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A Research Agenda

The Panel on Electrolytes and Water under the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes was charged with developing a research agenda to provide a basis for public-policy decisions related to recommended intakes of water, potassium, sodium, chloride, and sulfate. This chapter describes the approach used to develop the research agenda, briefly summarizes gaps in knowledge, and presents a list of research topics deemed of highest priority. Sections at the end of Chapters 4 through 7 present additional research topics.

APPROACH

During its deliberations, the panel critically reviewed the published literature on the health effects of water, potassium, sodium, chloride, and sulfate. Throughout the process of preparing this report, the panel:

1. Identified gaps in knowledge related to role of electrolytes and water in human health and their impact on functional and biochemical indicators used to assess requirements; methodological problems in measuring electrolyte and water intake and in assessing adequacy of intake; relationships of nutrient intake to chronic disease; and adverse effects from overconsumption of electrolytes and water.
2. Examined data to identify major discrepancies between intake

and the recommended intakes and consider possible reasons for such discrepancies.

3. Considered the need to protect individuals with extreme or distinct vulnerabilities due to disease conditions or genetic predisposition.

4. Weighed the alternatives and set priorities based on expert judgment.

MAJOR KNOWLEDGE GAPS

Requirements

To derive an Estimated Average Requirement (EAR), a criterion must be selected for a particular status indicator or combination of indicators that is consistent with impaired status as defined by some clinical consequence or accepted biomarker for that consequence.

- For sodium, potential biochemical indicators of adequate intake included increased plasma renin activity, adverse changes in lipid concentrations, and increased insulin resistance. Nonbiochemical indicators were nutrient inadequacy and sodium imbalance. In predominantly short-term studies, a reduced sodium intake increased plasma renin activity, but the clinical relevance of increased plasma renin activity is uncertain. The best available evidence did not support adverse changes to lipid concentrations. Data were insufficient to determine whether chronic ingestion of sodium in clinically relevant ranges led to deterioration in insulin resistance. Achieving an adequate intake of other nutrients is a potential concern at extremely low levels of intake. Sodium imbalance, that is, sodium losses that exceed intake, might occur when sweat sodium losses are high, as in the setting of extreme heat or extreme physical activity, particularly in persons who are unacclimatized to these environmental conditions. Overall, there was no single indicator that could be used to assess adequacy of intake, and thus a combination of indicators was used.
- For potassium, serum potassium concentration and hypokalemia are insensitive markers of inadequate intake. Biochemical markers of inadequate potassium intake are needed.
- For water, plasma or serum osmolality is an acceptable indicator of hydration status; however, trials that rigorously control and test different levels of total water intake, rather than allowing *ad libitum* intakes, have not been performed.

- For sulfate, there is no identified indicator of inadequate intake. Requirements for sulfate are met by meeting dietary protein and sulfur amino acid recommendations.
- For water, potassium, and sodium, useful data are lacking for setting requirements for infants, children, adolescents, pregnant and lactating women, and the elderly. As an example, there is a paucity of data on the relationship of dietary sodium and potassium intakes early in life on blood pressure and markers of bone health during adulthood. For water, research studies commonly tested the effects of inadequate intake in men of military age, but not in broad populations.

Methodology

In free-living persons, accurate measurement of dietary water and electrolytes intake is difficult, as are measurements of total body water and electrolytes. Potential sources of error in self-reported intake data include underreporting of portion sizes and frequency of intake, omission of foods and beverages, and use of food composition tables, which need to be continuously updated and expanded to include new foods and reformulated products.

For several reasons, assessment of sodium intake is problematic. Substantial additions can occur after processing. In fact, many diet collection methods do not collect information on the salt (sodium chloride) added during cooking or eating. More importantly, there is large day-to-day variation in sodium intake. The most accurate method to assess dietary sodium is to measure several timed urinary collections. However, this approach is cumbersome and prone to collection errors. Hence, practical tools to estimate sodium intake are needed.

Relationships of Intake to Chronic Disease

A substantial body of evidence, including results of clinical trials, has documented that reduced dietary sodium intake and increased potassium intake can lower blood pressure, which itself is a powerful risk factor for cardiovascular disease. Several, but not all, observational studies link increased dietary sodium and reduced potassium intake with subsequent cardiovascular disease. There is also evidence that increased dietary sodium intake and inadequate potassium intake increase urinary calcium excretion and affect calcium balance, but evidence of their effects on subclinical and clini-

cal outcomes, such as bone mineral density and osteoporosis, is limited.

Ideally, trials that test the effects of sodium reduction and increased potassium intake, alone and combined, on clinical outcomes should be conducted, potentially with multiple levels of intake. However, a critical issue is the feasibility of such efforts, an issue that pertains not just to sodium and potassium, but also to other nutrients (e.g., *trans* fatty acids and cholesterol) and nondietary factors (e.g., exercise and smoking) associated with the development of chronic disease. Feasibility concerns include the difficulties in sustaining a sufficient experimental contrast, large sample size, extended follow-up periods, and high cost. For these reasons, a trial that tests the effects of sodium reduction on clinical cardiovascular outcomes in hypertensive individuals, much less nonhypertensive individuals, is probably not possible. Still, debate on the overall health effects of sodium persists. Hence, a formal assessment of the feasibility of a trial of sodium reduction on clinical cardiovascular outcomes should be undertaken, and the results of this assessment should be published. For other research issues, such as the effects of increased potassium intake on stroke, kidney stones, or bone mineral density, clinical trials are more feasible. If possible, dose-response trials should be conducted.

For sulfate, a high priority is determining whether an increased sulfate intake increases the risk of inflammatory bowel disease. This research issue might be addressed in the setting of a case-control study or possibly a large, prospective observational study.

For water, there is a paucity of evidence on the effects of habitually low intakes on chronic disease outcomes (e.g., kidney stones, bladder cancer, and urinary tract infections). The effects of increased water intake as a means to prevent recurrent kidney stones and urinary tract infections could be tested in clinical trials, while the relationship between water intake and bladder cancer could be addressed in observational studies.

THE RESEARCH AGENDA

Three major types of information gaps were noted: (1) a paucity of data for estimating average requirements for electrolytes and water in presumably healthy humans; (2) an even greater dearth of evidence on the electrolyte and water needs in infants, children, adolescents, the elderly, and pregnant women; and (3) a lack of multidose trials to determine the effects of electrolyte and water intake on chronic diseases. There is also a critical need for research

on public health strategies that effectively reduce sodium intake and others that increase potassium intake in the general population.

Highest priority is given to research that has the potential to prevent or retard human disease processes and to prevent deficiencies with functional consequences. The following broad areas for research were deemed the highest priority (specific research recommendations are found at the conclusions of Chapters 4 through 7):

- Research on effective public health strategies to achieve and sustain a reduced sodium and increased potassium intake in the general population, including
  - behavioral change studies in individuals, and
  - community-based intervention studies.
- Research on alternative technologies that reduce the sodium content of foods, with a special emphasis on maintaining flavor, texture, consumer acceptability, safety, and low cost.
- Studies that test the effects of reduced sodium and increased potassium intake, alone and combined, on clinical outcomes (e.g., stroke, bone mineral density, and kidney stones). To the extent possible, clinical trials should be conducted. A formal assessment of the feasibility of a sodium reduction trial with clinical cardiovascular outcomes should be undertaken. In the absence of trials, methodologically rigorous observational studies that concomitantly collect electrolyte intake, other dietary information, and genetic information should be conducted.
- Studies to assess the potential for increased potassium intake to mitigate the adverse consequences of excess sodium intake and, vice versa, the potential for a reduced sodium intake to mitigate the adverse consequences of inadequate potassium intake. Potential outcomes include blood pressure, salt sensitivity, bone demineralization, and bone mineral density.
- Studies on the adverse effects of chronic, low-grade metabolic acidosis that results from an inadequate intake of potassium and its bicarbonate precursors. Potential outcomes include bone mineral density and kidney stones.
- Water, sodium, and potassium balance studies that enroll broad populations and that vary climate and physical activity levels. Populations of particular interest are children, as well as older persons with chronic, but stable, illnesses.
- Research to improve the assessment of sodium and potassium intake and total body stores.

- Studies to determine whether increased water intake can prevent kidney stones and urinary tract infections.
- Studies that assess the effects of sodium and potassium intake during childhood on the development of chronic diseases during adulthood.
- Studies to assess the relationship between sulfate intake and inflammatory bowel disease.