/d) increase is biologically warranted, the committee judged the second option was most appropriate. The potassium AI values for pregnant females are presented in Table 4-5.

Lactation

Little information exists on changes in body potassium content during lactation. Evidence from a study that measured total body potassium content found significantly greater losses in total body potassium content in lactating women, compared to nonlactating women (Butte and Hopkinson, 1998), suggesting that total body potassium content may decrease in lactating women. Potassium is excreted in breast milk (see the Infants

TABLE 4-5 Potassium Adequate Intakes, Pregnancy

DRI Age, Sex, and Life-Stage Group	Potassium Adequate Intake, mg/d
Pregnancy	
14–18 years	2,600
19–30 years	2,900
31–50 years	2,900

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. DRI = Dietary Reference Intake; mg/d = milligrams per day.

0–12 Months of Age section above), and the concentrations are determined by an electrical potential gradient (IOM, 1991). A systematic review assessing the effect of maternal diet on breast milk composition (Bravi et al., 2016) identified only one study in which potassium has been assessed; the study reported the correlation between maternal potassium intake and breast milk potassium composition to be –0.07 (Finley et al., 1985).

In the absence of evidence on differing requirements in lactation, the highest median usual potassium intake of lactating females in the two nationally representative surveys is presumed to be adequate. For lactating adolescent females, 14–18 years of age, the committee faced the same issues and concerns as for pregnant adolescent females (see above) and elected to take the same approach. The potassium AI values for lactating females are presented in Table 4-6.

SUMMARY OF UPDATED POTASSIUM ADEQUATE INTAKE VALUES

Aligned with the *2005 DRI Report*, limitations in the evidence precluded the committee from establishing potassium EARs and RDAs. As such, potassium AIs were established. This report has updated the potassium AI values across the DRI age, sex, and life-stage groups. The revisions reflect, in part, the expanded DRI model. The potassium AIs established

TABLE 4-6 Potassium Adequate Intakes, Lactation

DRI Age, Sex, and Life-Stage Group	Potassium Adequate Intake, mg/d
Lactation	
14–18 years	2,500
19–30 years	2,800
31–50 years	2,800

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. DRI = Dietary Reference Intake; mg/d = milligrams per day.

in the *2005 DRI Report* were derived from potassium supplement trials, which provided evidence that higher potassium intakes may confer benefits related to blood pressure and kidney stone reoccurrence. In the expanded DRI model, the committee has reviewed such evidence in context of establishing a potassium CDRR (see Chapter 6). A comparison of the potassium AIs established in this report and those that were established in the *2005 DRI Report* is presented in Table 4-7.

TABLE 4-7 Comparison of Potassium Adequate Intakes Established in This Report to Potassium Adequate Intakes Established in the *2005 DRI Report*

DRI Age, Sex, and Life-Stage Group	Potassium AI Established in the *2005 DRI Report* (mg/d)	Updated Potassium AI Values (mg/d)
Infants		
0–6 months	400	400
7–12 months	700	860
Children		
1–3 years	3,000	2,000
4–8 years	3,800	2,300
Males		
9–13 years	4,500	2,500
14–18 years	4,700	3,000
19–30 years	4,700	3,400
31–50 years	4,700	3,400
51–70 years	4,700	3,400
> 70 years	4,700	3,400
Females		
9–13 years	4,500	2,300
14–18 years	4,700	2,300
19–30 years	4,700	2,600
31–50 years	4,700	2,600
51–70 years	4,700	2,600
> 70 years	4,700	2,600
Pregnancy		
14–18 years	4,700	2,600
19–30 years	4,700	2,900
31–50 years	4,700	2,900
Lactation		
14–18 years	5,100	2,500
19–30 years	5,100	2,800
31–50 years	5,100	2,800

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. DRI = Dietary Reference Intake; mg/d = milligrams per day.

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5

Potassium: Dietary Reference Intakes for Toxicity

The Tolerable Upper Intake Level (UL) specifies the highest average daily intake level of a nutrient, consumed on a habitual basis, that is likely to pose no risk of adverse health effects for nearly all apparently healthy individuals in a given Dietary Reference Intake (DRI) age, sex, and life-stage group. The potential for adverse health effects increases as intakes increase above the UL. The UL is intended to provide guidance on intake levels that are safe; it is not intended to serve as an intake goal. The *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) recommended that the UL be retained in the expanded DRI model, but that it should characterize *toxicological* risk (NASEM, 2017). Although this conceptual revision narrows the scope of the UL, it allows for a more nuanced characterization of the different types of risk that can exist with intake of a nutrient or other food substance. This chapter presents the committee's review of the evidence on the toxicological effects of excessive potassium intake and its conclusion regarding establishing a potassium UL. For context, the committee's findings are preceded by a brief summary of the decision made regarding the potassium UL in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005).

POTASSIUM TOLERABLE UPPER INTAKE LEVELS IN THE *2005 DRI REPORT*

A potassium UL was not established in the *2005 DRI Report*. Potential indicators reviewed included gastrointestinal discomfort from certain forms

of potassium supplements and arrhythmia from hyperkalemia. Available evidence indicated that, in generally healthy individuals, excess potassium is excreted in the urine. Because they may have impaired potassium excretion, individuals with certain conditions (e.g., chronic kidney disease, end-stage renal disease, diabetes, severe heart failure, adrenal insufficiency) and individuals who use certain medications (e.g., angiotensin-converting enzyme inhibitors [ACE-Is] and angiotensin-receptor blockers [ARBs]) were identified as potentially vulnerable subpopulations in which potassium intakes at the AI may not be appropriate (IOM, 2005).

REVIEW OF POTENTIAL INDICATORS OF TOXICOLOGICAL ADVERSE EFFECTS OF EXCESSIVE POTASSIUM INTAKE

Although dietary potassium intake can be increased through behavioral change, there is a self-limiting aspect to such changes that makes toxic adverse effects from increases in dietary potassium intake unlikely. Reports and studies evaluating potassium supplements were therefore considered most useful to determine whether a potassium intake level that could lead to toxicity could be quantified. For ethical reasons, trials cannot be designed to evaluate whether an intervention will increase the incidence of adverse effects. Consequently, adverse effect data in trials are almost always secondary outcomes. These data, particularly if systematically and carefully reported, can provide useful information for evaluating the likelihood of adverse effects. However, as secondary outcomes, these trials may not be adequately powered to identify a statistically significant occurrence of an adverse effect. These strengths and limitations need to be taken into account when using data from trials for evaluating the potential for adverse effects.

Guided by the first step of the DRI organizing framework, the committee sought to identify potential indicators of toxicological adverse effects from excessive potassium intake. The section that follows describes the evidence the committee reviewed to identify indicators that could potentially inform the derivation of the potassium UL.

Evidence Reviewed to Identify Potential Toxicological Indicators

The committee conducted a literature scan to identify potential indicators that may be informative for the potassium DRIs (see Appendix D). Among the identified indicators were blood lipid concentrations and catecholamines. Based on the committee's supplemental literature search (see Appendix E), a systematic review was identified that compiled evidence from randomized controlled trials on these measures (Aburto et al., 2013). Meta-analyses of randomized controlled trial data found that increasing potassium intake did not increase blood lipids, plasma adrenaline, or

plasma noradrenaline concentrations among adults (Aburto et al., 2013). No other potential indicator of potassium toxicity was identified from the committee's literature scan.

Additional exploration of systematic reviews and case reports on toxicity, adverse effects, and poisonings from potassium intake were undertaken in an effort to identify potential toxicological adverse effects. From these efforts, the committee identified a collection of case reports on deaths and sublethal symptomology attributed to high levels of potassium intake. The committee also compiled reported adverse effects of the potassium trials included in the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), and the committee's supplemental literature searches. The committee notes that the doses used in trials are generally not high enough to cause serious adverse effects, as it would be unethical to randomize participants to such an exposure. The intent of these evidence searches was to identify specific indicators that could potentially inform the potassium UL. The evidence that was compiled is described below.

Case Reports of Death and Sublethal Symptomology

High, acute potassium intakes have been associated with symptoms related to neuromuscular dysfunction, including weakness, paralysis, nausea, vomiting, and diarrhea. These symptoms, however, do not consistently develop prior to life-threatening cardiac arrhythmias. Furthermore, consistent evidence to quantify potassium exposure that leads to these symptoms is lacking. Acute potassium intoxications and associated hyperkalemia have been consistently linked with cardiac conduction system abnormalities, which may be fatal. These include bradycardia, peaking of T waves and widening of the QRS complex on surface electrocardiography, wide complex arrhythmias, and ultimately asystole and death. These cardiac adverse effects are mediated through higher serum potassium concentrations influencing the electrical potential on cardiac tissues.

Several case reports of potassium intoxication have been published and summarized in the literature (Guillermo et al., 2014; Ray et al., 1999). Some of the case reports include death resulting from an overdose of potassium chloride tablets. For instance, a 32-year-old female who was consuming a liquid protein diet reportedly died after ingesting approximately 47 extended-release potassium chloride tablets (Wetli and Davis, 1978). In a summary of cases reported in the literature, a report was outlined of a 26-year-old male who died after consuming an estimated 12,500 mg (320 mmol) of potassium from extended-release potassium chloride tablets (Guillermo et al., 2014);

there was also co-ingestion of dextropropoxyphene-acetaminophen in this case, which complicates the interpretation.

Death is a particularly severe endpoint to use to establish a UL. As such, the committee sought to define doses of potassium supplementation associated with signs and symptoms that preceded death and thus could serve as early warning signs of toxicity. A case report described a 17-year-old male developing nausea, vomiting, and diarrhea in conjunction with hyperkalemia after consuming between 7,800 and 11,730 mg (200 and 300 mmol) of potassium from sustained-release potassium chloride tablets (Su et al., 2001). Another case report described a 67-year-old male who was revived from cardiac arrest after consuming approximately 2,730 mg/d (70 mmol/d) of potassium from a salt substitute for 1 week (Ray et al., 1999). The individual in this case report had recently increased the dose of an ACE-I and had mild acute kidney injury at the time of presentation, which could have influenced his ability to excrete excess potassium. Although not quantified, this individual reportedly consumed a high-potassium diet, in addition to the salt substitute.

Case reports of acute intoxications from potassium supplements are not suitable for establishing a potassium UL. Such reports generally do not evaluate habitual dietary intakes, are often confounded by concurrent medical conditions, and often can only provide estimates of the number of supplements or quantity of potassium consumed based on patient self-report or reports from others who witnessed the event. The accuracy of the dose of potassium in relation to clinical signs and symptoms may be suspect. Nevertheless, the case reports demonstrate that excessive potassium supplement intake can lead to adverse events and death, even in the absence of comorbid conditions that compromise potassium excretion.

Of note is the case report of adverse effects from salt-substitute intake (Ray et al., 1999). Although total potassium intake was not quantified, the amount reportedly consumed from the salt substitute is a level of intake that has been repeatedly studied in potassium supplement trials, wherein the risk of adverse events appears to be low among generally healthy populations (described below). The 2,730 mg/d (70 mmol/d) dose of salt substitute is likely too low to inform a potassium UL for the generally healthy population. However, this case report provides evidence that certain subpopulations are susceptible to adverse effects from elevated potassium intakes.

Adverse Events Reported in Potassium Supplementation Trials

The *AHRQ Systematic Review* did not have a key question regarding adverse events in potassium trials, but it provided a brief summary of commonly reported adverse events, including gastrointestinal discomfort. Build-

ing on this work, the committee reviewed descriptions of adverse events reported in trials meeting the inclusion criteria for the *AHRQ Systematic Review* and the committee's supplemental literature searches (see Table 5-1); trials that only assessed dietary interventions are omitted from the table. Because carefully designed feeding studies demonstrate that consuming diets high in potassium induces small but detectable increases in serum potassium concentrations in healthy individuals (Macdonald-Clarke et al., 2016), the committee's review also summarizes changes or groupwise differences in serum or plasma potassium concentrations reported in these trials.

The potassium supplement dose was frequently the same across trials, at or near 2,500 mg/d (64 mmol/d). The similarity in doses studied makes it challenging to identify intake–response relationships. These studies also systematically excluded individuals at risk for potassium toxicity, such as persons with chronic kidney disease, prior evidence of hyperkalemia, and in some instances individuals with diabetes or using antihypertensive medications. The duration of exposure was typically short term, 4 to 16 weeks, although there are some trials that lasted 1 year or longer. Under these conditions, only one study provided evidence on hyperkalemia and reported higher prevalence among those in the placebo group than in the potassium supplement group. The committee's findings on changes in blood potassium concentrations are augmented by a meta-analysis of potassium supplementation trials; it found that among relatively healthy individuals there were small increases in plasma or serum potassium concentrations (weighted mean difference: 0.14 mmol/L [95% confidence interval: 0.09, 0.19], I^2 = 57 percent) with moderate potassium supplementation (Cappuccio et al., 2016).[1] The meta-analysis, however, did not find evidence of a relationship of potassium dose or duration with circulating potassium concentrations. Although there were occasional reports of nausea or gastrointestinal upset, these were rare, and it was not possible to identify a potassium dose at which these symptoms develop.

The committee's review of potassium supplementation trials were limited in facilitating establishment of a UL for potassium owing to a lack of variability in doses of potassium that were studied. The adverse reports included in potassium supplementation trials did not reveal a specific indicator on which to base a potassium UL.

[1]The dose of potassium supplement used in the trials included in the meta-analysis ranged from 860–5,474 mg/d (22–140 mmol/d).

TABLE 5-1 Potassium Supplementation Trials Included in the *AHRQ Systematic Review* and the Committee's Supplemental Literature Search That Provided a Description of Adverse Events or Blood Potassium Concentrations

Reference	Duration, Weeks[a]	Participants	Intervention
Crossover Studies			
Patki et al., 1990	8	37 Indian adults, mean age 49.9 ± 7.6 years, with mild hypertension who did not take antihypertensive medications throughout trial	Placebo 60 mmol/d liquid K supplement
Graham et al., 2014	6	43 British adults, 40–70 years of age, at moderate cardiovascular disease risk	Placebo 64 mmol/d KCl
Richards et al., 1984	4–6	12 New Zealand adults, 19–52 years of age, with mild hypertension	Control period 140 mmol/d K supplement
He et al., 2010	4	42 British adults, 18–75 years of age, with untreated mild hypertension	Placebo 64 mmol/d KCl 64 mmol/d $KHCO_3$
Vongpatanasin et al., 2016	4	30 U.S. adults, mean age 54 ± 12 years, with prehypertension or stage I hypertension	Placebo 40 mmol/d KCl 40 mmol/d K_3Cit
Parallel Randomized Controlled Trials			
Barcelo et al., 1993	144	57 Spanish adults,[g] 27–64 years of age, with moderately severe active lithiasis and low/low-normal urinary citrate	Placebo 30–60 mmol/d K_3Cit

Mean Achieved Urinary Potassium Excretion, mmol/d			
Low[b]	High[c]	Description of Adverse Events	Blood Potassium Concentrations
60	82	3 placebo and 4 K supplement participants reported abdomen pain and nausea; resolved and did not require withdrawal of treatment	Serum K, by period (mmol/L) Baseline: 3.6 ± 0.42 Placebo: 3.6 ± 8.4 Potassium: 3.7 ± 8.5
87	104	4 KCl participants reported gastrointestinal irritation; resolved with reduction in supplementation	Serum K, by period (mmol/L): Baseline: 4.2 ± 0.04 Placebo: 3.9 ± 0.04 KCl: 4.1 ± 0.05 (p = .012 compared to placebo)
~50[d]	~180[d]	Completed without incident	Plasma K, by period (mmol/L): Control: 3.84 ± 0.05 Potassium: 3.99 ± 0.12
77	122/125[e]	No significant differences in hematocrit or plasma sodium, chloride, bicarbonate, creatinine, albumin, renin activity and aldosterone, or 24-hour urinary sodium and creatinine	Plasma K, by period (mmol/L): Placebo: 4.4 ± 0.3 KCl: 4.6 ± 0.2 (p < .01 compared to placebo) $KHCO_3$: 4.4 ± 0.3
58	95/84[f]	No report provided	Serum K, by period (mmol/L): Placebo: 4.2 ± 0.3 KCl: 4.4 ± 0.3 (p < .01 compared to placebo) K_3Cit: 4.3 ± 0.3 (p < .01 compared to placebo)
~61[h]	105[i]	1 placebo and 2 K_3Cit participants dropped out due to gastrointestinal intolerance 3 K_3Cit participants reported mild nausea, epigastric pain, or abdominal distention	No significant changes in serum K

continued

TABLE 5-1 Continued

Reference	Duration, Weeks[a]	Participants	Intervention
Jehle et al., 2013	104	201 healthy, Swiss adults, 65–80 years of age	Placebo 60 mmol/d K_3Cit
Macdonald et al., 2008	104	276 postmenopausal, British women, 55–65 years of age	Placebo 55.5 mmol/d K_3Cit 18.5 mmol/d K_3Cit 300 grams additional fruit and vegetables/d
Gregory et al., 2015	52	83 U.S. women, mean of 66 years of age,[l] with postmenopausal osteopenia	Placebo 40 mmol/d K_3Cit
Obel, 1989	16	48 black, Kenyan adults, 23–56 years of age, with mildly increased blood pressure	Placebo 64 mmol/d K supplement
Siani et al., 1987	15	37 Italian adults, 21–61 years of age, with SBP ≥ 160 mm Hg and/or DBP ≥ 90 mm Hg	Placebo 48 mmol/d K supplement
Chatterjee et al., 2017	12	29 African American adults, at least 30 years of age, with prediabetes	Placebo 40 mmol/d KCl
Bulpitt et al., 1985	12	33 British adults, mean of 55 years of age,[o] with hypertension, receiving a K-losing diuretic	Control 64 mmol/d K supplement[p]

Mean Achieved Urinary Potassium Excretion, mmol/d			
Low[b]	High[c]	Description of Adverse Events	Blood Potassium Concentrations
75	109	3 K_3Cit participants discontinued due to gastrointestinal discomfort, and 1 discontinued due to severe diarrhea Adverse events were of minor severity and balanced among groups	Plasma K, end of trial (mmol/L): Placebo group: 3.8 ± 0.3 K_3Cit group: 3.9 ± 0.3 ($p < .05$ compared to placebo)
51[j]	106/ 75/70[k]	K_3Cit generally well tolerated; minor side effects were reported (indigestion, bloating)	Trend for higher serum K in the 55.5 mmol/d K_3Cit, compared to other groups, although still in reference range
NR	NR	Moderate to severe gastrointestinal symptoms were more frequently reported in K_3Cit group as compared to placebo group (19.0 versus 9.8 percent, respectively)	Higher prevalence of hyperkalemia in the placebo group as compared to K_3Cit group (14.6 versus 4.8 percent, respectively; $p = .23$)
56	102[m]	No major adverse events	No significant change in serum K concentrations in K supplement group Placebo group had similar results
NR	87	No major adverse events	Plasma K, end of trial (mmol/L): Placebo group: 4.4 ± 0.1 K group: 4.3 ± 0.1
(−8.69)[n]	(+32.12)[n]	K supplement was well tolerated	Serum K, end of trial (mmol/L): Placebo group: 3.81 ± 0.2 K group: 4.00 ± 0.2 ($p < .05$ compared to placebo)
55	95	Plasma creatinine, end of trial (μmol/L)[q]: Control group: 110 ± 9 K group: 84 ± 5 1 patient in each group reported decreased appetite at end of trial	Plasma K, end of trial (mmol/L)[r]: Control group: 3.5 ± 0.09 K group: 3.8 ± 0.09 ($p < .05$ compared to placebo)

continued

TABLE 5-1 Continued

Reference	Duration, Weeks[a]	Participants	Intervention
Svetkey et al., 1987	8	116 U.S. adults, mean age of approximately 51 years, with DBP between 90 and 105 mm Hg, untreated during trial	Placebo 120 mmol/d K supplement
Braschi and Naismith, 2008	6	85 British adults, 22–65 years of age, with BP ≤ 160/105 mm Hg	Placebo 30 mmol/d KCl 30 mmol/d K_3Cit
Naismith and Braschi, 2003	6	59 British adults, 25–65 years of age	Placebo 24 mmol/d KCl
Franzoni et al., 2005	4	104 Italian adults, 35–65 years of age, with mild to moderate hypertension, untreated during trial	Control 30 mmol/d K-aspartate
Miller et al., 1987	4	38 pairs of identical twin, U.S. children, mean 11.6 ± 3.8 years of age	Placebo ~36–45 mmol/d liquid K supplement

Mean Achieved Urinary Potassium Excretion, mmol/d			
Low[b]	High[c]	Description of Adverse Events	Blood Potassium Concentrations
NR	NR	1 participant discontinued K supplement due to side effects 2 participants discontinued placebo due to side effects K supplement versus placebo, percent of participants reporting: abdominal pain (18 versus 9 percent, respectively), change in bowel habits (10 versus 14 percent, respectively), gas (20 versus 10 percent, respectively)	Not reported
67	90/98[s]	K capsules were well tolerated, with no clinically significant side effects	Plasma K, change from baseline (mmol/L): Placebo: –0.01 [–0.26, 0.23] KCl: 0.03 [–0.26, 0.32] K_3Cit: –0.20 [–0.43, 0.02]
NR	NR	1 KCl group participant reported increase in appetite 2 placebo group participants reported side effects (nausea, transitory polyuria); symptoms resolved during study	Not reported
58	82	No reported adverse effects from the K supplement	Serum K, end of trial (mmol/L)[t]: Control: 4.18 ± 0.46 K group: 4.38 ± 0.26 ($p < .001$ compared to control)
37	49	No major adverse effects Some reports of transient nausea on initiation of supplementation, subsided after a few days	Not reported

continued

TABLE 5-1 Continued

Reference	Duration, Weeks[a]	Participants	Intervention
Sundar et al., 1985	4	50 Indian adults, mean age of approximately 46 years, with mild to moderate hypertension, untreated during trial	Placebo ~60 mmol/d K supplement

NOTES: Mean achieved urinary potassium excretion values are presented in mmol. To convert the mmol value to milligrams, multiple the excretion level by 39.1. BP = blood pressure; DBP = diastolic blood pressure; K = potassium; K_3Cit = potassium citrate; KCl = potassium chloride; $KHCO_3$ = potassium bicarbonate; SBP = systolic blood pressure.

[a]For crossover trials, duration is per period.

[b]Represents usual intake, placebo, or control period or group.

[c]This group represents the period or group intended to have the highest level of potassium intake in the study.

[d]Estimated from a bar graph in the publication.

[e]Presented as potassium chloride and potassium bicarbonate estimates, respectively.

[f]Presented as potassium chloride and potassium citrate estimates, respectively.

[g]Only 38 completed all 36 months.

[h]No values for the placebo group were reported in the paper, but it was noted that the values did not change for the placebo group over time. Value in the table reflects pretreatment urinary potassium excretion of the potassium citrate group.

[i]Urinary potassium excretion at month 36 of treatment.

[j]Value is the mean baseline urinary potassium excretions plus mean change at 104 weeks.

THE COMMITTEE'S CONCLUSION REGARDING THE TOLERABLE UPPER INTAKE LEVEL FOR POTASSIUM

Short-term potassium supplementation of approximately 2,500 mg/d (64 mmol/d) on the background of a usual diet appears to be safe for generally healthy individuals. This level of potassium intake would likely be below the UL for individuals without kidney disease, diabetes, heart failure, adrenal insufficiency, or individuals using ACE-Is, ARBs, or other medications that may raise blood potassium concentrations to levels that could lead to adverse effects. There is evidence that very high doses of supplemental potassium ingestion can lead to adverse events, and in extreme cases has led to death, even in the absence of kidney disease or other factors that alter potassium excretion. However, without a specific indicator of a toxicological effect of high potassium intake, a potassium UL cannot be established.

Mean Achieved Urinary Potassium Excretion, mmol/d			
Low[b]	High[c]	Description of Adverse Events	Blood Potassium Concentrations
56	81	No report provided	Plasma K, end of trial (mmol/L): Placebo group: 3.93 ± 0.21 K group: 4.13 ± 0.26 ($p < .001$ compared to control)

[k]Values are the mean baseline urinary potassium excretions plus mean change at 104 weeks for the high K_3Cit, the low K_3Cit, and the vegetable/fruit intervention groups, respectively.

[l]Mean age 65.1 ± 5.9 years in supplementation group ($n = 42$), 66.1 ± 7.1 years in placebo group ($n = 41$).

[m]This group had higher urinary potassium excretion at baseline as compared to the control group.

[n]Change from baseline. Baseline urinary potassium concentrations were not provided.

[o]Mean age 56.1 ± 1.6 years in supplementation group ($n = 14$), 54.2 ± 1.9 years in control group ($n = 19$).

[p]Administered as slow-release potassium tablets.

[q]Plasma creatinine at baseline was 94 ± 6 µmol/L in the potassium supplement group and 104 ± 8 µmol/L in the control group.

[r]Plasma potassium at baseline was 3.7 ± 0.12 mmol/L in the potassium supplement group and 3.7 ± 0.08 mmol/L in the control group.

[s]Presented as potassium chloride supplementation group and potassium citrate supplementation group, respectively.

[t]Serum potassium at baseline was 4.14 ± 0.43 mmol/L in the potassium supplement group and 4.19 ± 0.50 mmol/L in the control group.

The committee concludes that there is insufficient evidence of potassium toxicity risk within the apparently healthy population to establish a potassium Tolerable Upper Intake Level (UL).

The limitations that exist in the evidence highlight the need for future monitoring and research opportunities (see Chapter 12). Given the relatively high prevalence of chronic kidney disease, diabetes, heart failure, and use of ACE-Is and ARBs in the U.S. and Canadian populations, these groups represent subpopulations in which potassium excess may be of concern (see Chapter 7).

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6

Potassium: Dietary Reference Intakes Based on Chronic Disease

This chapter presents the evidence on indicators that could potentially inform the potassium Dietary Reference Intakes (DRIs) based on chronic disease and the committee's determination regarding its ability to establish a potassium Chronic Disease Risk Reduction Intake (CDRR). In its application of the recommendations in the *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) (NASEM, 2017), the committee first reviewed the evidence on chronic disease indicators. For indicators with at least moderate strength of evidence for a causal relationship, the committee characterized the intake–response relationship. This evidence informed the committee's conclusion regarding the potassium CDRR.

REVIEW OF CHRONIC DISEASE INDICATORS

The *Guiding Principles Report* recommended:

> The ideal outcome used to establish chronic disease [DRIs] should be the chronic disease of interest, as defined by accepted diagnostic criteria, including composite endpoints, when applicable. Surrogate markers could be considered with the goal of using the findings as supporting information of results based on the chronic disease of interest. (NASEM, 2017, p. 123)

In accordance with this guidance and the first step of the DRI organizing framework (see Chapter 1, Box 1-2), the committee reviewed evidence for the causal relationship between potassium intake and indicators that

could potentially inform the potassium CDRRs, which included chronic disease endpoints and surrogate markers (see Table 6-1).

Evidence on the indicators reviewed in this chapter was drawn primarily from the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018). Therefore, the evidence reflects the methodologies used in the *AHRQ Systematic Review*, including the approach to the literature search, application of the inclusion/exclusion criteria, assessment of risk of bias, and determination of the strength of evidence. The committee also conducted supplemental literature searches for select indicators not included in the *AHRQ Systematic Review* (see Appendixes D and E).

Approach to Reviewing Indicators

Use of Different Study Designs

In its application of the *Guiding Principles Report* (NASEM, 2017), the committee considered the use of evidence from different study designs in its derivation of the potassium CDRRs. As compared to randomized controlled trials, observational studies are inherently weaker for establishing causal relationships and begin at a lower strength of evidence rating in the Grading of Recommendations Assessment, Development and Evalua-

TABLE 6-1 Potential Chronic Disease Indicators Reviewed for a Causal Relationship with Potassium Intake, in Order of Presentation

Indicator	*2005 DRI Report*	*AHRQ Systematic Review*	Committee's Supplemental Literature Search
All-cause mortality		X	
Cardiovascular disease		X	
Coronary heart disease	X	X	
Myocardial infarction		X	
Stroke	X	X	
Blood pressure	X	X	
Kidney stones	X	X	
Chronic kidney disease		X	
Osteoporosis and related indicators	X[a]		X
Type 2 diabetes, glycemic control, and insulin sensitivity			X

NOTE: AHRQ = Agency for Healthcare Research and Quality; DRI = Dietary Reference Intake.

[a]The *2005 DRI Report* reviewed evidence on bone demineralization.

tion (GRADE) system (Guyatt et al., 2011). The strength of evidence from observational studies can be upgraded, for instance, when the relationship cannot be explained by uncontrolled confounding, when there is a large effect size, or when there is a strong intake–response relationship.

In accordance with the first step of the DRI organizing framework and the guidance provided in the *Guiding Principles Report* (NASEM, 2017), the committee first sought to identify evidence intake of at least moderate strength that established causality between potassium intake and a chronic disease indicator. To that end, the committee placed the highest value on evidence from randomized controlled trials (i.e., evidence of effect). Evidence from observational studies (i.e., evidence of association) is described throughout this chapter to summarize the landscape of evidence on the relationship between potassium and chronic disease. In its application of the *Guiding Principles Report*, however, the committee recognized the challenges of using observational studies to derive a potassium CDRR, because it is difficult to establish causality from observational data and it is difficult to determine the independent effect of potassium, owing to its collinearity with other nutrients. The committee therefore decided that if there was sufficient strength of evidence from trials alone, only such evidence would be used to establish the potassium CDRRs. It also decided that individual observational studies rated as low risk of bias could serve as supportive evidence, particularly when evidence from randomized controlled trials was few or unavailable, but would not serve as the sole evidence used to derive the potassium CDRRs.

Committee-Conducted Meta-Analyses

The committee rated the *AHRQ Systematic Review* as being of moderate quality, as guided by AMSTAR 2 criteria (for additional details, see Appendix C).[1] One of the domains that the *AHRQ Systematic Review* did not adequately cover related to investigation and explanation of the causes of heterogeneity in the results of meta-analyses. The committee determined that exploring sources of heterogeneity was essential for fully evaluating the strength of evidence, particularly when inconsistency was a concern in the body of evidence (for an explanation of the importance of explaining heterogeneity, see Chapter 2). Thus, the committee undertook analyses to explore heterogeneity in the trial evidence on the relationship between potassium supplementation and blood pressure (for details, see the Blood Pressure section below).

[1]AMSTAR stands for A Measurement Tool to Assess Systematic Reviews.

Review of Evidence on Indicators

The committee sought evidence on the independent effect of potassium intake on chronic disease risk. In the *AHRQ Systematic Review*, Chang et al. (2006) was included as evidence for the effect of potassium on all-cause mortality, cardiovascular disease mortality, and coronary heart disease mortality. The study assessed the effect of potassium-enriched salt on outcomes among elderly male veterans living in five retirement homes in northern Taiwan. Because the intervention concomitantly reduced sodium intake while increasing potassium intake, evidence from Chang et al. (2006) is presented in the discussion of the moderating effect of potassium (see Chapter 3).

The sections that follow present the body of evidence for a relationship between potassium intake and the potential chronic disease indicators outlined in Table 6-1. For context, evidence and conclusions presented in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005) are summarized for each indicator.

All-Cause Mortality

All-cause mortality is a clearly defined endpoint that is not specific to any chronic disease, but is heavily influenced by chronic disease mortalities. As such, it was included in context of potentially informing the potassium CDRR.

Evidence presented in the *2005 DRI Report* The relationship between potassium intake and all-cause mortality was not reviewed in the *2005 DRI Report*.

Evidence provided in the *AHRQ Systematic Review* No randomized controlled trials meeting the *AHRQ Systematic Review* inclusion criteria evaluated the independent effect of potassium intake on all-cause mortality. Six observational studies assessed the association between potassium intake and all-cause mortality among generally healthy adults. Results were mixed among the four studies that assessed potassium intake through measurement of urinary potassium excretion—two studies did not find an association (Geleijnse et al., 2007; Kieneker et al., 2016b) while the other two reported an inverse relationship (BMJ, 1998; O'Donnell et al., 2014; Tunstall-Pedoe et al., 1997). Three studies that assessed potassium intake through self-report methods found an inverse relationship between potassium intake and all-cause mortality (Geleijnse et al., 2007; Seth et al., 2014; Yang et al., 2011). All studies were rated as having moderate

or high risk of bias. The *AHRQ Systematic Review* characterized the evidence as insufficient to identify an association between potassium intake and all-cause mortality.

The modifying effect of hypertension, established cardiovascular disease or high-risk diabetes, or chronic kidney disease on the relationship between potassium and all-cause mortality was also investigated. The *AHRQ Systematic Review* identified five observational studies (Dunkler et al., 2015; He et al., 2016; Leonberg-Yoo et al., 2017; O'Donnell et al., 2011; Yang et al., 2011). Findings across the studies were mixed, and all studies were rated as having moderate or high risk of bias. The *AHRQ Systematic Review* characterized the evidence on the modifying effect of chronic disease on the association between potassium intake and all-cause mortality as insufficient.

Committee's synthesis of the evidence The lack of randomized controlled trials in which potassium intake was the only component of the diet modulated limits the committee's ability to determine if potassium intake has an independent effect on all-cause mortality risk.

The observational studies included in the *AHRQ Systematic Review* were all rated as having moderate or high risk of bias and provided inconsistent evidence of an association between potassium intake and all-cause mortality. Studies that measured urinary potassium excretion varied in approach, and included collection of multiple 24-hour urines (Kieneker et al., 2016b), a single 24-hour urine (BMJ, 1998; Tunstall-Pedoe et al., 1997), timed overnight urine (Geleijnse et al., 2007), and a spot urine sample using the Kawasaki equation to estimate 24-hour potassium excretion (O'Donnell et al., 2014). The studies applied different statistical adjustments to control for potential confounders. The two studies that did not find an association (Geleijnse et al., 2007; Kieneker et al., 2016b) adjusted for a variety of demographic, lifestyle, and health factors, including urinary sodium excretion. The two studies that reported an inverse association made some of the statistical adjustments, but neither included urinary sodium excretion. One analysis only adjusted for age (Tunstall-Pedoe et al., 1997).

Studies based on self-reported dietary intake assessment methodologies found an inverse association between potassium intake and all-cause mortality. The risk-of-bias ratings for these studies were moderate or high. The analyses included statistical adjustments for various demographic, lifestyle, and health factors. Despite the consistency of the results from analyses based on dietary intake methodologies, the committee is unable to attribute the relationship to potassium intake because statistical adjustments may not be complete and causality cannot be determined.

Given the lack of randomized controlled trials and inconsistent results from observational studies that used a variety of potassium assessment

methodologies, had different statistical adjustments for potential confounding variables, and were rated as having moderate or high risk of bias, the committee is in agreement with the *AHRQ Systematic Review* assessment that there is insufficient evidence for a relationship between potassium intake and all-cause mortality.

Cardiovascular Disease

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* included evidence on the relationship between potassium intake and the prevention of cardiovascular disease, specifically stroke and coronary heart disease (described below individually). Evidence on the relationship between potassium intake and cardiovascular disease, broadly, was not specifically reviewed.

Evidence provided in the *AHRQ Systematic Review* No randomized controlled trials meeting the *AHRQ Systematic Review* inclusion criteria evaluated the independent effect of potassium intake on cardiovascular disease mortality and morbidity. Observational studies that assessed the association between urinary potassium excretion and composite cardiovascular disease outcomes among generally healthy adult populations mostly reported nonstatistically significant relationships (Cook et al., 2009; Kieneker et al., 2016b; O'Donnell et al., 2014). Similarly, no association was found between urinary potassium excretion and a composite cardiovascular disease outcome in a cohort of adults with mild to moderate chronic kidney disease (Mills et al., 2016). Among the studies reporting on combined cardiovascular disease morbidity and mortality, only one (Cook et al., 2009) was rated as having a low risk of bias; the other studies were rated as having a moderate or high risk of bias. Although generally similar, the definition of the composite cardiovascular disease outcome slightly varied across studies. The *AHRQ Systematic Review* characterized the evidence as insufficient to be able to identify an association between potassium intake and cardiovascular disease morbidity and mortality.

No randomized controlled trials meeting the *AHRQ Systematic Review* inclusion criteria evaluated the independent effect of potassium intake on cardiovascular disease mortality. Three observational studies in generally healthy adult populations provided mixed results regarding the association between potassium intake and cardiovascular disease mortality (Geleijnse et al., 2007; O'Donnell et al., 2014; Yang et al., 2011). These studies varied in potassium intake ascertainment that included spot urine sample, timed overnight urine sample, food frequency questionnaire, and 24-hour dietary recall. One study, conducted in adults with established cardiovascular disease or high-risk diabetes, did not find a statistically significant relationship

between baseline spot urine potassium excretion and risk of cardiovascular disease mortality (O'Donnell et al., 2011). All studies were rated as having a moderate or high risk of bias. The *AHRQ Systematic Review* characterized this evidence as insufficient to identify an association between potassium intake and cardiovascular disease mortality.

Committee's synthesis of the evidence The lack of randomized controlled trials in which potassium intake is the only component of the diet modulated limits the committee's ability to determine if potassium intake has an independent effect on the risk of cardiovascular disease mortality or combined cardiovascular outcomes.

The association between potassium intake and combined cardiovascular disease outcomes was not statistically significant in the observational studies included in the *AHRQ Systematic Review*. Findings were mixed among studies that assessed the association between urinary potassium excretion and cardiovascular mortality among various populations, with O'Donnell et al. (2014) reporting an inverse relationship, and Geleijnse et al. (2007) and a separate study by O'Donnell et al. (2011) reporting no significant associations. Studies with data collected through self-reported dietary intake methodologies were also mixed; an analysis based on food frequency questionnaires reported no significant relationship (Geleijnse et al., 2007) whereas an analysis based on 24-hour recalls reported an inverse relationship (Yang et al., 2011).

Since the release of the *AHRQ Systematic Review*, two additional observational studies meeting the *AHRQ Systematic Review* inclusion criteria have been published related to composite cardiovascular disease outcomes. Prentice et al. (2017) used data from the usual diet arm of the Women's Health Initiative (WHI) Dietary Modification Trial and from the WHI Observation Study to assess the relationship between potassium intake measured by a baseline food frequency questionnaire and total cardiovascular disease among 86,444 postmenopausal women (high risk of bias study). An inverse relationship was found between baseline potassium intake (calibrated using urinary excretion) and total cardiovascular disease (coronary heart disease and stroke; hazard ratio [HR] = 0.86 [95% confidence interval {CI}: 0.75, 0.98]).[2,3] The findings were slightly attenuated when using uncalibrated potassium intake (HR = 0.96 [95% CI: 0.94,

[2]To correct for biases in the self-reported dietary intake data, potassium intakes from the food frequency questionnaires were calibrated using an equation developed from 24-hour urine samples and potential confounding variables on a subsample of 450 participants in the WHI Observational Study.

[3]Findings were similar for an analysis expanding the definition of total cardiovascular disease to include coronary heart disease, stroke, coronary artery bypass graft, and percutaneous coronary intervention (HR = 0.87 [95% CI = 0.76, 0.99]).

0.98]). In an analysis of 6.5 years of follow-up in the Tehran Lipid and Glucose Study, baseline potassium intake as assessed by food frequency questionnaire was not associated with cardiovascular disease among 1,576 adults 30 years of age and older (high risk of bias study) (Mirmiran et al., 2018).

Given the lack of randomized controlled trials and inconsistent results among observational studies, all of which were rated as having a moderate or high risk of bias except one, the committee is in agreement with the *AHRQ Systematic Review* assessment that there is insufficient evidence for a relationship between potassium intake and either risk of combined cardiovascular disease mortality and morbidity or risk of cardiovascular disease mortality. The dietary assessment calibration approach used in Prentice et al. (2017) may have implications for future research, as the calibration can potentially correct for biases in the dietary intake assessment data, but this study alone is not strong enough to change the strength of the evidence grade.

Coronary Heart Disease

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* included evidence from three prospective cohort studies that assessed the relationship between potassium intake and coronary heart disease (Bazzano et al., 2001; Khaw and Barrett-Connor, 1987; Tunstall-Pedoe et al., 1997). Findings were mixed. Evidence for coronary heart disease was not used to determine, support, or justify the potassium reference values established in the *2005 DRI Report*.

Evidence provided in the *AHRQ Systematic Review* No randomized controlled trials meeting the *AHRQ Systematic Review* inclusion criteria evaluated the independent effect of potassium intake on coronary heart disease morbidity and mortality. Two observational studies assessing the association between potassium intake and combined coronary heart disease morbidity and mortality met inclusion criteria. One study reported no significant differences in risk by quintile of urinary potassium excretion, based on multiple samples; the study was rated as having a moderate risk of bias (Kieneker et al., 2016b). The other study reported an inverse relationship, based on a single 24-hour urinary potassium excretion at baseline and was rated as having a high risk of bias (BMJ, 1998; Tunstall-Pedoe et al., 1997). The *AHRQ Systematic Review* characterized the evidence as insufficient to identify an association between potassium intake and coronary heart disease morbidity and mortality.

No randomized controlled trials meeting the *AHRQ Systematic Review* inclusion criteria evaluated the independent effect of potassium intake on coronary heart disease mortality. Two observational studies assessed the

relationship between potassium intake and coronary heart disease mortality. Both reported an inverse relationship, with hazards of coronary heart disease mortality decreasing with increasing potassium excretion or intake, based on a single 24-hour urinary potassium excretion at baseline (BMJ, 1998; Tunstall-Pedoe et al., 1997) or intake 24-hour dietary recalls (Yang et al., 2011). The studies were rated as having a moderate and high risk of bias. The *AHRQ Systematic Review* characterized the evidence as insufficient to be able to identify an association between potassium intake and coronary heart disease mortality.

Committee's synthesis of the evidence The lack of randomized controlled trials in which potassium intake is the only component of the diet modulated limits the committee's ability to determine if potassium intake has an independent effect on the risk of coronary heart disease mortality or combined coronary heart disease morbidity and mortality.

Two studies included in the *AHRQ Systematic Review* assessed the association between potassium intake and combined coronary heart disease morbidity and mortality. One of the studies only adjusted for age in its analyses and did not report confidence intervals (Tunstall-Pedoe et al., 1997). The other study did not find a statistically significant association between the average of multiple 24-hour urinary potassium excretions and coronary heart disease morbidity and mortality (HR, per 1,017 mg/d [26 mmol/d] increase in urinary potassium excretion = 0.90 [95% CI: 0.77, 1.04]) (Kieneker et al., 2016b). Since the release of the *AHRQ Systematic Review*, an additional study meeting inclusion criteria has reported an inverse relationship between calibrated potassium intake and coronary heart disease (inclusive of nonfatal myocardial infarction and coronary death; HR = 0.85 [95% CI: 0.73, 0.99]), based on data from the WHI Dietary Modification Trial and from the WHI Observation Study (Prentice et al., 2017). The findings were slightly attenuated when using uncalibrated potassium intake (HR = 0.94 [95% CI: 0.92, 0.97]).

Two studies included in the *AHRQ Systematic Review* suggest there is an inverse association between potassium intake and coronary heart disease mortality. As described above, one of the studies had incomplete exploration and reporting of the analyses (Tunstall-Pedoe et al., 1997). The other study reported decreased hazard for coronary heart disease mortality for each quartile of intake, as compared to the first quartile of usual potassium intake at baseline (1,793 mg/d [80 mmol/d]) (Yang et al., 2011). Since the release of the *AHRQ Systematic Review*, an additional study meeting the inclusion criteria reported an inverse relationship between calibrated potassium intake and coronary death, with a decrease in risk for every 20 percent increase in calibrated potassium intake (HR = 0.84 [95% CI: 0.74, 0.98]) (Prentice et al., 2017). The findings were slightly attenuated when using uncalibrated potassium intake (HR = 0.93 [95% CI: 0.89,

0.97]). The analyses adjusted for a variety of demographic, lifestyle, and health factors;[4] however, neither body mass index nor incident hypertension were included in the disease risk model, to prevent overcorrection.

Given the lack of a randomized controlled trial and the observational studies having a moderate or high risk of bias the committee is in agreement with the *AHRQ Systematic Review* assessment that there is insufficient evidence on the relationship between potassium intake and coronary heart disease.

Myocardial Infarction

Evidence presented in the *2005 DRI Report* Evidence on the relationship between potassium intake and myocardial infarction was not reviewed in the *2005 DRI Report*.

Evidence provided in the *AHRQ Systematic Review* No randomized controlled trials meeting the *AHRQ Systematic Review* inclusion criteria evaluated the independent effect of potassium intake on myocardial infarction. Two observational studies assessed the relationship between potassium intake and myocardial infarction in a cohort of generally healthy adults (Geleijnse et al., 2007; O'Donnell et al., 2014). Neither study found a statistically significant relationship between potassium excretion and myocardial infarction. The *AHRQ Systematic Review* rated both studies as having a high risk of bias, and characterized the evidence on the association between potassium intake and myocardial infarction as insufficient.

The *AHRQ Systematic Review* also included studies that assessed the association between potassium intake and myocardial infarction in a cohort of adults with hypertension (Alderman et al., 1997), mild to moderate chronic kidney disease (Mills et al., 2016), or established cardiovascular disease or high-risk diabetes (O'Donnell et al., 2011). None of the studies identified a statistically significant association between potassium intake and myocardial infarction. The *AHRQ Systematic Review* rated the studies as having a moderate or high risk of bias, and characterized the evidence on the moderating effect of select chronic diseases on the association between potassium intake and myocardial infarction as insufficient.

Committee's synthesis of the evidence The lack of randomized controlled trials in which potassium intake is the only component of the diet modulated limits the committee's ability to determine if potassium intake has

[4]Adjusted for age, race/ethnicity, educational level, family history of premature cardiovascular disease, cigarette smoking status, treated diabetes, statin use, aspirin use, prior postmenopausal hormone therapy use, and an estimate of recreational physical activity.

an independent effect on the risk of myocardial infarction. None of the observational studies included in the *AHRQ Systematic Review* identified a statistically significant association between various measures of urinary potassium excretion and myocardial infarction. Since the release of the *AHRQ Systematic Review*, an additional study meeting inclusion criteria has reported an inverse relationship between calibrated potassium intake and nonfatal myocardial infarction (HR = 0.83 [95% CI: 0.72, 0.96]) (Prentice et al., 2017). The findings were slightly attenuated when using uncalibrated potassium intake (HR = 0.94 [95% CI: 0.92, 0.97]).

Given the lack of randomized controlled trials and the moderate or high risk of bias observational studies that, with the exception of one, did not find a statistically significant association between potassium intake and myocardial infarction, the committee is in agreement with the *AHRQ Systematic Review* assessment that there is insufficient evidence for a relationship between potassium intake and myocardial infarction.

Stroke

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* summarized eight observational studies on potassium intake and stroke (Ascherio et al., 1998; Bazzano et al., 2001; Fang et al., 2000; Green et al., 2002; Iso et al., 1999; Khaw and Barrett-Connor, 1987; Lee et al., 1988; Sasaki et al., 1995). Several, but not all, of the studies found an inverse relationship between potassium intake and stroke-associated morbidity and mortality.

Evidence provided in the *AHRQ Systematic Review* No randomized controlled trials met the *AHRQ Systematic Review* inclusion criteria for this outcome. Fifteen observational studies assessing the association between potassium intake and stroke were included.

Three studies assessed the association between urinary potassium excretion and stroke. Two of the studies did not find a statistically significant relationship (Geleijnse et al., 2007; Kieneker et al., 2016b). One study reported that the odds for stroke was significantly lower for those with estimated potassium excretions of 1,500–1,999 mg/d (38–51 mmol/d), as compared to those with urinary potassium excretions < 1,500 mg/d (< 38 mmol/d) (odds ratio [OR] = 0.82 [95% CI: 0.68, 0.99]); odds of stroke were not statistically lower for any of the higher categories of urinary potassium excretion, as compared to the < 1,500 mg/d (< 38 mmol/d) group (O'Donnell et al., 2014). The three studies were rated as having a moderate or high risk of bias. The *AHRQ Systematic Review* described the relationship between urinary potassium excretion and stroke as inconsistent.

Results from studies that used dietary intake assessment methodologies to assess the association between potassium intake and stroke were

also mixed. Three studies collected 24-hour dietary recalls. Bazzano et al. (2001) reported a statistically significant decrease in risk only between the first and second quartile of potassium intake (< 1,353 mg/d [< 34.6 mmol/d] versus 1,353–1,947 mg/d [35–50 mmol/d], respectively), but not at higher intake levels. Using data from the same cohort, Fang et al. (2000) found an inverse relationship between potassium intake and risk of stroke mortality among black males and white males; the relationship did not reach statistical significance among black females, white females, normotensive females, females with hypertension, or normotensive males. Another study, however, reported risk of stroke-related mortality to have an inverse relationship with potassium intake, particularly among women (Khaw and Barrett-Connor, 1987). Findings were mixed among studies that assessed potassium intake through food frequency questionnaire. Several did not find a statistically significant relationship between potassium intake and stroke (Adebamowo et al., 2015; Ascherio et al., 1998; Geleijnse et al., 2007; Larsson et al., 2008, 2011a; Sluijs et al., 2014). Some of the studies found a statistically significant relationship, notably in adults not using diuretics (Green et al., 2002) and normotensive postmenopausal women (Seth et al., 2014). All studies were rated as having a moderate or high risk of bias. The *AHRQ Systematic Review* characterized the statistical significance of the associations between potassium intake and stroke as mixed among studies that used dietary intake assessment methodologies.

The relationship between potassium intake and stroke was also assessed among population groups characterized by a chronic disease or condition. In an analysis based on the first National Health and Nutrition Examination Survey Epidemiological Follow-Up Study data, relative risk of stroke mortality was reported to be higher among hypertensive males with lower potassium intake, but such a relationship was not found among hypertensive females (Fang et al., 2000). Based on an analysis of data from the Swedish Mammography Cohort, relative risk of stroke tended to be lower among women with a history of hypertension with higher potassium intakes, although not all comparisons to the first quintile of intake reached statistical significance (Larsson et al., 2011a). Among postmenopausal women with hypertension participating in the WHI Observational Study, there were no statistically significant risk reductions in all comparisons to the first quartile of intake (< 1,925 mg/d [< 49 mmol/d]) (Seth et al., 2014). Statistically significant lower hazards of stroke were found among adults with established cardiovascular disease or high-risk diabetes with higher potassium excretion, as compared to those with the lowest potassium excretion (< 1,500 mg/d [< 38 mmol/d]) (O'Donnell et al., 2011). In an analysis of adults with mild to moderate chronic kidney disease, cumulative mean potassium excretion from three 24-hour urinary measurements was not associated with stroke risk (Mills et al., 2016). All studies were rated as having a moderate or high risk of bias.

The *AHRQ Systematic Review* concluded that there was insufficient evidence to identify associations of potassium intake with stroke. Evidence on the moderating effect of chronic diseases or conditions was also characterized as insufficient.

Committee's synthesis of the evidence The lack of randomized controlled trials in which potassium intake is the only component of the diet modulated limits the committee's ability to determine if potassium intake has an independent effect on stroke.

The association between potassium intake and risk of stroke did not reach statistical significance in many of the observational studies included in the *AHRQ Systematic Review*. Since the release of the *AHRQ Systematic Review*, an additional study meeting the inclusion criteria has been published suggesting that there was a nonstatistically significant inverse relationship between calibrated potassium intake and total stroke (HR for 20 percent increase in potassium intake = 0.88 [95% CI: 0.78, 1.01]) (Prentice et al., 2017).

The conclusion of insufficient evidence reached in the *AHRQ Systematic Review* appears to differ from conclusions reached in several recent systematic evidence reviews and meta-analyses of prospective cohort studies on potassium intake and risk of stroke (Aburto et al., 2013; D'Elia et al., 2014; Larsson et al., 2011b; Vinceti et al., 2016). The *AHRQ Systematic Review* considered these reviews by identifying individual studies within each that met its inclusion criteria (i.e., used them for reference mining). As such, the origin of the apparent different conclusions is not that the *AHRQ Systematic Review* considered a different collection of literature, but that it had different inclusion criteria and approach.[5] Unlike the other systematic reviews, the *AHRQ Systematic Review* did not conduct meta-analyses using the prospective cohort data; pooled estimates are, therefore, not available for comparison. A brief summary of methodologies and findings from other syntheses of the observational evidence on the relationship between potassium intake and risk of stroke is provided below:

- Larsson et al. (2011b) identified 10 prospective cohort studies, all of which collected either 24-hour dietary recalls or food frequency questionnaire data. No risk-of-bias assessment was described. The pooled relative risk for total stroke for 1,000 mg/d (26 mmol/d) increase in potassium was 0.89 ([95% CI: 0.83, 0.96], I^2 = 51 percent). Removing one of the studies (Khaw and Barrett-Connor, 1987) reduced the heterogeneity to 21 percent. Although the methodology

[5]For example, Umesawa et al. (2008) and Weng et al. (2008) were both listed as excluded from the *AHRQ Systematic Review* because "the intervention [was] not of interest."

was not provided, Adebamowo et al. (2015) reported updating this meta-analysis with new estimates from analyses of Nurses' Health Study I and II data and a study by Sluijs et al. (2014). The pooled relative risk for total stroke for 1,000 mg/d increase in potassium was 0.91 ([95% CI: 0.88, 0.94], I^2 was not reported).

- Aburto et al. (2013) reported that, based on nine cohort studies, risk of incident stroke was reduced with higher intake of potassium (risk ratio [RR] = 0.76 [95% CI: 0.66, 0.89], I^2 = 59 percent). Using the GRADE system, the strength of the evidence for a protective effect of higher potassium intake on incident stroke was graded as low.
- D'Elia et al. (2011) included nine studies that were assessed through an adapted quality scoring system from Downs and Black. Higher potassium intake (average weighted difference 1,640 mg/d [42 mmol/d]) had an inverse relationship with stroke (RR = 0.79 [95% CI: 0.68, 0.90], I^2 = 55 percent). None of the factors assessed through meta-regression (quality score, length of follow-up, recruitment year, population potassium intake at baseline, between group difference in potassium intake) had a significant influence on the estimate. A 2014 update of this systematic review added three additional analyses, including one analysis in which the potassium exposure was based on a baseline spot urine sample (D'Elia et al., 2014). Methodological details of the process by which the systematic review was updated were not provided. For every 1,000 mg/d (26 mmol/d) increase in potassium intake, there was a 10 percent reduction in stroke risk (RR = 0.90 [95% CI: 0.84, 0.96], I^2 = 47 percent).
- Vinceti et al. (2016) included 16 studies in their meta-analysis. The Newcastle-Ottawa assessment scale was used to assess the studies; any measure of urinary potassium excretion was considered higher quality. The authors multiplied baseline potassium exposure expressed as 24-hour urinary excretion by 1.3 to convert it to an estimate of dietary intake. The pooled risk ratio for stroke was estimated to be 0.87 ([95% CI: 0.80, 0.94], I^2 = 46 percent).[6] When stratified by type of potassium intake assessment methodology, the pooled risk ratio estimate of the four studies based on urinary excretion was higher and had wider confidence intervals than that of the pooled estimate based on 12 studies that assessed potassium exposure through dietary assessment methodologies. In a spline regression analysis, stroke risk reduced with increased intake to approximately 3,518 mg/d (90 mmol/d). The analyses suggested that the relationship between potassium intake and stroke may not

[6]Estimate is for the most adjusted model. Additional analyses also explore the implications of using estimates not adjusted for blood pressure or hypertension status.

be linear. Only two studies in the analysis, however, had estimates of potassium intakes of 4,691 mg/d (120 mmol/d) or greater.

Larsson et al. (2011b) and Vinceti et al. (2016) both explored whether the relationship between potassium intake and stroke varied by stroke type. Each produced pooled estimates from the subset of studies that provided such data. Both analyses suggested a significant inverse relationship with ischemic stroke. The relationship between potassium intake and hemorrhagic stroke was not statistically significant in either report, except in an analysis in which Vinceti et al. (2016) did not control for blood pressure or hypertension status.

There is some observational evidence to suggest that potassium intake may have an inverse relationship with risk of stroke and, based on the summaries above, limited evidence to suggest that the relationship may be more relevant to ischemic stroke, as opposed to hemorrhagic stroke (Larsson et al., 2011b; Vinceti et al., 2016). However, recent systematic reviews that have assessed the strength of evidence have graded the evidence as either insufficient (Newberry et al., 2018) or low (Aburto et al., 2013). The *Guiding Principles Report* recommended strength of evidence for a causal relationship should be at least moderate to be used to establish a DRI based on chronic disease. Given that the evidence on the relationship is entirely derived from analyses of observational data, and therefore limits the committee's ability to determine the independent effect of potassium, the strength of evidence on the causal relationship between potassium intake and stroke does not qualify for a moderate rating. The committee is in agreement with the *AHRQ Systematic Review* assessment that there is insufficient evidence on the association between potassium intake and stroke.

Blood Pressure

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* reviewed observational studies, interventional trials, and a meta-analysis to assess the relationship between potassium intake and blood pressure. Integral to the use of the blood pressure evidence in the *2005 DRI Report* were considerations regarding interpretation, which are outlined in Box 6-1.

Two findings on the relationship between potassium intake and blood pressure were described as part of the evidence base that informed the potassium AI for adults.[7] First, one intake–response trial reported that potassium intake of 4,700 mg/d (120 mmol/d), of which 3,519 mg/d (90 mmol/d)

[7]The potassium AI for adults 19–50 years of age served as the foundation for setting the potassium AI for children, adolescents, older adults, pregnant women, and lactating women.

BOX 6-1
Considerations That Informed the Interpretation of Blood Pressure Evidence in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*)

In the *2005 DRI Report*, evidence on the relationship between potassium intake and blood pressure was used to support the potassium Adequate Intake. Central to the interpretation of the evidence in that report were the following considerations:

- Given concomitant changes in other nutrients that accompany a potassium-rich diet (e.g., fiber, magnesium), evidence from studies on dietary potassium intake ought to be interpreted with caution.
- Some observational studies reported stronger relationships between the sodium-to-potassium ratio than to either electrolyte alone. The collinearity of other nutrients with potassium, however, made discerning the independent effect of potassium challenging.
- In some of the potassium supplement trials, the contribution of dietary potassium intake to total potassium intake was not described or accounted for in the analysis.
- The lack of multiple doses of potassium within the same trial limits an intake–response analysis from a single study.
- Because a relationship was reported in both observational studies (i.e., potassium from food sources) and supplementation trials (i.e., potassium chloride, a different anion than what typically occurs in foods), it was concluded that the effect on blood pressure was a result of potassium rather than its conjugate anion.

SOURCE: IOM, 2005.

was administered as potassium bicarbonate capsules, markedly reduced the prevalence of salt sensitivity among normotensive African American men (Morris et al., 1999).[8] Second, several clinical trials reported total potassium intake of approximately 3,100–4,700 mg/d (80–120 mmol/d) reduced blood pressure among normotensive adults; most studies included a potassium supplement. This evidence, together with evidence on the relationship between potassium intake and kidney stones, was used in the *2005 DRI Report* to establish the potassium Adequate Intake (AI) for adults at 4,700 mg/d (120 mmol/d).

[8]Morris et al. (1999) was not included in the *AHRQ Systematic Review*. There were no key questions about salt-sensitive blood pressure changes. Furthermore, the provision of potassium was only 3 weeks in length, which is shorter than the inclusion criteria for the *AHRQ Systematic Review*.

Evidence provided in the *AHRQ Systematic Review* The *AHRQ Systematic Review* included two key questions that sought to assess the relationship between potassium intake and blood pressure (see Chapter 1, Box 1-3). One of the key questions focused on the *effect* of potassium interventions on blood pressure (i.e., randomized controlled trials). Corresponding evidence included interventions in which participants received advice and coaching to increase dietary potassium intake and trials that used potassium supplements to increase potassium intake. The other key question assessed the evidence of an *association* between potassium intake and blood pressure (i.e., observational studies).

As the intent of this review of evidence is to evaluate the causality between potassium intake and a chronic disease indicator, the summary below focuses on the trial data. However, it is noted that the *AHRQ Systematic Review* concluded that there was low strength of evidence to suggest that higher potassium intake is inconsistently associated with lower adjusted blood pressure in adults, based on 10 analyses of observational data. There was no evidence to indicate that higher potassium intake is associated with a decrease in hypertension incidence. There was insufficient evidence to draw conclusions about the modifying effect of sex, age, race, ethnicity, hypertension status, or obesity status.

Adults The *AHRQ Systematic Review* identified three parallel randomized controlled trials (Miller et al., 2016; Nowson and Morgan, 1988; Siani et al., 1991) and one crossover trial (Berry et al., 2010) that examined the effect of increasing potassium intake from foods alone on blood pressure. All were conducted in adult participants with mild or well-controlled hypertension. Nowson and Morgan (1988) reported a significant effect of dietary potassium intake on blood pressure. Siani et al. (1991) found that, although there was no difference in blood pressure between groups at the end of the study, the dietary potassium intervention group had greater reductions in antihypertensive drug therapy, as compared to the control group ($p < .001$). The other two studies reported no statistically significant effect (Berry et al., 2010; Miller et al., 2016). The studies had various risk-of-bias ratings (low, moderate, high, and unclear). Grading the strength of the evidence as low, the *AHRQ Systematic Review* concluded that there was no evidence to suggest increasing dietary potassium through food alone affects blood pressure.

The *AHRQ Systematic Review* identified 10 parallel randomized controlled trials and 8 crossover trials that examined the effect of potassium supplements, as compared to placebo. A random-effects meta-analysis across the 18 trials resulted in a mean difference in systolic blood pressure of –6.43 mm Hg ([95% CI: –11.06, –1.80], I^2 = 94 percent). The high heterogeneity was noted. Omitting studies with high or unclear risk of bias

did not substantially change the pooled estimate. For diastolic blood pressure, the pooled estimate across the 18 trials resulted in a mean difference of –3.50 mm Hg ([95% CI: –6.10, –0.89], I^2 = 93 percent). The analyses were also stratified by hypertension status. The pooled effect estimates for normotensive adults suggested a possible beneficial effect on systolic and diastolic blood pressure, but it was no longer statistically significant. Pooled estimates among adults with prehypertension and hypertension were similar to those in the overall meta-analysis.

The *AHRQ Systematic Review* concluded that there was moderate strength of evidence that increased potassium intake from dietary supplements reduces blood pressure in adults with prehypertension and hypertension, and that there was low strength of evidence that potassium supplementation does not decrease blood pressure among normotensive adults. The *AHRQ Systematic Review* also determined that there was insufficient evidence to draw any conclusions about whether sex, race, or ethnicity modifies the effect of potassium supplementation on blood pressure among adults.

Children and adolescents One parallel randomized controlled trial and one controlled trial assessing the effect of potassium supplementation on blood pressure in children and adolescents met the *AHRQ Systematic Review* inclusion criteria. In the randomized controlled trial, 210 adolescents (mean: 13 years of age at baseline) in the top 15th percentile for blood pressure were randomized to a low-sodium diet, potassium chloride supplementation, or placebo control for 3 years (Sinaiko et al., 1993). The potassium supplement was scaled to body weight (39 mg/kg bodyweight/d [1 mmol/kg bodyweight/d], with a maximum of 3,128 mg/d [80 mmol/d]). Girls in the potassium supplement group had a significantly lower increase in systolic blood pressure, whereas the boys in the potassium supplement group did not have the same effect. The change in systolic and diastolic blood pressure at the end of the trial was not significantly different between the placebo and the potassium supplementation groups. The slope of change in blood pressure was significantly different between boys and girls in the potassium supplementation group. The other trial assessed 38 sets of homozygous twins (mean: 11.6 ± 3.8 years of age at baseline), during which one twin received potassium supplementation and the other twin received a placebo for a period of 4 weeks (Miller et al., 1987). There was no significant difference in blood pressure in paired comparisons. Based on this evidence, the *AHRQ Systematic Review* concluded that there was insufficient evidence to draw any conclusions about the effects of potassium supplementation on blood pressure in children and adolescents.

Committee's synthesis of the evidence The committee identified the lack of exploration of potential sources of heterogeneity as a key limitation of

the *AHRQ Systematic Review* report (for an explanation regarding heterogeneity, see Chapter 2, and for the committee's assessment of the *AHRQ Systematic Review*, see Appendix C). Given the extensive variation seen among the studies, the committee further explored heterogeneity in the trials of potassium supplementation and blood pressure. Two members of the committee reviewed the primary publications of the trials included in the *AHRQ Systematic Review*; relatively small transcription errors were corrected. Trials mentioned in the text of the *AHRQ Systematic Review* but not included in meta-analysis were also identified. A description of changes made are listed in Box 6-2.

The committee's analysis includes 16 trials of potassium supplements only. As described above, there were four trials of dietary intervention to increase potassium intake. The dietary trials, however, are excluded from this analysis owing to concerns about collinearity between potassium and other nutrients. Most of the potassium supplementation trials used potassium chloride. Some included potassium citrate or potassium bicarbonate, but potassium chloride was used primarily in the *AHRQ Systematic Review* and used preferentially in the committee's analysis. The analysis was a random-effects meta-analysis done using the metafor package in the software package R.[9] The Knapp-Hartung variance estimate is reported for all summary effects. Because the results from Obel (1989) were an apparent outlier, all analyses were repeated without this trial.

Updated results for blood pressure Despite some changes in the studies and corrections to individual study effects, the overall results were similar to those reported in the *AHRQ Systematic Review;* increased potassium intake through potassium supplementation decreased blood pressure. The estimated net difference in systolic blood pressure was –6.87 mm Hg [95% CI: –12.12, –1.61] (see Figure 6-1), and in diastolic blood pressure it was –3.57 mm Hg [95% CI: –6.52, –0.63] (see Figure 6-2). There was still much heterogeneity with overall I^2 values of 94 to 97 percent, with more heterogeneity in the parallel trials than the crossover trials (98 versus 71 percent for systolic blood pressure and 96 versus 66 percent for diastolic blood pressure, respectively). Restricting the included studies to those that used potassium chloride supplements made little difference. When the Obel (1989) trial was eliminated, there was only a small reduction in heterogeneity, though the estimated effects were smaller, with net differences of –4.42 mm Hg ([95% CI: –6.92, –1.91], I^2 = 83 percent) for systolic blood pressure and –2.53 mm Hg ([95% CI: –4.73, –0.32], I^2 = 86 percent) for diastolic blood pressure.

[9]A collection of functions for conducting meta-analyses is in the statistical software package R.

BOX 6-2
Decisions Made on Individual Trials in the Committee's Meta-Analyses on the Effect of Potassium Supplementation on Blood Pressure

The committee used the evidence provided in the *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) to further explore the effect of potassium supplement intake on blood pressure. The following decisions were made about individual trials in the committee's analysis:

- Becerra-Tomas et al. (2015) was an intervention comparing low-sodium wheat bread enriched by potassium citrate to traditional bread. Because this study is a combined intervention of sodium and potassium, it was not included in the committee's analysis.
- Berry et al. (2010) is a crossover trial of potassium citrate, which also had diet arms. The *AHRQ Systematic Review* reported the supine blood pressure measures. Since ambulatory blood pressure was chosen in the *AHRQ Systematic Review* for many other trials, it was substituted in the committee's analysis. The mean baseline ambulatory blood pressure also agrees with the hypertensive status at baseline. Note that this changed the blood pressure difference to a positive effect (1.8/1.4 mm Hg).
- He et al. (2010) is a three-period crossover trial of potassium chloride versus potassium bicarbonate versus placebo. The *AHRQ Systematic Review* included potassium bicarbonate in its analysis while most of the other studies included potassium chloride. The *AHRQ Systematic Review* reported a difference for ambulatory blood pressure of 0/+1 mm Hg. The actual mean difference for potassium chloride should be –3/–1 mm Hg, though nonsignificant. The same differences were seen in office blood pressure. The estimates for potassium chloride were substituted, along with the confidence intervals computed in the *AHRQ Systematic Review*.
- Nowson and Morgan (1988) was a dietary intervention trial, and is excluded from the committee's analysis of potassium supplements.
- Rahimi et al. (2007) was a dietary intervention, and was excluded from the committee's analysis of potassium supplements.
- Five of the eight crossover trials only reported the means and standard deviation at the end of the interventions, and did not report changes or their variation. The *AHRQ Systematic Review* computed confidence intervals from these trials, likely based on methods recommended in the Cochrane report that impute a correlation between the repeated measured of blood pressure. The estimated confidence intervals reported in the *AHRQ Systematic Review* were used in the committee's analysis.

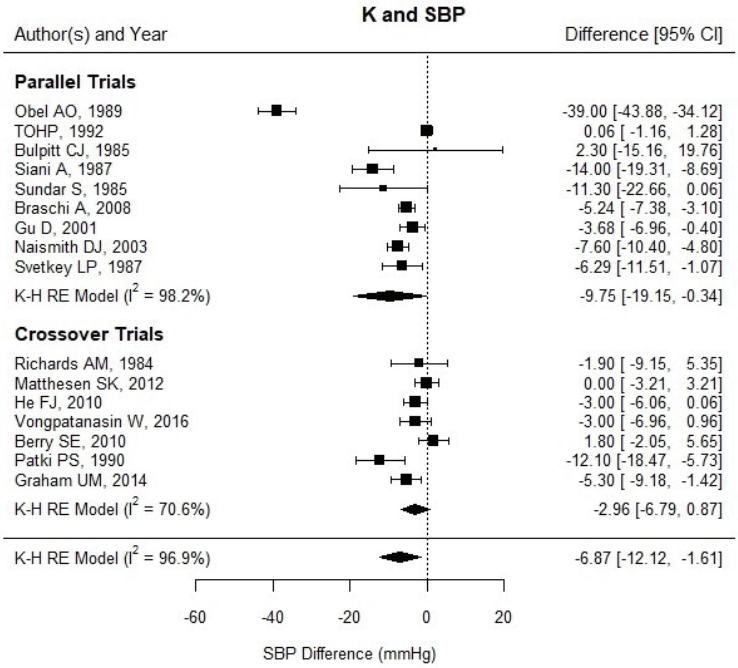

FIGURE 6-1 Random-effects meta-analysis of parallel and crossover trials of effects of potassium supplementation on systolic blood pressure. Meta-analysis was conducted in R with random-effects models in the metafor package using the Knapp-Hartung variance.
NOTES: Studies are listed by the last name of the first author and year of publication. CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K = potassium; K-H = Knapp-Hartung variance estimate; RE = random-effects; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention.

There were no differences in effect by achieved net differences in potassium excretion (see Figure 6-3), including after eliminating the Obel (1989) outlier, indicating a lack of an intake–response relationship. There were also no differences by sodium excretion, duration of trial, year, or sample size, including after eliminating the Obel (1989) outlier. There was a suggested difference in effect on net systolic blood pressure difference by baseline systolic blood pressure (slope = –0.245 per mm Hg, p = .046) (see Figure 6-4), but this was attenuated after eliminating Obel (1989) (slope = –0.085 per mm Hg, p = .26). The I^2 values remained high at 95 percent (82 percent without Obel, 1989). Effects were stronger among studies including any hypertensive participants with a net systolic difference of –8.16 mm Hg

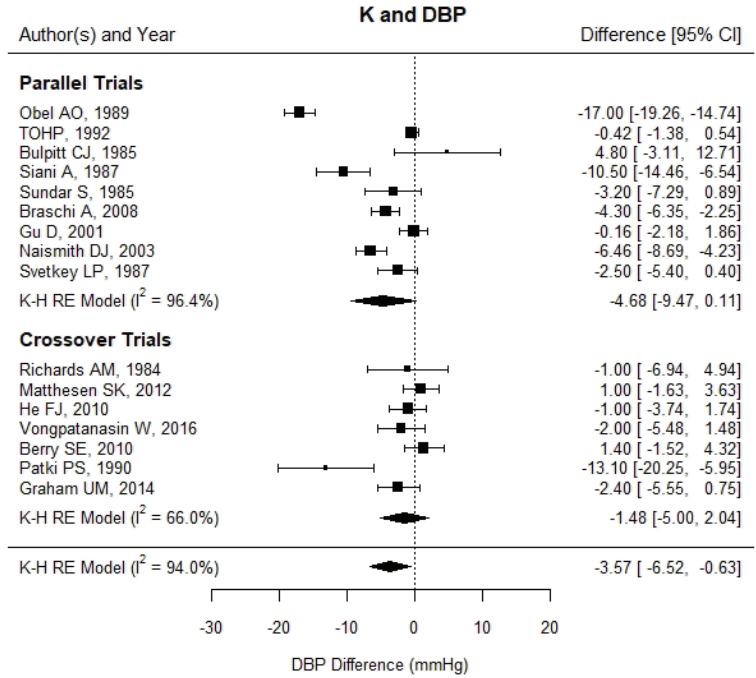

FIGURE 6-2 Random-effects meta-analysis of parallel and crossover trials of effects of potassium supplementation on diastolic blood pressure. Meta-analysis was conducted in R with random-effects models in the metafor package using the Knapp-Hartung variance.
NOTES: Studies are listed by the last name of the first author and year of publication. CI = confidence interval; DBP = diastolic blood pressure; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K = potassium; K-H = Knapp-Hartung variance estimate; RE = random-effects; TOHP = Trials of Hypertension Prevention.

[95% CI: –14.58, –1.74] (see Figure 6-5). In the three trials that did not include participants with hypertension, the net difference was not statistically significant. The lack of an intake–response relationship with net change in potassium excretion was observed in both those with and without hypertension at baseline. Similar results with respect to eliminating the outlier and separating studies by hypertension status were seen for diastolic blood pressure (see Figure 6-6).

Committee's interpretation Overall there was a significant reduction in both systolic and diastolic blood pressure with potassium supplementation, with an average difference of –6.87/–3.57 mm Hg (or –4.42/–2.53 mm Hg,

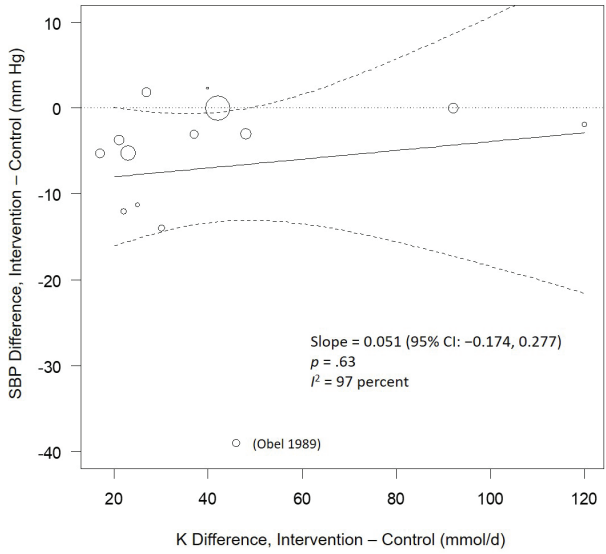

FIGURE 6-3 Meta-regression of trials of potassium supplementation showing the net effect of the potassium intake difference between intervention and control groups on the systolic blood pressure effect size.
NOTE: CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K = potassium; SBP = systolic blood pressure.

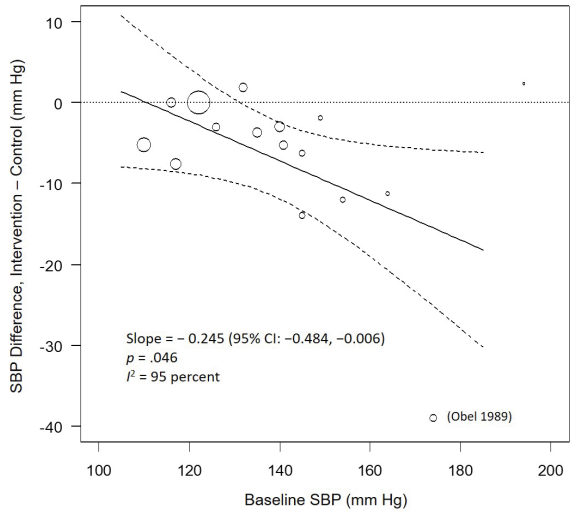

FIGURE 6-4 Meta-regression of trials of potassium supplementation showing the effect of the baseline systolic blood pressure on the systolic blood pressure effect size.
NOTE: CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; SBP = systolic blood pressure.

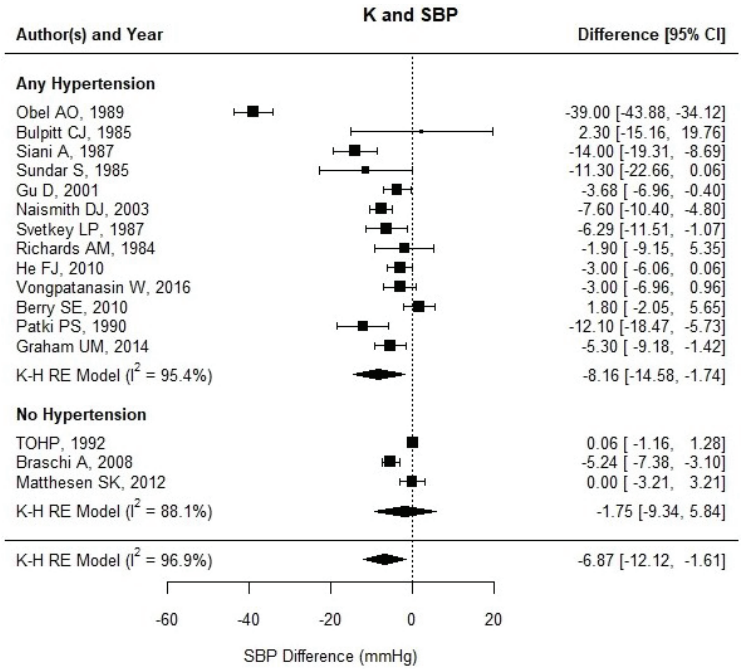

FIGURE 6-5 Random-effects meta-analysis of parallel and crossover trials of effects of potassium supplementation on systolic blood pressure, by hypertension status. Meta-analysis was conducted in R with random-effects models in the metafor package using the Knapp-Hartung variance.
NOTES: Studies are listed by the last name of the first author and year of publication. CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K = potassium; K-H = Knapp-Hartung variance estimate; RE = random-effects; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention.

after excluding Obel, 1989), respectively. The effect was somewhat stronger in parallel than crossover trials, and stronger among those with hypertension. There was a large amount of heterogeneity, however, with overall I^2 values of 94 to 97 percent. The heterogeneity was affected by one large outlier, but remained after excluding this trial. This variability could not be resolved by controlling for the other factors examined, including by intake–response relationship (net change in potassium level). These meta-analyses, however, are limited by their ecologic nature[10] and the lack of individual participant data.

[10]Meaning the unit of analysis is not individual-level data.

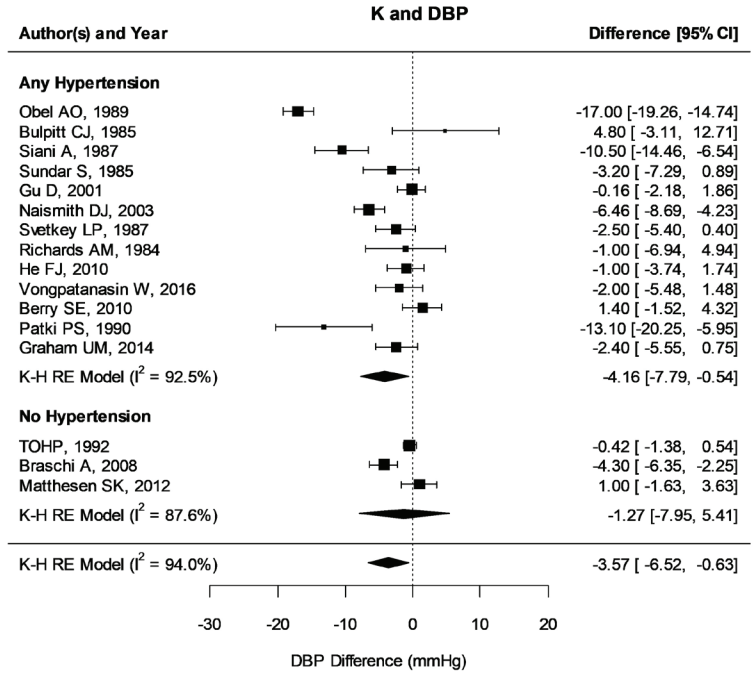

FIGURE 6-6 Random-effects meta-analysis of parallel and crossover trials of effects of potassium supplementation on diastolic blood pressure, by hypertension status. Meta-analysis was conducted in R with random-effects models in the metafor package using the Knapp-Hartung variance.
NOTES: Studies are listed by the last name of the first author and year of publication. CI = confidence interval; DBP = diastolic blood pressure; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K = potassium; K-H = Knapp-Hartung variance estimate; RE = random-effects; TOHP = Trials of Hypertension Prevention.

The committee's refinement of the *AHRQ Systematic Review* was not able to identify an explanation for the observed heterogeneity, and therefore the committee reaffirmed the *AHRQ Systematic Review* rating of the strength of evidence between increased potassium intake (achieved by potassium supplementation) and decreased blood pressure as moderate. This rating is based on a downgrade for unexplained inconsistency. Importantly, the committee's reanalysis could not discern an intake–response gradient where greater intervention was correlated with greater effect, and meta-regression suggested a nonsignificant inverse relationship (see Figure 6-3). Additionally, the observed effects of increased potassium intakes through potassium supplementation on blood pressure appeared to be

primarily limited to adults with hypertension with no significant effects in normotensive adults and adults with prehypertension.

The *Guiding Principles Report* recommended that surrogate markers could be used as supporting evidence for establishing the DRI based on chronic disease, but that the surrogate marker should meet the qualification criteria for their purpose and be specific to each nutrient (NASEM, 2017, p. 8). Pursuant to this guidance, the committee considered whether blood pressure could serve as a surrogate marker for the relationship between potassium intake and chronic disease endpoints. Qualification of blood pressure as a surrogate marker implies that studies measuring blood pressure as an outcome of increasing potassium intake can be used in support of establishing a CDRR. There is a lack of clear supporting benefit of potassium alone on cardiovascular and mortality outcomes. Without such evidence, the committee is unable to consider blood pressure as a qualified surrogate marker in the context of potassium interventions.

Given the lack of an intake–response relationship, and in accordance with guidance in the *Guiding Principles Report* on use of qualified surrogate markers in establishing DRIs based on chronic disease, the committee did not find the sufficient evidence to use blood pressure as an indicator to establish a potassium CDRR.

Kidney Stones

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* presented findings from a double-blind, placebo-controlled trial evaluating the effects of 30–60 mmol/d potassium citrate on recurrent kidney stones in 57 patients, 27–64 years of age (Barcelo et al., 1993). Usual diet was consumed throughout the trial, and dietary potassium intake was not directly assessed, although urinary potassium was measured. Estimated potassium intake in the treatment group from intake of the supplement and dietary sources was estimated to be 3,600–4,700 mg/d (92–120 mmol/d). After 3 years, the rate of stone formation in the treatment group was significantly lower than in the control group (0.1 stone/patient-year versus 1.1 stones/patient-year; $p < .001$).

The *2005 DRI Report* also cited three large studies with evidence of an association between potassium and kidney stones (Curhan et al., 1993, 1997; Hirvonen et al., 1999). A strong inverse relationship between potassium intake estimated from a food frequency questionnaire and risk of kidney stones was reported in analyses of observational data from the Health Professionals' Follow-Up Study and the Nurses' Health Study I (Curhan et al., 1993, 1997). A Finnish study of male smokers found that risk of kidney stones decreased between the first and second quartile of potassium intake, as assessed by food frequency questionnaire, but that higher intakes did not confer additional risk reduction (Hirvonen et al., 1999). The findings at

higher intakes in the Finnish study were noted as possibly being attributed to higher potassium intake than in the United States.

Evidence from the 3-year double-blind controlled trial of the effect of potassium citrate on kidney stone reoccurrence (Barcelo et al., 1993), coupled with the evidence on blood pressure, was used in the *2005 DRI Report* to establish the potassium AI for adults at 4,700 mg/d (120 mmol/d).

Evidence provided in the *AHRQ Systematic Review* One trial assessing the effect of potassium intake on the risk of kidney stones was included in the *AHRQ Systematic Review*. The study was the same trial used to establish the potassium AI in the *2005 DRI Report*, described above (Barcelo et al., 1993). No additional trials were identified. The *AHRQ Systematic Review* concluded that there was insufficient evidence to draw conclusions about the *effect* of higher potassium intake on the risk for kidney stones.

Two observational studies, which included analyses of four cohorts, met the inclusion criteria for the *AHRQ Systematic Review*. One of the studies was summarized in the *2005 DRI Report*, described above (Hirvonen et al., 1999). The other study expands on the other work described in the *2005 DRI Report* and assessed the association between dietary potassium intake and risk of incident kidney stones using three large cohort studies conducted in the United States—Health Professionals' Follow-Up Study, Nurses' Health Study I, and the Nurses' Health Study II (Ferraro et al., 2016). A significant inverse relationship between potassium intake and kidney stones was observed in all three cohorts. Due to heterogeneity, the cohorts were not pooled. The findings did not appear to differ significantly by sex. The *AHRQ Systematic Review* rated both of the included studies as having a high risk of bias and concluded that there was low strength of evidence to suggest that higher potassium exposure is associated with lower risk for kidney stones. The *AHRQ Systematic Review* also concluded that there was insufficient evidence to determine the moderating effect of hypertension or obesity status on the relationship between potassium intake and kidney stones.

Committee's synthesis of the evidence The available evidence on the relationship between potassium intake and kidney stone risk is similar to that which was reviewed in the *2005 DRI Report*. No new trials meeting the *AHRQ Systematic Review* inclusion criteria have since been published. The observational studies cannot independently confirm that potassium per se is the dietary component associated with observed benefits. The committee is in agreement with the *AHRQ Systematic Review* that the evidence on the effect (i.e., from trials) of potassium intake and kidney stones is insufficient. The committee also agrees with the *AHRQ Systematic Review* that there

is low strength of evidence that higher potassium intake may be associated with lower risk of kidney stones.

Chronic Kidney Disease

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* characterized patients with chronic kidney disease as a population in which the AI was not suitable owing to being predisposed to hyperkalemia, particularly those who use angiotensin-converting enzyme inhibitor therapy. Chronic kidney disease was not reviewed in the *2005 DRI Report* as a potential indicator for establishing a potassium DRI value.

Evidence provided in the *AHRQ Systematic Review* No randomized controlled trials meeting the *AHRQ Systematic Review* inclusion criteria evaluated the independent effect of potassium intake on the risk of chronic kidney disease.

Two observational studies assessed the association between potassium intake and chronic kidney disease. An inverse association between urinary potassium excretion and chronic kidney disease was identified among participants in the Prevention of Renal and Vascular End-Stage Disease cohort (Kieneker et al., 2016a); for each standard deviation decrease in urinary potassium excretion (821 mg/d [21 mmol/d]), risk of developing chronic kidney disease increased by 16 percent.[11] In another prospective cohort, the highest quintile of potassium intake (5,519 mg/d [141 mmol/d]), assessed by food frequency questionnaire at baseline, was associated with a reduced hazard of death attributable to renal cause and dialysis as compared to the lowest quintile of potassium intake (1,801 mg/d [46 mmol/d]) (Smyth et al., 2016). The *AHRQ Systematic Review* concluded that there was insufficient evidence to draw conclusions about the relationship between potassium intake and the risk for chronic kidney disease.

Committee's synthesis of the evidence The committee agrees with the *AHRQ Systematic Review* that the evidence is insufficient on the relationship between potassium intake and chronic kidney disease; the committee also agrees with the *2005 DRI Report* that patients with chronic kidney disease are not an appropriate population for establishing a DRI value, which are meant for the apparently healthy population. Due to the risk of hyperkalemia, patients with chronic kidney disease are further discussed as a special consideration in Chapter 7.

[11]Model adjusted for age; sex; height; weight; smoking status; alcohol consumption; parental history of chronic kidney disease; race; diabetes; baseline estimated glomerular filtration rate; and urinary sodium, calcium, urea, albumin, and creatinine excretion.

Osteoporosis and Related Indicators

One of the considerations previously factored into characterizing potassium intake needs centers around the concept of acid–base balance. Potassium-rich foods, such as fruits and vegetables, provide bicarbonate precursors, which are thought to play a role in neutralizing diet-induced acidosis. Diets that are higher in foods that produce noncarbonic acids (e.g., animal protein, cereal grains) and lower in foods that provide bicarbonate precursors, consumed over a long period of time, are thought to have negative metabolic effects owing to the body's attempt to counter the diet-induced acidosis. One such buffering mechanism is to dissolve the bone matrix. Given this biological plausibility, the committee reviewed the evidence presented in the *2005 DRI Report* and evidence that has since emerged.

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* included trials that explored the relationship between potassium intake and bone demineralization in consideration for establishing the potassium DRIs for adequacy. Sebastian et al. (1994) assessed the effect of potassium bicarbonate (60–120 mmol/d per 60 kg body weight) for a period of 18 days among 18 postmenopausal women. The study reported that concentrations of a marker of bone formation significantly increased and urinary marker of bone reabsorption significantly decreased during the supplementation period; urinary calcium excretion also decreased. Maurer et al. (2003) reported that, during 7 days of the bicarbonate salt supplementation, urinary markers of bone resorption decreased among nine healthy young adults; urinary calcium excretion also significantly decreased. Among 21 adult patients with recurrent kidney stones who were treated with potassium citrate for at least 11 months (range: 11–120 months), bone mineral density in L2 through L4 in the spine increased, but urinary calcium excretion did not change (Pak et al., 2002). Lemann et al. (1991) assessed the effect of 4 days of potassium chloride, potassium bicarbonate, sodium chloride, and sodium bicarbonate supplementation in healthy adults. Urinary calcium excretion decreased during potassium administrations, which was not seen during the sodium administrations.

The *2005 DRI Report* also included observational studies that explored the relationship between potassium intake and bone demineralization. Five cross-sectional studies and one longitudinal study provided evidence that potassium intake and/or urinary potassium excretion was positively associated with bone mineral density. The observational evidence for the relationship between potassium intake and bone loss was not used as the primary data to establish the potassium AI in the *2005 DRI Report*, but was described as being supporting evidence.

Evidence from the committee's supplemental literature search Evidence suggests that potassium intake has a hypocalciuric effect (Frassetto et al., 2005; Lemann et al., 1989), which potentially has implications for bone integrity. Urinary calcium excretion, however, can be affected by a variety of factors other than changes to the bone. Although evidence of a relationship between potassium intake and urinary calcium may point to a biological interdependence, the committee is unable to attribute it to an effect on the risk of osteoporosis. Studies have also assessed the relationship between potassium intake and bone turnover markers (Dawson-Hughes, 2009, 2015; He et al., 2010; Marangella et al., 2004; Moseley et al., 2013). Although bone turnover markers have the potential to clarify the biological mechanism by which a relationship exists, the committee was concerned about the validation of such markers and using such evidence to inform the potassium CDRR. The relationship between risk of fracture and bone formation marker (serum procollagen type I N propeptide) and a bone resorption marker (serum C-terminal cross-linking telopeptide of type I collagen) has been characterized as modest (Johansson et al., 2014). To that end, the committee's evidence review focused on outcomes related to osteoporosis (including osteoporotic fracture) and bone mineral density. Details of the committee's supplemental literature search, including inclusion criteria and summary tables of findings, are presented in Appendix E.

Osteoporotic facture No randomized controlled trials meeting the inclusion criteria evaluated the independent effect of potassium intake on the risk of osteoporotic fracture. One case-cohort study was identified. There were no statistically significant differences for risk of total, hip, spine, or wrist fracture across the sex-specific quintiles of potassium intake or evidence of a trend in fracture risk across the sex-specific quintiles of potassium intake (Hayhoe et al., 2015). The study was rated as having a moderate risk of bias.

Bone mineral density Three randomized controlled trials meeting the inclusion criteria evaluated the effect of potassium intake on bone mineral density. A 2-year placebo-controlled trial among 203 postmenopausal women reported no statistically significant differences in lumbar spine or total hip bone mineral density among participants receiving potassium citrate in high or low dose (Macdonald et al., 2008). The study was rated as having a low risk of bias. In a separate 2-year randomized controlled trial among 169 adults 65 years of age and older, participants in the potassium citrate supplementation group experienced a net increase of areal bone mineral density and, as compared to the placebo group, had a significant net effect on measures of total volumetric bone mineral density in the dominant and nondominant radium and tibia (Jehle et al., 2013). The study was

rated as having a low risk of bias. In a 1-year trial of 83 postmenopausal women with osteopenia, randomized to receive either potassium citrate or placebo, no significant changes in lumbar spine, total hip, or femoral net bone mineral density were found in either group (Gregory et al., 2015). The study was rated as having a low risk of bias.

Three observational studies on the association between potassium intake and bone mineral density were identified. In a study of 266 postmenopausal women, those in the highest quartile of urinary potassium excretion had higher total hip bone mineral density and total bone mineral density at year 5, as compared to those in the lowest quartile of potassium excretion (Zhu et al., 2009). The study was rated as having a high risk of bias. In a study of 891 healthy pre-, peri-, and postmenopausal women, there were significant positive correlations between energy-adjusted intake of several dietary components (including potassium) and change in femoral neck bone mineral density, but only among pre- and perimenopausal women who had never taken hormone replacement therapy (Macdonald et al., 2004). The study was rated as having a moderate risk of bias. In a 2-year study of 125 female competitive distance runners (18–26 years of age), potassium intake and other dietary components were associated with increases in whole-body bone mineral density (Nieves et al., 2010); controlling for calcium intake attenuated the relationships with potassium but did not change its statistical significance. The study was rated as having a moderate risk of bias.

Committee's synthesis of the evidence The committee's supplemental literature search did not reveal any randomized controlled trials assessing the effect of potassium intake on osteoporotic fracture, and one prospective cohort study did not reveal a statistically significant relationship. Evidence on the relationship between potassium intake and the outcome of osteoporosis is therefore considered insufficient.

Evidence of the relationship between potassium intake and bone mineral density was mixed among randomized controlled trials. Trials differed from each other with respect to the populations assessed, co-administration of calcium and vitamin D, and doses of potassium citrate provided, which potentially contributed to the inconsistent results. Findings from a trial by Jehle et al. (2006) suggest that the potassium citrate may have a different effect on bone mineral density than potassium chloride, which makes it difficult to attribute observed effects to potassium per se. This is particularly important when considering diet as the source of potassium, as many potassium-rich foods are high in bicarbonate precursors. It is difficult to discern if the effect on bone mineral density is attributable to potassium intake or influences of foods rich in bicarbonate precursors or other dietary constituents. Studies have found positive associations between potassium intake and bone mineral density, although other dietary components also

share a positive or negative relationship, as well. Given inconsistencies and a limited ability to attribute an effect to potassium per se, the committee determined the evidence on the relationship between potassium intake and bone mineral density as insufficient.

Type 2 Diabetes, Glycemic Control, and Insulin Sensitivity

Evidence presented in the *2005 DRI Report* The *2005 DRI Report* did not review evidence on the relationship between potassium intake and type 2 diabetes, glycemic control, or insulin sensitivity.

Evidence provided in the *AHRQ Systematic Review* The *AHRQ Systematic Review* included individuals with type 2 diabetes as a subgroup of consideration throughout the key questions. There was insufficient evidence to determine if potassium intake has a differential effect on individuals with diabetes, with respect to the cardiovascular and renal indicators. The *AHRQ Systematic Review* did not review evidence on the relationship between potassium intake and type 2 diabetes, glycemic control, or insulin sensitivity.

Evidence from the committee's supplemental literature search One randomized controlled trial on the effect of potassium supplementation on glucose control and tolerance was identified. A 12-week pilot study randomized 27 African American adults with prediabetes to receive either potassium chloride or placebo (Chatterjee et al., 2017). Fasting glucose levels were significantly improved for the potassium supplementation group as compared to the placebo group at the end of the study; statistically significant differences in glucose tolerance between the groups, however, were not identified at the end of the trial. The study was rated as having a low risk of bias.

Three prospective cohort studies that assessed the relationship between potassium intake and risk of type 2 diabetes were identified. One study, with 18 years of follow-up, did not find an association between baseline potassium excretion and risk of type 2 diabetes (Hu et al., 2005); the study was rated as having a high risk of bias. A separate study found participants in the lowest quintile of potassium excretion (238–1,380 mg/d [6–35 mmol/d]) had increased risk of incident diabetes (HR = 2.45 [95% CI: 1.08, 5.59]), as compared to the highest quintile of urinary potassium excretion (2,862–6,256 mg/d [73–160 mmol/d]) (Chatterjee et al., 2012). Dietary history data were also available on a subset of participants in this cohort; based on 20 years of follow-up, risk of incident diabetes was not significantly different across quintiles of dietary potassium intake, although there was evidence to suggest an inverse relationship existed among African American participants, but not white participants. Risk of bias for this

study was rated as moderate. Chatterjee et al. (2010) reported that, in models that adjusted for possible confounders, baseline potassium intake was not significantly associated with incident diabetes among 12,209 adults. This study was rated as having a high risk of bias.

Committee's synthesis of the evidence The committee's supplemental literature search identified one randomized controlled trial assessing the effect of potassium on a measure of glucose control. As a pilot study in a small group of participants for a relatively short period of time, the available trial data are insufficient for the committee to make a determination regarding whether potassium intake affects glucose control. Evidence on the relationship between potassium intake and incident diabetes risk was also explored. Findings across the observational studies are inconsistent. The evidence on the relationship between potassium intake and type 2 diabetes, glucose control, and insulin sensitivity is considered insufficient.

THE COMMITTEE'S CONCLUSION REGARDING CHRONIC DISEASE RISK REDUCTION INTAKES FOR POTASSIUM

The body of evidence for the relationship between potassium intake and chronic disease is limited. Many of the indicators reviewed by the committee had little to no data from randomized controlled trials, which prevented the committee from being able to establish a causal relationship with potassium. Diets rich in potassium are typically also rich in other micronutrients and dietary components that could contribute to an apparent effect attributed to potassium. For this reason, the committee gave greater emphasis to potassium supplementation data from clinical trials, even though potassium supplementation is not the source of usual potassium intake in the population.

The indicator with the most clinical trial data for potassium supplementation is blood pressure. Meta-analyses across these trials indicate that potassium intake has an overall beneficial effect on both systolic and diastolic blood pressure, particularly among adults with hypertension. However, the meta-analysis also showed a considerable amount of heterogeneity across trials. In its refinement of the analysis in the *AHRQ Systematic Review*, the committee explored multiple potential sources of heterogeneity, including the removal of an outlier study and consideration of an intake–response relationship, but none explained more than a small portion of the observed heterogeneity. Thus, the strength of evidence for potassium and blood pressure was rated as moderate owing to this unexplained inconsistency across studies.

Although a moderate strength of evidence would be sufficient to consider for supporting a CDRR, the committee did not use blood pressure

as an indicator for chronic disease risk for two key reasons. First, as per the guidance in the *Guiding Principles Report*, the ideal indicator for establishing a DRI based on chronic disease is a chronic disease endpoint; qualified surrogate markers are primarily intended to be used as supporting evidence. The strength of evidence to support a causal relationship between increased potassium intake and related chronic disease outcomes, such as cardiovascular disease outcomes or hypertension, was graded as low or insufficient. Without evidence on the relationship between increases in potassium intake and risk of chronic disease outcomes, blood pressure cannot be considered a qualified surrogate marker in the context of potassium interventions. Second, even if blood pressure could be used to establish a potassium CDRR, there is a lack of evidence of an intake–response relationship, as studies with greater contrasts in potassium intake between intervention and control groups did not tend to also have greater reductions in blood pressure. As described in the *Guiding Principles Report*, an intake–response relationship is one of the evidentiary components of establishing a DRI based on chronic disease. Therefore, because of the limitations of the body of evidence described above (lack of intake–response gradient, low or inadequate strength of evidence for related chronic disease outcomes), the committee judged that a potassium CDRR based solely on blood pressure evidence was not congruent with the guidance provided in the *Guiding Principles Report*.

> *The committee concludes that, although there is moderate strength of evidence for a causal relationship between potassium supplementation and reductions in blood pressure, heterogeneity across studies, lack of evidence for an intake–response relationship, and lack of supporting evidence for benefit of potassium on cardiovascular disease prevents the committee from establishing a potassium Chronic Disease Risk Reduction Intake (CDRR).*

The committee notes that its determination regarding the potassium CDRR should not be interpreted as statement about a *lack of an effect* of potassium intake on chronic disease outcomes. Rather, the committee's conclusion regarding the potassium CDRR likely reflects a *lack of evidence*. There is moderate strength of evidence on the relationship between potassium intake and blood pressure, based on potassium supplementation trials. There is a lack of evidence on the intake–response relationship between potassium intake and blood pressure and a lack of evidence regarding the relationship between potassium intake and chronic disease endpoints. Addressing these research gaps could provide a more definitive determination regarding the effect of potassium intake on chronic disease endpoints and thereby possibly inform the derivation of a potas-

sium CDRR in the future. The committee outlines such research gaps in Chapter 12.

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7

Potassium Dietary Reference Intakes: Risk Characterization and Special Considerations for Public Health

The final two steps of the Dietary Reference Intake (DRI) organizing framework provide public health context for the revised or newly established reference values. One of the hallmarks of these steps is to compare the DRI values to intake distributions in the United States and Canada for the nutrient of interest, to assess whether population intakes are likely to be adequate, and to determine if the population is at risk due to excessive intake. Use of biochemical and clinical measures, if available, can also supplement this risk characterization. With the expansion of the DRI model, this step now also examines intakes in relevant populations in relation to the Chronic Disease Risk Reduction Intake (CDRR), if established. This information is then used to describe the public health implications of the established DRI values. This chapter provides the committee's risk characterization and special considerations for public health as they relate to the potassium DRI values established in this report.

RISK CHARACTERIZATION BASED ON POTASSIUM INTAKE LEVELS IN THE U.S. AND CANADIAN POPULATIONS

Adequate Intakes (AIs) are usually established when the evidence is not sufficient to derive Estimated Average Requirements and Recommended Dietary Allowances. The potassium AIs were derived using the highest median usual potassium intakes across two nationally representative surveys among children and normotensive male and female adults. For infants, the potassium AIs were derived by estimating potassium intake of breastfed infants.

Because the committee lacked information as to how AIs relate to actual requirements, caution is needed in use and interpretation of the AI values (IOM, 2000, 2003). The potassium AIs were derived using median intakes of apparently healthy groups of people within the U.S. and Canadian populations. Therefore, "similar groups with mean intakes at or above the AI can be assumed to have a low prevalence of inadequate intakes. When mean intakes of groups are below the AI, it is not possible to make any assumptions about the extent of intake inadequacy" (IOM, 2000, p. 12).

The sections that follow compare the potassium AI values established in this report to current potassium intakes in the U.S. and Canadian populations. Appendix G provides methodological details about the surveys used for this comparison, namely the U.S. National Health and Nutrition Examination Survey (NHANES), Canadian Community Health Survey–Nutrition 2015 (CCHS Nutrition 2015), and the Feeding Infants and Toddlers Study 2016 (FITS 2016). Data are presented by sex and age groups, as provided in these data sources. Details regarding the bias of using 24-hour dietary recalls to estimate distributions of usual intake compared to 24-hour urinary potassium excretions are presented in Chapter 3 (see Figure 3-1). Supplementary figures for select comparisons are provided in Appendix H.

Characterization by DRI Age, Sex, and Life-Stage Groups

Infants 0–12 Months of Age

The committee was provided with evidence on the distribution of usual potassium intake of U.S. infants (see Table 7-1). Among NHANES 2009–2014 infants 0–6 months of age who did not consume breast milk, estimated median potassium intake was 763 mg/d (20 mmol/d). Among FITS 2016 infants, which include both infants who did and did not consume breast milk, estimated median potassium intake was 625 mg/d (16 mmol/d). These median potassium intakes exceed the AI, which was derived by estimating potassium intake of breastfed infants and assumes an average breast milk potassium concentration of 515 mg/L. The committee notes that its estimate of breast milk potassium concentration may be lower than the value used to estimate intakes in FITS 2016 (see Chapter 4 and Appendix F).

Intake estimates for infants 7–12 months of age include potassium intakes from either breast milk, formula, or other milks in addition to complementary foods. Median usual potassium intakes among infants 7–12 months of age ranged from approximately 900–1,300 mg/d (23–33 mmol/d) and varied by whether infants included in the analyses consumed breast milk (see Table 7-2). Slightly more than half of infants who consumed some breast milk and more than 75 percent of infants who

TABLE 7-1 Usual Potassium Intake Among U.S. Infants 0–6 Months of Age, as Compared to the Potassium Adequate Intake

					Percentile		
Comparison Data Source	Age Range (Months)	Breastfeeding Status of Infants	Adequate Intake (mg/d)	Mean (mg/d)[a]	25th (mg/d)	50th (mg/d)	75th (mg/d)
NHANES 2009–2014	0–6	Not BF	400	**801 (16)**	**618**	**763**	**941**
FITS 2016	0–5.9	All	400	**659 (10)**	**487**	**625**	**793**

NOTES: Bold indicates the value is higher than the Adequate Intake for the DRI age, sex, and life-stage group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. No analyses were identified that estimated usual potassium intake distribution for breastfed infants 0–6 months of age. FITS 2016 = Feeding Infants and Toddlers Study 2016; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey; Not BF = analysis of infants who did not consume breast milk.

[a]Presented as intake (standard error).

SOURCES: Bailey et al., 2018; NHANES 2009–2014 (unpublished).

did not consume breast milk in this age group exceed the potassium AI. Infants who did not consume breast milk had higher potassium intakes than breastfed infants. This difference may reflect both the lower potassium content of breast milk compared to infant formula, and higher energy intakes in infants who are not breastfed with concomitant higher potassium intakes (Heinig et al., 1993; Whitehead, 1995).

Children and Adolescents 1–18 Years of Age

The 50th and 75th percentiles from the estimated distributions of usual potassium intakes among U.S. and Canadian children and adolescents are summarized in Table 7-3. The potassium AIs for children and adolescents 1–18 years of age were established using the highest median usual intakes in the U.S. and Canadian population within each DRI group. Therefore, the 50th percentiles approach or meet the AI values within the DRI groups for children and adolescents. Because it is unknown how the AI value relates to actual requirements, interpretation of intakes below the AI in terms of inadequacy cannot be made.

Adults 19 Years of Age and Older

The 75th percentile of usual potassium intake exceeds the potassium AI for most adult DRI age, sex, and life-stage groups, indicating that between

TABLE 7-2 Usual Potassium Intake Among U.S. Infants 7–12 Months of Age, as Compared to the Potassium Adequate Intake

Comparison Data Source	Age Range (months)	Breastfeeding Status of Infants	Adequate Intake (mg/d)	Mean (mg/d)[a]	Percentile		
					25th (mg/d)	50th (mg/d)	75th (mg/d)
NHANES 2009–2014	7–12	Not BF	860	**1,305 (32)**	**1,039**	**1,263**	**1,526**
NHANES 2003–2010	7–11	Not BF	860	**1,257 (26)**	**1,051**	**1,212**	**1,418**
	7–11	BF[b]	860	**901 (41)**	742	**892**	**1,042**
FITS 2016	6–11.9	All	860	**1,125 (13)**	855	**1,074**	**1,342**
NHANES 2003–2010	7–11	All	860	**1,168 (21)**	**963**	**1,133**	**1,334**
NHANES 2009–2012	6–11	All[c]	860	**1,119 (21)**	844	**1,068**	**1,336**

NOTES: Bold indicates the value is higher than the Adequate Intake for the DRI age, sex, and life-stage group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. BF = analysis of infants who consumed breast milk; FITS 2016 = Feeding Infants and Toddlers Study 2016; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey; Not BF = analysis of infants who did not consume breast milk.

[a]Presented as intake (standard error).

[b]Consumption of at least some breast milk, as reported on the 24-hour dietary recall.

[c]Estimated 23.9 ± 3.3 percent of this sample reported consuming any breast milk.

SOURCES: Ahluwalia et al., 2016; Bailey et al., 2018; NHANES 2009–2014 (unpublished); Tian et al., 2013.

one-quarter and one-half of U.S. and Canadian adults exceed the AI (see Table 7-4). Median usual potassium intakes of the general U.S. and Canadian populations are lower than the observed median intakes in the normotensive population used to establish the potassium AI values. There were two adult DRI life-stage groups in which usual potassium intakes at the 75th percentiles were below the potassium AI: females 19–30 years of age in the United States and males older than 70 years of age in the United States and Canada. Because it is unknown how the AI relates to actual requirements, interpretation of intakes below the AI in terms of inadequacy cannot be made.

Characterization by Sex

On average, males had higher usual potassium intakes than females. As noted in Chapter 3, potassium intake is highly correlated with energy intake, leading to higher intakes of potassium with greater energy intakes.

TABLE 7-3 50th and 75th Percentiles of Usual Potassium Intake Among U.S. and Canadian Children and Adolescents 1–18 Years of Age, as Compared to the Potassium Adequate Intakes

DRI Group	AI (mg/d)	50th Percentile (mg/d)[a]	75th Percentile (mg/d)[a]	Percent > AI
Both sexes, 1–3 years				
U.S., both sexes	2,000	1,944 (24)	**2,279 (32)**	45
Canada, males	2,000	**2,042 (45)**	**2,450 (49)**	53
Canada, females	2,000	1,934 (51)	**2,324 (58)**	45
Both sexes, 4–8 years				
U.S., both sexes	2,300	2,094 (19)	**2,432 (24)**	33
Canada, males	2,300	**2,349 (49)**	**2,764 (56)**	53
Canada, females	2,300	2,134 (45)	**2,509 (54)**	37
Males, 9–13 years				
U.S.	2,500	2,331 (38)	**2,734 (55)**	38
Canada	2,500	**2,516 (44)**	**3,007 (55)**	50
Males, 14–18 years				
U.S.	3,000	2,628 (52)	**3,123 (74)**	30
Canada	3,000	2,984 (77)	**3,680 (97)**	49
Females, 9–13 years				
U.S.	2,300	2,050 (33)	**2,392 (53)**	30
Canada	2,300	2,263 (44)	**2,683 (55)**	47
Females, 14–18 years				
U.S.	2,300	1,914 (43)	2,267 (53)	23
Canada	2,300	2,255 (49)	**2,747 (58)**	47

NOTES: Bold indicates the value is higher than the Adequate Intake for the DRI age, sex, and life-stage group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. AI = Adequate Intake; mg/d = milligrams per day; U.S. = United States.

[a]Presented as intake (standard error).

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

The difference in intakes between males and females informed the committee's decision to stratify potassium AIs by sex for individuals 9 years of age and older. Although no statistical comparisons were carried out to explore differences, the percent of the population with intakes above the AI was relatively similar in males and females in each of the DRI age groups.

Characterization by Country

Although no statistical comparisons were carried out to explore differences, median and 75th percentile of potassium intakes are relatively comparable between the United States and Canada for many DRI age,

TABLE 7-4 50th and 75th Percentiles of Usual Potassium Intake Among U.S. and Canadian Adults 19 Years of Age and Older, as Compared to the Potassium Dietary Reference Intake Values

DRI Group	AI (mg/d)	50th Percentile (mg/d)[a]	75th Percentile (mg/d)[a]	Percent > AI
Males, 19–30 years				
U.S.	3,400	2,825 (40)	**3,475 (62)**	27
Canada	3,400	2,973 (87)	**3,540 (117)**	30
Males, 31–50 years				
U.S.	3,400	3,098 (31)	**3,703 (50)**	36
Canada	3,400	2,945 (59)	**3,618 (204)**	32
Males, 51–70 years				
U.S.	3,400	3,065 (32)	**3,709 (66)**	35
Canada	3,400	2,927 (51)	**3,576 (69)**	30
Males, > 70 years				
U.S.	3,400	2,783 (35)	3,324 (56)	22
Canada	3,400	2,615 (46)	3,169 (57)	17
Females, 19–30 years				
U.S.	2,600	2,119 (31)	2,509 (44)	20
Canada	2,600	2,296 (73)	**2,771 (125)**	32
Females, 31–50 years				
U.S.	2,600	2,366 (19)	**2,845 (30)**	36
Canada	2,600	2,404 (44)	**2,744 (80)**	34
Females, 51–70 years				
U.S.	2,600	2,425 (25)	**2,899 (33)**	40
Canada	2,600	2,418 (35)	**2,900 (41)**	39
Females, > 70 years				
U.S.	2,600	2,312 (27)	**2,805 (38)**	34
Canada	2,600	2,179 (41)	**2,652 (48)**	27
Pregnant				
U.S.	2,600/2,900[b]	2,533 (87)[c]	**3,090 (116)**[c]	32[c]
Canada	2,600/2,900[b]	2,876 (134)[c]	**3,294 (175)**[c]	48[c]
Lactating				
U.S.	2,500/2,800[d]	2,675 (104)[e]	**3,079 (110)**[e]	41[e]
Canada	2,500/2,800[d]	**2,814 (111)**[e]	**3,211 (158)**[e]	51[e]

NOTES: Bold indicates the value is higher than the AI for the DRI age, sex, and life-stage group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. AI = Adequate Intake; mg/d = milligrams per day.

[a]Presented as intake (standard error).

[b]Potassium AI presented by age groups, pregnant females 14–18 years of age/pregnant females 19 years of age and older.

[c]Intakes are compared to the AI for pregnant females 19 years of age and older.

[d]Potassium AI presented by age groups, lactating females 14–18 years of age/lactating females 19 years of age and older.

[e]Intakes are compared to the AI for lactating females 19 years of age and older.

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

sex, and life-stage groups (see Tables 7-3 and 7-4). An exception was the group of Canadian males 14–18 years of age, who reported a higher usual intake of potassium than the corresponding group in the United States. The difference for this group was more than 340 mg/d (9 mmol/d). Methods for collecting 24-hour dietary recalls, nutrient databases, and statistical methods used to estimate intakes were similar between the U.S. and Canadian surveys, and therefore would not be expected to explain these differences (CDC/NCHS, 2019; Statistics Canada, 2017; and see Appendix G for details of the methodology). Because it is unknown how the AI relates to actual requirements, and because there is no Tolerable Upper Intake Level (UL) for potassium, the implications of the differences cannot be inferred.

Characterization by Race and Ethnicity Groups

For the United States, distributions of the usual potassium intake were estimated by three race/ethnicity categories: non-Hispanic white, non-Hispanic black, and Hispanic (see Figures 7-1 and 7-2). Although no statistical comparisons were made, the median intakes were lowest for non-Hispanic blacks in each of the DRI age, sex, and life-stage groups. For some DRI groups, the differences were quite small (e.g., for females 19–30 years of age median intakes differed by 51 mg/d between non-Hispanic blacks and non-Hispanic whites); for other DRI groups, differences in median intakes were larger (e.g., for males older than 70 years of age, median intakes differed by more than 700 mg/d between non-Hispanic blacks and non-Hispanic whites). Almost all adult groups and children 14–18 years of age among Hispanics and among non-Hispanic blacks had usual daily intakes of potassium that are 500 mg/d or more below the AI. Although it is not known how the AI relates to requirements, these groups ought to be encouraged to increase their potassium intake to meet the AI. A comparable stratified analysis was not available for Canada.

Risk Characterization by Hypertension Status

Although the apparently healthy population used to derive the adult potassium AIs were normotensive, there is no indication that the AIs cannot be applied to hypertensive individuals, with the exception of those taking medications that may interfere with blood potassium levels (see Special Considerations section below).

For the United States and Canada, distributions of the usual potassium intakes were stratified by hypertension status. In the Canadian distributions, hypertension status was self-reported and stratified into two catego-

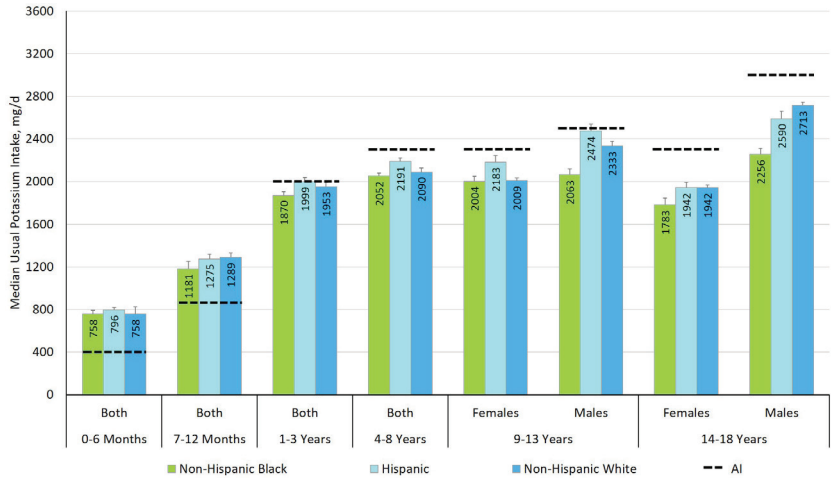

FIGURE 7-1 Median potassium intake among U.S. children and adolescents 0–18 years of age, by DRI age, sex, and life-stage group, stratified by race/ethnicity.
NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. AI = Adequate Intake; mg/d = milligrams per day.
SOURCE: NHANES 2009–2014 (unpublished).

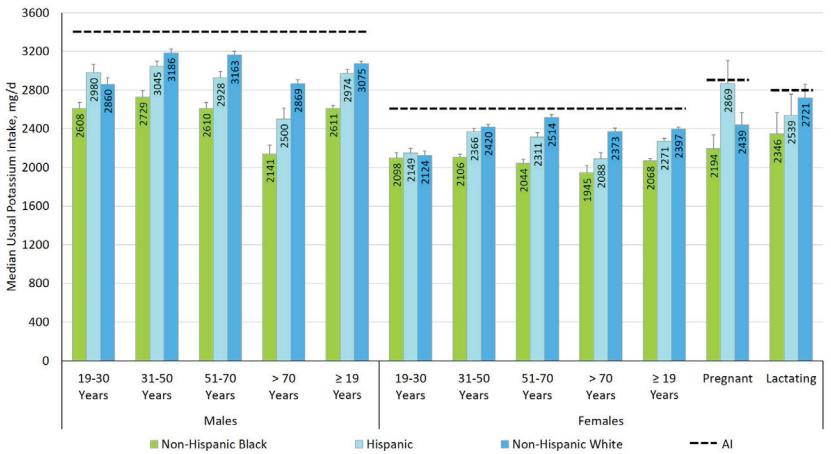

FIGURE 7-2 Median potassium intake among U.S. adults 19 years of age and older, by DRI age, sex, and life-stage group, stratified by race/ethnicity.
NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. AI = Adequate Intake; mg/d = milligrams per day.
SOURCE: NHANES 2009–2014 (unpublished).

ries, based on the question "Do you have high blood pressure?" (Statistics Canada, 2017). In the U.S. distributions, hypertension status was stratified into three categories—normotensive, elevated blood pressure, and hypertensive. Hypertension status was defined using the 2017 American College of Cardiology and the American Heart Association guidelines for adults (Whelton et al., 2018), based on the mean of up to three consecutive blood pressure measurements or use of hypertensive medications. In both analyses, individuals who self-reported having a history of cardiovascular disease were excluded.[1] For comparability between the United States and Canada, the elevated blood pressure group from the NHANES 2009–2014 data is omitted from this section.

In some DRI life-stage groups, median usual potassium intakes were higher in normotensive individuals compared to individuals with hypertension, particularly for males 51–70 years of age and females 51 years of age and older (see Figure 7-3). It is difficult to know why these groups differ. Possible explanations for the difference might be that those with higher potassium intakes have lower blood pressure, and/or those with hypertension taking angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), or renin inhibitor medications avoid potassium-rich food sources and potassium supplements because of the potassium-sparing effects of these drugs. Populations taking such medications are described below as a special consideration. Because it is unknown how the AI relates to actual requirements, and because there is no potassium UL, the implications of the differences cannot be inferred.

SOURCES OF POTASSIUM IN THE DIET

Various cycles of NHANES data have been used to characterize leading contributors of potassium intake (Hoy and Goldman, 2012; NIH/NCI, 2018b; O'Neil et al., 2012, 2018) (see Tables 7-5 through 7-8). The age-stratified analyses provide evidence that there are certain foods that commonly contribute a sizeable proportion of potassium intake in the diets of children, adolescents, and adults, including milk, white potatoes, and fruit. The age-stratified analyses also provide evidence of variation in relative contribution and some differences in top food contributors across age groups. Furthermore, the tables highlight how different approaches to grouping foods can lead to different rankings of the top contributors to

[1]The NHANES usual potassium intake distribution stratified by hypertension status excluded anyone who had reported that a doctor or other health professional had ever told them they had a stroke or heart attack (myocardial infarction). The CCHS Nutrition 2015 usual potassium intake distribution stratified by hypertension status excluded anyone who had reported that a health professional had ever told them they had heart disease. Participants who answered that they did not know or refused to answer were also excluded.

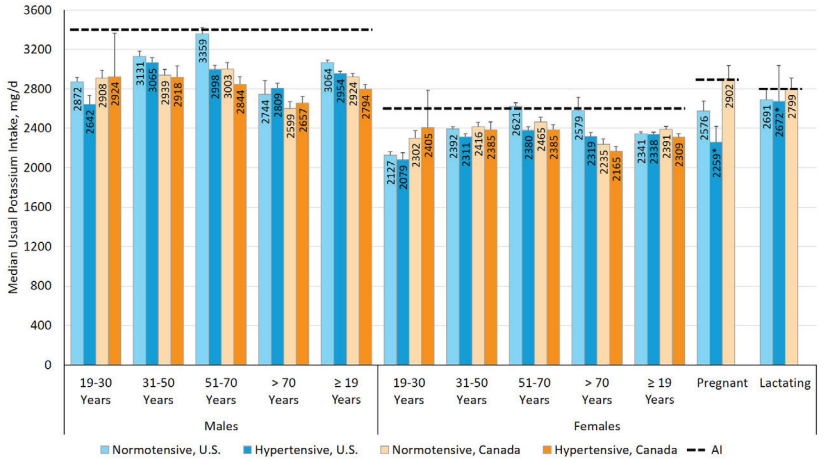

FIGURE 7-3 Median potassium intakes by U.S. and Canadian adults 19 years of age and older, stratified by hypertension status.
NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 39.1. * = estimate statistically unstable; AI = Adequate Intake; mg/d = milligrams per day. This note was revised since the prepublication release.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

potassium intake. Fruits, for instance, are broadly grouped in two of the analyses and appear among the top contributors across the age-stratified analyses (O'Neil et al., 2012, 2018). In contrast, the analysis in which fruits do not appear among the top contributors to potassium intake used several, more narrowly defined fruit groups (e.g., bananas, citrus fruits, grapes) (NIH/NCI, 2018a,b).

Table 7-9 presents foods with the highest amounts of potassium per standard food portion. Synthesizing this information with the evidence presented in Tables 7-5 through 7-8 shows that the foods that are among the highest in potassium content are not necessarily the top contributors to potassium intake in the diet. Foods with lower potassium content per standard portion can contribute to a substantial proportion of total potassium intake when such foods are consumed commonly and in large quantities. Similarly, foods that are high in potassium may not make a substantial contribution to total potassium intake if the food is not commonly consumed or is consumed only in small quantities.

Food fortification and dietary supplements contribute minimally to total potassium intake. An analysis of NHANES 2003–2006 data reported that, of 2,616 mg/d (67 mmol/d) potassium consumed among individuals

TABLE 7-5 Percent Contribution of Food Categories to Potassium Intake—National Health and Nutrition Examination Survey, 2009–2010

Food Categories	Individuals Reporting (%)[a]	Contribution to Potassium (%)
Fruits and vegetables	81	20
Milk and milk drinks[b]	55	11
Meats and poultry	66	10
Grain-based mixed dishes[c]	50	10
Coffee and tea	55	7
100 percent juices	25	5
Meat/poultry mixed dishes[d]	18	4
Plant-based protein foods[e]	27	4
Savory snacks[f]	45	3

NOTE: Data are from What We Eat In America, National Health and Nutrition Examination Survey 2009–2010, day 1 dietary intake data, weighted, excluding breastfed infants.

[a]Percent of individuals reporting the foods in the category at least once on the reporting day.

[b]Includes milk (all fat levels), flavored milk, milk substitutes, and milkshakes.

[c]Includes pasta mixed dishes, macaroni and cheese, rice mixed dishes, pizza, sandwiches, burritos, tacos, and tamales.

[d]Includes dishes in which meat or poultry is the main ingredient with grain and/or vegetables, gravies, or sauces.

[e]Includes beans or peas, mixed dishes with beans or peas, nuts and seeds, and soy products.

[f]Includes chips, crackers, popcorn, and pretzels.

SOURCE: Hoy and Goldman, 2012.

TABLE 7-6 Top 10 Food Categories Contributing to Potassium Intake Among U.S. Persons 2 Years of Age and Older, Ranked by Percent Contribution—National Health and Nutrition Examination Survey, 2005–2006 (N = 8,549[a])

Rank	Food Category	Percent Contribution[b]
1	Reduced-fat milk	5.9
2	Coffee	5.2
3	Chicken and chicken mixed dishes	4.5
4	Beef and beef mixed dishes	3.6
5	100 percent orange/grapefruit juice	3.4
6	Fried white potatoes	3.3
7	Potato/corn/other chips	3.2
8	Whole milk	2.9
9	Other white potatoes	2.9
10	Pasta and pasta dishes	2.7

[a]This number was revised since the prepublication release.

[b]Mean potassium intake for this analysis was 2,617 mg/d (67 mmol/d).

SOURCE: Adapted from NIH/NCI, 2018b.

TABLE 7-7 Top 10 Food Categories Contributing to Potassium Intake Among U.S. Persons 2–18 Years of Age, Ranked by Percent Contribution—National Health and Nutrition Examination Survey, 2011–2014 (*N* = 5,876)

	2–5 Years of Age (*n* = 1,511)	
Rank	Food Group	Percent Contribution[a]
1	Milk	21.1
2	Fruits	9.6
3	100 percent fruit juice	8.5
4	Flavored milk	5.1
5	Vegetables[d]	3.9
6	White potatoes	3.9
7	Grain-based mixed dishes	3.7
8	Poultry	3.5
9	Savory snacks	3.1
10	Sweetened beverages	3.0

NOTES: Food groups are from the 47 subgroups defined by the What We Eat In America food category classification system. The percent contributions reflected in the table were adjusted to disaggregate dairy intake from nondairy foods (e.g., mixed dishes) and reallocate them to the milk, cheese, and yogurt subgroups, as appropriate.

[a]Mean potassium intake for this group was 1,982 mg/d (51 mmol/d).

[b]Mean potassium intake for this group was 2,198 mg/d (56 mmol/d).

TABLE 7-8 Top 10 Food Categories Contributing to Potassium Intake Among U.S. Persons 19 Years of Age and Older, Ranked by Percent Contribution—National Health and Nutrition Examination Survey, 2003–2006 (*N* = 9,490)

	19–50 Years of Age (*n* = 5,429)	
Rank	Food Group	Percent Contribution[a]
1	Milk	9.7
2	Coffee, tea, other nonalcoholic beverages	7.0
3	White potatoes	6.9
4	Tomatoes, tomato/vegetable juice	6.1
5	Beef	5.7
6	Fruit juice	5.2
7	Fruit	4.5
8	Poultry	4.4
9	Crackers, popcorn, pretzels, chips	4.1
10	Other vegetables	3.4

NOTES: Food groups were defined by the U.S. Department of Agriculture Dietary Sources Nutrient database, which were collapsed into 51 categories for the analysis.

[a]Mean potassium intake for this group was 2,783 mg/d (71 mmol/d).

[b]Mean potassium intake for this group was 2,659 mg/d (68 mmol/d).

6–11 Years of Age (n = 2,193)		12–18 Years of Age (n = 2,172)	
Food Group	Percent Contribution[b]	Food Group	Percent Contribution[c]
Milk	15.6	Milk	15.0
Fruits	7.3	White potatoes	6.1
Flavored milk	5.7	Fruits	5.6
100 percent juice	5.3	100 percent fruit juice	4.6
White potatoes	4.5	Poultry	4.5
Savory snacks	4.0	Vegetables[d]	4.1
Poultry	3.9	Savory snacks	4.0
Pizza	3.7	Mexican mixed dishes	3.9
Grain-based mixed dishes	3.7	Grain-based mixed dishes	3.7
Mexican mixed dishes	3.6	Meats	3.7

[c]Mean potassium intake for this group was 2,308 mg/d (59 mmol/d).
[d]Excludes white potatoes.

SOURCE: Adapted from O'Neil et al., 2018. Reprinted with permission under the Creative Commons Attribution (CC BY) license (http://creative commons.org/licenses/by/4.0) (accessed January 18, 2019).

≥ 51 Years of Age (n = 4,061)	
Food Group	Percent Contribution[b]
Coffee, tea, other nonalcoholic beverages	10.8
Milk	9.5
Fruit	8.0
White potatoes	6.4
Tomatoes, tomato/vegetable juice	5.5
Fruit juice	4.8
Beef	4.4
Other vegetables	3.5
Poultry	3.2
Yeast breads and rolls	3.1

SOURCE: Adapted from O'Neil et al., 2012. Reprinted with permission under the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0) (accessed January 18, 2019).

TABLE 7-9 Food Sources Ranked by Amount of Potassium per Standard Portions, as Presented in the *2015 Dietary Guidelines Advisory Committee Report*

	Potassium (mg)		
Food	Standard Portion	Per Standard Portion	Per 100 grams
Potato, baked, flesh and skin	1 medium	941	544
Prune juice, canned	1 cup	707	276
Carrot juice, canned	1 cup	689	292
Passion-fruit juice, yellow or purple	1 cup	687	278
Tomato paste, canned	¼ cup	669	1,014
Beet greens, cooked from fresh	½ cup	654	909
Adzuki beans, cooked	½ cup	612	532
White beans, canned	½ cup	595	454
Plain yogurt, nonfat	1 cup	579	255
Tomato puree	½ cup	549	439
Sweet potato, baked in skin	1 medium	542	475
Salmon, Atlantic, wild, cooked	3 ounces	534	628
Clams, canned	3 ounces	534	628
Pomegranate juice	1 cup	533	214
Plain yogurt, low-fat	1 cup	531	234
Tomato juice, canned	1 cup	527	217

NOTES: This table presents an excerpt from the *2015 Dietary Guidelines Advisory Committee Report* of food sources with ≥ 500 mg potassium per standard portion. The data were cited as being from the U.S. Department of Agriculture National Nutrient Database for Standard Reference, Release 27. Potassium contents are presented in milligrams. To convert the milligram value to mmol, divided by 39.1. mg = milligrams.
SOURCE: Adapted from DGAC, 2015.

2 years of age and older, an average of 20 mg/d (0.5 mmol/d) came from fortification (Fulgoni et al., 2011). Potassium from fortification has been reported to contribute 0.2 to 0.6 percent of total potassium intake among children 2–18 years of age (Berner et al., 2014). Multivitamin and mineral supplements provide similarly small amounts of potassium. An analysis of NHANES 2007–2010 data of individuals 4 years of age and older found that multivitamin/mineral supplements provide approximately 11 mg/d (0.3 mmol/d) potassium to the overall estimated usual potassium intake of 2,606 mg/d (67 mmol/d) (Wallace et al., 2014). Use of multivitamin/mineral supplements containing potassium among adults 20 years of age and older appears to be declining. In 2011–2012, 18 percent [95% confidence interval (CI): 16, 19] of adults reported using a potassium-containing multivitamin/mineral supplement in the previous 30 days; the prevalence in 1999–2000 was estimated to be 28 percent [95% CI: 26, 30] (Kantor et al., 2016). Potassium-containing supplement use appears to be low among

older adults, with an estimated 1.7 percent of adults 60 years of age and older reported using a potassium-containing dietary supplement in the previous 30 days (Gahche et al., 2017).

PUBLIC HEALTH IMPLICATIONS AND SPECIAL CONSIDERATIONS

To interpret the findings from the risk characterization analysis presented above, consideration is given to the meaning and use of AIs. AIs are recommended average daily nutrient intake levels that are established when the intake distribution of requirements could not be established. To that end, an AI, including the potassium AIs established in this report, does not necessarily reflect requirements, but rather reflects the best estimate of intakes assumed to be adequate. Despite the uncertainties that exist with the potassium AIs, the values presented in this report reflect intake levels that are intended to be broadly applicable to the U.S. and Canadian populations. Nevertheless, there are certain situations and subpopulations in which potassium intakes may need to differ from the AI. Such special considerations are described below, and followed by a discussion of the implications of the updated potassium DRI values.

Special Considerations

Excessive Sweat Losses

Individuals who are exposed to high temperatures or those who engage in high levels of physical activity, especially at high temperatures, may require potassium intakes higher than the AI because of higher than usual losses of potassium through elevated sweat levels, ranging from 390–2,300 mg/d (10–60 mmol/d) (Consolazio et al., 1963; Costill et al., 1982; Malhotra et al., 1976, 1981). Typically, potassium concentrations in sweat in adults at ambient temperature and moderate levels of physical activity range from 100–300 mg/L (3–7 mmol/L) sweat, with total losses estimated to be approximately 78–137 mg/d (2–4 mmol/d) (EFSA NDA et al., 2016; IOM, 2005). Additionally, potassium sweat concentrations can increase up to 500 mg/L (14 mmol/L) sweat at high temperatures (Fukumoto et al., 1988), but they are less elevated in heat-acclimatized individuals exposed to high temperatures (40°C [104°F]), being approximately 200 mg/L (5 mmol/L) (Malhotra et al., 1976). Even in heat-acclimatized individuals exposed to high temperatures, total potassium sweat loss is still greater, at approximately 2,300 mg/d (60 mmol/d), owing to 20-fold greater sweat production of approximately 8 L/d (Malhotra et al., 1976).

Individuals Taking Medications That Affect Potassium Retention and Excretion

Recent major hypertension guidelines have recommended more intensive blood pressure lowering targets for individuals with hypertension; ACE-Is and ARBs are recommended among first-line pharmaceutical agents for hypertension treatment (Whelton et al., 2018). Using a systolic blood pressure threshold for treatment of ≥ 130 mm Hg, the proportion of the U.S. population that may require pharmacological antihypertensive therapy is estimated to be 36 percent (Muntner et al., 2018). ACE-Is and ARBs are also used frequently in heart failure populations; these individuals typically have high serum potassium concentrations, and are likely to have a higher risk of potassium toxicity.

Persons taking medications that alter regulation of potassium homeostasis through increased retention or excretion of potassium represent a special population for whom the applicability of the potassium AI is uncertain. For example, persons taking ACE-Is or ARBs may have a higher risk of developing hyperkalemia on a diet enriched with potassium (Cappuccio et al., 2016). Similar consideration needs to be given to persons taking other medications that influence potassium homeostasis, such as potassium-sparing diuretics. Conversely, many non-potassium-sparing diuretics induce urinary loss of potassium and can lower serum potassium concentrations in some individuals. Such individuals may require greater potassium intake. Some studies suggest that repletion of potassium in this setting may enhance the antihypertensive effects of these medications (Kaplan et al., 1985). In these cases and under the guidance of a health care provider, intakes that deviate from the AI may be warranted.

Heart failure is estimated to affect 5.7 million adults in the United States (Mozaffarian et al., 2016). Treatment for heart failure often includes treatment with ACE-Is/ARBs and diuretics; certain diuretic classes can cause hypokalemia or hyperkalemia (Pitt et al., 1999). These medications are often used in combination, and balancing the specific medications and their doses is often guided by serum potassium concentrations. Thus, it is uncertain if the potassium AI is applicable to individuals with heart failure.

Adrenal Insufficiency

Adrenal insufficiency is a rare condition; nonetheless, this disease is characterized by mineralocorticoid hormone levels below homeostatic requirements. Individuals with this condition are characterized by hyperkalemia. The potassium AI may not be appropriate in individuals with this condition.

Chronic Kidney Disease

Impaired renal potassium excretion commonly leads to hyperkalemia in patients with chronic kidney disease (CKD). On the other hand, use of potassium-wasting diuretics and restriction of potassium-rich foods, such as fruits and vegetables, in patients with CKD can lead to hypokalemia (Gilligan and Raphael, 2017; Kovesdy et al., 2017). Although hyperkalemia is a well-recognized complication of CKD, the prevalence of hyperkalemia (14 to 20 percent) and hypokalemia (12 to 18 percent) is similar in CKD patients (Gilligan and Raphael, 2017). Both hyperkalemia and hypokalemia are independently associated with increased risk of cardiovascular disease, hospitalization, and all-cause deaths among patients with CKD (Hoppe et al., 2018; Luo et al., 2016). In 3,939 patients with CKD from the Chronic Renal Insufficiency Cohort Study, the highest quartile of urinary potassium excretion (≥ 2,624 mg/d [≥ 67 mmol/d]) was significantly associated with increased risk of CKD progression but not all-cause mortality (He et al., 2016). A post-hoc analysis including 812 participants from the Modification of Diet in Renal Disease Study, however, reported higher baseline urinary potassium level being associated with a lower risk of all-cause mortality but not kidney failure (Leonberg-Yoo et al., 2017). Patients with CKD need to consult with their health care providers about individualized potassium intake recommendation, because of variations in the severity of kidney function decline, comorbidities, and use of medications such as ACE-I.

Type 2 Diabetes

The prevalence of type 2 diabetes is high and increasing in the general population. In 2011–2012, the estimated prevalence of diabetes was 12 to 14 percent among U.S. adults, depending on the criteria used (Menke et al., 2015). General population studies demonstrate that the presence of type 2 diabetes is associated with hyperkalemia (Hughes-Austin et al., 2017). This is likely attributable to the wide use of ACE-I/ARB and a higher prevalence of CKD among persons with type 2 diabetes. However, even among individuals with type 2 diabetes who do not have kidney disease and are not taking ACE-I/ARBs, hyperkalemia may be more common because of hyporeninemic hypoaldosteronism and other comorbidities or cotreatments (Dojki and Bakris, 2018). These data suggest that persons with diabetes may have an elevated risk of hyperkalemia and associated adverse health consequences if potassium intake is too high. However, higher potassium intake has also been associated with the slower decline of kidney function and lower incidence of cardiovascular complications in type 2 diabetic patients with normal renal function (Araki et al., 2015). Thus, the applica-

bility of the potassium AIs for persons with type 2 diabetes is uncertain, and its application will likely need to be individualized in consultation with a health care provider, with consideration of the individual's kidney function, medication use, and serum potassium concentrations.

Implications of the Potassium DRI Values in Context of the Previous Values and the Expanded DRI Model

The potassium DRI values in this report reflect the committee's synthesis of a broad range of evidence on adequate and safe levels of potassium intake and the relationship between potassium and chronic disease. To contextualize the public health implications, the committee provides comment on each of the DRI categories.

The potassium AIs, as with all AIs, are intake levels that do not necessarily reflect requirements, but rather are the best estimates for intake levels in apparently healthy individuals. The potassium AIs established in this report are almost all lower than the values established in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005). This change is underpinned by several factors. More rigorous data analysis methodologies for synthesizing data, for instance, have emerged and are now incorporated in the DRI process. This committee had available for its use a prepared systematic review that assessed risk of bias and strength of the evidence. Furthermore, this committee reviewed the evidence using an expanded DRI model, in which consideration of chronic disease risk reduction was separate from consideration of adequacy. The evolution of the data, processes, and DRI model led the committee to use the median intake of groups of apparently healthy people to derive the potassium AI values. The potassium AI values are no longer informed by evidence from potassium supplement trials on blunting the effects of salt-sensitive rise in blood pressure, which was the case with the levels established in the *2005 DRI Report*. Food pattern modeling evidence from the 2015 Dietary Guidelines Advisory Committee revealed that, for many energy levels, it was not possible to meet the potassium AI established in the *2005 DRI Report* while meeting intake requirement for other nutrients (DGAC, 2015). Given the basis of the potassium AIs in this report, potassium intakes at or above the AI through dietary intake alone are more feasible than the potassium AIs established in the *2005 DRI Report*.

There was insufficient evidence of toxicological risk to establish a potassium UL, aligned with what was concluded in the *2005 DRI Report*. The committee notes that the lack of a UL does not necessarily reflect a lack of risk, but rather a lack of evidence of risk. As noted above, there are select population groups in whom retention and excretion of potassium

are altered, which may put them at risk of hyperkalemia. At present, the available evidence suggests that dietary potassium intakes in the ranges currently consumed in the United States and in Canada appear to be safe and reflect little or insubstantial contribution from food fortification and dietary supplements.

The committee's inability to establish a potassium DRI based on chronic disease reflects limitations in the evidence. Although there was evidence that potassium supplements decreased blood pressure, notably in individuals with hypertension, an intake–response relationship could not be established and the heterogeneity across studies could not be explained. The committee was further limited in its ability to consider blood pressure a qualified surrogate marker, in context of potassium intake, as evidence on the independent effect of potassium intake on cardiovascular disease risk is lacking. Pursuant to the guidance and recommendations offered in the *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (NASEM, 2017), the committee did not establish a potassium DRI based on chronic disease. The committee recognizes that higher potassium intakes are related to blood pressure reductions, particularly among hypertensive adults. Although this relationship could not, for the reasons stated, be used to develop a potassium DRI based on chronic disease, or could not otherwise be quantified, it nevertheless suggests that higher potassium intake through the diet will likely benefit populations with elevated blood pressure. In the absence of quantitative intake–response data for the potassium and blood pressure relationship, all persons (except the at-risk subpopulations described above), and particularly hypertensive adults, might benefit from achieving intakes at the level of the AI and to consult with health care providers as to whether higher intakes might be needed.

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Part III

Part III of this report presents the evidence the committee reviewed to derive the Dietary Reference Intake (DRI) values for sodium. Based on the committee's review of the evidence on indicators of adequacy, toxicity, and chronic disease as they relate to sodium, the committee provides its recommendations. This part of the report consists of four chapters.

Chapter 8 follows steps 1 and 2 of the DRI organizing framework, provides the committee's review of the evidence on indicators of sodium adequacy, and presents the committee's rationale for updating some of the previously established Adequate Intake values.

Chapter 9 follows steps 1 and 2 of the DRI organizing framework, provides the committee's review of the evidence on indicators of sodium toxicity, and presents this committee's rationale for not establishing a Tolerable Upper Intake Level under the expanded DRI model.

Chapter 10 follows steps 1 and 2 of the DRI organizing framework, provides the committee's review of the evidence on the relationship between sodium intake and chronic disease risk, and provides the committee's rationale for establishing the sodium Chronic Disease Risk Reduction Intakes.

Chapter 11 follows steps 3 and 4 of the DRI organizing framework by characterizing risk in the U.S. and Canadian populations and by describing special considerations and public health implications, as they relate to the revised sodium DRI values.

8

Sodium: Dietary Reference Intakes for Adequacy

Sodium is a physiologically essential nutrient. Accordingly, the Dietary Reference Intakes (DRIs) for adequacy serve as an important reference value with a variety of applications. The extent to which an indicator of sodium adequacy has been identified and characterized in the apparently healthy population is at the crux of the committee's decision regarding which DRI for adequacy to establish and at what levels. For an Estimated Average Requirement (EAR) to be established, evidence of a causal relationship between intake of the nutrient and the indicator of adequacy, as well as evidence of an intake–response relationship, is needed to determine the distribution of requirement for adequacy in the population. As described in Chapter 1, once an EAR is determined, a Recommended Dietary Allowance (RDA) can be established. When there is insufficient evidence to establish an EAR and an RDA, a DRI for adequacy is still indispensable, as it provides a benchmark for dietary planning and assessment; in such cases, an Adequate Intake (AI) is established using other data-driven approaches and indicators.

Guided by the DRI organizing framework (see Chapter 1, Box 1-2) and the considerations under the expanded DRI model (see Chapter 2), this chapter describes the committee's review of indicators to inform the sodium DRIs for adequacy and presents its approach and determination of updated reference values for the DRI age, sex, and life-stage groups. The committee's decision was informed by its evaluation of evidence on sodium intake requirements in apparently healthy individuals, as well as its review of the evidence on adverse effects associated with continuing low sodium intakes. In addition to the indicators considered, the chapter includes conclusions

from the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), where relevant, and additional evidence from the committee's supplemental literature searches and information-gathering activities. This chapter presents the committee's rationale and conclusions regarding the suitability of these indicators to inform the sodium DRI for adequacy. For context, the committee's findings are preceded by a brief summary of the approach taken to establish the sodium AIs in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*).

SODIUM ADEQUATE INTAKE LEVELS ESTABLISHED IN THE *2005 DRI REPORT*

Collecting data to construct intake–response relationships for estimating sodium EARs is not feasible within the context of the current food supply because of the challenges in consuming extremely low levels of sodium. In 2005, an EAR and an RDA were not established for sodium because of inadequate intake–response evidence; instead, AIs were established with an approach that was different from that of other essential nutrients. The sodium AIs for adults 19–50 years of age were "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," with the assumption that the individual was moderately active in a temperate climate (IOM, 2005, p. 308). As supporting evidence, the AI was noted as exceeding sodium intake levels that had been associated with adverse effects on blood lipid concentrations and insulin resistance. Serum and plasma sodium concentrations, plasma renin activity, and blood pressure were explored as potential indicators but were not used to establish the sodium AIs. For children 1–18 years of age and older adults (51 years of age and older), AIs were extrapolated from the AI set for adults 19–50 years of age based on reported energy intake.

REVIEW OF POTENTIAL INDICATORS OF SODIUM ADEQUACY

The original intent of setting adequacy reference intake values for nutrients was to prevent deficiency diseases in the population; therefore, adequacy levels have been established based on such deficiency symptoms. However, health concerns in the United States and Canada have shifted toward the high prevalence of chronic diseases. Consequently, the idea of introducing chronic diseases as indicators to establishing reference values characterizing adequate intakes, either EARs and RDAs or AIs, has been implemented by various DRI committees. In contrast, the current committee

faces an expanded DRI model, in which the relationship between nutrient intake and chronic disease can be characterized in a separate DRI category, termed herein the Chronic Disease Risk Reduction Intake (CDRR). This committee interpreted the guidance provided in the *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) as differentiating considerations of adequacy and chronic disease. Pursuant to the first step of the DRI organizing framework (see Chapter 1, Box 1-2), the committee's review of the evidence to establish the sodium DRIs for adequacy focuses on identifying indicators of sodium adequacy. Despite this conceptual delineation, the committee recognized the importance of reviewing evidence of potential harmful health effects of low sodium intakes in establishing the sodium DRIs for adequacy. In this context, the evidence on the relationship between sodium intake and chronic disease was reviewed to ensure that the selected sodium adequacy DRI values did not potentially lead to detrimental effects. The committee considered this use as being different from using such evidence as an indicator to establish a sodium CDRR.

To explore which indicators could potentially be used to inform the sodium DRIs for adequacy, the committee first considered aspects of sodium physiology, including adaptations of blood sodium concentration to various conditions and hyponatremia. Hyponatremia is defined as a serum sodium concentration of less than 135 mmol/L, with severe hyponatremia being below 120 mmol/L (Sterns, 2015); the concentration of blood sodium at which symptoms of sodium deficiency (e.g., nausea, poor balance, decreased ability to think, headaches, confusion, seizures, or coma) appear are not well characterized. The human body tightly regulates water and sodium balance; however, in instances where these two homeostatic goals are at odds with one another, water and fluid balance are prioritized. As such, in most instances hypo- or hypernatremia are driven by disturbances in fluid balance, and its hormonal control, rather than by disturbances in sodium balance or by sodium intake (Andreoli, 2000). To that end, blood sodium concentration is not a reliable indicator of usual dietary sodium intake or status because most often it reflects inadequate or excessive intakes or losses of water from the body, increased vasopressin release, or occasionally drug effects (e.g., thiazide diuretics, synthetic vasopressin, nonsteroidal anti-inflammatory drugs, antidepressants).

From its information-gathering activities and scoping literature searches (see Appendix D), the committee was unable to identify a sensitive or specific biomarker of sodium status that could be used to determine the distribution of sodium requirements in the apparently healthy population. In the absence of such an indicator of sodium adequacy, the committee reviewed the evidence from balance studies and considered the context of potential harms of low sodium intake.

Balance Studies

Balance studies measuring total intake and losses have been used in the past to assess adequacy based on the concept that neutral balance reflects homeostasis for the nutrient in adults. Such a neutral balance can be, and has been for some nutrients, interpreted as meeting the physiological requirement and, thus, informative to specify an adequate intake level (NASEM, 2018). For example, the EAR for calcium in adults was specified on the basis of calcium balance (IOM, 2011). Applying this rationale to sodium would mean that for an adult to be in neutral balance, intake would be equal to the sum of all sodium losses (sweat, urine, fecal, and other). Individuals with intakes less than losses would be considered in negative balance, indicating deficient intakes. Individuals with intakes greater than losses would be considered in positive balance. In states of growth, positive balance might be necessary to support tissue accretion and, thus, be adequate; in adults, positive balance might indicate intakes above those meeting physiological requirements. To have confidence in such balance studies, intake of sodium and losses by all routes need to be rigorously determined for a sufficient duration in controlled feeding studies to ensure that homeostasis has been achieved. In addition, rigorous balance studies will minimize confounding factors, such as bioavailability and adaptation, that could affect the interpretation of balance.

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* provided an overview of topics related to sodium balance and considered the effects of heat and physical activity on sodium losses. Urinary sodium excretion was characterized as being approximately equal to sodium intake for individuals in a steady state of sodium and fluid balance. Excretion of sodium in feces was described as minimal, although it was noted that increases in sodium intake led to increases in fecal sodium excretion (Allsopp et al., 1998). Sodium losses in sweat were described as being widely variable and dependent on factors such as sweat rate, sodium intake, and heat acclimation. In the *2005 DRI Report* it was concluded that "free-living individuals can achieve sodium balance following acclimation under a variety of conditions, including low sodium intake and extreme heat" (IOM, 2005, p. 277).

Evidence from the Committee's Supplemental Literature Searches

As the committee reviewed the evidence from the limited balance studies available, the expected challenge of measuring total sodium losses from

the body was evident (see Table 8-1). Only two studies measured all sodium losses from total urine, feces, and whole body sweat (Alsopp et al., 1998; Palacios et al., 2004), and only one of these rigorously measured dietary sodium intake (Palacios et al., 2004). Palacios et al. (2004) examined sodium retention in black and white adolescent females consuming a low- (1,300 mg/d [57 mmol/d]) or high-sodium (4,000 mg/d [172 mmol/d]) diet in a randomized, crossover design. Although all losses were assessed, the study did not control for environmental parameters, such as humidity or temperature, and urinary sodium excretion showed high intra-individual variability. In addition to incomplete sodium loss measurements, a number of studies did not directly measure total sodium intake, but relied on food composition tables or manufacturers' labeled sodium content (Heer et al., 2000, 2009; Lerchl et al., 2015). Such failure to measure all sodium losses or reliance on food composition estimates of intake introduces uncertainty and imprecision in total sodium intake that limit the interpretation of balance.

The committee noted new challenges that have been identified based on the emerging data since 2005. First, one study reports high intra-individual variability in sodium losses on controlled intake of sodium and an infradian rhythm (i.e., lasting longer than 1 day) (Lerchl et al., 2015), which would require longer duration for a balance study to ensure that homeostasis is achieved and to enable appropriate consideration of the high intra-individual variability. The study suggested that at least 7 days of urinary sodium assessment are needed to achieve classification accuracy greater than 90 percent (Lerchl et al., 2015). Most balance studies, however, have been conducted only for 3 to 8 days. One exception is a study by Kirkendall et al. (1976) that was conducted for 4 weeks on each sodium intake level; this longer-duration study fed controlled intakes from liquid formula diet, which may be less relevant to food-based diets. Furthermore, high intra-individual variability may mean that randomized crossover (which will need longer periods to achieve equilibrium) or sequential study designs are essential for sodium balance studies and that parallel randomized designs are less appropriate for sodium balance studies. Second, evidence is emerging on sequestration of sodium in the skin concomitantly with water and muscle without concomitant water (Kopp et al., 2013; Xu et al., 2015). Sequestration may be influenced by age (Kopp et al., 2013), hypertensive status (Kopp et al., 2013), inflammation (Xu et al., 2015), and other factors. Thus, unmeasured sequestration might confound the interpretation of balance in these studies. The relationship of sequestration of sodium in skin or muscle to sodium intake is an important, but unexamined, concern relative to balance studies. Such confounding limits the interpretation in that negative balance might represent the loss of sodium from sequestration as opposed to actual deficiency and positive balance might represent sequestration to maintain a level of sodium in these sites.

TABLE 8-1 Sodium Balance Studies Summarized by Completeness of Assessment of Intake and Losses[a]

Reference	Population	Sodium Intake (mg/d)		
		Negative Balance	Neutral Balance	Positive Balance
Rigorous Complete Balance[b]				
Palacios et al., 2004	36 white and black American adolescent females, 11–15 years of age			1,300 4,000
Incomplete Balance—Limitation on Intake Assessment[c]				
Allsopp et al., 1998	25 British males, 18–40 years of age		1,525[d]	1,525[e] 4,004 8,013
Incomplete Balance—Limitation on Loss Assessment[f]				
Kodama et al., 2005[g]	109 Japanese males and females, 18–28 years of age[h]	2,210		6,870
Consolazio et al., 1963	3 healthy, young American adult males, ages not reported			8,729 10,229
Holbrook et al., 1984	12 healthy American adult males and 16 healthy American females, 20–53 years of age			4,200 (males)[i] 2,700 (females)[j]

Noted Design and Limitations

- Randomized crossover design with 3-week duration for each intake separated by 2-week period
- 31 participants completed the low-sodium period; 29 participants completed the high-sodium period
- 24-hour urinary sodium collected for 20 consecutive days
- Whole body sweat was collected after 2 weeks on diet
- No control for environmental parameters, such as humidity or temperature
- High intra-individual variability

- Participants consumed one of three sodium intakes (1,525 mg/d, n = 9; 4,004 mg/d, n = 9; 8,013 mg/d, n = 7) at two environmental temperature balance periods. The first 3 days at 25°C (77°F) with the next 5 days for 10 hours at 40°C (104°F) from 0800 hours to 1800 hours followed by 14 hours at 25°C (77°F) from 1800 hours to 0800 hours
- Sodium intake analyzed based on nutrient composition data and manufacturer's reported content, but was not directly analyzed

- Series of 11 mineral balance studies of 5–12 days duration with a 2–4-day adaptation period
- Sodium intake directly measured
- Urinary and fecal sodium losses measured; only arm sweat losses during physical activity measured

- Balance determined after a preliminary 8 days at 24°C (75°F) during three 4-day periods at 38°C (100°F), one period with intake of 10,229 mg/d and two periods with intakes of 8,729 mg/d
- Set amount of sodium provided and ad libitum sodium as sodium chloride was measured
- Dietary sodium intake and urinary and fecal sodium losses were chemically determined, but 24-hour whole body sweat was not measured; some sweat measurements from underarms collected during 38°C (100°F) periods. Balance did not include sweat losses given limitation of its measurement

- Sodium content of self-selected diet assessed for a period of 1 week, four times over the course of 1 year, chemically analyzed for duplicate samples of all food and beverage consumed
- Urinary and fecal sodium losses measured; no sweat losses were determined

continued

TABLE 8-1 Continued

Reference	Population	Sodium Intake (mg/d) Negative Balance	Neutral Balance	Positive Balance
Incomplete Balance—Limitation on Both Intake and Loss Assessment[k]				
Heer et al., 2000	6 German nonsmoker, nonathlete males, mean 24 years of age			5,060 10,120 15,180
Heer et al., 2009	9 German males, mean 25.7 years of age	1,151[l]		4,605[l] 12,663[l]
Lerchl et al., 2015	10 Russian males in simulated Mars environment			2,453 3,662 4,782–4,835
Kirkendall et al., 1976	7 American males, 24–47 years of age[m]	230		4,828 9,426

NOTE: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0.

[a]Only studies reporting balance using crossover or sequential designs in the same participants at studied intakes for a minimum of 3 days are included. Studies using randomized parallel design trials were not included because high intra-individual variability might confound results.

[b]Rigorous and complete balance measured directly sodium content of foods consumed and all losses (urinary, fecal using appropriate fecal markers, and whole body sweat).

[c]Incomplete balance studies were limited by the lack of direct measurement of sodium content in foods consumed and relied on nutrient composition data from various sources.

[d]Near neutral balance (4.6 ± 117.3 mg/d) at 40°C (104°F) for 10 hours per day for 5 days.

[e]Strong positive balance (535.9 ± 225.4) at 25°C (77°F) for 3 days.

[f]Incomplete balance studies were limited by lack of direct assessment of one or more sources of sodium loss, typically either fecal or whole body sweat or both.

[g]Also reported in part in Kodama et al. (2003) (primary for lowest sodium intake); Nishimuta et al. (1991) (primary for highest sodium intake; only published in Japanese).

Noted Design and Limitations
• Sequential study design with an 8-day duration at each level • Sodium intake assessed by nutrient composition data with direct measurement only of high-sodium foods • Sodium losses assessed only by urinary and fecal sodium after determination in three participants; whole body sweat losses were negligible under experimental conditions
• Controlled sequential feeding study 6- to 10-day duration at three levels • Unclear if sodium intake was chemically determined • No fecal sodium loss was determined
• Two series of studies, one for 105 days and one for 205 days duration, were conducted under conditions simulating a flight to Mars • Cumulative sodium chloride intake and urinary sodium for entire duration was reported • Fecal or whole body sweat sodium losses were not determined • Sodium intake was analyzed based on required regulatory analysis by manufacturer and was not directly determined in study • High intra-individual variability
• Controlled intakes through semipurified liquid formula diets during a 12-week period, consisting of 4 weeks each of three different levels of sodium intake (230, 4,828, and 9,426 mg/d). Formula sodium content was chemically determined on selected spot-checked samples • Urinary excretion measured; fecal losses assessed in three participants; no sweat losses were determined. Balance represents difference between intake and only urinary losses

[h]Sample size of all participants across a series of 11 balance studies. Across the 11 balance studies, participants consumed different levels of sodium; sample size in any given balance study is limited.

[i]Average sodium intake of male participants (n = 12), based on analysis of 1 week's worth of food and beverage samples collected four times over the course of 1 year.

[j]Average sodium intake of female participants (n = 16), based on analysis of 1 week's worth of food and beverage samples collected four times over the course of 1 year.

[k]Incomplete balance studies were limited by lack of direct measurement of sodium content in foods consumed and by lack of assessment of one or more sources of sodium losses as noted for each study.

[l]Intakes were reported as mmol/kg/d and estimated as total mg based on average body weight reported as 71.5 kg. For low sodium, 0.7 mmol/kg estimated total intake of 1,151 mg; for medium sodium, 2.8 mmol/kg estimated total intake of 4,605 mg; for high sodium, 7.7 mmol/kg estimated total intake of 12,663 mg.

[m]The study reported on 24-hour urinary excretion for 7 of the 8 participants.

Committee's Synthesis of the Evidence

Current balance studies have limitations and do not offer sufficient data for characterizing the distribution of sodium requirements in the apparently healthy population. Limitations of existing studies include uncertainties of the duration needed to allow for equilibration in light of high intra-individual variability and the potential confounding by sequestration of sodium in skin and muscle. As discussed in Chapter 12, evidence is needed from studies in which sodium intake is controlled and chemically determined in rigorous feeding studies of sufficient duration to encompass infradian rhythm and intra-individual variability. Such ideal studies would measure all losses of sodium including at a minimum urinary, whole body sweat, and fecal losses.

The better-designed balance studies summarized in Table 8-1 may be informative if considered in combination with other approaches for assessing adequacy. Despite the limitations of the balance studies, negative balance was reported with sodium intakes of 230–2,210 mg/d (10–96 mmol/d) across the eight studies conducted in adults. By comparison positive balance was reported with intakes as low as 1,525 mg/d (66 mmol/d; at 25°C [77°F]). Only one study reported an approximately neutral balance of intake and excretion (sodium balance reported as +4.6 ± 117.3 mg/d), and only for one sodium intake level (1,525 mg/d [66 mmol/d]) with daily heat stress (40°C [104°F] for 10 hours) (Allsopp et al., 1998). Only one study in adolescent females rigorously measured sodium intake and all sodium losses and reported positive balance with intakes of 1,300–4,000 mg/d (57–172 mmol/d).

ADDITIONAL EVIDENCE CONSIDERED: POTENTIAL HARMFUL HEALTH EFFECTS OF LOW SODIUM INTAKES

The committee's review of the evidence did not identify other potential indicators of sodium adequacy or deficiency that could be used to estimate sodium requirements in the apparently healthy population. However, data from observational studies have suggested an increase in risk of specific chronic diseases at low intake levels of sodium. Therefore, to minimize the potential for harmful health effects beyond deficiency at levels of intake around sodium adequacy, the committee considered the evidence related to the potential for such levels to increase biomarkers of chronic diseases (insulin resistance, blood pressure, and lipid concentrations), cardiovascular disease outcomes, and all-cause mortality. This section describes the committee's assessment of such evidence and its appropriateness and limitations for its use as support of the sodium DRIs for adequacy. The committee based its assessment using evidence from the *AHRQ Systematic Review* and

evidence from its supplemental literature searches. This section also summarizes findings from another systematic review for comparison (Eeuwijk et al., 2013).

Type 2 Diabetes, Glycemic Control, and Insulin Sensitivity

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* concluded that the effects of sodium reduction on insulin resistance were sparse and inconsistent. However, the potential adverse effects on insulin resistance at low sodium levels (700 mg/d [30 mmol/d]) were noted as a consideration for the selection of a sodium AI in the *2005 DRI Report*.

Evidence from the Committee's Supplemental Literature Search

A systematic review assessed evidence of relationships between low levels of sodium intake (230–1,953 mg/d [10–85 mmol/d] for 5–28 days, after a period of normal-to-high sodium intake of 4,596–6,894 mg/d [200–300 mmol/d]) and a variety of measures, including insulin resistance (Eeuwijk et al., 2013). Among the eight trials included in the systematic review studying insulin sensitivity, only three reported a lower insulin sensitivity with sodium reduction in the ranges listed above. The systematic review concluded such levels of sodium restriction may decrease insulin sensitivity, although results were inconsistent (Eeuwijk et al., 2013).

The committee reviewed the evidence from randomized clinical trials and prospective cohort studies published since 2003 on the relationship between sodium intake and blood glucose, insulin, and incident type 2 diabetes (for literature search details, see Appendix E). The committee identified two randomized controlled trials reviewing the effect of dietary sodium on insulin sensitivity and glucose tolerance (Meland and Aamland, 2009; Suckling et al., 2016) and one prospective cohort study examining the relationship between sodium intake and type 2 diabetes (Hu et al., 2005). The identified randomized clinical trials did not find differences in measures of glucose control or insulin production between groups on low and high sodium intakes. The prospective cohort study reported that high sodium intake was associated with higher risk of incident type 2 diabetes.

Committee's Synthesis of the Evidence

There is insufficient evidence to suggest that there is potential harm in lower sodium intakes with respect to incident type 2 diabetes, and measures of glucose and insulin status.

Blood Pressure

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* noted that some investigators have found blood pressure increases as a result of reducing sodium intake levels. The apparent rise in blood pressure in some individuals was described as potentially being a pressor response, potentially caused by an overactive renin-angiotensin-aldosterone system (RAAS), intrinsic variability in blood pressure, or imprecise blood pressure measurements. The *2005 DRI Report* concluded that, given these considerations, the apparent rise in blood pressure with reductions in sodium intake could not be used as an indicator of sodium adequacy.

Evidence Provided in the AHRQ Systematic Review

The *AHRQ Systematic Review* included one observational cohort study in Taiwanese adult men and women with evidence of an increase in hypertension risk with lower sodium intakes. Compared with individuals in the second quartile of sodium intake (median of 2,367 mg/d [103 mmol/d]), those in the first quartile (median of 1,448 mg/d [63 mmol/d]) had a suggestive, but nonsignificant, increased risk of hypertension (relative risk = 1.24; p = .07) (Chien et al., 2008). Sodium was assessed through estimated 24-hour urinary sodium from a single overnight urine sample.[1] The *AHRQ Systematic Review* rated this study as having a high risk of bias. The *AHRQ Systematic Review* made no conclusion on whether lowering sodium intake could increase blood pressure.

Committee's Synthesis of the Evidence

Based on the committee's assessment of the trials that explored blood pressure as an outcome, there is moderate strength of evidence that the positive linear relationship between sodium intake and blood pressure extends downward to as low as 850–1,800 mg/d (37–78 mmol/d) (see Chapter 10). There is also insufficient evidence that low sodium intakes are associated with increased blood pressure.

[1]Chien et al. (2008) did not explicitly state how the overnight urine sample was used to estimate 24-hour urinary sodium excretion. A paper by Kawasaki et al. (1993) was cited in a general description of sample collection and is presumed to be the equation used.

Plasma Lipid Concentrations

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* described two systematic reviews that explored the relationship between reduced sodium intake and plasma lipid concentrations and that provided contrasting results (Graudal et al., 1998; He and MacGregor, 2002). One of the systematic reviews included trials with extreme reductions of sodium (Graudal et al., 1998), whereas the other included trials with moderate reductions in sodium (He and MacGregor, 2002). Reductions in sodium from high sodium intakes of 6,434 mg/d (280 mmol/d) to low intakes of 1,287 mg/d (56 mmol/d) resulted in significant increases in total and low-density lipoprotein (LDL) cholesterol concentrations (Graudal et al., 1998). Moderate reductions in sodium (net changes of sodium ranged from 920–2,714 mg/d [40–118 mmol/d]) did not result in such increases (He and MacGregor, 2002). These meta-analyses also differ in that trials of 1 week or less duration were included in Graudal et al. (1998), but not in He and MacGregor (2002). No studies were identified for which plasma lipid concentrations was the primary endpoint. The *2005 DRI Report* described the selected sodium AI for adults 19–50 years of age as a level above which some studies had reported increased plasma lipid concentrations.

Evidence Provided in the AHRQ Systematic Review

The *AHRQ Systematic Review* did not include plasma lipids in its outcomes of interest but recorded them from studies on an ad hoc basis when measured as an adverse event. The *AHRQ Systematic Review* identified four such publications (from three different trials) showing no significant difference in plasma lipid concentrations (total cholesterol, LDL, high-density lipoprotein [HDL], triglycerides) (Harsha et al., 2004; Meland and Aamland, 2009; Sacks et al., 2001; Sciarrone et al., 1992). Based on a low strength of evidence, the *AHRQ Systematic Review* concluded that sodium reduction does not appear to significantly affect plasma lipids concentrations.

Evidence from the Committee's Supplemental Literature Search

A systematic review assessed evidence of relationships between low levels of sodium intake (230–1,953 mg/d [10–85 mmol/d] for 5–28 days, after a period of normal-to-high sodium intake of 4,596–6,894 mg/d [200–300 mmol/d]) and a variety of measures including plasma lipids (Eeuwijk et al., 2013). The review concluded that there is (1) inconsistent evidence that sodium restriction significantly increases total cholesterol (from seven

randomized controlled trials) or LDL cholesterol (from five randomized controlled trials) and (2) no significant effect on HDL cholesterol (from four randomized controlled trials) or triglyceride (from five randomized controlled trials) concentrations (Eeuwijk et al., 2013).

The committee's supplemental literature searches identified three recent systematic reviews that examined relationships between sodium intake and plasma lipids concentrations (Aburto et al., 2013; Graudal et al., 2017; He et al., 2013). A brief summary of each is provided below and presented in Table 8-2:

- He et al. (2013), which included a Cochrane review and meta-analyses, concluded that there was no significant effect of sodium intake on plasma lipid concentrations based on 8 randomized controlled trials on total cholesterol, 5 randomized controlled trials on LDL cholesterol, 6 randomized controlled trials on HDL cholesterol, and 6 randomized controlled trials on plasma triglyceride concentrations. The major inclusion/exclusion criteria were
    1. randomized controlled trials designs;
    2. random allocation to modestly reduced salt intake or usual salt intake (control);
    3. a minimum intervention period of 4 weeks;
    4. exclusion of studies with concomitant interventions; and
    5. a reduction in 24-hour urinary sodium within a range of 920–2,760 mg/d (40–120 mmol/d).
- Aburto et al. (2013) found no significant effect of sodium reduction on plasma lipids concentrations based on 11 randomized controlled trials on total cholesterol, 6 studies on LDL cholesterol, and 9 studies on HDL cholesterol. The major inclusion/exclusion criteria were
    1. a minimum intervention period of 4 weeks;
    2. sodium intake difference of > 40 mmol/day;
    3. randomized controlled trials using 24-hour urinary sodium excretion for assessing sodium intake;
    4. inclusion of prospective cohort designs with duration longer than 1 year with any measure of sodium intake, if fewer than three intervention studies included;
    5. exclusion of studies with concomitant interventions; and
    6. exclusion of studies targeting acutely ill subjects.
- Graudal et al. (2017) reported significant increases in cholesterol and triglyceride concentrations with reduced sodium based on 26 crossover trials on total cholesterol, 17 crossover trials on LDL cholesterol, 19 crossover trials on HDL cholesterol, and 19 crossover trials on triglyceride concentrations. The major inclusion criteria were

TABLE 8-2 Results from Meta-Analyses of Randomized Controlled Trials, Effect of Decreases in Sodium Intake on Blood Lipid Concentrations

			Graudal et al., 2017[b]		Graudal et al., 2011[b]		
Measure	He et al., 2013[a]	Aburto et al., 2013[a]	Trials of Any Duration	Trials ≥ 1-Week Duration	Trials of Any Duration	Trials ≥ 2-Week Duration	Trials ≥ 4-Week Duration
Total Cholesterol, mmol/L							
Trials (Comparisons)	8	11	26 (27)	20	23 (25)	13	9
Participants	365	2,339	1,800	1,180	1,546	848	NR
Effect Estimate[c]	0.05 [−0.02, 0.11], I^2 = 0%	0.02 [−0.03, 0.07], I^2 = 0%	0.15 [0.06, 0.23],[d] I^2 = 0%	0.13 [0.03, 0.22],[d] I^2 = 0%	0.15 [0.06, 0.24],[d] I^2 = 0%	0.06 [−0.06, 0.18],[d] I^2 = 0%	0.08 [−0.06, 0.23],[d] I^2 = NR
LDL Cholesterol, mmol/L							
Trials (Comparisons)	5	6	17	12	15 (16)	8	6
Participants	262	1,909	1,358	864	1,172	546	NR
Effect Estimate[c]	0.05 [−0.01, 0.12], I^2 = 0%	0.03 [−0.02, 0.08], I^2 = 0%	0.08 [−0.01, 0.17],[d] I^2 = 0%	0.09 [−0.01, 0.20],[d] I^2 = 0%	0.07 [−0.03, 0.18],[d] I^2 = 0%	0.06 [−0.08, 0.21],[d] I^2 = 0%	0.10 [−0.07, 0.26],[d] I^2 = NR
HDL Cholesterol, mmol/L							
Trials (Comparisons)	6	9	19	14	16 (17)	11	8
Participants	278	2,031	1,442	948	1,210	684	NR
Effect Estimate[c]	−0.02 [−0.06, 0.01], I^2 = 16%	−0.01 [−0.03, 0.00], I^2 = 0%	−0.01 [−0.04, 0.03],[d] I^2 = 0%	−0.02 [−0.06, 0.02],[d] I^2 = 0%	0.00 [−0.04, 0.04],[d] I^2 = 0%	−0.02 [−0.07, 0.04],[d] I^2 = 0%	0.00 [−0.07, 0.06],[d] I^2 = NR

NOTES: Meta-analyses differ from each other with respect to inclusion/exclusion criteria. HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported.

[a]Intervention duration of ≥ 4 weeks.

[b]Graudal et al., 2017, is an update to Graudal et al., 2011. Because the update did not present analyses only on trials of longer durations (i.e., ≥ 2 and ≥ 4 weeks), both publications are presented.

[c]Presented as mean difference [95% confidence interval], I^2.

[d]Values were reported as mg/dL. These values were converted to mmol/L by multiplying the mg/dL value by 0.02586.

SOURCES: Aburto et al., 2013; Graudal et al., 2011, 2017; He et al., 2013.

1. randomized controlled trial designs;
2. diets containing any amount of sodium;
3. sodium assessment via 24-hour urinary sodium excretion or estimated from 8-hour excretion;
4. unhealthy patients were excluded; and
5. no exclusion based on the duration of the intervention.

Committee's Synthesis of the Evidence

The absolute effect of sodium intake on blood triglyceride concentrations appears to be small and of questionable biological significance when information about whether individuals had fasted or not is lacking (Stone et al., 2014). In addition, differences in the results of the three identified systematic reviews on the effects of sodium intake on lipid concentrations could result from differences in the inclusion/exclusion criteria such as the duration of the interventions. Although there is ample evidence to include only studies with sodium interventions of 4 weeks or more when blood pressure is the outcome of interest (Law et al., 1991), the limited evidence with serum lipid concentrations suggests that a minimum intervention period is also necessary for serum lipid levels to stabilize. For example, Table 8-2 shows results from different meta-analyses that included studies of various durations. Analyses with the criteria of at least 4 weeks (Aburto et al., 2013; Graudal et al., 2011; He et al., 2013) did not find a significant effect of sodium reduction on total cholesterol, whereas analyses that included studies of shorter duration found a significant mean difference (Graudal et al., 2011, 2017). Given these inconsistencies in the results of the three systematic reviews and the likelihood that study duration is affecting results, there is insufficient evidence about the relationship between a low sodium intake and detrimental effects on blood lipid concentrations.

Cardiovascular Disease Outcomes and All-Cause Mortality

The scientific community has generally supported the idea of a linear positive relationship between higher levels of sodium intake and cardiovascular disease risk, mostly based on studies measuring blood pressure as a biomarker for risk of cardiovascular disease. More recently, however, observational studies have emerged that suggest the possibility that lower intakes of sodium may increase the risk of harmful health outcomes. These studies suggest that the relationship between sodium intake and cardiovascular disease outcomes and mortality is not linear but presents a J or U shape. If confirmed, such a J- or U-shaped relationship might be supportive evidence to specify an AI that minimizes the risk of adverse outcomes at a low level of sodium intake. In contrast to shorter-term studies that evaluated the rela-

tionship of sodium intakes and blood pressure, randomized controlled trials of lifestyle interventions that directly measure a chronic disease outcome are less feasible owing to the larger sample size and longer follow-up required. In addition, achieving low intakes of sodium is particularly challenging within current dietary patterns. Hence, most of the evidence evaluating the relationship between lower sodium intake and direct health outcomes derives from observational cohort studies. Although cohort studies are ideal to explore some scientific questions (NASEM, 2017), they are at higher risk of biases, their interpretation requires great care, and their strength of evidence for causality is generally low. In the case of exploring the health effects of lower sodium intake, these methodological issues have fueled controversy. The committee reviewed evidence in the *AHRQ Systematic Review* to assess whether the J- or U-shaped relationships are caused by methodological limitations or are likely to occur and could be considered as supportive evidence to establish adequacy levels. As background, this section starts with conclusions from other groups who have evaluated this body of evidence.

A 2013 Institute of Medicine (IOM) consensus study report included a comprehensive review of the benefits and adverse effects of reducing sodium intake in the population particularly in the range of 1,500–2,300 mg/d (65–100 mmol/d). Its authors concluded that

> evidence from studies on direct health outcomes is inconsistent and insufficient to conclude that lowering sodium intakes below 2,300 mg per day either increases or decreases risk of cardiovascular disease outcomes (including stroke and cardiovascular disease mortality) or all-cause mortality in the general U.S. population. (IOM, 2013, p. 5)

This IOM report also found that the methodological quality of the studies linking lower dietary sodium intake with adverse health outcomes was highly variable and that this variability limited the ability to conduct comparisons. Other reviews have suggested a J-shaped relationship between sodium intake and health outcomes using meta-analyses (Graudal, 2016; Graudal et al., 2014) or qualitative assessments (Alderman and Cohen, 2012) of observational studies. The meta-analyses included studies with diverse methodologies (e.g., food frequency questionnaires, 24-hour urine excretions).

A systematic review of the evidence of associations between low levels of sodium intake and status or adverse health outcomes was conducted for the European Food Safety Authority in preparation for establishing dietary reference values for sodium. The authors reported that low sodium intake may be associated with increased mortality, particularly all-cause mortality and cardiovascular disease mortality (Eeuwijk et al., 2013). This conclusion

was based on two (out of three) National Health and Nutrition Examination Survey (NHANES) longitudinal follow-up studies showing an inverse relationship between sodium intake and all-cause mortality (Alderman et al., 1998; Cohen et al., 2006) and on three NHANES studies showing an inverse relationship between sodium intake and cardiovascular disease mortality (Alderman et al., 1998; Cohen et al., 2006, 2008). A major limitation for all three NHANES studies, however, is that estimates of sodium intake come from 24-hour dietary recall data (for limitation of different sodium intake measurement approaches, see Chapter 3).

A comprehensive assessment of cohort studies examining the relationships between sodium intake and health outcomes has provided an in-depth description of methodological issues and their potential contribution to the heterogeneity of the results (Cobb et al., 2014). The authors of the comprehensive assessment applied their criteria to the body of observational studies on sodium and disease outcomes. Based on the potential for both random and systematic error identified in the individual studies, the authors do not recommend the use of this body of evidence to set specific cut points for sodium intake recommendations. Furthermore, the authors concluded that given the multiplicity of different measures of intake and the lack of standardization, comparisons across studies is difficult.

Evidence Provided in the AHRQ Systematic Review

The *AHRQ Systematic Review* included observational studies that suggested J- or U-shaped relationships between sodium intake and health outcomes. These studies were rated as having high risk of bias based on the *AHRQ Systematic Review* risk-of-bias tool (see Appendix C, Annex C-1); the committee notes that the high risk of bias ratings closely aligned with the concepts described in Cobb et al. (2014). In addition, the *AHRQ Systematic Review* did not conduct intake–response meta-regressions with these studies owing to the lack of sufficient data (as specified in their criteria for conducting meta-analysis, three or more studies using 24-hour urinary excretion measures for each outcome). Instead, the *AHRQ Systematic Review* concluded that "observational studies had limited ability to control for pre-existing health conditions at study baseline that might have resulted in decreased sodium intakes, contributing to potentially spurious associations of lower sodium intakes with morbidity or mortality outcomes of interest" (Newberry et al., 2018, p. 192). Furthermore, the *AHRQ Systematic Review* notes that "observational studies may have residual confounding, as they could not adjust for all factors that may increase risk for [hypertension], [cardiovascular disease], or [coronary heart disease] outcomes" (Newberry et al., 2018, p. 192). The *AHRQ Systematic Review* also made the following qualitative conclusions in regard to the relationship between low intakes of

sodium and all-cause mortality, cardiovascular disease mortality, combined cardiovascular disease morbidity and mortality, and heart failure:

- *All-cause mortality:* The *AHRQ Systematic Review* concluded that there was insufficient evidence that sodium reduction decreases the risk for all-cause mortality (6 randomized controlled trials in the low intake range of 1,953–3,171 mg/d [85–138 mmol/d]). Out of 13 prospective cohort studies examining associations between sodium intake and all-cause mortality, a U-shaped association was reported in three multicountry studies with overlapping populations that used estimated 24-hour urinary sodium excretion and that were determined to have a high risk of bias (Lamelas et al., 2016; Mente et al., 2016; O'Donnell et al., 2014).
- *Cardiovascular disease mortality and combined cardiovascular disease morbidity and mortality:* Based on eight trials, the *AHRQ Systematic Review* concluded that sodium reduction may significantly decrease the risk for combined cardiovascular disease morbidity and mortality. However, the review also concluded that there is insufficient evidence to draw a conclusion regarding either linear or nonlinear associations between sodium intake levels and cardiovascular disease mortality or associations between sodium intake levels and risks of combined cardiovascular disease morbidity and mortality. Two studies with overlapping populations reported a J or U shape between sodium intake and cardiovascular disease mortality (Lamelas et al., 2016; O'Donnell et al., 2014) and three studies (Lamelas et al., 2016; Mente et al., 2016; O'Donnell et al., 2014) with overlapping populations reported a U-shaped relationship between sodium intake and combined cardiovascular disease morbidity and mortality. All studies were rated as having high risk of bias.
- *Heart failure:* The *AHRQ Systematic Review* reported on two studies that presented evidence on heart failure outcomes. One study reported a U-shaped association (Pfister et al., 2014); the other study reported higher risk of heart failure at higher sodium quartile intake level (He and Macgregor, 2002). Both studies were rated as having high risk of bias.

Committee's Synthesis of the Evidence

The committee notes that the *AHRQ Systematic Review* did not conduct meta-analyses on the results of observational studies. Pooling results from studies with such varied designs is not appropriate, particularly with different sodium intake assessment methods that carry different system-

atic and random errors (see Chapter 3 for strengths and weaknesses of the methods); such a pooling might result in spurious changes in size and directionality of the overall effect on the outcome of interest.

The method of sodium intake ascertainment in the observational studies that suggest inverse relationships between sodium intake and chronic diseases is of concern. Six out of seven of the studies that reported higher risk of adverse outcomes at low sodium intake levels in the *AHRQ Systematic Review* used spot urine sodium measurements converted to estimates of 24-hour urinary sodium excretion by using a formula (e.g., the Kawasaki formula). Two additional studies were published after the release of the *AHRQ Systematic Review* (Lelli et al., 2018; Mente et al., 2018). Mente et al. (2018) analyzed results from the ongoing Prospective Urban Rural Epidemiology study (for previous results from this study, see also O'Donnell et al., 2014), in which 82,544 individuals in 255 communities were assessed for cardiovascular outcomes during a median of 8.1 years. Morning fasting urine was used to estimate sodium intake using the Kawasaki formula. As with previous results from this ongoing study, a significant inverse association was reported between the lowest tertile of sodium intake (< 4,430 mg/d [< 193 mmol/d]) and cardiovascular disease. The study by Lelli et al. (2018) was conducted in a cohort of two Italian communities enrolled in the 1998–2000 Invecchiare in Chianti—Aging in the Chianti study. An inverse relationship between sodium intake and mortality was reported with higher mortality at sodium intakes below 6,250 mg/d (271 mmol/d). However, the inverse relation was particularly strong in the frail elderly and the group with the lowest sodium intake was older, more sedentary, had more dementia, and could potentially have other medical conditions as well as inadequate calorie intake. Based on the application of the *AHRQ Systematic Review* risk-of-bias criteria, the committee determined these two observational studies to have a high risk of bias (see Appendix E).

Although spot urine sodium measurements are simpler to obtain than multiple 24-hour urine collections, they introduce important biases that might alter intake–response curves exploring associations of sodium intake with health outcomes (Dougher et al., 2016; Mente et al., 2014). Past methodological studies have partly explained the strengths and limitations of various sodium intake assessment methods and are described in depth in Chapter 3. Some have specifically demonstrated that most sodium exposure measurement methods would result in incorrect levels of intake in individuals, which would lead to misinterpretations regarding associations with health outcomes. For example, Olde Engberink et al. (2017) found that hazard ratios for cardiovascular disease outcomes changed up to 85 percent depending on the sodium intake estimation used (baseline versus 1-year versus 5-year follow-up). A key finding from these validation studies is the systematic bias across the range of sodium intakes, such that

spot urine sodium estimates are particularly biased estimates of 24-hour urine sodium at the lower and upper extremes of sodium intake (Dougher et al., 2016; Mente et al., 2014). As the issue at hand is the relationship of low sodium intake with health outcomes, the committee considered the accuracy of spot urine sodium estimates at the low range of intakes as an important concern to this method. Another key piece of evidence for specifically explaining the apparent inverse relationship between sodium intake and mortality derives from recent analyses of data from the Trials of Hypertension Prevention I and II cohort studies (He et al., 2018). The authors compared four different methods of measuring sodium intake: averaged measured,[2] average estimated,[3] first measured,[4] and first estimated.[5] The averaged estimated value (a method frequently used in observational studies showing inverse relationships) overestimates sodium intake by about one-third overall. It also tends to overestimate at lower levels and underestimate at higher levels of sodium intake. In addition, whereas the measured value shows a linear relationship between sodium intake and mortality, the estimated value using the Kawasaki formula suggests a J-shaped relationship with mortality. These comparisons are valuable because they show clearly that the sodium exposure assessment can influence the nature of the relationship with endpoints, even when conducted in the same individuals at the same time. Moreover, such comparisons help explain how inaccurate sodium intake measurements could contribute to the apparent higher risk of adverse outcomes at low sodium intake levels observed in some studies.

More broadly, finding an inverse, J- or U-shaped relationship when a direct relationship is expected is not uncommon in the medical literature but it is often largely attributable to reverse causation or confounding. For example, a J- or U-shaped relationship with body mass index (BMI) and mortality has been documented in patients with diabetes, cardiovascular disease, chronic kidney disease, and heart failure. In-depth examination of potential drivers of the J-shaped relationship between BMI and mortality using approaches such as exclusion of those with early deaths or those who were ever smokers attenuated the J-shaped relationship (Tobias et al., 2014). When both ever smokers and those with early deaths were excluded, the expected direct relationship between BMI and all-cause mortality was seen.

Thus, the paradoxical J- and U-shaped relationships of sodium intake and cardiovascular disease and mortality are likely observed because of methodological limitations of the individual observational studies.

[2]From three to seven 24-hour urinary sodium measurements during the trial periods.

[3]From three to seven estimated 24-hour urinary sodium excretions from sodium concentration of 24-hour urine using the Kawasaki formula.

[4]From a 24-hour urinary sodium measured at the beginning of each trial.

[5]A 24-hour urinary sodium estimated from sodium concentration of the first 24-hour urine using the Kawasaki formula.

DIETARY REFERENCE INTAKES OF SODIUM ADEQUACY

The committee's review of the evidence on potential indicators to inform the sodium DRIs for adequacy revealed the following:

- There is no sensitive biomarker that can be used to characterize the distribution of sodium requirements in the apparently healthy population.
- The balance studies have a number of limitations, particularly related to the low number of studies and of subjects in each study, incomplete measurement of intake and losses, unknowns related to sodium sequestration in skin and muscle (storage) in the body, and short equilibration periods in light of emerging evidence of infradian rhythms and high intra-individual variation. These limitations precluded the committee from using such data to estimate median requirements and the distribution of requirements in the apparently healthy population. The balance studies, particularly those with stronger designs, can provide some insight into the levels of sodium intake that may lead to neutral balance.
- There is a limited and inconsistent body of evidence on the potential harms of low sodium intake. The heterogeneity appears to be caused, in part, by methodological approaches used in observational studies.

The AI is "a recommended average daily nutrient intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people who are assumed to be maintaining an adequate nutritional state" (IOM, 2006, p. 11). To establish sodium AIs for adults, which could then be extrapolated to other DRI age, sex, and life-stage groups, the committee drew on its review and synthesis of the evidence for this and the other DRI categories. In particular, as summarized in Chapter 9, randomized controlled trials on sodium included in the *AHRQ Systematic Review* did not reveal a pattern of reported adverse effects among the low-sodium groups, suggesting that levels of sodium intakes studied did not result in sodium deficiency. Furthermore, the committee established a sodium CDRR for adults 19 years of age and older at 2,300 mg/d (100 mmol/d) (see Chapter 10). In the committee's interpretation of the guidance provided in the *Guiding Principles Report*, the DRIs for adequacy would be established at or below the sodium CDRR; establishing the sodium AI above the CDRR would be inappropriate, as intakes above 2,300 mg/d (100 mmol/d) are expected to increase risk of cardiovascular disease. To that end, unlike the approach taken for the potassium AI, the committee could not use median population intakes

to inform the sodium AIs; median intakes across the DRI age, sex, and life-stage groups in both the United States and Canada exceed the CDRR (see Chapter 11). The committee therefore determined that the sodium AI for adults could be derived from trials with sodium intakes less than 2,300 mg/d (100 mmol/d) and that the strongest designed balance study could provide insight as to whether the selected sodium AI value was appropriate.

The committee concludes that none of the reviewed indicators of sodium requirements offer sufficient evidence to establish Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) values. Adequate Intakes (AIs) are therefore established. Median population intakes are not suitable for establishing the sodium AI because they exceed the sodium Chronic Disease Risk Reduction Intake (CDRR). The committee also concluded that the lowest levels of sodium intake evaluated in randomized trials and evidence from the best-designed balance study conducted among adults were congruent and are appropriate values on which to establish the sodium AIs.

The adult sodium AI value was extrapolated to children and adolescents 1–18 years of age, based on sedentary Estimated Energy Requirements (EERs). For infants 0–12 months of age, sodium intakes of breastfed infants were estimated and were used as the basis of the AI. The sections that follow present additional details on the committee's derivation of the sodium AIs for each of the DRI age, sex, and life-stage groups.

Infants 0–12 Months of Age

Details of the committee's approach to estimating the concentration of sodium in breast milk and the contributions of complementary foods to total sodium intake are provided in Appendix F. To establish the sodium AIs for infants 0–6 and 7–12 months of age, the committee estimated the sodium concentration in mature breast milk. Different concentrations are used for the two infant age groups in the estimates below, as the sodium content of breast milk changes over the course of the first year. To establish the sodium AI for infants 7–12 months of age, sodium intake from complementary foods was estimated and added to the estimated sodium intake from breast milk.

The sodium AI for infants 0–6 months of age is based on estimated sodium intake from breast milk alone. The mean sodium concentration of breast milk for this age group was estimated to be 140 mg/L (6 mmol/L). Assuming an average consumption of 780 mL/day, the sodium AI for infants 0–6 months is established at 110 mg/d (5 mmol/d).

TABLE 8-3 Sodium Adequate Intakes, Infants 0–12 Months of Age

DRI Age, Sex, and Life-Stage Group	Sodium Adequate Intake, mg/d
Infants	
0–6 months	110
7–12 months	370

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. DRI = Dietary Reference Intake; mg/d = milligrams per day.

The sodium AI for infants 7–12 months of age is based on estimated sodium intake from breast milk and complementary foods. The mean sodium concentration in breast milk for this age group was estimated to be 110 mg/L (5 mmol/L). Assuming an average breast milk consumption of 600 mL/d, approximately 70 mg/d (3 mmol/d) sodium is consumed from breast milk. Sodium intake from complementary foods was estimated to be 300 mg/d (13 mmol/d). The sodium AI for infants 7–12 months is therefore established at 370 mg/d (16 mmol/d). A summary of the infant sodium AIs is presented in Table 8-3.

Children and Adolescents 1–18 Years of Age

For children and adolescents 1–18 years of age, the sodium AIs were derived by extrapolating from the sodium AI for adults (1,500 mg/d [65 mmol/d]; see below). To extrapolate, the committee used rounded average EERs for sedentary children for each age group (see Table 8-4), as com-

TABLE 8-4 Estimated Energy Requirements for Sedentary Children and Adolescents 1–18 Years of Age, by Age Group

Age Group	Average EER (kcal/d)	Rounded Average EER (kcal/d)
1–3 years	1,000[a]	1,000[a]
4–8 years	1,280	1,300
9–13 years	1,640	1,600
14–18 years	2,040	2,000

NOTES: Unless otherwise noted, sedentary EERs were drawn from a summary table in the *2015–2020 Dietary Guidelines for Americans* (HHS/USDA, 2015), which were derived from the EER equations (IOM, 2002/2005). The average estimated requirements were determined by a simple average of the estimated energy needs for sedentary males and females within each age range. Average intakes were mathematically rounded. EER = Estimated Energy Requirement; kcal = kilocalorie.

[a]The *2015–2020 Dietary Guidelines for Americans* provides dietary guidance for individuals 2 years of age and older. The summary table of sedentary EERs did not include children 1 year of age. The committee considered the effect of the EER for children 1 year of age on the rounded average for the 1–3-year-old age group. The average of EERs for children 12–24 months are estimated to be below 1,000 kcal/d (IOM, 2002/2005, pp. 169–170), but they are not low enough to affect the rounded average EER. As such, 1,000 kcal/d was used in extrapolating the adult sodium AI to children 1–3 years of age.

TABLE 8-5 Sodium Adequate Intakes, Children and Adolescents 1–18 Years of Age

DRI Age, Sex and Life-Stage Group	Sodium Adequate Intake, mg/d
Children	
1–3 years	800
4–8 years	1,000
Males	
9–13 years	1,200
14–18 years	1,500
Females	
9–13 years	1,200
14–18 years	1,500

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. DRI = Dietary Reference Intake; mg/d = milligrams per day.

pared to an EER for adults of 2,000 kcal/d. EERs were used instead of self- or proxy-reported energy intake owing to potential biases in reported dietary intake data. Extrapolated sodium AIs were mathematically rounded to the nearest 100 mg/d increment. Table 8-5 summarizes the sodium AIs for children and adolescents 1–18 years of age.

Adults 19 Years of Age and Older

There was insufficient evidence to establish sodium EARs and RDAs for adults. Therefore, the following evidence informed the committee's judgment in establishing the sodium AI for adults:

- *Lowest sodium intakes from DASH-Sodium and other sodium trials:* The Dietary Approaches to Stop Hypertension (DASH)-Sodium trial was a randomized feeding trial in which 412 individuals were assigned to one of two diet arms, a DASH diet (a balanced eating plan) and control diet (a Western-style diet); within each assignment, participants consumed low-, intermediate-, and high-sodium-density foods in random order for 30 days each (Sacks et al., 2001). The range of sodium intakes during the low-sodium period of the DASH-Sodium trial was 985–2,452 mg/d (43–107 mmol/d; average: 1,495 mg/d [65 mmol/d]) among those in the DASH diet arm and 949–2,326 mg/d (41–101 mmol/d; average: 1,449 mg/d [63 mmol/d]) among those in the control diet arm (Murtaugh et al., 2018; Sacks et al., 2001). No deficiency symptoms were reported in this tightly controlled feeding study. In addition, the *AHRQ Systematic Review* included eight other randomized controlled trials in which sodium

TABLE 8-6 Trials That Studied the Effects of Sodium Intake Reduction to Low-Range Sodium Levels (850–1,800 mg/d)

Reference	Sodium Level Achieved (mg/d)	AHRQ Assigned Risk of Bias
Beard et al., 1982	851	High
Sciarrone et al., 1992	1,196	Low
Todd et al., 2012	1,233	Moderate
Sacks et al., 2001	1,472[a] 1,541[b]	Low
Parker et al., 1990	1,564	Low
Morgan and Anderson, 1987	1,725	Moderate
Puska et al., 1983	1,771	Low
Nestel et al., 1993	1,771[c]	Low
Todd et al., 2010	1,794	Moderate

NOTES: This table includes rounded values. Sodium level achieved values are presented in milligrams. To convert the milligram value to mmol, divide the level by 23.0. AHRQ = Agency for Healthcare Research and Quality; mg/d = milligrams per day.

[a]Control diet intervention group.

[b]DASH (Dietary Approaches to Stop Hypertension) diet intervention group.

[c]Among female participants.

intake was reduced to below 1,800 mg/d (see Table 8-6). No deficiency symptoms were reported among the participants in these trials, and there was no pattern of adverse effects (see Chapter 9, Table 9-1).

- *Balance studies:* All balance studies had design limitations. In addition, only one study identified a sodium intake level that resulted in an approximately neutral balance at sodium intake of 1,525 mg/d (66 mmol/d) with daily heat stress (40°C [104°F] for 10 hours per day for 5 days). In contrast, this same intake in the same participants without heat stress resulted in positive balance (Allsopp et al., 1998). The committee determined that, among those assessed, the balance study by Allsopp et al. (1998) had the best study design for assessing adults, in that losses from sweat, feces, and urine were accounted for; in addition, this study demonstrated both approximately neutral and positive balance at 1,525 mg/d (66 mmol/d) of intake, dependent on temperature. Negative balance was reported with intakes of sodium from 230–2,210 mg/d whereas positive balance was reported with intakes as low as 1,525 mg/d (66 mmol/d; at 25°C [77°F]) (see Table 8-1).
- *Consideration of potential harmful health effects:* There is insufficient evidence that low sodium intakes are associated with potential

harmful health effects. The paradoxical J- and U-shaped relationships of sodium intake and cardiovascular disease and mortality are likely observed because of methodological limitations of the individual observational studies, particularly their sodium intake assessment methods.

Based on the lowest level of sodium intakes studied in the DASH-Sodium feeding trial and other sodium reduction trials and on the best-designed balanced study, a sodium AI of 1,500 mg/d (65 mmol/d) is appropriate for adults at normal ambient temperatures and not engaged in high-intensity physical activity. For individuals at high ambient temperature and/or performing high-intensity physical activity, a higher sodium intake level than the AI may be needed, but such a level could not be estimated at this time. Several of the randomized controlled trials included in the *AHRQ Systematic Review* reported allowing participants older than 70 years of age to be included in the study (Appel et al., 2001; Cappuccio et al., 2006; Howe et al., 1994; Hwang et al., 2014; Meland and Aamland, 2009; Nakano et al., 2016; Nestel et al., 1993; Schorr et al., 1996; Wing et al., 1998), but none were exclusively conducted in individuals in that age group. In addition, none of the best-designed balance studies included individuals in this age range. Based on this limited information, there are insufficient data to establish a sodium AI for individuals > 70 years of age that is different from the younger adult population. Based on the evidence presented above, all adults 19 years of age and older have a sodium AI of 1,500 mg/d (65 mmol/d) (see Table 8-7).

TABLE 8-7 Sodium Adequate Intakes, Adults 19 Years of Age and Older

DRI Age, Sex, and Life-Stage Group	Sodium Adequate Intake, mg/d
Males	
19–30 years	1,500
31–50 years	1,500
51–70 years	1,500
> 70 years	1,500
Females	
19–30 years	1,500
31–50 years	1,500
51–70 years	1,500
> 70 years	1,500

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. DRI = Dietary Reference Intake; mg/d = milligrams per day.

Pregnancy

Starting early in pregnancy, there are considerable increases in plasma volume, interstitial space, and intercellular water (Hytten, 1985; Picciano, 2003). With these expansions, there are also decreases in plasma osmolality and plasma sodium concentrations (Cheung and Lafayette, 2013). Expansion of the extracellular fluid indicates an alteration in the homeostasis of the total body water. This change is accompanied by increased cardiac output, reduced systolic blood pressure, and increased vascular perfusion of organs and tissues, all of which result in increased kidney volume. Additionally, there are increases in renal blood flow, the glomerular filtration rate, and tubular reabsorption of sodium. There is increased renal clearance of low-molecular-weight solutes and creatinine clearance progressively increases throughout gestation (Cheung and Lafayette, 2013). These changes are highly influenced by progesterone. In addition to inducing smooth muscle relaxation and vasodilation, progesterone also reduces the response of the distal tubules to aldosterone, although aldosterone production also increases in early pregnancy (Soma-Pillay et al., 2016).

Circulating concentrations of all elements of the RAAS increase during pregnancy. In populations with extremely low salt intake (e.g., the Yanomamo tribe), pregnant women had higher plasma renin activity and serum aldosterone concentrations compared to nonpregnant women and no adverse gestational outcomes were reported (Oliver et al., 1981). The range of physiological adaptations during pregnancy is not fully understood, such as the production of hormones involved in the regulation of body water and a decreased responsiveness of receptors, such as the renin angiotensin system, to these hormones (Cheung and Lafayette, 2013). Additionally, the relationship between sodium intake and these volume changes is not clear, nor is the role of sodium in maintaining total body water volume during gestation fully understood (Brown and Gallery, 1994; Duvekot et al., 1993; Schrier and Briner, 1991).

Sodium accretion during pregnancy ranges from 2,100–2,300 mg (90–100 mmol) of additional sodium over the gestational period, estimated to amount to an additional 69 mg/d (3 mmol) (IOM, 2005). These cumulative gains in total body sodium provide for the products of conception (fetus, placenta, and amniotic fluid), and maintain the rise in plasma volume and interstitial space (Brown and Gallery, 1994).

The committee agrees with the *2005 DRI Report* that there is a lack of evidence to suggest that sodium requirements of pregnant females differ from that of nonpregnant females. Accordingly, the sodium AI for pregnant females is determined to be 1,500 mg/d (65 mmol/d) (see Table 8-8).

TABLE 8-8 Sodium Adequate Intakes, Pregnant Females

DRI Age, Sex, and Life-Stage Group	Sodium Adequate Intake, mg/d
Pregnancy	
14–18 years	1,500
19–30 years	1,500
31–50 years	1,500

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, the intake value is divided by 23.0. DRI = Dietary Reference Intake; mg/d = milligrams per day.

TABLE 8-9 Sodium Adequate Intakes, Lactating Females

DRI Age, Sex, and Life-Stage Group	Sodium Adequate Intake, mg/d
Lactation	
14–18 years	1,500
19–30 years	1,500
31–50 years	1,500

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. DRI = Dietary Reference Intake; mg/d = milligrams per day.

Lactation

There is limited evidence regarding maternal sodium requirements during lactation. Sodium is excreted in breast milk (see the Infants 0–12 Month of Age section above), but the concentrations are determined by an electrical potential gradient, rather than by maternal dietary intake (IOM, 1991). To that end, the sodium requirements for lactating females does not appear to differ from that of nonpregnant, nonlactating females. Accordingly, the sodium AI for lactating females is determined to be 1,500 mg/d (65 mmol/d) (see Table 8-9).

SUMMARY OF UPDATED SODIUM ADEQUATE INTAKE VALUES

Aligned with the *2005 DRI Report*, limitations in the evidence precluded this committee from establishing sodium EARs and RDAs. As such, the sodium AIs were updated. This committee's derivation of the sodium AI integrates consideration of a different collection of evidence than what was used in the *2005 DRI Report*. Particularly, the committee not only considered evidence from the DASH-Sodium trial, but other trials that achieved low sodium intakes that did not report sodium deficiency among its participants. This committee also integrated into its consideration the best available balance study conducted among adults. The committee's review of potential harmful effects of low sodium intake revealed a heterogeneous

body of evidence, which is insufficient to identify health risks associated with low sodium intakes. The sodium AIs have been revised for infants 0–6 months of age, children and adolescents 1–13 years of age, and adults 51 years of age and older.[6] For infants 0–6 months of age, updated sodium AI stems from this committee's approach to estimating sodium concentrations in breast milk. For children and adolescents 1–18 years of age, the committee used sedentary EERs to extrapolate from the adult AI. This extrapolation approach differs from the approach used in the *2005 DRI Report*, which used energy estimates from proxy- and self-reported 24-hour dietary recalls to extrapolate. Finally, the *2005 DRI Report* used self-reported energy intake to extrapolate the sodium AI for adults 19–50 years of age to adults 51 years of age and older. This committee did not extrapolate for older adults owing to limited evidence, particularly with older adults. For context, a comparison of the sodium AIs established in this report and those that were established in the *2005 DRI Report* are presented in Table 8-10.

[6]This text was revised since the prepublication release.

TABLE 8-10 Comparison of Sodium Adequate Intakes Established in This Report to Sodium Adequate Intakes Established in the *2005 DRI Report*

DRI Age, Sex, and Life-Stage Group	Sodium AI Established in the *2005 DRI Report* (mg/d)	Updated Sodium AI Values (mg/d)
Infants		
0–6 months	120	110
7–12 months	370	370
Children		
1–3 years	1,000	800
4–8 years	1,200	1,000
Males		
9–13 years	1,500	1,200
14–18 years	1,500	1,500
19–30 years	1,500	1,500
31–50 years	1,500	1,500
51–70 years	1,300	1,500
> 70 years	1,200	1,500
Females		
9–13 years	1,500	1,200
14–18 years	1,500	1,500
19–30 years	1,500	1,500
31–50 years	1,500	1,500
51–70 years	1,300	1,500
> 70 years	1,200	1,500
Pregnancy		
14–18 years	1,500	1,500
19–30 years	1,500	1,500
31–50 years	1,500	1,500
Lactation		
14–18 years	1,500	1,500
19–30 years	1,500	1,500
31–50 years	1,500	1,500

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. AI = Adequate Intake; DRI = Dietary Reference Intake; mg/d = milligrams per day.

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9

Sodium: Dietary Reference Intakes for Toxicity

The Tolerable Upper Intake Level (UL) specifies the highest average daily intake level of a nutrient, consumed on a habitual basis, that is likely to pose no risk of adverse health effects for nearly all apparently healthy individuals in a given Dietary Reference Intake (DRI) age, sex, and life-stage group. The potential for adverse health effects increases as intakes increase above the UL. The UL is intended to provide guidance on intake levels that are safe; it is not intended to serve as an intake goal. The *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) recommended that the UL be retained in the expanded DRI model, but that it should characterize *toxicological* risk (NASEM, 2017). Although this conceptual revision narrows the scope of the UL, it allows for a more nuanced characterization of the different types of risk that can exist with intake of a nutrient or other food substance. This chapter presents the committee's review of the evidence on the toxicological effects of excessive sodium intake and its conclusion regarding establishing a sodium UL. For context, the committee's findings are preceded by a brief summary of the decision made regarding the sodium UL in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005).

SODIUM TOLERABLE UPPER INTAKE LEVELS ESTABLISHED IN THE *2005 DRI REPORT*

To determine if a UL could be established, the *2005 DRI Report* assessed evidence on the relationship between sodium intake and the fol-

lowing indicators: blood pressure; stroke; coronary heart disease; left ventricular mass; calcium excretion, bone mineral density, and kidney stones; pulmonary function; and gastric cancer. Evidence for a relationship between sodium intake and blood pressure, which was described as "direct and progressive" (IOM, 2005, p. 378), ultimately served as the basis for the UL in the *2005 DRI Report*. The lowest-observed-adverse-effect level (LOAEL) was informed by three multidose sodium trials (Johnson et al., 2001; MacGregor et al., 1989; Sacks et al., 2001),[1] and it was determined to be the next lowest sodium intake level above the Adequate Intake (AI). A no-observed-adverse-effect level could not be identified owing to the continuous relationship between sodium intake and blood pressure. No uncertainty factor was applied to the LOAEL. A sodium UL of 2,300 mg/d (100 mmol/d) was set for all adult DRI age, sex, and life-stage groups; the UL for children and adolescents 1–18 years of age was extrapolated from the adult UL, based on median energy intake from the 1994–1996 Continuing Survey of Food Intakes by Individuals.

REVIEW OF POTENTIAL INDICATORS OF TOXICOLOGICAL ADVERSE EFFECTS OF EXCESSIVE SODIUM INTAKE

The expanded DRI model shifts consideration of evidence on the relationship between intake and chronic disease indicators to DRIs based on chronic disease. As such, the approach to establish the sodium UL in this report differs from the approach taken in the *2005 DRI Report*. For instance, evidence on the relationships between sodium intake and blood pressure, stroke, coronary heart disease, left ventricular mass, bone-related indicators, and kidney disease was reviewed in the *2005 DRI Report* as potentially informing the UL, but it is now considered in the context of establishing sodium Chronic Disease Risk Reduction Intakes (CDRRs; see Chapter 10). Similarly, evidence on relationships between sodium intake and pulmonary function and gastric cancer would now be considered as potentially informing the sodium CDRR; however, as described in Appendix D, the available evidence did not support use of these indicators.

For ethical reasons, trials cannot be designed to evaluate whether an intervention will increase the incidence of adverse effects. Consequently, adverse effect data in trials are almost always secondary outcomes. These data, particularly if systematically and carefully reported, can provide use-

[1]Sacks et al. (2001) was included in the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), but the other two studies were not. The *AHRQ Systematic Review* excluded Johnson et al. (2001) on the basis of the timing not being of interest and excluded MacGregor et al. (1989) on the basis of study design.

ful information for evaluating the likelihood of adverse effects. However, as secondary outcomes, these trials may not be adequately powered to identify a statistically significant occurrence of an adverse effect. These strengths and limitations need to be taken into account when using data from trials for evaluating the potential for adverse effects.

Guided by the first step of the DRI organizing framework, the committee sought to identify potential indicators of toxicological adverse effects from excessive sodium intake. The sections that follow describe the evidence the committee reviewed to identify indicators that could potentially inform the derivation of the sodium UL, as well as summarize the evidence on the potential indicator identified.

Evidence Reviewed to Identify Potential Toxicological Indicators

The committee conducted a literature scan to identify potential indicators that may be informative for the sodium DRIs (see Appendix D), but it did not reveal any potential indicator of sodium toxicity, separate from consideration of chronic disease–related indicators. Additional exploration of systematic reviews and case reports on toxicity, adverse effects, and poisonings from sodium intake were undertaken in an effort to identify potential toxicological adverse effects. From these efforts, the committee identified a collection of case reports on deaths attributed to high levels of sodium intake. The committee also compiled reported adverse effects of the sodium trials included in the Agency for Healthcare Research and Quality's systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), and the committee's supplemental literature searches. The committee notes that the doses used in trials are generally not high enough to cause serious adverse effects, as it would be unethical to randomize participants to such an exposure. The intent of these evidence searches was to identify specific indicators that could potentially inform the sodium UL. The evidence that was compiled is described below.

Case Reports of Death

Several case reports exist in the literature regarding lethal levels of sodium intake, primarily attributable to the ingestion of massive acute doses. A 2017 systematic review summarized evidence on 35 fatalities from acute ingestion of massive doses of salt (Campbell and Train, 2017). Explanations of the massive acute intakes included salt being mistaken for sugar, used as an emetic, used in exorcism rituals, or, in some of the case reports about children, administered by a parent. All cases that documented sodium blood concentrations reported concentrations exceeding 150 mmol/L, indi-

cating hypernatremia. Many, but not all, of the cases included co-ingestion of other potential toxins (e.g., medications for anxiety, depression, schizophrenia) and occurred in individuals with chronic conditions or illnesses (e.g., depression, psychiatric disease, Prader-Willi syndrome).

The estimated level of sodium intake varied across the case reports. The lowest level of sodium intake among the adult cases was estimated to be between 6,800 and 10,200 mg (296 and 444 mmol), ingested as a saline emetic for a suspected antipsychotic medication poisoning in a 48-year-old female (Gresham and Mashru, 1982). In a case of an 83-year-old female with hypertension and dementia, sodium intake was estimated to be between 13,600 and 20,400 mg (592 and 887 mmol) (Engjom and Kildahl-Andersen, 2008). Substantially higher intakes were also reported, including 273,000 mg (11,875 mmol) of sodium consumed by a 34-year-old female (Raya et al., 1992) and less than 400,000 mg (17,399 mmol) of sodium by a 20-year-old female with psychiatric disorders (Ofran et al., 2004). Among children, the lower levels of intake that resulted in death among the identified case reports included an estimated 5,000 mg (219 mmol) of sodium in a 7-month-old female (Martos Sanchez et al., 2000) and less than 7,000 mg (304 mmol) in a 2-year-old with gastrointestinal strictures (Scott and Rotondo, 1947). The estimated doses of sodium intake among children, however, were largely not reported.

Case reports provide evidence that acute ingestion of large doses of sodium, including rapid ingestion of salt in liquid solution, can lead to death. Collectively, the case reports provide information about limits of biological homeostatic controls related to sodium, but they do not necessarily reflect the toxicological effects of habitually elevated intake levels suitable for establishing a sodium UL. In many of the cases, sodium was co-ingested with other potential toxins (e.g., medications), and most poisonings occurred in individuals with coexisting conditions and illnesses. Not all of the case reports provided the dose of sodium ingested. In cases where the level of intake was reported, the amount was often estimated because it was not possible to determine the exact quantity consumed. The absence or imprecision of intake estimates leading to death, coupled with the acute nature of the excessive sodium intake, limits the committee's ability to use these case reports to inform the sodium UL.

Hypernatremia was also described in the case reports. In general, hypernatremia is associated with symptoms such as nausea, vomiting, headache, and fever but does not always result in death. Hypernatremia was determined not to be an informative indicator of sodium toxicity, as it is typically caused by severe dehydration rather than excessive sodium intake (Adrogué and Madias, 2000; Sterns, 2015). The case reports did not reveal any other potential indicators of sodium toxicity.

Adverse Events Reported in Sodium Trials

The *AHRQ Systematic Review* did not have a key question regarding adverse events in sodium trials, but it provided a brief summary of commonly reported adverse events in the context of sodium reduction. Building on this work, the committee reviewed descriptions of adverse events reported in trials meeting the inclusion criteria for the *AHRQ Systematic Review* and the committee's supplemental literature searches (see Table 9-1).

As outlined in Table 9-1, participants were varied and included healthy normotensive adults, adults with treated and untreated hypertension, pregnant women, and children. Several of the smaller studies did not report marked differences in adverse events between the high- and low-sodium intervention periods (crossover trials) or groups (parallel randomized controlled trials). There was little consistency of the types of adverse events reported and the extent to which they differed between the intervention periods or arms. However, two findings emerged from this review of evidence. First, the crossover studies by Todd et al. (2010, 2012) provide some evidence regarding the level of intake associated with adverse effects. This finding is further considered below. Second, among the reported adverse events, some trials reported reduction of headaches among those in the lower-sodium intervention period or arm. Given this, the committee explored the evidence on headaches as a potential indicator of sodium toxicity in the next section.

Todd et al. (2010) assessed 34 adults with hypertension during three different sodium interventions in a crossover study. Throughout, participants consumed a diet containing 1,380 mg/d (60 mmol/d) sodium. In a random order, participants added to their low-sodium diet 500 mL of tomato juice containing 0, 2,070, or 3,220 mg/d (0, 90, or 140 mmol/d) sodium for a period of 4 weeks each. The investigators reported that seven of the participants withdrew from the highest sodium period because of elevated blood pressure and other symptomology. Only one participant withdrew from the moderate sodium period. In Todd et al. (2012), the tomato juice trial was conducted in 23 normotensive adults. The design was similar to that which was conducted in adults with hypertension, except the highest dose of sodium provided in the tomato juice was 4,370 mg/d (190 mmol/d) rather than 3,220 mg/d (140 mmol/d). Nine of the first 10 participants who completed the highest sodium period reportedly experienced adverse effects, leading the investigators to reduce the amount of sodium in the tomato juice during the highest period to 3,220 mg/d (140 mmol/d). The reduction in sodium content of the tomato juice did not change reported bloating, but it did improve other symptoms experienced (included frequency of cramps

TABLE 9-1 Sodium Trials Included in the *AHRQ Systematic Review* and the Committee's Supplemental Literature Search That Provided a Description of Adverse Events

Reference	Duration, Weeks[a]	Participants
Crossover Studies		
Kwakernaak et al., 2014	6	45 Dutch adults, mean 65 ± 9 years of age, with type 2 diabetes nephropathy on ACE inhibitor
Wing et al., 1998	6	17 Australian adults, 37–74 years of age, with hypertension, administered ACE inhibitor throughout
Sacks et al., 2001[c,d]	4	390 U.S. adults, at least 22 years of age, with SBP 120–159 mm Hg and DBP 80–95 mm Hg
Weir et al., 2010	4	132 U.S. adults, ≤ 60 years of age, with SBP ≥ 135 but < 160 mm Hg, receiving antihypertensive medication
Todd et al., 2010	4	34 New Zealand adults, 20–65 years of age, with BP > 130/85 or treated with antihypertensive therapy
Todd et al., 2012	4	23 normotensive New Zealand adults, 24–61 years of age
Singer et al., 1991	4	21 British adults, mean 53.9 ± 2.5 years of age, with hypertension, treated with a converting enzyme inhibitor and a diuretic

Mean Achieved Urinary Sodium Excretion by Sodium Intake Group, mmol/d			
Low	Moderate	High[b]	Description of Adverse Events
148	N/A	224	No serious adverse events occurred
99	N/A	158	No significant differences in adverse events between periods
67/64[e]	107/106[e]	144/141[e]	Fewer symptoms reported during periods of reduced sodium intake Fewer reports of headache during the low-sodium period (DASH and control diets), as compared to high-sodium control period No difference in blood lipids[f]
85	N/A	208	Proportion of participants reporting an adverse event similar between both high- and low-sodium periods 1 participant withdrew during low-sodium period because of dizziness and asthenia During low-sodium period, slightly greater proportion reported dizziness, fatigue, and diarrhea During high-sodium period, slightly greater proportion reported headaches and musculoskeletal and connective tissue disorders
78[g]	173[g]	215[g]	1 participant withdrawn from moderate-sodium period because of elevated BP[b] and peripheral fluid retention 7 participants withdrawn from high-sodium period because of elevated BP and symptoms of headaches, nausea, vomiting, frequent bowel motions, fluid retention, or general ill feelings No differences in insulin sensitivity across periods
54[g]	144[g]	190[g]/240[i]	9 of 10 participants completing high sodium intake intervention at 5,750 mg/d (250 mmol/d) sodium experienced side effects Bloating did not change, but reporting of other symptoms reduced after content of high-sodium period was reduced from 5,750–4,600 mg/d (250–200 mmol/d) sodium[j]
104	N/A	195	All participants completed study without adverse effects

continued

TABLE 9-1 Continued

Reference	Duration, Weeks[a]	Participants
Schorr et al., 1996	4	16 healthy, normotensive German adults, 60–72 years of age
Parallel Randomized Controlled Trials		
Appel et al., 2001; Whelton et al., 1998	116[l]	639 U.S. adults, 60–80 years of age, with BP < 145/85 while receiving antihypertensive medication[m]
TOHP Collaborative Research Group, 1992	72	744 U.S. adults, 30–54 years of age, with high normal DBP, not taking antihypertensive medication[m]
Bulpitt et al., 1984	12	65 British adults, mean 54 years of age, on drug treatment for hypertension with DBP > 95 mm Hg
Beard et al., 1982	12	90 Australian adults, 25–69 years of age, with mild hypertension
Hwang et al., 2014[q]	8	242 nondiabetic, Korean adults with hypertension and albuminuria, mean 49.5 years of age, treated with angiotensin II blocker therapy throughout trial
Meland and Aamland, 2009	8	46 Norwegian adults, 20–75 years of age, with hypertension inadequately controlled by drug treatment
Sciarrone et al., 1992	8	91 hypertensive, Australian adults, 20–69 years of age, < 120% ideal body weight, BP > 130/80 mmHg (untreated) or 125/85 mm Hg (treated)
Puska et al., 1983	6	72 Finnish adults, 30–50 years of age, free from major health problems, not undergoing antihypertensive treatment at baseline[m]
Knuist et al., 1998	NR	361 nulliparous, Dutch women, mean 28 years of age, who had a rise in BP, excessive weight gain, or edema identified during a prenatal visit

Mean Achieved Urinary Sodium Excretion by Sodium Intake Group, mmol/d			
Low	Moderate	High[b]	Description of Adverse Events
105	N/A	125/175[k]	Sodium interventions did not have deleterious effects on metabolic parameters of glucose tolerance or plasma lipids Urinary calcium excretion decreased significantly during the sodium bicarbonate period, but increased during the sodium chloride period
99	N/A	140	Sodium reduction was associated with a significant decrease in the rate of headaches No between-group differences in number of individuals reporting other adverse events[n]
99	N/A	145	Significant improvements in the Psychological General Well-Being scale observed in the sodium-reduction group
102[o]	N/A	161[p]	Reports of transient unsteadiness and faintness increased in the low-sodium group and decreased in the high-sodium group
37	N/A	161	Lower sodium group reported they felt happier, had less depression, and used fewer analgesics Both groups reported slight improvements in mild and severe muscle cramps
122	N/A	146	2 participants in the low-sodium group dropped out because of elevated serum creatinine levels 1 participant in the high-sodium group withdrew because of headache
83[r]	N/A	126[r]	No differences in measures of insulin, glucose, and blood lipids
52	N/A	134	HDL-C slightly reduced in the low-sodium groups compared with the normal-sodium groups No significant difference in the change in total cholesterol to HDL-C ratio between sodium groups
77	NA	167	2 participants in the low-sodium group developed hypertension and began antihypertensive treatment[s] 1 participant in the low-sodium group developed significant polyuria
84	N/A	124	No difference in obstetric outcomes

continued

TABLE 9-1 Continued

Reference	Duration, Weeks[a]	Participants
van Buul et al., 1997	26[t]	242 healthy, nulliparous, pregnant, Dutch women, mean age 28 years
Steegers et al., 1991	26[t]	42 healthy, nulliparous, Dutch women, 20–35 years of age, with singleton pregnancies
Gillum et al., 1981	52	64 U.S. children, 6–9 years of age, with BP > 95th percentile for age and sex, but below 130/90 mm Hg[v]

NOTES: Adverse events in the table reflect those reported by the study authors. Omitted from this table are mortality or cardiovascular disease adverse events, unless such occurrences were included in the description of participant withdrawal from the study. Urinary excretion and intake values are presented in mmol. To convert the mmol value to milligrams, multiply the excretion or intake level by 23.0. ACE = angiotensin-converting enzyme; BP = blood pressure; DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein-cholesterol; mm Hg = millimeter mercury; N/A = not applicable; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention.

[a]For crossover trials, duration is per dietary period.

[b]This group represents the period or group intended to have the highest level of sodium intake in the study. In several studies, this group reflects usual sodium intake.

[c]Participants were assigned to either the DASH diet (n = 208) or a control diet (n = 204). Within the diet assignment, participants consumed three different levels of sodium.

[d]Daily sodium intake was proportionate to total energy intake of each individual participant.

[e]Presented as mean urinary sodium excretion for the DASH diet arm/control diet arm, respectively.

[f]This finding was reported in a separate publication (Harsha et al., 2004).

[g]Urinary sodium was reported as urinary sodium-to-creatinine ratio. Estimates in the table reflect the estimated amount of dietary sodium consumed. In both studies, participants consumed a low-sodium diet (60 mmol/d) and then received 0, 90, or 140 mmol/d of additional sodium through tomato juice.

[h]Threshold for withdrawal in the study was blood pressure > 160/100 mm Hg.

[i]Participants consumed a low-sodium diet (60 mmol/d) throughout the study. The highest dose of sodium provided in the tomato juice began at 190 mmol/d, but was reduced to 140 mmol/d due to adverse events.

[j]Included frequency of cramps upon exercising, joint pain, vomiting, headaches, shortness of breath, and other reported symptoms.

[k]Presented as 24-hour urinary sodium excretion during the high–sodium bicarbonate period and high–sodium chloride period, respectively.

[l]Median length of follow-up.

Mean Achieved Urinary Sodium Excretion by Sodium Intake Group, mmol/d			
Low	Moderate	High[b]	Description of Adverse Events
~70	N/A	~132	Maternal weight gain was lower in the low-sodium group No difference in obstetric outcomes
~50[u]	N/A	~145	Maternal weight gain was lower in the low-sodium group Dietary intake of nutrients significantly lower in the low-sodium group No difference in obstetric outcomes
~74[w,x]	N/A	~84[x,y]	No adverse effects of intervention on growth or development

[m]Publication included other intervention arms not specific to sodium only, which are not included in this table.

[n]As reported in Appel et al., 2001, examined adverse events included excessive weight loss, physical injury from exercise, palpitations, nonischemic chest pain, dizziness, edema, excessive weight gain, or other adverse events.

[o]The publication reported average 48-hour urine to be 204 ± 33 mmol. Value was divided in half to obtain the 24-hour estimate reported in this table.

[p]The publication reported average 48-hour urine to be 321 ± 36 mmol. Value was divided in half to obtain the 24-hour estimate reported in this table.

[q]Conventional low-salt diet education versus intensive low-salt intervention. Both groups received angiotensin II receptor blocker throughout the trial.

[r]Between-group difference in urinary sodium excretion was reported to be 38 mmol. Baseline urinary sodium excretion was 93 mmol/d in the low-sodium group and 98 mmol/d in the high-sodium group.

[s]Identified after the end of the study. Data were removed from analyses.

[t]Intervention was started in the 14th week of pregnancy and stopped at delivery. Duration in this table assumes length of pregnancy is 40 weeks.

[u]Publication states that urinary sodium excretion in the low-sodium group was approximately one-third that of the unrestricted group. Values could not be determined from the figure in the publication. Values in this table are based on baseline values of 24-hour sodium excretion in the unrestricted group.

[v]Number of participants in this table reflect the number of children randomized. Only 17 of the 41 randomized to the intervention completed the full program.

[w]Reflects 32 children randomized to the intervention, including those who dropped out. Baseline sodium excretion was lower among those who actively participated in the program than those in the control group and those who dropped out.

[x]Values expressed in the publication were mmol/10 hours, based on an overnight urine collection. Estimates presented in the publication were multiplied by 2.4 to approximate 24-hour excretion.

[y]Reflects 32 children randomized to the control group. Baseline sodium excretion was higher among those in the control group than those who actively participated in the program.

upon exercising, vomiting, joint pain, headaches, shortness of breath, and other symptoms).

The committee considered whether the two studies by Todd et al. (2010, 2012) could be used to derive a sodium UL, as both studies provide evidence of an intake–response relationship. Factoring into the committee's decision were the strengths and limitations of using the available data for such a purpose. The two studies are among the few publications included in the *AHRQ Systematic Review* that evaluated multiple doses of sodium intake, including an elevated intake level. Furthermore, the reported adverse effects were documented in both adults with hypertension and normotensive adults, suggesting implications for the general population. The studies, however, lacked key information about ingestion of the sodium and the adverse events. Neither the publications nor the clinical trial registry for the studies (ANZCTR, 2010) provided information regarding how participants were instructed to consume the tomato juice and how the participants operationalized the protocol. Interpretation of the reported adverse events would likely differ if participants consumed the 500 mL of tomato juice as a single bolus without food, as opposed to consuming portions over the course of the day with food. Furthermore, the derivation of a UL is driven by the identification of an indicator of toxicological adverse effects. The two studies did not sufficiently characterize the reported symptomology (e.g., level of severity, number of participants reporting each symptom, temporal relationship with ingestion of the tomato juice); furthermore, no specific indicator could be identified from either study. Todd et al. (2010, 2012) provide key evidence of adverse effects from consumption of concentrated sources of sodium. However, the uncertainties about the consumption of the sodium interventions and the limited characterization of the adverse effects prevented the committee from using these two studies to establish sodium ULs.

Review of Evidence on a Potential Indicator

Headaches[2]

In the Trial of Nonpharmacologic Interventions in the Elderly (TONE), 681 participants 60–80 years of age with hypertension (systolic blood pressure less than 145 mm Hg and diastolic blood pressure less than 85 mm Hg while taking one antihypertensive medication) were randomized to a reduced sodium intervention or control (Appel et al., 2001). On average, sodium intake in the intervention group was 920 mg/d (40 mmol/d) lower

[2]Evidence presented in this section were gathered through the committee's supplemental literature search and information-gathering activities (see Appendix E).

compared to the control group,[3] and systolic and diastolic blood pressures were 4.3 and 2.0 mm Hg lower, respectively. Headache was less frequently self-reported as an adverse event in the intervention group compared to the control group (35 versus 54 individuals, rates not given, $p = .04$). In a follow-up study of headache in 975 individuals in TONE,[4] of which 90 percent had some follow-up, cumulative incidence of headache in the group not randomized to a sodium reduction intervention (i.e., usual care or weight loss intervention) was 14.3 percent compared to 10.5 percent in those randomized to a sodium intervention (i.e., sodium reduction alone, or in combination with weight loss) ($p = .012$) (Chen et al., 2016). Adjustment for systolic and diastolic blood pressure did not have an appreciable impact on the study results. As compared to the usual care group, the intervention group that was only sodium reduction (i.e., excluding those in the combined sodium reduction and weight loss arm) had reduced hazards of headaches (hazard ratio = 0.61 [95% confidence interval {CI}: 0.39, 0.95]; $p = .03$). In analyses that considered 24-hour urinary sodium excretion, each 230 mg/d (10 mmol/d) increase in sodium excretion was associated with a 7 percent increase in the hazard for headaches ($p \leq .001$); this relationship persisted after adjustment for systolic and diastolic blood pressure. There was evidence of a nonlinear effect, with the greatest effect on headache above 3,449 mg/d (150 mmol/d) sodium.

In the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial, 412 participants who were classified as having prehypertension or stage I hypertension were randomized to one of two parallel diet arms (DASH versus control), and within these diet arms participants consumed three levels of sodium for 30 days each in a crossover feeding study (Sacks et al., 2001). In the control arm, headache occurred in 47 percent of participants during the high-sodium feeding period compared with 39 percent during the low-sodium period ($p < .05$). In a follow-up analysis of headache in the DASH-Sodium trial (Amer et al., 2014), headache incidence was 47, 41, and 39 percent for the high-, intermediate-, and low-sodium periods of the control diet arm, and 43, 38, and 36 percent for the high-, intermediate-, and low-sodium periods of the DASH diet arm. In models adjusted for age, sex, race, site, systolic blood pressure, body mass index, smoking, and carryover effects, there were no significant differences between the DASH diet and control diet within sodium level. Controlling for these same covariates, there were significant differences between high and low sodium within each

[3]As assessed through 24-hour urinary sodium excretion. Mean baseline 24-hour urinary excretion was 3,311 mg/d (144 mmol/d) among the intervention group, and 3,334 mg/d (145 mmol/d) among the control group.

[4]The sample size is larger in this report on TONE, as compared to Appel et al. (2001), as it includes participants who were randomized to the weight loss or combined weight loss and sodium reduction interventions.

diet arm (DASH, $p = .04$; control, $p = .05$). Although no test for trend was reported, the decreased headache incidence by sodium level across groups is supportive of an intake–response relationship.

Committee's synthesis of the evidence Headaches were reported to be reduced during the lower-sodium period or in the lower-sodium group in some of the trials included in the *AHRQ Systematic Review* (see Table 9-1). Headaches occur commonly among the general population for a variety of reasons, many of which are unknown. The available studies generally lacked detailed information about the type, severity, duration, and frequency of headaches. The persistence or transience of the headache response is also not well characterized. Although post-hoc statistical adjustments suggested that the headache effects may be independent of blood pressure effects, more data are needed to understand if and how headache and blood pressure effects are related and the interplay of sodium intake. Headache was prevalent at low sodium intakes and, as such, there is a lack of information that might be used to identify no-effect or minimum effect intakes for sodium-induced headaches, both of which are important for UL development. Thus, while the committee acknowledges that there is evidence of a relationship between sodium intake and headaches, the uncertainties in the evidence preclude using headaches as a critical adverse effect to establish a sodium UL. The committee, however, notes that the same studies used to evaluate headaches are also part of the evidence base used to establish the sodium CDRR. Therefore, this latter DRI value will cover the range of intakes associated with headache.

THE COMMITTEE'S CONCLUSION REGARDING THE TOLERABLE UPPER INTAKE LEVELS FOR SODIUM

Extreme intakes of sodium, especially ingested as a massive acute dose, have been shown to cause severe adverse effects, including death. Two studies provide evidence that a higher concentration of sodium delivered through tomato juice resulted in more adverse effects than when the same volume of tomato juice had a lower concentration of sodium or no sodium at all (Todd et al., 2010, 2012). Additionally, some sodium trials have indicated changes in the occurrence of headaches with changes in sodium intake, but questions remain regarding the nature and severity of the reported headaches. However, without a specific indicator of a toxicological effect of high sodium intake that can be used to establish a quantitative relationship, the committee concluded that a sodium UL cannot be established.

The committee concludes that there is insufficient evidence of sodium toxicity risk within the apparently healthy population to establish a sodium Tolerable Upper Intake Level (UL).

Cautions are in order regarding the possible adverse consequences of excessive sodium consumption, particularly in the concentrated doses. The limitations that exist in the evidence highlight the need for future monitoring and research opportunities (see Chapter 12).

Conclusion in the Context of the Expanded DRI Model

DRIs based on chronic disease allow for the relationship between intake and chronic disease risk to be characterized under a new DRI category, rather than being embedded in the decision-making process for other DRI categories (e.g., AI, UL). ULs previously have been established based on any type of critical adverse effect attributable to excessive intake of the nutrient or other food substance. As per the guidance provided in the *Guiding Principles Report*, the expanded DRI model now focuses the UL on characterizing toxicological risk attributable to excessive intake and the new DRI category on characterizing the relationship between intake and chronic disease risk.

In the expanded DRI model, there may be scenarios in which chronic disease risk is reduced by increasing intake of a nutrient or other food substance (see Chapter 2, Figure 2-1). Conceptually, a UL could have added value in such a scenario to ensure increases in intakes are not entering a range in which the benefits of reducing chronic disease risk are outweighed by the risk of inducing a toxic response. In the case of sodium, however, the CDRR indicates that risks of cardiovascular disease decrease with reductions in sodium intake (see Chapter 10). Because the sodium CDRR indicates there are benefits from decreasing intakes, the committee views the absence of a sodium UL as less critical. Nonetheless, the absence of a sodium UL does not necessarily mean excessive sodium intakes pose no risks, but rather likely reflects a lack of evidence on adverse toxicological effects.

Conclusion in the Context of the Sodium DRIs Established in the *2005 DRI Report*

The committee's decision not to establish a sodium UL may appear to be a departure from the decisions made in the *2005 DRI Report*. However, this apparent change cannot be meaningfully interpreted without considering the recent expansion of the DRI model. In the absence of recommendations or guidance on how to use chronic disease endpoints in the DRI

process, the sodium UL established in the *2005 DRI Report* was based on the direct and progressive relationship between sodium intake and blood pressure. Blood pressure was characterized as being a biomarker for "several diseases of substantial public health importance," including cardiovascular diseases and end-stage renal disease (IOM, 2005, p. 376). With the expansion of the DRI model, evidence that was used to derive the sodium UL in the *2005 DRI Report* was considered by this committee in context of deriving a sodium CDRR (see Chapter 10). Thus, the lack of a sodium UL does not reflect a change in the state of the evidence of the risk associated with excessive sodium intake; rather it reflects a change in the model on how risk is characterized in the DRIs.

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10

Sodium: Dietary Reference Intakes Based on Chronic Disease

This chapter presents the evidence on indicators to inform the sodium Chronic Disease Risk Reduction Intake (CDRR) and the committee's derivation of CDRR reference values for the Dietary Reference Intake (DRI) age, sex, and life-stage groups. In its application of the *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) (NASEM, 2017), the committee first reviewed the evidence on potential indicators and assessed the strength of evidence for causal relationships using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. This assessment informed the selection of biologically interrelated indicators with moderate or high strength of evidence for causal relationships. The committee characterized and graded the intake–response relationships between sodium intake and the selected indicators, which informed the sodium CDRR values.[1]

REVIEW AND SELECTION OF CHRONIC DISEASE INDICATORS

The *Guiding Principles Report* recommended:

> The ideal outcome used to establish chronic disease [DRIs] should be the chronic disease of interest, as defined by accepted diagnostic criteria,

[1]The terminology "intake–response" is used for consistency with the DRI organizing framework (see Chapter 1, Box 1-2) and the *Guiding Principles Report* (NASEM, 2017). Terminology commonly used in the literature and under the GRADE system is "dose–response."

> including composite endpoints, when applicable. Surrogate markers could be considered with the goal of using the findings as supporting information of results based on the chronic disease of interest. (NASEM, 2017, p. 123)

In accordance with this guidance and the first step of the DRI organizing framework (see Chapter 1, Box 1-2), the committee reviewed evidence for the causal relationship between sodium intake and indicators that could potentially inform the sodium CDRRs, which included chronic disease endpoints and surrogate markers (see Table 10-1).

Evidence on the relationship between sodium intake and the potential indicators reviewed in this chapter was drawn primarily from the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018). The evidence contained herein therefore reflects the methodologies taken in the *AHRQ Systematic Review*, including the approach to the literature search and application of the inclusion/exclusion criteria. The section that follows describes the committee's approach to using the evidence provided in the

TABLE 10-1 Potential Chronic Disease Indicators Reviewed for a Causal Relationship with Sodium Intake, in Order of Presentation

Indicator	*2005 DRI Report*	*AHRQ Systematic Review*	Committee's Supplemental Literature Search
Cardiovascular disease morbidity and mortality		X	
Hypertension	X	X	
Blood pressure	X	X	
Cardiovascular disease mortality[a]	X	X	
Stroke[a]	X	X	
Myocardial infarction[a]		X	
Left ventricular mass and gross morbidity[a]	X[b]	X	
Osteoporosis and related indicators[a]	X[c]		X
Kidney disease[a]		X	
All-cause mortality[a]		X	

NOTE: AHRQ = Agency for Healthcare Research and Quality; DRI = Dietary Reference Intake.

[a]Indicators were reviewed as potentially informing the sodium CDRRs, but were ultimately not selected. A summary of evidence on these indicators is presented in Annex 10-1.

[b]The *2005 DRI Report* reviewed evidence on left ventricular mass.

[c]The *2005 DRI Report* reviewed evidence on bone demineralization.

AHRQ Systematic Review. The committee also conducted supplementary literature searches for select indicators not included in the *AHRQ Systematic Review* (for additional information, see Appendixes D and E).

Approach to Reviewing Indicators

Use of Different Study Designs

In its application of the *Guiding Principles Report* (NASEM, 2017), the committee considered the use of evidence from different study designs in its derivation of the sodium CDRRs. As compared to randomized controlled trials, observational studies are inherently weaker for establishing causal relationships and begin at a lower strength of evidence rating in the GRADE system (Guyatt et al., 2011a). The strength of evidence from observational studies can be upgraded, for instance, when the relationship cannot be explained by uncontrolled confounding, when there is a large effect size, or when there is a strong intake–response relationship.

Observational studies exploring relationships between sodium intake and chronic disease outcomes often have methodological issues (Cobb et al., 2014). The *AHRQ Systematic Review* accounted for such issues by assessing the risk of bias of individual studies, which was one of the domains used to determine the strength-of-evidence grade for the body of evidence. Nearly all observational studies that met the inclusion criteria for the *AHRQ Systematic Review* were rated as having moderate or high overall risk of bias (Newberry et al., 2018). The *AHRQ Systematic Review*, in turn, rated the strength of the body of evidence for associations between sodium intake and each of the indicators was assessed as either low or insufficient (Newberry et al., 2018). The *AHRQ Systematic Review* did not conduct meta-analyses on the results of these observational studies, as pooling results from observational studies with varied designs is not appropriate.

The committee reviewed the evidence from observational studies included in the *AHRQ Systematic Review* on potential J- or U-shaped relationships between sodium intake and health outcomes (for details on the committee's assessment of the evidence, see Chapter 8). Certain intake assessment methodologies that are often used in observational studies produce estimates of sodium intake with systematic and random errors that can lead to spurious changes in size and directionality of the overall effect on the outcome of interest (for strengths and limitations of common sodium intake assessment methodologies, see Chapter 3). Therefore, in agreement with the *AHRQ Systematic Review*, the committee found insufficient evidence for an inverse relationship between low sodium intake levels (below 2,300 mg/d [100 mmol/d]) and risk of

the following health outcomes: all-cause mortality, cardiovascular disease mortality, combined cardiovascular disease morbidity and mortality, and heart failure.

Given the limitations of the observational studies outlined above, the committee agreed with a concept described in the *AHRQ Systematic Review*, which stated that "if the [randomized controlled trial] evidence is robust, observational studies may not contribute to strengthening the evidence unless they are high quality studies with large, precise effect sizes" (Newberry et al., 2018, p. 23). The committee therefore decided that if there was sufficient strength of evidence from trials alone, only such evidence would be used to establish the sodium CDRRs. Individual observational studies rated as having low risk of bias could serve as supportive evidence, particularly when evidence from randomized controlled trials were few or unavailable, but such studies would not serve as the sole evidence used to derive the sodium CDRRs. The committee acknowledges that relying primarily on randomized controlled trials limits the range of sodium intakes that have been evaluated. For example, the only studies on cardiovascular disease outcomes meeting the inclusion criteria of the *AHRQ Systematic Review* that characterized groups with sodium intakes below 2,300 mg/d (100 mmol/d) and above 4,100 mg/d (178 mmol/d) were observational. However, the insufficient strength of this body of evidence precluded the committee from using it to establish the sodium CDRRs. In sum, the committee focused primarily on evidence from randomized controlled trials and, as necessary, observational studies rated as having a low risk of bias.

Committee-Conducted Meta-Analyses

The committee rated the *AHRQ Systematic Review* as being of moderate quality, as guided by AMSTAR 2 criteria (for additional details, see Appendix C).[2] One of the domains that the *AHRQ Systematic Review* did not adequately cover relates to the investigation and explanation of the causes of heterogeneity in the results of meta-analyses. The committee determined that exploring sources of heterogeneity was essential for fully evaluating the strength of evidence, particularly when inconsistency was a concern in the body of evidence (for an explanation of the importance of explaining heterogeneity, see Chapter 2). Thus, the committee undertook analyses to explore any heterogeneity for four indicators:

[2]AMSTAR stands for A Measurement Tool to Assess Systematic Reviews.

cardiovascular disease morbidity and mortality, hypertension, systolic blood pressure, and diastolic blood pressure. Box 10-1 provides an overview of the committee's approach to the meta-analyses it conducted. For meta-analyses of more than 10 trials, the committee examined publication bias, which was not assessed in the *AHRQ Systematic Review* (see Box 10-1 for overview of methods used by the committee). The committee's approach also included evidence-based revisions to some of the data included in the *AHRQ Systematic Review* meta-analyses (see Box 10-2).

BOX 10-1
Overview of the Committee's Approach to Conducting Meta-Analyses and Assessing Publication Bias

Extracting Data

The committee extracted data from the studies included in the *AHRQ Systematic Review* meta-analyses, making corrections and extracting additional information as appropriate. Where available, hazard ratios from survival analysis were used rather than the relative risks calculated from proportions in the *AHRQ Systematic Review*.*

Conducting Meta-Analyses

The committee conducted random-effects meta-analyses, following standard procedures recommended for Cochrane reviews (Deeks et al., 2008) and AHRQ reviews (AHRQ, 2014), but it recognizes the diversity of opinions in the scientific community regarding which is the most appropriate model. For example, when using a random-effects model, the small outlier studies may receive disproportionate weight in the overall effect size, particularly when the between-study variance is high (Deeks et al., 2008). Recognizing this limitation of random-effects meta-analyses, the committee also reports results using fixed-effects models for the overall effect of sodium reduction intake on cardiovascular disease incidence, hypertension incidence, systolic blood pressure, and diastolic blood pressure. The fixed-effects and random-effects models produced similar overall effect estimates. For comparison, the fixed-effects model results are provided as notes throughout this chapter, but the committee presents random-effects model estimates as its primary results, following currently recommended standard procedures (AHRQ, 2014; Deeks et al., 2008).

continued

BOX 10-1 Continued

Estimating Variance

The committee also considered the methods for estimating variance, particularly given the challenges involved in conducting meta-analyses of small numbers of studies (Bender et al., 2018; Gonnermann et al., 2015). Like the *AHRQ Systematic Review*, the committee's meta-analyses were conducted using random-effects models with the metafor package of R (a package to conduct meta-analyses with the statistical software environment R). However, whereas the *AHRQ Systematic Review* used the Knapp-Hartung variance estimate throughout, the committee used the approach detailed in a February 2018 update on recommended methods for quantitative assessment published by AHRQ (Morton et al., 2018). In this approach the Knapp-Hartung estimate is used when heterogeneity is present ($I^2 > 0$ percent), but the restricted maximum likelihood (REML) estimate is used when no heterogeneity is exhibited ($I^2 = 0$ percent). This modification is recommended because of the documented erratic behavior and lack of power for the Knapp-Hartung estimate when heterogeneity is low, especially with a small number of studies (Bender et al., 2018; Gonnermann et al., 2015; Jackson et al., 2017), as well as the appropriate error rates observed under the null exhibited using the REML estimator when studies are homogeneous (Gonnerman et al., 2015; IntHout et al., 2014). The committee used the REML estimate for analyses of cardiovascular disease incidence and hypertension incidence, which exhibited no heterogeneity. For blood pressure, the Knapp-Hartung variance estimate was used for all summary effects because of the large number of studies available as well as the presence of detectable heterogeneity throughout most analyses.

Explaining Heterogeneity in Meta-Analysis

The committee's analysis included subgrouping and meta-regression, with a focus on the following variables:

- the net reduction in sodium intake achieved by the intervention versus control groups or the average achieved sodium intake in each group separately;
- hypertension status (inclusion/exclusion of participants with hypertension); and
- baseline levels of systolic and diastolic blood pressure.

Analyses were conducted with and without trials that used a salt substitute (usually a low-sodium, high-potassium salt substitute) to explore the potential interaction of potassium in the outcome. Although the committee recognizes the potential heterogeneity caused by the diversity in blood pressure measurement methods, accounting for this potential source of heterogeneity was not feasible owing to additional analyses needed and potential challenges in the interpretation of the results.

Assessing Publication Bias

Egger and colleagues (1997) and others have noted that asymmetry in the results with seemingly missing small effects in studies with reduced sample size can be attributable to publication bias or possible other reasons, including selective outcome and/or selective analysis reporting; spurious large effects in studies of reduced sample size due to poor methodological quality of such studies; heterogeneity leading to an association between the size of the effect with the size of the study; or simple sampling variation. The patterns in the data can be evaluated for publication bias using a number of different approaches, with the funnel plot being the most common. Although there are concerns using funnel plots and associated statistics for assessing publication bias (Sterne et al., 2011), the assessment of this bias is fundamental to the consideration of meta-analysis results. In particular, following the GRADE approach, the strength of evidence can be rated down if there is serious concern that the body of evidence has a high risk of publication bias (Guyatt et al., 2011b). The committee assessed asymmetry in the results when a body of evidence in a meta-analysis consists of at least 10 studies. Moreover, the above caveats are noted in the interpretation. Publication bias was assessed using funnel plots and Egger's regression test for funnel plot asymmetry (Egger et al., 1997). The potential effect of publication bias was assessed using the "trim-and-fill" method of Duval and Tweedie (2000).

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*Survival analysis is a set of statistical techniques to analyze a time-to-event outcome variable and reflects the time until a participant has an event of interest (e.g., heart attack, death). This technique may adjust for imbalances at baseline, reflecting better the survival distribution.

BOX 10-2
The Committee's Revisions to Data from Individual Trials, as Compared to the *AHRQ Systematic Review*

- Applegate et al. (1992): The intervention in this trial combined weight reduction, sodium restriction, and increased physical activity. It was excluded from the committee's meta-analyses.
- Beard et al. (1982): Diastolic blood pressure data were added to the committee's meta-analyses.
- Bulpitt et al. (1984): Diastolic blood pressure data were added to the committee's meta-analyses.
- Cappuccio et al. (2006): This is a cluster-randomized trial of villages in Ghana. The effects were replaced with the adjusted effects.
- He et al. (2000): This publication reported on Trials of Hypertension Prevention (TOHP) I results from only one of the clinics. It was replaced by the full results from TOHP I (TOHP Collaborative Research Group, 1992b).
- Meuleman et al. (2017): This trial was conducted in patients with kidney disease. It was excluded from the committee's meta-analyses.
- Nakano et al. (2016): For this trial, a correction was applied for baseline blood pressure; diastolic blood pressure data were added to the committee's meta-analyses.
- Nowson and Morgan (1988): Diastolic blood pressure data were added to the committee's meta-analyses.
- Sacks et al. (2001): This is a crossover trial with low-, medium-, and high-sodium arms. Contrasts of low versus medium sodium intake levels, and

Review of Evidence on Indicators

The sections that follow present the body of evidence for a causal relationship between sodium intake and four indicators: cardiovascular disease incidence, hypertension incidence, systolic blood pressure, and diastolic blood pressure. For context, evidence and conclusions presented in the *2005 DRI Report* and in the *AHRQ Systematic Review* are summarized for each of the indicators; the committee, however, relied on its analyses to assess the strength of the evidence. Potential indicators that were reviewed by the committee but not selected to inform the sodium CDRRs are presented as an annex to this chapter (see Annex 10-1).

Cardiovascular Disease Morbidity and Mortality

As summarized in Box 10-3, evidence on the relationship between sodium intake and cardiovascular disease morbidity and mortality was included in both the *2005 DRI Report* (IOM, 2005) and the *AHRQ Sys-*

medium versus high sodium intake levels were included in the committee's meta-analyses.

- Santos et al. (2010): A multicomponent crossover trial of high versus low mineral water with calcium and magnesium. It was excluded from the committee's meta-analyses.
- Seals et al. (2001): This trial compares reduced salt interventions to an exercise intervention, not to usual care. It was excluded from the committee's meta-analyses.
- Silman et al. (1983): Diastolic blood pressure data were added to the committee's meta-analyses.
- Takahashi et al. (2006): In this trial, the intervention group was coached to decrease sodium intake and increase vitamin C and carotene intake. It was excluded from the committee's meta-analyses.
- Todd et al. (2010): This is a crossover trial with three periods, in which participants consumed tomato juice containing 0, 2,070, and 3,220 mg/d (0, 90, and 140 mmol/d) sodium. All arms were included. This publication also had slight discrepancies in the numbers presented in the table, text, and abstract. The committee used the numbers in the publication table.
- Todd et al. (2012): This is a crossover trial with three periods, in which participants consumed tomato juice containing 0, 2,070, and 3,220 mg/d (0, 90, and 140 mmol/d) sodium. All arms were included. This trial compared high- to low-sodium periods. The sign of these was reversed in the publication.
- Xie et al. (1998): The intervention in this trial included weight reduction, salt moderation, physical exercise, alcohol moderation, and biofeedback. It was excluded from the committee's meta-analyses.

tematic Review (Newberry et al., 2018). The committee's assessment of the evidence built on the meta-analyses presented in the *AHRQ Systematic Review*. The committee reviewed the trials in the meta-analyses included in the *AHRQ Systematic Review* for two outcomes: (1) "any cardiovascular disease" and (2) "combined cardiovascular disease morbidity and mortality." Many of the studies were short term, some lasting only 8 weeks, with very few cardiovascular disease events, some as low as one to three outcomes. The *AHRQ Systematic Review* included these studies using a continuity correction, leading to very wide confidence intervals (CIs) and an appearance of heterogeneity. Because a nutritional intervention in healthy individuals is unlikely to lead to effects on cardiovascular disease incidence or mortality within a very short period of time, the committee reanalyzed the evidence restricting inclusion to studies lasting at least 1 year. Trials of cardiovascular disease mortality among those with preexisting cardiovascular disease were also excluded. With these changes, the results of the committee's meta-analysis is based on five trials.

BOX 10-3
Summary of Evidence Presented in the *2005 DRI Report* and the *AHRQ Systematic Review* on Cardiovascular Disease Morbidity and Mortality

2005 DRI Report

Cardiovascular disease morbidity and mortality were explored as separate outcomes, but neither were selected as the critical adverse effects to inform the sodium Tolerable Upper Intake Levels (ULs) because of the lack of data from trials (IOM, 2005).

AHRQ Systematic Review

The *AHRQ Systematic Review* identified nine trials that reported some cardiovascular disease mortality or mortality endpoint or a combination of morbidity and mortality (Appel et al., 2001; Chang et al., 2006; Charlton et al., 2008; Cook et al., 2007; CSSSCG, 2007; Gilleran et al., 1996; Morgan et al., 1978; Sarkkinen et al., 2011). Meta-analyses showed an overall beneficial effect of reducing sodium intake, whether the outcome was any cardiovascular disease event reported (pooled risk ratio [RR] = 0.80 [95% confidence interval {CI}: 0.67, 0.96]; I^2 = 0 percent) or the combination of cardiovascular disease morbidity and mortality (pooled RR = 0.81 [95% CI: 0.67, 0.98], I^2 = 0 percent). The *AHRQ Systematic Review* concluded that there is a low strength of evidence to support an effect of sodium reduction on any cardiovascular disease event or the combination of morbidity and mortality. The rationale for downgrading the rating to a low strength of evidence was inconsistency in direction of effects and imprecision among effect sizes.

The *AHRQ Systematic Review* determined that there was insufficient evidence of the moderating effects of sex, race/ethnicity, diabetes status, kidney disease, or obesity and overweight on cardiovascular disease morbidity and mortality.

Results from the committee's analyses The inclusion of small studies of short duration in the *AHRQ Systematic Review* led to the appearance of inconsistency and imprecision. As presented in Figure 10-1, using the five trials of at least 1 year and hazard ratios from survival analyses led to stronger results (risk ratio [RR] = 0.72 [95% CI: 0.59, 0.89]) than were reported in the *AHRQ Systematic Review* analyses for trials of any cardiovascular disease incidence and/or cardiovascular disease mortality.[3] The revised analyses exhibited no heterogeneity across trials (I^2 = 0 percent). When trials using salt substitutes were excluded from the meta-analysis, three large trials of

[3]Cardiovascular disease events actually collected in the individual five studies were myocardial infarction, angina, congestive heart failure, coronary revascularization, stroke, transient ischemic attack, arrhythmia, or other.

cardiovascular disease incidence remained,[4] and the overall risk ratio was 0.74 ([95% CI: 0.58, 0.93], I^2 = 0 percent) (see Figure 10-2). There were too few studies to evaluate potential publication bias. These three studies are long-term follow-ups of randomized controlled trials of various lifestyle

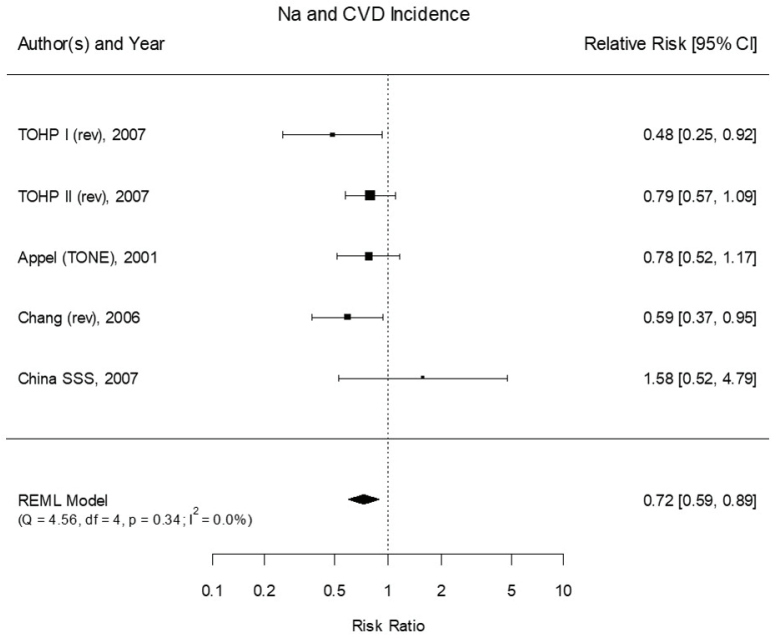

FIGURE 10-1 Random-effects meta-analysis of trials of effects of sodium reduction on cardiovascular disease incidence.

NOTES: Studies using salt substitutes are included. Meta-analysis was conducted in R with random-effects models in the metafor package. The variance was estimated using the REML approach. For comparison, in a fixed-effects meta-analysis the overall risk ratio was 0.72 [95% CI: 0.59, 0.89]. China SSS = China Salt Substitute Study; CI = confidence interval; CVD = cardiovascular disease; df = degrees of freedom; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium; Q = Q statistic; REML = restricted maximum likelihood; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention; TONE = Trial of Nonpharmacologic Interventions in the Elderly.

SOURCES: Appel et al., 2001; Chang et al., 2006; Cook et al., 2007; CSSSCG, 2007.

[4]Cardiovascular disease event collected in the individual three studies were myocardial infarction, angina, congestive heart failure, coronary revascularization, stroke, transient ischemic attack, arrhythmia, or other.

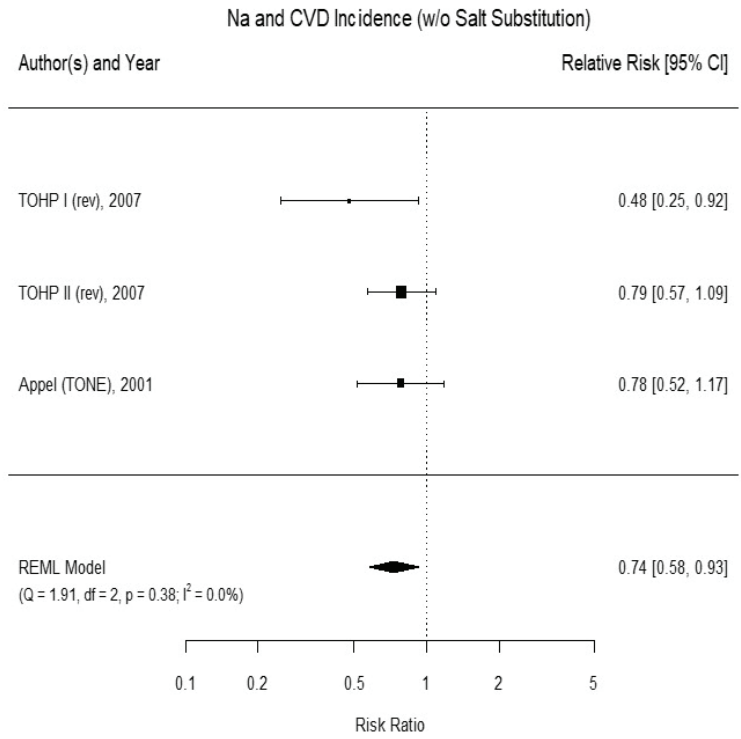

FIGURE 10-2 Random-effects meta-analysis of trials of effects of sodium reduction on cardiovascular disease incidence, excluding trials where the intervention was the consumption of a salt substitute.
NOTES: Meta-analysis was conducted in R with random-effects models in the metafor package. The variance was estimated using the REML approach. For comparison, in a fixed-effects meta-analysis the overall risk ratio was 0.74 [95% CI: 0.58, 0.93]. CI = confidence interval; CVD = cardiovascular disease; df = degrees of freedom; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium; Q = Q statistic; REML = restricted maximum likelihood; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention; TONE = Trial of Nonpharmacologic Interventions in the Elderly; w/o = without.
SOURCES: Appel et al., 2001; Cook et al., 2007.

interventions, including interventions with a single aim of sodium intake reduction as summarized below:

- For Trials of Hypertension Prevention (TOHP) I and II, the interventions in the initial trial period were dietary and behavioral counseling on reducing sodium intake without changing other

nutrient intakes. Participants in the control group followed their usual diets in addition to general guidance on healthy eating. The objective of the initial sodium reduction interventions in TOHP I and II was to examine the effect on blood pressure, whereas the follow-up studies compared cardiovascular disease events (15–18 years of follow-up) and mortality (23–26 years of follow-up) between the sodium intake reduction groups and the control groups. These follow-up studies, which are extensions of the TOHP I and II trials, have the randomized attributes of trials. That is, in contrast to observational studies in which selection bias will lead to distinct groups—and methods to adjust for baseline differences are paramount—allocation into the intervention groups is unbiased (i.e., selection bias is controlled) and baseline characteristics of the intervention groups should be similar. With respect to outcome assessment and compliance, the lack of measures to ensure compliance and the assessment of outcomes based on intention-to-treat in the TOHP I and II follow-up studies would bias the results to the null; therefore, if a difference between interventions can be found under the conditions of these follow-up studies then these differences will likely be found also under the strict follow-up schedule and compliance considered in a trial.

- Similar to TOHP I and II, the sodium reduction intervention in the Trial of Nonpharmacologic Interventions in the Elderly (TONE) was focused on modifying only sodium intake rather than a comprehensive diet change, with the objective of examining the effect on blood pressure. The initial trial examined the effects of sodium reduction on blood pressure among patients with hypertension who were withdrawn from medication. During the long-term follow-up period (mean 27.8 months), cardiovascular events were compared between the control and intervention groups.

Updated strength-of-evidence evaluation Using GRADE and the additional analyses described above, the committee reassessed the strength of evidence for the causal relationship between sodium intake reduction and reduction in cardiovascular disease incidence (see Table 10-2). The strength of evidence was assessed as moderate owing to imprecision related to the relatively low total number of events observed across studies (< 300) when excluding salt-substitute studies. The committee recognizes that the evidence derived from three studies that are long-term follow-ups to trials with lifestyle interventions to reduce sodium intake. Thus, there are two possible ways in which factors other than sodium intake contribute to differences in effects on cardiovascular disease incidence. One possibility is that the lifestyle interventions resulted in changes in dietary patterns other than reduced sodium intake. The

TABLE 10-2 GRADE Assessment Table: Sodium Reduction and Cardiovascular Disease Incidence

GRADE Criteria	Rating[a]
Outcome: Incidence of Cardiovascular Disease Events	
Study design	High
Risk of bias	No (0)
Inconsistency	No (0)
Indirectness	No (0)
Imprecision	Serious (–1)
Publication bias	Not measured
Other	None (0)

[a]Table format adapted from Ryan and Hill (2016). Possible ratings as follows:

- For Study Design, strength-of-evidence rating for randomized controlled trials starts as "High" and for nonrandomized controlled trials starts as "Low"
- For Risk of Bias, Inconsistency, Indirectness, and Imprecision, the possible ratings are "No (0)" (no change), "Serious (–1)" (downgrade one level), or "Very serious (–2)" (downgrade two levels)

other possibility is that the intervention only occurred during the initial trial, so it is possible that sodium intake changed during the long-term follow-up period. Under GRADE, if these possibilities were considered serious, the strength of evidence could be down rated because of indirectness. However, these concerns were not serious enough to warrant a down rating due to the following three reasons. First, the counseling interventions in the TOHP and TONE trials were highly targeted and designed specifically to reduce sodium without changing other foods or nutrients (Appel et al., 2001; Kumanyika et al., 2005). Second, any deviation during the follow-up period from the

Reasons for Rating	Strength of Evidence[b]
Randomized controlled trials.	
All studies have low or moderate risk of bias.	
No statistical heterogeneity was detected. All study point estimates were in the same direction.	
Evidence directly answers the question of interest in terms of relevant populations, interventions, comparators, and outcomes. No change in overall results with inclusion of salt-substitution studies, which are more indirect because they also involve increases in other nutrients, usually potassium. Although interventions were not continued during long-term follow-up, post-intervention changes to sodium intake would tend to bias toward the null. Moreover, adherence and loss to follow-up were nondifferential and unlikely to introduce bias.	⊕⊕⊕○ Moderate
Statistically significant summary effect, with meaningful size of effect (26–28 percent change in hazard ratio). However, when salt-substitution studies are excluded, upper confidence bound of 0.93 would imply a substantially smaller size of effect (7 percent change) and total cardiovascular disease events number < 300 across studies.	
Too few studies for analysis of publication bias.	
No additional upgrading factors.	

- For Publication Bias, the ratings are "Undetected (0)" (no change) or "Strongly suspected (–1)" (downgrade one level)
- Other ratings, if present, are "Large effect," "Intake–response," and/or "No plausible confounding" along with "(+1)" or "(+2)" depending on whether upgrade is one or two levels

[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

interventions' intent of reducing sodium intake would tend to bias toward the null and therefore reduce the effect size. Finally, adherence rate and loss to follow-up in the control and intervention groups were not different enough to raise concerns about introducing bias in the results.

Hypertension

As summarized in Box 10-4, evidence on the relationship between sodium intake and hypertension was included in both the *2005 DRI Report*

(IOM, 2005) and the *AHRQ Systematic Review* (Newberry et al., 2018). The committee's assessment of the evidence built on the meta-analyses presented in the *AHRQ Systematic Review*. The committee's meta-analysis of hypertension is based on the three trials in nonpregnant individuals that were included in the *AHRQ Systematic Review*. Each trial was evaluated for appropriate inclusion and revisions were made, as summarized in Box 10-2.

BOX 10-4
Summary of Evidence Presented in the *2005 DRI Report* and the *AHRQ Systematic Review* on Hypertension

2005 DRI Report

Three trials on the relationship between sodium intake and incidence of hypertension were explored in the *2005 DRI Report* (IOM, 2005): the Hypertension Prevention Trial (HPTRG, 1990), the Trials of Hypertension Prevention (TOHP) Phase I (TOHP Collaborative Research Group, 1992a,b), and TOHP II (TOHP Collaborative Research Group, 1997). The *2005 DRI Report* focused on the TOHP II trial because it was specifically designed with hypertension incidence as an outcome. The TOHP II investigators concluded that the decreased hypertension incidence by the end of the 3 to 4 years of follow-up was indicative of the effectiveness of a behavioral intervention on sodium intake. These results were used in the *2005 DRI Report* to support the selection of blood pressure as an indicator for the sodium Tolerable Upper Intake Level (UL).

AHRQ Systematic Review

The *AHRQ Systematic Review* (Newberry et al., 2018) identified four trials that assessed the relationship between sodium reduction and incidence of hypertension, one of them with gestational hypertension in pregnant women, as the outcome. The trial on pregnant women failed to show any significant effects on gestational hypertension (van Buul et al., 1997). A meta-analysis of the results from the trials in nonpregnant individuals (He et al., 2000; HPTRG, 1990; TOHP Collaborative Research Group, 1997) resulted in a nonsignificant effect of sodium reduction in incidence of hypertension (pooled RR = 0.83 [95% CI: 0.67, 1.03], I^2 = 0 percent). Based on the low number of trials, the imprecision in the results, and the variation in the definition of hypertension, the *AHRQ Systematic Review* concluded that there was insufficient strength of evidence that reducing sodium intake reduces the incidence of hypertension.

One analysis from the TOHP II trial (Kumanyika et al., 2005) showed no differences in sodium reduction on incidence of hypertension when stratified by sex or race. Based on this limited body of evidence, the *AHRQ Systematic Review* concluded there is insufficient evidence regarding the effects of sex or race on incidence of hypertension.

Results from the committee's analyses With the committee's selection of studies and updated extracted data, the overall estimate of the effect of a sodium reduction on hypertension was strengthened. The revised estimated relative risk was 0.79 [95% CI: 0.67, 0.93], with no apparent heterogeneity across studies (I^2 = 0 percent) (see Figure 10-3). There were too few studies to evaluate potential publication bias.

Updated strength-of-evidence evaluation Using GRADE and the additional analysis described above, the committee reassessed the strength of evidence for a causal relationship between sodium intake reduction and reduction in hypertension incidence (see Table 10-3). The strength of evidence was

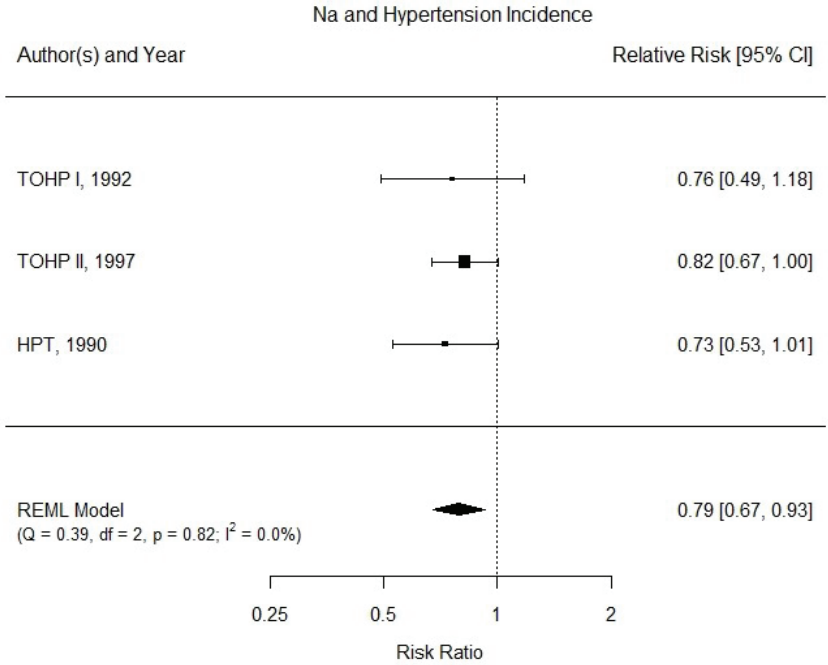

FIGURE 10-3 Random-effects meta-analysis of trials of effects of sodium reduction on hypertension incidence.
NOTES: Meta-analysis was conducted in R with random-effects models in the metafor package. The variance was estimated using the REML approach. For comparison, fixed-effects meta-analysis overall risk ratio was calculated to be 0.80 [95% CI: 0.69, 0.94]. CI = confidence interval; df = degrees of freedom; HPT = Hypertension Prevention Trial; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium; Q = Q statistic; REML = restricted maximum likelihood; TOHP = Trials of Hypertension Prevention.
SOURCES: HPTRG, 1990; TOHP Collaborative Research Group, 1992a,b, 1997.

TABLE 10-3 GRADE Assessment Table: Sodium Reduction and Incidence of Hypertension

GRADE Criteria	Rating[a]
Outcome: Incidence of Hypertension	
Study design	High
Risk of bias	No (0)
Inconsistency	No (0)
Indirectness	No (0)
Imprecision	Serious (–1)
Publication bias	Not measured
Other	None (0)

[a]Table format same as Table 10-2.
[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

assessed as moderate owing to the relatively small size of effect (< 25 percent risk reduction) and the upper CI being close to 1.0.

Blood Pressure

As summarized in Box 10-5, evidence on the relationship between sodium intake and blood pressure was included in both the *2005 DRI Report* (IOM, 2005) and the *AHRQ Systematic Review* (Newberry et al., 2018). The committee's assessment of the evidence built on the meta-analyses presented in the *AHRQ Systematic Review*. In particular, the committee sought to explore heterogeneity in sodium reduction trials and blood pressure that was not explored in the *AHRQ Systematic Review*. As noted in Box 10-1, the sources of heterogeneity caused by the diversity in methods to measure blood pressure was not explored.

Methods for exploring heterogeneity The committee's analyses are based on the studies of systolic and diastolic blood pressure, focusing on study-specific characteristics that were collected in the *AHRQ Systematic Review*.

Reasons for Rating	Strength of Evidence[b]
Randomized controlled trials. All studies have low or moderate risk of bias. No statistical heterogeneity was detected. All study point estimates were in the same direction.	
Evidence directly answers the question of interest in terms of relevant populations, interventions, comparators, and outcomes. Statistically significant summary effect, with total events numbering > 1,000 across studies. However, the 20 percent change in hazard ratio is less than the 25 percent considered "appreciable" under GRADE (Guyatt et al., 2011c), with an upper confidence limit of 0.93 that is close to 1.00. Too few studies for analysis of publication bias. No additional upgrading factors.	⊕⊕⊕○ Moderate

BOX 10-5
Summary of Evidence Presented in the *2005 DRI Report* and the *AHRQ Systematic Review* on Blood Pressure

2005 DRI Report

Based on the number of trials that found a positive relationship between sodium intake and blood pressure and the persuasive data of blood pressure as a biomarker of cardiovascular disease, blood pressure was selected as the indicator of adverse effects from excessive sodium intake in the *2005 DRI Report* (IOM, 2005). The sodium Tolerable Upper Intake Level (UL) was established based on the results of the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial (Sacks et al., 2001), which demonstrated that blood pressure at the lowest sodium intake (intake target of approximately 1,200 mg/d [50 mmol/d]) was significantly lower than at a target sodium intake of 2,300 mg/d (100 mmol/d).

continued

BOX 10-5 Continued

AHRQ Systematic Review

Adults

The *AHRQ Systematic Review* identified 47 sodium reduction comparisons (35 from parallel trials and 12 from crossover trials) that met the inclusion criteria and examined the effect of reducing sodium intake on systolic and diastolic blood pressure in adults. The results of the random-effects meta-analyses presented in the *AHRQ Systematic Review* are presented in Table 10-4. The *AHRQ Systematic Review* noted the substantial heterogeneity ($I^2 > 30$ percent in all meta-analyses).

TABLE 10-4 Random-Effects Meta-Analyses Presented in the *AHRQ Systematic Review* on Effects of Sodium Reduction on Blood Pressure Among Adults

	Systolic Blood Pressure		Diastolic Blood Pressure	
Study Type Included	MD [95% CI], mm Hg	I^2	MD [95% CI], mm Hg	I^2
Parallel trials	–2.68 [–3.59, –1.77]	39%	–2.04 [–2.71, –1.18]	50%
Crossover trials	–3.77 [–5.45, –2.08]	89%	–2.51 [–4.07, –0.95]	86%
All trials	–3.23 [–4.07, –2.38]	77%	–2.26 [–2.91, –1.60]	72%

NOTE: CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; MD = mean difference.
SOURCE: Newberry et al., 2018.

Owing primarily to inconsistency in the direction of effect and high heterogeneity across the individual studies, the *AHRQ Systematic Review* downgraded the strength of evidence for an effect of sodium reduction on both systolic and diastolic blood pressure in adults to moderate.

Children and Adolescents 1–18 Years of Age

Eight parallel trials were included in the *AHRQ Systematic Review* that assessed the relationship between sodium reduction and systolic blood pressure and seven trials assessed the relationship between sodium reduction and diastolic blood pressure in children and adolescents. The overall effects were nonsignificant. For systolic blood pressure, mean difference (MD) was –0.73 mm Hg ([95% confidence interval {CI}: –1.83, 0.37], I^2 = 48 percent); for diastolic blood pressure, the MD was –2.10 mm Hg ([95% CI: –4.75, 0.55], I^2 = 79 percent). However, when the high-risk-of-bias studies were excluded, the overall effect on diastolic blood pressure between the control and the intervention became sig-

nificant (MD = –1.54 mm Hg [95% CI: –2.57, –0.51], I^2 = 0 percent). The *AHRQ Systematic Review* concluded that there was low strength of evidence that sodium reduction may not significantly lower systolic blood pressure in children and adolescents and that there was low strength of evidence that sodium reductions reduce diastolic blood pressure (based only on low- and moderate-risk-of-bias studies).

Other Population Groups

Three sodium reduction trials included in the *AHRQ Systematic Review* were conducted in pregnant women—one trial in women with pregnancy-induced hypertension (Knuist et al., 1998) and two trials in normotensive women (Steegers et al., 1991; van Buul et al., 1997). None showed a reduction in systolic or diastolic blood pressure with sodium intake reduction. Because of this heterogeneity in study participants and the small number of participants, the *AHRQ Systematic Review* concluded that the evidence was insufficient for assessing the effects of sodium reduction on blood pressure in pregnant women. No trials in the *AHRQ Systematic Review* included or reported results on lactating women.

The *AHRQ Systematic Review* also assessed the effect of sodium reduction on blood pressure by hypertension status. Random-effects meta-analyses found that sodium reduction reduced systolic blood pressure in normotensive participants (MD: –1.52 mm Hg [95% CI: –2.77, –0.26], I^2 = 43 percent; based on 9 randomized controlled trials) and prehypertension, mild hypertension, and more severe hypertension (MD: –4.14 mm Hg [95% CI: –5.21, –3.07], I^2 = 75 percent; based on 36 randomized controlled trials). In contrast, sodium reduction did not significantly reduce diastolic blood pressure in studies of normotensive individuals (MD: –0.61 mm Hg [95% CI: –1.28, 0.06], I^2 = 12 percent; based on 10 randomized controlled trials) but significantly reduced diastolic blood pressure in those with prehypertension and hypertension (MD: –2.59 mm Hg [95% CI: –3.27, –1.90], I^2 = 69 percent; based on 37 randomized controlled trials).

The *AHRQ Systematic Review* concluded that there was a moderate strength of evidence that sodium reduction lowers systolic blood pressure in individuals with hypertension and normotensive individuals; the strength-of-evidence rating was down rated owing to inconsistency. For diastolic blood pressure, the *AHRQ Systematic Review* concluded that there was a moderate strength of evidence that sodium reduction lowers diastolic blood pressure in individuals with hypertension; for normotensive individuals, the *AHRQ Systematic Review* concluded that there was low strength of evidence that sodium reduction may not reduce diastolic blood pressure.

Based on random-effects meta-analyses of eight trials stratified by sex, the *AHRQ Systematic Review* concluded that there is a low strength of evidence that there may not be a moderating effect of sex on the effect of sodium reduction on systolic or diastolic blood pressure. The evidence was determined to be insufficient to support the moderating effects of race/ethnicity, diabetes status, kidney disease, or obesity and overweight.

Specifically, nine variables were extracted from the evidence tables and quality assessment tables included in the *AHRQ Systematic Review*[5]: study type (parallel or crossover), year, risk of bias, sample size, duration, net change in sodium, average sodium in control, type of intervention (dietary advice, salt supplement, or food provided), and blood pressure level and status at baseline (hypertension and antihypertensive medication use). The committee corrected some of the data it extracted from the *AHRQ Systematic Review* (see Box 10-2) and also extracted additional variables from the original study publications.

To examine effect by hypertension status, the committee classified studies into "Hypertension" (any participants with hypertension) and "No Hypertension" (no participants with hypertension). Studies including participants described as having "high normal" blood pressure or with "prehypertension" were included in the group without hypertension. In addition, the committee's meta-analyses extracted from the original studies an indicator of whether participants on antihypertensive medication were eligible. These categorizations are approximate because individual participant data were not available and a single blood pressure category for the study as a whole was used. In addition, the definitions for hypertension have changed over time and so may not be consistent from study to study or with current guidelines.

Results from the committee's analyses on systolic blood pressure The meta-analyses results using the revised data were similar to those in the *AHRQ Systematic Review*. As presented in Figure 10-4, the committee's overall estimate was a systolic blood pressure change of –3.34 mm Hg ([95% CI: –4.17, –2.52], I^2 = 76 percent); the *AHRQ Systematic Review* estimate was –3.23 mm Hg ([95% CI: –4.07, –2.38], I^2 = 77 percent). Much heterogeneity remained in the committee's meta-analysis and was larger in the crossover trials (I^2 = 88 percent) than in the parallel trials (I^2 = 49 percent). In meta-regressions, both the net reduction in sodium and the baseline systolic blood pressure level were significantly associated with the size of the reduction in systolic blood pressure, though the control sodium level was not (see Figures 10-5, 10-6, and 10-7). The change in sodium and hypertension status at baseline helped to explain much of the heterogeneity, and the overall I^2 value was reduced to 52 percent in meta-regressions including these three variables (net reduction in sodium, baseline systolic blood pressure level, and control sodium level). There was also a difference in the effects by categories of baseline blood pressure (see Figure 10-8). Although the effect estimates were larger among studies with any participants with hypertension (mean difference [MD] = –4.08 mm Hg [95% CI: –5.03, –3.13], I^2 = 69 percent)

[5]The referenced tables correspond to Appendixes C and E in the *AHRQ Systematic Review* (Newberry et al., 2018).

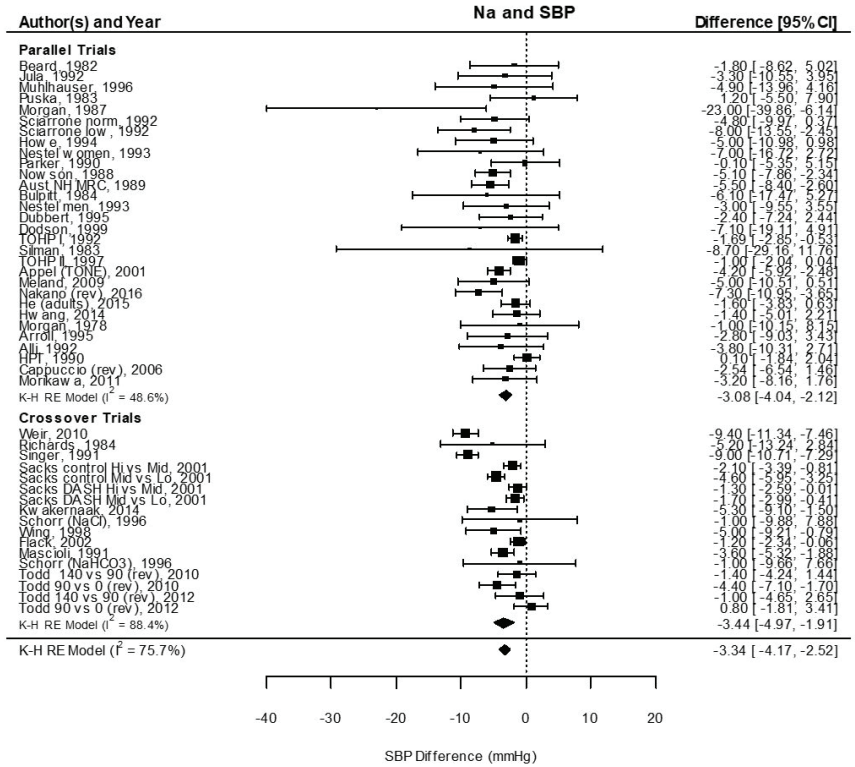

FIGURE 10-4 Random-effects meta-analysis of parallel and crossover trials of effects of sodium reduction on systolic blood pressure.

NOTES: Meta-analysis was conducted in R with random-effects models in the meta-for package using the Knapp-Hartung variance. For comparison, fixed-effects meta-analysis overall MD was calculated to be –2.77 mm Hg [95% CI: –3.13, –2.42] for all, –2.26 mm Hg [95% CI: –2.81, –1.72] for parallel trials, and –3.13 mm Hg [95% CI: –3.60, –2.68] for crossover trials. Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; HPT = Hypertension Prevention Trial; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K-H = Knapp-Hartung variance estimate; Na = sodium; RE = random-effects; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention.

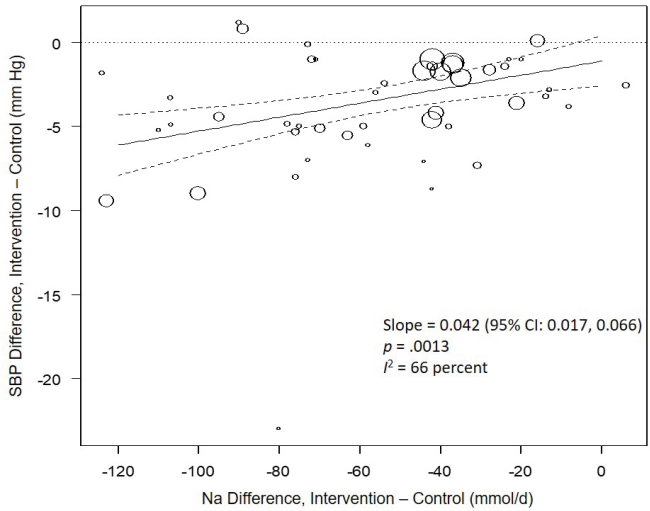

FIGURE 10-5 Meta-regression of trials of sodium intake reduction showing the net effect of the sodium intake difference between intervention and control groups on the systolic blood pressure effect size.
NOTES: Na differences in the figure are urinary sodium excretions, which were presented in the *AHRQ Systematic Review* in mmol/d. To convert to milligrams, multiply the mmol value by 23.0. CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium; SBP = systolic blood pressure.

versus those without hypertension (MD = –1.32 mm Hg [95% CI: –2.22, –0.43], I^2 = 39 percent), the overall effect was statistically significant in both subgroups. The slope of change in sodium was larger and significant in trials including participants with hypertension (slope = 0.051 mm Hg per mmol change in sodium, $p < .0001$), but was null in those without hypertension (slope = –0.022 mm Hg per mmol change in sodium, $p = .30$). In regressions accounting for baseline systolic blood pressure and the net difference in sodium among participants with hypertension, the I^2 value was reduced to 41 percent (see Table 10-5).

No publication bias was detected ($p > .05$) for all studies together as well as separately in trials including participants with hypertension and in those that did not. Summary estimates obtained by trim and fill remained statistically significant.

Given the evidence for an intake–response gradient for sodium intake and systolic blood pressure from meta-regression analyses, the committee also evaluated whether effects of sodium reduction on systolic blood pres-

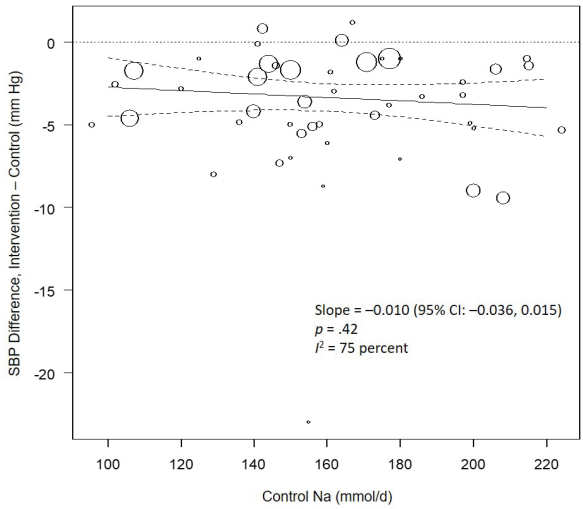

FIGURE 10-6 Meta-regression of trials of sodium intake reduction showing the effect of the control sodium intake on the systolic blood pressure effect size.
NOTES: Control Na values in the figure are urinary sodium excretions, which were presented in the *AHRQ Systematic Review* in mmol/d. To convert to milligrams, multiply mmol value by 23.0. CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium; SBP = systolic blood pressure.

sure were linear using semiparametric restricted cubic spline regression.[6] For splines with between three and five knots, the nonlinear terms were not statistically significant. Additionally, likelihood ratio tests comparing the (null) linear meta-regression model with each of these spline regression models were not statistically significant ($p = .27$), supporting linearity of the effect on systolic blood pressure over the range of sodium intake levels. The Global Burden of Diseases Nutrition and Chronic Diseases Expert Group used a similar approach and reached similar conclusions about linearity (Mozaffarian et al., 2014). Based on these results, the committee focused on a linear model in its intake–response assessment.

Results from the committee's analyses on diastolic blood pressure For diastolic blood pressure, the overall effects were similar to those in the *AHRQ*

[6]Spline-based meta-regression was conducted using the R metafor and rms packages. Different splines were evaluated with knots placed at quantiles (0.1, 0.5, 0.9; 0.25, 0.5, 0.75; 0.1, 0.4, 0.6, 0.9; and 0.05, 0.25, 0.5, 0.75, 0.95). Maximum likelihood estimates for both linear and restricted cubic splines were compared using the likelihood ratio test through analysis of variance.

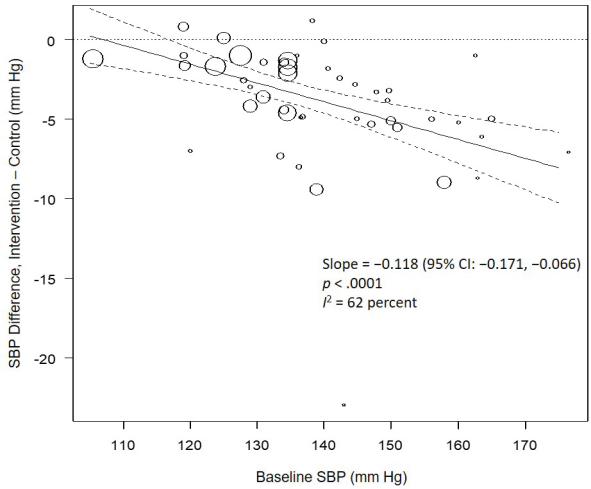

FIGURE 10-7 Meta-regression of trials of sodium intake reduction showing the effect of the baseline systolic blood pressure on the systolic blood pressure effect size. NOTE: CI = confidence interval; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; SBP = systolic blood pressure.

Systematic Review. As presented in Figure 10-9, the committee's overall estimate was a diastolic blood pressure change of –2.16 mm Hg ([95% CI: –2.84, –1.48], I^2 = 79 percent), which was a smaller change than what was estimated for systolic blood pressure. Heterogeneity was larger in cross-over studies (I^2 = 90 percent) than in parallel arm trials (I^2 = 62 percent). There was some intake–response relationship with change in sodium, but this was not statistically significant (see Figure 10-10). The effect varied by baseline diastolic blood pressure (see Figure 10-11). The overall I^2 remained at 73 percent after accounting for these two factors (see Table 10-5). Although the diastolic blood pressure changes were larger among studies with any participants with hypertension (MD: –2.68 mm Hg [95% CI: –3.50, –1.86], I^2 = 78 percent) as compared to studies of participants without hypertension (MD: –0.72 mm Hg [95% CI: –1.20, –0.24], I^2 = 0 percent), the results reached statistical significance in both subgroups (see Figure 10-12). The remaining heterogeneity was largely driven by studies with larger, more negative effect sizes. Restricting to studies with point estimates greater than –4.0 mm Hg (i.e., removing the quartile with the largest, most negative effect sizes) reduced heterogeneity (I^2 = 37 percent); the summary estimate remained statistically significant (MD: –1.32 mm Hg [95% CI: –1.71, –0.94]). Thus, the observed heterogeneity relates to the size of the effect (large or small) rather than the direction of the effect.

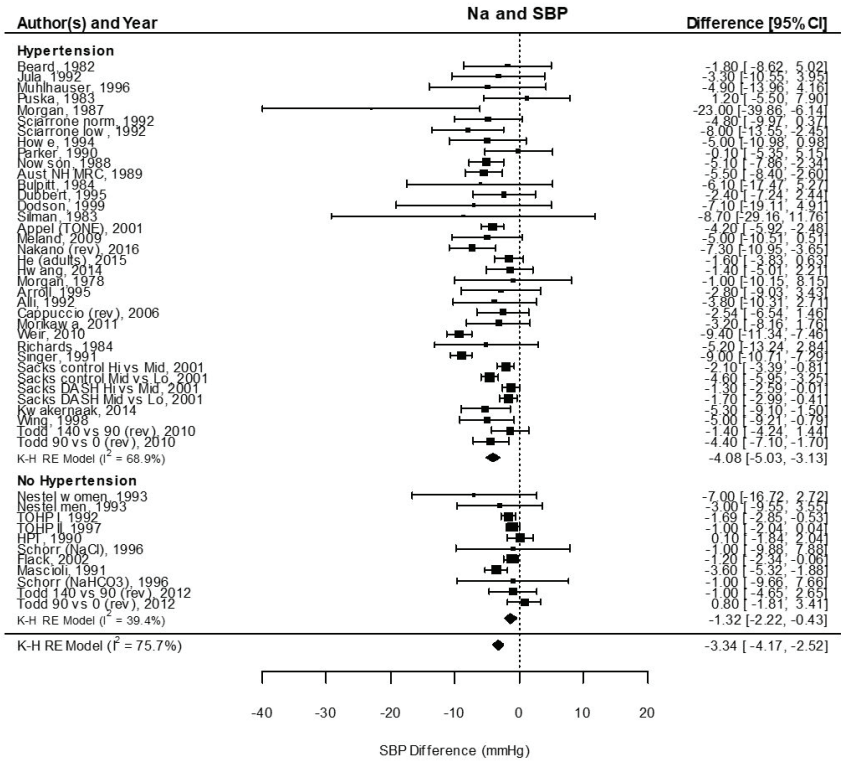

FIGURE 10-8 Random-effects meta-analysis of trials of effects of sodium intake reduction on systolic blood pressure by hypertension status.
NOTES: Meta-analysis was conducted in R with random-effects models in the metafor package using the Knapp-Hartung variance. For comparison, fixed-effects meta-analysis overall MD was calculated to be –3.79 mm Hg [95% CI: –4.24, –3.33] for studies that included participants with hypertension and –1.33 mm Hg [95% CI: –1.88, –0.78] for studies that did not include participants with hypertension. Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. CI = confidence interval; HPT = Hypertension Prevention Trial; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K-H = Knapp-Hartung variance estimate; Na = sodium; RE = random-effects; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention.

Some nonsignificant publication bias (funnel plots not included) was suggested (p = .06) for all studies together but not by hypertension status. Summary estimates obtained by trim and fill remained statistically significant in all these cases.

TABLE 10-5 Estimated Mean Blood Pressure Change with Given Change in Sodium Excretion by Baseline Blood Pressure

	Mean Blood Pressure Change by Change in Sodium Excretion, mm Hg			
Baseline Blood Pressure Level, mm Hg	0 mmol/d Change in Sodium Excretion	−50 mmol/d Change in Sodium Excretion	−100 mmol/d Change in Sodium Excretion	Residual I^2
Systolic Blood Pressure[a]				41%
110	−0.60	−0.60	−0.60	
120	−1.19	−1.19	−1.19	
130	−0.94	−3.25	−5.56	
140	−1.54	−3.85	−6.16	
150	−2.14	−4.45	−6.76	
Diastolic Blood Pressure[b]				73%
70	−0.38	−0.95	−1.51	
80	−1.13	−1.70	−2.26	
90	−1.88	−2.45	−3.01	
100	−2.63	−3.20	−3.76	

NOTES: Sodium excretions in the table are presented as mmol/d. To convert to milligrams, multiply the mmol value by 23.0.

[a]The model to estimate systolic blood pressure change included baseline systolic blood pressure, hypertension, and the change in sodium only among those with hypertension because this variable was significant only in those with hypertension.

[b]The model to estimate diastolic blood pressure change included baseline diastolic blood pressure and change in sodium.

Updated strength-of-evidence evaluation Overall there was a significant reduction in both systolic blood pressure and diastolic blood pressure with sodium reduction, though there was sizeable heterogeneity among trials. Much of the heterogeneity in systolic blood pressure could be explained by the intake–response (net change in sodium) as well as baseline systolic blood pressure level, which reduced the heterogeneity substantially. The net blood pressure difference was stronger among those with hypertension at baseline for both systolic blood pressure and diastolic blood pressure but was apparent in both subgroups. There was no apparent effect of baseline sodium level on either measure, suggesting a similar effect of sodium reduction throughout the baseline range of sodium examined.

Publication bias was not detected for systolic blood pressure, but it was suggested in diastolic blood pressure. However, all the diastolic blood pressure studies also reported systolic blood pressure, so the appearance of publication bias for diastolic blood pressure may instead reflect differential effect sizes between systolic blood pressure and diastolic blood pressure. Moreover, in all cases, the statistical significance of the summary estimates

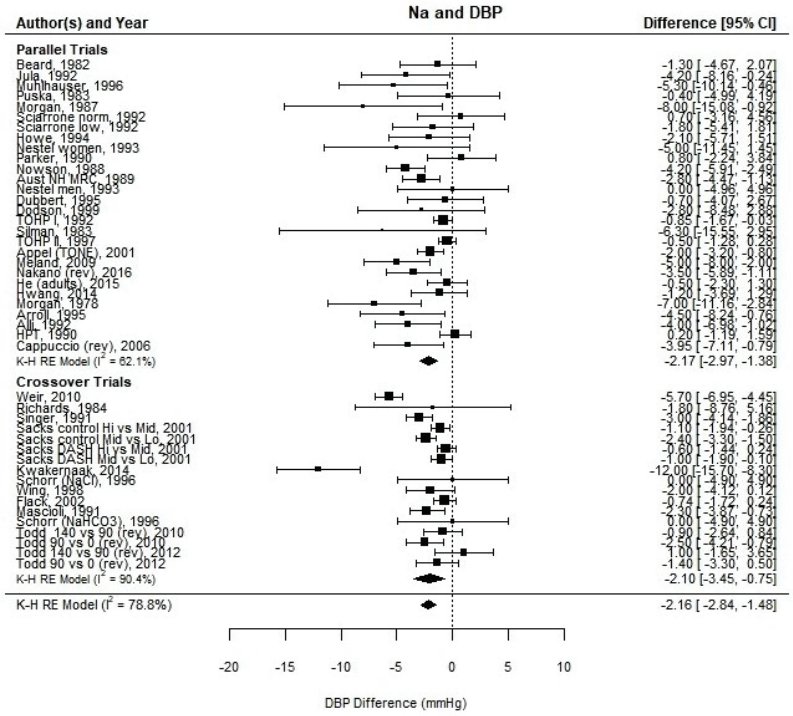

FIGURE 10-9 Random-effects meta-analysis of parallel and crossover trials of effects of sodium intake reduction on diastolic blood pressure.
NOTES: Meta-analysis was conducted in R with random-effects models in the metafor package using the Knapp-Hartung variance. For comparison, fixed-effects meta-analysis overall MDs were calculated to be –1.64 mm Hg [95% CI: –1.89, –1.40] for all trials, –1.48 mm Hg [95% CI: –1.86, –1.10] for parallel trials and –1.76 mm Hg [95% CI: –2.09, –1.44] for crossover trials. Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. CI = confidence interval; DBP = diastolic blood pressure; HPT = Hypertension Prevention Trial; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K-H = Knapp-Hartung variance estimate; Na = sodium; RE = random-effects; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention.

remained when using trim and fill to account for potentially missing studies. Therefore, the effect of potential publication bias is not likely to be large enough to affect the overall strength of the evidence.

Using GRADE and the committee's analyses, the committee reassessed the strength of evidence that reducing sodium intake reduces systolic blood pressure or diastolic blood pressure (see Tables 10-6 and 10-7, respectively).

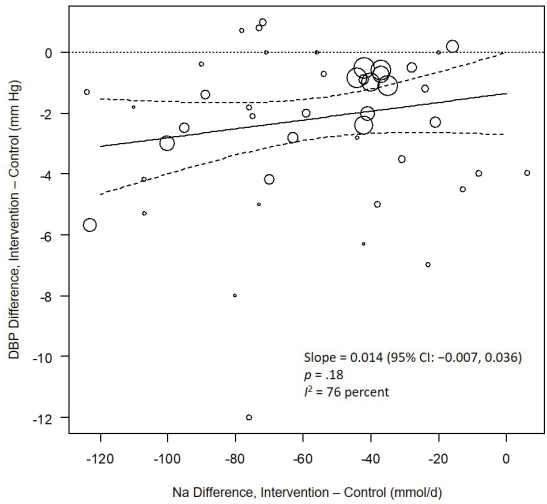

FIGURE 10-10 Meta-regression of trials of sodium intake reduction showing the effect of the net sodium intake difference between intervention and control on the diastolic blood pressure effect size.
NOTES: Na differences in the figure are urinary sodium excretions, which were presented in the *AHRQ Systematic Review* in mmol/d. To convert to milligrams, multiply the mmol value by 23.0. CI = confidence interval; DBP = diastolic blood pressure; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium.

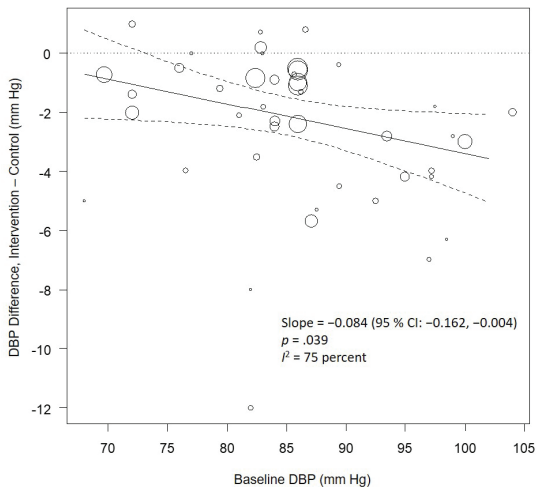

FIGURE 10-11 Meta-regression of trials of sodium intake reduction showing the effect of the baseline diastolic blood pressure on the diastolic blood pressure effect size.
NOTE: CI = confidence interval; DBP = diastolic blood pressure; I^2 = statistic that describes the percent of variation across studies due to heterogeneity.

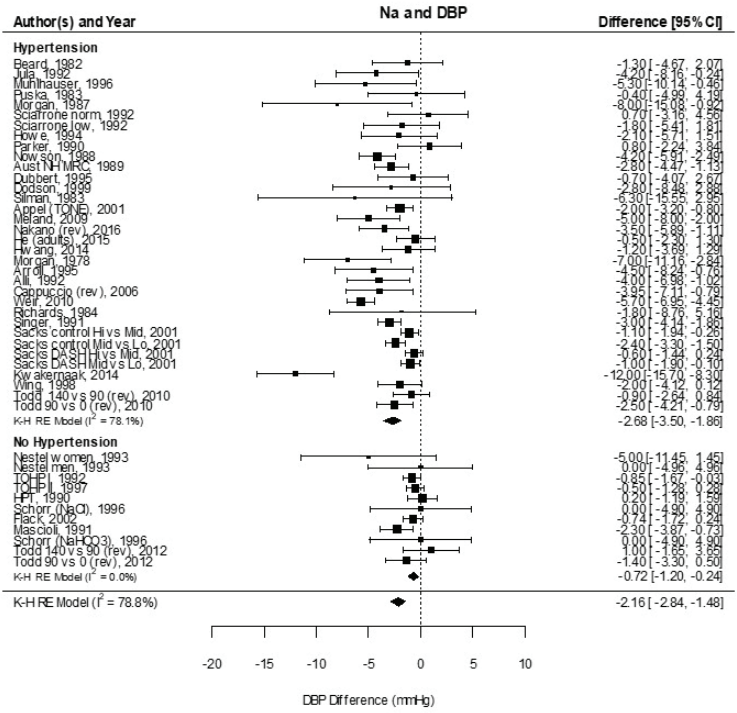

FIGURE 10-12 Random-effects meta-analysis of trials of effects of sodium intake reduction on diastolic blood pressure by hypertension status.

NOTES: Meta-analysis was conducted in R with random-effects models in the metafor package using the Knapp-Hartung variance. For comparison, fixed-effects meta-analysis overall MDs were calculated to be –2.12 mm Hg [95% CI: –2.42, –1.82] for studies that included participants with hypertension and –0.72 mm Hg [95% CI: –1.14, –0.29] for studies that did not include participants that did not include participants with hypertension. Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. CI = confidence interval; DBP = diastolic blood pressure; HPT = Hypertension Prevention Trial; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; K-H = Knapp-Hartung variance estimate; Na = sodium; RE = random-effects; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention.

TABLE 10-6 GRADE Assessment Table: Sodium Reduction and Systolic Blood Pressure

GRADE Criteria	Rating[a]	Reasons for Rating	Strength of Evidence[b]
Outcome: Change in Systolic Blood Pressure			
Study design	High	Randomized controlled trials.	
Risk of bias	No (0)	Results similar if high-risk-of-bias studies are excluded.	
Inconsistency	No (0)	Although the overall summary estimate had substantial heterogeneity, with I^2 = 76 percent, meta-regression and subgroup analyses showed that most of the heterogeneity is explained by the difference in sodium intake between control and intervention groups and hypertension status and/or baseline systolic blood pressure. The residual I^2 = 41 percent is considered "moderate."[c]	
Indirectness	No (0)	Evidence directly answers the question of interest in terms of relevant populations, interventions, comparators, and outcomes.	⊕⊕⊕⊕
Imprecision	No (0)	Statistically significant and biologically meaningful summary effect sizes across all studies and within subgroups, including those with and without individuals with hypertension.	High
Publication bias	Undetected (0)	No detectable publication bias; summary results remained statistically significant when additional studies added using trim-and-fill procedure.	
Other	Intake–response (+1)	Meta-regression showed that larger contrast in sodium intake between control and intervention groups were associated with larger effect sizes. Additionally, the intercept term was not statistically significant, consistent with a linear intake–response relationship down to zero contrast in sodium intake.	

[a]Table format same as Table 10-2.

[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

[c]This text was revised since the prepublication release.

TABLE 10-7 GRADE Assessment Table: Sodium Reduction and Diastolic Blood Pressure

GRADE Criteria	Rating[a]	Reasons for Rating	Strength of Evidence[b]
Outcome: Change in Diastolic Blood Pressure			
Study design	High	Randomized controlled trials.	
Risk of bias	No (0)	Results similar if high-risk-of-bias studies are excluded.	
Inconsistency	No (0)	Meta-regression showed that the substantial heterogeneity of the overall summary estimate (I^2 = 79 percent) is partially explained by baseline diastolic blood pressure and to a small extent by the difference in sodium intake between control and intervention groups. The residual I^2 = 73 percent is considered substantial. However, excluding the studies with the largest effect sizes further reduced heterogeneity to "moderate," with I^2 = 37 percent. Thus, the observed heterogeneity involves differences between small and large beneficial effects, not whether an effect exists or whether an effect is beneficial or harmful. Thus, this heterogeneity is not considered serious for the strength-of-evidence grading for a causal relationship, and no downgrade for inconsistency was applied.	
Indirectness	No (0)	Evidence directly answers the question of interest in terms of relevant populations, interventions, comparators, and outcomes.	⊕⊕⊕⊕ High
Imprecision	No (0)	Statistically significant and biologically meaningful summary effect size across all studies and within subgroups, including those with and without individuals with hypertension.	
Publication bias	Detected, but no impact (0)	Some publication bias was detected; summary results remained statistically significant when additional studies added using trim-and-fill procedure.	
Other	None (0)	No upgrade for intake–response was applied. In all trials and crossover trials alone meta-regression of showed a nonstatistically significant trend ($p > .05$) of increased effect size with increased contrast in sodium intake between control and intervention groups. In parallel trials alone, no trend was evident (slope = 0, $p > .99$). The contrast in sodium intake explained very little of the heterogeneity.	

[a]Table format same as Table 10-2.

[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

In both cases, the updated strength of evidence was assessed as high. Additionally, the evidence for systolic blood pressure exhibited an intake–response gradient across studies.

Selection of Chronic Disease Indicators

Table 10-8 presents the overall GRADE summary of findings for the four indicators with a moderate or high strength of evidence for a causal relationship with sodium intake that the committee selected to inform the sodium CDRRs. Although the strength of evidence for all-cause mortality was rated as moderate (see Annex 10-1), this indicator was not selected because it is nonspecific and because the effect sizes were notably smaller than for cardiovascular disease and hypertension. For each of the four selected indicators, the committee's reevaluated strength of the evidence was rated higher than the rating in the *AHRQ Systematic Review*. For cardiovascular disease and hypertension, the higher strength-of-evidence ratings were attributable to the more stringent exclusion of short-term trials as well as the committee's use of hazard ratios rather than relative risks based on raw counts. This difference in the analytical approach led to statistically significant summary results with no observed heterogeneity. For systolic and diastolic blood pressure, the higher strength-of-evidence ratings were attributable to the additional exploration of heterogeneity that enabled apparent inconsistencies to be explained. For systolic blood pressure, these analyses revealed that heterogeneity could be largely explained by differences across studies in the magnitude of sodium intake reduction associated with the intervention, the presence/absence of participants with hypertension in the studied populations, and baseline systolic blood pressure levels. For diastolic blood pressure, these factors reduced, but could not fully explain, the observed heterogeneity. However, the heterogeneity for diastolic blood pressure was largely the result of some studies showing large beneficial effect sizes. Removing these large effect studies reduced heterogeneity to a low to moderate level, and there remained a statistically significant reduction in diastolic blood pressure.

Based on the committee's synthesis of the evidence, as well as the *Guiding Principles Report* recommendation that there should be at least moderate strength of evidence of a causal relationship between intake and chronic disease, the committee selected cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure as the indicators that would inform the sodium CDRRs. Although the *Guiding Principles Report* recommended that, in general, a "single outcome indicator on the causal pathway" be selected, the report acknowledged the possibility of using "multiple indicators of chronic disease" if there is "strong evidence suggesting that multiple indicators point to risk of a chronic disease"

TABLE 10-8 GRADE Summary of Findings Used to Determine the Causal Relationship Between Reduction in Sodium Intake and Chronic Disease Risk

Indicator	Duration of Study or Follow-Up	Study Results and Measurements	Strength of Evidence
Cardiovascular disease event incidence	2.5 to 12 years	Relative risk: 0.74 [95% CI: 0.58, 0.93]	Moderate, due to imprecision
Hypertension incidence	2.5 to 4 years	Relative risk: 0.79 [95% CI: 0.67, 0.93]	Moderate, due to imprecision
Systolic blood pressure	4 weeks to 4 years	See Table 10-6	High
Diastolic blood pressure	4 weeks to 4 years	See Table 10-7	High

(NASEM, 2017, p. 10). The committee judged that such evidence exists, as the four indicators of cardiovascular disease incidence, hypertension incidence, systolic blood pressure, and diastolic blood pressure are all biologically interrelated. The committee developed a framework for chronic disease outcomes to illustrate the interrelationships among sodium intake and the four indicators (see Figure 10-13). The evidence for the relationships between reductions in sodium intake and the four indicators was evaluated using GRADE as described above. Pursuant to the *Guiding Principles Report* recommendation on the use of surrogate markers, the committee further considered whether blood pressure could serve as a qualified surrogate marker in context of sodium intake reduction interventions. The evidence and rationale for qualifying systolic blood pressure and diastolic blood pressure as surrogate markers for predicting the effects of changes in sodium intake on changes in the incidence of hypertension and cardiovascular disease is presented in Annex 10-2.

ASSESSMENT OF INTAKE–RESPONSE FOR CHRONIC DISEASE INDICATORS

The *Guiding Principles Report* outlines two key steps in evaluating evidence related to characterizing an intake–response relationship. First, it is necessary to frame the question appropriately by identifying any differences in the body of evidence to evaluate intake–response as compared to the body of evidence used previously to evaluate causality. Second, the strength of the body of evidence needs to be reevaluated under GRADE specifically in the context of intake–response, a process that may lead to different ratings for different ranges of intake. The results of these two steps as performed by the committee are described below.

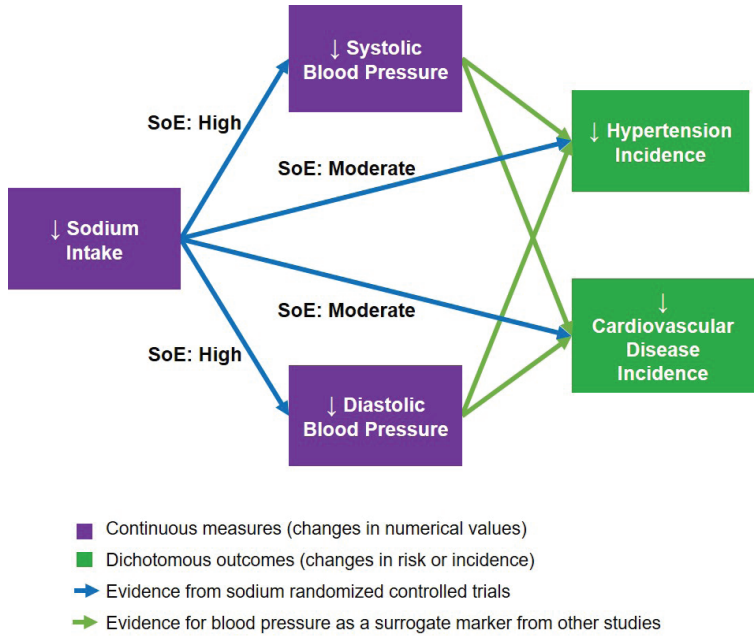

FIGURE 10-13 Framework for the relationships between sodium intake and chronic disease indicators.
NOTES: For the committee's evaluation of blood pressure as a qualified surrogate marker of hypertension and cardiovascular disease in context of sodium intake interventions, see Annex 10-2. SoE = strength of evidence.

Framing the Question

Combining Indicators of Chronic Disease Endpoints

As described above, the committee considered four indicators together as indicators of chronic disease risk. Cardiovascular disease incidence and hypertension incidence are direct measures of chronic disease risk. As discussed in Annex 10-2, blood pressure was considered a qualified surrogate marker for cardiovascular disease and hypertension incidence in the context of sodium reduction interventions. Of these two blood pressure measures, systolic blood pressure is more strongly related to cardiovascular disease risk than is diastolic blood pressure. Although any of these indicators alone may be adequate for supporting an intake–response relationship between sodium and chronic disease risk, the committee considered the evidence to be stronger if there were consistency across these four indicators in accordance with the relationships depicted in the framework for sodium chronic disease outcomes (see Figure 10-13).

Intake–Response Meta-Analysis

The first framing issue is considering the need to characterize a continuous intake–response relationship rather than to evaluate the presence or absence of an effect with a specific intervention. The committee applied intake–response meta-analysis methods to perform this characterization (see Box 10-6).

Sodium Intake Levels Studied in Eligible Randomized Controlled Trials

The second framing issue is to characterize the range of sodium intakes over which the available studies have examined the selected indicators of cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure. The *Guiding Principles Report* states

> Rating the certainty in intake–response relationships has an additional dimension in that the level of certainty may differ across the range of intakes due to different reasons. For example, the precision of the intake–response estimate might differ across the range of intakes or by differing population characteristics. (NASEM, 2017, p. 215)

Therefore, to the extent to which the body of evidence differs in different intake ranges, the determination of the strength of evidence of a positive, negative, or zero slope also needs to be separately evaluated in different intake ranges.

Figure 10-14 summarizes the intake ranges studied for each indicator, which were primarily based on validated measures such as 24-hour urinary sodium excretions (see Chapter 3). The intake ranges for cardiovascular disease (2,300–4,100 mg/d [100–178 mmol/d]) and hypertension (2,400–4,100 mg/d [104–178 mmol/d]) are substantially narrower than the ranges for systolic blood pressure and diastolic blood pressure (850–5,200 mg/d [37–226 mmol/d]).[7] Importantly, evidence was available for all four in the intake range from approximately 2,300–4,100 mg/d (100–178 mmol/d);[8] evidence from trials outside of this range (< 2,300 mg/d [< 100 mmol] and > 4,100 mg/d [178 mmol/d]) was available only for blood pressure. Therefore, the committee separately evaluated the evidence for intake–response in the three intake ranges: 2,300–4,100, < 2,300, and > 4,100 mg/d (100–178, < 100, and > 178 mmol/d, respectively) (see Figure 10-14).

[7]In the committee's intake–response analyses, the sodium intake level of approximately 850 mg/d (37 mg/d) was rounded to 1,000 mg/d (43 mmol/d) and the sodium intake level of approximately 5,200 mg/d (226 mmol/d) was rounded to 5,000 mg/d (217 mmol/d).

[8]The committee considered the lower end of the hypertension range of 2,400 mg/d (104 mmol/d) sufficiently close to 2,300 mg/d (100 mmol/d) to use the latter value for both.

BOX 10-6
Intake–Response Meta-Analyses

Intake–response (or dose–response) meta-analyses have most commonly been applied to observational data and dichotomous endpoints, following the methods of Greenland and Longnecker (1992) and Berlin et al. (1993). For instance, Del Gobbo et al. (2013) applied such methods to examine the intake–response relationship between circulating and dietary magnesium and risk of cardiovascular disease, standardizing effect sizes to a uniform increment of 0.2 mmol/L or 200 mg/d. More recently, such methods have been extended to continuous endpoints and clinical trials (Crippa and Orsini, 2016; Del Gobbo et al., 2015). The most common approach for such meta-analyses is a two-stage approach (Crippa and Orsini, 2016). In the first stage, parameters for an intake–response model (e.g., linear, E-max, spline) are estimated for each study separately; in the second stage, a traditional meta-analysis is performed on the study-specific model parameters.

One of the challenges to applying intake–response meta-analysis in the case of sodium is that virtually all of the randomized controlled trials involve a single contrast between control and intervention. Thus, the committee could only use a linear model for a common intake–response model across studies. This limitation was not considered critical, especially because meta-regressions performed by the committee for systolic blood pressure favored the linear model as compared to nonlinear models as represented by restricted cubic splines (as shown by the evaluation of the intake–response gradient for sodium intake and systolic blood pressure with meta-regression analyses described above). The use of a linear model with a single contrast also simplifies the first stage of the procedure: the slope parameter and its confidence interval can be derived directly from the point estimate and confidence interval for the reported log(hazard ratio) (for dichotomous endpoints) or mean difference (for continuous endpoints) by dividing by the difference in sodium intake between study arms. Therefore, for each indicator (cardiovascular disease incidence, hypertension incidence, systolic blood pressure, and diastolic blood pressure), the committee calculated the slope as the original effect estimate standardized to a 1,000 mg/d (43 mmol/d) decrease in sodium intake. A decrease of 1,000 mg/d (43 mmol/d) of sodium is close to the median amount of intake reduction across the cardiovascular disease, hypertension, and blood pressure trials, and appears to be achievable in a clinical setting based on dietary intervention studies. The intake–response slopes were then analyzed using standard meta-analysis methods, including investigation of sources of heterogeneity, as was performed previously in the evaluation of causality. An important part of the exploration of heterogeneity is investigation of differences in slopes and at different intake levels, which may indicate potential nonlinearity and/or differences in the strength of the body of evidence across different intake ranges. A similar approach, but standardized to 2,300 mg/d (100 mmol/d) reduction rather than 1,000 mg/d (43 mmol/d) reduction, was employed for the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (Mozaffarian et al., 2014).

Supporting Selection of the CDRR

The final framing issue is ensuring that the approach appropriately supports selection of a DRI based on chronic disease, as outlined by the *Guiding Principles Report*. First, the *Guiding Principles Repor*t recommended "Intake–response relationships should be defined as different ranges of the intake–response relationship where risk is at minimum, is decreasing, and/or is increasing (*i.e., slope = 0, negative, or positive*) [emphasis added]" (NASEM, 2017, p. 11). The committee's use of "slope" as the study outcome of interest for intake–response assessment is consistent with this recommendation. The *Guiding Principles Report* further noted

> In the simplest case, when the relationship appears linear, this characterization could include the slope of the relationship (amount of change in risk for a given change in intake), the range over which this relationship is supported, and the CIs for each of these. (NASEM, 2017, p. 219)

The committee's approach to intake–response meta-analysis directly addresses this recommendation by evaluating outcomes based on a standardized change in sodium intake and thereby translating effect sizes into a slope. Specifically, for each intake range considered, the key question was the strength of evidence of a positive slope—that is, reductions in sodium intake reduce chronic disease risk.

Rating Evidence for Chronic Disease Intake–Response

The committee rated the evidence for chronic disease intake–response separately for the three different sodium intake ranges (2,300–4,100, > 4,100, and < 2,300 mg/d [100–178, > 178, and < 100 mmol/d, respectively]). For each intake range, the available evidence is described, followed by an intake–response meta-analysis for each indicator, using methods described above in Box 10-6. The evidence for a chronic disease intake–response relationship is then rated using GRADE, taking into account the special considerations for intake–response outlined in the *Guiding Principles Report*. The committee recognized that individual trials involving three or more sodium intake levels provide a stronger characterization of intake–response than using a series of individual trials at different intake levels comparing a control and a single intervention. However, in keeping with the *Guiding Principles Report* and the use of systematic reviews in evaluating the body of evidence, the committee used the totality of the evidence rather than focusing on the results of individual studies. Intake–response relationships characterized in individual studies can provide additional supportive evidence. The *AHRQ Systematic Review* identified three

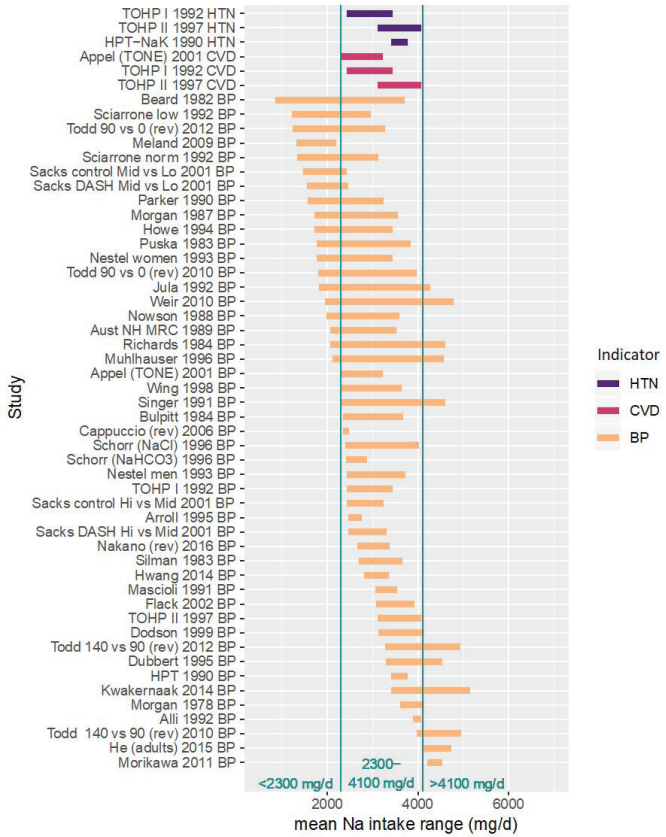

FIGURE 10-14 Intake ranges studied in randomized controlled trials of sodium intake and chronic disease indicators.

NOTES: The committee separately evaluated the strength of evidence for intake–response in three intake ranges, as indicated, owing to the differing indicators for which evidence is available. Specifically, in the middle range from 2,300–4,100 mg/d, the body of evidence consists of trials of incident cardiovascular disease, incident hypertension, and blood pressure. In the lower (< 2,300 mg/d) and upper (> 4,100 mg/d) ranges, the body of evidence used by the committee consists only of trials of blood pressure. Studies are listed by the last name of the first author, year of publication, and indicator represented in the figure. For studies with multiple contrasts, a description of the comparison represented in the figure follows the author's name. Intake values are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. BP = blood pressure; CVD = cardiovascular disease; DASH = Dietary Approaches to Stop Hypertension; HPT = Hypertension Prevention Trial; HTN = hypertension; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention; TONE = Trial of Nonpharmacologic Interventions in the Elderly.

trials with more than two sodium intake levels (Sacks et al., 2001; Todd et al., 2010, 2012). The intake–response results from these trials, as well as their limitations, are described in Box 10-7.

Sodium Intakes 2,300–4,100 mg/d (100–178 mmol/d)

Eligible studies All studies for which *both* the control and the intervention sodium intake level (rounded to the nearest 100 mg/d [4 mmol/d]) were within the range 2,300–4,100 mg/d (100–178 mmol/d) were considered eligible, as these provide direct evidence of intake–response in this intake range (see Figure 10-15). Evidence was available for all four of the selected chronic disease indicators.

Intake–response meta-analysis Intake–response meta-analyses on the slope for each of the four selected indicators are shown in Figures 10-16 through 10-20. For cardiovascular disease,[9] the intake–response slopes from randomized controlled trials were statistically significant with no heterogeneity (I^2 = 0 percent) (see Figure 10-16), similar to the results from evaluating evidence for causality. The linear slope reported by Cook et al. (2014),[10] based on observational data for cardiovascular disease, is consistent with the slope derived from randomized controlled trials. Combining these studies together led to virtually the same results as using randomized controlled trials alone, with no observed heterogeneity (see Figure 10-17).

For hypertension, the intake–response slopes were statistically significant with little heterogeneity (I^2 = 6 percent) (see Figure 10-18), similar to the results from evaluating evidence for causality. As with the analysis for causality, because of the small numbers of studies and low heterogeneity, random-effects estimates did not include the Knapp-Hartung modification.

For systolic blood pressure, the intake–response slope was statistically significant with moderate heterogeneity (I^2 = 47 percent). Heterogeneity was reduced (I^2 = 32 percent) when Nakano et al. (2016), the one study with high risk of bias, was excluded. Presence or absence of participants with hypertension in the study group contributed to this heterogeneity, with within-subgroup I^2 of 35 and 42 percent, respectively (see Figure 10-19). Additional subgroup analyses found that the presence or absence of individuals being treated with blood pressure medication explained most of the heterogeneity (within subgroup I^2 = 23 and 22 percent, respectively). The systolic blood pressure slope in all subgroup analyses remained sta-

[9]Cardiovascular disease events collected in the individual studies included myocardial infarction, angina, congestive heart failure, coronary revascularization, stroke, transient ischemic attack, arrhythmia, or other.

[10]This observational study was rated as low risk of bias in the *AHRQ Systematic Review*.

BOX 10-7
Intake–Response from Randomized Controlled Trials with More Than Two Sodium Intake Levels

Three studies were identified in the *AHRQ Systematic Review* that included more than two sodium intake levels:

- Sacks et al. (2001) was a multicenter, randomized, crossover feeding trial comparing the effects on blood pressure of three levels of sodium density (1,150, 2,300, and 3,450 mg/d [50, 100, and 150 mmol/d] for a 2,100 kcal/d energy intake). Participants were randomized to one of two types of diet arms—the Dietary Approaches to Stop Hypertension (DASH) diet and a control diet. Each sodium level was consumed for 30 days within each diet arm. Participants (n = 412) were adults with blood pressure exceeding 120/80 mm Hg, including those with stage 1 hypertension (a systolic blood pressure of 140–159 mm Hg or a diastolic blood pressure of 90–95 mm Hg).
- Todd et al. (2010) was a smaller (n = 34) randomized, crossover feeding trial with a single low-sodium diet supplemented with tomato juice that contained 0, 2,070, or 3,220 mg/d (0, 90, or 140 mmol/d) sodium. Measured total sodium intake was 1,794, 3,979, and 4,945 mg/d (78, 173, and 215 mmol/d). Each sodium level was consumed for 4 weeks. All participants had hypertension with systolic blood pressure > 130 mm Hg and diastolic blood pressure > 85 mm Hg or were currently on antihypertensive therapy.
- Todd et al. (2012) was a smaller (n = 23) randomized, crossover feeding trial with a single low-sodium diet supplemented with tomato juice that contained 0, 2,070, or 3,220 mg/d (0, 90, or 140 mmol/d) sodium.* Measured total sodium intake was 1,233, 3,287, and 4,936 mg/d (54, 143, and 215 mmol/d), respectively. Each sodium level was consumed for 4 weeks. All participants were normotensive with systolic blood pressure ≤ 130 mm Hg and diastolic blood pressure ≤ 85 mm Hg and were not on antihypertensive therapy.

tistically significant. The funnel plot asymmetry test for publication bias was not statistically significant (p = .09). The overall effect remained statistically significant after adjusting for possible publication bias using the trim-and-fill method. All estimates for systolic blood pressure used the Knapp-Hartung modification.

For diastolic blood pressure, the intake–response slope was statistically significant with moderate to substantial heterogeneity (I^2 = 59 percent). The presence or absence of participants with hypertension in the study group contributed to this heterogeneity; the subgroup of studies without participants with hypertension had I^2 of 2 percent, whereas studies that included participants with hypertension had I^2 of 68 percent (see Figure 10-20). Addi-

Both Sacks et al. (2001) and Todd et al. (2010) reported reductions in blood pressure with reductions in sodium intake. Sacks et al. (2001) additionally reported that the reduction was greater between the middle and low intake levels than between the high and middle intake levels, although the *p* values were not highly significant ($p = .03$ and .045 for control and DASH diets, respectively). Additionally, when stratified by energy intake levels, the intake–response relationships appeared linear (Murtaugh et al., 2018). Todd et al. (2010) also reported that the reduction was greater between the middle and low intake levels than between the high and middle intake levels, but this was likely caused by five participants having to withdraw from the high intake intervention because of excessively high blood pressure (> 160/100 mm Hg). Todd et al. (2012) reported no changes in blood pressure between groups with different sodium intakes.

Thus, none of these studies individually provides strong evidence of nonlinearity. Additionally, Sacks et al. (2001) concludes that reducing sodium intake below 2,300 mg/d (100 mmol/d) substantially reduces blood pressure, but Todd et al. (2012) concluded that dietary sodium has no effect on blood pressure. The conclusions from Todd et al. (2010) regarding intakes below 2,300 mg/d (100 mmol/d) are less clear, because the low intake level only extends to approximately 1,800 mg/d (78 mmol/d) while the middle sodium intake level was much higher at approximately 4,000 mg/d (174 mmol/d). Moreover, these studies have several limitations, such as relatively short duration (30 days or less) and, for the Todd et al. (2010, 2012) studies, small sample size and use of tomato juice to deliver sodium. The committee considered these studies as part of its GRADE evaluation of the body of evidence for different intake ranges, described in the main text.

*In Todd et al. (2012), the sodium content of the tomato juice in the highest intervention period was initially 4,370 mg/d (190 mmol/d); 10 participants completed the intervention at this level. Because of side effects, the sodium content was reduced to 3,220 mg/d (140 mmol/d) for the remaining participants. Results were pooled in the study.

tional subgrouping did not substantially reduce this heterogeneity. However, the diastolic blood pressure slope in all subgroup analyses remained statistically significant. The funnel plot asymmetry test for publication bias was not statistically significant ($p = .054$). The overall effect remained statistically significant after adjusting for possible publication bias using the trim-and-fill method. All estimates for diastolic blood pressure used the Knapp-Hartung modification.

Evidence rating for intake–response Following guidance in the *Guiding Principles Report*, the committee did not develop an effect estimate for a composite endpoint. That is, the overall GRADE rating, while taking into

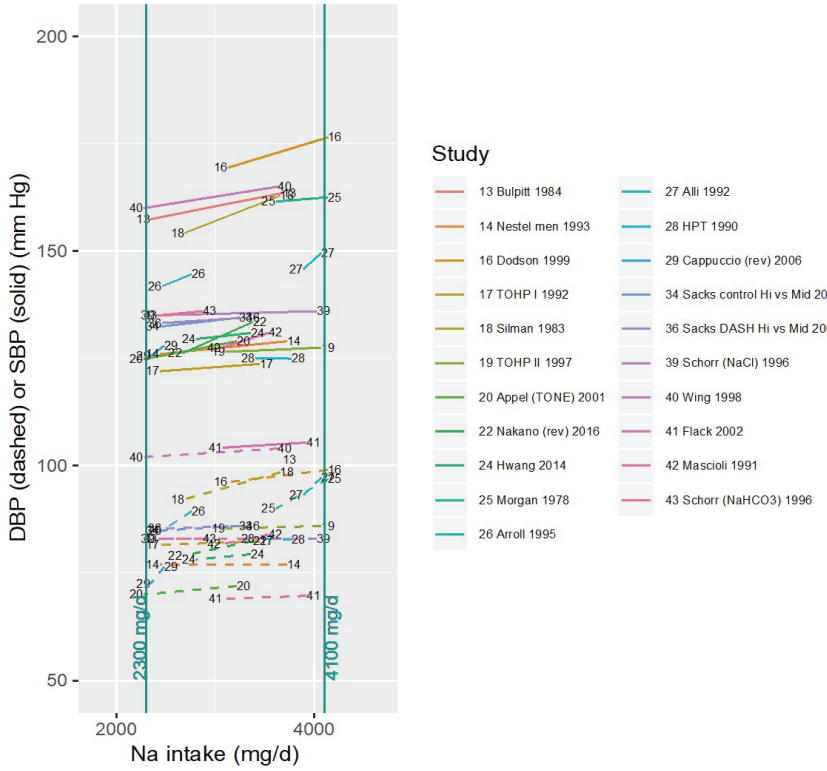

FIGURE 10-15 Intake–response slopes for blood pressure in intake range 2,300–4,100 mg/d.

NOTES: For each study considered within this intake range, the control and intervention systolic and diastolic blood pressures along with the corresponding sodium intake values are connected by a line segment (solid line for systolic blood pressure, dashed line for diastolic blood pressure). Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the figure follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic blood pressure; HPT = Hypertension Prevention Trial; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention; TONE = Trial of Nonpharmacologic Interventions in the Elderly.

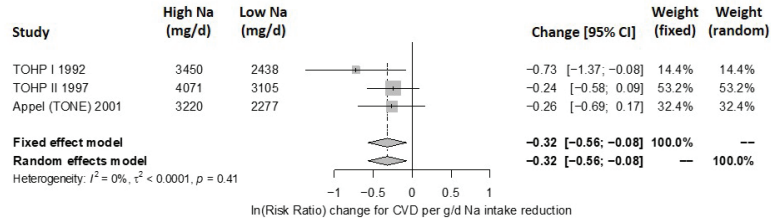

FIGURE 10-16 Intake–response meta-analysis for cardiovascular disease risk in the intake range 2,300–4,100 mg/d using randomized controlled trials alone.
NOTES: Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; CVD = cardiovascular disease; g/d = gram per day; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; TOHP = Trials of Hypertension Prevention; TONE = Trial of Nonpharmacologic Interventions in the Elderly.
SOURCES: Appel et al., 2001; TOHP Collaborative Research Group, 1992a,b, 1997.

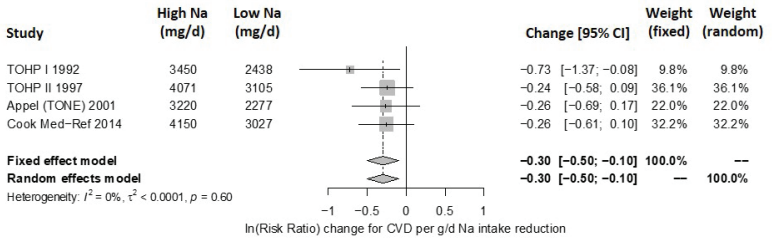

FIGURE 10-17 Intake–response meta-analysis for cardiovascular disease risk in intake range 2,300–4,100 mg/d combining randomized controlled trials with a low-risk-of-bias observational study.
NOTES: Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; CVD = cardiovascular disease; g/d = gram per day; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; TOHP = Trials of Hypertension Prevention; TONE = Trial of Nonpharmacologic Interventions in the Elderly.
SOURCES: Appel et al., 2001; Cook et al., 2014; TOHP Collaborative Research Group, 1992a,b, 1997.

account the multiple indicators, does not combine effect sizes for different endpoints. Instead, the effect estimates are calculated separately for each outcome (cardiovascular disease incidence, hypertension incidence, systolic blood pressure, and diastolic blood pressure). However, because the goal of the intake–response analysis is to determine the strength of evidence of

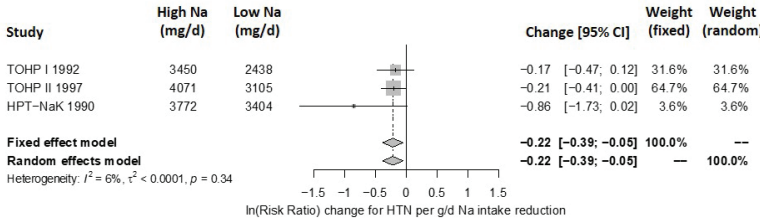

FIGURE 10-18 Intake–response meta-analysis for hypertension risk in intake range 2,300–4,100 mg/d.
NOTES: Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; g/d = gram per day; HPT = Hypertension Prevention Trial; HTN = incident hypertension; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; TOHP = Trials of Hypertension Prevention.
SOURCES: HPTRG, 1990; TOHP Collaborative Research Group, 1992a,b, 1997.

a *positive/negative/zero slope*, rather than a specific effect size, the committee determined it appropriate to examine all four indicators together in the GRADE table for intake–response. In that manner, using GRADE and trials results from 3 comparisons on cardiovascular disease risk, 3 comparisons on risk of hypertension, and 21 comparisons on systolic and diastolic blood pressure, the committee assessed the strength of evidence that reducing sodium intake reduces chronic disease risk in the intake range 2,300–4,100 mg/d (100–178 mmol/d). The overall rating is high, with details as to the rationale summarized in Table 10-9.

Sodium Intakes Above 4,100 mg/d (178 mmol/d)

Eligible studies No randomized controlled trials of cardiovascular disease and hypertension involving average intakes above 4,100 mg/d (178 mmol/d) were available. The *AHRQ Systematic Review* rated the observational studies in this intake range as having a low strength of evidence; as discussed earlier in this chapter, the committee decided not to establish sodium CDRRs based only on observational studies owing to such studies' potential for various biases. The one observational study of cardiovascular disease with low risk of bias (Cook et al., 2014) included intakes above 4,100 mg/d (178 mmol/d). The included comparison from this study was between two groups: one with sodium intakes 3,600 to < 4,800 mg/d (157 to < 209 mmol/d; mean intake 4,100 mg/d [178 mmol/d]) and the other with sodium intakes ≥ 4,800 mg/d (≥ 209 mmol/d; mean intake 5,800 mg/d [252 mmol/d]).

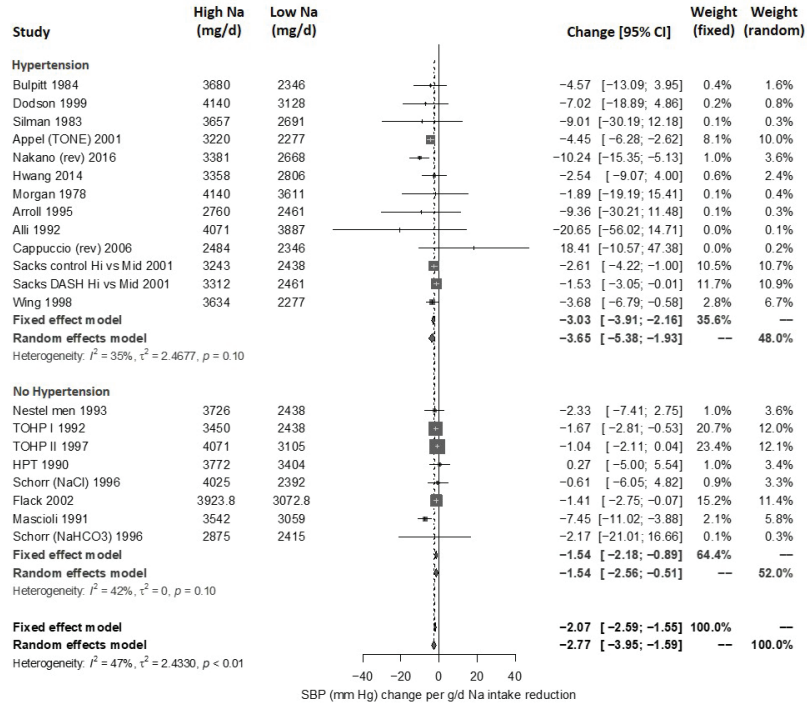

FIGURE 10-19 Intake–response meta-analysis for systolic blood pressure change in intake range 2,300–4,100 mg/d.
NOTES: Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; g/d = gram per day; HPT = Hypertension Prevention Trial; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention.

Two blood pressure trials (He et al., 2015; Morikawa et al., 2011) involved *both* the control and the intervention sodium intake level (rounded to the nearest 100 mg/d [4 mmol/d]) being above 4,100 mg/d (178 mmol/d). These studies were rated as having moderate risk of bias (He et al., 2015) and high risk of bias (Morikawa et al., 2011). Using the less stringent criteria that the *midpoint* of the control and intervention studies be above 4,100 mg/d (178 mmol/d) yielded four studies; using the least stringent criteria that only the control (high) intake level be above 4,100 mg/d (178 mmol/d) yielded 11

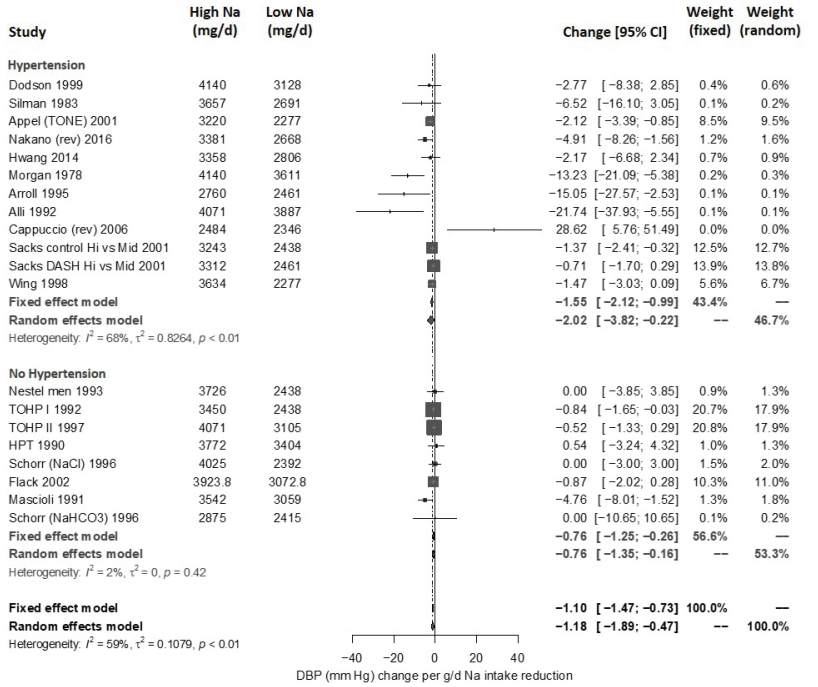

FIGURE 10-20 Intake–response meta-analysis for diastolic blood pressure change in intake range 2,300–4,100 mg/d.
NOTES: Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic blood pressure; g/d = gram per day; HPT = Hypertension Prevention Trial; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention.

studies (see Figure 10-21). To the extent that there may be nonlinearity in the intake–response relationship, these studies may be more indirect because the intake–response slope includes effects of reducing intake below 4,100 mg/d (178 mmol/d). This potential indirectness was taken into consideration in the committee's evidence rating, as described below. Additionally, there are no data above intakes of approximately 5,000 mg/d (217 mmol/d), so this evaluation only applies to intakes up to this value.

Intake–response meta-analysis For cardiovascular disease, Cook et al. (2014) found a hazard ratio of 1.05 [95% CI: 0.68, 1.62] for the high-intake group as compared to the reference group,[11] which translates to a slope of –0.03 [95% CI: –0.29, 0.23] in units of ln(risk ratio) per 1,000 mg/d (43 mmol/d) sodium intake reduction. This value is not statistically significant, and is smaller than the effect found from this study and from randomized controlled trials in the lower intake range of 2,300–4,100 mg/d (100–178 mmol/d). As only one study is available, no intake–response meta-analysis was performed.

For systolic blood pressure, the intake–response slope was statistically significant with low heterogeneity (I^2 = 29 percent) (see Figure 10-22). This heterogeneity was completely explained by the one study in participants without hypertension (Todd et al., 2012), which reported no statistically significant difference in systolic blood pressure between groups. Separating this one study resulted in no observed heterogeneity in the remaining studies (I^2 = 0 percent). The summary intake–response slope did not depend on whether or not the midpoint of the intake range was > 4,100 mg/d (> 178 mmol/d), consistent with a linear relationship extending from below to above 4,100 mg/d (178 mmol/d). A subgroup difference was found for blood pressure medication, with a larger slope in studies that included individuals being treated with blood pressure medication; however, the intake–response slope remained statistically significant in both subgroups. Results did not change with the exclusion of the one study with high risk of bias. The funnel plot asymmetry test for publication bias was not statistically significant (p = .059). Overall effect remained statistically significant after adjusting for possible publication bias using the trim-and-fill method. All estimates used the Knapp-Hartung modification.

For diastolic blood pressure, the intake–response slope was statistically significant with substantial or considerable heterogeneity (I^2 = 76 percent) (see Figure 10-23). No studies were rated as having a high risk of bias. The heterogeneity was completely explained by two studies: Todd et al. (2012), which is the only study with nonhypertensive participants that reported no effect on diastolic blood pressure, and Kwakernaak et al. (2014), which was a study of patients with type 2 diabetic nephropathy that reported a very large change in diastolic blood pressure. Excluding these two, there is no observed heterogeneity in the remaining studies (I^2 = 0 percent). The summary intake–response slope did not depend on whether the midpoint of the intake range was > 4,100 mg/d (> 178 mmol/d), consistent with a linear relationship extending from below to above 4,100 mg/d (178 mmol/d). No

[11]As described above, the high intake group consumed ≥ 4,800 mg/d (≥ 209 mmol/d) sodium, while the reference group in this comparison consumed 3,600 to < 4,800 mg/d (157 to < 209 mmol/d) sodium.

TABLE 10-9 GRADE Assessment Table for Intake–Response in Range 2,300–4,100 mg/d (100–178 mmol/d)

GRADE Criteria	Rating[a]
Outcome: Reduced chronic disease risk per 1,000 mg/d (43 mmol/d) sodium intake reduction, as indicated by cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure, in the intake range 2,300–4,100 mg/d (100–178 mmol/d).	
Study design	High
Risk of bias	No (0)
Inconsistency	No (0)
Indirectness	No (0)
Imprecision	No (0)
Publication bias	Undetected (0)
Other	No (0)

[a]Table format same as Table 10-2.
[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

Reasons for Rating	Strength of Evidence[b]
Randomized controlled trials.	
No cardiovascular disease or hypertension studies had high risk of bias. For systolic blood pressure and diastolic blood pressure, summary slope remains statistically significant, with lower heterogeneity when removing the one study with high risk of bias.	
Little or no heterogeneity for cardiovascular disease or hypertension. For systolic blood pressure, moderate heterogeneity overall (I^2 = 47 percent), which was largely explained by hypertension or blood pressure medication status. Effects were greater in populations that included individuals with hypertension or that included those taking blood pressure medication, but effects remained statistically significant for populations without these characteristics. Heterogeneity was low to moderate within subgroups (I^2 between 22 and 42 percent). For diastolic blood pressure, there was moderate to substantial heterogeneity overall (I^2 = 59 percent), which can only be partially explained by hypertension or blood pressure medication status. Heterogeneity within subgroups varied from low to substantial (I^2 between 2 and 68 percent). Overall, no downgrade was applied because the two more direct indicators of chronic disease risk—cardiovascular disease and hypertension—had little or no unexplained heterogeneity.	⊕⊕⊕⊕ High
All studies used control and intervention intake levels within the specified intake range. Cardiovascular disease and hypertension are direct measures of chronic disease risk; systolic blood pressure and diastolic blood pressure are indirect but serve as qualified surrogate markers.	
Statistically significant and biologically meaningful summary effect sizes for all indicators, across all studies and within subgroups, including those with and without individuals with hypertension.	
No publication bias detected; results similar if adjusted for possible publication bias using trim-and-fill procedure.	
Outcome already specified as an intake–response slope, so no additional upgrade for intake–response gradient.	

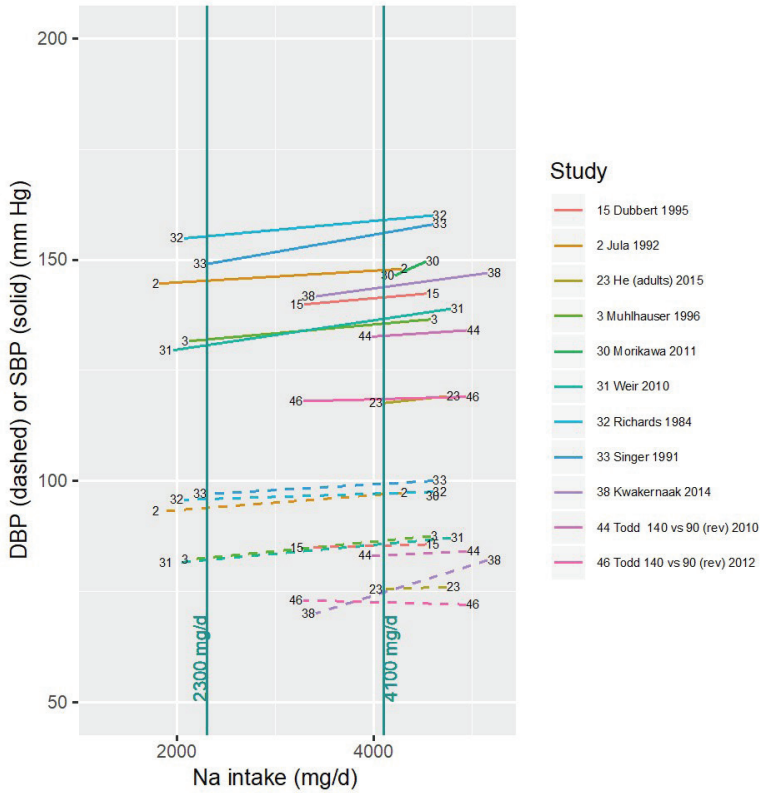

FIGURE 10-21 Intake–response slopes for blood pressure in intake range > 4,100 mg/d.

NOTES: For each study considered within this intake range, the control and intervention systolic and diastolic blood pressures along with the corresponding sodium intake values are connected by a line segment (solid for systolic blood pressure, dashed for diastolic blood pressure). Studies were included if the control (high) sodium intake level was > 4,100 mg/d. Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the figure follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. DBP = diastolic blood pressure; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure.

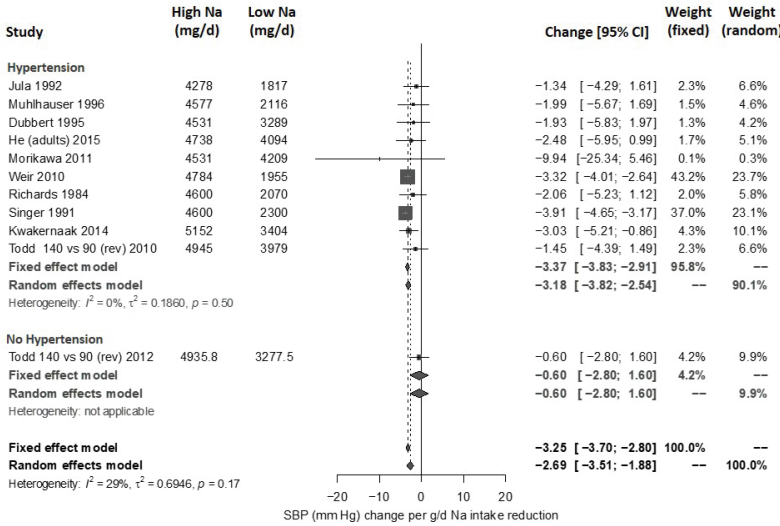

FIGURE 10-22 Intake–response meta-analysis for systolic blood pressure change in intake range > 4,100 mg/d.
NOTES: Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; g/d = gram per day; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure.

subgroup differences were found based on blood pressure medication. After excluding the two outliers, all studies included individuals with hypertension. A funnel plot asymmetry test for publication bias was not statistically significant (p = .94). Overall effect remains statistically significant after adjusting for possible publication bias using the trim-and-fill method. All estimates used the Knapp-Hartung modification.

Evidence rating for intake–response Using GRADE, the committee assessed the strength of evidence that reducing sodium intake reduces chronic disease risk in the intake range above 4,100 mg/d (178 mmol/d). The overall rating was moderate owing to concerns about indirectness, with details as to the rationale summarized in Table 10-10. Because of lack of data above 5,000 mg/d (217 mmol/d), this rating only applies for sodium intakes up to this value.

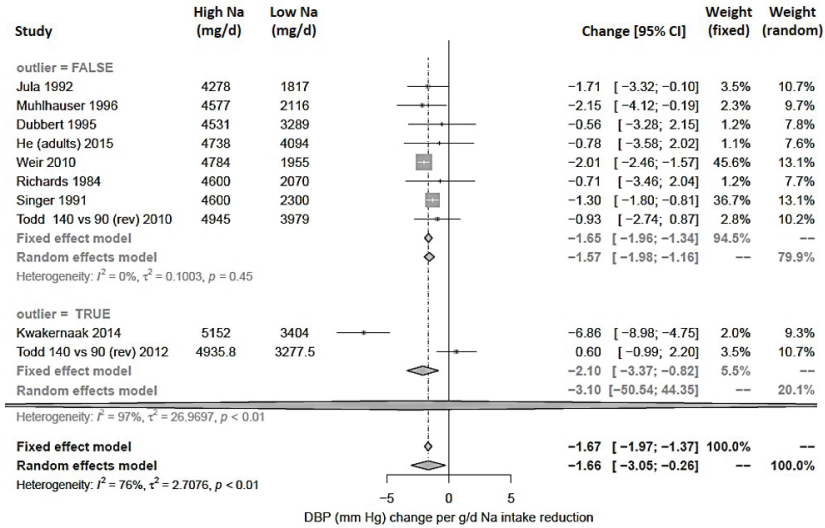

FIGURE 10-23 Intake–response meta-analysis for diastolic blood pressure change in intake range > 4,100 mg/d.
NOTES: Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; DBP = diastolic blood pressure; g/d = gram per day; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*.

The *AHRQ Systematic Review* identified a number of observational studies of blood pressure, cardiovascular disease, and hypertension that included participants with intakes above 5,000 mg/d (217 mmol/d). Overall, the *AHRQ Systematic Review* rated the strength of evidence that sodium intake was associated with these outcomes as low or insufficient owing to their observational design and concerns about risk of bias. Additionally, the *AHRQ Systematic Review* concluded that there was insufficient data to characterize the nature of the intake–response relationship based on observational studies. The committee, however, recognized that a portion of the general population consumes sodium at levels of intake exceeding 5,000 mg/d (217 mmol/d) (see Chapter 11, Tables 11-4 and 11-6). Although the magnitude of the risk reduction is uncertain, the committee used its expert judgment to assume that reducing sodium intakes above 5,000 mg/d (217 mmol/d) reduces chronic disease risk. Therefore, those consuming sodium

TABLE 10-10 GRADE Assessment Table for Intake–Response in Range Above 4,100 mg/d (178 mmol/d)

GRADE Criteria	Rating[a]	Reasons for Rating	Strength of Evidence[b]
Outcome: Reduced chronic disease risk per 1,000 mg/d (43 mmol/d) sodium intake reduction, as indicated by cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure, in the intake range above 4,100 mg/d (178 mmol/d).			
Study design	High	Randomized controlled trials.	
Risk of bias	No (0)	Only one study, for systolic blood pressure, had high risk of bias; results did not change with exclusion of this study.	
Inconsistency	No (0)	For systolic blood pressure, there was low heterogeneity overall (I^2 = 29 percent), which is completely explained by the one study that excluded individuals with hypertension. Effects were greater in studies that included those taking blood pressure medication, but effects remained statistically significant in both groups of studies. For diastolic blood pressure, there was substantial heterogeneity overall (I^2 = 76 percent), all of which is explained by two studies: one study that excluded adults with hypertension, and one study reporting large effects in patients with type 2 diabetic nephropathy. Overall, no downgrade was applied because all the observed heterogeneity could be explained.	⊕⊕⊕◯ Moderate up to 5,000 mg/d (217 mmol/d); Insufficient[c] above 5,000 mg/d (217 mmol/d)[d]
Indirectness	Serious (–1)	Only one low-risk-of-bias observational study was available in this intake range for cardiovascular disease, one of the more direct measures of chronic disease risk. No data in this intake range was available for hypertension. For systolic blood pressure and diastolic blood pressure, the midpoint of control and intervention intakes were > 4,100 mg/d (> 178 mmol/d) for only 4 of the 11 randomized controlled trials studies of systolic blood pressure and diastolic blood pressure; these studies were all < 6 months in duration. All but one of the studies of systolic blood pressure and diastolic blood pressure included adults with hypertension, with the one study in normotensives reporting no effect.	

continued

TABLE 10-10 Continued

GRADE Criteria	Rating[a]	Reasons for Rating	Strength of Evidence[b]
		Overall, a downgrade for indirectness was applied owing to the lack of studies fully (or mostly) within this intake range, the lack of studies in normotensives, and the lack of randomized controlled trials on cardiovascular disease and hypertension providing more direct evidence of reduced chronic disease risk.	
Imprecision	No (0)	Statistically significant and biologically meaningful summary effect sizes for systolic blood pressure and diastolic blood pressure, across all studies and within all subgroups that included adults with hypertension.	
Publication bias	Undetected (0)	No publication bias detected; results similar if adjusted for possible publication bias using trim-and-fill procedure.	
Other	No (0)	Outcome already specified as an intake–response slope, so no additional upgrade for intake–response gradient.	

[a]Table format same as Table 10-2.

[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

[c]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system *is very low certainty* or *quality of the evidence*.

[d]For intakes above 5,000 mg/d (217 mmol/d), based on the totality of the evidence, the committee exercised expert judgment in assuming that, for the purposes of public health decision making, reducing sodium intake would reduce chronic disease risk.

at levels of intake exceeding 5,000 mg/d (217 mmol/d) would be expected to benefit from reducing sodium intake.

Sodium Intakes Below 2,300 mg/d (100 mmol/d)

Eligible studies No randomized controlled trials of cardiovascular disease and hypertension involving average sodium intakes in this range were available. The one observational study of cardiovascular disease with a low risk of bias included intakes below 2,300 mg/d (100 mg/d) (Cook et al., 2014). The included comparison from this study was between two groups: one with intakes 3,600 to < 4,800 mg/d (157 to < 209 mmol/d; mean intake

4,100 mg/d [178 mmol/d]) and the other < 2,300 mg/d (< 100 mmol/d; mean intake 1,900 mg/d [83 mmol/d]).

One blood pressure study involved *both* the control and the intervention sodium intake level (rounded to the nearest 100 mg/d) below 2,300 mg/d (100 mmol/d) (Meland and Aamland, 2009). Using the less stringent criterion that the *midpoint* of the control and intervention studies be below 2,300 mg/d (100 mmol/d) yielded five studies with a total of seven comparisons; using the least stringent criterion that only the intervention (low) intake level be below 2,300 mg/d (100 mmol/d) yielded 17 studies with 19 comparisons (see Figure 10-24). To the extent that there may be nonlinearity in the intake–response relationship, these studies may be more indirect because the intake–response slope includes effects of reducing intake above 2,300 mg/d (100 mmol/d). This potential indirectness was taken into consideration in the committee's evidence rating, as described below. Additionally, there are no data below intakes of approximately 1,000 mg/d (43 mmol/d), so this evaluation only applies to intakes down to this value.

Intake–response meta-analysis For cardiovascular disease, Cook et al. (2014) found a hazard ratio of 0.68 [95% CI: 0.34, 137] for the low sodium intake group as compared to the reference group,[12] which translates to a slope of –0.17 [95% CI: –0.48, 0.14] in units of ln(risk ratio) per 1,000 mg/d (43 mmol/d) sodium intake reduction. This value is not statistically significant, but it is about the same as the effect found from this study and from randomized controlled trials in the higher intake range of 2,300 to 4,100 mg/d (100 to 178 mmol/d). As only one study is available, no intake–response meta-analysis was performed.

For systolic blood pressure, the intake–response slope was statistically significant with substantial heterogeneity (I^2 = 67 percent) (see Figure 10-25). Studies for which the midpoint of intakes between the control and intervention groups was < 2,300 mg/d (< 100 mmol/d) were more heterogeneous than studies for which the midpoint intake was ≥ 2,300 mg/d (≥ 100 mmol/d; I^2 = 82 versus 38 percent, respectively) (see Figure 10-25). Some of the heterogeneity was attributable to one of the two studies that included participants without hypertension that reported no statistically significant difference in systolic blood pressure between groups (Todd et al., 2012). Separating this one study resulted in less, but still moderate, heterogeneity in the remaining studies (I^2 = 47 percent); however, studies for which the midpoint of intakes between the control and intervention groups was < 2,300 mg/d (< 100 mmol/d) were still more heterogeneous (I^2 = 65

[12]As described above, the low intake group consumed < 2,300 mg/d (< 100 mmol/d) sodium, while the reference group in this comparison consumed 3,600 to < 4,800 mg/d (157 to < 209 mmol/d) sodium.

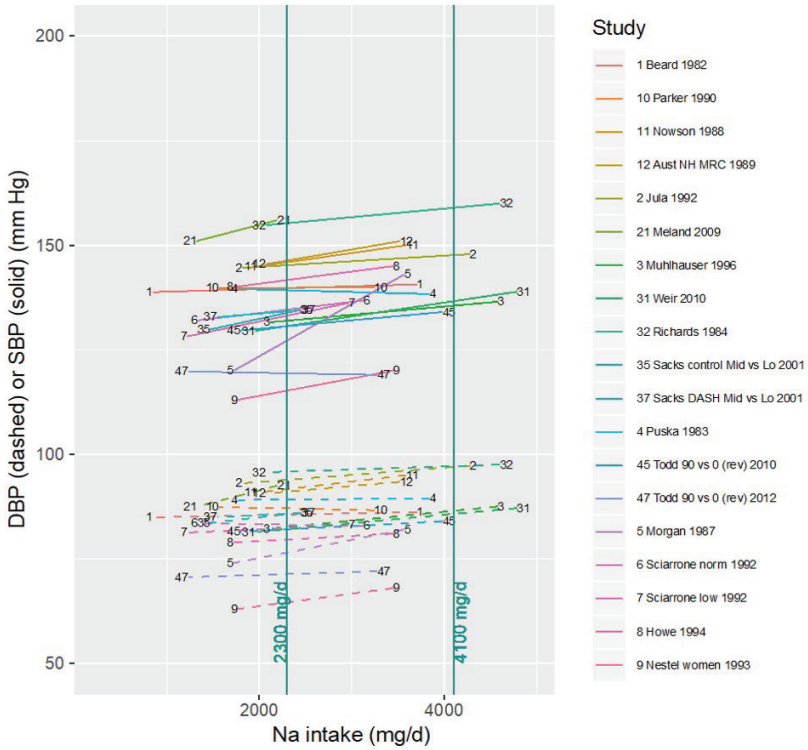

FIGURE 10-24 Intake–response slopes for blood pressure in intake range < 2,300 mg/d.

NOTES: For each study considered within this intake range, the control and intervention systolic and diastolic blood pressures along with the corresponding sodium intake values are connected by a line segment (solid line for systolic blood pressure, dashed line for diastolic blood pressure). Studies were included if the intervention (low) sodium intake level was < 2,300 mg/d. Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the figure follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. DASH = Dietary Approaches to Stop Hypertension; DBP = diastolic blood pressure; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure.

percent). Some, but not all, subgroups by hypertension status or blood medication had somewhat lower heterogeneity (I^2 = 23 to 68 percent), but subgroup differences were not statistically significant. Meta-regression by baseline blood pressure and control sodium intake level also could not explain observed heterogeneity. The summary intake–response slope did not

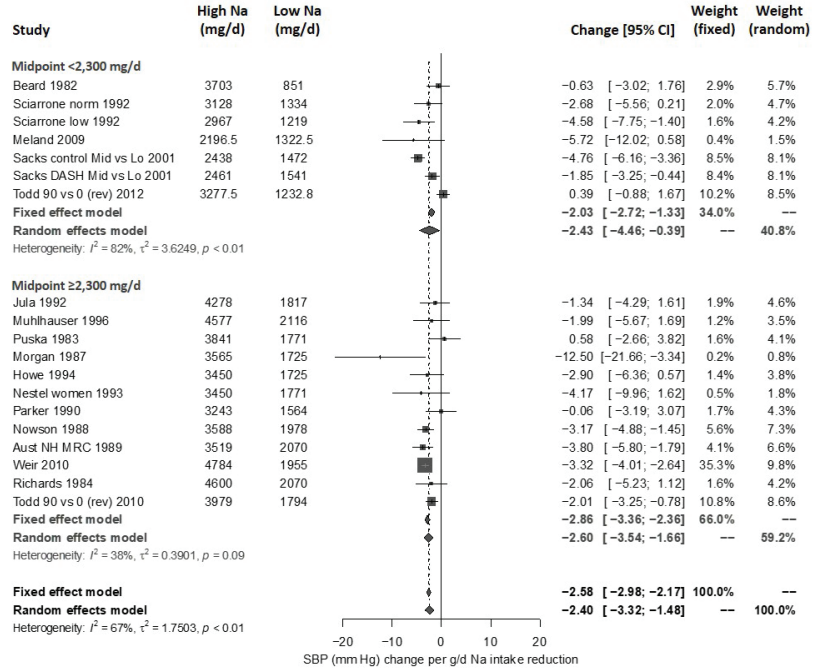

FIGURE 10-25 Intake–response meta-analysis for systolic blood pressure change in intake range < 2,300 mg/d.
NOTES: Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. Sodium intake levels are presented in milligrams To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; g/d = gram per day; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; SBP = systolic blood pressure.

depend on whether or not the midpoint of the intake range was < 2,300 mg/d (< 100 mmol/d), consistent with a linear relationship extending from above to below 2,300 mg/d (100 mmol/d). Results did not change with the exclusion of the one study with a high risk of bias. The funnel plot asymmetry test for publication bias was not statistically significant (p = .86). The overall effect remains statistically significant after adjusting for possible publication bias using the trim-and-fill method. All estimates used the Knapp-Hartung modification.

For diastolic blood pressure, the intake–response slope was statistically significant with moderate heterogeneity (I^2 = 54 percent; see Figure 10-26).

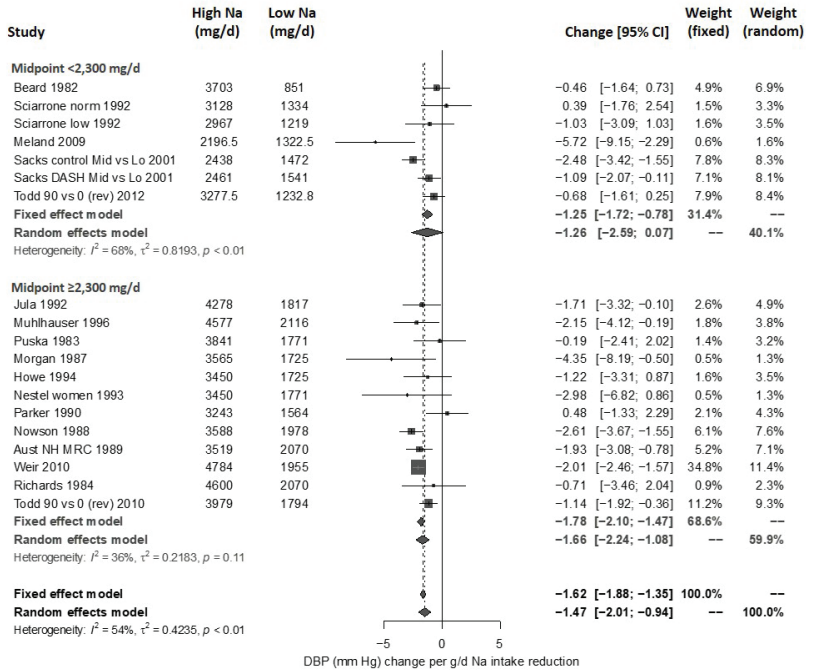

FIGURE 10-26 Intake–response meta-analysis for diastolic blood pressure change in intake range < 2,300 mg/d.
NOTES: Studies are listed by the last name of the first author and year of publication. For studies with multiple contrasts, a description of the comparison represented in the meta-analysis follows the author's name. Sodium intake levels are presented in milligrams. To convert to mmol, divide the milligram value by 23.0. CI = confidence interval; DBP = diastolic blood pressure; g/d = gram per day; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; mg/d = milligrams per day; Na = sodium; rev = revised as compared to estimate used in the *AHRQ Systematic Review*.

Studies for which the midpoint of intakes between the control and intervention groups was < 2,300 mg/d (< 100 mmol/d) were more heterogeneous (I^2 = 68 percent) than studies for which the midpoint intake was ≥ 2,300 mg/d (≥ 100 mmol/d; I^2 = 36 percent). Some, but not all, subgroups by hypertension status or blood pressure medication had somewhat lower heterogeneity (I^2 = 41 to 76 percent). Meta-regression by baseline blood pressure and control sodium intake level also could not explain observed heterogeneity. The summary intake–response slope did not depend on whether the midpoint of the intake range was < 2,300 mg/d (< 100 mmol/d) or not, consistent with a linear relationship extending from above to below

2,300 mg/d (100 mmol/d). Results did not change with the exclusion of the one study with a high risk of bias. A funnel plot asymmetry test for publication bias was not statistically significant ($p = .57$). The overall effect remained statistically significant after adjusting for possible publication bias using the trim-and-fill method. All estimates used the Knapp-Hartung modification.

Evidence rating for intake–response Using GRADE, the committee assessed the strength of evidence that reducing sodium intake reduces chronic disease risk in the intake range below 2,300 mg/d (100 mmol/d). The overall rating is low owing to concerns about inconsistency and indirectness, with details as to the rationale summarized in Table 10-11. Because of lack of data below 1,000 mg/d (43 mmol/d), this rating only applies for intakes down to this value.

Summary of Intake–Response Assessment

Table 10-12 presents the overall GRADE summary of findings for the intake–response relationship between the three sodium intake ranges evaluated above and cardiovascular chronic disease:

- The strongest evidence is in the intake range from 2,300–4,100 mg/d (100–178 mmol/d), with a high strength of evidence for chronic disease intake–response. In this intake range, a 1,000 mg/d (43 mmol/d) reduction of intake is expected to reduce chronic disease risk, as indicated by risk reduction for cardiovascular disease and hypertension, as well as by lowering of systolic blood pressure and diastolic blood pressure. These four related indicators, illustrated in the framework for sodium chronic disease outcomes (see Figure 10-13), are all concordant, pointing to decreased risk of chronic disease with decreased sodium intake in this range.
- Chronic disease intake–response for intakes of sodium above 4,100 mg/d (178 mmol/d) has a moderate strength of evidence up to a sodium intake of 5,000 mg/d (217 mmol/d). In this intake range, a 1,000 mg/d (43 mmol/d) intake reduction is expected to reduce chronic disease risk, as indicated by lowering of systolic blood pressure and diastolic blood pressure. Uncertainty in this intake range is primarily attributable to indirectness of evidence, including the lack of studies directly measuring cardiovascular disease or hypertension risk reduction, and lack of studies in which both control and intervention intake levels are above 4,100 mg/d (178 mmol/d). Additionally, the control intakes in the available studies only extended up to approximately 5,000 mg/d (217 mmol/d).

TABLE 10-11 GRADE Assessment Table for Intake–Response in Range Below 2,300 mg/d (100 mmol/d)

GRADE Criteria	Rating[a]	Reasons for Rating	Strength of Evidence[b]
Outcome: Reduced chronic disease risk per 1,000 mg/d (43 mmol/d) sodium intake reduction, as indicated by cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure, in the intake range below 2,300 mg/d (100 mmol/d).			
Study design	High	Randomized controlled trials.	
Risk of bias	No (0)	Only one study, for systolic blood pressure and diastolic blood pressure, had high risk of bias; results did not change with exclusion of this study.	
Inconsistency	Serious (–1)	For systolic blood pressure, there was substantial heterogeneity overall (I^2 = 67 percent), which could only be partially explained. Removing one study reduced heterogeneity to moderate (I^2 = 47 percent). Some, but not all, subgroups based on hypertension status or blood pressure medication use had lower heterogeneity, though subgroup differences were not statistically significant. For diastolic blood pressure, there was moderate heterogeneity overall (I^2 = 54 percent), which could only be partially explained. Subgroups based on hypertension status or blood pressure medication use had moderate or substantial heterogeneity, though subgroup differences were not statistically significant. For both systolic blood pressure and diastolic blood pressure, several individual studies showed no effect. Additionally, studies more directly informative of intake–response in this range (where the midpoint of the intakes between the control and intervention was < 2,300 mg/d [< 100 mmol/d]) had substantial heterogeneity (I^2 > 60 percent). Overall, a downgrade was applied because heterogeneity remained moderate after sources of heterogeneity were explored and was substantial in more directly informative studies; additionally, several studies individually showed no effect.	

Indirectness	Serious (–1)	Only one observational study with low risk of bias was available in this intake range for cardiovascular disease, one of the more direct measures of chronic disease risk. No data in this intake range were available for hypertension.	
		For systolic blood pressure and diastolic blood pressure, the midpoint of control and intervention intakes were < 2,300 mg/d for only 4 of the 17 randomized controlled trials studies of systolic blood pressure and diastolic blood pressure considered, totaling 6 comparisons; these 4 studies were all < 6 months in duration. All but 2 of the studies of systolic blood pressure and diastolic blood pressure included adults with hypertension, with the summary estimate for normotensives not statistically significant. Overall, a downgrade for indirectness was applied owing to the lack of studies fully (or mostly) within this intake range, the lack of studies in normotensives, and the lack of randomized controlled trials on cardiovascular disease and hypertension providing more direct evidence of reduced chronic disease risk.	⊕⊕◯◯ Low down to 1,000 mg/d (43 mmol/d); Insufficient below 1,000 mg/d (43 mmol/d)[c]
Imprecision	No (0)	Statistically significant and biologically meaningful summary effect sizes for systolic blood pressure and diastolic blood pressure, across all studies and within all subgroups that included adults with hypertension.	
Publication bias	Undetected (0)	No publication bias detected; results similar if adjusted for possible publication bias using trim-and-fill procedure.	
Other	No (0)	Outcome already specified as an intake–response slope, so no additional upgrade for intake–response gradient.	

[a]Table format same as Table 10-2.

[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

[c]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *very low certainty* or *quality of the evidence*.

Above this level of intake, the committee identified three studies with intakes up to approximately 8,000 mg/d (348 mmol/d) (He et al., 2009; Koolen et al., 1983; Takeshita et al., 1982). However, the interventions in these studies were of short duration (only up to 2 weeks) and therefore were excluded from the evidence. The absence of evidence above 8,000 mg/d (348 mmol/d) and the paucity of evidence between 5,000 and 8,000 mg/d (217 and 348 mmol/d) is not to be interpreted as indicating a safe level of intake. It is likely that cardiovascular disease risk will continue to increase above intake levels for which randomized controlled trial data are available.

- For intakes of sodium below 2,300 mg/d (100 mmol/d), there was a low strength of evidence for a chronic disease intake–response down to an intake of 1,000 mg/d (43 mmol/d). In this intake range, reduction in sodium intake may reduce chronic disease risk, as indicated by lowering of systolic blood pressure and diastolic blood pressure. Uncertainty in this intake range is primarily attributable to unexplained inconsistency across studies and indirectness of evidence. Failure to identify chronic disease risk reduction at intakes below 2,300 mg/d (100 mmol/d) likely reflects a lack of evidence rather than a lack of effect.

These ratings are consistent with the only available observational study rated as having low risk of bias that measured cardiovascular disease risk with sodium intake reduction (Cook et al., 2014). The findings from this study are consistent with the available randomized controlled trial data; linear regression that treats intakes as continuous indicated a 17 percent risk reduction [95% CI: 0, 36] per 1,000 mg/d (43 mmol/d) reduction in sodium intake. Additionally, as shown in Figure 10-27, results from spline regression indicated that the CIs begin to diverge below approximately 2,300 mg/d (100 mmol/d), consistent with the committee's determination of a low strength of evidence from randomized controlled trial data in this intake range. As noted above, the committee did not use the evidence from observational studies on the potential J- or U-shaped relationships between sodium intake and health outcomes owing to the insufficient strength of evidence (see Chapter 8).

CHRONIC DISEASE RISK REDUCTION INTAKES FOR SODIUM

In the sections above, the committee reviewed the evidence on potential indicators to inform the sodium DRIs based on chronic disease, which included consideration of both causal and intake–response relationships

(see Tables 10-8 and 10-12 for summary). Specifically, the committee's review of evidence for the four indicators above revealed the following:

- The committee's meta-analyses and reassessment of the evidence provided in the *AHRQ Systematic Review* indicated a moderate strength of evidence for a causal relationship between reductions in sodium intake and any cardiovascular event. Likewise, there was a moderate strength of evidence from randomized controlled trials to suggest that reducing sodium intake reduces hypertension incidence.
- The committee's meta-analyses and reassessment of the evidence provided in the *AHRQ Systematic Review* indicated a high strength of evidence from randomized controlled trials that reducing sodium intake reduces systolic and diastolic blood pressure. Much of the observed heterogeneity among trials examining systolic blood pressure could be explained by the net reduction in sodium (intake–response) and the baseline systolic blood pressure level. Among trials examining diastolic blood pressure, heterogeneity was mainly related to the difference in the size rather than in direction of the effect. The effect of sodium reduction was greater among adults with hypertension, but it was also evident among nonhypertensive adults.

The committee concludes there is moderate to high strength of evidence for both a causal relationship and an intake–response relationship between sodium and several interrelated chronic disease indicators: cardiovascular disease, hypertension, systolic blood pressure, and diastolic blood pressure. Evidence from these indicators can be synthesized to inform the development of a sodium Chronic Disease Risk Reduction Intake (CDRR).

The committee carefully considered how the guidance in the *Guiding Principles Report* applied to the evidence on the relationship between sodium intake and chronic disease. As introduced in Chapter 2, the committee encountered challenges in implementing the *Guiding Principles Report* recommendation that the DRI based on chronic disease be established as a range rather than a single value (see Chapter 2, Box 2-1, Recommendation 6). Based on the analyses in the preceding section, the committee could characterize an intake–response relationship of at least moderate strength up to sodium intakes of approximately 5,000 mg/d (217 mmol/d), but the committee did not have sufficient evidence from randomized controlled trials or low-risk-of-bias observational studies for sodium intakes above this level. The *Guiding Principles Report* anticipated that there may be

TABLE 10-12 Summary of Evidence Used to Determine the Intake–Response Relationship Between Reduction in Sodium Intake and Reduction in Chronic Disease Risk

Sodium Intake Range, mg/d	Chronic Disease Indicator	Evidence Informing Intake–Response Relationship[a]	Intake–Response, per 1,000 mg/d Reduction in Sodium Intake		Strength of Evidence for an Intake–Response Relationship Between Sodium Intake Reduction and Chronic Disease Risk Reduction[b]
			Estimate	[95% CI]	
> 8,000	CVD, HTN, SBP, DBP	No eligible RCTs or low-risk-of-bias observational studies extend into this intake range	—	—	Insufficient, due to lack of eligible RCTs and no low-risk-of-bias observational studies
5,000–8,000	CVD, HTN, SBP, DBP	No eligible RCTs extend into this intake range; 1 low-risk-of-bias observational study on cardiovascular disease extends into this intake range	—	—	Insufficient, due to lack of eligible RCTs and only 1 low-risk-of-bias observational study
4,100–5,000	CVD	No eligible RCTs extend into this intake range; 1 low-risk-of-bias observational study extends into this intake range	—	—	Moderate, due to indirectness
	HTN	No eligible RCTs or low-risk-of-bias observational studies extend into this intake range	—	—	
	SBP	11 RCTs extend into this range (2 fully in this range)	2.7 mm Hg reduction	[1.9, 3.5]	
	DBP	10 RCTs extend into this range (1 fully in this range)	1.7 mm Hg reduction	[0.3, 3.1]	
2,300–4,100	CVD	3 RCTs fully in this range; 1 low-risk-of-bias observational study extends into this intake range	27% risk reduction[c]	[8, 43]	High

	HTN	3 RCTs fully in this range	20% risk reduction[d]	[5, 32]	
	SBP	21 RCTs fully in this range[e]	2.8 mm Hg reduction	[1.6, 4.0]	
	DBP	20 RCTs fully in this range[f]	1.2 mm Hg reduction	[0.5, 1.9]	
1,000–2,300	CVD	No eligible RCTs extend into this intake range; 1 low-risk-of-bias observational study extends into this range	—	—	Low, due to inconsistency and indirectness
	HTN	No eligible RCTs or low-risk-of-bias observational studies extend into this intake range	—	—	
	SBP	19 RCTs extend into this range (1 fully in this range)[g]	2.4 mm Hg reduction	[1.5, 3.3]	
	DBP	19 RCTs extend into this range (1 fully in this range)[g]	1.5 mm Hg reduction	[0.9, 2.0]	
< 1,000	CVD, HTN, SBP, DBP	No eligible RCTs or low-risk-of-bias observational studies extend into this intake range	—	—	Insufficient, due to lack of eligible RCTs and no low-risk-of-bias observational studies

NOTES: Sodium intake levels are present in mg/d. To convert to mmol, divide the milligram value by 23. CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure; HTN = hypertension; RCT = randomized controlled trial; SBP = systolic blood pressure.

[a]The number of studies do not directly correspond to the strength of the evidence rating. For details on the evidence rating, see Tables 10-9, 10-10, and 10-11.

continued

TABLE 10-12 Continued

[b]The purpose of the intake–response analysis is to determine the strength of evidence of a positive/negative/zero slope. All four indicators were examined together for assessing the strength of evidence for an intake–response relationship.

[c]To calculate the percent reduction from the size effect ln(RR) = –0.32 in cardiovascular disease incidence the following conversion was made: RR = exp(–0.32) = 0.726; 0.726 corresponds to a 27 percent reduction in cardiovascular disease (1.0 – 0.27 = 0.73).

[d]To calculate the percent reduction from the size effect ln(RR) = –0.22 in hypertension incidence the following conversion was made: RR = exp(–0.22) = 0.803; 0.803 corresponds to a 20 percent risk reduction in hypertension incidence (1.0 – 0.20 = 0.80).

[e]Number of comparisons from 19 different studies.

[f]Number of comparisons from 18 different studies.

[g]Number of comparisons from 17 different studies.

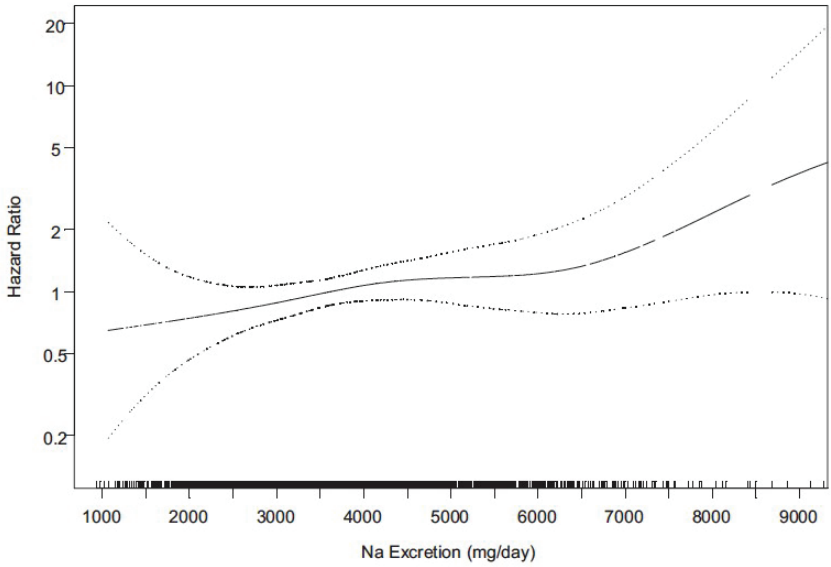

FIGURE 10-27 Spline plot of the hazard ratio for cardiovascular disease by mean sodium excretion from observational follow-up of Trials of Hypertension Prevention studies.
SOURCE: Cook et al., 2014. Reprinted with permission from Wolters Kluwer Health, Inc.

instances in which a lower strength of evidence could be used in the derivation of the DRI based on chronic disease, particularly when the nutrient increases chronic disease risk. The committee applied this guidance and assumed that sodium intakes above 5,000 mg/d (217 mmol/d) are likely to pose a continuing risk. Given the committee's concerns that specifying an upper end of a range could be interpreted as suggesting that higher sodium intakes are not associated with chronic disease risk, the committee expressed the sodium CDRR as the lowest intake level for which there was sufficient evidence to characterize chronic disease risk reduction (see Box 10-8). For additional details regarding the committee's selection of nomenclature and the conceptual underpinnings of the CDRR, see Chapter 2.

In addition, pursuant to the guidance in the *Guiding Principles Report*, the committee assessed the evidence by population subgroups defined by characteristics such as demographics and health status. The *AHRQ Systematic Review* concluded that there was insufficient strength of evidence that sex, age, ethnicity/race, diabetes status, kidney disease, or obesity and overweight moderate the effect of sodium intake on cardiovascular disease, hypertension, or blood pressure (see Boxes 10-3 through 10-5). Although

BOX 10-8
Chronic Disease Risk Reduction Intake for Sodium

Context: The sodium Chronic Disease Risk Reduction Intake (CDRR) is the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. The concept of a range is embedded in the expression of the sodium CDRR in that for intakes above the CDRR, reduction in sodium intake is expected to reduce chronic disease risk.

For sodium, the CDRR is the intake above which intake reduction is expected to reduce chronic disease risk within an apparently healthy population.

stronger effects of sodium intake have been reported among African Americans and older individuals (He et al., 2009; Vollmer et al., 2001; Weinberger and Fineberg, 1991; Weinberger et al., 1982; Wright et al., 2003), such evidence is based on short-term trials of blood pressure effects with little or no data on chronic disease outcomes. Thus, in keeping with the guidance in the *Guiding Principles Report*, the committee had insufficient basis to establish a different CDRR for specific population subgroups. The committee did not have access to individual patient data that may have allowed for additional analyses with respect to population subgroups and consideration of sodium CDRRs specific to them. The committee identified this limitation as a future direction in Chapter 12.

Specification of the Sodium CDRR Values

In the sections that follow, the committee specifies the sodium CDRR values for adults 19–70 years of age, and provides its rationale for extrapolating the sodium CDRR to adults > 70 years of age, to pregnant and lactating females, and to children and adolescents 1–18 years of age. A summary of the sodium CDRRs is presented at the end of this chapter.

Adults 19–70 Years of Age

In the sodium intake range 2,300–4,100 mg/d (100–178 mmol/d), there was high strength of evidence that reducing sodium intake reduces chronic disease risk, based on evidence of reduction in cardiovascular disease incidence, reduction in hypertension incidence, and lowering of systolic and diastolic blood pressure. At sodium intake levels above 4,100–5,000 mg/d (178–217 mmol/d), there was moderate strength of evidence of an intake–response relationship that reductions in sodium intake reduce chronic dis-

ease risk, based on evidence of reductions in systolic and diastolic blood pressure and one low-risk-of-bias observational study on cardiovascular disease. There were no eligible randomized controlled trials on cardiovascular disease, hypertension, or blood pressure identified at sodium intakes above 5,000 mg/d (217 mmol/d). The committee determined that the evidence for intakes above 5,000 mg/d (217 mmol/d) was insufficient, but assumed that sodium intakes above 5,000 mg/d (217 mmol/d) are likely to pose a continuing risk. For intakes below 2,300 mg/d (100 mmol/d), there is low strength of evidence that reducing sodium intakes reduces chronic disease risk, based on evidence of reductions in systolic and diastolic blood pressure down to 1,000 mg/d (43 mmol/d) and one low-risk-of-bias observational study on cardiovascular disease. There were, however, no eligible randomized controlled trials on cardiovascular disease, hypertension, or blood pressure identified at sodium intakes below 1,000 mg/d (43 mmol/d); therefore, the evidence was determined to be insufficient. Furthermore, for intakes below 2,300 mg/d (100 mmol/d), there was insufficient strength of evidence that reducing sodium intake is associated with harm, such as increased risk in mortality (for the committee's review of this evidence, see Chapter 8). Finally, because the sodium AI for adults 19 years of age and older was established at 1,500 mg/d (65 mmol/d) (see Chapter 8), the committee restricted the options for the sodium CDRR to be at least this value or higher.

The committee considered two options for establishing the sodium CDRR for adults 19–70 years of age:

Option 1: Use 2,300 mg/d (100 mmol/d) as the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. Establishing a sodium CDRR at this level is expected to reduce the risk of chronic disease, as supported by evidence on the relationship between sodium intake and risk for cardiovascular disease and risk for hypertension. This intake level is further supported by evidence on the relationship between sodium intake and systolic and diastolic blood pressure, which the committee considered qualified surrogate markers for cardiovascular disease and hypertension in the context of sodium intake.

Option 2: Use 1,500 mg/d (65 mmol/d), the sodium AI for adults, as the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. Establishing a sodium CDRR at this level is expected to reduce the risk of chronic disease, specifically cardiovascular disease and hypertension as mediated by blood pressure. This intake level is supported by evidence

on the relationship between sodium intake and systolic and diastolic blood pressure, which the committee considered qualified surrogate markers for cardiovascular disease and hypertension in the context of sodium intake.

Based on its synthesis of the evidence and its interpretation of the guidance provided in the *Guiding Principles Report*, the committee selected Option 1 for the following reasons:

- The committee conceptualized the sodium CDRR as the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. In its identification of the lowest level of intake, the committee followed the *Guiding Principles Report* recommendation that a DRI based on chronic disease be based on at least moderate strength of evidence for both the causal and the intake–response relationships. Such strength of evidence existed for sodium intakes down to 2,300 mg/d (100 mmol/d).
- For sodium intakes below 2,300 mg/d (100 mmol/d) down to the sodium AI for adults (1,500 mg/d [65 mmol/d]), there was evidence from randomized controlled trials that reducing sodium intake lowers blood pressure. Although blood pressure was considered a qualified surrogate maker in the context of sodium intake reductions (see Annex 10-2), the strength of evidence for an intake–response relationship between reductions in sodium intake and reductions in chronic disease risk was rated as low.
- Observational studies on associations between sodium intakes below 2,300 mg/d (100 mmol/d) and chronic disease endpoints are sparse. Such observational studies are also diverse in design and can have methodological issues that create challenges in interpreting their body of evidence as a whole (see Chapter 8).

Although there might be long-term health benefits of reducing usual sodium intake below 2,300 mg/d (100 mmol/d), there was enough uncertainty to not establish the CDRR below this intake level. A sodium CDRR of reducing intakes if above 2,300 mg/d (100 mmol/d) is supported by multiple indicators in study populations that include normotensive individuals, individuals with prehypertension, and individuals with hypertension. There was insufficient evidence to specify different CDRRs based on parameters such as baseline systolic or diastolic blood pressure. Likewise, there was insufficient evidence of a moderating effect of sex, age, or race/ethnicity. In addition, based on the *AHRQ Systematic Review* conclusion that the evidence is insufficient about the moderating effects of diabetes status, kidney

disease, or obesity and overweight, the committee was unable to determine whether the sodium CDRR applies to groups with those conditions. The sodium CDRR is applicable to adults with and without hypertension, irrespective of sex, age, or race/ethnicity.

Extrapolation to Other DRI Age and Life-Stage Groups

Adults > 70 years of age The *AHRQ Systematic Review* concluded that there was insufficient evidence to determine a moderating effect of age on the effects of sodium reduction on cardiovascular disease. Several of the randomized controlled trials included in the committee's analyses reported allowing participants older than 70 years of age to be included in the study (Appel et al., 2001; Cappuccio et al., 2006; Howe et al., 1994; Hwang et al., 2014; Meland and Aamland, 2009; Nakano et al., 2016; Nestel et al., 1993; Schorr et al., 1996; Wing et al., 1998). None of the studies were conducted exclusively in individuals in this age range. One study reported on a subgroup analysis among participants 70–80 years of age (Appel et al., 2001). Systolic and diastolic blood pressure were not statistically different after 3.5 months in the sodium reduction group (n = 66), as compared to the usual lifestyle group (n = 66) (systolic MD = –1.5 mm Hg [95% CI: –5.4, 2.4], p = .46; diastolic MD = –1.4 mm Hg [95% CI: –3.9, 1.0], p = .25). During a mean of 27.8 months of follow-up, risk of the trial endpoints (high blood pressure, resumption of antihypertensive medications, or cardiovascular event) was not statistically significant (relative HR = 0.75 [95% CI: 0.50, 1.14], p = .18). The investigators suggested that the lack of statistical significance could have been caused by small sample size. No other studies included in the committee's analyses reported results specifically on this age group.

Given the high risk of hypertension and cardiovascular disease and the higher prevalence of hypertension and use of any antihypertensive medications with increasing age (Carson et al., 2011; Fang et al., 2018; Fryar et al., 2017; Gu et al., 2012), the committee considered it appropriate from a public health context to extrapolate the sodium CDRR to this age group. Therefore, the committee established a sodium CDRR for individuals > 70 years of age as reducing intakes if above 2,300 mg/d (100 mmol/d).[13]

Pregnancy and lactation There was insufficient evidence that a different CDRR is needed for pregnant or lactating females. The committee establishes the same CDRR for pregnant and lactating females as for their nonpregnant, nonlactating age group counterparts.

[13]This text was revised since the prepublication release.

Children and adolescents 1–18 years of age As described in Box 10-5, the *AHRQ Systematic Review* concluded that there was low strength of evidence that reductions in sodium intake may not decrease systolic blood pressure and low strength of evidence that reductions in sodium intake reduce diastolic blood pressure (based on only low and moderate risk of bias studies). Given that this strength of evidence is not of sufficient strength, based on GRADE, to derive sodium CDRRs for children, the committee considered other evidence to determine if extrapolation was appropriate.

In addition to the randomized controlled trials included in the *AHRQ Systematic Review*, the committee also assessed the evidence from prospective cohort studies that examined the association of sodium intake (urinary excretion or dietary assessment) and longitudinal change in blood pressure in children and adolescents (Buendia et al., 2015; Geleijnse et al., 1990; Setayeshgar et al., 2017; Shi et al., 2014). Setayeshgar et al. (2017) followed 448 schoolchildren 10–17 years of age for 2 years and reported borderline significance in the association between sodium intake and diastolic but not systolic blood pressure. None of the other studies reported a significant change in either systolic or diastolic blood pressure. These observational studies were rated as having a high risk of bias. Based on the findings from the randomized controlled trials and the prospective cohort studies, there was insufficient evidence to assess the relationship between sodium intake and blood pressure in children and adolescents.

Longitudinal cohort studies have documented blood pressure tracking from childhood to adulthood (Chen and Wang, 2008; Toschke et al., 2010). In a systematic review and meta-analysis of 50 longitudinal cohort studies, pooled correlation coefficients of blood pressure tracking from childhood to adulthood were 0.38 for systolic blood pressure and 0.28 for diastolic blood pressure (Chen and Wang, 2008). The tracking correlation coefficients varied significantly according to baseline age (0.18, 0.40, 0.42, and 0.43 for systolic blood pressure and 0.09, 0.29, 0.29, and 0.32 for diastolic blood pressure among children < 5, 5–9, 10–14, and ≥ 15 years of age, respectively). In another meta-analysis, Toschke et al. (2010) assessed 29 studies among individuals 10 years of age or older and reported higher pooled tracking correlation coefficients of 0.37–0.47 for systolic and 0.36–0.46 for diastolic blood pressure. In addition, several prospective cohort studies have reported that elevated blood pressure in childhood predicted the subsequent risk of hypertension in adulthood (Bao et al., 1995; Gillman et al., 1993; Xi et al., 2017). Despite results from two trials in newborn infants suggesting a relationship between dietary sodium intake and blood pressure during the first few months of life (Hofman et al., 1983; Pomeranz et al., 2002), blood pressure tracking from children younger than 5 years of age to adulthood is weak (Chen and Wang, 2008). There is also a lack

of data on the association between blood pressure in children 1–3 years of age and the subsequent risk of hypertension and cardiovascular disease in adulthood.

Despite the insufficient evidence to assess the relationship between sodium intake and chronic disease risk in children and adolescents, and the uncertainties about the long-term chronic disease benefits of reduced sodium intake beginning in childhood, the committee considered the risk of not setting a CDRR to outweigh the risk of setting a sodium CDRR for children and adolescents. The committee rationale for extrapolating the sodium CDRR to children and adolescents 1–18 years of age is based on evidence of blood pressure tracking to adulthood, the public health importance, and consideration of salt-taste sensitivity and preferences starting to develop as early as 3–4 months of age (Liem, 2017; Stein et al., 2012).

The sodium CDRR for children and adolescents was extrapolated from the adult sodium CDRR. To extrapolate, the committee used rounded average Estimated Energy Requirements (EERs) for sedentary individuals for each age group (see Table 10-13), as compared to an EER for adults of 2,000 kcal/d. EERs were used instead of self- or proxy-reported energy intake owing to potential biases in reported dietary intake data. Extrapolated sodium CDRRs were mathematically rounded to the nearest 100 mg/d increment.

TABLE 10-13 Estimated Energy Requirements for Sedentary Children and Adolescents 1–18 Years of Age, by Age Group

Age Group	Average EER (kcal/d)	Rounded Average EER (kcal/d)
1–3 years	1,000[a]	1,000[a]
4–8 years	1,280	1,300
9–13 years	1,640	1,600
14–18 years	2,040	2,000

NOTES: Unless otherwise noted, sedentary EERs were drawn from a summary table in the *2015–2020 Dietary Guidelines for Americans* (HHS/USDA, 2015), which were derived from the EER equations (IOM, 2002/2005). The average estimated requirements were determined by a simple average of the estimated energy needs for sedentary males and females within each age range. Average intakes were mathematically rounded. EER = Estimated Energy Requirement; kcal = kilocalorie.

[a]The *2015–2020 Dietary Guidelines for Americans* provides dietary guidance for individuals 2 years of age and older. The summary table of sedentary EERs did not include children 1 year of age. The committee considered the effect of the EER for children 1 year of age on the rounded average for the 1–3-year-old age group. The average of EERs for children 12–24 months are estimated to be below 1,000 kcal/d (IOM, 2002/2005, pp. 169–170), but are not low enough to affect the rounded average EER. As such, 1,000 kcal/d was used in extrapolating the adult sodium Adequate Intake (AI) to children 1–3 years of age.

TABLE 10-14 Chronic Disease Risk Reduction Intake (CDRR) by Age Group

Nutrient	Population Group	Recommendation
Sodium	Children, 1–3 years	Reduce intakes if above 1,200 mg/day[a]
	Children, 4–8 years	Reduce intakes if above 1,500 mg/day[a]
	Adolescents, 9–13 years	Reduce intakes if above 1,800 mg/day[a]
	Adolescents, 14–18 years	Reduce intakes if above 2,300 mg/day[a]
	Adults, ≥ 19 years	Reduce intakes if above 2,300 mg/day

NOTES: The sodium CDRRs are presented in milligrams. To convert to mmol, divide the milligram value by 23.0.

[a]Extrapolated from the adult CDRR based on sedentary Estimated Energy Requirements.

SUMMARY

The sodium CDRRs are established through a synthesis of evidence from sodium reduction trials and outcomes of incident cardiovascular disease, incident hypertension, systolic blood pressure, and diastolic blood pressure. The sodium CDRR is the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. For sodium, the CDRR is the intake above which intake reduction is expected to reduce chronic disease risk within an apparently healthy population. Among adults, further reductions in sodium intake below the CDRR have demonstrated a lowering effect on blood pressure, but the effect on chronic disease risk could not be characterized. A summary of the sodium CDRRs is presented in Table 10-14.

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ANNEX 10-1
INDICATORS REVIEWED BUT NOT SELECTED

Cardiovascular Disease Mortality

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* (IOM, 2005) discussed results from one prospective study (Alderman et al., 1998) that reported an inverse relationship between sodium intake and cardiovascular disease mortality, based on follow-up data from National Health and Nutrition Examination Survey (NHANES) I participants. The *2005 DRI Report* noted that the analytical model variables in this study were correlated with sodium intake, such as energy intake. The results of this study were inconsistent with other studies in which no significant relationship was found (e.g., Cohen et al., 1999) and with a different analysis of the same NHANES I data in which individuals with a history of cardiovascular disease or under treatment were excluded because of possible reverse causation (He et al., 1999). In the *2005 DRI Report*, cardiovascular disease mortality was considered but not selected as the critical adverse outcome to inform the sodium UL.

Evidence Provided in the AHRQ Systematic Review

Two trials were identified in the *AHRQ Systematic Review* (Newberry et al., 2018) that examined cardiovascular disease mortality as an endpoint of reducing sodium intake. Morgan et al. (1978) studied a moderate restriction in sodium for 2 years; although blood pressure decreased in the intervention group, the cardiovascular disease mortality rate was similar in the control and intervention groups. Chang et al. (2006) conducted a trial in elderly men and found a significant decrease in cardiovascular disease mortality in the experimental group that used a potassium-rich salt substitute (age-adjusted hazard ratio [HR] = 0.59 [95% CI: 0.37, 0.95]). Because of inconsistency in the results and dearth of studies, the evidence was determined to be insufficient to assess the effect of sodium reduction on cardiovascular disease mortality.

Committee's Synthesis of the Evidence

The committee is in agreement with the assessment of the evidence in the *AHRQ Systematic Review*. The committee also notes that the salt substitute used as the intervention in the Chang et al. (2006) trial does not allow attribution of effects to sodium reduction because of the concurrent

increase in potassium intake. There is insufficient evidence to be able to assess the effect of sodium reduction on cardiovascular disease mortality and, therefore, cardiovascular disease mortality could not be used as an indicator to inform the sodium CDRRs.

Stroke

Evidence Presented in the 2005 DRI Report

In the exploration of adverse effects related to excessive sodium intake, the *2005 DRI Report* presented evidence from observational studies that measured stroke as an outcome. Results varied from no significant effects of sodium intake on stroke (Kagan et al., 1985), to a significant increase in stroke with increasing sodium intake only in overweight individuals (He et al., 1999), to a negative relationship between sodium intake and stroke (Alderman et al., 1997). The *2005 DRI Report* stated concerns over observational studies, which show high intra-individual variability owing to intake measurement methods, contributing to low statistical power to observe effects. In the *2005 DRI Report*, stroke was considered, but was not selected as the critical adverse effect to inform the sodium UL.

Evidence Provided in the AHRQ Systematic Review

Three sodium-reduction trials were included in the *AHRQ Systematic Review* that explored stroke as an outcome among adults (Appel et al., 2001; Charlton et al., 2008; Gilleran et al., 1996). None of the studies showed any significant effect of sodium reduction in stroke whether results were considered either separately or pooled in a meta-analysis (pooled RR = 0.72 [95% CI: 0.05, 9.88]; I^2 = 0 percent). The *AHRQ Systematic Review* concluded that there is a low strength of evidence that sodium reduction in adults may not decrease the risk of stroke.

Committee's Synthesis of the Evidence

The committee is in agreement with the assessment of the strength-of-evidence rating in the *AHRQ Systematic Review*, and, therefore, stroke could not be used as an indicator to inform the sodium CDRRs.

Myocardial Infarction

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* described results from one prospective study (Alderman et al., 1995) that reported a significant inverse association between sodium intake and incident myocardial infarction. The *2005 DRI Report* noted limitations of the study, particularly in the likelihood of variables that confounded the results and the potential for incomplete measurement of sodium intake. In the *2005 DRI Report*, myocardial infarction was considered but was not selected as the critical adverse effect to inform the sodium UL.

Evidence Provided in the AHRQ Systematic Review

One trial, TONE (Appel et al., 2001), examined myocardial infarction as an adverse effect in older adults. A nonsignificant lower event rate, four compared to two events, was observed in the group consuming less sodium after a mean follow-up of 27.8 months. Based on the low number of studies, the *AHRQ Systematic Review* concluded that there was insufficient evidence that sodium reduction has an effect on risk of myocardial infarction.

Committee's Synthesis of the Evidence

The committee is in agreement with the assessment of the strength of evidence in the *AHRQ Systematic Review*, and, therefore, myocardial infarction could not be used as an indicator to inform the sodium CDRRs.

Left Ventricular Mass and Gross Morbidity

Evidence Presented in the 2005 DRI Report

Left ventricular mass was discussed in the *2005 DRI Report* because of its potential as a predictor of cardiovascular disease morbidity and mortality, as well as it being mechanistically related to increases in blood pressure. In particular, two cross-sectional studies were described that reported on left ventricular mass and sodium intake, but the results were not consistent (Alderman et al., 1997; du Cailar et al., 2002). Only one trial was identified, which reported that reduction in sodium intake resulted in small decreases in left ventricular mass, whereas no change occurred in the control group (Jula and Karanko, 1994). In the *2005 DRI Report*, left ventricular mass was considered but was not selected as the critical adverse effect to inform the sodium UL.

Evidence Provided in the AHRQ Systematic Review

Two studies that examined the relationship between sodium intake reduction and gross morbidity (HPTRG, 1990) and left ventricular mass (Xie et al., 1998) met the *AHRQ Systematic Review* inclusion criteria. No significant difference in these outcomes was reported with sodium reduction. The *AHRQ Systematic Review* could not make conclusions based on this evidence.

Committee's Synthesis of the Evidence

The committee is in agreement with the assessment of the evidence in the *AHRQ Systematic Review*, and therefore neither gross morbidity nor left ventricular mass could be used as indicators to establish the sodium CDRRs (for the committee's rationale for excluding left ventricular mass from its supplementary literature search, see Appendix D).

Osteoporosis and Related Indicators

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* summarized the findings from four observational studies on the relationship between sodium intake and bone mineral density (Devine et al., 1995; Greendale et al., 1994; Jones et al., 1997; Matkovic et al., 1995), but it noted that the role of sodium intake was unclear and that there was no evidence on the relationship between sodium intake and fracture.

Evidence from the Committee's Supplemental Literature Search

One trial examining the relationship between sodium intake and bone mineral density in postmenopausal women was identified. The intervention group received dietary advice to lower sodium intake to 1,500 mg/d (65 mmol/d) whereas the control group was advised to maintain sodium intake of 3,000 mg/d (130 mmol/d) (Ilich et al., 2010). After 3 years, there was no statistically significant difference in mean bone mineral density.

Committee's Synthesis of the Evidence

The committee considered the evidence insufficient and therefore osteoporosis and related indicators could not be used as indicators to establish the sodium CDRRs.

Kidney Disease

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* did not review evidence on kidney disease as an indicator of adverse effect of excessive sodium intake.

Evidence Provided in the AHRQ Systematic Review

One observational study based on data from the Prevention of Renal and Vascular End-Stage Disease study (Kieneker et al., 2016) was identified that assessed the association between sodium intake and kidney disease. The observational study found no association between sodium intake and risk of chronic kidney disease, as measured by either estimated glomerular filtration rate or urinary albumin excretion. No other studies on kidney disease outcomes met the *AHRQ Systematic Review* inclusion criteria. The *AHRQ Systematic Review* concluded there was insufficient evidence on the relationship between sodium intake and kidney disease.

Committee's Synthesis of the Evidence

The committee is in agreement with the assessment of the evidence in the *AHRQ Systematic Review* and, therefore, kidney disease could not be used as an indicator to inform the sodium CDRRs.

All-Cause Mortality

Evidence Presented in the 2005 DRI Report

The *2005 DRI Report* described results from one prospective study (Alderman et al., 1998) that reported an inverse relationship between sodium intake and all-cause mortality, based on an analysis of follow-up data from NHANES I participants. As discussed above, the *2005 DRI Report* noted concerns about the analytical model used and the inclusion of individuals with chronic diseases. Using a different analytical model, He et al. (1999) found higher sodium intakes to be associated with all-cause mortality in overweight individuals. In the *2005 DRI Report*, all-cause mortality was considered but was not selected as the critical adverse effect to inform the sodium UL.

Evidence Provided in the AHRQ Systematic Review

The *AHRQ Systematic Review* identified seven trials that examined the relationship between sodium intake and all-cause mortality, either as the

outcome of interest (Chang et al., 2006; Cook et al., 2016; Morgan et al., 1978) or as an adverse effect (CSSSCG, 2007; de Brito-Ashurst et al., 2013; Weir et al., 2010). A random-effects meta-analysis of the trials found a nonsignificant effect of sodium reduction on decreasing the risk of all-cause mortality (pooled RR = 0.97 [95% CI: 0.94, 1.00], I^2 = 0 percent). Despite seven trials being identified, the *AHRQ Systematic Review* determined the evidence to be insufficient because the outcomes were not powered to assess mortality and the results showed inconsistency in the direction of the size effect, as well as imprecision of the effect across studies.

Committee's Synthesis of the Evidence

The committee reviewed the analyses of trials of sodium and all-cause mortality included in the *AHRQ Systematic Review*. Some of the trials were short term, one lasting only 4 weeks with no deaths (Weir et al., 2010). One trial lasted for 6 months and had only one death (de Brito-Ashurst et al., 2013). The *AHRQ Systematic Review* included these studies by using a continuity correction, leading to very wide CIs and an appearance of no heterogeneity. Because a nutritional intervention in healthy individuals is unlikely to lead to effects on mortality within such a short timeframe, the committee conducted a meta-analysis that restricted inclusion to studies lasting at least 1 year and in healthy participants with no preexisting cardiovascular disease. For the committee's revisions to data from individual trials, as compared to the *AHRQ Systematic Review*, see Box 10-2.

Results from the committee's analyses Use of hazard ratios from survival analyses led to a nonsignificant RR of 0.89 [95% CI: 0.78, 1.01], with no detectable heterogeneity across trials (I^2 = 0 percent) (see Figure 10-28). The inclusion in the *AHRQ Systematic Review* of small studies of short duration led to the appearance of inconsistency and imprecision. When trials using salt substitutes were excluded, the meta-analysis led to an overall RR of 0.85 [95% CI: 0.66, 1.08], with no heterogeneity (see Figure 10-29). This is consistent with the analysis of the pooled TOHP I and II data that reported a RR of 0.85 [95% CI: 0.66, 1.09] (Cook et al., 2016). There were too few studies to evaluate potential publication bias.

Updated strength-of-evidence evaluation Using GRADE and the committee's additional analyses, the committee reassessed the strength of evidence that reducing sodium intake reduces all-cause mortality (see Table 10-15). The strength of evidence was rated as moderate owing to imprecision related to small effect size, lack of statistical significance, and the relatively low total number of events observed across studies (< 300). Despite the evidence being

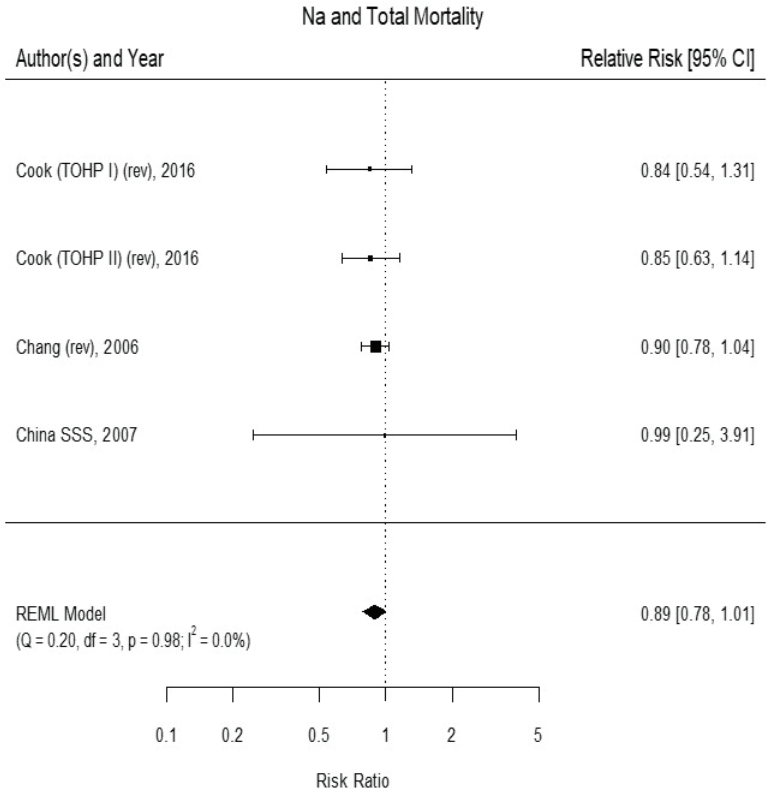

FIGURE 10-28 Random-effects meta-analysis of trials of effects of sodium reduction on all-cause mortality.
NOTES: Studies using salt substitutes are included. Meta-analysis was conducted in R with random-effects models in the metafor package. The variance was estimated using the REML approach. China SSS = China Salt Substitute Study; CI = confidence interval; df = degrees of freedom; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium; Q = Q statistic; REML = restricted maximum likelihood; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention.
SOURCES: Chang et al., 2006; Cook et al., 2016; CSSSCG, 2007.

rated as moderate strength, the committee did not use all-cause mortality because of its nonspecificity and the existence of more specific endpoints, described in Chapter 10.

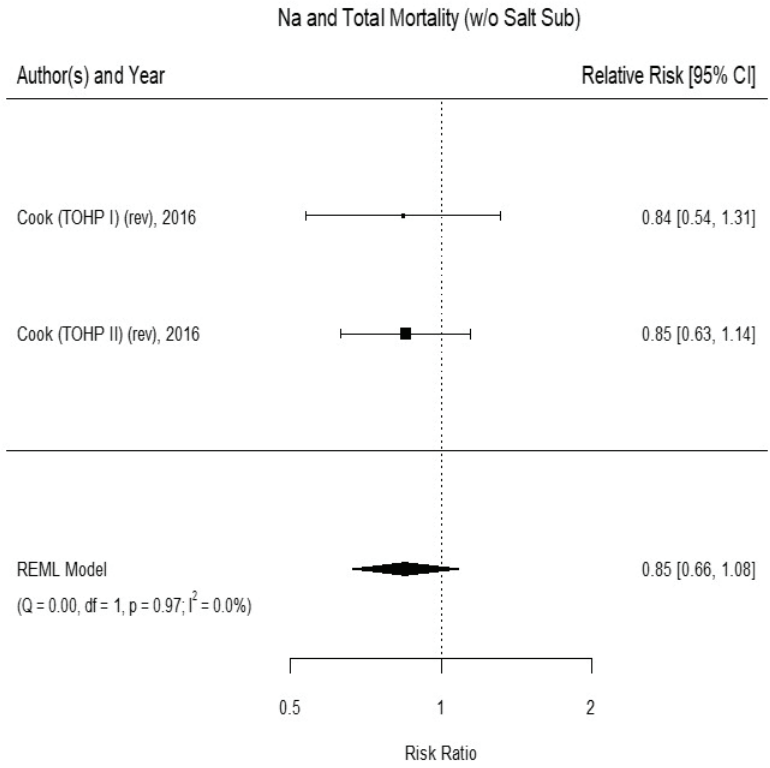

FIGURE 10-29 Random-effects meta-analysis of trials of effects of sodium reduction on all-cause mortality, excluding trials where the intervention was the consumption of a salt substitute.
NOTES: Meta-analysis was conducted in R with random-effects models in the metafor package. The variance was estimated using the REML approach. CI = confidence interval; df = degrees of freedom; I^2 = statistic that describes the percent of variation across studies due to heterogeneity; Na = sodium; Q = Q statistic; REML = restricted maximum likelihood; rev = revised as compared to estimate used in the *AHRQ Systematic Review*; TOHP = Trials of Hypertension Prevention; w/o = without.
SOURCE: Cook et al., 2016.

TABLE 10-15 GRADE Assessment Table: Sodium Reduction and All-Cause Mortality

GRADE Criteria	Rating[a]	Reasons for Rating	Strength of Evidence[b]
Outcome: All-Cause Mortality			
Study design	High	Randomized controlled trial.	
Risk of bias	No (0)	All studies have low or moderate risk of bias.	
Inconsistency	No (0)	No statistical heterogeneity was detected. All study point estimates were in the same direction.	
Indirectness	No (0)	Evidence directly answers the question of interest in terms of relevant populations, interventions, comparators, and outcomes. No change in overall results with inclusion of salt-substitution studies, which are more indirect because they also involve increases in other nutrients, usually potassium.	⊕⊕⊕◯ Moderate
Imprecision	Serious (–1)	Summary effect not statistically significant, whether including or excluding salt-substitution studies. Additionally, effect size is relatively small (11–15 percent change in hazard ratio), and the total number of events number < 300 across studies.	
Publication bias	Not measured	Too few studies for analysis of publication bias.	
Other	None (0)	No additional upgrading factors.	

[a]Table format adapted from Ryan and Hill (2016). Possible ratings as follows:

- For Study Design, strength-of-evidence rating for randomized controlled trial starts as "High" and for nonrandomized controlled trial starts as "Low"
- For Risk of Bias, Inconsistency, Indirectness, and Imprecision, the possible ratings are "No (0)" (no change), "Serious (–1)" (downgrade one level), or "Very serious (–2)" (downgrade two levels)
- For Publication Bias, the ratings are "Undetected (0)" (no change) or "Strongly suspected (–1)" (downgrade one level)
- Other ratings, if present, are "Large effect," "Intake–response," and/or "No plausible confounding" along with "(+1)" or "(+2)" depending on whether upgrade is one or two levels

[b]This terminology was used for consistency with the *AHRQ Systematic Review*. Preferred terminology under the GRADE system is *certainty of the evidence* or *quality of the evidence*.

ANNEX 10-1 REFERENCES

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ANNEX 10-2
EVALUATION OF BLOOD PRESSURE AS A SURROGATE MARKER OF HYPERTENSION AND CARDIOVASCULAR DISEASE FOR SODIUM INTAKE INTERVENTIONS

The *Guiding Principles Report* recommends that, in general, a DRI based on chronic disease be developed when there is at least moderate strength of evidence for both causality and intake–response (NASEM, 2017). Based on its review of the evidence, there is moderate strength of evidence relating sodium intake to both hypertension and cardiovascular disease (see Chapter 10); accordingly, this moderate rating satisfies the causality criterion for establishing a sodium CDRR. However, the evidence on the intake–response relationship between sodium intake and both hypertension and cardiovascular disease is less robust. As such, the committee considered whether evidence on the relationship between sodium intake and blood pressure could be used together with the evidence on hypertension and cardiovascular disease, in support of setting the sodium CDRR. There is high strength of evidence relating sodium intake to blood pressure and the available evidence on blood pressure can help in characterizing an intake–response relationship. However, unlike hypertension and cardiovascular disease, blood pressure is not a chronic disease endpoint. Blood pressure therefore has different considerations in its use for establishing a CDRR. These considerations were described in the *Guiding Principles Report*, which offered the following recommendation:

> Surrogate markers could be considered with the goal of using the findings as supporting information of results based on the chronic disease of interest. To be considered, surrogate markers should meet the qualification criteria for their purpose. Qualification of surrogate markers must be specific to each nutrient or other food substance, although some surrogates will be applicable to more than one causal pathway. (NASEM, 2017, p. 8)

Pursuant to the guidance in the *Guiding Principles Report*, the committee explored whether blood pressure could serve as a surrogate marker for the relationship between sodium intake, hypertension, and cardiovascular disease.[14] Qualification of blood pressure as a surrogate marker implies that studies measuring blood pressure as an outcome of reducing sodium intake can be used in support of establishing a CDRR. The committee's evaluation of blood pressure as a surrogate marker for cardiovascular

[14]A surrogate marker (e.g., blood pressure) is "a biomarker that is intended to substitute for a clinical endpoint" (e.g., cardiovascular disease risk) by accurately predicting the effect of a measured intervention (e.g., sodium intake) on an unmeasured clinical outcome (e.g., cardiovascular disease risk) (IOM, 2010, p. 250).

disease and hypertension with sodium intake reduction was guided by the 2010 Institute of Medicine (IOM) report *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease* (hereafter referred to as the 2010 IOM Report), which recommends a three-step process for evaluation of biomarkers: analytical validation, qualification, and utilization. Analytic validation concerns "analyses of available evidence on the analytical performance of an assay." Analytic validation of blood pressure is well established in clinical practice and research (IOM, 2010, p. 2), so it will not be discussed further. The discussion below thus focuses on the "Qualification" and "Utilization" steps.

Qualification

Qualification involves "assessment of available evidence on associations between the biomarker and disease states, including data showing effects of interventions on both the biomarker and clinical outcomes" (IOM, 2010, p. 2). The 2010 IOM Report further recommends that this step involve two components: evaluating the "prognostic value of the biomarker–disease relationship" and "gather available evidence showing the biomarker's ability to predict the effects of interventions on clinical endpoints of interest" (IOM, 2010, p. 9). This section focuses on blood pressure as the potential surrogate marker for hypertension and cardiovascular disease because of its relevance in the committee's assessment of the evidence about the relationship between sodium intake and those health outcomes (see Figure 10-13). Therefore, the specific questions in this case are (1) Does blood pressure have a prognostic value for hypertension and cardiovascular disease? and (2) Does blood pressure accurately predict the effect of interventions on hypertension and cardiovascular disease? The evaluations are based on probabilistic rather than deterministic reasoning as it is likely that not all contributing factors will be fully understood. These evaluations generally require robust, adequately controlled study data that include studies that measure clinical outcomes.

Evidence of Blood Pressure's Prognostic Value

The 2010 IOM Report noted that "blood pressure is often looked to as an exemplar surrogate endpoint for cardiovascular mortality and morbidity due to the levels and types of evidence that support its use" (IOM, 2010, p. 39). The 2010 IOM Report further summarized the extensive epidemiological and clinical trial literature on the relationship between blood pressure and cardiovascular disease outcomes. In brief, epidemiological studies, including meta-analyses summarizing outcomes from hundreds of thousands of individuals, consistently demonstrate this relationship to be

highly robust. Additionally, both placebo- and active-controlled clinical trials robustly demonstrate that pharmacological reductions in blood pressure lead to reductions in cardiovascular mortality and morbidity.

Evidence That Blood Pressure Accurately Predicts the Effect of Interventions

Drug trials involving more than 75 different hypertensive agents from nine drug classes with varying mechanisms of action have consistently shown that reductions in blood pressure will reduce the risk of cardiovascular disease (Israili et al., 2007). The benefits were observed across different assessment variables (e.g., systolic alone, diastolic alone, and systolic and diastolic together) and in diverse populations (e.g., different sexes, across a range of adult age groups, in different races and ethnicities, and among both participants with and without hypertension) (Desai et al., 2006). Thus, blood pressure lowering, per se, had a beneficial effect on cardiovascular disease risk. As a consequence, blood pressure guidelines have underscored the central role of blood pressure reduction during antihypertensive drug treatment (Mancia et al., 2013; Whelton et al., 2018). The results from blood pressure–lowering agents, as well as the abundant observational data linking hypertension to cardiovascular events, provided the basis for use of blood pressure as a surrogate endpoint for antihypertensive drugs by the Food and Drug Administration (Desai et al., 2006; Temple, 1999).

The effect of interventions on blood pressure "may or may not capture an intervention's entire risk–benefit balance" (IOM, 2010, p. 40). For instance, there may be beneficial effects of an intervention that are independent of the effects on blood pressure. Additionally, there may be adverse effects that run counter to the beneficial effects owing to changes in blood pressure. Ultimately, however, the 2010 IOM Report concluded that "the fact that pharmacologically distinct agents have directionally similar effects on cardiovascular outcomes has provided more support for the use of blood pressure as a surrogate endpoint" (IOM, 2010, p. 41). However, these issues are to be revisited in the "Utilization" step, specifically in the context of use considered for the surrogate endpoint—in this case for interventions involving reduced sodium intake—discussed next.

Utilization

Utilization involves "contextual analysis based on the specific use proposed and the applicability of available evidence to this use. This includes a determination of whether the validation and qualification conducted provide sufficient support for the use proposed" (IOM, 2010, p. 2). The need for this "fit-for-purpose" evaluation stemmed from the recognition

that caution is needed when generalizing surrogate marker qualification status from one context to another (IOM, 2010; Yetley et al., 2017). Consistent with the criteria that surrogate markers need to be fit for purpose (i.e., qualified for a specific intake and outcome context) (IOM, 2010), the *Guiding Principles Report* recommended that "qualification of surrogate markers must be specific to each nutrient or other food substance, although some surrogates will be applicable to more than one causal pathway" (NASEM, 2017, p. 8). The 2010 IOM Report provided detailed guidance and recommendations as to the critical and important factors to consider in this "Utilization" step. The committee's evaluation of blood pressure presented below is organized by these seven factors.

1. Is the Biomarker Being Used as a Surrogate? (Critical Factor)

The 2010 IOM Report noted that "If the biomarker is used as a surrogate, enhanced scrutiny would be necessary" (IOM, 2010, p. 112). In this case, the answer to this question is "Yes," as blood pressure is to be used as a surrogate for hypertension and cardiovascular disease. The need for "enhanced scrutiny" is the reason that this detailed evaluation is being conducted as to whether use of blood pressure as a surrogate is "fit for purpose" in the context of establishing a sodium DRI based on chronic disease.

2. What Is the Prevalence of the Disease? What Are the Morbidities and Mortalities Associated with This Disease? (Critical Factor)

The 2010 IOM Report noted that "A highly prevalent or serious disease might have a lower threshold for use of biomarkers in clinical and regulatory decisions" (IOM, 2010, p. 112). In this case, hypertension and cardiovascular disease have high prevalence, with high associated morbidity and mortality (Bundy et al., 2018; Padwal et al., 2016). Therefore, the committee took into account the possibility of requiring a "lower threshold of use," particularly with respect to the extent to which effects of sodium intake reduction on blood pressure could account for the full extent of the benefits with respect to hypertension and cardiovascular disease (discussed further below in factor 5).

3. What Are the Risks and Benefits Associated with the Intervention? Has Due Attention Been Paid to Both Safety and Efficacy? (Critical Factor)

The 2010 IOM Report noted that "The benefits of the intervention must be weighed against the risks of biomarker failure to define a range of tolerable biomarker performance for each specific biomarker" (IOM, 2010, p. 112). The evidence for the risks and benefits of reducing sodium intake were

reviewed extensively throughout this chapter. Moreover, the question of balancing benefits and harms was explicitly discussed, as the question of the safety of interventions reducing sodium intake has been studied extensively. The committee found no evidence suggesting benefits from increasing intake above 2,300 mg/d (100 mmol/d), and that studies suggesting increased risks from decreasing intake below 2,300 mg/d (100 mmol/d) suffer from high risk of bias. Therefore, no concerns are raised with respect to unintended risks that would argue against using blood pressure as a surrogate endpoint in the case of sodium intake reduction, at least as low as the Adequate Intake of 1,500 mg/d (65 mmol/d). Thus, based on the committee's assessment, the benefits of reducing sodium intake to specific levels as specified by the CDRR outweigh the possible concerns about harms.

4. What Are the Advantages and Disadvantages Associated with Use of the Biomarker When Compared with the Best Available Alternative? How Does the Biomarker Benefit Management and Outcomes? (Critical Factor)

The 2010 IOM Report reported noted that "The evaluation may proceed differently depending upon whether a variety of valid treatment options are available compared to if no treatments have yet been developed, for example" (IOM, 2010, p. 112). In this case, the advantages of using blood pressure as a surrogate endpoint, as opposed to only using data on hypertension and cardiovascular disease incidence, are three-fold:

- First, the range of intakes over which clinical trial data for sodium reduction are available is much wider for blood pressure than it is for hypertension and cardiovascular disease. Thus, blood pressure data have much wider applicability to the populations of interest.
- Second, there is much more intake–response information for blood pressure, owing to the fact that clinical trial data for blood pressure involve a wide range of intervention sizes from less than 100 mg/d (4 mmol/d) reduction to almost 3,000 mg/d (130 mmol/d) reduction. By contrast, almost all the interventions for hypertension and cardiovascular disease were clustered around an intervention size of 1,000 mg/d (43 mmol/d) reduction.
- Third, use of blood pressure as a surrogate endpoint is beneficial to management and outcomes because it is a continuous marker, and thus can be used as a target for prevention.

Together, these factors support that using blood pressure as a surrogate endpoint has many comparative advantages to using the best available alternatives of hypertension incidence and cardiovascular disease incidence.

5. Is the Biomarker for Drugs, Biologics, or Device Development; for Relationships Between Diet or Nutrients and Disease; or for Public Health Monitoring and Interventions? (Critical Factor)

The 2010 IOM Report noted that "While the highest level of scientific rigor is needed in biomarker evaluations for all uses, each category of use has different risks and regulatory frameworks, which carry implications for appropriate evidence thresholds and requirements for biomarker use" (IOM, 2010, p. 112). In this case, blood pressure is used as a biomarker for relationships between "nutrients and disease" and "public health … interventions." The appropriate evidence thresholds were previously delineated in the *Guiding Principles Report* (NASEM, 2017), and applied rigorously by the committee in Chapter 10.

One key issue has been whether blood pressure is on the causal pathway between sodium intake reduction and hypertension or cardiovascular disease risk such that it reliably predicts changes in hypertension and cardiovascular disease risk when sodium intake is reduced. To address this question, the committee evaluated the results of three long-term follow-ups to previously completed large intervention trials that measured both blood pressure and cardiovascular outcomes (Appel et al., 2001; Cook et al., 2016). The study participants for the TOHP I and II trials were adults 30–54 years of age with prehypertension (Cook et al., 2016). The participants in the TONE trial (Appel et al., 2001) were 60–80 years of age with hypertension. Assessments of sodium intakes in all three trials were obtained from multiple 24-hour urine samples, the methodology considered to be the most accurate. The original trials all showed reductions in systolic and diastolic blood pressure and in the incidence of hypertension after 18–36 months in which reduced sodium intakes were compared to control (usual) intakes. Information on the long-term follow-ups of participants was collected via questionnaires with additional data collected from medical records and the national death index.

To be able to measure cardiovascular outcomes, the available evidence is from long-term follow-up data from randomized controlled trials. In those studies, the interventions in the initial trial period were aimed at reducing blood pressure through dietary and behavioral counseling to reduce sodium intake (without changing other nutrient intakes) (see also the description of the evidence in the Chapter 10 section Cardiovascular Disease Morbidity and Mortality, Updated Strength-of-Evidence Evaluation). The consistency in both the direction and the persistence of these effects over relatively long periods of time provides some of the strongest evidence that blood pressure is on the causal pathway between sodium intake and cardiovascular disease risk. However, given the lack of quantitative information on the sodium intakes of study participants between the completion

of these trials and the follow-up data on cardiovascular outcomes, it is not possible to estimate whether the blood pressure changes due to sodium intake reductions explain a significant portion of the effect of sodium on cardiovascular disease risk or if there are additional effects of sodium that occur outside the blood pressure pathway.

Thus, while the available data clearly meet almost all criteria for qualifying a surrogate marker for a specific context (Prentice, 1989), there remains some uncertainty as to whether blood pressure fully explains the effect of sodium intake reductions on cardiovascular risk. In considering whether blood pressure is a qualified surrogate marker for predicting the effect of sodium intakes on cardiovascular disease risk within the DRI context, this uncertainty does not negate the committee's ability to qualify blood pressure as a surrogate marker for the purposes of establishing a CDRR for sodium and cardiovascular disease. Although the available data cannot accurately estimate what fraction of disease prevention from sodium reduction is directly attributable to blood pressure reduction, the directionality of the relationship is consistent, and appears persistent for up to 18 years of follow-up. These results are also consistent with drug trials relating blood pressure to cardiovascular disease, in which different classes of drugs with different mechanisms of action for lowering blood pressure had consistent effects on cardiovascular disease risk. Overall, the committee considered blood pressure to be a sufficiently accurate surrogate specifically for the purposes of establishing the positive slope of the intake–response relationship between sodium intake and chronic disease risk. Pursuant to the guidance provided in the *Guiding Principles Report*, the blood pressure data served as supporting evidence. The committee did not solely rely on the biomarker of blood pressure in making its decisions, but instead used blood pressure in tandem with trial-based evidence on incident hypertension and cardiovascular disease in determining the sodium CDRR.

6. What Is the Biomarker's Purpose with Respect to Phase of Development in Clinical Trials? (Important Factor)

This factor is not applicable in this case.

7. Is the Biomarker for Primary or Secondary Disease Prevention? (Important Factor)

The 2010 IOM Report noted that "Biomarkers used for these purposes carry especially high risk and should be evaluated with this consideration in mind" (IOM, 2010, p. 112). In this case, the biomarker is being used for primary disease prevention, although the context is public health interventions rather than patient-level interventions. The "high-risk" nature of

using a biomarker for primary prevention informed the committee's decision to use blood pressure in tandem with hypertension and cardiovascular disease in establishing the sodium CDRR. Thus, the committee did not solely rely on the biomarker in making its decisions.

Summary

In the main body of Chapter 10, the committee rigorously evaluated the evidence supporting the fact that blood pressure is on the causal pathway between sodium intake and cardiovascular risk and accurately predicts the directional benefits of sodium intake reduction on cardiovascular disease risk. In this annex, the committee evaluated whether blood pressure is qualified to serve as a surrogate marker within the DRI context when sodium is the intervention of interest and chronic disease is the outcome of interest (i.e., is fit for purpose). Based on the committee's evaluation, the overall scientific evidence provides a sufficient basis both to *qualify* blood pressure as a surrogate marker for predicting the effects on hypertension and cardiovascular disease as well as to *utilize* blood pressure as a surrogate endpoint specifically in the case of interventions to reduce sodium intake. Therefore, the committee uses blood pressure as a surrogate marker for hypertension and cardiovascular disease in establishing the sodium CDRR.

ANNEX 10-2 REFERENCES

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11

Sodium Dietary Reference Intakes: Risk Characterization and Special Considerations for Public Health

The final two steps of the Dietary Reference Intake (DRI) organizing framework provide public health context for the revised or newly established reference values. One of the hallmarks of these steps is to compare the DRI values to intake distributions in the United States and Canada for the nutrient of interest, to assess whether population intakes are likely to be adequate, and to determine if the population is at risk due to excessive intake. Use of biochemical and clinical measures, if available, can also supplement this risk characterization. With the expansion of the DRI model, this step now also examines intakes in relevant populations in relation to the Chronic Disease Risk Reduction Intake (CDRR), if established. This information is then used to describe the public health implications of the established DRI values. This chapter provides the committee's risk characterization and special considerations for public health as they relate to the sodium DRI values established in this report.

RISK CHARACTERIZATION BASED ON SODIUM INTAKE LEVELS IN THE U.S. AND CANADIAN POPULATIONS

Adequate Intakes (AIs) are usually established when the evidence is not sufficient to derive Estimated Average Requirements and Recommended Dietary Allowances. The sodium AIs were derived using evidence from the lowest level of sodium intakes evaluated in trials and evidence from the best-designed balance study in adults, and were extrapolated to children and adolescents based on sedentary Estimated Energy Requirements (EERs). Because the committee lacked information as to how the AIs relate to actual

requirements, caution is required in use and interpretation of the AI values (IOM, 2000, 2003). With sodium, the AI represents a level of intake that, based on the lack of adverse effects, appears to be adequate. Therefore, "similar groups with mean intakes at or above the AI can be assumed to have a low prevalence of inadequate intakes. When mean intakes of groups are below the AI, it is not possible to make any assumptions about the extent of intake inadequacy" (IOM, 2000, p. 12).

Reducing sodium intakes that are above the CDRR is expected to reduce the risk of chronic disease. Evidence on the effect of sodium reduction on risk of cardiovascular disease, risk of hypertension, and blood pressure was synthesized in order to establish the sodium CDRR. Assessing the public health context of usual sodium intakes of the U.S. and Canadian populations requires an assessment of the distribution of intakes above the CDRR to determine what proportion of the population might benefit from reductions in usual sodium intakes.

The sections that follow compare the sodium AIs and CDRRs established in this report to current sodium intakes in the U.S. and Canadian populations. Appendix G provides methodological details about the surveys used for these comparisons, namely the U.S. National Health and Nutrition Examination Survey (NHANES), Canadian Community Health Survey–Nutrition 2015 (CCHS Nutrition 2015), and the Feeding Infants and Toddlers Study 2016 (FITS 2016). Data are presented by sex and age groups, as provided in these data sources. Estimates from NHANES and CCHS Nutrition 2015 exclude salt added at the table or sodium intakes from supplements or medications, which would be expected to lead to a slight underestimation of intake (CDC/NCHS, 2019; Statistics Canada, 2017). Supplementary figures for select comparisons are provided in Appendix H.

Characterization by DRI Age, Sex, and Life-Stage Groups

Infants 0–12 Months of Age

The committee was provided with evidence on the distribution of usual sodium intake of U.S. infants (see Table 11-1). Among NHANES 2009–2014 infants 0–6 months of age who did not consume breast milk, estimated median sodium intake was 215 mg/d (9 mmol/d). Among FITS 2016 infants, which include both infants who did and did not consume breast milk, estimated median sodium intake was 195 mg/d (8 mmol/d). These median sodium intakes exceed the AI, which was derived by estimating sodium intake of breastfed infants and assumes an average sodium concentration in breast milk of 140 mg/L and an average consumption of 780 mL of breast milk per day (for additional details, see Chapter 8 and Appendix F).

TABLE 11-1 Usual Sodium Intake Among U.S. Infants 0–6 Months of Age, as Compared to the Sodium Adequate Intake

Comparison Data Source	Age Range (Months)	Breastfeeding Status of Infants	Adequate Intake (mg/d)	Mean (mg/d)[a]	Percentile		
					25th (mg/d)	50th (mg/d)	75th (mg/d)
NHANES 2009–2014	0–6	Not BF	110	**230 (7)**	**169**	**215**	**275**
FITS 2016	0–5.9	All	110	**214 (4)**	**143**	**195**	**265**

NOTES: Bold indicates the value is higher than the Adequate Intake for the DRI age, sex, and life-stage group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. No analyses were identified that estimated usual sodium intake distribution for breastfed infants 0–6 months of age. FITS 2016 = Feeding Infants and Toddlers Study 2016; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey; Not BF = analysis of infants who did not consume breast milk.

[a]Presented as intake (standard error).

SOURCES: Bailey et al., 2018; NHANES 2009–2014 (unpublished).

Intake estimates for infants 7–12 months of age include sodium intakes from breast milk, formula, and/or other milks in addition to complementary foods. Median usual sodium intakes among infants 7–12 months of age ranged from approximately 341–537 mg/d (15–23 mmol/d) and varied by the survey and by whether infants included in the analyses consumed breast milk (see Table 11-2). Infants in the NHANES 2003–2010 analysis who consumed some breast milk and FITS 2016 infants of all breastfeeding statuses had median intake slightly below the sodium AI; median sodium intakes for all other survey groups exceeded the AI. Estimated sodium intake was slightly higher in the analyses that did not include breastfed infants. This difference may reflect both the lower sodium content of breast milk compared to infant formula, as well as lower energy intakes (Heinig et al., 1993; Whitehead, 1995). Because breast milk is considered to be nutritionally adequate, the intake of breastfed infants in this age group is not a public health concern.

Children and Adolescents 1–18 Years of Age

Because it is unknown how the AI relates to actual requirements, caution must be exercised when interpreting the prevalence of intakes above or below the AI in terms of adequacy. However, Table 11-3 indicates that more than 95 percent, and in many cases almost all, of U.S. and Canadian children and adolescents consume sodium at levels above the AI. The occurrence of a relatively low prevalence of intakes less than the AI for some groups in Table 11-4 cannot be interpreted as inadequate (IOM, 2000, 2003). Thus, the high prevalence of intakes above the AI likely reflect a low chance of inadequacy.

TABLE 11-2 Usual Sodium Intake Among U.S. Infants 7–12 Months of Age, as Compared to the Sodium Adequate Intake

Comparison Data Source	Age Range (months)	Breastfeeding Status of Infants	Adequate Intake (mg/d)	Mean (mg/d)[a]	Percentile		
					25th (mg/d)	50th (mg/d)	75th (mg/d)
NHANES 2009–2014	7–12	Not BF	370	**680 (38)**	334	**537**	**861**
NHANES 2003–2010	7–11	Not BF	370	**538 (22)**	**370**	**484**	**650**
	7–11	BF[b]	370	**383 (53)**	254	341	**463**
FITS 2016	6–11.9	All	370	**400 (60)**	273	367	**492**
NHANES 2003–2010	7–11	All	370	**500 (19)**	320	**438**	**614**
NHANES 2009–2012	6–11	All[c]	370	**497 (25)**	247	**395**	**625**

NOTES: Bold indicates the value is higher than the Adequate Intake for the DRI age, sex, and life-stage group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. BF = analysis of infants who consumed breast milk; FITS 2016 = Feeding Infants and Toddlers Study 2016; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey; Not BF = analysis of infants who did not consume breast milk.

[a]Presented as intake (standard error).

[b]Consumption of at least some breast milk, as reported on the 24-hour dietary recall.

[c]Estimated 23.9 ± 3.3 percent of this sample reported consuming any breast milk.

SOURCES: Ahluwalia et al., 2016; Bailey et al., 2018; NHANES 2009–2014 (unpublished); Tian et al., 2013.

The sodium CDRR represents the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. The sodium CDRR, therefore, is the intake above which intake reduction is expected to reduce chronic disease risk within an apparently healthy population. For children and adolescents, the sodium CDRRs were extrapolated from the adult value, based on sedentary EERs. For all DRI groups for children and adolescents 1–18 years of age, the 50th percentile of sodium intake exceeded the CDRR and in some cases, even the 5th percentile intake is greater than the CDRR (see Table 11-4). More than 80 percent of U.S. children and adolescents 1–18 years of age exceed the CDRR. Similarly, more than 80 percent of Canadian children and adolescents 1 year of age and older exceed the CDRR, with the exception of females 14–18 years of age, for whom more than 60 percent exceeded the CDRR. These results indicate that the majority of U.S. and Canadian children and adolescents may benefit from reduction in sodium intake. Reductions from current high levels of sodium intakes down to the CDRR

TABLE 11-3 5th and 50th Percentiles of Usual Sodium Intake Among U.S. and Canadian Children and Adolescents 1–18 Years of Age, as Compared to the Sodium Dietary Reference Intake Values

DRI Group	AI (mg/d)	CDRR (mg/d)[a]	5th Percentile (mg/d)[b]	50th Percentile (mg/d)[b]
Both sexes, 1–3 years				
U.S., both sexes	800	1,200	**1,169 (50)**	***1,935 (24)***
Canada, males	800	1,200	**948 (141)**	***1,645 (49)***
Canada, females	800	1,200	**872 (137)**	***1,547 (55)***
Both sexes, 4–8 years				
U.S., both sexes	1,000	1,500	***1,800 (33)***	***2,663 (23)***
Canada, males	1,000	1,500	***1,845 (243)***	***2,406 (63)***
Canada, females	1,000	1,500	***1,692 (228)***	***2,212 (53)***
Males, 9–13 years				
U.S.	1,200	1,800	***2,348 (96)***	***3,320 (51)***
Canada	1,200	1,800	***1,871 (107)***	***2,910 (61)***
Males, 14–18 years				
U.S.	1,500	2,300	***2,434 (117)***	***3,905 (77)***
Canada	1,500	2,300	***2,380 (138)***	***3,519 (77)***
Females, 9–13 years				
U.S.	1,200	1,800	***2,002 (72)***	***2,894 (36)***
Canada	1,200	1,800	**1,672 (88)**	***2,555 (51)***
Females, 14–18 years				
U.S.	1,500	2,300	**1,883 (152)**	***2,886 (61)***
Canada	1,500	2,300	**1,546 (88)**	***2,499 (67)***

NOTES: Bold indicates the value is higher than the AI for the DRI age, sex, and life-stage group; italics indicates the value is higher than the CDRR for the DRI group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day.

[a]The sodium CDRR represents the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. If sodium intakes are above the CDRR, intake reduction is expected to reduce chronic disease risk within an apparently healthy population. The sodium CDRRs for children and adolescents were extrapolated from the adult CDRR based on sedentary Estimated Energy Requirements.

[b]Presented as intake (standard error).

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

TABLE 11-4 Percent of U.S. and Canadian Children and Adolescents 0–18 Years of Age Exceeding the Adequate Intake, Chronic Disease Risk Reduction Intake, and Select Sodium Intake Levels

			% of Population with Sodium Intake							
			> AI		> CDRR		> 4,100 mg/d		> 5,000 mg/d	
DRI Group	AI (mg/d)	CDRR (mg/d)[a]	U.S.	Canada	U.S.	Canada	U.S.	Canada	U.S.	Canada
Both sexes, 0–6 months	120	N/A	94	—[b]	N/A	N/A	1	—[b]	1	—[b]
Both sexes, 7–12 months	370	N/A	70	—[b]	N/A	N/A	1	—[b]	1	—[b]
Both sexes, 1–3 years	800	1,200	99	97	94	81	1	1	1	1
Both sexes, 4–8 years	1,000	1,500	99	99	99	99	2	1	1	1
Males, 9–13 years	1,200	1,800	99	99	99	96	13	8	1	1
Males, 14–18 years	1,500	2,300	99	99	96	96	42	24	17	5
Females, 9–13 years	1,200	1,800	99	99	98	91	3	1	1	1
Females, 14–18 years	1,500	2,300	99	95	81	62	5	2	1	1

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; N/A = not applicable.

[a]The sodium CDRR represents the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. If sodium intakes are above the CDRR, intake reduction is expected to reduce chronic disease risk within an apparently healthy population. The sodium CDRRs for children and adolescents were extrapolated from the adult CDRR based on sedentary Estimated Energy Requirements.

[b]CCHS Nutrition 2015 did not collect dietary intake data on children younger than 1 year of age (Statistics Canada, 2017).

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

intake levels are expected to benefit the population's health. This would be unlikely to increase the risk of inadequacy because the sodium CDRR is higher than the AI.

Adults 19 Years of Age and Older

The vast majority of U.S. and Canadian adults have usual sodium intakes higher than the AI (see Tables 11-5 and 11-6). In the United States,

the 5th percentile of usual sodium intake exceeds the AI for all adult DRI groups. In Canada, the 5th percentile of usual sodium intake exceeds the AI for all adult DRI groups with the exception of females 51 years of age or older, and the combined category of females 19 years of age and older. Because the AI is not based on the distribution of requirements, caution must be exercised when interpreting the prevalence of intakes above or below the AI in terms of adequacy. However, more than 90 percent, and in many cases almost all, of U.S. and Canadian adults are consuming sodium at values above the AI (see Table 11-6), indicating a very low probability of inadequacy of sodium. Because of uncertainties in how the AI relates to requirements, prevalence of intakes below the AI cannot be interpreted as being inadequate.

The sodium CDRR is the intake above which intake reduction is expected to reduce chronic disease risk within an apparently healthy population. For the U.S. population, the 50th percentile sodium intake exceeded the CDRR for all adult DRI groups; in many cases, the 5th percentile is greater than the CDRR. For the Canadian population, the 50th percentile exceeded the CDRR, except for females 51 years of age or older, and the combined category of females 19 years of age and older (see Tables 11-5 and 11-6). At least half or more of the U.S. and Canadian adult populations consume more sodium than the CDRR for most DRI groups, putting them at increased risk of cardiovascular disease. More than 80 percent of U.S. adult females, 97 percent of U.S. male adults, and, combined, 88 percent of all U.S. adults exceed the CDRR. Among Canadian adults, 80 percent of males and 46 percent of females exceed the CDRR, with 65 percent of all adults above the CDRR. Among U.S. and Canadian adults, the proportion above the CDRR tended to decline with increasing age, with the lowest proportion in adults 71 years of age and older. These high sodium intakes for all adults are a public health concern, as cardiovascular disease is a major health burden. These results indicate that the majority of U.S. and Canadian adults could benefit from sodium reduction, which would be expected to decrease risk of cardiovascular disease in the population.

Characterization by Sex and Life Stage

On average, males have higher usual intakes of sodium than women, and pregnant and lactating females have higher usual sodium intakes than nonpregnant or lactating females. These relationships are likely attributed to higher energy intakes in males than females, and pregnant and lactating females as compared to their nonpregnant and nonlactating counterparts. As noted in Chapter 3, sodium intake is highly correlated with energy intake, leading to higher intakes of sodium with greater energy intakes.

TABLE 11-5 5th and 50th Percentiles of Usual Sodium Intake Among U.S. and Canadian Adults 19 Years of Age and Older, as Compared to the Sodium Dietary Reference Intake Values

DRI Group	AI (mg/d)	CDRR (mg/d)[a]	5th Percentile (mg/d)[b]	50th Percentile (mg/d)[b]
Males, 19–30 years				
U.S.	1,500	2,300	***2,688 (91)***	***4,271 (54)***
Canada	1,500	2,300	***2,307 (490)***	***3,547 (136)***
Males, 31–50 years				
U.S.	1,500	2,300	***2,709 (76)***	***4,275 (44)***
Canada	1,500	2,300	**1,630 (298)**	***3,149 (74)***
Males, 51–70 years				
U.S.	1,500	2,300	***2,397 (57)***	***3,837 (47)***
Canada	1,500	2,300	**1,798 (260)**	***2,972 (65)***
Males, > 70 years				
U.S.	1,500	2,300	**2,093 (57)**	***3,256 (39)***
Canada	1,500	2,300	**1,705 (93)**	***2,626 (52)***
Males, ≥ 19 years				
U.S.	1,500	2,300	***2,487 (39)***	***4,027 (24)***
Canada	1,500	2,300	**1,723 (62)**	***3,093 (42)***
Females, 19–30 years				
U.S.	1,500	2,300	**2,082 (77)**	***3,055 (38)***
Canada	1,500	2,300	**1,565 (138)**	***2,326 (86)***
Females, 31–50 years				
U.S.	1,500	2,300	**1,900 (42)**	***2,995 (21)***
Canada	1,500	2,300	**1,649 (135)**	***2,383 (48)***
Females, 51–70 years				
U.S.	1,500	2,300	**1,803 (61)**	***2,813 (26)***
Canada	1,500	2,300	1,264 (55)	**2,150 (33)**
Females, > 70 years				
U.S.	1,500	2,300	**1,610 (56)**	***2,547 (33)***
Canada	1,500	2,300	1,241 (63)	**2,054 (39)**
Females, ≥ 19 years				
U.S.	1,500	2,300	**1,846 (26)**	***2,888 (13)***
Canada	1,500	2,300	1,425 (46)	**2,253 (25)**

TABLE 11-5 Continued

DRI Group	AI (mg/d)	CDRR (mg/d)[a]	5th Percentile (mg/d)[b]	50th Percentile (mg/d)[b]
Pregnant				
U.S.	1,500	2,300	**2,294 (224)**	***3,337 (88)***
Canada	1,500	2,300	**1,782 (421)**	***2,579 (164)***
Lactating				
U.S.	1,500	2,300	***2,721 (325)***	***3,633 (135)***
Canada	1,500	2,300	**1,849 (418)**	***2,708 (119)***

NOTES: Bold indicates the value is higher than the AI for the DRI age, sex, and life-stage group; italics indicates the value is higher than the CDRR for the DRI group. Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day.

[a]The sodium CDRR represents the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. If sodium intakes are above the CDRR, intake reduction is expected to reduce chronic disease risk within an apparently healthy population.

[b]Presented as intake (standard error).

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

Characterization by Country

Because the DRIs are established jointly for use in the U.S. and Canadian populations, there is interest in whether intakes vary by country. The 50th percentile of usual sodium intake was lower in Canada than in the United States for all of the DRI age, sex, and life-stage groups. Methods for collecting 24-hour dietary recalls, nutrient databases, and statistical methods used to estimate intakes were similar between the U.S. and Canadian surveys, and therefore would not be expected to explain these differences (CDC/NCHS, 2019; Statistics Canada, 2017; and see Appendix G for details of the methodology). Although no statistical comparisons were made, in many cases, the sodium intakes were substantially lower in Canada. For example, the median intake among adult males 19 years of age and older was more than 900 mg/d lower in Canada compared to the United States, and the median intake among adult females 19 years of age and older was more than 600 mg/d lower in Canada compared to the United States. The vast majority of both the U.S. and Canadian populations are above the AI so inadequate intakes are not a concern. Although the majority of the U.S. and Canadian populations have usual sodium intakes above the CDRR, the percent exceeding the CDRR were consistently equivalent or lower in the Canadian population.[1] Notably, 80 percent of U.S. women and 46 percent

[1]This text was revised since the prepublication release.

TABLE 11-6 Percent of U.S. and Canadian Adults 19 Years of Age and Older Exceeding the Adequate Intake, Chronic Disease Risk Reduction Intake, and Select Sodium Intake Levels

			% of Population with Sodium Intake							
			> AI		> CDRR		> 4,100 mg/d		> 5,000 mg/d	
DRI Group	AI (mg/d)	CDRR (mg/d)[a]	U.S.	Canada	U.S.	Canada	U.S.	Canada	U.S.	Canada
Males, 19–30 years	1,500	2,300	99	99	98	95	56	26	25	6
Males, 31–50 years	1,500	2,300	99	96	98	79	56	21	26	7
Males, 51–70 years	1,500	2,300	99	98	96	80	39	11	14	2
Males, > 70 years	1,500	2,300	99	98	90	70	17	2	3	1
Males, ≥ 19 years	1,500	2,300	99	97	97	80	47	17	20	5
Females, 19–30 years	1,500	2,300	99	96	89	51	7	1	1	1
Females, 31–50 years	1,500	2,300	99	97	83	56	9	1	1	1
Females, 51–70 years	1,500	2,300	98	87	78	41	5	1	1	1
Females, > 70 years	1,500	2,300	96	85	65	34	2	1	1	1
Pregnant	1,500	2,300	99	98	94	70	16	1	2	1
Lactating	1,500	2,300	99	98	99	76	22	1	1	1
Females, ≥ 19 years	1,500	2,300	99	92	80	46	6	1	1	1
Both sexes, ≥ 19 years	1,500	2,300	99	94	88	65	27	7	9	1

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. AI = Adequate Intake; CDRR = Chronic Disease Prevention Intake; mg/d = milligrams per day.

[a]The sodium CDRR represents the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. If sodium intakes are above the CDRR, intake reduction is expected to reduce chronic disease risk within an apparently healthy population.

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

of Canadian women exceed the CDRR. Additionally, although overall 5 percent of adult men in Canada exceed an average sodium intake of 5,000 mg/d, 20 percent of adult males in the United States exceed this intake level. Nevertheless, the evidence indicates that reducing sodium intakes if they are above the CDRR is warranted for both the Canadian and U.S. populations.

Characterization by Race and Ethnicity Groups

For the United States, distributions of the usual sodium intake were estimated by three race/ethnicity categories: non-Hispanic white, non-Hispanic black, and Hispanic (see Figures 11-1 and 11-2). Although no statistical comparisons were made, in nonpregnant and nonlactating adults, non-Hispanic whites tended to have highest sodium intakes; this pattern was not seen in children and adolescents.

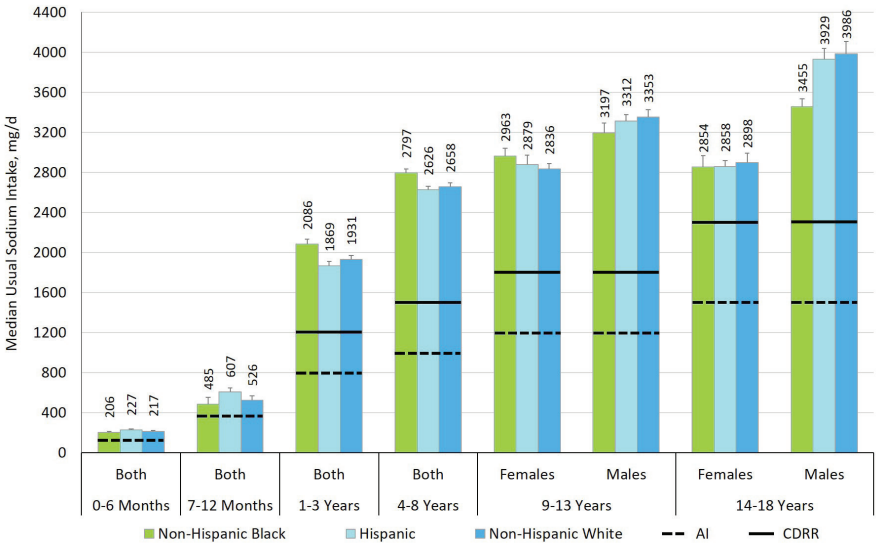

FIGURE 11-1 Median usual sodium intakes among U.S. children and adolescents 1–18 years of age, by race/ethnicity.
NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day.
SOURCE: NHANES 2009–2014 (unpublished).

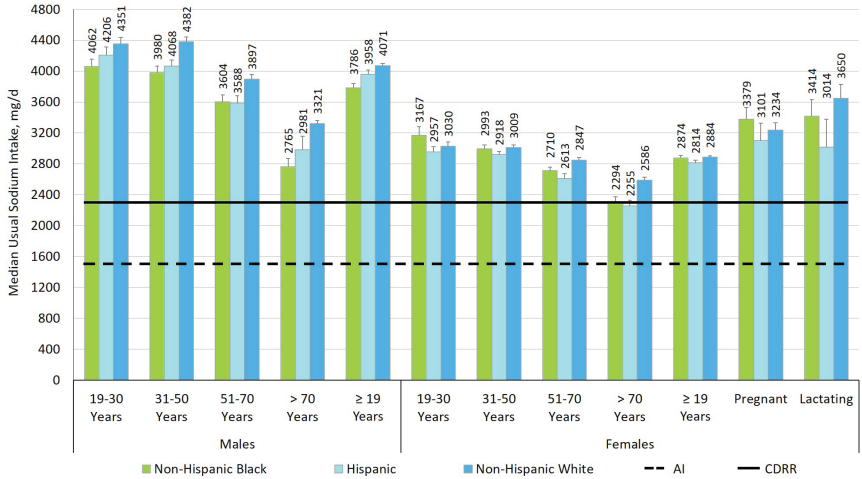

FIGURE 11-2 Median usual sodium intakes among U.S. adults 19 years of age and older, by race/ethnicity.
NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day.
SOURCE: NHANES 2009–2014 (unpublished).

Characterization by Hypertension Status

Distributions of the usual sodium intakes in the United States and Canada were stratified by hypertension status. In the Canadian distributions, hypertension status was self-reported and stratified into two categories based on the question "Do you have high blood pressure?" (Statistics Canada, 2017). In the U.S. distributions, hypertension status was stratified into three categories—normotensive, elevated blood pressure, and hypertensive. Hypertension status was defined using the 2017 American College of Cardiology and the American Heart Association guidelines for adults (Whelton et al., 2018), based on the mean of up to three consecutive blood pressure measurements or use of hypertensive medications. In both analyses, individuals who self-reported having a history of cardiovascular disease were excluded.[2] For comparability between the United States and Canada,

[2]The NHANES usual sodium intake distribution stratified by hypertension status excluded anyone who had reported that a doctor or other health professional had ever told them they had a stroke or heart attack (myocardial infarction). The CCHS Nutrition 2015 usual sodium intake distribution stratified by hypertension status excluded anyone who had reported that a health professional had ever told them they had heart disease. Participants who answered that they did not know or refused to answer were also excluded.

the elevated blood pressure group from the NHANES 2009–2014 data are omitted in this characterization.

Although no statistical comparisons were made, in some DRI age, sex, and life-stage groups, usual sodium intakes were comparable in normotensive adults and in adults with hypertension (see Figure 11-3). However, median usual sodium intakes were higher among normotensive adult males and females (≥ 19 years of age and older) compared to their hypertensive counterparts. Normotensive pregnant women also had higher median sodium intakes compared to hypertensive women in the United States. Estimates of usual sodium intake among hypertensive pregnant women were statistically unstable in the U.S. data and were too variable to be reported in the Canadian data. Both hypertensive and normotensive population groups in the United States and Canada have sodium intakes that exceed the CDRR; reductions in usual sodium intakes above the CDRR are expected to reduce risk of chronic disease in the apparently healthy population.

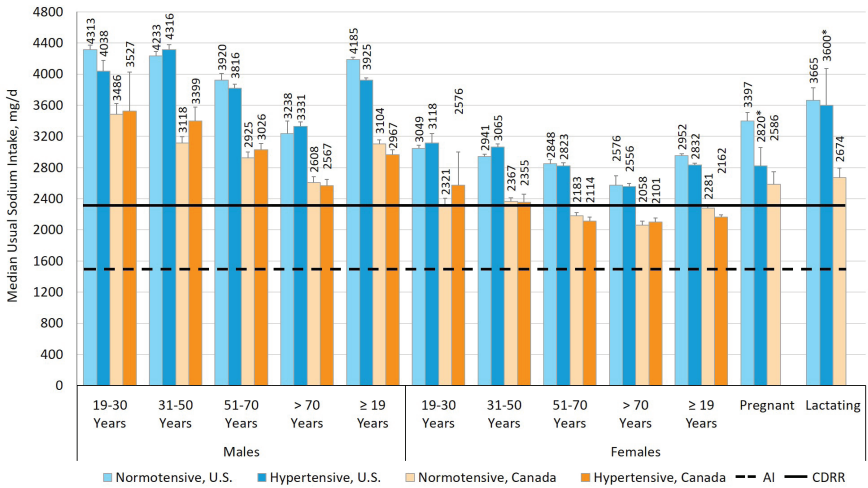

FIGURE 11-3 Median usual sodium intakes among U.S. adults 19 years of age and older, by hypertension status.
NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake level by 23.0. * = estimate is statistically unstable; AI = Adequate Intake; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

THE ROLE OF SODIUM IN THE FOOD SUPPLY AND SOURCES OF SODIUM IN THE DIET

The sections that follow further contextualize sodium intake levels in the U.S. and Canadian populations by first considering the roles of sodium in the food supply and then reviewing the evidence regarding the top contributors to sodium intake.

Roles of Sodium in the Food Supply

To understand the top contributors of sodium in the diet, the roles of sodium in the food supply are useful to consider. Sodium, typically in the form of sodium chloride (commonly referred to as "salt"), has many functional applications and imparts desirable qualities. Brief summaries of some of those key roles are described below.

Preserving and Fermenting Foods

Salt has long been used to preserve food. As water is critical for the growth of microorganisms, a primary mechanism by which salt can preserve food is by reducing water content. The binding of salt to water reduces water's chemical and biological activity and makes it unavailable to microorganisms. The water activity of foods can be decreased by means of osmotic gradients that promote migration of water out of the food (e.g., surface application of dry salt crystals, brining) or direct addition of salt into a food formulation. Salt can also slow microbial growth by disrupting the activity of enzymes and DNA replication. Salt added during processing can selectively inhibit the growth of food pathogens such as *Salmonella* or *Clostridium botulinum*. These beneficial effects are attributed to inhibition of bacterial growth rather than cell death.

Salt is a critical ingredient in food fermentations. Food fermentation in products like sauerkraut, cheese, and salami is aided by the presence of salt, which selectively promotes the growth of lactic acid bacteria. Lactic acid–producing bacteria are tolerant of high-salt environments and thus can grow in the presence of salt faster than other spoilage microorganisms and food pathogens. Lactic acid is produced by these bacteria as they metabolize (ferment) carbohydrates, which decreases the pH of the food. Thus, the salting of vegetables, cheese, and meats allows for selective bacterial lactic acid fermentation and creates a low-pH environment that preserves the food.

Altering the Texture of Foods

Salt can alter the texture of foods, especially meats. During the brining of a meat product, salt migrates into the muscle where it increases the solubil-

ity of meat proteins. When the meat is cooked, the solubilized proteins can entrap water and produce a juicer texture. The solubilized proteins can form gels that further entrap water. Brining of meat increases its salt content. For instance, brined fresh pork contains more than 350 mg of sodium per 100 grams of meat whereas unbrined pork has 50 mg sodium per 100 g of meat.

Salt can also interact with proteins to increase their association with water to make them more water soluble (salting-in) and can also interact with proteins to decrease their charge, change their structure, and produce protein aggregation, which results in decreased water solubility (salting-out). Salting-in is important to the production of processed meat. The proteins in meats (myofibrillar proteins) have very low solubility in water with low sodium levels. Adding salt to meats increases protein solubility and thus the ability of myofibrillar proteins to associate with other components in the foods such as water and fat. When solubilized myofibrillar proteins are heated, they form gels that can entrap both water and fat droplets. This is the premise behind why meat products, such as emulsified sausages (e.g., hot dogs), require high levels of salt. If salt is not present in these products, the protein does not form gels and emulsify fat, resulting in separation of the water and fat from the protein to form a defective product. In other meat products, salt solubilization of the proteins allows the meat to bind together forming a cohesive product that does not fall apart (e.g., breakfast sausages and deli meats).

The quality of bread produced by yeast fermentation is also influenced by salt. Salt binds water and can penetrate yeast cells to modify the growth rate, slowing the fermentation process. Salt also alters the functionality of bread proteins (gluten) and promotes formation of a physical matrix that slows bread rising, entraps gas, and resists collapsing. This occurs because salt decreases the extendibility of gluten networks and thereby increases stability. Salt also helps decrease water activity, which both decreases spoilage and affects the flavor of bread products (Silow et al., 2016). Typical salt concentrations in bread are around 2 percent of the flour weight.

Imparting and Enhancing Flavor

Salt is added to food as a flavoring agent and can enhance the perception of other flavors by acting as a flavor modifier. Even in applications where it is added to affect microbial growth or the functional properties of food components, salt also contributes to flavor (see illustrative example in Box 11-1). In some processed foods, the amount of salt needed to affect flavor can be higher if the salt migrates into large pieces of food and associates with other food components. This internalized salt might not migrate to the taste buds during food consumption and thus is not perceived as flavor. This can result in the need for higher salt concentrations to obtain the desired salty flavor in many processed foods.

BOX 11-1
An Illustrative Example of the Multiple Roles of Salt in Food

Cheese production serves as an illustrative example of how salt can have multiple roles in a food product. First, salt is important in cheese production because it favors the growth of lactic acid bacteria over spoilage organisms and pathogens. Second, salt is added to fresh cheese curds to help draw out water to create a firmer texture. The addition of salt also causes milk proteins to aggregate, which can be used in creating the desired texture. The salt also helps decrease water activity, thereby minimizing spoilage by microorganisms and contributing to long shelf lives. Finally, salt produces desired flavors and enhances perception of other flavors in the final product.

Other Forms of Sodium Used in Food Production

In addition to sodium chloride, sodium in foods can originate from food ingredients that are in the form of sodium salts. For example, phosphates are commonly added to foods to improve protein solubility, inhibit lipid oxidation, alter pH, and control bacterial growth. The most common forms of phosphates are sodium pyrophosphate and sodium tripolyphosphates. Sodium lactate and sodium diacetate are commonly added to precooked, processed meats along with sodium chloride to reduce or prevent the growth of the food pathogens (Seman et al., 2002). Sodium bicarbonate is used in chemically leavened baked goods (e.g., cakes) as a source of carbon dioxide. Sodium caseinate is a water-soluble form of the dairy protein casein. Sodium caseinate is used as a light-scattering agent to form a white appearance in products such as nondairy creamers, an emulsifier in salad dressing and sauces, and as a water binder in meats. Sodium benzoate and sodium proprionate are common antimicrobial agents added to foods. Sodium bisulfite and metabisulfite are added to food to prevent browning. Nonsodium salts (e.g., potassium) are available for most of these food ingredients, but their use can be limited by lower solubility, higher costs, and off flavors.

Source of Sodium in the Diet

Sources of Sodium Intake

The various roles of sodium in the food supply provide context for understanding the evidence on the various sources of sodium intake. In a 26-week study of 62 adult participants who reported regularly using

discretionary salt, estimated median sodium intake came from the following sources: 77 percent was from processing-added sources, 11.6 percent was inherent in the food, 6.2 percent was added at the table, 5.1 percent was added during cooking, and 0.1 percent was from water (Mattes and Donnelly, 1991). A more recent evaluation of 450 adults in three geographic locations in the United States reported similar findings: 70.9 percent of sodium intake came from sources outside the home, 14.2 came from sodium inherent in food, 5.6 percent came from in-home preparation, and 4.9 percent came from salt added at the table (Harnack et al., 2017). Tap water has small amounts of sodium, and along with dietary supplements and nonprescription antacids each contributed less than 0.5 percent to total sodium intake (Harnack et al., 2017). Findings from these studies indicate that the majority of sodium intake is not from sodium naturally inherent in the food, added during cooking, or at the table; rather, it is added during commercial processing and preparation.

Top Contributors to Sodium Intake in the United States and Canada

Various cycles of NHANES data have been used to characterize leading contributors of sodium intake in the U.S. population (O'Neil et al., 2012, 2018; Quader et al., 2017) (see Tables 11-7 through 11-9). Sources of dietary sodium among Canadians have been characterized using CCHS Nutrition 2015 data (Health Canada, 2018) (see Figure 11-4). The food categories in each analysis differ, making direct comparisons challenging. In Table 11-8, for instance, cheese is the top contributor to sodium intake, as the analysis disaggregated dairy intake from nondairy food (e.g., mixed dishes). Without this disaggregation of dairy intake, cheese would have been ranked as the 8th top sodium contributor among children 2–5 years of age and the 10th top contributor among children 6–11 and 12–18 years of age (O'Neil et al., 2018), a similar ranking as to what is found among the U.S. population (Quader et al., 2017). Thus, disaggregation of the different components of mixed dishes (e.g., the bread in sandwiches, cheese on pizza) would likely change the rankings of specific foods or food categories. This level of precision, however, does not currently exist in the available data.

In general, the major sources of sodium in the diet come from foods in which sodium chloride serves a functional purpose, including baked goods, processed meats, and cheese. The age-stratified analyses provide evidence that there are certain foods that commonly contribute a sizeable proportion of sodium intake in the diets of children, adolescents, and adults, but that there is variation in relative contribution and some differences in top food contributors.

TABLE 11-7 Top 10 Food Categories Contributing to Sodium Intake Among U.S. Persons 2 Years of Age and Older, Ranked by Percent Contribution—National Health and Nutrition Examination Survey, 2013–2014 (*N* = 8,067)

Rank	Food Category[a]	Percent Contribution[b]
1	Yeast bread[c]	6.2
2	Pizza	5.9
3	All single code sandwiches[d]	5.7
4	Cold cuts and cured meats	5.4
5	Soups	3.8
6	Burritos and tacos	3.8
7	All savory snacks[e]	3.7
8	Chicken, whole pieces	3.7
9	Cheese[f]	3.5
10	Eggs and omelets	2.6

[a]What We Eat In America food categories are available at http://www.ars.usda.gov/Services/docs.htm?docid=23429 (accessed October 22, 2018).

[b]The percent sodium consumed is defined as the sum of the amount of sodium consumed from each specific What We Eat In America food category for all participants 2 years of age and older, divided by the sum of sodium consumed from all food categories for all participants 2 years of age and older, multiplied by 100. All estimates use one 24-hour dietary recall, take into account the complex sampling design, and use the 1-day diet sample weights to account for nonresponse and weekend/weekday recalls.

[c]Yeast breads, rolls, buns, bagels, and English muffins.

[d]Sandwiches, identified by a single What We Eat In America food code, include burgers, frankfurter sandwiches, chicken/turkey sandwiches, egg/breakfast sandwiches, and other sandwiches.

[e]Chips, popcorn, pretzels, snack mixes, and crackers.

[f]Natural and processed cheese.

SOURCE: Adapted from Quader et al., 2017.

TABLE 11-8 Top 10 Food Categories Contributing to Sodium Intake Among U.S. Persons 2–18 Years of Age, Ranked by Percent Contribution—National Health and Nutrition Examination Survey, 2011–2014 (*N* = 5,876)

	2–5 Years of Age (*n* = 1,511)		6–11 Years of Age (*n* = 2,193)		12–18 Years of Age (*n* = 2,172)	
Rank	Food Group	Percent Contribution[a]	Food Group	Percent Contribution[b]	Food Group	Percent Contribution[c]
1	Cheese	8.3	Cheese	9.1	Cheese	8.8
2	Cured meats/ poultry	8.0	Mixed dishes, pizza	6.8	Cured meats/ poultry	6.5
3	Breads, rolls, tortillas	6.4	Cured meats/ poultry	6.5	Mixed dishes, pizza	6.4
4	Mixed dishes, grain-based	6.2	Breads, rolls, tortillas	6.4	Breads, rolls, tortillas	6.2
5	Milk	5.9	Mixed dishes, sandwiches	6.0	Poultry	5.7
6	Poultry	5.8	Poultry	5.6	Mixed dishes, sandwiches	5.7
7	Mixed dishes, sandwiches	4.1	Mixed dishes, Mexican	5.5	Mixed dishes, grain-based	5.3
8	Sweet bakery products	4.0	Mixed dishes, grain-based	5.4	Mixed dishes, Mexican	5.3
9	Mixed dishes, Mexican	3.9	Sweet bakery products	4.2	Condiments and sauces	4.3
10	Savory snacks	3.8	Milk	3.6	Mixed dishes, meat/poultry/ fish	3.8

NOTES: Food groups are from the 47 subgroups defined by the What We Eat In America food category classification system. The percent contributions reflected in the table were adjusted to disaggregate dairy intake from nondairy foods (e.g., mixed dishes) and reallocate them to the milk, cheese, and yogurt subgroups, as appropriate.

[a]Mean sodium intake for this group was 2,267 mg/d (99 mmol/d).

[b]Mean sodium intake for this group was 3,036 mg/d (132 mmol/d).

[c]Mean sodium intake for this group was 3,395 mg/d (148 mmol/d).

SOURCE: Adapted from O'Neil et al., 2018. Reprinted with permission under the Creative Commons Attribution (CC BY) license (http://creative commons.org/licenses/by/4.0) (accessed January 18, 2019).

TABLE 11-9 Top 10 Food Categories Contributing to Sodium Intake Among U.S. Persons 19 Years of Age and Older, Ranked by Percent Contribution—National Health and Nutrition Examination Survey, 2003–2006 (N = 9,490)

	19–50 Years of Age (n = 5,429)		≥ 51 Years of Age (n = 4,061)	
Rank	Food Group	Percent Contribution	Food Group	Percent Contribution
1	Salt	23.0	Salt	21.7
2	Yeast breads and rolls	8.0	Yeast breads and rolls	10.1
3	Cheese	7.9	Cheese	6.4
4	Frankfurters, sausages, luncheon meats	6.6	Frankfurters, sausages, luncheon meats	6.4
5	Condiments and sauces	5.7	Pork, ham, bacon	4.9
6	Biscuits, corn bread, pancakes, tortillas	4.4	Condiments and sauces	4.4
7	Pork, ham, bacon	4.3	Soup, broth, bouillon	3.9
8	Crackers, popcorn, pretzels, chips	4.2	Cake, cookies, quick bread, pastry, pie	3.8
9	Cake, cookies, quick bread, pastry, pie	3.1	Crackers, popcorn, pretzels, chips	3.7
10	Tomatoes, tomato/ vegetable juice	2.8	Biscuits, corn bread, pancakes, tortillas	3.5

NOTES: Food groups were defined by the U.S. Department of Agriculture Dietary Sources Nutrient database, which were collapsed into 51 categories for the analysis. This text was revised since the prepublication release.

SOURCE: Adapted from O'Neil et al., 2012. Reprinted with permission under the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0) (accessed January 18, 2019).

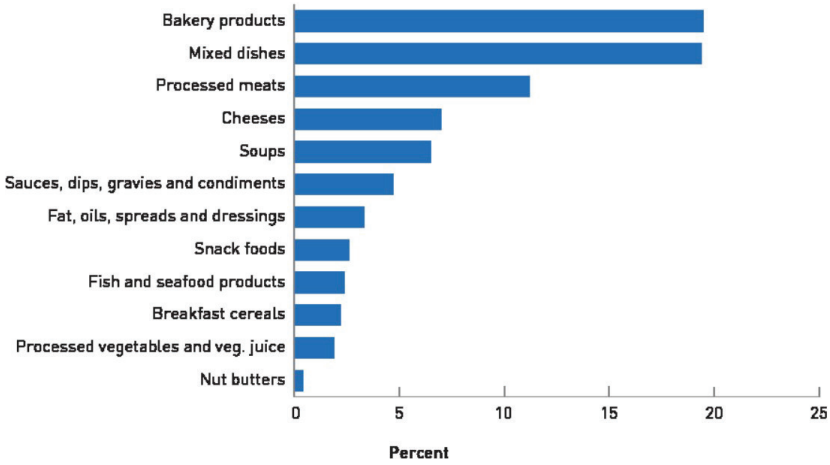

FIGURE 11-4 Percent contribution of major food categories to the average daily sodium intake of Canadians.
NOTE: Figure based on 2015 Canadian Community Health Survey, Health Canada Food Label Data 2017, and Canadian Nutrient File 2015 for top categories as classified in Health Canada's 2012 sodium reduction targets.
SOURCE: © All rights reserved. *Sodium Intake of Canadians in 2017*. Health Canada. Adapted and reproduced with permission from the Minister of Health, 2018.

PUBLIC HEALTH IMPLICATIONS AND SPECIAL CONSIDERATIONS

To interpret the findings from the risk characterization analysis presented above, consideration is given to the meaning and use of AIs and the new DRI category, the CDRR. AIs are recommended average daily nutrient intake levels that are established when the intake distribution of requirements could not be established. To that end, an AI, including the sodium AI established in this report, does not necessarily reflect requirements; rather, it reflects the best estimate of intakes assumed to be adequate for an apparently healthy population. Despite the uncertainties that exist with the sodium AIs, the values presented in this report reflect intake levels that are broadly applicable to the U.S. and Canadian populations. The CDRR for sodium, in contrast, is the intake above which intake reduction is expected to reduce chronic disease risk within an apparent healthy population.

Sodium inadequacy is not a concern in the U.S. or Canadian populations. The vast majority of the U.S. and Canadian populations consume more sodium than what is recommended by the CDRR, which indicates that cardiovascular disease risk in the population is expected to be reduced with reductions in current sodium intakes. Most of the DRI age, sex, and

life-stage groups exceed the CDRR, indicating that the need for sodium reduction is broadly applicable in the population.

Despite the sodium CDRR not characterizing absolute risk for an individual, the public health implications are apparent. Hypertension and cardiovascular disease are prevalent in both the United States and Canada (Bundy et al., 2018; Padwal et al., 2016). Hypertension prevalence increases with age, and is more prevalent among non-Hispanic black adults than among non-Hispanic white, non-Hispanic Asian, and Hispanic adults (Bundy et al., 2018). Heart disease is the leading cause of death in the United States and the second leading cause of death in Canada (Health Canada, 2018; NCHS, 2017); cerebrovascular diseases are also among the leading causes of death in both countries (Health Canada, 2018; NCHS, 2017). Given the prevalence and effect of hypertension and cardiovascular disease, the public health context for the sodium CDRR is clear: *Reductions in sodium intakes above the CDRR are expected to reduce chronic disease risk within the apparently healthy population.*

Special Considerations

Normotensive and Hypertensive Individuals

A meta-analysis in the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*), found that reducing sodium intakes led to a larger reduction in blood pressure among those with hypertension at baseline than among those who were normotensive at baseline (Newberry et al., 2018). This was verified by the committee's reanalysis, as well as by an intake–response relation with baseline blood pressure in continuous form. It is plausible that those with hypertension may be particularly susceptible to the effects of sodium because of an increased sodium sensitivity (He et al., 2009; Wright et al., 2003). The prevalence of hypertension in the United States and Canada is high and increases with age. An estimated 45.4 percent [95% confidence interval (CI): 43.9, 46.9] of the U.S. general population 20 years of age and older have hypertension (blood pressure ≥ 130/80 mm Hg) (Bundy et al., 2018). The prevalence of hypertension increased to 49.6 percent [95% CI: 47.1, 52.2] among those 40–59 years of age, and to 73.7 percent [95% CI: 70.7, 76.7] among those 60 years of age and older. Approximately 90 percent of U.S. and Canadian adults will develop hypertension in their lifetimes (Vasan et al., 2002).

Although larger effects of sodium reduction on blood pressure have been seen in adults with hypertension as compared to normotensive adults, the benefits of sodium intake reduction are applicable to both. Moreover,

considering approximately 90 percent of adults will develop hypertension in their lifetimes (Vasan et al., 2002) and the currently excessive intakes of sodium by the majority of U.S. and Canadian adults, a population-based approach will likely significantly improve public health. The sodium CDRR, therefore, applies to those both with and without existing hypertension in order to lower blood pressure and reduce the incidence of both hypertension and its cardiovascular sequelae.

Excessive Sweat Losses

Individuals who are exposed to high temperatures or who engage in high levels of physical activity, especially at high temperatures, may require higher intakes of sodium than the AI owing to elevated sodium loss through higher sweat loss (Allsopp et al., 1998; Baker, 2017; Bates and Miller, 2008; Cogswell et al., 2015; Sharp, 2006). As an example, the sodium same intake of 1,525 mg/d (66 mmol/d) resulted in a positive sodium balance at ambient temperature, but it resulted in an approximately neutral balance at high temperatures (40°C [104°F]) because of increased sweat losses (Allsopp et al., 1998).

Sodium concentration in sweat among adults varies widely from 230–3,358 mg/L (10–146 mmol/L) (Sawka and Montain, 2000; Verde et al., 1982) with an average of 1,012 mg/L (44 mmol/L) (Kaptein et al., 2016). Sodium concentrations can vary with overall diet, sodium intake, sweating rate, hydration status, heat exposure and stress, heat acclimatization, duration and intensity of physical activity, and intra-individual variability of sodium reabsorption in the sweat gland (Allan and Wilson, 1971; Brouns, 1991; Brown et al., 2011; Palacios et al., 2004). Older adults likely have similar sweat sodium concentrations based on limited evidence (Inoue et al., 1999).

At ambient temperatures with moderate physical activity, several studies suggest sweat sodium losses are limited to a few mmol per day (Heer et al., 2000; Palacios et al., 2004). In a balance study in adolescent females, Palacios et al. (2004) reported that sodium sweat loss was 3 percent of a high sodium intake (4,000 mg/d [174 mmol/d]) and 10 percent of a low sodium intake (1,300 mg/d [57 mmol/d]), both within the estimated range of loss. Limited evidence suggests that pregnant women may have greater sweat losses than nonpregnant women possibly attributable to the onset of sweating at a lower temperature (Clapp, 1991). Sodium sweat concentrations increase up to 1,932–2,829 mg/L (84–123 mmol/L) at high temperatures (Fukumoto et al., 1988), but sodium sweat concentrations are lower in heat-acclimatized individuals exposed to high temperatures (Allsopp et al., 1998; Bates and Miller, 2008; Buono et al., 2007, 2018; Consolazio et al., 1963). Furthermore, heat acclimatization occurs rapidly and results in

a linear decrease in sweat sodium concentration over time (Buono et al., 2018). Even in heat-acclimatized individuals exposed to high temperatures and high physical activity, total sodium sweat loss is still greater because of greater sweat losses—up to 8 L/d (Malhotra et al., 1976). Because of the variability in heat acclimatization and sweat sodium losses, an individualized approach considering intensity of physical activity, temperature exposure, and sweat loss is needed.

Orthostatic Hypotension

Orthostatic hypotension is often related to dehydration and it tends to be transient. It can also be associated with specific diseases, such as advanced diabetes or Parkinson's disease. These conditions are often characterized by symptomatic low blood pressure, which may increase risk of falls. Although the prevalence is debated (Saedon et al., 2018), objective measurement in the Systolic Blood Pressure Intervention Trial (SPRINT) reported that among 14,692 hypertensive patients screened for the SPRINT, 2.4 percent showed low standing systolic blood pressure (< 110 mm Hg) (Wright et al., 2015). In individuals with these conditions, ingestion of low-sodium diets may be ill advised; therefore, targeted guidance from health care providers on sodium intake is needed for individuals with orthostatic hypotension.

Implications of the Sodium DRI Values in Context of the Previous Values and the Expanded DRI Model

The sodium DRI values in this report reflect the committee's synthesis of a broad range of evidence on adequate and safe levels of sodium intake and the relationship between sodium and chronic disease. To contextualize the public health implications, the committee provides comment on each of the DRI categories.

The sodium AIs, as with all AIs, are intake levels that do not necessarily reflect requirements; rather they are the best estimates for intake levels that are associated with health. The adult sodium AIs established in this report are similar to the values established in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005). For adults 51 years of age and older, the committee did not extrapolate the sodium AI values downward based on energy intake. This departure from decisions made in the *2005 DRI Report* reflects insufficient evidence specific to the sodium requirements in older individuals and a limited number of clinical trials conducted in older individuals at sodium intakes below 1,500 mg/d (65 mmol/d). The sodium AIs for children and adolescents were also updated, and the values are now extrapolated based

on EERs for sedentary individuals, rather than being based on reported energy intake. This decision was guided by concerns over measurement bias in self-reported energy intake and a possible disconnect between actual intakes and requirements. The different approach to extrapolating the sodium AI for adults to children resulted in slightly lower values for children 1–13 years of age[3] than those established in the *2005 DRI Report*.

In contrast to the approach taken in the *2005 DRI Report*, chronic disease–related indicators were not considered for the sodium Tolerable Upper Intake Level (UL) in this report. This difference in approach stems from the expansion of the DRI model, as the UL now focuses on toxicological risks from excessive intake. The committee was unable to identify a specific toxicological risk outcome associated with high levels of sodium intake, except in extreme circumstances that do not necessarily reflect risk of habitual intake. The committee acknowledges that the absence of evidence is not necessarily an absence of effect. However, because sodium has a CDRR that characterizes chronic disease risk reduction with reductions in intake, the absence of a UL may be less problematic for sodium than for a nutrient that has an inverse relationship between intake and chronic disease risk.

The expansion of the DRI model now allows for the relationship between nutrient intake and chronic disease risk reduction to be characterized in a separate DRI category. Sodium is one of the first two nutrients to be considered under this expanded model, and is the first nutrient for which there was sufficient evidence to guide the selection CDRR values. Although the CDRR values are similar to the ULs established in the *2005 DRI Report*, the methodological approach and the process of evaluating the totality of the evidence differs. The new DRI category provides specificity of the nature and direction of the relationship—in this case a positive relationship between sodium intake and cardiovascular disease risk. There was sufficient evidence from randomized controlled trials to support sodium reductions down to 2,300 mg/d (100 mmol/d) for adults. Although the evidence was insufficient to further define the CDRR by characteristics such as age, weight status, race/ethnicity, or comorbidities, the committee notes that there are population groups with higher prevalence and risk for hypertension and cardiovascular disease (e.g., older individuals, certain race/ethnicity groups, particularly non-Hispanic blacks). Reducing sodium intake toward the CDRR level is expected to be particularly beneficial for these groups. However, with evidence in both normotensive adults and adults with hypertension, the sodium CDRR is broadly applicable.

Guided by evidence on the tracking of blood pressure from childhood into adulthood, the committee extrapolated the sodium CDRR for adults to children and adolescents 1–18 years of age. There is less certainty in

[3]This text was revised since the prepublication release.

the evidence regarding the long-term benefits of sodium reductions among children. However, the continuity of lower sodium intake from childhood into adulthood was viewed as prudent for public health, as there is insufficient evidence to determine when sodium reductions are most effective or become beneficial. Moreover, salt preferences develop in childhood and therefore can affect longer-term sodium intakes. The sodium CDRRs for children and adolescents was extrapolated based on EERs for sedentary individuals, rather than being based on reported energy intake. Although they are not equivalent DRI categories, compared to the sodium ULs established in the *2005 DRI Report*, the sodium CDRRs for children are lower. From an applications standpoint, the committee acknowledges that these lower sodium DRIs may pose challenges for those developing diets and food programs for children.

Significant reductions in sodium intake are needed to alleviate the major public health burden associated with cardiovascular disease and to ensure that burden does not persist or worsen into the future. It was beyond the scope of this committee's task to determine how the reductions are best achieved; however, based on the evidence reviewed herein regarding sources of sodium in the diet, continued efforts to reduce sodium intake in the population are warranted, such as those previously recommended (IOM, 2010). The evidence guiding the committee's decision to establish the sodium CDRRs, coupled with evidence that intakes are above the sodium CDRRs for the vast majority of the population, indicate that both the U.S. and Canadian populations would benefit from reducing sodium intakes.

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Part IV

Part IV of this report offers this committee's perspective on knowledge gaps it revealed through its review of the evidence. This part of the report consists of one chapter.

Chapter 12 synthesizes the committee's assessment of the evidence to identify where research gaps exist related to the understanding of potassium and sodium intake levels that are adequate, are toxic, and reduce chronic disease risk. The committee also describes its experience of undertaking a Dietary Reference Intake (DRI) study that incorporated recommendations from the 2017 National Academies report *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* and used an externally prepared systematic evidence review. Based on its experience, the committee highlights opportunities to enhance the DRI process.

12

Knowledge Gaps and Future Directions

This chapter presents the committee's interpretation of the state of the science for deriving the Dietary Reference Intakes (DRIs) for potassium and sodium, including strengths, limitations, and research needs. Support from federal agencies and research institutions to address these knowledge gaps is expected to facilitate the work of the next DRI committee that reviews the evidence on potassium and sodium. This chapter also includes the committee's suggestions to enhance the DRI process, based on its experience implementing recommendations from the *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) (NASEM, 2017) and using an externally commissioned systematic review to inform its work.

KNOWLEDGE GAPS AND RESEARCH NEEDS

Strengthen Methods to Measure Potassium and Sodium Intake

Collection of multiple 24-hour urinary sodium excretions with quality control methods is considered the most accurate method for quantifying usual sodium intake in an individual (Holbrook et al., 1984; Lerchl et al., 2015). Even when conducted correctly, this method has limitations. Like all urinary sodium assessments, 24-hour urinary excretion does not capture all modes of sodium loss (e.g., sweat, fecal), and therefore underestimates the true quantity of sodium consumed. Furthermore, collection of 24-hour urine samples is burdensome for participants, which often makes this assessment method challenging to use in a large, free-living population.

Spot urine samples collected at a single point in time are more convenient to collect than 24-hour urinary excretions, but they are subject to multiple errors owing to intra- and inter-day variations in urine osmolality, sodium excretion, meal timing, fluid intake, ambient temperature, physical activity, and diuretic use (Ji et al., 2012). Spot urine samples have also demonstrated systematic bias as compared to 24-hour urine samples—underestimating 24-hour urinary sodium excretion at high intake levels, and overestimating 24-hour urinary sodium excretion at low intake levels—both in the general population and in individuals with chronic kidney disease (Dougher et al., 2016; He et al., 2018; Huang et al., 2016; Mente et al., 2014).

The alternative to determining sodium intake from urinary samples is to use self-reported dietary intake assessment methods, such as 24-hour dietary recalls or food frequency questionnaires. These methods also have limitations. Sodium intake is highly correlated with energy intake, so underreporting energy intake is likely to result in underreporting of sodium intake (Bailey et al., 2007). The majority of sodium is consumed from sources prepared outside the home (Harnack et al., 2017). Unless specific brands of foods and beverages are reported and updated food composition databases are used to analyze the data, the results are subject to inaccuracies. Furthermore, methods are lacking for quantifying sodium added at home during food preparation or during consumption (Anderson et al., 2010).

Estimating potassium intake is also challenging. Compared to sodium, a lower proportion of potassium consumed is recovered in urine (Aburto et al., 2013; Tasevska et al., 2006). This incomplete recovery may systematically differ across population groups and may depend on intake of other nutrients in the diet (Turban et al., 2013; Weaver et al., 2016), making it difficult to control for these differences. Short-term, self-reported assessment methods, particularly multiple 24-hour dietary recalls, provide reasonably accurate estimates of usual potassium intake because potassium content in foods is generally naturally occurring and not added during food preparation or consumption, and therefore is not as variable and brand specific as sodium. As discussed in Chapter 3, one of the challenges of attributing health effects to potassium is its collinearity with other nutrients in the diet.

To strengthen methodological approaches and improve the accuracy for estimating potassium and sodium intake, especially if the two nutrients are considered jointly, future research is needed to do the following:

- Identify or develop methods to minimize systematic biases between spot and 24-hour urine collections (e.g., nonlinear modeling). If successful, these data could be used to derive new equations to pre-

dict 24-hour potassium and sodium exposure from spot urine samples, by groups defined by sex, age, and ethnicity, if appropriate.
- Collect multiple 24-hour urine samples from subsamples of large cohorts to permit calibration of spot urine samples collected from the majority of participants.
- Identify individual-level and environment-level attributes (e.g., age, sex, ethnicity, body mass index, physical activity, ambient temperature) that affect the proportion of consumed potassium and sodium excreted in the urine. Using this information, determine whether equations can be developed to adjust each individual's 24-hour urine excretion information.
- Determine whether and to what extent the use of multiple spot urine samples collected at various times on different days improves calibration over a single spot urine sample for both potassium and sodium.
- Develop methodological approaches for capturing, analyzing, and synthesizing data that can characterize complex dietary interactions, especially between potassium and other nutrients in the diet.

Determine Potassium and Sodium Requirements and Toxicological Outcomes

Potassium and sodium are physiologically essential nutrients, and their concentrations in the blood are tightly regulated through homeostatic controls. This regulation, coupled with the pervasiveness of these nutrients in the food supply, makes it challenging to characterize the distribution of potassium and sodium requirements in the population. Without such information, the DRI for adequacy for each nutrient will remain an Adequate Intake (AI) rather than an Estimated Average Requirement (EAR) and a Recommended Dietary Allowance (RDA). Future DRI committees' efforts to derive EARs and RDAs for potassium and sodium would be facilitated by rigorously designed balance studies that assess intake levels of potassium and sodium needed to achieve balance across the lifespan. These balance studies would do the following:

- Determine an optimal study duration to accurately assess potassium and sodium balance, accounting for both infradian rhythm (i.e., lasting longer than 1 day) and potentially high intra-individual variability in urinary excretion.
- Provide participants with intake levels that have been chemically determined so that intake can be accurately assessed.
- Measure all excretion modes, including urinary, fecal, and sweat.

- Characterize sequestration of sodium in the skin and muscle and its relationship to intake, as well as to characteristics such as life stage and degree of adiposity.

The applicability of the potassium AI is uncertain for subpopulations prone to hyperkalemia or hypokalemia, such as individuals taking certain medications (e.g., angiotensin-converting-enzyme inhibitors [ACE-Is], angiotensin II receptor blockers [ARBs], diuretics) or individuals with adrenal insufficiency, chronic kidney disease, or type 2 diabetes. Health care providers may need to individualize potassium intake recommendations for these individuals, given the clinical context. The committee's inability to determine the applicability of the potassium AI to such subpopulations is due in part to a lack of data on how key biological and drug effects influence (1) potassium balance and (2) the effect of potassium intake on serum potassium concentrations. Furthermore, individuals with such conditions are typically excluded from potassium supplementation trials. To better characterize the potassium intake needs in these at-risk subpopulations, future research would do the following:

- Evaluate the effect of potassium supplementation on balance, serum potassium concentrations, blood pressure, and cardiovascular disease in individuals taking common medications that influence potassium homeostasis (e.g., ACE-Is, ARBs, diuretics), and in individuals with chronic kidney disease, diabetes, and heart failure.

In the expanded DRI model, the Tolerable Upper Intake Level (UL) is intended to characterize toxicological risk. In an effort to identify a toxicological indicator, the committee reviewed adverse effects from trials and case reports. Ethical considerations preclude human studies that are designed to produce toxic effects as the primary outcome. Thus, secondary reports of adverse events that are observed in studies of beneficial effects are likely to be a critical source of information for future DRI committees. Detailed and systematic collection of such information may elucidiate patterns and trends, and provide evidence for an indicator not previously considered. To further characterize the effects of high intakes of potassium and sodium, future research would do the following:

- Support the use of animal and in vitro studies for evaluating potential toxicological effects.
- Collect and report adverse effects in human studies in a systematic manner.
- Report and thoroughly describe case studies related to potassium and sodium overconsumption.

- Identify reliable indicators of excess potassium and sodium intake.

Strengthen the Evidence on the Relationship Between Potassium Intake and Chronic Disease Risk

There is moderate strength of evidence for a causal relationship between increased potassium intake (achieved by potassium supplementation) and decreased blood pressure among adults with hypertension. However, a lack of an intake–response relationship, coupled with a lack of direct evidence of a causal relationship between potassium intake and cardiovascular disease, precluded the committee from establishing a Chronic Disease Risk Reduction Intake (CDRR) for potassium. To strengthen the evidence on the relationship between potassium and chronic disease risk, future research would accomplish the following:

- Assess the effect of different doses and forms of potassium (e.g., dietary potassium, potassium chloride supplements, potassium bicarbonate supplements) on blood pressure so that an intake–response relationship can be established.
- Conduct an adequately powered trial of sufficient duration to study the effect of potassium supplementation on cardiovascular disease with concurrent measures of blood pressure, particularly among populations in which there is minimal risk of adverse effects from potassium supplementation.
- Conduct pooled meta-analyses that combine individual-level data to identify subgroup differences and comprehensively evaluate intake–response relationships.
- Conduct trials to further evaluate the interrelationships of potassium and other nutrients (e.g., calcium, magnesium) to determine the independent effects of each on blood pressure and cardiovascular disease.

Strengthen the Evidence on the Relationship Between Sodium Intake and Chronic Disease Risk

The meta-analyses used in this report helped the committee consider the totality of the evidence, but were limited by their ecological nature—that is, the studies were the unit of analysis rather than pooled individual-level data. Without access to individual-level data, the committee was unable to conduct analyses to draw conclusions about the differential effects of sodium reductions among population subgroups. To leverage existing data and overcome this limitation, future research would do the following:

- Conduct meta-analyses combining individual-level data across various trials so that subgroup differences, particularly for sodium and blood pressure, can be more comprehensively evaluated (e.g., by age, sex, race/ethnicity, baseline blood pressure, genetics). Both mean effects and differences in the intake–response relationship are of interest.

Although the committee characterized the relationship between sodium intake and chronic disease risk as at least moderate, additional studies are still needed on the effects of sodium intake reductions on chronic disease risk. There are a number of design and execution challenges to such trials, especially those that evaluate long-term effects of behavioral modification of dietary intake on chronic disease endpoints. Given the limitations and uncertainties in the current evidence, future research would do the following:

- Explore the feasibility of conducting large, methodologically rigorous randomized controlled trials that study the effect of sodium intake levels (ideally a range) on chronic disease endpoints, with particular attention to subpopulations that may have different responses to sodium intake.

Blood pressure changes in response to a sodium intervention are variable, roughly following a bell-shaped curve (He et al., 2009). Defining individuals with moderate to high sodium sensitivity remains a challenge (Elijovich et al., 2016). Sodium sensitivity is most often defined as a proportional change (e.g., ≥ 3 percent, ≥ 10 percent) or an absolute change (e.g., ≥ 3 mm Hg, ≥ 10 mm Hg) in mean arterial pressure during sodium intervention. A common method to define sodium sensitivity is to assess acute blood pressure response to rapid sodium loading (e.g., intravenous administration of 2 L normal [0.9 percent] saline over 4 hours) and depletion (e.g., a 10 mmol sodium diet and three doses of oral furosemide over 24 hours). Another common method of assessing sodium sensitivity is to measure the blood pressure response to low (e.g., < 50 mmol/d) and high (e.g., > 250 mmol/d) sodium intake over 1–2 weeks. In general, the dietary approach is considered the most rigorous approach for the characterization of sodium sensitivity, and evidence suggests that the blood pressure response has long-term reproducibility and stability in the general population (Gu et al., 2013). Several genes have been identified as being associated with increased sodium sensitivity, both in rats and humans, which suggests a genetic basis for salt sensitivity (Kelly and He, 2012). The Genetic Epidemiology Network of Salt Sensitivity study estimated that heritabilities for blood pressure response to high sodium were 0.22, 0.33,

and 0.33 for systolic, diastolic, and mean arterial pressure, respectively (Gu et al., 2007).

The ability to accurately characterize sodium sensitivity among individuals could inform future updates to the sodium CDRR. Given current limitations in characterizing sodium sensitivity, future research would do the following:

- Characterize how blood pressure response to changes in sodium intake varies by age, sex, race/ethnicity, adiposity, genotype, and clinical conditions such as hypertension, diabetes, and chronic kidney disease.
- Identify both rare and common genetic variants that will help identify individuals who are predisposed to sodium sensitivity.
- Improve methods for identifying sodium-sensitive individuals—including through discovery and validation of biomarkers in the blood or urine and use of proteomics and metabolomics—to increase accuracy and facilitate implementation in clinical and public health settings.

Several prospective cohort studies have reported a significant positive association between sodium intake and cardiovascular disease risk and all-cause mortality, independent of blood pressure (Cook et al., 2007; He et al., 1999; Mills et al., 2016). Mechanisms underlying this blood pressure–independent association are not well studied. Observational studies have reported significant positive associations between sodium intake and left ventricular hypertrophy, endothelial dysfunction, and arterial stiffness, independent of blood pressure (Avolio et al., 1986; DuPont et al., 2013; Rodriguez et al., 2011; Todd et al., 2010). Little evidence exists from randomized controlled trials on the effect of sodium intake on cardiovascular risk factors other than blood pressure. To better characterize the relationship between sodium intake and chronic disease, future research would do the following:

- Test the effects of different sodium intake levels on endothelial and vascular function.

Explore Potassium and Sodium in Relation to Each Other and Other Dietary Components

Sodium-to-Potassium Ratio

If a DRI were established as a sodium-to-potassium ratio, it could potentially convey that increases in potassium intake without a concomi-

tant reduction in sodium intake (thereby decreasing the ratio) would confer health benefits. At this time, the evidence is insufficient to characterize the relationship between the sodium-to-potassium ratio and health outcomes. Limitations in the available data precluded the committee from establishing the potassium and sodium DRIs as a ratio, and from assessing the behavioral implications of recommending a ratio. Nevertheless, potassium and sodium are inextricably biologically linked, and further exploration into their interactions is needed.

The sodium-to-potassium ratio may overcome some of the methodological inaccuracies of measuring either nutrient alone. When comparing spot urine samples with 24-hour urine samples, for example, the sodium-to-potassium ratios are more closely aligned than either nutrient alone (Iwahori et al., 2017). The sodium-to-potassium ratio was more accurately captured in both 24-hour dietary recalls and food frequency questionnaires than either individual nutrient (Freedman et al., 2015). In addition, the sodium-to-potassium ratio has been reported to have a higher correlation with blood pressure than either nutrient alone (Iwahori et al., 2017), although evidence from trials is limited.

The ratio may be more robust to systematic errors in urine collection or in self-reported intakes than either nutrient alone. For instance, the sodium-to-potassium ratio may partially account for the confounding effect of energy when estimating the association between the minerals and blood pressure outcomes. Errors that occur during the measurement process (e.g., underreporting, other biases associated with the respondent) tend to be correlated across nutrients, so taking the ratio of the two nutrients partially cancels out these errors.

To better characterize the interrelationships of potassium and sodium, future research would do the following:

- Determine if and how the infradian rhythms (i.e., lasting longer than 1 day) of urinary potassium and sodium excretion affect the sodium-to-potassium ratio.
- Explore the relationship between the sodium-to-potassium ratio and outcomes and surrogate markers (e.g., blood pressure) at different doses of potassium and sodium intake, and assess whether the ratio is a better measure than either nutrient alone.
- Identify individual-level attributes that affect the urinary sodium-to-potassium ratio (e.g., age, race/ethnicity, body mass index, genotype) and determine how that information can be used to calibrate adjustment equations.
- Improve statistical methods for estimating the distribution of the usual intake for the sodium-to-potassium ratio.

Sodium Density

The Dietary Approaches to Stop Hypertension-Sodium trial was designed using a sodium density approach (i.e., milligrams sodium per kilocalorie energy intake); the primary results, however, were reported in terms of absolute sodium (milligrams of sodium per day), based on a 2,100 kilocalorie diet (Sacks et al., 2001). A secondary analysis of the study reported that the association between sodium intake and blood pressure varied by energy intake (Murtaugh et al., 2018). Specifically, higher sodium intakes among individuals with lower energy intakes led to a greater increase in blood pressure than higher sodium intakes among individuals with higher energy intakes. This finding suggests that it may be important to consider sodium density in addition to absolute sodium intake when assessing the relationship between sodium intake and health outcomes. This approach has had limited application to date. Valid estimates of sodium density may be difficult to obtain without biomarkers for both sodium and energy, unless carefully controlled feeding studies are conducted. To clarify this relationship, future research would do the following:

- Identify biomarkers of sodium and energy intake that would be feasible to collect in large population studies.
- Determine the intake–response relationship of different levels of sodium intake with both blood pressure and cardiovascular disease and determine whether optimal levels differ by sex, age, and adiposity corresponding to differences in energy needs or intakes of kilocalories.
- Explore the feasibility of directly examining sodium intake density to obtain an estimate of the optimal level of sodium intake, either as an absolute amount (milligrams sodium) or as a density (milligrams sodium per kilocalorie energy).

Evaluate Developmental Origins of Health and Disease Related to Potassium and Sodium

The developmental origins of health and disease (DoHAD) posits that the in utero and early infant environment, including nutrition or stress, alters the long-term risk for chronic disease of the adult offspring. Studies in both human and animal models demonstrate that it is not only the immediate in utero environment for a fetus, but also the in utero environment of the fetus's parents that can result in DoHAD-enhanced risk for chronic disease (Mandy and Nyirenda, 2018). Different potassium and sodium intake levels during early life may affect chronic disease risk as one ages. At present, however, the longitudinal effects of potassium and sodium intake

are not well characterized. One study reported an increased risk of hypertension in adult offspring of rats fed either a low-sodium or high-sodium diet during pregnancy and lactation (Koleganova et al., 2011). To clarify the long-term effects of potassium and sodium exposure, future research would accomplish the following:

- Evaluate the first- and second-generation effects of high and low potassium and sodium intakes of both the mother and father in order to identify optimal intakes of these nutrients during reproductive stages of life and characterize the variability of risk for chronic disease in the population.

Explore Opportunities in the Food Supply

Reducing Sodium

Sodium (in the form of salt and other sodium-containing compounds) is added to foods for reasons related to food safety, functionality, and taste. Making lower-sodium foods with high consumer acceptability is critical to reducing population-wide sodium intake, but there are conflicting data on how it is best accomplished (Israr et al., 2016). A prior Institute of Medicine committee explored food technology considerations and strategies for reducing sodium in the food supply in greater detail (IOM, 2010); these topics are discussed here only briefly.

A number of strategies have been implemented to enhance salt taste perception in reduced-sodium products, including use of different forms of salt crystals and addition of certain food additives that either impart salty taste without sodium or enhance the perception of salty taste. For example, hollow salt crystals that are less dense than regular crystals dissolve faster upon consumption and increase sodium perception. These crystals are useful only in dry surface applications (e.g., potato chips) because if they dissolve, they lose the advantage of their lower sodium density. Potassium chloride may be used to provide salt taste in lower-sodium products, but this ingredient presents challenges for individuals who have health conditions that reduce clearance of potassium from the blood. It can also have a bitter and metallic taste, but these off flavors can be decreased by adding flavor modifiers or by blending it with sodium chloride. A flavor enhancer to help reduce sodium is free glutamate, used mainly in the form of monosodium glutamate (MSG). MSG is not believed to pose a health risk at the levels used in a typical serving of food.

Given that most sodium comes from foods prepared away from home and that there is a relationship between sodium intake and chronic disease risk, future research would do the following:

- Develop novel solutions, including through technological innovations, to decrease sodium in the food supply.

Ensuring Iodine Nutriture

The native iodine content of foods and beverages tends to be low and is dependent on the geographic location where the ingredients were grown (Ershow et al., 2018). As a result, Canada has established a mandatory table salt fortification program and the United States allows for the voluntary fortification of salt if products are appropriately labeled (CFIA, 2019; Leung et al., 2012). Efforts to reduce sodium intake have led to concerns that iodine consumption will become inadequate in some individuals. However, available data indicate that sodium reductions have not resulted in inadequate iodine intakes (Musso et al., 2018). This finding may be attributed to the low use rates of iodized salt, both among consumers and in commercially prepared and processed food and to the iodine contribution of some common food additives. To continue to explore the possible effect of sodium reduction efforts on iodine consumption, future research would do the following:

- Determine whether current approaches to reducing sodium intake in the population decrease intake of iodized salt from sources such as table salt, salt used in processed foods, or both, and assess whether decreases in sodium intake affect iodine consumption and status.
- Monitor the iodine status of the U.S. and Canadian populations, and if some subpopulations are found to have inadequate or marginal iodine intakes, identify potential fortificants other than salt as a vehicle for delivering iodine to these specific subpopulations.
- Chemically analyze the iodine content of representative diets (such as the Total Diet Study) and compare these estimated iodine intakes to estimates using food composition tables to determine the accuracy of food composition data for iodine. Because salt is not added to the representative diets, this would provide information on iodine contributed from both naturally occurring sources and from iodine-containing food additives other than iodized salt.

OPPORTUNITIES TO ENHANCE THE DRI PROCESS

The DRI process has evolved over time, and each iteration has revealed opportunities for improvement. As the first DRI committee to apply the guidance from the *Guiding Principles Report*, the committee identified the future opportunities summarized below.

Defining Healthy Populations Relative to the DRI Model When Prevalence of Chronic Disease Is High

The DRI model focuses on healthy populations, but an ongoing challenge in both the United States and Canada is the high prevalence of chronic disease, including obesity, type 2 diabetes, hypertension, and cardiovascular disease in adults, and the increasing prevalence of obesity and type 2 diabetes in children. In adults, the healthy population is the minority, rather than majority, of the total. Describing the focus of the DRIs as "apparently healthy population" does not fully resolve this challenge; high prevalence of these chronic diseases is accompanied by high prevalence of medication and medical nutrition therapy to manage them.

The expansion of the DRI model to include DRIs based on chronic disease magnifies the challenge of high chronic disease prevalence. DRIs based on chronic disease focus on primary prevention of chronic disease, but issues of secondary prevention and disease management are also pressing public health problems. An ongoing challenge and knowledge gap is how to assess if the DRI specified is relevant to the substantive proportion of the population that might be considered "apparently healthy" with appropriate medical management. A related challenge is discerning when and how to include these populations in the DRI framework of assessment of indicators and intake–response relationships. Future DRIs would benefit from the following:

- Further research and evaluation to determine whether the population focus of the DRI for each nutrient should be redefined and, if so, how.

Integrating an Externally Conducted Systematic Review into the DRI Process

To enhance the effectiveness of an externally conducted systematic review, alignment of the needs of the DRI committee (evidence users) with the information from evidence providers (e.g., Agency for Healthcare Research and Quality) is critical. This synchronization requires that the information in the systematic review meet the needs of the DRI committee and that the process minimizes the likelihood that bias or conflicts of interest adversely affect the usefulness and integrity of the systematic review. Involving the DRI committee in the development of the systematic evidence review, to the extent that best practices allow, has the potential to create a more efficient DRI process. This interaction is often handled with protocols that are developed prior to initiation of data collection for the review. Such protocols describe appropriate interactions among the

contributors—in this case, between the DRI committee, the sponsors, and the scientists conducting the systematic review. Appropriate interactions may include finalizing key questions related to DRI decisions, identifying inclusion/exclusion criteria, reaching a general agreement on table formats and information to be provided, and discussing the overall approach and methodologies to be applied. Once the appropriate interactions have been completed and protocols agreed upon, the evidence providers would then conduct the review independent of the DRI committee. This independence is necessary to minimize the perception that the evidence users and evidence generators exerted bias in the conduct of the review. To create greater efficiency in the process and usability of the final systematic reviews for DRI applications, future DRI reviews would do the following:

- Develop a priori protocols for how and when the DRI committee, the sponsors, and those who design and execute the systematic review coordinate at key points in the process, as guided by systematic review best practices.

As described in Chapter 2 and Appendix C, the committee assessed the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), in a variety of ways prior to using and building on the evidence it provided. The committee determined that this step was necessary because the *AHRQ Systematic Review* was externally conducted and the committee was not involved in its design. The committee's independent assessment of the *AHRQ Systematic Review* included evaluating the fidelity of the methodology, the transparency of reporting, and the subjective decisions made. Through this process, the committee identified the need to further investigate sources of heterogeneity in meta-analyses and to reassess the strength-of-evidence ratings for selected indicators. Moreover, the *Guiding Principles Report* recommended that intake–response assessment also be evaluated using the Grading of Recommendations Assessment, Development and Evaluation system. Because key questions in the *AHRQ Systematic Review* focused only on issues of causality between nutrient intakes and chronic disease indicators, the committee performed additional analyses to evaluate intake–response relationships. For sodium, the CDRR was informed by the committee's intake–response analyses across multiple chronic disease indicators. Future DRI committees will likely need to critically evaluate the methods and conclusions of the systematic evidence review as they apply to both issues of causality and intake–response. The committee also anticipates that it is unlikely that future DRI committees will be able to avoid conducting some additional analyses, particularly with respect to

intake–response assessment. Thus, future systematic reviews could in principle conduct some intake–response analyses, but future DRI committees may need to perform additional or alternative analyses and employ expert judgment. To better integrate externally conducted systematic reviews into the process, future DRI reviews would do the following:

- Develop protocols for conducting post-hoc analyses of systematic reviews to confirm the fidelity of the review, to update the externally conduced review, and to meet unanticipated committee needs in a manner that is transparent and justified.

Collecting Evidence to Supplement the Externally Conducted Systematic Reviews

In the first step of the DRI organizing framework, the committee assessed the current state of the evidence on potential indicators for the DRIs for adequacy, the DRIs for toxicity, and DRIs based on chronic disease. The *AHRQ Systematic Review* was limited to a review of potassium and sodium intakes on chronic disease outcomes and related risk factors. This meant that the committee had comprehensive data summaries for chronic disease (with the exception of a few potential chronic disease indicators not included in the review), but lacked similar systematic reviews or a sufficient context for evaluating indicators of adequacy and toxicity. The committee performed several scoping literature searches to determine if there were indicators not included in the *AHRQ Systematic Review* that could potentially inform any of the DRI categories for either potassium or sodium (see Appendix D). The literature scans led the committee to perform comprehensive literature searches for select indicators (see Appendix E). To better integrate different sources of information, future DRI reviews would do the following:

- Develop approaches for DRI committees to compile and evaluate available evidence for potential indicators not included in the independently conducted systematic review, to ensure the quality and completeness of the review while minimizing the potential for bias or conflicts of interest.

Integrating the Recommendations in the *Guiding Principles Report* into the DRI Process

The *Guiding Principles Report* was indispensable to the committee's derivation of the sodium CDRR values, as well as its decision not to establish a CDRR for potassium. Nonetheless, as the committee reviewed the

evidence for these two nutrients, it needed to adapt some of the approaches and recommendations outlined by the *Guiding Principles Report*.

First, with respect to indicators of chronic disease, the *Guiding Principles Report* recommended selection of a single outcome indicator on the causal pathway, but acknowledged the possibility of using multiple indicators (NASEM, 2017). Rather than using any single outcome indicator as the basis for the sodium CDRR, the committee integrated evidence from multiple indicators (cardiovascular disease incidence, hypertension incidence, systolic blood pressure, and diastolic blood pressure), particularly because these indicators are known to be causally linked and evidence supports the relationship between sodium and each indicator. Future DRI committees may find it useful to use multiple, causally linked indicators for establishing DRIs based on chronic disease, to the extent that such evidence is available for the nutrient or food substance under investigation.

Second, the *Guiding Principles Report* provided guidance that is more applicable to situations in which observational data are used to assess intake–response relationships. For sodium, the strongest data were from randomized controlled trials, with the limitation that most trials only involved a single contrast. Thus, the committee needed to adapt existing intake–response meta-analysis methods to combine multiple trials with different sodium intake levels for the control and intervention groups. Future DRI committees will likely refine the approaches to assess intake–response relationships, depending on available evidence.

Third, in the case of sodium, the committee adapted the *Guiding Principles Report* recommendation that DRIs based on chronic disease be expressed as a range instead of a single number. This recommendation was based on the premise that chronic disease risk varies with intake, and that there is a range over which increasing or decreasing intakes will reduce risk. The *Guiding Principles Report* noted that expressing the DRI as a single number might be misconstrued as suggesting the existence of a sharp dividing line between risk and no risk. Conversely, expressing the sodium CDRR as a range might lead to the false impression that any intake within that range is acceptable, as opposed to being a range where reducing intakes is beneficial.

As it considered the guidance and recommendations in the *Guiding Principles Report* to develop the new DRI category—the CDRR—the committee saw the need to provide a description of how the CDRR would apply to sodium. For the reasons stated in Chapter 2, the committee adapted the guidance in the *Guiding Principles Report* and expressed the sodium CDRR as the lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction. As more experience with establishing DRIs based on chronic disease is gained, future DRI efforts would do the following:

- Balance the need for consistency over time with the need for refinements as new and unanticipated challenges are encountered.
- Develop a general or standardized description of the DRI based on chronic disease category.

Providing Additional Guidance on the Expanded DRI Model as Experience Is Gained

The *Guiding Principles Report* provided limited comment on how DRIs based on chronic disease affect or interact with the other DRI categories. The committee's experience clarified that the review of the evidence and the decisions about DRIs based on chronic disease can have implications for the other DRI categories. For potassium, the evidence that was previously considered for the AI in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005) was considered in this report for the purposes of establishing a DRI based on chronic disease. This shift, caused by the expansion of the DRI model, narrowed the evidence the committee considered for establishing the potassium DRIs for adequacy. Ultimately, the lack of a specific indicator of potassium adequacy or status led the committee to establish AIs for all DRI age, sex, and life-stage groups. For sodium, the committee considered evidence on chronic disease–related indicators as context for the adequacy DRI, to ensure the selected intake levels would not increase chronic disease risk. Pursuant to a recommendation in the *Guiding Principles Report*, the committee considered only toxicological adverse effects for establishing ULs. The meaning of UL in this report, therefore, is fundamentally different than the definition used in the *2005 DRI Report*. Although it was imperative for the committee to use its collective expert judgment regarding the interrelationship between DRIs based on chronic disease and the other DRI categories for potassium and sodium, it is beyond the scope of this report to determine how future DRI committees can systematically make such decisions.

To create more conceptually consistent DRIs moving forward, future DRI efforts would do the following:

- Provide additional guidance on how to address the interrelationship between DRIs based on chronic disease and the other DRI categories, particularly the AI. A decision-making framework that can be consistently applied to various scenarios would have broad application for future DRI committees.

The committee's methodologies reflect the state of the evidence on potassium and sodium, and do not necessarily establish a definitive meth-

odological blueprint for future DRIs. The type and quantity of evidence, as well as specific health outcomes, will vary for each nutrient and food substance considered under the expanded DRI model. Approaches taken for future DRIs will be determined on a case-by-case basis at the expense of consistency across nutrients and DRI committees. As future DRI committees gain experience with the expanded DRI model with other nutrients and food substances, there will likely be greater clarity on which approaches are broadly applicable, as well as which recommendations in the *Guiding Principles Report* need to be adapted. To this end, future DRI efforts would do the following:

- Update and revise the guiding principles, as experience establishing DRIs based on chronic disease is gained.

It is beyond the scope of this study to provide definitive guidance on the proper clinical, educational, research, and public health applications of the DRI values in the expanded model. As the sodium CDRR and future DRIs based on chronic disease are used, a greater understanding will emerge of the strengths, limitations, usefulness, and misapplications of this new DRI category. Translating this information for DRI users will help bolster the use and understanding of the expanded DRI model. As such, DRI users would likely benefit from receiving the following:

- Revised guidance on using the expanded DRI model for dietary assessment and dietary planning.

CONCLUDING REMARKS

The committee identified a range of knowledge gaps and critical research needs related to the first two steps of the DRI organizing framework. A prevailing theme was that methods for assessing potassium and sodium intake need to be strengthened to improve accuracy. The committee found it challenging to characterize potassium and sodium requirements and toxicological effects. As the first to apply the guidance in the *Guiding Principles Report*, the committee determined that evidence on the relationship between sodium intake and chronic disease risk was sufficient to introduce a new DRI category. There remains a need to strengthen the evidence on the relationship between potassium and/or sodium intake and chronic disease risk. With the expansion of the DRI model, opportunities exist to continue to enhance the process and to provide DRI users with additional guidance on proper application of the reference values.

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Appendix A

Acronyms and Abbreviations

µmol/L	micromoles per liter
^{23}Na MRI	sodium magnetic resonance imaging
ACE-I	angiotensin-converting enzyme inhibitor
AHRQ	Agency for Healthcare Research and Quality
AI	Adequate Intake
AMDR	Acceptable Macronutrient Distribution Range
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ARB	angiotensin-receptor blocker
BMI	body mass index
CCHS	Canadian Community Health Survey
CDC	Centers for Disease Control and Prevention
CDRR	Chronic Disease Risk Reduction Intake
CI	confidence interval
CKD	chronic kidney disease
DASH	Dietary Approaches to Stop Hypertension
df	degrees of freedom
DNA	deoxyribonucleic acid
DoHAD	developmental origins of health and disease
DRI	Dietary Reference Intake
DRV	Dietary Reference Value

EAR	Estimated Average Requirement
EER	Estimated Energy Requirement
EFSA	European Food Safety Authority
FITS	Feeding Infants and Toddlers Study
FNDDS	Food and Nutrient Database for Dietary Studies
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	hazard ratio
IOM	Institute of Medicine
kg/m^2	kilograms per meter square
$KHCO_3$	potassium bicarbonate
LDL	low-density lipoprotein
LOAEL	lowest-observed-adverse-effect level
LVH	left ventricular hypertrophy
MD	mean difference
mg	milligrams
mg/d	milligrams per day
mg/L	milligrams per liter
mL	milliliters
mm Hg	millimeter of mercury
mmol	millimoles
mmol/d	millimoles per day
mmol/L	millimoles per liter
MSG	monosodium glutamate
NCI	National Cancer Institute
NDSR	Nutrition Data System for Research
NEAP	net endogenous acid production
NHANES	National Health and Nutrition Examination Survey
NHE3	sodium hydrogen exchange 3
OR	odds ratio

PAHO	Pan American Health Organization
PICO	population, intervention, comparator, and outcome
RAAS	renin-angiotensin-aldosterone system
RDA	Recommended Dietary Allowance
REML	restricted maximum likelihood
RR	risk ratio
SPRINT	Systolic Blood Pressure Intervention Trial
TOHP	Trials of Hypertension Prevention
TONE	Trial of Nonpharmacologic Interventions in the Elderly
UL	Tolerable Upper Intake Level
USDA	U.S. Department of Agriculture
WHI	Women's Health Initiative
WIC	Special Supplemental Nutrition Program for Women, Infants, and Children

Appendix B

Open Session Agendas

The committee held three meetings that were open to the public. The first took place on December 6, 2017, and was held as an online conference. The second took place on March 7, 2018, in Washington, DC. The third took place on March 9, 2018, and was held as an online conference. The agendas for all three of these meetings are below.

Committee to Review the Dietary Reference Intakes for Sodium and Potassium
Open Meeting 1

Wednesday, December 6, 2017
2:30–3:30 PM ET

2:30–2:35 PM ET	**Introductory Remarks** Virginia Stallings, Committee Chair
2:35–2:55 PM	**Sponsors' Statement** Amanda MacFarlane, Health Canada David Klurfeld, U.S. Department of Agriculture
2:55–3:30 PM	**Committee Discussion with the Sponsors** *Sponsor Representatives* Mary Cogswell, Centers for Disease Control and Prevention Janet de Jesus, National Institutes of Health

David Klurfeld, U.S. Department of Agriculture
Linda Greene-Finestone, Public Health Agency of Canada
Amanda MacFarlane, Health Canada
Essie Yamini and Robin McKinnon, Food and Drug Administration

3:30 PM **Adjourn Open Session**

Committee to Review the Dietary Reference Intakes for Sodium and Potassium
Open Meeting 2: Public Workshop

Wednesday, March 7, 2018
8:00 AM–5:15 PM ET

7:30–8:00 AM ET **Registration**

SESSION 1: WELCOME AND SPONSOR PANEL

8:00–8:15 AM **Welcome and Opening Remarks**
Virginia Stallings, Committee Chair

8:15–9:00 AM **Perspectives from Sponsor Representatives**
David Klurfeld, U.S. Department of Agriculture
Hasan Hutchinson, Health Canada
Kristy Mugavero, Centers for Disease Control and Prevention
Janet de Jesus, National Institutes of Health
Robin McKinnon, Food and Drug Administration
Linda Greene-Finestone, Public Health Agency of Canada

SESSION 2: EXISTING SCIENTIFIC REVIEWS TO ESTABLISH SODIUM AND POTASSIUM DIETARY REFERENCE INTAKES

9:00–9:20 AM **Development of 2005 Dietary Reference Intakes for Sodium and Potassium**
Larry Appel, Johns Hopkins University

9:20–9:40 AM	**Agency for Healthcare Research and Quality (AHRQ) Systematic Review: Process, Protocol, Findings, and Conclusions** Sydne Newberry, RAND Corporation (remote)
9:40–10:15 AM	**Panel Discussion and Committee Questions**
10:15–10:30 AM	Break

SESSION 3: BACKGROUND, PHYSIOLOGY, METHODOLOGICAL ISSUES, AND CURRENT SODIUM AND POTASSIUM INTAKE

10:30–10:50 AM	**Sodium/Potassium Interaction in the Kidney, Blood Vessels, Brain, and Beyond** Horacio J. Adrogue, Baylor College of Medicine
10:50–11:10 AM	**Methodological Issues Related to Measuring Sodium and Potassium Intake** Catherine Loria, National Institutes of Health
11:10–11:30 AM	**Sodium and Potassium Intake: National Health and Nutrition Examination Survey (NHANES) and Other Data** Mary Cogswell, Centers for Disease Control and Prevention
11:30 AM–12:00 PM	**Panel Discussion and Committee Questions**
12:00–12:45 PM	Break for Lunch

SESSION 4: CURRENT KNOWLEDGE OF THE HEALTH CONSEQUENCES OF SODIUM AND POTASSIUM EXPOSURE

12:45–1:15 PM	**Safety of Sodium Reduction and Potassium Supplementation in Various Populations** Paul Whelton, Tulane University
1:15–1:45 PM	**Association of Sodium and Potassium to Cardiovascular Disease and Mortality** Salim Yusuf, McMaster University

1:45–2:15 PM	**As Essential Nutrients, What Are the Risks of Breaching the General Population's Lower and Upper Limits of Sodium and Potassium?** David McCarron (remote)
2:15–2:45 PM	**Challenges in Conducting Clinical Trials on the Association Between Sodium and Health Effects** Bruce Neal, The George Institute for Global Health, Australia (remote)
2:45–3:15 PM	**Panel Discussion and Committee Questions**
3:15–3:30 PM	Break

SESSION 5: CONSIDERATIONS FOR ESTABLISHING DIETARY REFERENCE INTAKES

3:30–3:50 PM	**Sodium and Potassium Intake and Cardiovascular and Bone Health: How Important Is the Ratio?** Connie Weaver, Purdue University
3:50–4:20 PM	**Committee Questions**
4:20–4:30 PM	Break

SESSION 6: PUBLIC COMMENT

4:30–5:15 PM*	**Public Comments**
5:15 PM	**Adjourn Workshop**

*The session will conclude once all public comments have been delivered.

Committee to Review the Dietary Reference Intakes for Sodium and Potassium
Open Meeting 3

Friday, March 9, 2018
9:30–10:30 AM ET

9:30–9:40 AM ET	**Opening Remarks** Virginia Stallings, Committee Chair
9:40–10:00 AM	**Considerations for Dietary Reference Intakes for Specific Populations** Shiriki Kumanyika, Drexel University (remote)
10:00–10:30 AM	**Committee Questions**
10:30 AM	**Adjourn Open Session**

Appendix C

Committee's Assessment of the *Agency for Healthcare Research and Quality Systematic Review*

In accordance with its Statement of Task (see Chapter 1, Box 1-1), the committee was asked to consider the Agency for Healthcare Research and Quality (AHRQ) systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), in its derivation of the Dietary Reference Intake (DRI) values for potassium and sodium. The *AHRQ Systematic Review* included both the selection of literature and the investigators' assessment of the strength of evidence for each indicator.

Prior to using the *AHRQ Systematic Review*, the committee assessed its overall quality and methodology. As anticipated in the *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (*Guiding Principles Report*) (NASEM, 2017), the committee reassessed the evidence for some relevant indicators in the *AHRQ Systematic Review*. The details of the additional data analyses conducted by the committee for the purposes of the expanded assessment are included in Chapters 6 and 10. This appendix includes the committee's approach to reviewing the quality of the *AHRQ Systematic Review* and to expanding the assessment of the evidence as the fundamental basis for the deliberations regarding establishing Chronic Disease Risk Reduction Intakes for potassium and sodium.

ASSESSMENT OF OVERALL QUALITY

The committee assessed the overall quality of the *AHRQ Systematic Review* using the AMSTAR 2 tool (Shea et al., 2017).[1] The committee determined the *AHRQ Systematic Review* met the majority of the 16 domains and that it was of overall moderate quality.[2] Domains that the *AHRQ Systematic Review* did not adequately cover related to investigating and explaining the causes of heterogeneity in the results, which in some cases is essential in order to interpret the results of meta-analysis.

ASSESSMENT OF METHODOLOGICAL APPROACH

As prescribed in the AHRQ guidance, a protocol was prepared and published for the *AHRQ Systematic Review* used in this study (AHRQ, 2017). The committee reviewed the protocol and determined that the PICO questions[3] and the inclusion/exclusion criteria for each indicator included were complete, clear, and appropriate. The committee also reviewed the strength-of-evidence domains and their definitions in the AHRQ guidance (AHRQ, 2014) and determined that they were complete, clear, and appropriate.

The protocol specified the tools and criteria used for assessing the evidence. The AHRQ guidance scores the body of evidence separately for randomized controlled trials and observational studies and provides guidance for randomized controlled trials. However, the guidance provides flexibility and directs the evidence-based practice centers conducting the systematic review to specify risks of bias specific to the content area. Accordingly, the *AHRQ Systematic Review* protocol is particularly detailed at describing its constructs and implementation in the risk-of-bias (or study limitations) domain for randomized controlled trials and observational studies separately. Judging risk of bias in an objective and standardized manner is essential to the interpretation and weighing of a study (or a body of evidence) (for explanations of the importance of the risk-of-bias tool, see Chapter 2).

In spite of using assessment tools that are objective and formally accepted by the scientific community, the committee recognizes that all assessments regarding determination of risk of bias for individual studies and strength of the evidence for the body of evidence for a specific outcome entail a certain

[1]AMSTAR stands for A Measurement Tool to Assess Systematic Reviews.

[2]The AMSTAR 2 tool is not intended to result in an overall score. Instead, the tool can be used for a qualitative assessment, where different factors can be weighted differently, depending on the importance or relevance to the research question(s).

[3]PICO is a mnemonic device for the important parts of a well-built clinical question. PICO stands for population (or problem or patient), intervention, comparison, and outcome.

degree of interpretation and judgment. With this in mind, the committee performed two tasks to explore its degree of agreement in the application of these assessment tools with the decisions and judgments of the *AHRQ Systematic Review*. The committee performed spot checks of the *AHRQ Systematic Review*'s risk-of-bias assessment and strength-of-evidence rating. The committee understood that it is its prerogative to perform additional analyses and to potentially reach a different strength-of-evidence determination, as long as there is transparency and a scientific basis in its rationale for doing so.

Spot Check of the Risk-of-Bias Assessment

The committee generally agreed with the risk-of-bias tools criteria for both randomized controlled trials and observational studies, as defined in the *AHRQ Systematic Review* (for the criteria, see Annex C-1). To check the application of the risk-of-bias criteria, six studies were selected at random; the selected studies were determined by the AHRQ investigators to have low, moderate, and high level of risk of bias (one of each risk-of-bias level for randomized controlled trials and one of each risk-of-bias level for observational studies). Two members of the committee independently assessed the risk of bias for each study by following the AHRQ risk-of-bias criteria. Discrepancies were minor between the committee members' and the *AHRQ Systematic Review*'s risk-of-bias rating for each study. Given previous reports regarding the inconsistent application of the risk-of-bias tools and the large discrepancies in how risk of bias is being evaluated for some specific domains (Jordan et al., 2017), the committee accepted these minor discrepancies as typical and determined that based on this limited spot check, the application of the risk-of-bias tools in the *AHRQ Systematic Review* was appropriate.

Assessing the Application of Strength-of-Evidence Domains

The committee conducted a number of checks related to the *AHRQ Systematic Review*, particularly for outcomes that would likely be relevant for setting DRI values (e.g., blood pressure, cardiovascular disease). In that regard, the committee noted that the conclusions in some relevant recent systematic reviews differ from the conclusions in the *AHRQ Systematic Review*. For example, the strength of the evidence for an effect of a reduction of sodium intake on reducing blood pressure, an outcome for which a substantial body of evidence exists, was determined as high in past systematic reports (Graudal et al., 2017; NHLBI, 2013; WHO, 2012a). Even if using the same strength-of-evidence domains (e.g., risk of bias, inconsistency, imprecision, and indirectness), the *AHRQ Systematic Review* rated the strength of evidence as moderate. This discrepancy might

give the appearance that the strength of the evidence for the relationship between sodium intake and blood pressure has changed over the past few years. However, the reason for this discrepancy could lie in various other factors, including the strength-of-evidence assessment.

To understand this discrepancy, the committee examined salient systematic reviews on sodium and blood pressure and cardiovascular disease outcomes (NHLBI, 2013; WHO, 2012a,b) and an additional systematic review on sodium and blood pressure (Graudal et al., 2017). The committee found a number of differences in the systematic reviews, such as those related to the approach in the literature search, the populations of interest, and various inclusion/exclusion criteria compared to the *AHRQ Systematic Review*. A major difference that could have led to differences in the final determination, however, was in the application of the inconsistency domain, which refers to the unexplained heterogeneity or variability of study results in a body of evidence, or the imprecision domain.

For example, the World Health Organization's 2012 systematic review concluded that randomized controlled trials on the relationship between sodium intake and blood pressure did not show a serious inconsistency (based on inconsistency in the direction or the size of the effect), which led to a determination of high quality (WHO, 2012a). Conversely, the meta-analysis of the relationship between sodium reduction and systolic and diastolic blood pressure conducted by the *AHRQ Systematic Review* resulted in high inconsistency owing to heterogeneity in the meta-analysis. The *AHRQ Systematic Review* did not perform further analyses and downgraded the strength of the evidence to moderate based on the existence of inconsistency (for how the *AHRQ Systematic Review* defined inconsistency, see Box C-1). The committee decided that, in order to understand the nuances and have more clarity in interpreting the evidence, it was essential to explore the sources of heterogeneity in the body of evidence on the relationship between sodium intake and blood pressure. The committee performed sensitivity analyses to investigate sources of heterogeneity. These analyses informed the committee's assessment of the strength of the evidence for a relationship between sodium intake and systolic and diastolic blood pressure, which it rated as high (for additional details, see Chapter 10).

The above example presents one case where analyses beyond those conducted in the *AHRQ Systematic Review* were helpful in resolving an important question for assessing the evidence for an indicator of interest. The committee conducted additional analyses on select results of the *AHRQ Systematic Review* to clarify its interpretation of the results as needed in order to complete the committee's task; the additional analyses are described in Chapters 6 and 10.

BOX C-1
Application of Inconsistency in the *AHRQ Systematic Review*

For randomized controlled trials: The strength of evidence was downgraded based on inconsistency in the direction of effect (beneficial or not) as reported in meta-analysis. Sensitivity analysis was conducted to explore whether the inconsistency (and the heterogeneity, as reflected by the I^2 statistic [a statistic that describes the percent of variation across studies due to heterogeneity]) was caused by study quality or subgroup differences (e.g., hypertensive individuals versus normotensives). The heterogeneity seen in meta-analysis could not be explained by inclusion of lower-quality studies. When studies of participants with normal blood pressure were pooled separately from studies of participants with high-normal blood pressure or hypertension to assess the effects of sodium reduction interventions on blood pressure, heterogeneity was substantially lower for the pooled analyses of normotensives than for the studies of participants with hypertension and for the meta-analyses of all studies. However, inconsistency was still observed in the effect sizes. Thus, the strength of evidence was downgraded for each conclusion because of "unexplained heterogeneity." If the subgroup analyses that were conducted or additional subgroup analyses that were not conducted (e.g., based on different blood pressure methodology, use of antihypertensive medications, or differences in achieved sodium intake) had resulted in consistency across effect sizes as well as significant falls in heterogeneity (as indicated by the I^2 values), the authors would not have downgraded the strength of evidence, as the reasons for the heterogeneity would be explained. Generally, clinical/biological heterogeneity is larger in nutrition trials compared to drug trials.

For observational studies: Based on inconsistency on (a) direction of effect (beneficial or not) and (b) size of effect (magnitude of change).

SOURCE: Personal communication, S. Newberry, RAND Corporation, April 3, 2018.

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ANNEX C-1
RISK OF BIAS CRITERIA USED IN THE *AGENCY FOR HEALTHCARE RESEARCH AND QUALITY SYSTEMATIC REVIEW*

The two sections that follow are the risk-of-bias criteria used in the Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (Newberry et al., 2018). These criteria were developed independent of this committee.

RISK OF BIAS ASSESSMENT FOR RANDOMIZED CONTROLLED TRIALS

Random Sequence Generation (Selection Bias)

For randomized controlled trials, is the sequence generation (recruitment) described as being random?

For controlled clinical trials, is the allocation described in such a way that it appears to be free of obvious (intentional) bias?

For crossover trials, was the order of receiving treatments randomized adequately?

- *Low risk:* The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
- *High risk:* The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach; for example, sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example: allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; allocation by availability of the intervention.

- *Unclear risk:* Insufficient information about the sequence generation process to permit judgment of "Low risk" or "High risk."

Allocation Concealment

Was the group allocation concealed (such that assignments could not be predicted)?

- *Low risk:* Use of a third party and opaque envelopes or their equivalent are low risk. Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, Web-based, and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- *High risk:* Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g., a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g., if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
- *Unclear risk:* Insufficient information to permit judgment of "Low risk" or "High risk." This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment; for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
- *Not applicable:* Study is a controlled clinical trial.

Blinding of Participants and Personnel

Were participants and key study personnel blinded to their intervention or exposure status?

- *Low risk:* Any one of the following: no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- *High risk:* Any one of the following: no blinding of outcome assessment, and the outcome is likely to be influenced by lack of blinding;

blinding of participants and key study personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
- *Unclear risk:* Any one of the following: insufficient information to permit judgment of "Low risk" or "High risk"; the study did not address this outcome. Just mentioning "placebo" = "unclear."

Blinding of Outcome Assessment

- *Low risk:* Any one of the following: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. Apply same criteria as for patients.
- *High risk:* Any one of the following: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
- *Unclear risk:* Any one of the following: insufficient information to permit judgment of "Low risk" or "High risk"; the study did not address this outcome; "double blind" and no further information on assessor (e.g., external assessor).

Incomplete Outcome Data (Attrition Bias)

For randomized controlled trials and clinical controlled trials, could high attrition or uneven attrition across study arms have contributed to bias?

For crossover studies, only, was outcome reporting complete for all phases?

- *Low risk:* Similar loss to follow-up across groups OR analyses took loss to follow-up into account (e.g., by intent-to-treat [ITT] analysis, "censoring," imputing missing data [e.g., by carrying the last observation forward] or qualitatively or quantitatively comparing the characteristics of people who dropped out with those who remained in the analysis).
- *High risk:* Differential loss to follow-up across groups with no attempt to take into account or to assess differences between dropouts and retained participants.
- *Unclear risk:* Nothing mentioned about evaluating impacts or taking into account in analysis.

Selective Reporting of Outcome Data

For studies that purport to be reporting the prespecified study outcomes, do the outcomes reported match those listed in the Methods section under "Outcomes," or does the article state that some of the prespecified outcomes will be reported in subsequent articles?

- *Low risk:* Any of the following: the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
- *High risk:* Any one of the following: not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- *Unclear risk:* Insufficient information to permit judgment of "Low risk" or "High risk." It is likely that the majority of studies will fall into this category.
- *Not applicable:* Article reports on post-hoc analysis of data from a study initially published elsewhere.

Other: Adherence

Did the investigators describe rates of adherence to the intervention or some measure of adherence?

- *Low risk:* Adherence was described as high (e.g., based on biomarkers) or as greater than or equal to 80 percent.
- *High risk:* Adherence was described as low.
- *Unclear risk:* Nothing about adherence was mentioned.

Other: Unequal Distribution Among Groups of Potential Confounders at Baseline

Was distribution of demographics (e.g., age, gender, race/ethnicity), comorbidities, and other potentially critical confounding factors (e.g., blood pressure, use of antihypertensives) similar across study arms at baseline (or if not, does the analysis control for baseline characteristics)?

- *Yes (Low risk):* No significant difference between arms in demographic and important comorbidity characteristics (e.g., blood pressure) according to table and/or described by investigators, or difference(s) taken into account in analysis.
- *No (High risk):* Significant difference between arms in age, race, gender, important comorbidity with no attempt to control for the differences.

Demonstration That Outcome of Interest Was Not Present at Start of Study for All Participants

For example, analysis of the number of people with stroke includes patients that had a stroke before start of study not after the intervention or had a recurring stroke. Note: Incidence versus recurrence. This item is a trigger for excluding individual studies from analyses. Please specify for which outcome this is an issue.

- *Low risk:* No problem.
- *High risk:* People with an outcome of interest were not excluded (specify the outcome, and exclude study for that analysis).

Other: Valid Method of Exposure Assessment

Was exposure to intervention assessed using a valid method?

- *Low risk:* For sodium or sodium-to-potassium ratio, exposure was assessed with at least one 24-hour urinary analysis with reported quality control measure. For potassium, exposure was assessed using at least one 24-hour urinary analysis with reported quality control measure, chemical analysis of diet or food diary with intervention/exposure adherence measure, or composition of potassium supplement with intervention/exposure adherence measure.

- *High risk:* For sodium or sodium-to-potassium ratio or potassium, exposure was assessed with chemical analysis of diet, composition of salt substitute, or food diaries. Exposure was assessed less than 24 hours or through a published food frequency questionnaire.
- *Moderate risk or unclear:* For sodium, 24-hour urinary analysis without reported quality control measure. Chemical analysis of diet without intervention/exposure adherence measure, or composition of potassium supplement without intervention/exposure adherence measure. For potassium, use of food diaries without quality control.

Other: Valid Method of Outcome Assessment

Were outcomes assessed using valid methods?

- *Low risk:* Definitions of outcomes are provided by investigators, outcomes are not self-reported, and method of ascertainment is described.
- *High risk:* Definitions are not provided (e.g., for cardiovascular disease morbidity); one or more outcomes is described as self-reported.
- *Unclear risk:* No description of outcome definitions, no mention of method of ascertainment.

Other: Valid Statistical Assessment (for Crossover Trials Only)

Did the authors report how they did their analysis, and did they do the correct analysis for a crossover (a paired analysis of some type)?

- *Yes*, they report how they analyzed the data, and they report a paired analysis of some type.
- *No*, they report an analysis but it was not paired.
- *Unclear:* They do not report how the analysis was done and the outcomes do not appear to have come from pairing people with themselves.

RISK OF BIAS CRITERIA FOR OBSERVATIONAL STUDIES

Representativeness of the Exposed Cohort

- *Low risk:* Truly representative of the average named cohort in the community.
- *High risk:* Select group (e.g., only doctors).

- *Moderate risk or unclear:* Somewhat representative of average named population or no description of the derivation of the cohort.

Selection of the Nonexposed Cohort

- *Low risk:* The recruitment or allocation strategy was similar across exposure groups (drawn from the same community as exposed cohort).
- *High risk:* Drawn from a different source.
- *Unclear risk:* No description.

Ascertainment of Sodium and Potassium Exposure (Dietary Assessment/Urinary Assessment)

- *Low risk of bias:*
  - Multiple days (more than 4 on average, preferably nonconsecutive) 24-hour urines with reported quality control measures (e.g., instructions given and measure of completeness of collection such as creatinine, urine volume, questionnaire)
- *Moderate risk of bias:*
  - Two to four 24-hour urine specimens with reported quality control measures or correction for regression dilution bias with repeated 24-hour urine collection on a sample of participants
  - Multiple days of food diaries
  - Multiple nonconsecutive days (more than 4) 24-hour diet recalls or food records or correction for regression dilution bias with repeated (nonconsecutive) 24-hour diet recalls for a sample of participants
- *High risk of bias:*
  - 24-hour urine without any reported quality control measures
  - A single 24-hour urine collection (high random error)
  - Timed-urine collection of less than 24 hours
  - Food frequency questionnaire
  - Single-day food diaries/records or 24-hour diet recalls
  - Spot urine with or without use of a prediction equation for estimating 24-hour excretion

Potassium Exposure Assessment

- *Low risk of bias:*
  - Multiple nonconsecutive days (more than 4) 24-hour diet recalls or food records

- Multiple (more than four, preferably nonconsecutive) 24-hour urines with reported quality control measures (e.g., instructions given and measure of completeness of collection, such as creatinine, urine volume, questionnaire)

- *Moderate risk of bias:*
  - Two to four 24-hour urine specimens or correction for regression dilution bias with repeated 24-hour urine collection on a sample of participants
  - Two to four nonconsecutive 24-hour recalls/food records or correction for regression dilution bias with repeated (nonconsecutive) 24-hour diet recalls for a sample of participants
  - Food frequency questionnaire validated for potassium intake within a subset of the study population against duplicate diets or multiple 24-hour urine collections
- *High risk of bias:*
  - Single 24-hour urine specimen
  - Use of more than one 24-hour urine specimen without any reported quality control measures
  - Timed-urine collection of less than 24 hours
  - Food frequency questionnaire other than that specified above under "Moderate risk of bias"
  - Single-day food records
  - Single day of 24-hour recall
  - Spot urine specimen(s) with or without use of an equation for estimating 24-hour excretion

Demonstration That Outcome of Interest Was Not Present at Start of Study for All Participants

For example, analysis of the number of people with stroke includes patients that had a stroke before the start of the study, not after the intervention, or had a recurring stroke (incidence versus recurrence). This item is a trigger for excluding individual studies from analyses. Please specify for which outcome this is an issue.

Comparability

Comparability of cohorts on the basis of the design or analysis (Was distribution of health status, demographics, and other critical confounding factors similar across study groups at baseline or did the analysis control for baseline differences between groups?)

- *Low risk:* Study provides explanation for and controls for the most important factors likely to affect outcomes, including blood pressure for non–blood pressure studies or body mass index.
- *High risk:* Study does not control for blood pressure or other important factors (e.g., demographics).
- *Moderate risk or unclear:* Study does not describe the exact factors controlled for in analysis.

Assessment of Outcome

Ascertainment of outcome should be appropriate for the type of outcome.

- *Low risk:* The authors describe independent or blind assessment or confirmation of the outcome by reference to secure records (e.g., X-rays, medical records) or use of record linkage (e.g., identification of outcome through the *International Statistical Classification of Diseases and Related Health Problems* [ICD] codes on database records).
- *High risk:* Outcomes are described as being self-reported.
- *Moderate risk or unclear:* No description.

REFERENCE

Newberry, S. J., M. Chung, C. A. M. Anderson, C. Chen, Z. Fu, A. Tang, N. Zhao, M. Booth, J. Marks, S. Hollands, A. Motala, J. K. Larkin, R. Shanman, and S. Hempel. 2018. *Sodium and potassium intake: Effects on chronic disease outcomes and risks*. Rockville, MD: Agency for Healthcare Research and Quality.

Appendix D

Indicators Not Relevant for Establishing Dietary Reference Intake Values

The Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), served as a foundational evidence source for this study. However, the committee needed to consider additional evidence to inform each of the Dietary Reference Intake (DRI) categories. Accordingly, supplemental literature searches were performed.

In the first step of the DRI organizing framework, potential indicators for establishing the reference values are identified and reviewed. The committee used a multipronged approach to create a comprehensive list of indicators that have been assessed for having a relationship with either potassium and/or sodium intake. The list was compiled with the intent of determining which indicators not included in the *AHRQ Systematic Review* would merit further consideration and, as appropriate, supplemental literature searches. By assessing the scope of evidence on the relationship between the identified indicator and potassium and/or sodium intake and through expert judgment, the committee determined which of the identified indicators had the potential to be relevant for establishing potassium and sodium DRI values.

This appendix describes the committee's approach to compiling the comprehensive list of indicators and performing scoping literature searches for the identified indicators. For each indicator the committee determined to be not relevant for establishing potassium or sodium DRI values, a brief description of the evidence gathered and the committee's rationale for not further evaluating the indicator are provided.

METHODOLOGICAL APPROACH

The committee first compiled a comprehensive list of indicators not included in the *AHRQ Systematic Review* by gathering information from a variety of sources. Then, through its assessment of the evidence coupled with expert judgment, the committee determined which indicators were not relevant for establishing potassium or sodium DRI values.

Creating a Comprehensive List of Indicators Not Included in the *AHRQ Systematic Review*

To approach the first step of the DRI organizing framework, the committee undertook several efforts to identify a wide range of indicators that could potentially inform potassium or sodium DRI values. The multipronged approach included reviewing relevant Institute of Medicine (IOM) reports, conducting an abbreviated search of recent systematic reviews, reviewing international reference intake values reports, and circulating a call for relevant grey literature. These efforts informed the comprehensive list of potential indicators.

Reviewing Relevant Institute of Medicine Reports

The committee reviewed indicators included in three key reports from the IOM: *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005); *Strategies to Reduce Sodium Intake in the United States* (IOM, 2010); and *Sodium Intake in Populations: Assessment of Evidence* (*Sodium Intake in Populations*) (IOM, 2013). Indicators not included in the *AHRQ Systematic Review* were added to the comprehensive list.

Conducting an Abbreviated Search of Recent Systematic Reviews

An abbreviated literature search of recent systematic reviews was conducted to identify additional indicators not included in the *AHRQ Systematic Review*. Because the intent was only to identify indicators, systematic reviews were not assessed for quality and the strength of evidence in the relationship with the nutrient was not considered at this stage. Searches were conducted in PubMed using the sodium and potassium search strings

presented in the *AHRQ Systematic Review*.[1,2] Using PubMed filters, the searches were limited to systematic reviews published between January 1, 2012, through December 31, 2017 (for sodium), and systematic reviews published between January 1, 2003, through December 31, 2017 (for potassium). The article type was selected to facilitate an efficient identification of indicators of current interest and investigation that would potentially have a sufficient amount of evidence that could inform the derivation of DRI values. The date range of the searches was selected based on the most recent review of the evidence for the nutrients by an IOM consensus committee. For sodium, *Sodium Intake in Populations* (IOM, 2013) served as the most recent evaluation. As such, a start date of January 1, 2012, was selected to account for articles that were in press or published during the production of the *Sodium Intake in Populations* report. For potassium, the *2005 DRI Report* (IOM, 2005) was the most recent IOM review of the evidence. Accordingly, a start date of January 1, 2003, was selected. The potassium and sodium searches of recent systematic reviews resulted in 559 and 386 results, respectively.

The titles and abstracts of the systematic reviews were screened for relevance. Citations were excluded if they were not published in English, if they did not assess the relationship between one or more indicators and either or both of the nutrients, or if the only relationship(s) assessed were explored in the *AHRQ Systematic Review*. For reviews that passed the initial screening, the indicator was drawn from the title, abstract, and, when ambiguous from the title and abstract, the full text article. For sodium, 35 articles addressed one or more indicators not included in the *AHRQ Systematic Review*, while 18 articles contained an additional indicator for potassium. Several of the articles assessed the same indicator. Accordingly, fewer than 35 and 18 indicators were identified for sodium and potassium, respectively, through this abbreviated literature search of systematic reviews.

[1]The PubMed search was conducted using the systematic review filter and the following search string: (((“Sodium Chloride”[Mesh] OR “Sodium Glutamate”[Mesh] OR “monosodium glutamate”[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract] OR intake[Text Word] OR “urinary excretion”) OR “Diet, Sodium-Restricted”[Mesh] OR “Sodium, Dietary”[Mesh])).

[2]The PubMed search was conducted using the systematic review filter and the following search string: (“Potassium, Dietary”[Mesh] OR potassium[tiab] OR KLOR-CON[tiab] OR KCL[tiab]).

Reviewing International Reference Intake Values Reports

The committee also reviewed international nutrient intake value reports for potassium and sodium to identify indicators that have been used by other groups, including the European Food Safety Authority (EFSA, 2017; EFSA et al., 2016); the Australian Government Department of Health and the New Zealand Ministry of Health (NHMRC, 2006, 2017); reference values for nutrient intake for Austria, Germany, and Switzerland (Strohm et al., 2017a,b); and the DRIs for Koreans (Paik, 2008).

Circulating a Public Call for Relevant Grey Literature

The committee gathered grey literature by asking sponsors, stakeholders, and interested members of the public for relevant reports that do not appear in the peer-reviewed literature. The request was posted to the National Academies of Sciences, Engineering, and Medicine website and an email announcement was circulated through the study listserv. This public call for information was in addition to the existing public comment mechanism, in which the public could provide written comments for the committee's consideration throughout the duration of the study.

Integrating Expert Input

To gain additional insight, the committee hosted a 1-day public workshop in Washington, DC, on March 7, 2018, and a 1-hour open session on March 9, 2018 (for agendas of these public sessions, see Appendix B). The workshop and open session included presentations on a variety of topics relevant to the committee's Statement of Task and included a range of scientific perspectives. In-person workshop attendees had an opportunity to address the committee by providing remarks up to 3 minutes in length. Interested members of the public were also able to submit written public comment throughout the duration of the study. Indicators revealed through the workshop, public comments, and information-gathering public sessions were compared to the comprehensive list of indicators, and indicators not previously identified were added.

Compiling the Comprehensive List of Indicators Not Included in the AHRQ Systematic Review

The comprehensive list of indicators not included in the *AHRQ Systematic Review* was compiled from the information-gathering activities described in the preceding sections (see Table D-1).

TABLE D-1 Comprehensive List of Potential Indicators Not Included in the *AHRQ Systematic Review* That Have Been Recently Assessed in Relation to Sodium and/or Potassium, Presented in Alphabetical Order

Indicator	Potassium	Sodium
Age-related cataracts		X
Age-related macular degeneration		X
Arterial stiffness	X	X
Ascites		X
Blood lipids[a]	X	X
Bone health[b]	X	X
Cancer		X
Catecholamines	X	X
Creatinine[c]	X	
Depression		X
Diabetes[d]	X	X
Diabetic retinopathy	X	X
Endothelial dysfunction		X
Gastroesophageal reflux		X
Genitourinary symptoms		X
Headache		X
Heart rate	X	X
Hyperhomocysteinemia		X
Left ventricular mass		X
Leg cramps		X
Maternal and birth outcomes[e]		X
Metabolic syndrome	X	X
Nonalcoholic fatty liver disease		X
Obesity	X	X
Pulmonary function[f]	X	X
Quality of life		X
Renin-angiotensin-aldosterone system	X	X
Rheumatoid arthritis		X
Sarcopenia	X	X

continued

TABLE D-1 Continued

Indicator	Potassium	Sodium
Serum or plasma concentrations of the nutrient	X	X
Severe acute malnutrition	X	
Small vessel disease		X

[a]Includes cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein.
[b]Includes bone mineral density and osteoporosis.
[c]Serum or plasma creatinine.
[d]Includes insulin sensitivity and glucose intolerance.
[e]Includes miscarriage, preeclampsia, and other adverse pregnancy or birth outcomes.
[f]Includes asthma.

Determining Which Indicators Have Potential Relevance

A wide range of indicators have been assessed in the literature as potentially having a relationship with potassium and/or sodium. The committee, therefore, decided to triage the identified indicators to determine which indicators potentially had relevance for establishing potassium or sodium DRI values. The steps included an initial assessment through expert judgment, then a broad assessment of the literature through scoping searches.

Using Expert Judgment

In the first wave of consideration, the committee used its expert judgment to remove from consideration any indicator that would not fit the DRI paradigm. Consideration was given as to whether the relationship between the indicator and the nutrient had biological underpinnings or if the indicator only exists in a disease state or population (i.e., would not be relevant to an apparently healthy population). The committee also used expert judgment to identify indicators that merited a more thorough consideration.

Reviewing Evidence Collected Through Information-Gathering Activities

In the next wave of considerations, the committee reviewed the remaining indicators in light of findings in previous IOM consensus study reports—specifically the *2005 DRI Report* (IOM, 2005) and *Sodium Intake in Populations* (IOM, 2013)—and evidence presented at the March 2018 public workshop and public session.

The committee also conducted scoping searches. The searches sought to provide an overview of evidence on the relationship between the nutrients

and the identified indicators, beyond what was provided in the previous consensus study reports. The scoping searches were performed in PubMed. The committee followed the general approach described in the *AHRQ Systematic Review*, which consisted of three different types of searches per indicator in PubMed. One search type was to identify systematic reviews for reference mining. A second search type was intended to identify evidence of *effect* of the nutrient on the indicator. Aligned with the approach taken in the *AHRQ Systematic Review*, this consisted of searching for parallel arm or crossover randomized controlled trials. A third search type was intended to identify evidence of the *association* between the nutrient and the indicator. Aligned with the approach taken in the *AHRQ Systematic Review*, this consisted of searching for prospective cohort studies and nested case-control studies.

The structure of the searches aligned with those presented in the *AHRQ Systematic Review*, with the indicator-specific search terms varying across the searches. Table D-2 presents the general search strategy. Indicator-specific search strings are presented as footnotes in the presentation of the evidence. The timeframe of literature assessed varied depending on if and when the indicator was last reviewed in an IOM consensus study report. For example, if the indicator was included in *Sodium Intake in Populations* (IOM, 2013), the scoping search only extended to January 1, 2012. For all other indicators, the scoping searches extended to January 1, 2003.

Two independent reviewers screened the titles and abstracts of the results from each of the searches for relevance, with disagreements resolved through discussion. The criteria for the title and abstract screening were broad, as to be generally inclusive. A citation was included if it was a study of humans that included an assessment of a relationship between the nutrient and indicator (for systematic reviews), an effect of the nutrient on the indicator, or an association between the nutrient and the indicator. An article was excluded if it exclusively reported on patients with end-stage renal disease, heart failure, HIV, or cancer, or reported on intake in which sodium and/or potassium could not be disaggregated from other components of the diet (e.g., studies that assess dietary patterns in which sodium is not the only component). Articles that remained after the title and abstract screening went on to full-text screening, using the same criteria as the title and abstract screening. Information about the population, intervention/intake, comparators/outcomes, timing, setting, and study design were extracted from each of the included articles. As is common for scoping review-type searches, risk of bias for each article was not formally assessed, although information on key components that would affect risk of bias (population, measurement of exposure, and measurement of outcome) was captured through data extraction.

TABLE D-2 General Search Strategy Used for Conducting Scoping Searches in PubMed, as Informed by Search Strategy Used in the *AHRQ Systematic Review*

Purpose of Search	Sodium
Identify systematic reviews for reference mining	((“Sodium Chloride”[Mesh] OR “Sodium Glutamate”[Mesh] OR “monosodium glutamate”[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract]OR intake[Text Word] OR “urinary excretion”) OR “Diet, Sodium-Restricted”[Mesh] OR “Sodium, Dietary”[Mesh]) AND (humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND (Indicator-specific search terms)[a] Filters: Systematic Reviews
Gather evidence on the association between the nutrient and the indicator	((“Sodium Chloride”[Mesh] OR “Sodium Glutamate”[Mesh] OR “monosodium glutamate”[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract]OR intake[Text Word] OR “urinary excretion”) OR “Diet, Sodium-Restricted”[Mesh] OR “Sodium, Dietary”[Mesh]) AND (humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND “Prospective Studies”[Mesh] OR “Case-Control Studies”[Mesh:NoExp] OR “prospective cohort” OR “nested case-control” OR “metabolic study” OR experiment*[tiab] OR clinical trial* AND (Indicator-specific search terms)[a]

Potassium
("Potassium, Dietary"[Mesh] OR potassium[tiab] OR KLOR-CON[tiab] OR KCL[tiab]) AND (humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND (Indicator-specific search terms)[a] Filters: Systematic Reviews
("Potassium, Dietary"[Mesh] OR potassium[tiab] OR KLOR-CON[tiab] OR KCL[tiab]) AND (humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh:NoExp] OR "prospective cohort" OR "nested case-control" OR "metabolic study" OR experiment*[tiab] OR clinical trial* AND (Indicator-specific search terms)[a]

continued

TABLE D-2 Continued

Purpose of Search	Sodium
Gather evidence on the effect of the nutrient on the indicator	((“Sodium Chloride”[Mesh] OR “Sodium Glutamate”[Mesh] OR “monosodium glutamate”[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract]OR intake[Text Word] OR “urinary excretion”) OR “Diet, Sodium-Restricted”[Mesh] OR “Sodium, Dietary”[Mesh]) AND (humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND random* OR randomized controlled trial[pt] OR randomized controlled trials OR rct* OR blind* OR double-blind* OR single-blind* AND (Indicator-specific search terms)[a]

[a]The search terms were specific to each indicator under consideration and are noted as footnotes throughout this appendix.
SOURCE: Search strings adapted from Newberry et al., 2018.

The committee reviewed the evidence from previous IOM reports, the March 2018 public workshop and public session, and the scoping searches to make a determination about whether the indicator potentially had relevance for deriving potassium or sodium DRI values. Indicators the committee determined to have evidence to suggest it may be of relevance progressed to a more thorough consideration and, as necessary, comprehensive literature search (see Appendix E). Evidence and rationale for not further pursuing indicators are described in the section that follows.

INDICATORS NOT RELEVANT FOR ESTABLISHING POTASSIUM OR SODIUM DIETARY REFERENCE INTAKE VALUES

Through the methodology described in the preceding section, the committee made an informed decision regarding the relevance of the identified indicators for the purposes of establishing potassium and sodium DRI values. The sections that follow provide the evidence and rationale that support those decisions.

Relevance Determined by Expert Scientific Judgment

In its initial review of the comprehensive list of indicators, the committee used its collective expert judgment to identify seven indicators that

Potassium
("Potassium, Dietary"[Mesh] OR potassium[tiab] OR KLOR-CON[tiab] OR KCL[tiab]) AND (humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti])) AND random* OR randomized controlled trial[pt] OR randomized controlled trials OR rct* OR blind* OR double-blind* OR single-blind* AND (Indicator-specific search terms)[a]

were relevant to its task: blood lipids, bone health, catecholamines, diabetes, headaches, the renin-angiotensin-aldosterone system, and serum or plasma levels of the nutrients.[3] The committee also had clear rationale for not further pursuing several of the indicators, in context of the evidence provided in the *AHRQ Systematic Review* and in context of the type of evidence needed to derive DRI values. Rationale for those decisions are provided below.

Arterial Stiffness

Arterial stiffness was identified as a potential sodium and potassium indicator through the abbreviated search of recent systematic reviews. The relationship between sodium and arterial stiffness was not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013). Measures of arterial stiffness have become more frequently used in research and in clinical settings in the past 20 years (Townsend, 2017). The rapid expansion and use of measures of arterial stiffness created a need for standardization of methodologies, for which guidelines were recently released (Townsend et al., 2015). If it were to be considered as a potential

[3]This text was revised since the prepublication release.

indicator, arterial stiffness would likely be used for establishing a DRI based on chronic disease, namely cardiovascular disease. Given the strength of evidence for blood pressure and for the hard endpoints of cardiovascular disease morbidity and mortality, the committee determined that currently available evidence on arterial stiffness would not further inform the derivation of the sodium DRI values. For potassium, arterial stiffness would need to be considered a qualified surrogate marker in context of potassium (see Chapter 2). Given the limited data on the relationship between potassium intake and cardiovascular disease risk, the committee determined that current evidence does not support considering arterial stiffness for the derivation of a potassium DRI based on chronic disease.

Ascites

Ascites is a condition in which fluid accumulates in the peritoneal cavity and occurs when an excess of sodium and fluid is retained in the body. Ascites is often caused by liver disease, but it is also found in other patient populations including those with congestive heart failure, advanced kidney disease, or advance cancers of abdominal organs. Because it occurs as a complication to a chronic disease and generally necessitates medical management, ascites does not fit the paradigm of an indicator that could inform a DRI value for the apparently healthy population.

Cancer

The Continuous Update Project of the World Cancer Fund and the American Institute for Cancer Research summarizes current evidence on factors related to the development and progression of cancer. The third expert report, *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective*, reported that there was strong, probable evidence that consumption of Cantonese-style salted fish increases the risk of nasopharyngeal cancer and that consumption of foods preserved by salting increases the risk of stomach cancer (WCRF/AICR, 2018b). With respect to the DRIs, the committee determined that the evidence related to the Cantonese-style salted fish (which is consumed as part of a traditional diet in the Pearl River Delta region in southern China) does not have broad public health relevance to U.S. and Canadian populations. Furthermore, the evidence supporting the relationship between salt-preserved foods and stomach cancer was primarily from studies conducted in Asian populations with heterogeneous classification of what qualified as a salt-preserved food (WCRF/AICR, 2018a). It was reported that there was insufficient evidence to conduct an intake–response meta-analysis. The systematic literature review that supported the conclusion on stomach cancer also investigated total salt intake

(Norat et al., 2015). Six studies were identified, and all collected sodium exposure through food frequency questionnaires. The meta-analysis of the six studies resulted in no significant relationship between total salt intake and stomach cancer; no intake–response meta-analysis was conducted. The findings in the 2018 edition of the *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective* report are in contrast to those in the 2007 edition, which indicated that it was probable that "total salt consumption, from processed foods, including salty and salted foods, and also salt added in cooking and at the table" increases the risk of stomach cancer (WCRF/AICR, 2007, p. 141). Based on this collection of evidence, the committee determined that the evidence currently does not support the use of stomach or nasopharyngeal cancer as a potential indicator for a sodium DRI.

Creatinine (Serum or Plasma)

Creatinine was identified as a potential indicator for potassium through the abbreviated search of recent systematic reviews. The relationship was not explored in the *2005 DRI Report* (IOM, 2005). Serum or plasma creatinine levels are used as markers of kidney function. The *AHRQ Systematic Review* included evidence on the relationship between potassium intake and risk of kidney stones and kidney disease morbidity and mortality. A recent meta-analysis of potassium supplementation trials found that moderate supplementation did not lead to changes in circulating creatinine levels (Cappuccio et al., 2016). Based on the evidence included in the *AHRQ Systematic Review* and the finding from Cappuccio et al. (2016), the committee determined that the evidence currently does not support the use of serum or plasma creatinine as a potential indicator for establishing potassium DRI values.

Endothelial Dysfunction

Endothelial function is a broad category that has been assessed using a variety of measures and techniques, each with noted advantages and disadvantages (Flammer et al., 2012). The American College of Cardiology Foundation and the American Heart Association joint practice guidelines do not recommend an endothelial function test as a tool for risk prediction or risk classification of cardiovascular disease in asymptomatic adults (Greenland et al., 2010). If it were to be considered as a potential indicator for sodium, measures of endothelial dysfunction would likely be used for deriving DRIs based on chronic disease. Endothelial dysfunction would need to be considered a qualified surrogate marker of cardiovascular disease in the context of sodium reduction. Given the strength of evidence for blood pressure and for the hard endpoints of cardiovascular disease morbidity

and mortality, the committee determined that the evidence currently does not support the use of measures of endothelial dysfunction as a potential indicator for establishing sodium DRI values.

Heart Rate

Heart rate is often measured and reported in trials related to sodium intake. The committee identified one recent systematic review that reported reduced dietary sodium intake increases heart rate (Graudal et al., 2016). Given that the systematic review included 63 randomized controlled trials, the committee did not think it was efficient to use the review for reference mining, as was done for other potential indicators under consideration. Instead, the committee assessed the quality of the review using the AMSTAR 2 tool.[4] Based on its appraisal, the committee identified critical weaknesses in the systematic review, particularly in the description and documentation of the search strategy. Furthermore, the criteria used in the systematic review did not align with the inclusion and exclusion criteria for the *AHRQ Systematic Review* (e.g., at least 4 weeks in duration, crossover trials with at least 2 weeks of washout).

If it were to be considered as a potential indicator, heart rate would likely be used for establishing DRIs based on chronic disease, namely cardiovascular disease. Given the strength of evidence for blood pressure and for the hard endpoint of cardiovascular disease, the committee determined that the evidence currently does not support the use of heart rate as a potential indicator for establishing sodium DRI values.

One recent meta-analysis of randomized controlled trials (Gijsbers et al., 2016), identified through the committee's literature scan, assessed evidence on the relationship between increased potassium intake (through potassium supplementation) and heart rate in healthy adults. Gijsbers et al. (2016) reported that the meta-analysis of 22 trials (1,086 participants) yielded no overall effect, no intake–response relationship, and no subgroup differences. The evidence, therefore, does not support considering heart rate for the derivation of potassium DRI values.[5]

Left Ventricular Mass

Increased left ventricular mass, a subclinical form of cardiovascular disease, is considered to be a structural adaptation of the heart as a compensatory mechanism for increased blood pressure and wall stress. Factors that are associated with blood pressure, such as sodium and potassium

[4]AMSTAR stands for A Measurement Tool to Assess Systematic Reviews.
[5]This text was revised since the prepublication release.

intake, are also associated with increased left ventricular mass. Direct evidence, particularly from longitudinal studies and randomized controlled trials, is sparse.

In the *2005 DRI Report*, left ventricular mass was explored as an adverse effect of overconsumption of sodium. Nearly all of the identified observational studies reported a statistically significant positive relationship between urinary sodium excretion and left ventricular mass (Daniels et al., 1990; du Cailar et al., 1989, 1992, 2002; Kupari et al., 1994; Langenfeld et al., 1998; Liebson et al., 1993; Schmieder et al., 1988, 1990, 1996). Four clinical trials were also identified. The comparison group in three of the trials received antihypertensive drug therapy (Fagerberg et al., 1991; Ferrara et al., 1984; Liebson et al., 1995). The fourth trial specifically assessed the effect of sodium reduction and reported significant reductions in left ventricular mass, as compared to a nonintervention group (Jula and Karanko, 1994). The *2005 DRI Report* noted that while the cross-sectional studies consistently showed an association between urinary sodium excretion and left ventricular mass, additional trials were needed. Left ventricular mass, therefore, was not used to derive the sodium Tolerable Upper Intake Level (UL) in the *2005 DRI Report*.

Through the scoping searches, three articles on crossover clinical trials and two articles on prospective cohort studies were identified as exploring the relationship between sodium intake and left ventricular mass. For the crossover trials, Williams et al. (2005) and Vaidya et al. (2009) reported on the results from participants with hypertension from an international consortium (HyperPath Project), while Larson et al. (2012) reported on results from normotensive adults. All three reports used the same protocol for high (≥ 200 mmol/d) and low (≤ 10 mmol/d) sodium exposure, which consisted of participants consuming 1 week of each diet, in random order. There was some indication that the low-sodium diet had a beneficial effect on left ventricular hypertrophy among the participants with hypertension, but such a finding was not reported among the evaluated normotensive adults. The high- and low-sodium diet intervention in these crossover trials only lasted for 1 week, which is unlikely to alter left ventricular mass. In addition, these trials used electrocardiography to measure left ventricular hypertrophy (LVH), which has low sensitivity; the majority of cases with true anatomical LVH could be misclassified by using electrocardiography criteria of LVH (Bacharova et al., 2014).

In the Coronary Artery Risk Development in Young Adults study, Rodriguez et al. (2011) reported that higher urinary sodium excretion and sodium-to-potassium ratio were significantly associated with greater left ventricular mass among relatively healthy young adults. These relationships were independent of blood pressure and persisted through 5 years of follow-up. Urinary sodium and potassium excretion were assessed using

the average of three 24-hour urinary samples. The Strong Heart Study, conducted in American Indian communities, reported that baseline sodium intake, as ascertained by a food frequency questionnaire, was not associated with changes in left ventricular mass over a 4-year period among normotensive participants (Haring et al., 2015). Sodium-to-potassium ratio, however, was associated with left ventricular mass index among participants with prehypertension and hypertension. The evidence from the Strong Heart Study was limited by use of a food frequency questionnaire to gather dietary sodium intake exposure data.

The committee determined that, although there is some evidence to suggest that lower dietary sodium intake or sodium-to-potassium ratio is related to lower left ventricular mass or risk of LVH, there is insufficient evidence at this time to support an intake–response relationship. Therefore, the evidence currently does not support the use of left ventricular mass as a potential indicator for establishing potassium or sodium DRI values. The committee, however, notes that future clinical trials are warranted to clarify the relationship between sodium intake and left ventricular mass.

Obesity

Obesity as an outcome was identified as a potential indicator for sodium and potassium through the abbreviated search of recent systematic reviews. The relationship between potassium and sodium and obesity was not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013). Potassium and sodium are not energy-providing nutrients but are correlated with energy intake (see Chapter 3). The majority of sodium intake in the diet comes from processed foods (see Chapter 11), whereas major contributors to potassium intake are fruits and vegetables. The interpretation of evidence on an apparent relationship between either nutrient and incident obesity is complicated, and has a high likelihood of being confounded. Accordingly, the committee elected to review evidence on obesity as a subpopulation who could be differentially affected by potassium or sodium intake (i.e., weight status as an effect modifier on relationships between intake and chronic disease outcomes), but determined it was not an appropriate indicator to inform the potassium or sodium DRI values.

Quality of Life

Quality of life is a broad, multidimensional concept. The instruments, scales, and tools used to assess quality of life capture an individual's or a group's perceptions. Owing to the lack of a biological mechanism to support the relationship between the nutrients and quality of life, the commit-

tee determined that such a subjective measure does not fit the paradigm of an indicator that could inform a DRI value for the apparently healthy population.

Severe Acute Malnutrition

Severe acute malnutrition is a condition characterized by severe wasting, caused by sudden shortage of food. Severe acute malnutrition contributes to the burden of disease globally, particularly among young children. The prevalence of wasting among children younger than 5 years of age in the United States is 0.5 percent (UNICEF/WHO/World Bank Group, 2017); it does not appear to be a widespread public health issue in North America.[6] In contrast, the prevalence of wasting among young children in Southern Asia is 15.4 percent. Accordingly, the committee determined that severe acute malnutrition would not have relevance for establishing DRI values for populations in the United States and Canada, but it acknowledges that it may have implications for nutrient reference values in other regions of the world.

Relevance Determined by Committee's Review of Evidence

To make an informed decision regarding the remaining indicators on the comprehensive list, the committee assessed a broad range of evidence. Information gathered on each of the indicators and the committee's rationale for why each was determined to not have relevance for establishing potassium or sodium DRI values is presented in the sections that follow.

Age-Related Cataracts, Age-Related Macular Degeneration, and Diabetic Retinopathy

Three eye-related conditions were identified as being potential indicators for sodium and potassium from the abbreviated search of recent systematic reviews. The potential indicators included age-related cataracts, age-related macular degeneration, and diabetic retinopathy. None of the eye-related indicators were reviewed in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013).

Sodium Through the scoping searches and reference mining of three systematic reviews for sodium (Dow et al., 2018; Wong et al., 2016, 2018), three articles that analyzed prospective cohort data were identified (Cundiff

[6]No estimate was available for Canada.

and Nigg, 2005; Horikawa et al., 2014; Roy and Janal, 2010).[7] Two of the studies were conducted in individuals with type 1 diabetes (Cundiff and Nigg, 2005; Roy and Janal, 2010), and were considered to have limited applicability for the purposes of establishing DRI values for the apparently healthy population. Horikawa et al. (2014) followed 1,588 Japanese patients who had type 2 diabetes, 40–70 years of age, for 8 years. Intake was assessed by food frequency questionnaires collected at baseline and 5 years after registration. Odds of incident retinopathy were not significantly different when those in the highest quartile of sodium intake were compared to those in the lowest quartile of sodium intake (odds ratio [OR]: 1.10 [95% confidence interval {CI}: 0.75, 1.61], $p = .64$). Based on this scoping search, the committee determined that the evidence currently does not support the use of age-related cataracts, age-related macular degeneration, or diabetic retinopathy as indicators to inform the sodium DRI values.

Potassium Through the scoping searches and reference mining of one systematic review for potassium (Dow et al., 2018), one relevant prospective cohort analysis was identified (Tanaka et al., 2013).[8] The analysis assessed 978 Japanese patients, 40–70 years of age, with type 2 diabetes. Dietary intake was collected through food frequency questionnaires and 24-hour dietary recall. The relationship between potassium intake and incidence diabetic retinopathy was not significant. The committee, therefore, determined that the evidence currently does not support the use of age-related cataracts, age-related macular degeneration, or diabetic retinopathy as indicators to inform the potassium DRI values.

Depression

Depression was assessed as an outcome in *Sodium Intake in Populations* (IOM, 2013), in which it was determined that conclusions about the relationship could not be drawn because only one study that prospectively

[7]The different scoping searches (see Table D-2) returned 3 results for the systematic review search, 26 results for the association search, and 25 results for the effect search, which were screened for relevance. The indicator-specific search string was (((((“eye”[MeSH Terms] OR “eye”[All Fields]) AND (“health”[MeSH Terms] OR “health”[All Fields])) OR (“eye diseases”[MeSH Terms] OR (“eye”[All Fields] AND “diseases”[All Fields]) OR “eye diseases”[All Fields] OR (“eye”[All Fields] AND “disease”[All Fields]) OR “eye disease”[All Fields])) OR (“retinal diseases”[MeSH Terms] OR (“retinal”[All Fields] AND “diseases”[All Fields]) OR “retinal diseases”[All Fields] OR “retinopathy”[All Fields])) OR (“cataract”[MeSH Terms] OR “cataract”[All Fields]).

[8]The different scoping searches (see Table D-2) returned 4 results for the systematic review search, 71 results for the association search, and 43 results for the effect search, which were screened for relevance. The indicator-specific search string was the same as for the sodium search.

assessed patients with heart failure was identified (Song, 2009). The relationship between sodium intake and depression was not explored in the *2005 DRI Report* (IOM, 2005).

Sodium The scoping searches did not reveal any publications on trials, prospective cohorts, or nested case-control studies on the independent relationship between sodium intake and depression that have been published since January 1, 2012.[9] This committee therefore determined that the evidence currently does not support the use of depression as an indicator to inform the sodium DRI values.

Gastroesophageal Reflux

Gastroesophageal reflux was assessed as an outcome in *Sodium Intake in Populations* (IOM, 2013), in which it was determined that conclusions about the relationship could not be drawn because only two studies on the topic were identified (Aanen et al., 2006; Nilsson et al., 2004). The relationship was not explored in the *2005 DRI Report* (IOM, 2005).

Sodium The scoping searches did not reveal any publications on trials, prospective cohorts, or nested case-control studies on this topic that have been published since January 1, 2012.[10] Accordingly, the committee determined that the evidence currently does not support the use of gastroesophageal reflux as an indicator to inform the sodium DRI values.

Genitourinary Symptoms

Genitourinary symptoms (including kidney stone formation and urinary tract infection) were assessed in both in the *2005 DRI Report* (IOM, 2005) and in *Sodium Intake in Populations* (IOM, 2013). The *AHRQ Systematic Review* included renal-related outcomes in key questions 3 and 4 for sodium and in key questions 5–8 for potassium (for the list of key

[9]The different scoping searches (see Table D-2) returned 0 results for the systematic review search, 9 results for the association search, and 8 results for the effect search, which were screened for relevance. The indicator-sepcific search string was ((((“depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depression”[All Fields] OR “depression”[MeSH Terms])) OR depressed)).

[10]The different scoping searches (see Table D-2) returned 2 results for the systematic review search, 2 results for the association search, and 1 result for the effect search, which were screened for relevance. The indicator-specific search string was ((“gastroesophageal reflux”[MeSH Terms] OR (“gastroesophageal”[All Fields] AND “reflux”[All Fields]) OR “gastroesophageal reflux”[All Fields] OR (“gastroesophageal”[All Fields] AND “reflux”[All Fields] AND “disease”[All Fields]) OR “gastroesophageal reflux disease”[All Fields]) OR “acid reflux”[All Fields])).

questions in the *AHRQ Systematic Review*, see Chapter 1, Box 1-3). This section, therefore, only describes the evidence on the relationship between sodium intake and urinary tract infection, which was not captured by the *AHRQ Systematic Review*.

Sodium In *Sodium Intake in Populations* (IOM, 2013), four articles on the relationship between sodium intake and genitourinary symptoms were identified, but only one was on the topic of urinary tract infections. In a cross-sectional assessment of 1,545 men 30–79 years of age in the Boston Area Community Healthy survey (2002–2005), Maserejian et al. (2009) reported that sodium intake, as measured by a food frequency questionnaire, had a significant positive association with lower urinary tract symptoms (p for trend = .007). In *Sodium Intake in Populations* (IOM, 2013), it was concluded that, given the inconsistent methodological approach and results, there was insufficient evidence to draw conclusions regarding the relationship between sodium intake and genitourinary symptoms. The scoping searches did not reveal any new randomized controlled trials, prospective cohorts, or nested case-cohort studies.[11] Accordingly, the committee determined that the evidence currently does not support the use of urinary tract infections as an indicator to inform the sodium DRI values.

Hyperhomocysteinemia

Hyperhomocysteinemia was identified as a potential indicator for sodium through the abbreviated search of recent systematic reviews. The relationship was not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013).

Sodium Through the scoping searches, one study was identified as exploring the relationship between sodium intake and hyperhomocysteinemia.[12] Wan et al. (2017) conducted a trial in rural China among 47 normotensive adults. Participants consumed three different diets in sequence, each for

[11]The different scoping searches (see Table D-2) returned 4 results for the systematic review search, 46 results for the association search, and 36 results for the effect search, which were screened for relevance. The indicator-specific search string was (urinary tract infection OR lower urinary tract OR cystitis).

[12]Instead of three individual scoping searches, a single search was conducted and led to 40 total results that were screened for relevance. The search string was (((((“Sodium Chloride”[Mesh] OR “Sodium Glutamate”[Mesh] OR “monosodium glutamate”[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract]OR intake[Text Word] OR “urinary excretion”) OR “Diet, Sodium-Restricted”[Mesh] OR “Sodium, Dietary”[Mesh]))) AND ((Hyperhomocysteinemia) OR homocysteine)) AND ((humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti]))).

1 week (low salt [3 grams sodium chloride per day], high salt [18 grams sodium chloride per day], and high salt with potassium supplementation [18 grams sodium chloride per day and 4.5 grams potassium chloride per day]); there was no washout period between the diets. Plasma homocysteine increased during salt loading among salt-sensitive participants (n = 19), whereas it did not significantly change among salt-resistant subjects (n = 28). The effects of salt loading among the salt-sensitive participants were ameliorated by the potassium supplementation.

Although the Wan et al. (2017) study suggests there is a relationship between sodium intake and plasma homocysteine levels in salt-sensitive individuals, the duration of the dietary intervention was short and there was no washout period between the different diets. Furthermore, given challenges in identifying salt-sensitive individuals (see Chapter 3), the committee did not use salt sensitivity as a characteristic to define subpopulations. Accordingly, the committee determined that the evidence currently does not support the use of hyperhomocysteinemia as an indicator to inform the sodium DRI values.

Leg Cramps

Leg cramps were identified as a potential indicator for sodium through the abbreviated search of recent systematic reviews. The relationships between the nutrients and leg cramps were not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013).

Sodium The scoping search revealed two systematic reviews published since January 1, 2003, that explore the relationship between leg cramps and sodium intake (Young, 2009, 2015).[13] The only primary study cited in the systematic reviews was Robinson (1947), and it was noted in those reviews that this study was of poor quality. No other articles were identified. Given the lack of recent data, the committee determined that the evidence currently does not support the use of leg cramps as an indicator to inform the sodium DRI values.

Maternal and Birth Outcomes

Maternal and birth outcomes (e.g., miscarriage, preeclampsia) were identified as a potential indicator for sodium through the abbreviated search of recent systematic reviews. In the *2005 DRI Report* (IOM, 2005,

[13]The different scoping searches (see Table D-2) returned 2 results for the systematic review search, 0 results for the association search, and 1 result for the effect search, which were screened for relevance. The indicator-specific search string was (leg cramp*).

p. 383), it was determined that the "available evidence indicates that reducing sodium intake has little impact on preventing hypertensive disorders of pregnancy or their complications." Pregnancy-related outcomes were not addressed in *Sodium Intake in Populations* (IOM, 2013).

Sodium Through the scoping searches and reference mining of three systematic reviews (Duley, 2008, 2011; Duley et al., 2005), five studies were identified as exploring the relationship between sodium intake and maternal and birth outcomes (see Table D-3).[14] The outcomes explored were varied and provided limited evidence of effect of sodium intake. The committee determined that the evidence currently does not support the use of maternal or birth outcomes as indicators to inform the sodium DRI values.

Metabolic Syndrome

Metabolic syndrome as an outcome was identified as a potential indicator for sodium and for potassium through the abbreviated search of recent systematic reviews. The relationships between the nutrients and metabolic syndrome were not explored in the *2005 DRI Report* (IOM, 2005). In *Sodium Intake in Populations* (IOM, 2013), two cross-sectional studies examining the association between sodium intake and risk of metabolic syndrome were identified, but the studies did not meet the criteria for further evaluation (Rodrigues et al., 2009; Teramoto et al., 2011).

Sodium The scoping searches and reference mining of three systematic reviews (Cai et al., 2016; Kang et al., 2016; Soltani et al., 2017) did not reveal any articles on trials, prospective cohorts, or nested case-control studies exploring the relationship between sodium intake and metabolic syndrome.[15] Accordingly, the committee determined that the evidence cur-

[14]The different scoping searches (see Table D-2) returned 4 results for the systematic review search, 27 results for the association search, and 20 results for the effect search, which were screened for relevance. The indicator-specific search string was (((((“pre-eclampsia”[MeSH Terms] OR “pre-eclampsia”[All Fields] OR “preeclampsia”[All Fields]) OR (“abortion, spontaneous”[MeSH Terms] OR (“abortion”[All Fields] AND “spontaneous”[All Fields]) OR “spontaneous abortion”[All Fields] OR “miscarriage”[All Fields])) OR (“pregnancy outcome”[MeSH Terms] OR (“pregnancy”[All Fields] AND “outcome”[All Fields]) OR “pregnancy outcome”[All Fields])) OR “pregnancy-induced hypertension”[All Fields]) OR “hypertensive pregnancy”[All Fields])).

[15]The different scoping searches (see Table D-2) returned 6 results for the systematic review search, 36 results for the association search, and 34 results for the effect search, which were screened for relevance. The indicator-specific search string was ((“metabolic syndrome”[MeSH Terms] OR (“metabolic”[All Fields] AND “syndrome”[All Fields]) OR “metabolic syndrome”[All Fields]) OR MetS[All Fields])).

rently does not support the use of metabolic syndrome as an indicator to inform the sodium DRI values.

Potassium The scoping searches and reference mining of one systematic review (Cai et al., 2016) did not reveal any articles on trials, prospective cohorts, or nested case-control studies exploring the relationship between potassium intake and metabolic syndrome.[16] Accordingly, the committee determined that the evidence currently does not support the use of metabolic syndrome as an indicator to inform the potassium DRI values.

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease was identified as a potential indicator for sodium through the abbreviated search of recent systematic reviews. The relationship between sodium and nonalcoholic fatty liver disease was not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013).

Sodium The scoping searches and reference mining of one systematic review (Wong et al., 2017) did not reveal any articles on trials, prospective cohorts, or nested case-control studies exploring the relationship between sodium intake and nonalcoholic fatty liver disease.[17] Accordingly, the committee determined that the evidence currently does not support the use of nonalcoholic fatty liver disease as an indicator to inform the sodium DRI values.

Pulmonary Function

Pulmonary function was assessed in both in the *2005 DRI Report* (IOM, 2005) and in *Sodium Intake in Populations* (IOM, 2013).

[16]The different scoping searches (see Table D-2) returned 3 results for the systematic review search, 45 results for the association search, and 38 results for the effect search, which were screened for relevance. The indicator-specific search string was the same as for the sodium search.

[17]The different scoping searches (see Table D-2) returned 1 result for the systematic review search, 6 results for the association search, and 6 results for the effect search, which were screened for relevance. The indicator-specific search string was ("non-alcoholic fatty liver disease"[MeSH Terms] OR ("non-alcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "non-alcoholic fatty liver disease"[All Fields] OR ("nonalcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "nonalcoholic fatty liver disease"[All Fields])).

TABLE D-3 Evidence on the Relationship Between Sodium Intake and Maternal and Birth Outcomes, Identified Through Scoping Searches

Reference	Population	Sodium Exposure
Crossover Trials		
Nielsen et al., 2016	• 7 women with preeclampsia • 15 healthy pregnant women • 13 healthy nonpregnant women Location: Denmark	Low-salt diet (50–60 mmol NaCl/d) throughout, and received the following in random order: • Salt tablets (172 mmol NaCl/d) for 4 days • Placebo for 4 days 24-hour urinary sodium measured the day before the study day for each period
Prospective Cohort		
Inoue et al., 2016	• 184 pregnant women Location: Japan	Measured before 20th week of gestation: • 24-hour home urine collection • Early morning urine sample Measured after 20th week, at each pregnancy check-up visit: • Early morning urine sample
Hassanzadeh et al., 2016	• 620 pregnant women Location: Iran	Completed at the 11th–15th, 26th, and 34th–37th weeks of gestation: • 48-hour dietary recalls

Maternal and Birth Outcome	Results
Measured at the end of each period: • Renin and angiotensin II concentrations • Aldosterone • Brain natriuretic peptide • Uterine and umbilical artery indices • Creatinine clearance	• Difference in 24-hour urinary sodium excretion between high- and low-salt intakes was significantly smaller in women with preeclampsia compared with nonpregnant women. • Urinary sodium-to-potassium ratios changed by the intervention in all three groups, but the changes were significantly higher in the two pregnant groups compared to the nonpregnant group. • High-salt diet significantly decreased renin and angiotension II concentrations in healthy pregnant women ($p < .03$) and nonpregnant women ($p < .001$), but did not in women with preeclampsia ($p = .58$). • Decreases in aldosterone and increases in brain natriuretic peptide were similar in all groups. • No adverse changes in uterine or umbilical artery indices during the low-salt diet among women with preeclampsia. • Creatinine clearance was significantly lower in women with preeclampsia with no change by salt intake.
Measured on 7 consecutive days before 20th week and after 30th week gestation: • Home blood pressure Infant outcome: • Light-for-date at birth	• 14 women developed pregnancy-induced hypertension and 8 developed pregnancy-induced hypertension with proteinuria.[a] • Estimated urinary salt excretion was not significantly correlated with either home blood pressure before the 20th gestational week or home blood pressure after the 30th gestational week. • Logistic regression: Neither urinary salt excretion averaged until the 30th gestational week nor change in urinary salt excretion was associated with the development of pregnancy-induced hypertension. • Maternal urinary salt excretion was not associated with the likelihood of light-for-date infants.
Collected through patient record: • PPROM	• 17 patients were diagnosed with PPROM. • Mean sodium intakes in the second trimester among women with PPROM were significantly more than intakes of healthy pregnant women (4,253 ± 2,845 versus 3,081 ± 1,622, $p = .004$).[b] • Logistic regression: Odds of PPROM was increased with increased sodium intake in the second trimester (Wald statistic 1.650; OR: 1.002).

continued

TABLE D-3 Continued

Reference	Population	Sodium Exposure
Watson and McDonald, 2007	• 197 pregnant women Location: New Zealand	Assessed during months 4 and 7 of pregnancy: • 8-day weighed diet record (two 4-day periods, 8 days apart)
Lagiou et al., 2005	• 222 Caucasian women with singleton pregnancies Location: United States	Collected at approximately 27 weeks gestation: • Semiquantitative food frequency questionnaire, asking about intake throughout the second trimester of pregnancy

NOTE: CI = confidence interval; NaCl = sodium chloride; OR = odds ratio; PPROM = preterm premature rupture of membranes.

[a]Pregnancy-induced hypertension defined as gestational hypertension (rise in BP to ≥ 140/90 mm Hg); preeclampsia (newly developed hypertension ≥ 140/90 mm Hg with proteinuria ≥ 300 mg/day); or superimposed preeclampsia after the 20th gestational week on chronic hypertension (BP rise to ≥ 160/110 mm Hg, and/or new-onset or worsening proteinuria ≥ 300 mg/day).

Sodium In the *2005 DRI Report*, pulmonary function was explored as an adverse effect of overconsumption of sodium. The five cross-sectional analyses on the topic identified had mixed results regarding the relationship between pulmonary function and sodium intake (Britton et al., 1994; Burney et al., 1986; Schwartz and Weiss, 1990; Tribe et al., 1994; Zoia et al., 1995). Evidence from three trials suggested that high salt intake adversely affected people with asthma (Carey et al., 1993; Gotshall et al., 2000; Medici et al., 1993). The evidence on the relationship between sodium intake and pulmonary function ultimately was characterized as sparse and was not used in the derivation of the UL in the *2005 DRI Report*.

In *Sodium Intake in Populations* (IOM, 2013), four articles on the relationship between sodium intake and pulmonary function were identified (Gotshall et al., 2004; Hirayama et al., 2010; Mickleborough et al., 2005; Sausenthaler et al., 2005). It was concluded that, given the inconsistent methodological approach and results, there was insufficient evidence to draw conclusions regarding the relationship between sodium intake and pulmonary function.

The scoping searches and reference mining of one systematic review (Forte et al., 2018) did not reveal any additional articles on trials, pro-

Maternal and Birth Outcome	Results
Infant outcome, obtained from health records: • Birth weight • Birth head circumference • Weight, length, and head circumference at 6 and 12 months	• Sodium exhibited sinusoidal variation by season, with intake being highest in the winter and lowest in the summer. • Among spring births, infants' head circumference at birth had a positive relationship with maternal sodium intake during month 4 of pregnancy (p = .047).
Infant outcome, measured at delivery: • Birth weight • Placental weight • Birth length • Head circumference	• Per standard deviation increase of sodium intake, adjusted mean change[c]: o Head circumference, +0.48 cm [95% CI: +0.02, +0.93], p = .04. o Placental weight, birth weight, and birth length not statistically significant.

[b]During the second trimester, women with PPROM were also reported to consume more energy, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, vitamin A, vitamin C, beta-carotene, carotenoids, calcium, and iron.

[c]Adjusted for energy intake, maternal age, maternal education, parity, maternal height, prepregnancy body mass index, pregravid oral contraceptive use, smoking during pregnancy, exact gestational age at delivery, and gender of the baby.

spective cohorts, or nested case-control studies exploring the relationship between sodium intake and pulmonary function as being published since January 1, 2012.[18] Accordingly, the committee determined that the evidence currently does not support the use of pulmonary function as an indicator to inform the sodium DRI values.

Potassium In the *2005 DRI Report*, prevention of impaired pulmonary function was explored as an indicator for estimating the requirement for potassium. The evidence on the relationship between potassium and pulmonary function was mixed for adults (Tribe et al., 1994; Zoia et al., 1995) and for children (Gilliland et al., 2002; Pistelli et al., 1993). Pulmonary function was not used in the derivation of the potassium Adequate Intake values.

[18]The different scoping searches (see Table D-2) returned 5 results for the systematic review search, 34 results for the association search, and 29 results for the effect search, which were screened for relevance. The indicator-specific search string was ((((((((((((((Asthma) OR Chest tightness) OR Cough) OR Dyspnoea) OR FEV1) OR Forced expiratory volume) OR Forced vital capacity) OR FVC) AND Lung function) OR PEF) OR Pulmonary function) OR Respiratory symptoms) OR Spiromet*) OR wheez*))).

The scoping searches and reference mining did not reveal any articles on randomized controlled trials, prospective cohorts, or nested case-cohort studies exploring the relationship between potassium intake and pulmonary function.[19] Accordingly the committee determined that the evidence currently does not support the use of pulmonary function as an indicator to inform the potassium DRI values.

Rheumatoid Arthritis

Rheumatoid arthritis was identified as a potential indicator for sodium through the abbreviated search of recent systematic reviews. The relationship between sodium and rheumatoid arthritis was not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013).

Sodium Through the scoping searches and reference mining of one systematic review (Wong et al., 2016), one nested case-control study was identified as exploring the relationship between sodium intake and rheumatoid arthritis.[20] The analysis included 386 cases of rheumatoid arthritis examined for a median of 7.7 years before the onset of symptoms and 1,886 matched controls (Sundström et al., 2015). The cases and controls were drawn from data collected through the Västerbotten Intervention Programme, a population-based screening and health counseling program in Sweden. Sodium intake was assessed by a semiquantitative food frequency questionnaire. Risk of developing rheumatoid arthritis did not significantly differ by tertile of sodium intake. When stratified by smoking status, however, the risk for developing rheumatoid arthritis was elevated among smokers in the highest tertile of sodium intake, as compared to the lowest tertile of intake (OR = 2.26 [95% CI: 1.06, 4.81], p = .036).

It was estimated that 54 percent of the increased risk of developing rheumatoid arthritis was attributed to the interaction between high sodium intake and smoking. Despite the statistically significant finding among smokers reported in Sundström et al. (2015), the study had limitations, including the methodology for capturing sodium intake. The com-

[19]The different scoping searches (see Table D-2) returned 6 results for the systematic review search, 263 results for the association search, and 180 results for the effect search, which were screened for relevance. The indicator-specific search string was the same as for the sodium search.

[20]The different scoping searches (see Table D-2) returned 2 results for the systematic review search, 9 results for the association search, and 1 result for the effect search, which were screened for relevance. The indicator-specific search string was ("arthritis, rheumatoid"[MeSH Terms] OR ("arthritis"[All Fields] AND "rheumatoid"[All Fields]) OR "rheumatoid arthritis"[All Fields] OR ("rheumatoid"[All Fields] AND "arthritis"[All Fields])).

mittee, therefore, determined that the evidence currently does not support the use of rheumatoid arthritis as an indicator to inform the sodium DRI values.

Sarcopenia

Sarcopenia was identified as a potential indicator for sodium and for potassium through the abbreviated search of recent systematic reviews. The relationship between sodium and sarcopenia was not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013).

Sodium The scoping searches and reference mining of one systematic review (van Dronkelaar et al., 2018) did not reveal any randomized controlled trials, prospective cohorts, or nested case-control studies published since January 1, 2003, on the relationship between sodium intake and sarcopenia.[21] The committee, therefore, determined that the evidence currently does not support the use of sarcopenia as an indicator to inform the sodium DRI values.

Potassium Through the scoping searches and reference mining of one systematic review (van Dronkelaar et al., 2018), two primary research articles were identified as exploring the relationship between sodium intake and sarcopenia-related measures that had been published since January 1, 2003.[22]

Ceglia and Dawson-Hughes (2017) conducted an 84-day randomized, placebo-controlled potassium bicarbonate ($KHCO_3$) trial among 233 men and women, 60 years of age and older. Participants were randomized to a placebo arm, a low-dose arm (1 mmol/kg/d $KHCO_3$), or a high-dose arm (1.5 mmol/kg/d $KHCO_3$). Using a ratio of urinary nitrogen excretion to concurrent nitrogen intake as a marker of muscle breakdown, the study found greater reductions in the marker with escalating doses of $KHCO_3$, although only the comparison between the highest dose and placebo arms was significant. The premise of this study, however, was not to investigate the effect of potassium, but rather the conjugate anion (bicarbonate) as a

[21]The different scoping searches (see Table D-2) returned 1 result for the systematic review search, 21 results for the association search, and 13 results for the effect search, which were screened for relevance. The indicator-specific search string was (((“sarcopenia”[MeSH Terms] OR “sarcopenia”[All Fields]) OR ((“muscles”[MeSH Terms] OR “muscles”[All Fields] OR “muscle”[All Fields]) AND loss[All Fields])))).

[22]The different scoping searches (see Table D-2) returned 16 results for the systematic review search, 48 results for the association search, and 18 results for the effect search, which were screened for relevance.

means for reducing metabolic acidosis. Measures and assessment of potassium intake or excretion were not reported.

In an analysis of prospective cohort data from 3,122 adults 65 years of age and older living in Hong Kong, dietary intake was assessed at baseline using a validated food frequency questionnaire (Chan et al., 2015). The investigators assessed the relationship of dietary protein-to-potassium ratio (as a measure of net endogenous acid production [NEAP]) and declines in muscle mass over a 4-year period. The results found slower declines with lower measure of NEAP. The premise of the study was to use the measure of NEAP, rather than evaluating the independent effect of potassium. The investigators also demonstrated that the energy-adjusted NEAP estimates were significantly correlated with the intake of several nutrients (e.g., vitamin C, calcium, fiber) and food groups (e.g., fish and shellfish, fruits and dried fruits, vegetables).

The scoping literature search revealed that studies on sarcopenia, as they relate to intake of potassium, focus on metabolic acidosis and the role of bicarbonate that is associated with potassium, as part of the supplement ($KHCO_3$) or in potassium-containing foods (e.g., assessed by NEAP). As the independent relationship between potassium intake and sarcopenia does not appear to be pervasive in the literature, the committee determined that the evidence currently does not support the use of sarcopenia as an indicator to inform the potassium DRI values.

Small Vessel Disease

Small vessel disease was identified as a potential indicator for sodium through the abbreviated search of recent systematic reviews. The relationships between sodium and small vessel disease was not explored in the *2005 DRI Report* (IOM, 2005) or in *Sodium Intake in Populations* (IOM, 2013).

Sodium The scoping searches and reference mining of a systematic review (Makin et al., 2017) did not reveal any articles on trials, prospective cohorts, or nested case-control studies exploring the relationship between

sodium intake and small vessel disease.[23] Accordingly, the committee determined that the evidence currently does not support the use of small vessel disease as an indicator to inform the sodium DRI values.

SUMMARY

A wide range of intermediates, surrogates, and clinical outcomes have been assessed as having a relationship with sodium and with potassium. While each may be of scientific and clinical interest, not all are relevant for the purposes of informing the potassium or sodium DRI values. Through expert judgment and scoping literature searches for recent evidence, the committee determined that several of the potential indictors that exist in the literature do not align with the DRI paradigm or have limited data at present, and as such do not support their use as indicators to inform the potassium or sodium DRI values.

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[23]Instead of three individual scoping searches, a single search was conducted and led to 25 total results that were screened for relevance. The search string was (((((“Sodium Chloride”[Mesh] OR “Sodium Glutamate”[Mesh] OR “monosodium glutamate”[Title/Abstract] OR salt[Title/Abstract] OR salt[Text Word] OR sodium[Title/Abstract] OR sodium[Text Word]) AND (diet[MeSH Terms] OR diet[Title/Abstract] OR diet[Text Word] OR food[Text Word] OR food[Title/Abstract] OR intake[Title/Abstract]OR intake[Text Word] OR “urinary excretion”) OR “Diet, Sodium-Restricted”[Mesh] OR “Sodium, Dietary”[Mesh]))) AND ((((“Small”[Journal] OR “small”[All Fields]) AND (“blood vessels”[MeSH Terms] OR (“blood”[All Fields] AND “vessels”[All Fields]) OR “blood vessels”[All Fields] OR “vessel”[All Fields]) AND (“disease”[MeSH Terms] OR “disease”[All Fields]))) OR (((“small vessel disease”) OR “microvascular Disease”) OR “small artery disease”))) AND ((humans[MESH]) OR (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb] NOT (mice[ti] OR mouse[ti] OR rats[ti] OR dogs[ti]))).

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Appendix E

Supplemental Literature Searches

The Agency for Healthcare Research and Quality systematic review, *Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks* (*AHRQ Systematic Review*) (Newberry et al., 2018), served as a foundational source of evidence for the committee. However, additional literature searches were needed in order to inform the committee's decision regarding the different Dietary Reference Intake (DRI) categories. This appendix provides a description of the additional literature searches conducted for indicators not included in the *AHRQ Systematic Review* but considered potentially relevant. This appendix also includes the committee's search for studies that would have qualified for the *AHRQ Systematic Review*, but were published after the last literature search conducted by the *AHRQ Systematic Review* investigators.

SUPPLEMENTAL LITERATURE SEARCH FOR POTASSIUM AND SODIUM BALANCE STUDIES

In order to minimize the duplication of resources, the committee's supplemental literature search for balance studies drew from the references presented in three sources: *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005), the 2016 European Food Safety Authority (EFSA) *Diet Reference Values (DRVs) for Potassium* (EFSA, 2016), and the 2018 draft of the EFSA *DRVs for Sodium* (EFSA, 2018). These three sources were selected as each provided thorough summaries of evidence on balance studies and descriptions of losses in the urine, feces, and sweat. As the EFSA resources were

recently prepared, the committee expected both to reflect evidence on balance studies that had emerged since the *2005 DRI Report*. Nevertheless, the committee also considered evidence provided through its other information-gathering activities, including comments submitted by the public and its public workshops. The committee notes that the EFSA DRVs for sodium report was in draft form at the writing of this report. The draft contained a comprehensive summary of evidence on sodium, but did not establish the reference values. The committee reviewed the summary of public comments on the intermediate draft of the DRVs for sodium, and did not find evidence that crucial studies had been omitted from the balance study summary (EFSA, 2017). The committee therefore determined that the DRVs for sodium draft report was a suitable resource from which to draw references on balance studies.

The committee compiled the references from each of the three sources cited in sections of those reports that summarized evidence on balance studies and losses in urine, feces, and sweat; one additional reference was submitted to the committee through the public comment mechanism. Across sodium and potassium, 77 references were identified. References were then reviewed using the following inclusion criteria: primary research study; crossover or sequential design; conducted for a minimum of 3 days; and conducted in normotensive, apparently healthy participants similar to the U.S. and Canadian populations. Studies using randomized parallel design trials were not included because high intra-individual variability might confound results. Summary tables of the literature are presented in Chapters 4 and 8.

SUPPLEMENTAL LITERATURE SEARCHES FOR EVIDENCE ON THE RELATIONSHIP BETWEEN SODIUM INTAKE AND HEADACHES

In its search for evidence to inform the sodium Tolerable Upper Intake Level, the committee identified headache as a potentially informative indicator. Evidence of the potential relationship was presented to the committee during its March 2018 public workshop (Whelton, 2018); in particular, three references were cited (Amer et al., 2014; Appel et al., 2001; Chen et al., 2016). To supplement the evidence presented to the committee, a supplementary literature search was conducted. The search strategy was aligned with the literature scans described in Appendix D (see Table D-2), which was modeled after the search strategy conducted in the *AHRQ Systematic Review* (Newberry et al., 2018). Specifically, three searches were conducted in PubMed to identify potentially relevant evidence of effect (i.e., randomized controlled trials), evidence of association (i.e., prospective cohorts and case-cohorts), and systematic reviews to reference

mine.[1] The searches resulted in 58 references for the effect-related search, and 59 references for the association-related search; after deduplication, 87 unique references remained. The search also identified 14 systematic reviews, of which 1 was relevant to the relationship between sodium intake and headaches; reference mining the review article, however, did not reveal any additional studies. Titles and abstracts were screened by two independent reviewers for potential relevance to sodium intake and headaches; discrepancies were resolved through discussion. The title/abstract screening removed 85 publications. The remaining studies were presented to the committee at its March 2018 workshop. As such, the supplementary literature search on headaches revealed no additional studies. The committee's assessment of the evidence on the relationship between sodium intake and headaches is presented in Chapter 9.

SUPPLEMENTAL LITERATURE SEARCHES ON ADDITIONAL INDICATORS IDENTIFIED THROUGH THE LITERATURE SCAN

The committee drew from diverse evidence sources to compile a comprehensive list of indicators that had been assessed in the literature as potentially having a relationship with potassium and sodium intakes (see Appendix D). Through literature scans, scoping searches, and expert scientific judgment, the committee narrowed the list and selected the following indicators for supplemental literature searches: blood lipids; bone health (fractures and bone mineral density); catecholamines; type 2 diabetes, glucose intolerance, and insulin sensitivity; and plasma renin activity.

Identifying High-Quality Systematic Reviews

To minimize the duplication of resources, the committee's supplemental literature searches began with a search for recent, high-quality systematic reviews on all indicators of interest. The search was conducted in MEDLINE and the Cochrane Database of Systematic Reviews and was limited to systematic reviews published since January 1, 2013. The committee determined that systematic reviews older than 5 years would not be considered recent. Systematic reviews were included if they reported a literature search strategy, described study eligibility criteria, included a risk-of-bias assessment, and had a potassium or sodium exposure. The search returned

[1]The indicator-specific terminology for headache was ((“headache”[MeSH Terms] OR “headache”[All Fields]) OR (“head”[All Fields] AND “pain”[All Fields]) OR “head pain”[All Fields]) OR (“cephalodynia”[All Fields]) OR (“cephalalgia”[All Fields]) OR (“hemicranias”[All Fields]) OR (“migraine disorders”[MeSH Terms] OR (“migraine”[All Fields] AND “disorders”[All Fields]) OR “migraine disorders”[All Fields] OR “migraine”[All Fields]).

127 initial results. After removing duplicates, 90 were excluded based on a dual title/abstract screening, and an additional 23 were excluded after a full-text screening, leaving 6 relevant systematic reviews. Each of these systematic reviews was evaluated using the AMSTAR 2 tool (Shea et al., 2017) (see Table E-1).[2] The AMSTAR 2 evaluation was conducted by two independent reviewers, and any conflicts were resolved through discussion. After considering the AMSTAR 2 assessment, one systematic review assessing the relationship between potassium intake and the risk of type 2 diabetes was excluded owing to failure to assess the effect of the risk of bias in the synthesis of evidence (Peng et al., 2017). Additionally, one systematic review assessing the effect of supplemental alkaline potassium salts on bone metabolism was identified (Lambert et al., 2015); however, it was not selected as a source of evidence because it had a narrow scope and would have necessitated a broader search to be conducted. These two systematic reviews were, however, used for reference mining to identify potentially relevant primary research articles. The remaining four systematic reviews were included and used to inform the committee's evidence review (Aburto et al., 2013a,b; Graudal et al., 2017; He et al., 2013). The included systematic reviews addressed three of the committee's indicators of interest: blood lipids, catecholamines, and plasma renin activity. Because of variations in the inclusion and exclusion criteria for the reviews, as well as the results, the committee was unable to combine the reviews. Instead, the committee evaluated each review independently with regard to the questions of interest, and included population and duration of included studies in order to synthesize the available information and draw conclusions.

Searching for Primary Studies

Because no high-quality, recent systematic reviews were identified on the relationship between sodium and potassium intakes and bone health or type 2 diabetes, glucose tolerance, and insulin sensitivity, a literature search to identify primary studies was conducted in Ovid MEDLINE to identify relevant randomized controlled trials and prospective cohort studies published since January 1, 2003, up to April 2018. The committee searched back to 2003 in order to include anything published since the *2005 DRI Report*. The searches were limited to humans and English language publications.

[2]AMSTAR stands for A Measurement Tool to Assess Systematic Reviews.

TABLE E-1 Summary of AMSTAR 2 Evaluation of Identified Systematic Reviews

Reference	AMSTAR 2		Use in Committee's Review
	Criteria[a] Partially Met	Not Met	
Aburto et al., 2013a	List and justification of excluded studies	None	Source of evidence
Aburto et al., 2013b	List and justification of excluded studies	None	Source of evidence
Graudal et al., 2017	None	None	Source of evidence
He et al., 2013	None	Sources of funding reported	Source of evidence
Lambert et al., 2015	Included studies described	Review methods established prior to review Duplicate data extraction Sources of funding reported Publication bias assessed if quantitative synthesis was done	Reference mining
Peng et al., 2017	Included studies described	Review methods established prior to review List and justification of excluded studies Sources of funding reported Impact of risk of bias assessed in evidence synthesis	Reference mining

NOTE: AMSTAR = A Measurement Tool to Assess Systematic Reviews.

[a]Unless otherwise noted as partially met or not met, all criteria were deemed to be met according to the AMSTAR 2 criteria. The AMSTAR 2 criteria for quality assessment is available at https://amstar.ca/docs/AMSTAR-2.pdf (accessed August 15, 2018).

Search Terms

The search strategy was aligned with the approach taken in the *AHRQ Systematic Review*. The search was conducted in MEDLINE using comprehensive search terms for bone health[3] and type 2 diabetes.[4] Comprehensive search terms were also used to capture all forms of sodium and potassium (e.g., supplements, sodium or potassium compounds), aligned with terms used in the *AHRQ Systematic Review*.

Inclusion/Exclusion Criteria

The search was limited to articles published since January 1, 2003. Randomized controlled trials and prospective cohort studies were included if they had a sodium or potassium intervention or exposure, or measured sodium or potassium intake. Other study designs were excluded, as were interventions where the effect of sodium or potassium could not be disaggregated from other effects. The complete inclusion/exclusion criteria are outlined in Tables E-2 through E-5 for sodium and potassium intakes and bone health outcomes, and in Tables E-6 through E-9 for sodium and potassium intakes and type 2 diabetes, glucose tolerance, and insulin sensitivity outcomes. The inclusion/exclusion criteria for population, intervention/intake, comparators, setting, and study design were generally aligned with criteria used in the *AHRQ Systematic Review*. Owing to differences in outcomes being searched, some revisions were made. For example, studies assessing bone mineral density outcomes were limited to 1-year duration or longer in order to reliably assess results, whereas other outcomes had a minimum duration of 4 weeks.

Screening and Selection

The search for these outcomes returned 2,287 results. After removing duplicates, dual screening titles and abstracts, and screening full-text articles, 14 relevant references were identified. Of these references, eight were on relationships with bone health outcomes (fracture and bone mineral density) and six were on type 2 diabetes, glucose tolerance, and insulin sensitivity outcomes. The characteristics of the studies are summarized in Tables E-10 through E-16.

[3]Including bone density, mineralization, osteoporosis, bone mineral content, fracture, falls, rickets, and tooth loss.

[4]Including prediabetes, insulin resistance, and glucose tolerance.

TABLE E-2 Inclusion Criteria for Studies to Assess the Effect of Sodium Intake on Bone Health Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies evaluating interventions to reduce dietary sodium intake that specify the oral consumption from food or supplements of quantified amounts of sodium and sodium chloride (salt) or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/– 3 percent or more. Interventions simultaneously addressing sodium and potassium intake that document sodium-to-potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.
Comparators	Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of sodium intake, or studies that alter sodium-to-potassium ratio in other ways will be included if they control for other nutrient levels.
Outcomes	Studies reporting on bone health outcomes (including fractures, falls, or performance measures of strength, and bone mineral density) will be eligible for inclusion.
Timing	Studies with a duration of more than 1 year will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Randomized controlled trial (crossover or parallel arm).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-3 Inclusion Criteria for Studies to Assess the Association Between Sodium Intake and Bone Health Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies that measure the intake (oral consumption from food or supplements of quantified amounts of sodium and sodium chloride [salt] or sodium-to-potassium ratio) with validated measures or that use biomarker values to assess sodium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of salt substitute with intervention/exposure adherence measure, and food diaries with reported validation [adherence check, electronic prompts]) will be eligible. Observational studies that report a weight change of +/– 3 percent or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies relying only on serum sodium levels, composition of salt substitute without intervention/exposure adherence measure, food diaries without reported validation, use of a published food frequency questionnaire, or partial or spot urine without reported prediction equation will be excluded.
Comparators	Studies comparing groups with different documented sodium intake or biomarker values for sodium will be eligible. Studies where differences in sodium intake or values are not reported independently of alteration of other nutrient levels will be excluded.
Outcomes	Studies reporting on bone health outcomes (including fractures, falls, or performance measures of strength, and bone mineral density) will be eligible for inclusion.
Timing	Studies with a duration of more than 1 year will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Prospective cohort studies (including case-cohort studies).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-4 Inclusion Criteria for Studies to Assess the Effect of Potassium Intake on Bone Health Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies evaluating interventions to increase dietary potassium intake that specify the oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/– 3 percent or more among adults. Interventions simultaneously addressing sodium and potassium intake that document sodium-to-potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.
Comparators	Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of potassium intake, or studies that alter sodium-to-potassium ratio in other ways will be included if they control for other nutrient levels.
Outcomes	Studies reporting on bone health outcomes (including fractures, falls, or performance measures of strength, and bone mineral density) will be eligible for inclusion.
Timing	Studies with a duration of more than 1 year will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Randomized controlled trial (crossover or parallel arm).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-5 Inclusion Criteria for Studies to Assess the Association Between Potassium Intake and Bone Health Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies that measure intake (oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio) with validated measures or use biomarker values to assess potassium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of potassium supplement with intervention/exposure adherence measure, use of a published food frequency questionnaire, and food diaries) will be eligible. Observational studies that report a weight change of +/– 3 percent or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies measuring potassium intake by reporting chemical analysis of diet without intervention/ exposure adherence measures, composition of potassium supplement without intervention/exposure measure, or serum potassium will be excluded.
Comparators	Studies comparing groups with different documented potassium intake, serum potassium levels, or urinary potassium excretion will be eligible. Studies where differences in potassium intake or values are not reported independently of alteration of other nutrient levels will be excluded.
Outcomes	Studies reporting on bone health outcomes (including fractures, falls, or performance measures of strength, and bone mineral density) will be eligible for inclusion.
Timing	Studies with a duration of more than 1 year will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Prospective cohort studies (including case-cohort studies).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-6 Inclusion Criteria for Studies to Assess the Effect of Sodium Intake on Type 2 Diabetes, Glucose, and Insulin Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies evaluating interventions to reduce dietary sodium intake that specify the oral consumption from food or supplements of quantified amounts of sodium and sodium chloride (salt) or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/– 3 percent or more. Interventions simultaneously addressing sodium and potassium intake that document sodium-to-potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.
Comparators	Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of sodium intake, or studies that alter sodium-to-potassium ratio in other ways will be included if they control for other nutrient levels.
Outcomes	Studies reporting on type 2 diabetes mellitus, glucose intolerance, or insulin sensitivity will be eligible for inclusion. Studies reporting on type 1 diabetes and gestational diabetes will be excluded.
Timing	Studies with a duration of more than 4 weeks will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Randomized controlled trial (crossover or parallel arm).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-7 Inclusion Criteria for Studies to Assess the Association Between Sodium Intake and Type 2 Diabetes, Glucose, and Insulin Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies that measure the intake (oral consumption from food or supplements of quantified amounts of sodium and sodium chloride [salt] or sodium-to-potassium ratio) with validated measures or that use biomarker values to assess sodium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of salt substitute with intervention/exposure adherence measure, and food diaries with reported validation [adherence check, electronic prompts]) will be eligible. Observational studies that report a weight change of +/– 3 percent or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies relying only on serum sodium levels, composition of salt substitute without intervention/exposure adherence measure, food diaries without reported validation, use of a published food frequency questionnaire, or partial or spot urine without reported prediction equation will be excluded.
Comparators	Studies comparing groups with different documented sodium intake or biomarker values for sodium will be eligible. Studies where differences in sodium intake or values are not reported independently of alteration of other nutrient levels will be excluded.
Outcomes	Studies reporting on type 2 diabetes mellitus, glucose intolerance, or insulin sensitivity will be eligible for inclusion. Studies reporting on type 1 diabetes and gestational diabetes will be excluded.
Timing	Studies with a duration of more than 4 weeks will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Prospective cohort studies (including case-cohort studies).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-8 Inclusion Criteria for Studies to Assess the Effect of Potassium Intake on Type 2 Diabetes, Glucose, and Insulin Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies evaluating interventions to increase dietary potassium intake that specify the oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/– 3 percent or more among adults. Interventions simultaneously addressing sodium and potassium intake that documents sodium-to-potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.
Comparators	Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of potassium intake, or studies that alter sodium-to-potassium ratio in other ways will be included if they control for other nutrient levels.
Outcomes	Studies reporting on type 2 diabetes mellitus, glucose intolerance, or insulin sensitivity will be eligible for inclusion. Studies reporting on type 1 diabetes and gestational diabetes will be excluded.
Timing	Studies with a duration of more than 4 weeks will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Randomized controlled trial (crossover or paralleled).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-9 Inclusion Criteria for Studies to Assess the Association Between Potassium Intake and Type 2 Diabetes, Glucose, and Insulin Outcomes

Component	Criteria
Population	Studies in humans, except those exclusively in patients with end-stage renal disease, heart failure, HIV, cancer, patients with fractures, or patients who have undergone transplantation, or bariatric or gastric bypass.
Intervention/ Intake	Studies that measure intake (oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio) with validated measures or use biomarker values to assess potassium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of potassium supplement with intervention/exposure adherence measure, use of a published food frequency questionnaire, and food diaries) will be eligible. Observational studies that report a weight change of +/– 3 percent or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies measuring potassium intake by reporting chemical analysis of diet without intervention/exposure adherence measures, composition of potassium supplement without intervention/exposure measure, or serum potassium will be excluded.
Comparators	Studies comparing groups with different documented potassium intake, serum potassium levels, or urinary potassium excretion will be eligible. Studies where differences in potassium intake or values are not reported independently of alteration of other nutrient levels will be excluded.
Outcomes	Studies reporting on type 2 diabetes mellitus, glucose intolerance, or insulin sensitivity will be eligible for inclusion. Studies reporting on type 1 diabetes and gestational diabetes will be excluded.
Timing	Studies with a duration of more than 4 weeks will be eligible for inclusion.
Setting	Studies in outpatient settings will be eligible.
Study Design	Prospective cohort studies (including case-cohort studies).

NOTE: HIV = human immunodeficiency virus.
SOURCE: Criteria adapted from Newberry et al., 2018.

TABLE E-10 Randomized Controlled Trial Assessing the Effect of Sodium Intake on Bone Health Outcomes

Reference (*Location*)	Participants	Intervention(s)	Control	Duration	Results
Parallel Arm Randomized Controlled Trial					
Ilich et al., 2010 (*United States*)	97 healthy, postmenopausal, Caucasian women	Dietary advice to lower sodium intake to 1,500 mg/d; received ~630 mg/d calcium and ~400 IU/d vitamin D supplementation	Received dietary advice to maintain sodium intake to 3,000 mg/d; received ~630 mg/d calcium and ~400 IU/d vitamin D supplementation	3 years	No statistical difference observed in mean BMD of the forearm (p = .417), hip (p = .411), or spine (p = .695) between groups at baseline and 3 years.

NOTE: BMD = bone mineral density; IU/d = International Units per day; mg/d = milligrams per day.

TABLE E-11 Randomized Controlled Trials Assessing the Effect of Potassium Intake on Bone Health Outcomes

Reference (*Location*)	Participants	Intervention(s)	Control or Comparison Group	Duration	Results
Gregory et al., 2015 (*United States*)	83 postmenopausal women, with osteopenia[a]	Received 40 mmol/d K citrate plus daily supplementation with Citracal (630 mg/d calcium citrate and 400 IU/d vitamin D3)	Received daily placebo capsules and supplementation with Citracal (630 mg/d calcium citrate and 400 IU/d vitamin D3)	12 months	• Mean BMD remained stable over the 12-month study period in subjects treated with K citrate and control.
Jehle et al., 2013 (*Switzerland*)	169 adults, 65–80 years of age, without current treatment for low bone mineral density[b]	Received 60 mmol/d K citrate plus daily supplementation with calcium (500 mg/d) and vitamin D3 (400 IU/d)	Received placebo tablets plus daily supplementation with calcium (500 mg/d) and vitamin D3 (400 IU/d)	24 months	• aBMD increased at all skeletal sites in the K citrate group with no trend to plateau. • After 24 months, aBMD at L2–L4 increased by 1.7% ([95% CI: 1.0, 2.3], $p < .001$), net of placebo. Corresponding increases were 1.6% [95% CI: 1.1, 2.2] at femoral neck, 1.0% [95% CI: 0.5, 1.5] at total hip, and 1.3% [95% CI: 0.8, 1.7] in total body.
Macdonald et al., 2008 (*United Kingdom*)	203 postmenopausal women, 49–54 years of age	Three treatment groups: High-dose group received 55.5 mmol/d K citrate Low-dose group received 18.5 mmol/d K citrate	Received placebo tablets	24 months	• Mean BMD loss at the spine in the placebo group was 1.8 ± 3.9% over 2 years.[c] • Apparently greater BMD loss (2.1 ± 3.2%)[c] in the treatment groups was not significant ($p = .88$). • For mean total hip, BMD loss was less in the placebo group (1.3 ± 2.3%)[c] than in the low-dose K citrate group (2.2 ± 2.3%),[c] but the difference was not significant ($p = .14$).

Reference (*Location*)	Participants	Intervention(s)	Control or Comparison Group	Duration	Results
		Diet group received additional 300 g/d fruit and vegetables			

NOTE: aBMD = areal bone mineral density; BMD = bone mineral density; CI = confidence interval; g/d = grams per day; IU/d = International Units per day; K citrate = potassium citrate; mg/d = milligram per day; mmol/d = millimoles per day.

[a]Defined as a T-score at the lumbar spine or hip between –1.0 and –2.5.

[b]Defined as a T-score at lumbar spine, L2 through L4, of less than –2.5.

[c]Values presented as mean ± standard deviation.

TABLE E-12 Prospective Cohort and Case-Cohort Studies Assessing the Association Between Potassium Intake and Bone Health Outcomes

Reference (*Location*)	Participants[a]	Length of Follow-Up	Intake Assessment	Results
Hayhoe et al., 2015 (*United Kingdom*)	4,713 adults, 40–79 years of age	13.4 years[b]	7-day food diary	• Positive trend in calcaneal BUA for women across increasing quintiles of potassium intake, not apparent in men; individual statistics did not remain significant with adjustment for multiple comparisons. • No statistically significant associations between potassium intake and risk of fracture.
Zhu et al., 2009 (*Australia*)	266 healthy women, 70–80 years of age[c]	5 years[d]	One 24-hour urine assessment, conducted at baseline	• Women in highest quartile of potassium excretion had a higher total hip BMD at year 1 (5%) and year 5 (6%), and significantly higher total body BMD (4%) and distal tibia total (7%) and trabecular vBMD (11%) at 5 years than those in the lowest quartile.[e]
Nieves et al., 2010 (*United States*)	125 healthy women, 18–26 years of age[f]	24 months[g]	Modified 97-item FFQ administered at baseline and each follow-up visit	• There was a positive relationship between increased intake of potassium and significant increases in hip and whole body BMD.[h]
Macdonald et al., 2004 (*United Kingdom*)	891 pre-, peri-, and postmenopausal healthy women, 50–59 years of age at follow-up	5–7 years	FFQ, validated, conducted at baseline and follow-up	• In premenopausal women only, significant positive association between BMD at femoral neck and energy-adjusted potassium intake.[i] • In analysis of all women, no evidence of association between nutrient intake and BMD.

NOTE: BMD = bone mineral density; BUA = broadband ultrasound attenuation; FFQ = food frequency questionnaire; vBMD = volumetric bone mineral density.

[a]Total number of participants included in the analysis.

[b]Mean length of follow-up.

[c]Mean age at baseline was 75.0 ± 2.7.

[d]This is an intervention study; however, it is reported with cohort studies because the effect of potassium was not the basis of the intervention.

[e]Analyses adjusted for baseline values of age, height, weight, calcium treatment group, energy intake, calcium intake, protein intake, and physical activity levels.

[f]Mean age at baseline was 22.1 ± 2.6 years.

[g]This is an intervention study; however, it is reported with cohort studies because the effect of potassium was not the basis of the intervention.

[h]Analyses adjusted for age, clinical site, annual menses, and treatment assignment.

[i]Analyses adjusted for age, height, weight, annual percentage change in weight, physical activity level, smoking status, socioeconomic status, and baseline femoral neck BMD.

TABLE E-13 Randomized Controlled Trials Assessing the Effect of Sodium Intake on Type 2 Diabetes, Glucose, and Insulin Outcomes

Reference (*Location*)	Participants	Intervention(s)	Control	Duration	Results
Parallel Study Design					
Meland and Aamland, 2009 (*Norway*)	46 men and women, aged 20–75 years with uncontrolled hypertension	Received NaCl capsules to equal 50 mmol/d and counseled to follow a moderate reduced-salt diet	Received placebo capsules and counseled to follow a moderate reduced-salt diet	8 weeks	No significant differences in changes of fasting and postload glucose and insulin C-peptide levels between low-salt (placebo) and high-salt (intervention) groups.
Crossover Study Design					
Suckling et al., 2016 (*United Kingdom*)	46 men and women, aged 30–80 years with type 2 diabetes or impaired glucose tolerance	Received salt tablets to equal 90 mmol/d and instructed to follow reduced salt diet of approximately 90 mmol/d	Received placebo tablets and instructed to follow reduced salt diet of approximately 90 mmol/d	12 weeks	No significant change in fasting glucose or insulin concentration observed from intervention to placebo period.

NOTE: mmol/d = millimoles per day; NaCl = sodium chloride.

TABLE E-14 Prospective Cohort Study Assessing the Association Between Sodium Intake and Type 2 Diabetes, Glucose, and Insulin Outcomes

Reference (*Location*)	Participants[a]	Length of Follow-Up	Potassium Assessment	Results
Hu et al., 2005 (*Finland*)	1,935 men and women aged 35–64 years	18.1 years	Measured by one 24-hour urine sample at baseline	Multiple-adjusted hazard ratio for diabetes for the highest versus combined lower quartiles of 24-hour urinary sodium excretion was 2.05 [95% CI: 1.43, 2.96].[b]

NOTE: CI = confidence interval.

[a]Total number of participants included in the analysis.

[b]Analyses adjusted for age, sex, study year, body mass index, physical activity, systolic blood pressure, antihypertensive drug treatment, education, smoking and coffee, alcohol, fruit, vegetable, sausage, bread, and saturated fat consumption.

TABLE E-15 Randomized Controlled Trial Assessing the Effect of Potassium Intake Supplements on Type 2 Diabetes, Glucose, and Insulin Outcomes

Reference (*Location*)	Participants	Intervention(s)	Control	Duration	Results
Chatterjee et al., 2017 (*United States*)	27 African American men and women with prediabetes	Received 40 mmol/d KCl	Received daily placebo capsules	12 weeks	• KCl supplement reduced fasting glucose by 7.2 mg/dL (p = .03). • No significant differences in 2-hour postload glucose, insulin, or C-peptide. • No significant difference in insulin sensitivity indexes or hemoglobin A1c.

NOTE: KCl = potassium chloride; mg/d = milligrams per day; mmol/d = millimoles per day.

TABLE E-16 Prospective Cohort Study Assessing the Association Between Potassium Intake and Type 2 Diabetes, Glucose, and Insulin Outcomes

Reference (*Location*)	Participants[a]	Length of Follow-Up	Potassium Assessment	Results
Hu et al., 2005 (*Finland*)	1,935 men and women aged 35–64 years	18.1 years	Measured by one 24-hour urine sample at baseline	Potassium excretion was not associated with the risk of type 2 diabetes.
Chatterjee et al., 2010 (*United States*)	12,209 men and women, aged 45–65 at baseline	9 years	Measured by FFQ at baseline	Dietary potassium intake was not significantly associated with risk of incident diabetes in multivariable models.[b]
Chatterjee et al., 2012 (*United States*)	4,754 men and women, aged 18–30 years	20 years	Dietary potassium measured by FFQ at baseline, year 7, and year 20; 3 consecutive 24-hour urines collected in subsample of 1,066 participants at year 5	In multivariable models, participants in the lowest urinary potassium quintile were more than twice as likely to develop diabetes as their counterparts in the highest quintile (HR = 2.45 [95% CI: 1.08, 5.59]).[c]

NOTE: CI = confidence interval; FFQ = food frequency questionnaire; HR = hazard ratio.

[a]Total number of participants included in the analysis.

[b]Analyses adjusted for age, sex, race, clinical center, body mass index, waist circumference, serum magnesium, calcium, and creatinine levels, physical activity, parental history of diabetes, presence of hypertension, systolic blood pressure, fasting glucose and insulin levels, income, and use of β-blockers, diuretics, and angiotensin-converting enzyme inhibitors.

[c]Analyses adjusted for age, sex, race, body mass index, family history of diabetes, systolic blood pressure, physical activity level, education level, and the average of three 24-hour urinary creatinine measures.

Assessing the Risk of Bias of Included Studies

To align with the *AHRQ Systematic Review* (Newberry et al., 2018), the committee assessed the risk of bias of each of the 14 references identified, using the same criteria used in the *AHRQ Systematic Review* (for criteria, see Appendix C, Annex C-1) (see Tables E-17 through E-20). The assessment was conducted by one reviewer, in line with principles of a rapid review.

TABLE E-17 Risk-of-Bias Assessment of Sodium Trials

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data (Attrition Bias)	Selective Reporting of Outcome Data	Adherence	Unequal Distribution Among Groups of Potential Confounders at Baseline
Meland and Aamland, 2009	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Suckling et al., 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk

NOTE: BPUK = Blood Pressure U.K.; CASH = Consensus Action on Salt and Health; COI = conflict of interest; N/A = not applicable; WASH = World Action on Salt and Health.

[a]Neither author received funding from any of the organizations.

Demonstration That Outcome of Interest Was Not Present at Start of Study for All Participants	Valid Method of Exposure Assessment	Valid Method of Outcome Assessment	Valid Statistical Assessment (for Crossover Trials)	Funding Source (Sponsor)	Other: Funding Source (Author COI)	Funding Source (Private Source)	Overall Risk of Bias
Low risk	Unclear risk	Low risk	N/A	Public and private	"The authors have no competing interests to declare."	N/A	Low
Low risk	Low risk	Low risk	Low risk	Public	F.J. He is a member of the CASH and WASH; G.A. MacGregor is Chairman of BPUK, CASH, WASH, and Action on Sugar[a]	N/A	Low

TABLE E-18 Risk-of-Bias Assessment for Sodium Observational Studies

Author, Year	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Sodium Exposure	Outcome of Interest Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis
Hu et al., 2005	Moderate risk	Low risk	High risk	Low risk	Low risk
Illich et al., 2010	Moderate risk	Low risk	Low risk	Low risk	Low risk

NOTE: COI = conflict of interest; N/A = not applicable; NR = not reported.

Assessment of Outcome	Adequacy of Follow-Up	Funding Source (Sponsor)	Funding Source (Author COI)	Funding Source (Private Source)	Overall Risk of Bias
Low risk	High risk	Public	NR	N/A	High
Low risk	High risk	Public	"The authors declare that they have no conflict of interest."	"Bayer HealthCare LLC, Morristown, NJ, USA"	Moderate

TABLE E-19 Risk-of-Bias Assessment of Potassium Trials

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data (Attrition Bias)	Selective Reporting of Outcome Data	Adherence	Unequal Distribution Among Groups of Potential Confounders at Baseline
Chatterjee et al., 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gregory et al., 2015	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Moderate risk
Jehle et al., 2013	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Macdonald et al., 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

NOTE: COI = conflict of interest; N/A = not applicable; NR = not reported.
[a]Included statement of no involvement of the study.
[b]SLN and HMM correspond to initials of the publication authors.

Demonstration That Outcome of Interest Was Not Present at Start of Study for All Participants	Valid Method of Exposure Assessment	Valid Method of Outcome Assessment	Valid Statistical Assessment (for Crossover Trials)	Funding Source (Sponsor)	Other: Funding Source (Author COI)	Funding Source (Private Source)	Overall Risk of Bias
Low risk	Low risk	Low risk	N/A	Public	NR	N/A	Low
Low risk	Unclear	Low risk	N/A	Public and private incorporation[a]	NR	N/A	Low
Low risk	Moderate risk	Low risk	N/A	Public and private incorporation[a]	"The authors have no conflicts of interest to report."	Yes	Low
Low risk	Low risk	Low risk	N/A	Public	SLN principal grant holder on a grant from GlaxoSmithKline to examine one of the company's products; HMM involved in interpreting the results of that study; none of the other authors had personal or financial COI[b]	N/A	Low

TABLE E-20 Risk-of-Bias Assessment for Potassium Observational Studies

Author, Year	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Potassium Exposure	Outcome of Interest Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis
Chatterjee et al., 2010	Moderate risk	Low risk	High risk	Low risk	Low risk
Chatterjee et al., 2012	Low risk	Low risk	Moderate risk	Low risk	Low risk
Hayhoe, 2015	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Hu et al., 2005	Moderate risk	Low risk	High risk	Low risk	Low risk
Macdonald et al., 2004	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Nieves et al., 2010	Low risk	Low risk	Moderate risk	Low risk	Moderate risk
Zhu et al., 2009	Low risk	Low risk	High risk	Low risk	Moderate risk

NOTE: COI = conflict of interest; N/A = not applicable.
[a]Included statement of no involvement of the study.

Assessment of Outcome	Adequacy of Follow-Up	Funding Source (Sponsor)	Funding Source (Author COI)	Funding Source (Private Source)	Overall Risk of Bias
Low risk	Low risk	Public	None reported financial disclosure	N/A	High
Low risk	Low risk	Public	"The authors declare that there is no duality of interest associated with this manuscript."	N/A	Moderate
Low risk	Unclear	Public	"None of the authors had a financial or personal conflict of interest relevant to this research at the time of writing."	N/A	Moderate
Low risk	High risk	Public	NR	N/A	High
Low risk	Low risk	Public	"None of the authors had financial or commercial interest in any company or organization sponsoring the research."	N/A	Moderate
Low risk	Low risk	Public and private incorporation[a]	All authors claimed: nothing to disclose	No	Moderate
Low risk	High risk	Public	"None reported conflict of interest."	N/A	High

UPDATE OF THE *AHRQ SYSTEMATIC REVIEW*

The *AHRQ Systematic Review* included evidence that was available as of March 2017. The *AHRQ Systematic Review* investigators extended the search to identify eligible publications published between March and December 2017, using the same literature search strategy and screening process that was used to identify the original collection of studies. The list of eligible publications was not included in the *AHRQ Systematic Review*, but it was provided to the committee (personal communication, S. Newberry, RAND Corporation, May 30, 2018). The committee further extended this search, based on the PubMed search strategy presented in the *AHRQ Systematic Review*, and it identified studies that met the inclusion criteria, published between December 2017 and June 2018. One additional study was provided to the committee via the public comment mechanism. Across these sources, 20 articles were identified as meeting the *AHRQ Systematic Review* inclusion criteria. Table E-21 provides a brief summary of the committee's assessment of the applicability of each study to its evidence review.

TABLE E-21 References Identified as Meeting the *AHRQ Systematic Review* Inclusion Criteria, Published Between March 2017 and June 2018

Reference	Notes About the Study
Lelli et al., 2018	• High-risk-of-bias article based on AHRQ quality assessment criteria • High-risk-of-bias observational studies did not inform the committee's decision making for the sodium CDRR for adults
Lelong et al., 2017	• High-risk-of-bias article based on AHRQ quality assessment criteria • High-risk-of-bias observational studies did not inform the committee's decision making for the sodium CDRR for adults • High-risk-of-bias observational studies did not inform the committee's decision making related to blood pressure or incident hypertension for potassium CDRR for adults
Mente et al., 2018	• High-risk-of-bias article based on AHRQ quality assessment criteria • High-risk-of-bias observational studies did not inform the committee's decision making for the sodium or potassium CDRR for adults
Mirmiran et al., 2018	• High-risk-of-bias article based on AHRQ quality assessment criteria • Used a food frequency questionnaire to assess dietary intake; evidence based on food frequency questionnaires was excluded from the sodium intake-related key questions, but was included in the potassium-related key questions
Pathak et al., 2017	• Study conducted in patients with chronic kidney disease • Given insufficient evidence on effect modification of kidney disease, study did not inform the sodium DRIs

TABLE E-21 Continued

Reference	Notes About the Study
Prentice et al., 2017	• High-risk-of-bias article based on AHRQ quality assessment criteria • Used a food frequency questionnaire to assess dietary intake; evidence based on food frequency questionnaires was excluded from the sodium intake-related key questions, but was included in the potassium-related key questions
Saran et al., 2017	• Study conducted in patients with stage 3–4 chronic kidney disease • Given insufficient evidence on effect modification of kidney disease, study did not inform the sodium DRIs
Saulnier et al., 2017	• Study conducted in individuals with type 2 diabetes • High-risk-of-bias article based on AHRQ quality assessment criteria • High-risk-of-bias observational studies did not inform the committee's decision making for the sodium CDRR for adults
Setayeshgar et al., 2017	• High-risk-of-bias article based on AHRQ quality assessment criteria • Study was part of a collection of evidence that informed the committee's rationale regarding extrapolation of the sodium CDRR to children
Tabara et al., 2017	• Study only reported on sodium-to-potassium ratio; independent relationship with sodium and potassium not reported
Torres et al., 2017	• Study conducted in patients with autosomal dominant polycystic kidney disease • Given insufficient evidence on effect modification of kidney disease, study did not inform the sodium DRIs
Zhao et al., 2017	• Study population was adults with suspected coronary heart disease, and therefore could not be used to estimate relationship with incident cardiovascular disease
Chen et al., 2016; Cheng et al., 2018; Juraschek et al., 2017; Murtaugh et al., 2018	• Primary analyses of trials already included in the *AHRQ Systematic Review*
Allaert, 2017; Hu et al., 2018; Janda et al., 2018; Yang et al., 2018	• Studies used salt substitutes; independent effects of sodium and potassium could not be determined • Studies did not inform the sodium or potassium DRIs

NOTE: AHRQ = Agency for Healthcare Research and Quality; CDRR = Chronic Disease Risk Reduction Intake; DRI = Dietary Reference Intake.

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Appendix F

Estimates of Potassium and Sodium Intakes from Breast Milk and Complementary Foods

In accordance with methodologies established and used in previous Dietary Reference Intake (DRI) reports, the committee reviewed evidence on breast milk composition and complementary food intake to estimate the potassium and sodium Adequate Intakes (AIs) for infants 0–6 and 7–12 months of age. As many of the studies and analyses were similar for potassium and sodium, this appendix is organized by category of intake (i.e., estimating contributions of breast milk and complementary food) rather than by nutrient.

ESTIMATING THE POTASSIUM AND SODIUM CONTENT OF BREAST MILK

The committee first reviewed the evidence on the concentration of potassium and sodium in breast milk. These estimates were then used to establish the AIs for infants 0–6 months of age and were used in conjunction with estimates of potassium and sodium intake from complementary foods (described later in this appendix) to establish the AIs for infants 7–12 months of age. The committee's process for estimating the potassium and sodium content of breast milk is described in the sections that follow.

Identifying Relevant Studies

The committee sought to identify studies that reported potassium and/or sodium concentrations in breast milk. Specifically, the committee focused on studies of mature breast milk from females with term infants conducted

in countries that have populations assumed to be similar to those in Canada and the United States. As breast milk composition has been evaluated and summarized by various groups and investigators, the committee elected to leverage these resources rather than conducting a de novo literature search. Accordingly, the committee identified relevant studies by reviewing citations in the *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (*2005 DRI Report*) (IOM, 2005), the European Food Safety Authority (EFSA) Dietary Reference Values (DRVs) for potassium (EFSA, 2016), the January 2018 draft of the EFSA DRVs for sodium (EFSA, 2018), and a recent review article on breast milk composition (Wu et al., 2018).

Characteristics of the identified studies meeting the committee's inclusion criteria are summarized in Tables F-1 and F-2 for potassium and sodium, respectively. Many of the identified studies provided repeated measurements of the concentrations over time among a cohort of women assessed at several time points (identified as longitudinal studies) or among different cohorts of women assessed at different time points (identified as cross-sectional studies). The concentration at each specific time point at which an assessment was made in each study was considered.

TABLE F-1 Mean Potassium Concentration in Mature Breast Milk from Women with Term Infants[a]

Reference (Country)	Methodology	*N*[b]	Breastfeeding Status	Stage of Lactation, Duration Postpartum (*N*)	Mean Potassium Concentration, mg/L	
					0–6 Months	7–12 Months
Longitudinal Studies						
Gross et al., 1980 (United States)	Milk expressed manually or by mechanical emptying; analyzed by atomic emission spectrophotometry	11	Not indicated	28 days (11)	587 (27)*	
Picciano et al., 1981 (United States)	Milk expressed manually or by hand pump; atomic absorption spectrophotometry	26	Exclusive[c]	1 month (26) 2 moths (26) 3 moths (26)	466 (93) 427 (87) 407 (80)	

TABLE F-1 Continued

Reference (Country)	Methodology	N^b	Breastfeeding Status	Stage of Lactation, Duration Postpartum (*N*)	Mean Potassium Concentration, mg/L	
					0–6 Months	7–12 Months
Lemons et al., 1982 (United States)	Milk expressed using an electric pump; flame emission spectrophotometry	7	Not indicated	21 days (7) 28 days (7)	545 (21)* 508 (20)*	
Dewey and Lonnerdal, 1983 (United States)	Manual milk expression at second feeding; flame atomic absorption spectrophotometer, emission mode	20	19 exclusive[d] 19 exclusive 16 exclusive 13 exclusive 11 exclusive 11 exclusive	1 month (13) 2 months (16) 3 moths (18) 4 months (16) 5 months (14) 6 months (15)	527 (70) 477 (79) 470 (81) 464 (89) 460 (85) 430 (63)	
Dewey et al., 1984 (United States)	Milk expressed manually or using a manual pump at second feeding; flame atomic absorption spectrophotometer using emission mode	15	Mothers were producing ≥ 500 mL/d	4–6 months (15 women, 38 samples)	443 (71)	
				7–11 months (8 women, 26 samples)		389 (41)
Morriss et al., 1986 (United States)	Milk expressed using a breast pump; flame photometry	52	Not indicated	14–21 days (10 samples)	669 (23)*	
				120–180 days (10 samples)	500 (19)*	
Allen et al., 1991 (United States)	Milk expressed manually; ion-selective electrodes verified by flame emission photometry	13	Exclusive	21 days (13) 45 days (13) 90 days (13) 180 days (10)	633 (18)* 590 (16)* 543 (16)* 485 (16)*	
Holt, 1993 (United Kingdom)	Manual expression; flame photometry	4	Not indicated	5–16 weeks (28 samples)	594 (86)	
Motil et al., 1997 (United States)	Milk expressed by manual or mechanical pumping; atomic absorption spectroscopy	11[e]	Exclusive Exclusive Partial Partial	6 weeks (11) 12 weeks (11) 18 weeks (11) 24 weeks (11)	545 (43) 524 (69) 494 (73) 498 (67)	

continued

TABLE F-1 Continued

Reference (Country)	Methodology	N^b	Breastfeeding Status	Stage of Lactation, Duration Postpartum (*N*)	Mean Potassium Concentration, mg/L	
					0–6 Months	7–12 Months
Wack et al., 1997 (United States)[f]	Manual expression or breast pump; inductively coupled plasma-atomic emission spectrometry	30	Not indicated	14–60 days (27)	585 (124)	
				61–120 days (20)	490 (85)	
				121–180 days (25)	485 (66)	
				181–240 days (29)		473 (63)
				241–300 days (17)		470 (72)
				301–360 days (14)		445 (53)
Bauer and Gerss, 2011 (Germany)	Milk expressed using an electric pump; absorption spectrometer and colorimetric assay	10	Not indicated	0–8 weeks (10)	450[g] (74)	
Perrin et al., 2017 (United States)	Spectroscopy	16	Not indicated	11 months (16) 12 months (16)		370 (51) 380 (69)
Cross-Sectional Studies						
Keenan et al., 1982 (United States)	Milk expressed using an electric pump; flame photometry	28	Not indicated	3.5–6 weeks (14)	594 (70)	
				8.5–18 weeks (14)	540 (51)	
				20–32 weeks (12)		520 (43)
Fly et al., 1998 (United States)	Milk expressed using an electric breast pump; inductively coupled plasma atomic emission spectroscopy	14	Not indicated	2–8 months At rest (14) After exercise (14)	 461 (24)* 447 (16)*	

TABLE F-1 Continued

Reference (Country)	Methodology	N[b]	Breastfeeding Status	Stage of Lactation, Duration Postpartum (N)	Mean Potassium Concentration, mg/L	
					0–6 Months	7–12 Months
Bjorklund et al., 2012 (Sweden)	Manual breast pump and/or a passive breast milk sampler; inductively coupled plasma mass spectrometry	60	Not indicated	2–3 weeks (60)	633[b] (40)	
Parr et al., 1991[i] (Hungary)	Milk expressed using a breast pump; atomic absorption spectrophotometry	71†	Partial	3 months (71†)	554‡ (9)	
Parr et al., 1991[i] (Sweden)	Milk expressed using a breast pump; atomic absorption spectrophotometry	29†	Partial	3 months (29†)	548‡ (19)	

NOTES: Breast milk potassium concentrations are presented as mg/L. To convert the mg/L value to mmol/L, divide the concentration by 39.1. Unless otherwise noted, concentrations are presented as mean (standard deviation). * = standard error; † = number of observations; ‡ = median; cross-sectional = different women at each time point; longitudinal = same women at each time point; mg/L = milligrams per liter.

[a]Mature human milk is defined as ≥ 21 days postpartum. Only data on milk for full-term (> 37 weeks) infants are included.

[b]Number of women in the sample.

[c]All infants were exclusively breastfed, except for one infant at 2 and 3 months postpartum and one other infant at 3 months postpartum.

[d]Exclusive breastfeeding was defined as ≤ 50 kcal from other sources.

[e]Values are for adults. Publication also has values for adolescents 16.5 ± 0.6 years of age, but they are not presented here.

[f]There is a discrepancy in this study about the time period of milk collection. The text states that milk samples were obtained starting at 2 weeks postpartum; however, their data table gives a time period of 0–60 days postpartum.

[g]Values are the average of the first 8 weeks postpartum.

[h]Based on collection of milk from each mother during 7 days of sampling.

[i]Values for Guatemala, Nigeria, the Philippines, and Zaire were also presented in the publication, but they are not presented here.

TABLE F-2 Mean Sodium Concentration in Mature Breast Milk from Women with Term Infants[a]

Reference (Country)	Methodology	N[b]	Breastfeeding Status	Stage of Lactation, Duration Postpartum (N)	Mean Sodium Concentration, mg/L	
					0–6 Months	7–12 Months
Longitudinal Studies						
Gross et al., 1980 (United States)	Milk expressed manually or by mechanical emptying; atomic emission spectrophotometry	11	Not indicated	28 days (11)	195 (41)*	
Picciano et al., 1981 (United States)	Milk expressed manually or by hand pump; atomic absorption spectrophotometry	26	Exclusive[c]	1 month (26)	151 (55)	
				2 month (26)	121 (50)	
				3 month (26)	126 (47)	
Lemons et al., 1982 (United States)	Milk expressed using an electric pump; flame emission spectrophotometry	7	Not indicated	21 days (7)	157 (23)*	
				28 days (7)	162 (22)*	
Dewey and Lonnerdal, 1983 (United States)	Manual milk expression at second feeding; flame atomic absorption spectrophotometer using emission mode	20	19 exclusive[d]	1 month (13)	227 (152)	
			19 exclusive	2 months (16)	264 (223)	
			16 exclusive	3 months (18)	184 (139)	
			13 exclusive	4 months (16)	175 (138)	
			11 exclusive	5 months (14)	166 (130)	
			11 exclusive	6 months (15)	134 (78)	
Garza et al., 1983 (United States)	Milk expressed using a breast pump; atomic absorption spectrophotometry	6	Exclusive at 24 weeks; Partial at all other weeks	24 weeks (5)[e]	136 (16)*	
				26 weeks (6)		119 (7)*
				28 weeks (5)		123 (8)*
				30 weeks (6)		121 (6)*
				32 weeks (5)		168 (23)*
				34 weeks (6)		203 (19)*
				36 weeks (5)		297 (57)*

TABLE F-2 Continued

Reference (Country)	Methodology	N^b	Breastfeeding Status	Stage of Lactation, Duration Postpartum (*N*)	Mean Sodium Concentration, mg/L	
					0–6 Months	7–12 Months
Butte et al., 1984 (United States)	Milk expressed using a breast pump; atomic absorption spectrometry	13	The majority were exclusively breastfed	4 weeks (13)	184 (54)	
				6 weeks (13)	173 (65)	
				8 weeks (13)	153 (47)	
				10 weeks (13)	150 (49)	
				12 weeks (13)	130 (41)	
Dewey et al., 1984 (United States)	Milk expressed manually or using a manual pump at second feeding; flame atomic absorption spectrophotometer using emission mode	15	Mothers were producing ≥ 500 mL/d	4–6 months (15 women, 36 samples)	113 (69)	
				7–11 months (8 women, 26 samples)		84 (42)
Morriss et al., 1986 (United States)	Milk expressed using a breast pump; flame photometry	52	Not indicated	14–21 days (10 samples)	168 (12)*	
				120–180 days (10 samples)	110 (23)*	
Allen et al., 1991 (United States)	Milk expressed manually; ion-selective electrodes verified by flame emission photometry	13	Exclusive	21 days (13)	212 (9)*	
				45 days (13)	165 (9)*	
				90 days (13)	145 (9)*	
				180 days (10)	138 (9)*	
Holt, 1993 (United Kingdom)	Manual expression; flame photometry	4	Not indicated	5–16 weeks (28 samples)	107 (29)	
Motil et al., 1997 (United States)	Milk expressed by manual or mechanical pumping; atomic absorptiometry	11[f]	Exclusive	6 weeks (11)	94 (27)	
			Exclusive	12 weeks (11)	71 (23)	
			Partial	18 weeks (11)	70 (16)	
			Partial	24 weeks (11)	75 (23)	

continued

TABLE F-2 Continued

Reference (Country)	Methodology	N^b	Breastfeeding Status	Stage of Lactation, Duration Postpartum (*N*)	Mean Sodium Concentration, mg/L	
					0–6 Months	7–12 Months
Wack et al., 1997 (United States)[g]	Manual expression or breast pump; inductively coupled plasma atomic emission spectrometry	30	Not indicated	14–60 days (27)	182 (83)	
				61–120 days (20)	129 (61)	
				121–180 days (25)	136 (76)	
				181–240 days (29)		139 (142)
				241–300 days (17)		124 (65)
				301–360 days (14)		122 (123)
Bauer and Gerss, 2011 (Germany)	Milk expressed using an electric pump; absorption spectrometer and colorimetric assay	10	Not indicated	0–8 weeks (10)	258[b] (48)	
Perrin et al., 2017 (United States)	Spectroscopy	19	Not indicated	11 months (16)		70 (19)
				12 months (16)		70 (24)
Cross-Sectional Studies						
Keenan et al., 1982 (United States)	Milk expressed using an electric pump; flame photometry	28	Not indicated	3.5–6 weeks (14)	182 (69)	
				8.5–18 weeks (14)	108 (46)	
				20–32 weeks (12)		124 (30)
Koo and Gupta, 1982 (Australia)	Manual milk expression; flame photometer	45	Not indicated	15–28 days (48 samples)	159 (5)*	
Fly et al., 1998 (United States)	Milk expressed using an electric breast pump; inductively coupled plasma atomic emission spectroscopy	14	Not indicated	2–8 months		
				At rest (14)	115 (11)*	
				After exercise (14)	109 (5)*	

TABLE F-2 Continued

Reference (Country)	Methodology	N^b	Breastfeeding Status	Stage of Lactation, Duration Postpartum (*N*)	Mean Sodium Concentration, mg/L	
					0–6 Months	7–12 Months
Bjorklund et al., 2012 (Sweden)	Manual breast pump and/or a passive breast milk sampler; inductively coupled plasma mass spectroscopy	60	Not indicated	2–3 weeks (60)	217[i] (77)	
Parr et al., 1991[j] (Hungary)	Milk expressed using a breast pump; atomic absorption spectrophotometry	71†	Partial	3 months (7†)	105‡ (6)	
Parr et al., 1991[j] (Sweden)	Milk expressed using a breast pump; atomic absorption spectrophotometry	29†	Partial	3 months (29†)	88‡ (17)	

NOTES: Breast milk sodium concentrations are presented as mg/L. To convert the mg/L value to mmol/L, divide the concentration by 23.0. Unless otherwise noted, concentrations are presented as mean (standard deviation). * = standard error; † = number of observations; ‡ = median; longitudinal = same women at each time point; cross-sectional = different women at each time point.

[a]Mature human milk is defined as ≥ 21 days postpartum. Only data on milk for full-term (> 37 weeks) infants are included.

[b]Number of women in the sample.

[c]All infants were exclusively breastfed, except for one infant at 2 and 3 months postpartum and one other infant at 3 months postpartum.

[d]Exclusive breastfeeding was defined as ≤ 50 kcal from other sources.

[e]Milk was collected before weaning began (24 weeks postpartum) and at 2 week intervals for 12 weeks.

[f]Values are for adults. Publication also has values for adolescents aged 16.5 ± 0.6 years, but they are not presented here.

[g]There is a discrepancy in this study about the time period of milk collection. The text states that milk samples were obtained starting at 2 weeks postpartum; however, their data table gives a time period of 0–60 days postpartum.

[h]Values are the average of the first 8 weeks postpartum.

[i]Based on collection of milk from each mother during 7 days of sampling.

[j]Values for Guatemala, Nigeria, the Philippines, and Zaire were also presented in the publication, but they are not presented here.

Synthesizing the Evidence Across Studies to Estimate Breast Milk Composition

The committee conducted meta-analyses to estimate potassium and sodium concentrations of breast milk. Because many of the studies measured the potassium and/or sodium breast milk concentrations at several time points across the two intervals of interest (0–6 months and 7–12 months), a meta-analysis of these measurements faced two obstacles that needed to be taken into consideration in order to make full use of the available data: (1) the correlation between observations at successive time points and (2) the trend in the measures over time.

In a setting in which not all the data are used, an exemplar for each study is taken, being the measure closest to the midpoint of the time interval of interest (3 months for the 0–6-month time interval; and 9 months for the 7–12-month interval). These midpoint meta-analyses are presented in Figures F-1 and F-2 for the mean potassium concentration in the time intervals of 0–6 months and 7–12 months, respectively. The rounded mean potassium concentration is 515 mg/L for the 0–6-month interval and 435 mg/L for the 7–12-month interval. For context, both the *2005 DRI Report* and EFSA approximated the potassium concentration of mature breast milk to be 500 mg/L (EFSA, 2016; IOM, 2005); the U.S. Department of Agriculture (USDA) National Nutrient Database for Standard Reference estimates potassium concentration of mature breast milk to be 523 mg/L (USDA/ARS, 2018). The mean sodium concentration in the time interval 0–6 months and 7–12 months are presented in Figures F-3 and F-4, respectively. The rounded mean sodium concentration is 140 mg/L for the 0–6-month interval and 110 mg/L for the 7–12-month interval. For context, the *2005 DRI Report* estimated the sodium concentrations of breast milk to be 160 and 130 mg/L for 0–6 and 7–12 months postpartum, respectively (IOM, 2005). The EFSA draft DRVs for sodium approximated the sodium concentration of mature breast milk to be 150 mg/L (EFSA, 2018). The USDA National Nutrient Database for Standard Reference provides an estimate of the sodium concentration of mature breast milk of 174 mg/L (USDA/ARS, 2018). The I^2 is large, indicating a high degree of heterogeneity of the results across the studies.[1] There are opinions that I^2 for a meta-analysis for the type of analysis considered here needs to be considered from a different perspective (Mills et al., 2015), that is, when the focus of the meta-analysis is not to combine the effect measures (for instance, when two interventions are compared), but rather to combine a characteristic of a population of interest, such as the prevalence of an event or, as in this case, the mean of a concentration.

[1]The I^2 statistic is a test of heterogeneity.

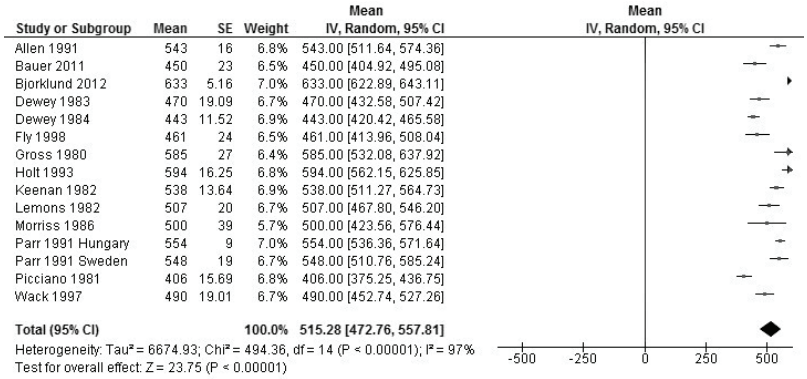

FIGURE F-1 Mean potassium concentration (mg/L) in mature breast milk from women with term infants: 0–6 months.
NOTES: Breast milk potassium concentrations are presented as mg/L. To convert the mg/L value to mmol/L, divide the concentration by 39.1. CI = confidence interval; SE = standard error.

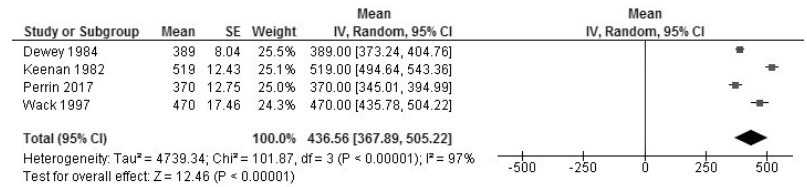

FIGURE F-2 Mean potassium concentration (mg/L) in mature breast milk from women with term infants: 7–12 months.
NOTES: Breast milk potassium concentrations are presented as mg/L. To convert the mg/L value to mmol/L, divide the concentration by 39.1. CI = confidence interval; SE = standard error.

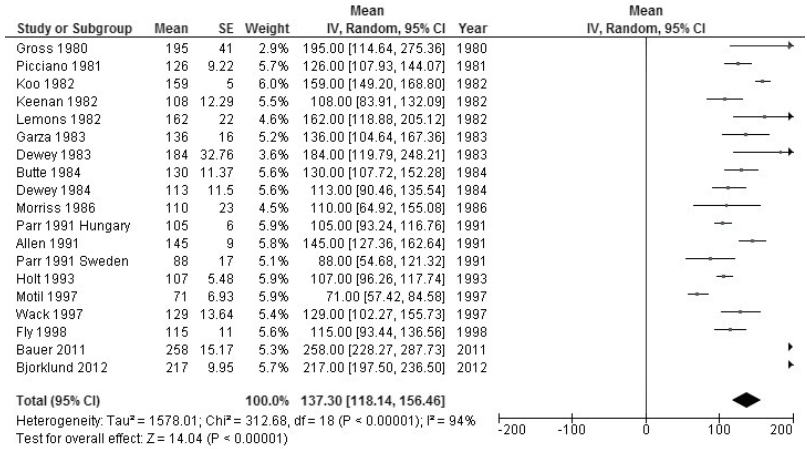

FIGURE F-3 Mean sodium concentration (mg/L) in mature breast milk from women with term infants: 0–6 months.
NOTES: Breast milk sodium concentrations are presented as mg/L. To convert the mg/L value to mmol/L, divide the concentration by 23.0. CI = confidence interval; SE = standard error.

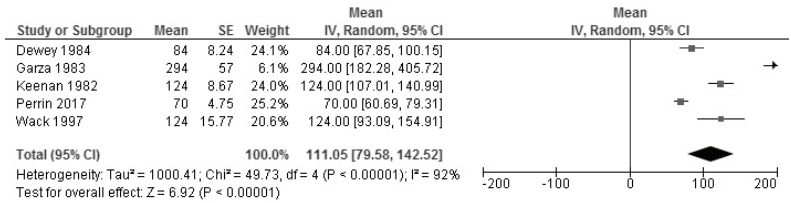

FIGURE F-4 Mean sodium concentration (mg/L) in mature human milk from women with term infants: 7–12 months.
NOTES: Breast milk sodium concentrations are presented as mg/L. To convert the mg/L value to mmol/L, divide the concentration by 23.0. CI = confidence interval; SE = standard error.

The committee conducted additional supporting meta-analyses in which the correlations and trends in the measures were not considered. First, in the study-specific analysis, a meta-analysis was conducted on the measures within a study in order to get a single measure for the study. These results for each study were then meta-analyzed to derive an overall concentration estimate. Four analysis scenarios were considered depending on the studies included (1) all studies, (2) only longitudinal studies, (3) only cross-sectional studies, and (4) all studies in which the individual participants were the unit of analysis.[2] These results are provided in Table F-3, and all yield concentration levels that were derived using the midpoint analysis. Second, in the time-specific analysis, a meta-analysis was conducted on the measures for a specific month across the studies in order to get a single measure for that month. The results for each month were then meta-analyzed to derive an overall concentration. Again, the four analysis scenarios described above were considered. These results are provided in Table F-3, and all yield concentration levels that were derived using the midpoint analysis. Methods have been identified that attempt to take the correlation between observations at successive time points and/or the trend in the measures over time (Peters and Mengersen, 2008). The Bayesian approach has been reviewed and is expected to yield similar results as those found for the midpoint analysis. In total, the additional meta-analyses support the concentrations of potassium and sodium in breast milk that the committee selected.

[2]Excludes two studies in which the breast milk samples were unit of analysis.

TABLE F-3 Potassium and Sodium Concentrations in Mature Breast Milk from Women with Term Infant, Estimated Using Various Meta-Analysis Scenarios

Meta-Analysis Scenario	Estimated Potassium Concentration, mg/L		Estimated Sodium Concentration, mg/L	
	0–6 Months	7–12 Months	0–6 Months	7–12 Months
Study Specific				
All studies included	526 [483, 568]	436 [375, 496]	145 [125, 166]	109 [79, 139]
Only longitudinal studies	511 [474, 547]	409 [355, 462]	149 [123, 174]	105 [72, 139]
Only cross-sectional studies	552 [470, 634]	519 [495, 543]	138 [101, 175]	124 [107, 141]
Only studies in which the participants were unit of analysis	518 [473, 564]	436 [375, 496]	148 [125, 171]	109 [79, 139]
Time Specific				
All studies included	504 [471, 536]	428 [365, 491]	139 [109, 169]	107 [74, 140]
Only longitudinal studies	489 [465, 514]	424 [366, 481]	144 [116, 172]	107 [74, 140]
Only cross-sectional	555 [479, 632]	519 [495, 543]	131 [104, 158]	124 [107, 141]
Only studies in which the participants were unit of analysis	497 [468, 526]	428 [365, 491]	140 [111, 169]	107 [74, 140]

NOTES: Values are presented as mean [95% confidence interval]. Breast milk concentrations are presented as mg/L. To convert the mg/L value to mmol/L, divide the concentration by 39.1 for potassium and 23.0 for sodium.

ESTIMATING POTASSIUM AND SODIUM INTAKE FROM COMPLEMENTARY FOODS

The committee reviewed evidence on potassium and sodium intake from complementary foods among infants 7–12 months of age and estimated intakes from three analyses that are briefly described below[3]:

- Tian et al. (2013) assessed potassium and sodium intake among infant and preschool-aged National Health and Nutrition Examination Survey (NHANES) 2003–2010 participants. The analysis provided estimates of usual total intake and estimates of intake from complementary foods among infants 7–11 months of age, stratified by breastfeeding status. Complementary foods were defined as any food or beverages other than breast milk, infant formula, or other milks (e.g., cow's milk). Breastfeeding status was classified based on whether the infant had reportedly consumed breast milk, as documented in the 24-hour dietary recalls. The committee considered the estimates, as provided in the publication.
- Maalouf et al. (2015) assessed the top sources of sodium intake among NHANES 2003–2010 participants from birth to 24 months of age. The analysis was not stratified by breastfeeding status. Breast milk, infant formula, and milk were among the top food categories contributing to sodium intake among infants 6–11.9 months of age. The proportion of total sodium intake that came from each of these food categories, along with the total sodium intake among this age group, were reported. The committee used this information to estimate the amount of sodium intake that came from complementary foods (i.e., sources other than breast milk, infant formula, and milk).
- The committee was provided with results from an analysis that assessed the sources of potassium and sodium intake among Feeding Infants and Toddlers Study (FITS) 2016 participants. The provided analysis did not stratify by breastfeeding status. The committee used the estimates of total potassium and sodium intake and subtracted the estimated contributions from breast milk, infant formula, and other milks to estimate the contributions from complementary foods.

[3]The brief summaries included herein only describe the portion of the analyses applicable to the committee's estimation of potassium and sodium intake from complementary foods for infants 7–12 months of age.

The estimates of potassium and sodium intakes from complementary foods are presented in Tables F-4 and F-5, respectively. Based on these analyses, the committee estimated that complementary foods contributed approximately 600 mg/d potassium and 300 mg/d sodium for infants 7–12 months of age. These estimates were used in combination with estimates of intake from breast milk to establish the AIs for potassium and sodium for infants 7–12 months of age.

TABLE F-4 Estimates of Potassium Intake from Complementary Foods, Infants 7–12 Months of Age

Data Source	Age Range, Months	Breastfeeding Status of Infants	Potassium Intake from Complementary Food, mg/day[a]
NHANES 2003–2010	7–11	Not BF	633 ± 21
	7–11	BF[b]	546 ± 34
FITS 2016	6–11.9	All	594 ± 27[c]

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake value by 39.1. BF = stratified analysis of infants who consumed breast milk; FITS = Feeding Infants and Toddlers Study; NHANES = National Health and Nutrition Examination Survey; Not BF = stratified analysis of infants who did not consume breast milk.

[a]Mean ± standard error.

[b]Consumption of at least some breast milk, as reported on the 24-hour dietary recall.

[c]Value from subtraction, approximate standard error.

SOURCES: FITS 2016 (unpublished); Tian et al., 2013.

TABLE F-5 Estimates of Sodium Intake from Complementary Foods, Infants 7–12 Months of Age

Data Source	Age Range, Months	Breastfeeding Status of Infants	Sodium Intake from Complementary Food, mg/day[a]
NHANES 2003–2010	7–11	Not BF	337 ± 27
	7–11	BF[b]	267 ± 36
	6–11.9	All	341 ± 31[c]
FITS 2016	6–11.9	All	294 ± 23[c]

NOTES: Intake values are presented in milligrams. To convert the milligram value to mmol, divide the intake value by 23.0. BF = stratified analysis of infants who consumed breast milk; FITS = Feeding Infants and Toddlers Study; NHANES = National Health and Nutrition Examination Survey; Not BF = stratified analysis of infants who did not consume breast milk.

[a]Mean ± standard error.

[b]Consumption of at least some breast milk.

[c]Value from subtraction, approximate standard error.

SOURCES: FITS 2016 (unpublished); Maalouf et al., 2015; Tian et al., 2013.

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Appendix G

Sources of Evidence for Potassium and Sodium Intake Distributions

This appendix provides an overview of the sources of evidence the committee used for potassium and sodium intake distributions.[1] These data were used to inform the Adequate Intake (AI) values for potassium (see Chapter 4), to inform the infant AI values for sodium (see Chapter 8), and to perform the third step of the Dietary Reference Intake (DRI) organizing framework (intake assessment; see Chapters 7 and 11). Three surveys provided estimates of usual intake of potassium and sodium from dietary sources: the National Health and Nutrition Examination Survey (NHANES), the Canadian Community Health Survey–Nutrition 2015 (CCHS Nutrition 2015), and the Feeding Infants and Toddlers Study (FITS) 2016 (Anater et al., 2018; CDC/NCHS, 2018; Statistics Canada, 2017). Estimates from NHANES 2009–2014 were computed for all DRI age, sex, and life-stage groups; however, the estimates excluded breastfed infants and children. The CCHS Nutrition 2015 did not include data on infants 0–12 months of age (Statistics Canada, 2017). Therefore, FITS 2016 data and additional published analyses of NHANES data were used to inform the intake estimates for infants (Ahluwalia et al., 2016b; Maalouf et al., 2015; Tian et al., 2013).

[1]Intake distribution tables are available by request from the National Academies of Sciences, Engineering, and Medicine's Public Access Records Office. For more information, email PARO@nas.edu.

NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

NHANES is a representative survey of the noninstitutional civilian population of the United States. NHANES has been a continuous survey since 1999, surveying approximately 5,000 people per year from 15 counties in the United States, and releasing data in 2-year intervals. Because it is continuous, the data may be combined across years. NHANES is the primary source of monitoring of dietary intakes for the United States. Since 2002, when the two national dietary surveys in the United States—the U.S. Department of Agriculture (USDA) Continuing Survey of Food Intakes by Individuals and NHANES—were integrated, two 24-hour dietary recall interviews have been collected on participants using the USDA Automated Multiple-Pass Method (Ahluwalia et al., 2016a; Moshfegh et al., 2008; Raper et al., 2004); the first years of public data release were in 2003–2004. The first 24-hour dietary recall is conducted in the Mobile Examination Center by an interviewer (CDC, 2014), and the second is collected by telephone within 3–10 days (CDC, 2013). Interviews are conducted with a proxy for participants younger than 6 years of age, are conducted with a proxy with the participant present for participants 6–8 years of age, are conducted with the participant with a proxy present for participants 9–11 years of age, and are conducted independently for participants 12 years of age and older. Each interview is coded as being reliable, as assessed by the interviewer. Dietary data are coded and linked to the Food and Nutritient Database for Dietary Studies (FNDDS) using the Survey Net system (Raper et al., 2004); data summarized as nutrient intake per day are publicly available.

Intake Distributions for All DRI Age, Sex, and Life-Stage Groups

Distributions of usual intake of potassium and sodium from NHANES 2009–2014 were provided to the committee (CDC, unpublished data).[2] The distributions included each of the DRI age, sex, and life-stage groups. The data were analyzed using the National Cancer Institute (NCI) method (Tooze et al., 2010). All individuals with a reliable 24-hour recall from the exam were included in the analytic sample, with the exception of infants and children who were breastfed and women whose pregnancy or lactation

[2]Intake distribution tables included estimates for all participants, estimates stratified by race/ethnicity, and estimates stratified by hypertension status. For the hypertension-stratified intake distributions, the blood pressure status of children and adolescents was categorized using the 2017 American Academy of Pediatrics guidelines (Flynn et al., 2017); the blood pressure status of adults was categorized using the 2017 American College of Cardiology and the American Heart Association guidelines (Whelton et al., 2018). Participants who reported that a doctor or other health professional had ever told them that they had a stroke or heart attack (myocardial infarction) were excluded from the hypertension-stratified intake distributions. This footnote was added since the prepublication release.

status was uncertain. Pregnant and lactating women were only included in analyses of those specific categories. Usual intake estimates of potassium and sodium from NHANES 2009–2014 exclude salt added at the table and potassium and sodium intakes from supplements or medications. This information is, however, queried in NHANES.

Additional NHANES Analyses Specific to Infants

Although the distributions of usual intake of potassium and sodium described above included the DRI age categories of infants 0–6 and 7–12 months of age, the estimates excluded NHANES participants who were breastfed. The committee, therefore, sought additional analyses of usual potassium and sodium intake that included NHANES participants 0–12 months of age who were breastfed. For infants 7–12 months of age, the committee also sought additional analyses that provided estimates of potassium and sodium intakes from complementary foods. Key methodologies used in the identified publications are briefly described below:

- Tian et al. (2013) used the Iowa State University method (Nusser et al., 1996) to estimate the distribution of usual intakes of potassium and sodium using NHANES 2003–2010 data. Estimates were presented for three age groups (7–11 months, 1–3 years, and 4–5 years) and, as applicable, stratified by breastfeeding status. Among infants consuming breast milk, the volume of breast milk was assumed to be 600 mL/d in those fed only breast milk, and 600 mL/d minus the volume of infant formula plus other milk for infants who were not exclusively breastfed. Potassium and sodium concentrations in breast milk were assumed to be 177 mg/L and 531 mg/L, respectively, from the USDA National Nutrient Database for Standard Reference 25 values for 1,000 mL of mature human milk (USDA/ARS, 2018). Estimates were also presented for usual potassium and sodium intake from complementary foods, which was defined in the publication as foods and beverages other than breast milk, infant formula, and other milks (e.g., cow's milk).
- Maalouf et al. (2015) examined food sources of sodium among NHANES 2003–2010 participants, birth to 24 months of age. The methodology for estimating sodium intake from breast milk was the same as in Tian et al. (2013). The publication provided estimated contribution of breast milk, infant formula, and cow's milk to the sodium intake of infants 6–11.9 months, along with estimated total sodium intake per day. Based on this information, the committee estimated the contribution of complementary foods to total sodium intake among older infants.

- Ahluwalia et al. (2016b) used the NCI method to estimate the distribution of usual intakes of a range of nutrients using NHANES 2009–2012 data. Estimates of the distribution of usual potassium and sodium intakes were presented for two age groups (6–11 months, 12–23 months) and included participants who consumed breast milk. The methodology for estimating intake from breast milk was the same as in Tian et al. (2013). This analysis did not present estimates for the contribution of complementary foods to usual potassium and sodium intake.

CANADIAN COMMUNITY HEALTH SURVEY–NUTRITION 2015

The CCHS Nutrition 2015 was the second nationally representative nutrition survey of the 21st century of the people of Canada, with the prior survey conducted in 2004 (Health Canada, 2017; Statistics Canada, 2017). The CCHS Nutrition is a focused survey collected occasionally with the CCHS Annual Component Survey, which samples 65,000 people each year. The CCHS Nutrition 2015 included a sample of all private-living individuals in the 10 Canadian provinces 1 year of age and older, with more than 20,000 respondents. Computer-assisted interviews conducted primarily in participants' homes were conducted during 2015 on all days of the week. Interviews for children 1–5 years of age were conducted with a parent or guardian, those 6–11 years of age included the participant and a parent or guardian, and those 12 years of age or older were interviewed independently. All participants completed an unannounced 24-hour recall using the USDA Automated Multiple-Pass Method at the first interview, and a random subset (approximately 7,600) were invited to complete a second interview by phone 3–10 days later on a different day of the week using a food model booklet. Nutrients were extracted from the Canadian Nutrient File Version 2015 (CNF, ref 16), a recipe file based on FNDDS 5.0 and 2011–2012 and modified for the Canadian food supply, and survey foods reported in the survey that were not in the CNF but had some nutrient information available.

Distributions of usual intake of potassium and sodium from CCHS Nutrition 2015 data were provided to the committee (Statistics Canada, unpublished).[3] The distributions included each of the DRI age, sex, and life-stage group for individuals 1 year of age and older. The data were analyzed using the NCI method. Because the NCI method allows for esti-

[3]Intake distribution tables included estimates for all participants and estimates stratified by hypertension status. For the hypertension-stratified intake distributions, blood pressure status was categorized based on the participant's response to the question, "Do you have high blood pressure?" Participants who reported that a health professional had ever told them they had heart disease were excluded from the hypertension-stratified intake distributions. This footnote was added since the prepublication release.

mates to be made for subpopulations, data from the previous CCHS 2004 (cycle 2.2) were combined with the CCHS Nutrition 2015 data to increase the sample size and improve model precision, but estimates from the 2015 cycle were estimated separately using covariates.[4] All individuals with a reliable 24-hour recall from the exam were initially included in the analytic sample. An outlier detection strategy was then applied, which identified observations where the differences between the first and second recall were large. The second recall was removed from the analysis, as it is generally considered less reliable than the first because of learning effects or the Hawthorne effect. Observations were removed if they were within ± 2, 2.5, or 3 standard deviations from the mean distribution of the difference of the first and second recall values, with the cutoff providing the greatest improvement in the within/between-person variance ratio chosen.[5,6] Pregnant and lactating women were included in analyses of those specific categories, but were excluded from other analyses. Usual intake estimates of potassium and sodium from CCHS Nutrition 2015 excluded salt added at the table and potassium and sodium intakes from supplements or medications. This information, however, is queried in CCHS Nutrition 2015 (Statistics Canada, 2017).

FEEDING INFANTS AND TODDLERS STUDY 2016

FITS 2016 is a cross-sectional study of the caregivers of infants and children younger than 4 years of age who live in the United States. Two previous FITS studies were conducted in 2002 and 2008 (Anater et al., 2018). Dietary intake data were collected using a 24-hour recall collected by telephone on all participants; 25 percent were invited to participate in a second 24-hour recall. The 24-hour recalls were collected using the Nutrition Data System for Research (NDSR) using certified dietary interviewers from the University of Minnesota Nutrition Coordinating Center. Participants were mailed a booklet to aid with the estimation of portion size. Although it is not a national probability sample, households were selected using stratified random sampling, and sampling weights that were calibrated to population totals for census divisions; the Special Supplemental Nutrition Program for

[4]Three records missing the first day of recall were removed from CCHS 2004.

[5]For potassium: 1- to 3-year-old ± 2.5 standard deviations was selected (n = 31 recalls removed); 31- to 50-year-old males ± 2 standard deviations was selected (n = 63 recalls removed); and 71-year-old and older males, ± 3 standard deviations was selected (n = 15 recalls removed).

[6]For sodium: 19- to 30-year-old males, ± 2 standard deviations was selected (n = 39 recalls removed); 19- to 30-year-old females, ± 3 standard deviations was selected (n = 9 recalls removed); and 31- to 50-year-old females, ± 3 standard deviations was selected (n = 20 recalls removed).

Women, Infants, and Children (WIC) participation status; sex of child; race/ethnicity of child; and educational attainment of the caregiver. Nutrient data were analyzed using NDSR, which made updates to baby foods and infant formulas prior to the start of the study, and brand-name products were updated using user recipes during data collection. A total of 3,235 interviews were completed for the first 24-hour recall, including 600 infants aged 0–5.9 months, 902 infants aged 6–11.9 months, and 1,733 infants aged 1–47.9 months; 799 participants completed the second 24-hour recall.

Direct breastfeeding volumes were assessed using the methods of FITS 2008 (Ponza et al., 2004). Specifically, exclusively breastfed infants younger than 6 months were assumed to consume 780 mL of breast milk per day; for those who had both breast milk and formula, the volume of formula was subtracted from 780 mL to estimate daily breast milk consumption. For infants 6–11.9 months, the same method was used using 600 mL of breast milk per day. Expressed breast milk was quantified.

An analysis of potassium and sodium intake by food source was conducted for the FITS 2016 data from the first 24-hour recall. From these estimates, intakes from complementary foods, which include all food and beverage intakes other than baby milk (breast milk, infant formula, or toddler drinks) or other milk sources (e.g., cow's milk), were estimated.

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Appendix H

Supplemental Risk Characterization Figures

In Chapters 7 and 11, the committee compared the potassium and sodium Dietary Reference Intake (DRI) values established in this report to reported usual intakes in U.S. and Canadian populations. Figures in this appendix, which supplement the information presented in those chapters, use data from the National Health and Nutrition Examination Survey (NHANES) 2009–2014 and the Canadian Community Health Survey–Nutrition 2015 (CCHS Nutrition 2015) (for additional details about these data sources, see Appendix G). The figures contained in this appendix are as follows:

- **FIGURE H-1** Median and 75th percentile of usual potassium intakes among U.S. and Canadian children and adolescents 1–18 years of age, by DRI age, sex, and life-stage group.
- **FIGURE H-2** Median and 75th percentile of usual potassium intakes among U.S. and Canadian adults 19 years of age and older, by DRI age, sex, and life-stage group.
- **FIGURE H-3** Fifth percentile and median usual sodium intakes among U.S. and Canadian children and adolescents 1–18 years of age, as compared to the sodium DRIs.
- **FIGURE H-4** Usual sodium intakes among U.S. and Canadian children and adolescents 1–18 years of age and older, as compared to the sodium DRIs and select intake levels.
- **FIGURE H-5** Fifth percentile and median usual sodium intakes among U.S. and Canadian adults 19 years of age and older, as compared to the sodium DRIs.

- **FIGURE H-6** Usual sodium intakes among U.S. and Canadian males 19 years of age and older, as compared to the sodium DRIs and select intake levels.
- **FIGURE H-7** Usual sodium intakes among U.S. and Canadian females 19 years of age and older, as compared to the sodium DRIs and select intake levels.

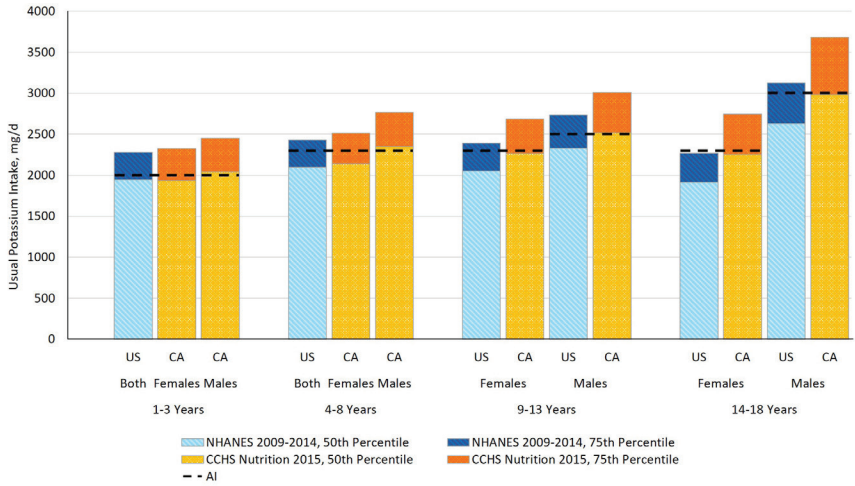

FIGURE H-1 Median and 75th percentile of usual potassium intakes among U.S. and Canadian children and adolescents 1–18 years of age, by DRI age, sex, and life-stage group.
NOTE: AI = Adequate Intake; CA = Canada; CCHS Nutrition 2015 = Canadian Community Health Survey–Nutrition 2015; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

FIGURE H-2 Median and 75th percentile of usual potassium intakes among U.S. and Canadian adults 19 years of age and older, by DRI age, sex, and life-stage group.

NOTE: AI = Adequate Intake; CCHS Nutrition 2015 = Canadian Community Health Survey–Nutrition 2015; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey.

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

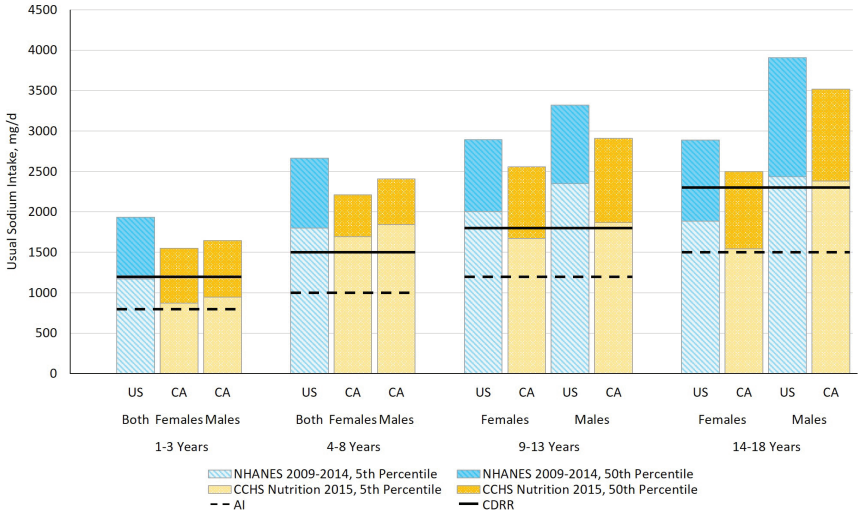

FIGURE H-3 Fifth percentile and median usual sodium intakes among U.S. and Canadian children and adolescents 1–18 years of age, as compared to the sodium DRIs.

NOTE: AI = Adequate Intake; CA = Canada; CCHS Nutrition 2015 = Canadian Community Health Survey–Nutrition 2015; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

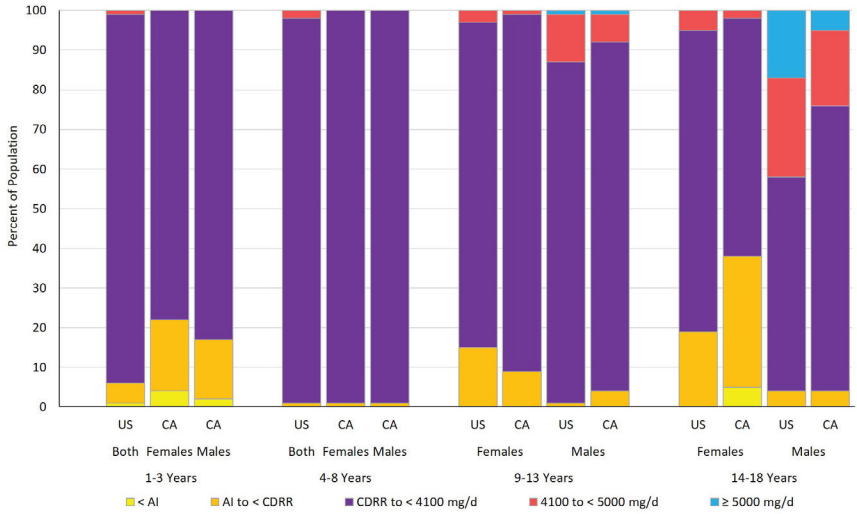

FIGURE H-4 Usual sodium intakes among U.S. and Canadian children and adolescents 1–18 years of age and older, as compared to the sodium DRIs and select intake levels.
NOTE: AI = Adequate Intake; CA = Canada; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; U.S. = United States.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

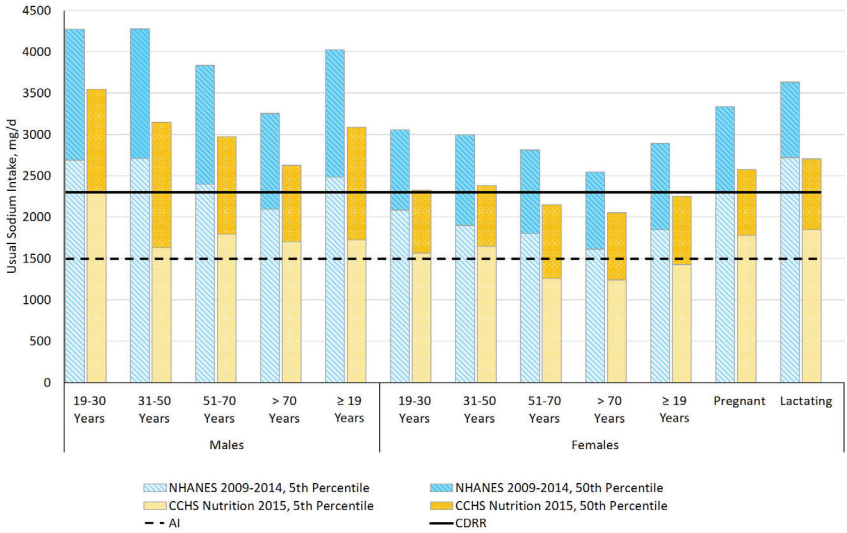

FIGURE H-5 Fifth percentile and median usual sodium intakes among U.S. and Canadian adults 19 years of age and older, as compared to the sodium DRIs.
NOTE: AI = Adequate Intake; CCHS Nutrition 2015 = Canadian Community Health Survey–Nutrition 2015; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; NHANES = National Health and Nutrition Examination Survey.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

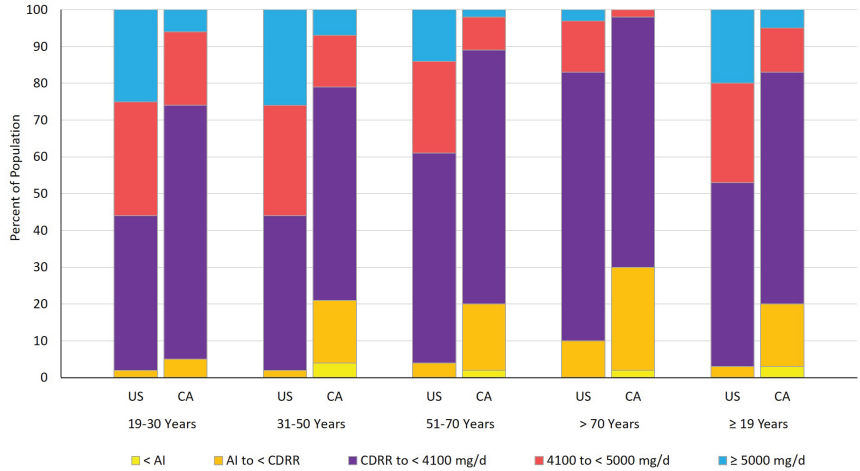

FIGURE H-6 Usual sodium intakes among U.S. and Canadian males 19 years of age and older, as compared to the sodium DRIs and select intake levels.
NOTE: AI = Adequate Intake; CA = Canada; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; U.S. = United States.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

FIGURE H-7 Usual sodium intakes among U.S. and Canadian females 19 years of age and older, as compared to the sodium DRIs and select intake levels.
NOTE: AI = Adequate Intake; CA = Canada; CDRR = Chronic Disease Risk Reduction Intake; mg/d = milligrams per day; U.S. = United States.
SOURCES: CCHS Nutrition 2015 (unpublished); NHANES 2009–2014 (unpublished).

Appendix I

Committee Member Biographical Sketches

Virginia A. Stallings, M.D. (*Chair*), is Professor of Pediatrics at the University of Pennsylvania Perelman School of Medicine, and Director of the Nutrition Center and the Jean A. Cortner Endowed Chair in Gastroenterology and Nutrition at Children's Hospital of Philadelphia. Her research interests include pediatric nutrition, evaluation of dietary intake and energy expenditure, and nutrition-related chronic disease. Dr. Stallings has served on several National Academies of Sciences, Engineering, and Medicine committees, including the Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy; Committee on Nutrition Standards for National School Lunch and Breakfast Programs; Committee on Nutrition Services for Medicare Beneficiaries; Committee on the Scientific Basis for Dietary Risk Eligibility Criteria for Women, Infants, and Children (WIC) Programs; Committee to Review the WIC Food Packages (2003); and the Committee to Review Child and Adult Care Food Program Meal Requirements. She is a former member (1997–2000) and co-Vice Chair (2000–2002) of the Food and Nutrition Board. Dr. Stallings is board certified in pediatrics and clinical nutrition. She received the Fomon Nutrition Award from the American Academy of Pediatrics. Dr. Stallings earned a B.S. in nutrition and foods from Auburn University, an M.S. in human nutrition and biochemistry from Cornell University, and an M.D. from the University of Alabama at Birmingham School of Medicine. She is a member of the National Academy of Medicine.

Cheryl A. M. Anderson, Ph.D., M.P.H., is Associate Professor and Interim Chair of the Department of Family Medicine and Public Health at the

University of California, San Diego. Dr. Anderson's research centers on nutrition and chronic disease prevention in underserved populations. Dr. Anderson has received National Institutes of Health funding to study the effects of dietary sodium and potassium intake on subclinical and clinical cardiovascular disease. Her research also focuses on identifying nutritional risk factors for progressive kidney disease and cardiovascular events in individuals with chronic kidney disease, and the conduct of clinical trials of nutritional factors on cardiovascular risk factors. Dr. Anderson is principal investigator of a study testing a unique biomarker, using carbon isotopic data, of intake of sweets. Dr. Anderson served on four National Academies of Sciences, Engineering, and Medicine committees: Committee on the Development of Guiding Principles for the Inclusion of Chronic Disease Endpoints in Future Dietary Reference Intakes, Committee on Consequences of Sodium Reduction in Populations, Committee on Strategies to Reduce Sodium Intake, and Committee on Use of Dietary Supplements by Military Personnel. She has a B.S. from Brown University, an M.P.H. from the University of North Carolina at Chapel Hill, and an M.S. in epidemiology and a Ph.D. in nutritional sciences from the University of Washington School of Public Health and Community Medicine.

Patsy M. Brannon, Ph.D., R.D., is currently Visiting Professor, and was Professor until her retirement in June 2018, in the Division of Nutritional Sciences at Cornell University, where she has also served as Dean of the College of Human Ecology. Prior to moving to Cornell University, Dr. Brannon was Chair of the Department of Nutrition and Food Science at the University of Maryland. She has also served as Visiting Professor at the Office of Dietary Supplements at the National Institutes of Health. Her research focus includes nutritional and metabolic regulation of gene expression, especially as relating to human development, the placenta, and exocrine pancreas. She was a member of the National Academies of Sciences, Engineering, and Medicine's Committee on Dietary Reference Intakes for Vitamin D and Calcium, and she is currently a member of the National Academies' Food and Nutrition Board and serves on the Workshop Planning Committee for Special Nutritional Requirements. Dr. Brannon is a member of a number of professional and scientific associations and has served on the Executive Board of the American Society for Nutrition. She has received numerous awards, including the Pew Faculty Scholar in Nutrition award as well as the Centennial Laureate award from Florida State University. Dr. Brannon received her Ph.D. from Cornell University in nutritional biochemistry.

Alicia Carriquiry, Ph.D., is Distinguished Professor of Liberal Arts and Sciences and Professor of Statistics at Iowa State University. She also holds the

President's Chair in Statistics and is Director of the Center for Statistics and Applications in Forensic Evidence, a National Institute of Standards and Technology Center of Excellence. Dr. Carriquiry is an elected member of the National Academy of Medicine and a Fellow of the American Association for the Advancement of Science. She is also an elected member of the International Statistical Institute, a Fellow of the American Statistical Association, a Fellow of the Institute of Mathematical Statistics, and a Fellow of the International Society for Bayesian Analysis. Currently, she serves in the Advisory Board for the Division of Behavioral and Social Sciences and Education and in the Report Review Committee of the National Academies. Dr. Carriquiry's research is in applications of statistics in human nutrition, bioinformatics, forensic sciences, and traffic safety. She participated in the National Academies of Sciences, Engineering, and Medicine's process to develop the Dietary Reference Intakes and maintains an active research and training program in the area of dietary assessment and planning. Dr. Carriquiry has published more than 120 peer-reviewed articles in journals in statistics, economics, nutrition, bioinformatics, mathematics, animal genetics, and several other areas, and has raised tens of millions of dollars in sponsored research funding. Dr. Carriquiry teaches courses at every level (undergraduate and graduate) in statistics at Iowa State University and has been invited to teach short courses in many organizations around the world as well as in the federal government. Dr. Carriquiry was born in Uruguay, where she graduated as an engineer in 1982. After coming to the United States, she received an M.Sc. in animal science from the University of Illinois (1985) and an M.Sc. in statistics (1986) and a Ph.D. in statistics and animal genetics (1989), both from Iowa State University.

Weihsueh A. Chiu, Ph.D., is Professor of Veterinary Integrative Biosciences in the College of Veterinary Medicine and Biomedical Sciences at Texas A&M University. Before joining the university, he worked at the U.S. Environmental Protection Agency for more than 14 years, most recently as chief of the Toxicity Pathways Branch in the Integrated Risk Information System Division of the National Center for Environmental Assessment. His research focuses on human health risk assessment, including systematic review methods, pharmacokinetic modeling, dose–response assessment, characterizing uncertainty, and addressing individual susceptibility to better protect sensitive subpopulations. He is currently Chair of the Dose-Response Specialty Group of the Society for Risk Analysis. He has served on several National Academies of Sciences, Engineering, and Medicine committees, including the Committee on Predictive-Toxicology Approaches for Military Assessments of Acute Exposures, the Committee on Endocrine-Related Low-Dose Toxicity, and as a consultant to the Committee on the Development of Guiding Principles for the Inclusion of Chronic Disease

Endpoints in Future Dietary Reference Intakes. Dr. Chiu received an A.B. in physics from Harvard University, and an M.A. and a Ph.D. in physics from Princeton University.

Nancy R. Cook, Sc.D., is a biostatistician and Professor in the Department of Medicine at the Brigham & Women's Hospital and Harvard Medical School, and Professor of Epidemiology at the Harvard T.H. Chan School of Public Health. Dr. Cook is involved in the design, conduct, and analysis of several large randomized trials, including the Women's Health Study, the Physicians' Health Study, and the Vitamin D and OmegA-3 TriaL. She leads the Trials of Hypertension Prevention (TOHP) Follow-Up Study, an observational follow-up of participants in Phases I and II of TOHP. Dr. Cook's methodological efforts focus on the predictive modeling of observational data and developing risk prediction scores using clinical biomarkers. She was a member of the Institute of Medicine Committee on the Consequences of Sodium Reduction in Populations. She received her M.S. and Sc.D. at the Harvard School of Public Health.

Eric A. Decker, Ph.D., is Professor and Head of the Department of Food Science at the University of Massachusetts Amherst. Dr. Decker is actively conducting research to characterize mechanisms of lipid oxidation, antioxidant protection of foods, and the health implications of bioactive lipids. Dr. Decker has more than 400 publications, and has been listed as one of the Most Highly Cited Scientists in Agriculture since 2005. Dr. Decker has served on numerous committees for institutions such as the Food and Drug Administration, Institute of Medicine, Institute of Food Technologist, U.S. Department of Agriculture, and American Heart Association. He has received widespread recognition for his research, including awards from the American Oil Chemist Society, the Agriculture and Food Chemistry Division of the American Chemical Society, the International Life Science Institute, and the Institute of Food Technologist.

Jiang He, M.D., Ph.D., is Professor and Joseph S. Copes, M.D., Chair of Epidemiology at Tulane University. Dr. He is a nationally and internationally well-known expert in the clinical, translational, and epidemiological research of cardiovascular and kidney diseases. He has conducted novel studies in obesity, hypertension, diabetes, stroke, cardiovascular disease, and chronic kidney disease funded by the National Institutes of Health (NIH). He has been the principal investigator and co-investigator for more than 40 major research awards from NIH. Dr. He has authored more than 475 scientific articles and has published in first-class biomedical journals, including the *New England Journal of Medicine*, *Journal of the American Medical Association*, *The Lancet*, and *Nature Genetics*. He has received

many awards from local, national, and international academic institutions and professional societies. He is teaching clinical trials and advanced epidemiological methods. Dr. He received his M.S. from Tulane University, his Ph.D. from Johns Hopkins University, his D.M.S. from Peking Union Medical College, and his M.D. from Jiangxi Medical College.

Joachim H. Ix, M.D., M.A.S., is Professor and Chief of the Division of Nephrology-Hypertension at the University of California, San Diego. He is a nephrologist, epidemiologist, and clinical trialist. His research focuses in two main areas, novel therapies in chronic kidney disease mineral bone disorders (CKD-MBD) and noninvasive assessment of kidney tubule health. Chronic kidney disease (CKD) leads to altered homeostasis of calcium, phosphate, and associated regulatory hormones that are strongly associated with vascular calcification and cardiac structural abnormalities. His team has used large observational epidemiological studies to quantify the strength of associations of these factors with cardiovascular disease and related outcomes in CKD patients. The strength and consistency of these findings makes interventions to improve CKD-MBD an important target in lowering cardiovascular disease event risk in CKD patients. He is now evaluating the safety and efficacy of novel therapies that lower intestinal phosphate absorption in CKD patients in multicenter randomized clinical trials. Second, his team is interested in identifying novel noninvasive markers of kidney tubule cell health. Pathological studies demonstrate that kidney tubule atrophy and fibrosis are important determinants of kidney disease progression, but they are poorly captured by glomerular markers of kidney health. Dr. Ix and his team have evaluated a number of blood and urine proteins that noninvasively assess the health of kidney tubule cells, and are working to determine if these markers improve assessment of risk of future kidney disease progression and cardiovascular disease risk. Dr. Ix served on the Institute of Medicine Committee on Consequences of Sodium Reduction in Populations. Dr. Ix received his B.S. from the University of California, San Diego; his M.D. from the University of Chicago Pritzker School of Medicine; and his M.A.S. from the University of California, San Francisco.

Alice H. Lichtenstein, D.Sc., is Stanley N. Gershoff Professor of Nutrition Science and Policy in the Friedman School of Nutrition Science and Policy and Director and Senior Scientist of the Cardiovascular Nutrition Laboratory at the U.S. Department of Agriculture's Jean Mayer Human Nutrition Research Center on Aging, both at Tufts University. She holds a secondary appointment as a Professor of Medicine at the Tufts University School of Medicine. Dr. Lichtenstein's research group focuses on assessing the interplay between diet and heart disease risk factors. Past and current

work includes addressing, primarily in postmenopausal females and older males, issues related to *trans* fatty acids, soy protein and isoflavones, sterol/stanol esters, and novel vegetable oils differing in fatty acid profile, glycemic index, and carbohydrate type. Selected issues are investigated in animal models and cell systems with the aim of determining the mechanisms by which dietary factors alter cardiovascular disease risk. Additional work is focused on population-based studies to address the relationship of cholesterol homeostasis and nutrient biomarkers on cardiovascular disease risk and on the application of systematic review methods to the field of nutrition. Dr. Lichtenstein is a member of the American Society for Nutrition, American Heart Association, and American Society for Biochemistry and Molecular Biology. She is a past Chair of the American Heart Association Committee on Nutrition and served as a member of the U.S. Department of Health and Human Services/U.S. Department of Agriculture 2000 Dietary Guidelines Advisory Committee and Vice Chair of the 2015 Dietary Guidelines Advisory Committee, the Institute of Medicine Committee on the Consequences of Sodium Reduction in Populations, Committee on Examination of Front-of-Package Nutrition Rating Systems and Symbols (Phase I), Dietary Reference Intake macronutrient panel, and the Food Forum. She received her D.Sc. in nutritional biochemistry from the Harvard School of Public Health and received postdoctoral training in the field of lipid metabolism at the Cardiovascular Institute at the Boston University School of Medicine.

Joseph V. Rodricks, Ph.D., is Founding Principal (1982) of Ramboll Environ. An expert in toxicology and risk analysis, Dr. Rodricks has consulted for hundreds of manufacturers and government agencies and for the World Health Organization in the evaluation of health risks associated with human exposure to chemical substances of all types. Before Ramboll, Dr. Rodricks served for 15 years as a scientist at the Food and Drug Administration; in his last 4 years, he served as Associate Commissioner for Health Affairs. His experience extends from pharmaceuticals, medical devices, consumer products, and foods to occupational chemicals and environmental contaminants. He has served on the National Academies of Sciences, Engineering, and Medicine's Board on Environmental Studies and Toxicology and on 36 committees of the National Academies, including the committees that produced the seminal works *Risk Assessment in the Federal Government: Managing the Process* (1983) and *Science and Decisions: Advancing Risk Assessment* (2009). He served for 8 years on the National Academies' committees on Dietary Reference Intakes and on the committee that produced the report *Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease* (2017). Dr. Rodricks has 150 scientific publications and has received honorary awards from three professional societies

for his contributions to toxicology and risk analysis. Dr. Rodricks earned his Ph.D. in biochemistry from the University of Maryland, College Park, and was a postdoctoral scholar at the University of California, Berkeley.

Janet A. Tooze, Ph.D., M.P.H., is Professor in the Department of Biostatistics and Data Science, Division of Public Health Sciences, at the Wake Forest School of Medicine. She is a biostatistician with expertise in longitudinal data analysis and nonlinear mixed-effects models. She has developed methods for estimating the usual intake of foods and nutrients in a unified framework with applications to nutritional surveillance and epidemiology, termed the "NCI Method," the foundation of which is a statistical model developed by Dr. Tooze for repeated measures data with excess zeroes. She developed an SAS macro to fit this model, which has been used by researchers across the United States and in 13 foreign countries. She has received three National Institutes of Health Merit Awards in recognition of her work in the advancement of dietary assessment. She has also published articles on statistical methods for analyzing data with excess zeroes, validation of dietary assessment measures, dietary patterns, nutritional status, nutritional epidemiology, a physical activity measurement error model, and energy expenditure, and serves on the editorial board of the *Journal of the Academy of Nutrition and Dietetics*. Dr. Tooze is the Associate Director of the Biostatistics Shared Resource of the Wake Forest Baptist Comprehensive Cancer Center, and provides design, analytic support, and subject-matter expertise on other research studies in the areas of nutrition, obesity, aging, and cancer control and prevention. Dr. Tooze received an M.P.H from the Harvard School of Public Health and a Ph.D. in biometrics from the University of Colorado.

George A. Wells, Ph.D., is a Professor of the School of Epidemiology and Public Health at the University of Ottawa. He is also a Professor in the Department of Medicine, Senior Scientist at the Ottawa Health Research Institute, and Director, Cardiovascular Research Methods Centre at the University of Ottawa Heart Institute. Dr. Wells's research interests are in the design and analysis of clinical trials, statistical methodology related to disease processes and health care delivery, systematic reviews and meta-analysis, economic evaluations, the development and assessment of decision support technologies for patients and practitioners, and quality assessment of comparative studies. Dr. Wells has worked extensively with national and international government and nongovernment research organizations, as well as private pharmaceutical and biotechnology industries. He has been on the executive and steering committees of national and international research programs as well as on committees with the following focus: external safety and efficacy monitoring, scientific grant review, editorial,

and scientific advisory. He is currently an Associate Editor of the *Journal of Clinical Epidemiology* and on the Editorial Committee for the *Canadian Medical Association Journal*. He has received several research awards including the Investigator of the Year award and University of Ottawa Heart Institute in 2015, the University of Ottawa Excellence in Research Award in 2014, and the Canadian Society for Clinical Investigation Distinguished Scientist Award in 2007. Dr. Wells received his B.Sc. in mathematics and his M.Sc. in mathematical statistics from McMaster University, and his Ph.D. in epidemiology and biostatistics from the University of Western Ontario.

Elizabeth A. Yetley, Ph.D., joined the Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) in February 2004 as a Senior Nutrition Research Scientist and retired in June 2008. Subsequently, she served as a nutrition science consultant to the ODS (2009–2017). Her responsibilities included (1) the development of a research and science-based strategy for the role of nutrients in health promotion and disease prevention, and (2) collaboration with other national and international agencies to facilitate the application of science-based approaches to evaluations of nutrient safety and adequacy. Prior to joining the ODS, Dr. Yetley was employed by the Center for Food Safety and Applied Nutrition (CFSAN) of the Food and Drug Administration (FDA). Dr. Yetley joined CFSAN as a senior staff fellow in 1980. She held subsequent positions as Section and Branch Chiefs and as Deputy Director for the Office of Nutrition and Food Sciences. In 1992, Dr. Yetley was appointed as Director of the Office of Special Nutritionals where she had regulatory and scientific responsibilities for three product areas: dietary supplements, medical foods, and infant formulas. Between January 2000 and February 2004, Dr. Yetley served as FDA's Lead Scientist for Nutrition. In 1996, Dr. Yetley became the first member of CFSAN to receive an appointment to FDA's Senior Biomedical Research Service. She also served for almost 10 years as the lead of the U.S. delegation to the United Nations–sponsored Codex Committee on Nutrition and Foods for Special Dietary Uses. Dr. Yetley is the recipient of numerous awards from NIH, FDA, and the U.S. Department of Health and Human Services. She is also the recipient of the Bernice K. Watt endowed lectureship at Iowa State University and the Virginia A. Beal honorarium at the University of Massachusetts. She was appointed a Fellow of the American Society for Nutrition (ASN) in 2009 and received the ASN's Conrad Elvehjem Award for Public Service in Nutrition in 2010. Dr. Yetley received her B.S., M.S., and Ph.D. degrees in human nutrition from Iowa State University.

Appendix J

Dietary Reference Intakes Summary Tables

Dietary Reference Intakes (DRIs): Estimated Average Requirements
Food and Nutrition Board, National Academies

Life-Stage Group	Calcium (mg/d)	CHO (g/d)	Protein (g/kg/d)	Vitamin A (μg/d)[a]	Vitamin C (mg/d)	Vitamin D (μg/d)	Vitamin E (mg/d)[b]	Thiamin (mg/d)	Ribo-flavin (mg/d)	Niacin (mg/d)[c]
Infants										
0–6 mo										
7–12 mo			1.0							
Children										
1–3 y	500	100	0.87	210	13	10	5	0.4	0.4	5
4–8 y	800	100	0.76	275	22	10	6	0.5	0.5	6
Males										
9–13 y	1,100	100	0.76	445	39	10	9	0.7	0.8	9
14–18 y	1,100	100	0.73	630	63	10	12	1.0	1.1	12
19–30 y	800	100	0.66	625	75	10	12	1.0	1.1	12
31–50 y	800	100	0.66	625	75	10	12	1.0	1.1	12
51–70 y	800	100	0.66	625	75	10	12	1.0	1.1	12
> 70 y	1,000	100	0.66	625	75	10	12	1.0	1.1	12
Females										
9–13 y	1,100	100	0.76	420	39	10	9	0.7	0.8	9
14–18 y	1,100	100	0.71	485	56	10	12	0.9	0.9	11
19–30 y	800	100	0.66	500	60	10	12	0.9	0.9	11
31–50 y	800	100	0.66	500	60	10	12	0.9	0.9	11
51–70 y	1,000	100	0.66	500	60	10	12	0.9	0.9	11
> 70 y	1,000	100	0.66	500	60	10	12	0.9	0.9	11
Pregnancy										
14–18 y	1,000	135	0.88	530	66	10	12	1.2	1.2	14
19–30 y	800	135	0.88	550	70	10	12	1.2	1.2	14
31–50 y	800	135	0.88	550	70	10	12	1.2	1.2	14
Lactation										
14–18 y	1,000	160	1.05	885	96	10	16	1.2	1.3	13
19–30 y	800	160	1.05	900	100	10	16	1.2	1.3	13
31–50 y	800	160	1.05	900	100	10	16	1.2	1.3	13

NOTES: An Estimated Average Requirement (EAR) is the average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a group. EARs have not been established for vitamin K, pantothenic acid, biotin, choline, chromium, fluoride, manganese, potassium, sodium, chloride, 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 two-fold 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.

Vitamin B_6 (mg/d)	Folate (µg/d)[d]	Vitamin 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
0.4	120	0.7	260	65	3.0	65	13	380	17	2.5
0.5	160	1.0	340	65	4.1	110	17	405	23	4.0
0.8	250	1.5	540	73	5.9	200	26	1,055	35	7.0
1.1	330	2.0	685	95	7.7	340	33	1,055	45	8.5
1.1	320	2.0	700	95	6	330	34	580	45	9.4
1.1	320	2.0	700	95	6	350	34	580	45	9.4
1.4	320	2.0	700	95	6	350	34	580	45	9.4
1.4	320	2.0	700	95	6	350	34	580	45	9.4
0.8	250	1.5	540	73	5.7	200	26	1,055	35	7.0
1.0	330	2.0	685	95	7.9	300	33	1,055	45	7.3
1.1	320	2.0	700	95	8.1	255	34	580	45	6.8
1.1	320	2.0	700	95	8.1	265	34	580	45	6.8
1.3	320	2.0	700	95	5	265	34	580	45	6.8
1.3	320	2.0	700	95	5	265	34	580	45	6.8
1.6	520	2.2	785	160	23	335	40	1,055	49	10.5
1.6	520	2.2	800	160	22	290	40	580	49	9.5
1.6	520	2.2	800	160	22	300	40	580	49	9.5
1.7	450	2.4	985	209	7	300	35	1,055	59	10.9
1.7	450	2.4	1,000	209	6.5	255	36	580	59	10.4
1.7	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); *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005); and *Dietary Reference Intakes for Calcium and Vitamin D* (2011). These reports may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins
Food and Nutrition Board, 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*	10*[h]	4*	2.0*	0.2*
7–12 mo	500*	50*	10*[h]	5*	2.5*	0.3*
Children						
1–3 y	**300**	**15**	**15**	**6**	30*	**0.5**
4–8 y	**400**	**25**	**15**	**7**	55*	**0.6**
Males						
9–13 y	**600**	**45**	**15**	**11**	60*	**0.9**
14–18 y	**900**	**75**	**15**	**15**	75*	**1.2**
19–30 y	**900**	**90**	**15**	**15**	120*	**1.2**
31–50 y	**900**	**90**	**15**	**15**	120*	**1.2**
51–70 y	**900**	**90**	**15**	**15**	120*	**1.2**
> 70 y	**900**	**90**	**20**	**15**	120*	**1.2**
Females						
9–13 y	**600**	**45**	**15**	**11**	60*	**0.9**
14–18 y	**700**	**65**	**15**	**15**	75*	**1.0**
19–30 y	**700**	**75**	**15**	**15**	90*	**1.1**
31–50 y	**700**	**75**	**15**	**15**	90*	**1.1**
51–70 y	**700**	**75**	**15**	**15**	90*	**1.1**
> 70 y	**700**	**75**	**20**	**15**	90*	**1.1**
Pregnancy						
14–18 y	**750**	**80**	**15**	**15**	75*	**1.4**
19–30 y	**770**	**85**	**15**	**15**	90*	**1.4**
31–50 y	**770**	**85**	**15**	**15**	90*	**1.4**
Lactation						
14–18 y	**1,200**	**115**	**15**	**19**	75*	**1.4**
19–30 y	**1,300**	**120**	**15**	**19**	90*	**1.4**
31–50 y	**1,300**	**120**	**15**	**19**	90*	**1.4**

NOTES: 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 (*). An RDA is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97–98 percent) healthy individuals in a group. It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. For healthy breastfed infants, an AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all healthy individuals in the groups, 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 two-fold 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]Under the assumption of minimal 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 from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

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**[i]	5*	30*	550*
1.3	**16**	**1.7**	**400**	**2.4**[i]	5*	30*	550*
0.9	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
1.0	**14**	**1.2**	**400**[j]	**2.4**	5*	25*	400*
1.1	**14**	**1.3**	**400**[j]	**2.4**	5*	30*	425*
1.1	**14**	**1.3**	**400**[j]	**2.4**	5*	30*	425*
1.1	**14**	**1.5**	**400**	**2.4**[i]	5*	30*	425*
1.1	**14**	**1.5**	**400**	**2.4**[i]	5*	30*	425*
1.4	**18**	**1.9**	**600**[k]	**2.6**	6*	30*	450*
1.4	**18**	**1.9**	**600**[k]	**2.6**	6*	30*	450*
1.4	**18**	**1.9**	**600**[k]	**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*

[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]Life-stage groups for infants were 0–5.9 and 6–11.9 months.

[i]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}.

[j]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.

[k]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 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); *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005); and *Dietary Reference Intakes for Calcium and Vitamin D* (2011). These reports may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Elements
Food and Nutrition Board, 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	200*[a]	0.2*	200*	0.01*	110*	0.27*	30*
7–12 mo	260*[a]	5.5*	220*	0.5*	130*	**11**	75*
Children							
1–3 y	**700**	11*	**340**	0.7*	**90**	**7**	**80**
4–8 y	**1,000**	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	**1,000**	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**

NOTES: 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 (*). An RDA is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97–98 percent) healthy individuals in a group. It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. For healthy breastfed infants, an AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all healthy individuals in the groups, 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 (mg/d)	Sodium (mg/d)	Chloride (g/d)
0.003*	2*	100*	15*	2*	400*	110*	0.18*
0.6*	3*	275*	20*	3	860*	370*	0.57*
1.2*	17	460	20	3	2,000*	800*	1.5*
1.5*	22	500	30	5	2,300*	1,000*	1.9*
1.9*	34	1,250	40	8	2,500*	1,200*	2.3*
2.2*	43	1,250	55	11	3,000*	1,500*	2.3*
2.3*	45	700	55	11	3,400*	1,500*	2.3*
2.3*	45	700	55	11	3,400*	1,500*	2.3*
2.3*	45	700	55	11	3,400*	1,500*	2.0*
2.3*	45	700	55	11	3,400*	1,500*	1.8*
1.6*	34	1,250	40	8	2,300*	1,200*	2.3*
1.6*	43	1,250	55	9	2,300*	1,500*	2.3*
1.8*	45	700	55	8	2,600*	1,500*	2.3*
1.8*	45	700	55	8	2,600*	1,500*	2.3*
1.8*	45	700	55	8	2,600*	1,500*	2.0*
1.8*	45	700	55	8	2,600*	1,500*	1.8*
2.0*	50	1,250	60	12	2,600*	1,500*	2.3*
2.0*	50	700	60	11	2,900*	1,500*	2.3*
2.0*	50	700	60	11	2,900*	1,500*	2.3*
2.6*	50	1,250	70	13	2,500*	1,500*	2.3*
2.6*	50	700	70	12	2,800*	1,500*	2.3*
2.6*	50	700	70	12	2,800*	1,500*	2.3*

[a]Life-stage groups for infants were 0–5.9 and 6–11.9 months.

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); *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and* Sulfate (2005); *Dietary Reference Intakes for Calcium and Vitamin D* (2011); and *Dietary Reference Intakes for Sodium and Potassium* (2019). These reports may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Total Water and Macronutrients
Food and Nutrition Board, 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**

NOTES: 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 (*). An RDA is the average daily dietary intake level sufficient to meet the nutrient requirements of nearly all (97–98 percent) healthy individuals in a group. It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. For healthy breastfed infants, an AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all healthy individuals in the groups, 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]*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) and *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). These reports may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Acceptable Macronutrient Distribution Ranges

Food and Nutrition Board, 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). The report may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Additional Macronutrient Recommendations

Food and Nutrition Board, 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[a]	Limit to no more than 25% of total energy

[a]Not a recommended intake. A daily intake of added sugars that individuals should aim for to achieve a healthful diet was not set.

SOURCE: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005). The report may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Chronic Disease Risk Reduction Intakes

Food and Nutrition Board, National Academies

Nutrient	Population Group	Recommendation
Sodium	Children, 1–3 y	Reduce intakes if above 1,200 mg/day[a]
	Children, 4–8 y	Reduce intakes if above 1,500 mg/day[a]
	Adolescents, 9–13 y	Reduce intakes if above 1,800 mg/day[a]
	Adolescents, 14–18 y	Reduce intakes if above 2,300 mg/day[a]
	Adults, ≥ 19 y	Reduce intakes if above 2,300 mg/day

[a]Extrapolated from the adult Chronic Disease Risk Reduction Intake (CDRR) based on sedentary Estimated Energy Requirements (EERs).

SOURCE: *Dietary Reference Intakes for Sodium and Potassium* (2019). The report may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Vitamins
Food and Nutrition Board, National Academies

Life-Stage Group	Vitamin A (µg/d)[a]	Vitamin C (mg/d)	Vitamin D (µg/d)	Vitamin E (mg/d)[b,c]	Vitamin K	Thiamin	Riboflavin
Infants							
0–6 mo	600	ND[e]	25[f]	ND	ND	ND	ND
7–12 mo	600	ND	38[f]	ND	ND	ND	ND
Children							
1–3 y	600	400	63	200	ND	ND	ND
4–8 y	900	650	75	300	ND	ND	ND
Males							
9–13 y	1,700	1,200	100	600	ND	ND	ND
14–18 y	2,800	1,800	100	800	ND	ND	ND
19–30 y	3,000	2,000	100	1,000	ND	ND	ND
31–50 y	3,000	2,000	100	1,000	ND	ND	ND
51–70 y	3,000	2,000	100	1,000	ND	ND	ND
> 70 y	3,000	2,000	100	1,000	ND	ND	ND
Females							
9–13 y	1,700	1,200	100	600	ND	ND	ND
14–18 y	2,800	1,800	100	800	ND	ND	ND
19–30 y	3,000	2,000	100	1,000	ND	ND	ND
31–50 y	3,000	2,000	100	1,000	ND	ND	ND
51–70 y	3,000	2,000	100	1,000	ND	ND	ND
> 70 y	3,000	2,000	100	1,000	ND	ND	ND
Pregnancy							
14–18 y	2,800	1,800	100	800	ND	ND	ND
19–30 y	3,000	2,000	100	1,000	ND	ND	ND
31–50 y	3,000	2,000	100	1,000	ND	ND	ND
Lactation							
14–18 y	2,800	1,800	100	800	ND	ND	ND
19–30 y	3,000	2,000	100	1,000	ND	ND	ND
31–50 y	3,000	2,000	100	1,000	ND	ND	ND

NOTES: A Tolerable Upper Intake Level (UL) is 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. Because of a 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 a UL, extra caution may be warranted in consuming levels above recommended intakes. Members of the general population should be advised not to routinely exceed the UL. 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.

[a]As preformed vitamin A only.

[b]As α-tocopherol; applies to any form of supplemental α-tocopherol.

[c]The ULs for vitamin E, niacin, and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of the two.

Niacin (mg/d)[c]	Vitamin B_6 (mg/d)	Folate (µg/d)[c]	Vitamin B_{12}	Pantothenic Acid	Biotin	Choline (g/d)	Carotenoids[d]
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
15	40	400	ND	ND	ND	1.0	ND
20	60	600	ND	ND	ND	2.0	ND
30	80	800	ND	ND	ND	3.0	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND
20	60	600	ND	ND	ND	2.0	ND
30	80	800	ND	ND	ND	3.0	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND
30	80	800	ND	ND	ND	3.0	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND
30	80	800	ND	ND	ND	3.0	ND
35	100	1,000	ND	ND	ND	3.5	ND
35	100	1,000	ND	ND	ND	3.5	ND

[d]β-Carotene supplements are advised only to serve as a provitamin A source for individuals at risk of vitamin A deficiency.

[e]ND = Not determinable owing 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.

[f]Life-stage groups for infants were 0–5.9 and 6–11.9 months.

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 Calcium and Vitamin D* (2011). These reports may be accessed via www.nap.edu.

Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Elements
Food and Nutrition Board, National Academies

Life-Stage Group	Arsenic[a]	Boron (mg/d)	Calcium (mg/d)	Chromium	Copper (µg/d)	Fluoride (mg/d)	Iodine (µg/d)	Iron (mg/d)	Magnesium (mg/d)[b]	Manganese (mg/d)
Infants										
0–6 mo	ND[f]	ND	1,000[g]	ND	ND	0.7	ND	40	ND	ND
7–12 mo	ND	ND	1,500[g]	ND	ND	0.9	ND	40	ND	ND
Children										
1–3 y	ND	3	2,500	ND	1,000	1.3	200	40	65	2
4–8 y	ND	6	2,500	ND	3,000	2.2	300	40	110	3
Males										
9–13 y	ND	11	3,000	ND	5,000	10	600	40	350	6
14–18 y	ND	17	3,000	ND	8,000	10	900	45	350	9
19–30 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11
31–50 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11
51–70 y	ND	20	2,000	ND	10,000	10	1,100	45	350	11
> 70 y	ND	20	2,000	ND	10,000	10	1,100	45	350	11
Females										
9–13 y	ND	11	3,000	ND	5,000	10	600	40	350	6
14–18 y	ND	17	3,000	ND	8,000	10	900	45	350	9
19–30 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11
31–50 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11
51–70 y	ND	20	2,000	ND	10,000	10	1,100	45	350	11
> 70 y	ND	20	2,000	ND	10,000	10	1,100	45	350	11
Pregnancy										
14–18 y	ND	17	3,000	ND	8,000	10	900	45	350	9
19–30 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11
31–50 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11
Lactation										
14–18 y	ND	17	3,000	ND	8,000	10	900	45	350	9
19–30 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11
31–50 y	ND	20	2,500	ND	10,000	10	1,100	45	350	11

NOTES: A Tolerable Upper Intake Level (UL) is 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. Because of a lack of suitable data, ULs could not be established for arsenic, chromium, potassium, silicon, sulfate, or sodium. In the absence of a UL, extra caution may be warranted in consuming levels above recommended intakes. Members of the general population should be advised not to routinely exceed the UL. 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.

[a]Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements.

[b]The ULs for magnesium represent intake from a pharmacological agent only and do not include intake from food and water.

[c]Although silicon has not been shown to cause adverse effects in humans, there is no justification for adding silicon to supplements.

[d]Although vanadium in food has not been shown to cause adverse effects in humans, there is no justification for adding vanadium to food and vanadium supplements should be used with caution. The UL is

Molybdenum (µg/d)	Nickel (mg/d)	Phosphorus (g/d)	Potassium	Selenium (µg/d)	Silicon[c]	Sulfate	Vanadium (mg/d)[d]	Zinc (mg/d)	Sodium[e]	Chloride (g/d)
ND	ND	ND	ND[b]	45	ND	ND	ND	4	ND[b]	ND
ND	ND	ND	ND[b]	60	ND	ND	ND	5	ND[b]	ND
300	0.2	3	ND[b]	90	ND	ND	ND	7	ND[b]	2.3
600	0.3	3	ND[b]	150	ND	ND	ND	12	ND[b]	2.9
1,100	0.6	4	ND[b]	280	ND	ND	ND	23	ND[b]	3.4
1,700	1.0	4	ND[b]	400	ND	ND	ND	34	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
2,000	1.0	3	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
1,100	0.6	4	ND[b]	280	ND	ND	ND	23	ND[b]	3.4
1,700	1.0	4	ND[b]	400	ND	ND	ND	34	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
2,000	1.0	3	ND[b]	400	ND	ND	1.8	40	ND[b]	3.6
1,700	1.0	3.5	ND[b]	400	ND	ND	ND	34	ND[b]	3.6
2,000	1.0	3.5	ND[b]	400	ND	ND	ND	40	ND[b]	3.6
2,000	1.0	3.5	ND[b]	400	ND	ND	ND	40	ND[b]	3.6
1,700	1.0	4	ND[b]	400	ND	ND	ND	34	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	ND	40	ND[b]	3.6
2,000	1.0	4	ND[b]	400	ND	ND	ND	40	ND[b]	3.6

based on adverse effects in laboratory animals, and this data could be used to set a UL for adults but not children and adolescents.

[c]The lowest level of intake for which there was sufficient strength of evidence to characterize a chronic disease risk reduction was used to derive the sodium Chronic Disease Risk Reduction Intake (CDRR) values.

[f]ND = Not determinable owing 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.

[g]Life-stage groups for infants were 0–5.9 and 6–11.9 months.

[b]ND = Not determinable owing to a lack of data of a specific toxicological adverse effect.

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); *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005); *Dietary Reference Intakes for Calcium and Vitamin D* (2011); and *Dietary Reference Intakes for Sodium and Potassium* (2019). These reports may be accessed via www.nap.edu.