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Vitamin C, Vitamin E, Selenium, and β-Carotene and Other Carotenoids: Methods

METHODOLOGICAL CONSIDERATIONS

Types of Data Used

A number of disciplines have made key contributions to the evidence linking antioxidants to outcomes that may relate to human health (e.g., Hennekens and Buring, 1987). Basic biological research often involving animal models, provides crucial information on mechanisms that may link nutrient consumption to beneficial or adverse health outcomes. Clinical and epidemiological observational studies likewise play a valuable role in generating and testing hypotheses concerning the health risks and benefits of nutrient intake patterns. Randomized clinical trials in population groups of interest have the potential to provide definitive comparisons between selected nutrient intake patterns and subsequent health-related outcomes. Note, however, that randomized trials attempting to relate diet to disease states also have important limitations, which are elaborated below.

Animal Models

Basic research using experimental animals affords considerable advantage in terms of control of nutrient exposures, environmental factors, and even genetics. In contrast, the relevance to free-living humans may be unclear. In addition, dose levels and routes of administration that are practical and possible in animal experiments may differ greatly from those that are relevant to or possible with

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humans. Nevertheless, results from animal feeding experiments regarding vitamin C, vitamin E, selenium, and β-carotene and other carotenoids were included in the evidence reviewed in developing the decisions concerning the ability to specify the Dietary Reference Intakes (DRIs) for these nutrients.

Human Feeding Studies

Controlled feeding studies, usually in a confined setting such as a metabolic ward, can yield valuable information on the relationship between nutrient consumption and health-related biomarkers. Much of the understanding of human nutrient requirements to prevent deficiencies is based on studies of this type. Studies in which the subjects are confined allow for close control of both intake and activities. Complete collections of nutrient losses through urine and feces are possible, as is recurring sampling of biological materials such as blood. Nutrient balance studies measure nutrient status in relation to intake, whereas depletion-repletion studies measure nutrient status while subjects are maintained on diets containing marginally low or deficient levels of a nutrient, followed by correction of the deficit with measured amounts of the nutrient. However, these studies have several limitations: typically they are limited in time to a few days or weeks, so longer-term outcomes cannot be measured with the same level of accuracy. In addition, subjects may be confined, and therefore findings cannot be generalized to free-living individuals. Finally, the time and expense involved in such studies usually limit the number of subjects and the number of doses or intake levels that can be tested.

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

Observational Studies

In comparison, observational epidemiological studies are frequently of direct relevance to free-living humans but lack the controlled setting of human feeding studies. Hence they may be able to establish convincing evidence of an association between the consumption of a nutrient and disease risk, but they are limited in their ability to ascribe a causal relationship. A judgment of causality may be supported by a consistency of association among studies in di-

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verse populations and may be strengthened by the use of laboratory-based tools to measure exposures and confounding factors, rather than other means of data collection such as personal interviews. In recent years, rapid advances in laboratory technology have made possible the increased use of biomarkers of exposure, susceptibility, and disease outcome in molecular epidemiological research. For example, one area of great potential in advancing current knowledge of the effects of diet on health is the study of genetic markers of disease susceptibility (especially polymorphisms in genes that encode metabolizing enzymes) in relation to dietary exposures. This development is expected to provide more accurate assessments of the risk associated with different levels of intake of both nutrients and nonnutritive food constituents.

While analytic epidemiological studies (studies that relate exposure to disease outcomes in individuals) have provided convincing evidence of an associative relationship between selected nondietary exposures and disease risk, there are a number of other factors that limit study reliability in research relating nutrient intakes to disease risks. First, the variation in nutrient intake may be rather limited in populations selected for study. This feature alone may yield modest relative risk trends across intake categories in the population, even if the nutrient is an important factor in explaining large disease rate variations among populations.

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

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the avoidance of systematic bias, although important sources of bias (e.g., confounding) may remain.

Randomized Clinical Trials

By allocating subjects to the (nutrient) exposure of interest at random, clinical trials eliminate the confounding that may be introduced in observational studies by self-selection. The unique strength of randomized trials is that, if the sample is large enough, the study groups will be comparable with respect not only to those confounding variables known to the investigators, but also to any unknown factors that might be related to risk of the disease. Thus, randomized trials achieve a degree of control of confounding that is simply not possible with any observational design strategy and thus allow for the testing of small effects that are beyond the ability of observational studies to detect reliably.

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

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

Weighing the Evidence

As a principle, only studies published in peer-reviewed journals have been used in this report. However, studies published in other scientific journals or readily available reports were considered if they appeared to provide important information not documented

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elsewhere. To the extent possible, original scientific studies have been used to derive the DRIs. Based on a thorough review of the scientific literature, clinical and functional indicators of nutritional adequacy and excess were identified for each nutrient.

The quality of the studies was considered in weighing the evidence. The characteristics examined included the study design and the representativeness of the study population; the validity, reliability, and precision of the methods used for measuring intake and indicators of adequacy or excess; the control of biases and confounding factors; and the power of the study to demonstrate a given difference or correlation. Publications solely expressing opinions were not used in setting DRIs. The assessment acknowledged the inherent reliability of each type of study design as described above and applied standard criteria concerning the strength, dose-response, and temporal pattern of estimated nutrient-disease or adverse effect associations; the consistency of associations among studies of various types; and the specificity and biological plausibility of the suggested relationships (Hill, 1971). For example, biological plausibility would not be sufficient in the presence of a weak association and lack of evidence that exposure preceded the effect.

Data were examined to determine whether similar estimates of the requirement resulted from the use of different indicators and different types of studies. For a single nutrient, the criterion for setting the Estimated Average Requirement (EAR) may differ from one life stage group to another because the critical function or the risk of disease may be different. When no or very poor data were available for a given life stage group, extrapolation was made from the EAR or Adequate Intake (AI) set for another group, by making explicit and logical assumptions about relative requirements. Because EARs can be used for multiple purposes, they were established whenever sufficient supporting data were available.

Data Limitations

Although the reference values are based on data, the data were often scanty or drawn from studies that had limitations in addressing the various questions that confronted the panel. Therefore, many of the questions raised about the requirements for and recommended intakes of these nutrients cannot be answered fully because of inadequacies in the present database. Apart from studies of overt deficiency diseases, there is a dearth of studies that address specific effects of inadequate intakes on specific indicators of health status, and thus a research agenda is proposed (see Chapter 10).

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Thus, after careful review and analysis of the evidence, including examination of the extent of congruent findings, scientific judgment was used to determine the basis for establishing the values. The reasoning used is described for each nutrient in Chapters 5 through 8.

Pathways to Nutrient Requirements

The possible pathways that were considered in determining the requirement for each nutrient include the following:

1. The availability of a convincing totality of evidence, including randomized clinical trial data, that the nutrient reviewed reduces the risk of important health outcomes—demonstration that a biomarker of exposure influences a specific health outcome constitutes a key component of this body of evidence.
2. The availability of a convincing totality of evidence, including randomized clinical trial data, that the nutrient reviewed favorably affects a selected functional marker—this pathway was used with caution in view of the many examples where intervention effects on an intermediate outcome (biomarker) proved to be inconsistent with intervention effects on the chronic disease of interest.
3. The presence of a clinically important deficiency disease or nutritional syndrome that has been demonstrated to relate specifically to an inadequate intake of the nutrient reviewed—this pathway is facilitated by considering intakes needed to ensure adequate body stores or reserves of the nutrient or of pertinent compounds that the body produces in response to adequate intake of the nutrient.

Method to Determine the Adequate Intake for Infants

The AI for young infants is generally taken to be the average intake by full-term infants who are born to apparently healthy, well-nourished mothers and are exclusively fed human milk. The extent to which the intake of a nutrient from human milk may exceed the actual requirements of infants is not known, and the ethics of experimentation preclude testing the levels known to be potentially inadequate. Using the infant exclusively fed human milk as a model is in keeping with the basis for earlier recommendations for intake (e.g., Health Canada, 1990; IOM, 1991). It also supports the recommendation that exclusive intake of human milk is the preferred method of feeding for normal full-term infants for the first 4 to 6 months of life. This recommendation has been made by the Cana-

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dian Paediatric Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), the Institute of Medicine (IOM, 1991), and many other expert groups, even though most U.S. babies no longer receive human milk by age 6 months.

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

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

Ages 0 through 6 Months

To derive the AI value for infants ages 0 through 6 months, the mean intake of a nutrient was calculated based on (1) the average concentration of the nutrient from 2 to 6 months of lactation using consensus values from several reported studies, if possible, and (2) an average volume of milk intake of 0.78 L/day. This volume was reported from studies that used test weighing of full-term infants. In this procedure, the infant is weighed before and after each feeding (Allen et al., 1991; Butte et al., 1984; Chandra, 1984; Hofvander et al., 1982; Neville et al., 1988). Because there is variation in both the composition of milk and the volume consumed, the computed value represents the mean. It is expected that infants will consume increased volumes of human milk during growth spurts.

Ages 7 through 12 Months

During the period of infant growth and gradual weaning to a mixed diet of human milk and solid foods from ages 7 through 12 months, there is no evidence for markedly different nutrient needs for this group of nutrients. The basis of the AI values derived for this age category was the sum of (1) the content of the nutrient provided by 0.60 L/day of human milk, which is the average volume of milk reported from studies of infants who receive only human milk in this age category (Heinig et al., 1993), and (2) that provided by the usual intakes of complementary weaning foods consumed by infants in this age category. Such an approach is in keeping with current recommendations of the Canadian Paediatric

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Society (Health Canada, 1990), the American Academy of Pediatrics (AAP, 1997), and the Institute of Medicine (IOM, 1991) for continued feeding of infants with human milk through 9 to 12 months of age, with appropriate introduction of solid foods. Selenium and vitamin C had published information about the intake from solid foods for infants aged 7 through 12 months, and thus followed this method.

For vitamin E, which did not have intake data from solid foods, the AI was calculated by extrapolating upward from the AI for infants ages 0 through 6 months, adjusting for metabolic body size and growth, and adding a factor for variability. The method is described below.

Method for Extrapolating Data from Adults to Children

Setting the EAR or AI

For vitamin C, vitamin E, and selenium, data were not available to set the EAR and RDA for children ages 1 year and older and adolescents. Because vitamin C is a water-soluble vitamin and boys have a larger lean body mass and total body water than girls, the adult EAR was adjusted for children and adolescents on the basis of differences in reference weights from Table 1-1. For vitamin E and selenium, the EAR has been extrapolated downward using an adjustment for metabolic body size and growth. The method relies on at least four assumptions:

1. Maintenance needs for vitamin E and selenium expressed with respect to body weight ([kilogram of body weight]$^{0.75}$) are the same for adults and children. Scaling requirements to the 0.75 power of body mass adjusts for metabolic differences demonstrated to be related to body weight, as described by Kleiber (1947) and explored further by West et al. (1997). By this scaling, a child weighing 22 kg would require 42 percent of what an adult weighing 70 kg would require—a higher percentage than if the requirement were based on body weight to a power of one.
2. The EAR for vitamin E and selenium for adults is an estimate of maintenance needs.
3. The percentage of extra vitamin E and selenium needed for growth is comparable with the percentage of extra protein needed for growth.
4. On average, total needs do not differ substantially for males compared to females until age 14, when reference weights differ.

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The formula for the extrapolation is

$$EAR_{child} = EAR_{adult}\ (F),$$

where F = $(Weight_{child}/Weight_{adult})^{0.75}$ (1 + growth factor). Reference weights from Table 1-1 are used. If the EAR differs for men and women, the reference weight used for adults in the equation differs by gender; otherwise, the average for men and women is used unless the value for women is derived from data on men. The approximate proportional increase in protein requirements for growth (FAO/WHO/UNA, 1985) is used as an estimate of the growth factor as shown in Table 3-1. If only an AI has been set for adults, it is substituted for the EAR in the above formula, and an AI is calculated; no RDA is set.

Setting the RDA for Children

To account for variability in requirements because of growth rates and other factors, a 10 percent coefficient of variation (CV) for the requirement is assumed unless data are available to support another value, as described in Chapter 1.

Method for Extrapolating Data from Young to Older Infants

This adjustment, the metabolic weight ratio method, involves metabolic scaling but does not adjust for growth because it is based on a value for a growing infant. To extrapolate from the AI for infants ages 0 through 6 months to an AI for infants ages 7 through 12 months, the following formula is used:

$$AI_{7\text{–}12\ mo} = AI_{0\text{–}6\ mo}\ (F),$$

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

TABLE 3-1 Estimated Growth Factor by Age Group

Age Group	Growth Factor
7 mo–3 y	0.30
4–8 y	0.15
9–13 y	0.15
14–18 y	
Males	0.15
Females	0.0

SOURCE: Proportional increase in protein requirements for growth from FAO/WHO/UNA (1985) used to estimate the growth factor.

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Methods for Determining Increased Needs for Pregnancy

It is known that the placenta actively transports vitamin C, vitamin E, and selenium from the mother to the fetus (Hytten and Leitch, 1971). However, for these three nutrients, experimental data that could be used to set an EAR and RDA for pregnancy are lacking. In these cases the potential of increased need for these nutrients during pregnancy is based on theoretical considerations, including obligatory fetal transfer, if data are available, and increased maternal needs related to increases in energy or protein metabolism, as applicable.

Methods to Determine Increased Needs for Lactation

For vitamin C, vitamin E, and selenium, it is assumed that the total requirement of lactating women equals the requirement for the nonpregnant, nonlactating woman of similar age plus an increment to cover the amount of the nutrient needed for milk production. To allow for inefficiencies in use of these nutrients, the increment may be somewhat greater than the amount of the nutrient contained in the milk produced. Details are provided in each nutrient chapter.

ESTIMATES OF LABORATORY VALUES

Substantial changes in analytical methods have occurred during the more than 40 years of studies considered in this report. Although the requirement for vitamin C is based on recent data, the studies that were utilized to determine the vitamin E requirement are 40 years old. Methodological problems have been documented for vitamin E intake assessment from food (see Chapter 6).

NUTRIENT INTAKE ESTIMATES

Reliable and valid methods of food composition analysis are crucial in determining the intake of a nutrient needed to meet a requirement. For vitamin E and selenium, analytic methods to determine the content of the nutrient in food have serious limitations, the specifics of which are discussed in Chapters 5 through 8.

Methodological Considerations

The quality of nutrient intake data varies widely across studies. The most valid intake data are those collected from metabolic study protocols in which all food is provided by the researchers, amounts

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consumed are measured accurately, and the nutrient composition of the food is determined by reliable and valid laboratory analyses. Such protocols are usually possible with only a small number of subjects. Thus, in many studies, intake data are self-reported (e.g., through 24-hour recalls of food intake, diet records, or food frequency questionnaires).

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

Four sources of measurement error are particularly important with regard to vitamin E intake: (1) energy intake is underreported in national surveys (Mertz et al., 1991), and fat intake (which serves as a major carrier for vitamin E) is likely to be more underreported than energy intake in the Third National Health and Nutrition Examination Survey (NHANES III) (Briefel et al., 1997); (2) the amount of fats and oils added during food preparation (and absorbed into the cooked product) is difficult to assess using diet recall methodologies, yet it contributes substantially to vitamin E intake; (3) uncertainties about the particular fats or oils consumed, particularly when food labels do not indicate the specific fat or oil in the product (e.g. "this product may contain partially hydrogenated soybean and/or cottonseed oil or vegetable oil") necessitate a reliance on default selections (and thus assumptions about the relative content of α- and γ-tocopherols; and (4) due to the small number of samples, the vitamin E content of food sources in the Continuing Survey of Food Intakes by Individuals (CSFII) and NHANES III databases is quite variable (J. Holden, Agricultural Research Service, USDA, personal communication, April 13, 1999).

Food composition databases that are used to calculate nutrient intake from self-reported and observed intake data introduce errors due to random variability, genetic variation in the nutrient content, analytical errors, and missing or imputed data. In general, when nutrient intakes for groups are estimated, the effect of errors in the composition data is probably considerably smaller than the effect of errors in the self-reported intake data (NRC, 1986). It is not known to what extent this is true for vitamin C, vitamin E, selenium, or β-

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carotene and other carotenoids. However, adult men and women participating in NHANES III underreported energy intake by about 23 percent, as well as fat intake (which serves as a carrier for vitamin E) when expressed as a percentage of total energy intake (Briefel et al., 1997).

Adjusting for Day-to-Day Variation

Because of day-to-day variation in dietary intakes, the distribution of 1-day (or 2-day) intakes for a group is wider than the distribution of usual intakes even though the mean intake may be the same (for further elaboration, see Chapter 9). To reduce this problem, statistical adjustments have been developed (NRC, 1986; Nusser et al., 1996) that require at least 2 days of dietary data from a representative subsample of the population of interest. However, no accepted method is available to adjust for the underreporting of intake, which may average as much as 20 percent for energy (Mertz et al., 1991).

DIETARY INTAKES IN THE UNITED STATES AND CANADA

Sources of Dietary Intake Data

The major sources of current dietary intake data for the U.S. population are the Third National Health and Nutrition Examination Survey (NHANES III), which was conducted from 1988 to 1994 by the U.S. Department of Health and Human Services, and the Continuing Survey of Food Intakes by Individuals (CSFII), which was conducted from 1994 to 1996 by the U.S. Department of Agriculture (USDA). NHANES III examined 30,000 subjects aged 2 months and older. A single 24-hour diet recall was collected for all subjects. A second recall was collected for a 5 percent nonrandom subsample to allow adjustment of intake estimates for day-to-day variation. The 1994 to 1996 CSFII collected two nonconsecutive 24-hour recalls from approximately 16,000 subjects of all ages. Both surveys used the food composition database developed by USDA to calculate nutrient intakes (Perloff et al., 1990). National survey data for Canada are not currently available, but data for vitamin C have been collected in Québec and Nova Scotia. The extent to which these data are applicable nationwide is not known.

Appendix D gives the mean and the first through ninety-ninth percentiles of dietary intakes of vitamin C and vitamin E by age from the CSFII, adjusted for day-to-day variation by the method of Nusser et al. (1996). Appendix C provides comparable information

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for vitamin C, vitamin E, and selenium from NHANES III, adjusted by methods described by the National Research Council (NRC, 1986) and by Feinleib et al. (1993) for persons aged 6 years and older. Appendix E provides means and selected percentiles of dietary intakes of vitamin C for individuals in Québec and Nova Scotia.

Sources of Supplement Intake Data

Although subjects in the CSFII are asked about the use of dietary supplements, quantitative information is not collected. Data on supplement intake obtained from NHANES III were reported as a part of total nutrient intake (Appendix C). NHANES III data on overall prevalence of supplement use are also available (LSRO/FASEB, 1995). In 1986, the National Health Interview Survey queried 11,558 adults and 1,877 children on their intake of supplements during the previous 2 weeks (Moss et al., 1989). The composition of the supplement was obtained directly from the product label whenever possible. Table 3-2 shows the percentage of adults, by age, taking supplements of vitamin C, vitamin E, or selenium.

Food Sources of Vitamin C, Vitamin E, Selenium, and Carotenoids

For some nutrients in this report, two types of information are provided about food sources of nutrients: identification of the foods that are the major contributors of the nutrient to diets in the United States and food sources of the nutrient. The determination of foods that are major contributors depends on both the nutrient

TABLE 3-2 Percentage of Persons Taking Vitamin Supplements by Sex, Age, and Type of Vitamin Used: National Health Interview Survey, United States, 1986

	Females				Males			
Supplement Taken	All Adults 18+ y	18–44 y	45–64 y	65+ y	All Adults 18+ y	18–44 y	45–64 y	65+ y
Vitamin C	33.6	32.7	35.7	33.3	27.8	27.7	28.4	27.2
Vitamin E	28.9	28.5	30.3	27.9	23.1	22.4	24.4	23.9
Selenium	10.3	10.5	10.2	10.2	8.1	8.3	7.1	8.7

NOTE: The high use of supplements by pregnant women is not reflected in this table.
SOURCE: Moss et al. (1989).

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content of a food and the total consumption of that food (amount and frequency). Therefore, a food that has a relatively low concentration of the nutrient might still be a large contributor to total intake if it is consumed in relatively large amounts. In contrast, the food sources listed are those with the highest concentration of the nutrient; no consideration is given to the amount consumed.

SUMMARY

General methods for examining and interpreting the evidence on requirements for vitamin C, vitamin E, and selenium, with special attention given to infants, children, and pregnant and lactating women; methodological problems; and dietary intake data are presented in this chapter. Relevant detail is provided in the nutrient chapters.

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