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A Research Agenda

The Panel on Macronutrients and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes were charged with developing a research agenda to provide a basis for public-policy decisions related to recommended intakes of energy, fat, carbohydrate, and protein. This chapter describes the approach used to develop the research agenda, briefly summarizes gaps in knowledge, and presents a prioritized research agenda. Sections at the end of Chapters 5 through 10 and Chapter 12 presented prioritized lists of research topics.

APPROACH

The following approach resulted in the research agenda identified in this chapter.

1. Identify gaps in knowledge to understand the role of macronutrients in human health, functional and biochemical indicators to assess macronutrient requirements, methodological problems related to the assessment of intake of these macronutrients and to the assessment of adequacy of intake, relationships of nutrient intake to chronic disease, and adverse effects of macronutrients.
2. Examine data to identify major discrepancies between intake and recommended intakes and consider possible reasons for such discrepancies.
3. Consider the need to protect individuals with extreme or distinct vulnerabilities due to genetic predisposition or disease conditions.
4. Weigh the alternatives and set priorities based on expert judgment.

MAJOR KNOWLEDGE GAPS

Requirements

To derive an Estimated Average Requirement (EAR), the criterion must be known for a particular status indicator or combination of indicators that is consistent with impaired status as defined by some clinical consequence. For some of the macronutrients considered in this report, such as *n*-6 and *n*-3 polyunsaturated fatty acids, there is a dearth of information on the biochemical values that reflect abnormal function. A priority should be to determine if there is a correlation between existing status indicators and clinical endpoints in the same subjects. For some macronutrients, such as indispensable amino acids, more data are needed using clinical endpoints or intermediate endpoints of impaired function to determine their requirements in regard to long-term health. For determining energy requirements, more information is needed on the form, frequency, intensity, and duration of exercise that is consistent with a healthy body weight for all age groups. The number of doubly labeled water studies for the determination of total energy expenditure in certain life stage and gender categories is limited and should be expanded.

For many of the essential macronutrients, useful data are seriously lacking for setting requirements for infants, children, adolescents, pregnant and lactating women, and the elderly. As an example, more information is needed on the role of *n*-3 polyunsaturated fatty acids in the neurodevelopment of term infants. Studies should use graded levels of nutrient intake and a combination of response indexes, and they should consider other points raised above. For some of the macronutrients, studies should examine whether the requirement varies substantially by trimester of pregnancy. Data are lacking about gender issues with respect to metabolism and requirements of macronutrients.

Methodology

For some macronutrients, serious limitations exist in the methods available to analyze laboratory values indicative of energy balance and macronutrient status. For instance, biological markers of risk of excess weight gain in children and young adults are needed, as are the standardization and validation of indicators in relation to functional outcome. As an example, to better understand the relationship between fiber and colon cancer, there needs to be increased validation of intermediate markers such as polyp recurrence and the assessment of functional markers (e.g., fecal bulk) of fiber intake. These methodological limitations have slowed progress in conducting or interpreting studies of energy and macronutrient requirements.

Potential sources of error in self-reported intake data include underreporting of portion sizes and frequency of intake, omission of foods, and inaccuracies related to the use of food composition tables. It is not possible to adjust intakes based on underreporting, and much work is needed to develop an acceptable method to do so. Reliable methods to track dietary energy intakes of populations need to be developed. Furthermore, expansion and revision of food composition tables are needed to allow for further understanding of the relationship between macronutrient intake and health. As an example, a comprehensive database for the *trans* fatty acid content and glycemic index of foods consumed in North America is needed.

Relationships of Intake to Chronic Disease

There are major gaps in knowledge linking the intake of some macronutrients and the prevention and retardation of certain chronic diseases common in North America. Because the relationship between macronutrient intake and risk of chronic disease is a trend, it is difficult to ascertain the optimal range of intake for each macronutrient. Long-term, multi-dose clinical trials are needed to ascertain, for instance, the optimal range of total, saturated, and unsaturated fatty acids intake to best prevent chronic diseases such as coronary heart disease, obesity, cancer, and diabetes. Dose–response studies are also needed to determine the intake level of fiber to promote optimum laxation. To resolve whether or not fiber is protective against colon cancer in individuals or a subset of individuals, genotyping and phenotyping of individuals in fiber/colon cancer trials is needed. Long-term clinical trials are needed to further understand the role of glycemic index in the prevention of chronic disease.

Adverse Effects

There is a body of evidence to suggest that high intakes of total fat, saturated fatty acids, *trans* fatty acids, and cholesterol increase the risk of adverse health effects (e.g., elevated low-density lipoprotein [LDL] cholesterol concentration); however, a Tolerable Upper Intake Level could not be established for any of the fats or cholesterol because of the linear trend that often exists between intake and degree of adverse effect. Therefore, more clinical research is needed to ascertain clearly defined intake levels at which significant risk can occur for adverse health effects. In addition, further information is needed on the various factors that contribute to the wide inter-individual variation in LDL cholesterol response to dietary cholesterol. There is some animal data to suggest that high intakes of *n*-6 polyunsaturated fatty acids can increase the risk of certain types of cancer.

This information is lacking in humans and is much needed. Research is needed to identify intake levels at which adverse effects begin to occur with the chronic consumption of high levels of protein and of the long-chain *n*-3 polyunsaturated fatty acids: eicosapentaenoic acid and docosahexaenoic acid.

THE RESEARCH AGENDA

Four major types of information gaps were noted: (1) a lack of data designed specifically to estimate average requirements in presumably healthy humans, (2) a lack of data on the nutrient needs of infants, children, adolescents, the elderly, and pregnant women, (3) a lack of multidose, long-term studies to determine the role of macronutrients in reducing the risk of certain chronic diseases, and (4) a lack of studies designed to detect adverse effects of chronic high intakes of these nutrients.

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 five areas for research were assigned the highest priority (other research recommendations are found at the ends of Chapters 5 through 10 and Chapter 12):

- Dose–response studies to help identify the requirements of macronutrients that are essential in the diet (e.g., indispensable amino acids and *n*-6 and *n*-3 polyunsaturated fatty acids) for all life-stage and gender groups. It is recognized that it is not possible to identify a defined intake level of fat for optimal health; however, it is recognized that further information is needed to identify acceptable ranges of intake for fat, as well as for protein and carbohydrate based on prevention of chronic disease and optimal nutrition;
- Studies to further understand the beneficial roles of *Dietary* and *Functional Fibers* in human health;
- Information on the form, frequency, intensity, and duration of exercise that is successful in managing body weight in children and adults;
- Long-term studies on the role of glycemic index in preventing chronic diseases, such as diabetes and coronary heart disease, in healthy individuals, and;
- Studies to investigate the levels at which adverse effects occur with chronic high intakes of carbohydrate, fiber, fat, and protein. For nutrients such as saturated fatty acids, *trans* fatty acids, and cholesterol, biochemical indicators of adverse effects can occur at very low intakes. Thus, more information is needed to ascertain defined levels of intakes at which relevant health risks may occur.