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Nutrient and energy intakes for the European Community

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1. Introduction

Mandate

To advise on the establishment of European Recommended Dietary Allowances for a number of purposes, including nutrition labelling and Community programmes on research and nutrition, and to make recommendations.

Policy of the Committee

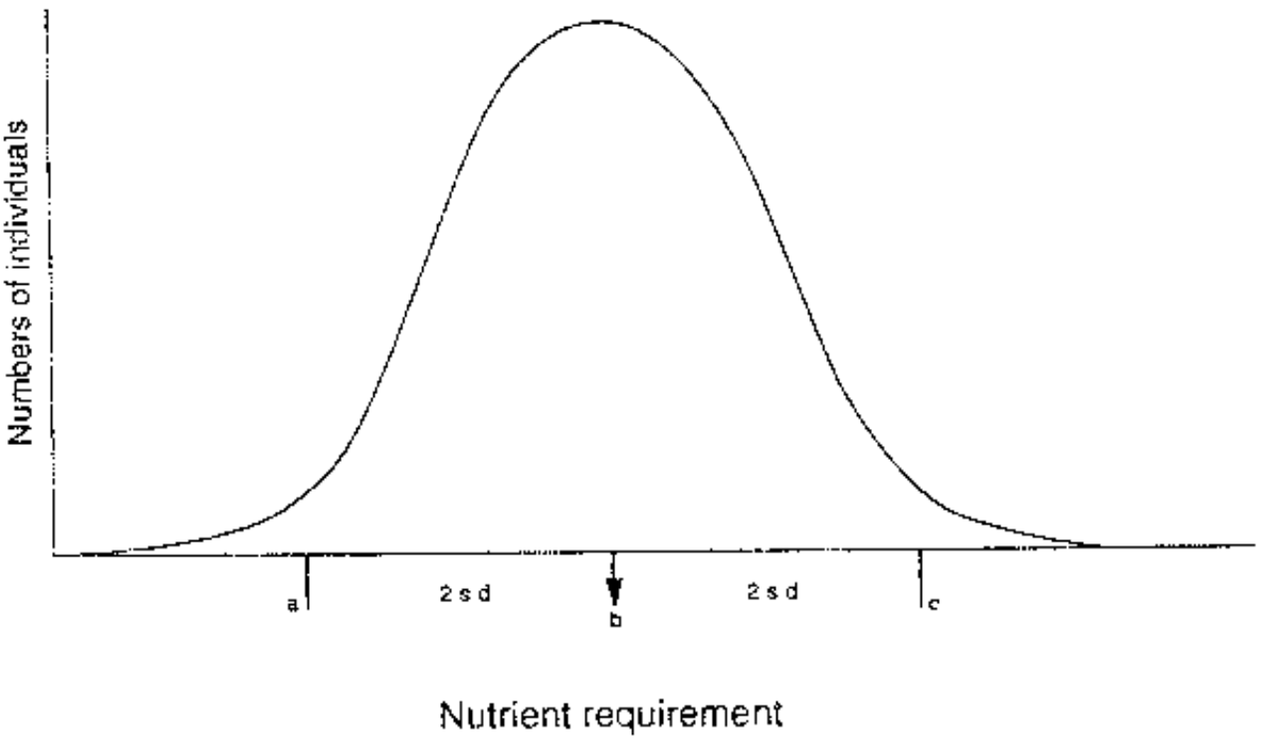
Almost all countries of the European Community have independently convened committees of experts to derive values for nutritional recommendations. These experts, drawing from a common pool of data, have used physiological and biochemical knowledge to estimate nutrient requirements. In many cases the data are limited and the expert committees have had to make decisions on the balance of evidence.

For most nutrients the derived requirements are fairly similar across the Community [1]. Not surprisingly, however, committees can assess the evidence from slightly divergent viewpoints and arrive at different values for nutrient requirements. This can raise problems for food manufacturers, food regulators and consumers. The Committee set up a working group, representative of various views on the interpretation of the available evidence, to compile a set of recommendations that could be used across the Community for a variety of purposes.

The working group consisted of 19 experts who operated in four sub-groups covering (i) energy and protein, (ii) water-soluble vitamins, (iii) fat-soluble vitamins, and (iv) minerals and trace elements. The sub-groups met several times, and the full working group met on seven occasions.

The Committee debated at length how to present their recommendations in the most helpful way. Their decisions are described in the section below on Recommendations and Nomenclature. The Committee drew on the experience of a number of expert committees, of member countries, of non-member countries [2,3], and of international agencies [4,5]. They did not, however, just try to harmonise existing national reports of member states, but sought instead to consider the data afresh, including the most recent, and sometimes still unpublished, work.

Fig 1.1 The frequency distribution of individual requirements for a nutrient



Point **b** is the mean requirement of the group. Point **c** (mean + 2 SD) is the intake that will meet the needs of nearly all healthy people in a group. Point **a** (mean - 2 SD) is the intake below which nearly all individuals will be unable to maintain metabolic integrity according to the criterion chosen.

In this report, point **b** will be called the **Average Requirement (AR)**. Points **c** and **a** will roughly correspond to the **Population Reference Intake (PRI)** and the **Lowest Threshold Intake (LTI)** respectively.

Recommendations and nomenclature

Many countries in the world have produced quantitative dietary recommendations under a variety of names such as recommended daily amounts, recommended daily allowances, recommended daily intakes, recommended dietary intakes and recommended nutrient intakes, among others. In this report they will be referred to by the generic term RDA.

A major problem in formulating a RDA is that nutrient requirements differ between individuals. They are conventionally assumed to have a normal Gaussian distribution, as depicted in Figure 1.1, with a peak at the mean requirement (point b in Fig. 1.1). Experimental evidence supporting this for humans is scanty, and a clear exception is known in the iron requirements of menstruating women, which are skewed, with a long tail of higher values. Nevertheless the basic assumption serves as a useful concept on which to base discussions of variations between individuals.

The policy adopted for most nutrients over many years by bodies promulgating RDAs was to choose a single value at, or more likely beyond, the top end of the distribution range, i.e. to give an intake that would cover the needs of all or almost all members of the group. Notionally this is often described as the mean requirement of the group plus two standard deviations (SD), i.e. covering at least 97.5 % of the population (point c in Fig. 1.1).

This approach had great merits for the original use of RDAs – to set a standard for an adequate diet for groups of the population; it is simple, and one can check by observation if the RDA has been set high enough. A single value RDA however is often misinterpreted or misused; it is sometimes regarded as the lowest acceptable intake, despite being clearly defined as substantially more than individual needs for the great majority of the population.

The more recent extensions of the use of RDAs to other purposes highlight the shortcomings of the single RDA. Reviewing bodies are therefore tending to move away from single RDA values. Agreeing with that view, this Committee is attempting to give, as far as possible, three values to indicate the spread of needs, corresponding to points c, b and a in Figure 1.1.

Point c, that intake which will meet the needs of virtually all healthy people in a group, corresponds conceptually with the traditional RDA. Since the Committee is producing more than one value, it seems inappropriate to retain a term such as recommended dietary allowance for this value alone. The use of the adjective 'recommended' has been criticised as potentially misleading, for intakes can be recommended only on a basis of probability. Even though always clearly stated, this

is not always recognised by users, perhaps because of the prescriptive overtones of 'recommended', and reviewing bodies have been introducing other terms. This Committee will call the intake that is enough for virtually all healthy people in a group the **Population Reference Intake (PRI)**.

Point b in Figure 1.1 is the **Average Requirement (AR)** for the group, according to the criterion chosen.

Point a in Figure 1.1 is the intake below which, on the basis of our current knowledge, almost all individuals will be unlikely to maintain metabolic integrity according to the criterion chosen for each nutrient. The Committee will call this the **Lowest Threshold Intake (LTI)**.

As mentioned previously, the schematic Figure 1.1 represents a conceptual framework, which may be adjusted to deal with the information available on specific nutrients. For example, the PRI is set notionally as the mean requirement plus two standard deviations, and thus about 2.5 % of the population would be inadequately supplied by that intake. In practice, this is not so; the mean and the standard deviation cannot be established reliably, and it is common to incorporate a safety factor by fixing the PRI at the lowest level above which all subjects appear to be adequately supplied.

In the absence of more reliable information, the LTI values in this report have been calculated as the mean minus two standard deviations. If more direct evidence is available to provide other figures, this has been used. Because deficiencies of most nutrients are fortunately relatively rare, data from which to estimate the LTI are often very inadequate, and the criteria chosen as indicators of deficiency may vary somewhat in stringency. In this report LTIs are often set on the prudent side, being not those intakes below which frank deficiency is almost certain, but rather those intakes below which there may be cause for concern for a substantial section of the population.

Consequently, the PRI and LTI values are not always the means plus and minus two standard deviations. Furthermore, there is much uncertainty about what the standard deviation should be. Many biological characteristics have a coefficient of variation of 15 %, and this is often assumed in this report. Nevertheless for some nutrients other coefficients of variation have been used, because there is direct evidence to that effect, or to allow a larger safety factor, or where the calculated values fit uneasily with observations.

The Committee has given only one value for increases during pregnancy or lactation; it considers it has inadequate information to give more with any confidence.

For nutrients where the requirements are given in terms of energy intake, there is the problem of how to give meaningful PRIs and LTIs as a weight of nutrient per day. The convention adopted in this report is to give the PRIs and LTIs for average energy intakes.

Use of values proposed

Multiple values are of greater utility than just a single RDA. For any particular use, one or other of the values may be appropriate:

Assessing the diets of individuals

Any individual who habitually has an intake equal to or greater than the PRI will almost certainly be provided for adequately. As the habitual intake falls below the PRI towards the LTI, the chances of being inadequately provided for increase. If the habitual intake falls below the LTI, further investigation of the nutritional status of the individuals being studied may need to be carried out.

Considerable caution should be exercised in judging an individual's diet in this way. Measurements of habitual intake of a nutrient are often not very accurate and the proposed reference values in this report are subject to some uncertainties.

Assessing the diets of groups

The risk of deficiency in a group can be estimated from the numbers and the intakes of those in the group habitually consuming less than the PRI. As the number of individuals with intakes below the PRI increases, so does the likelihood of the group being inadequately provided for.

For prescribing diets or provisions of food supplies

When diets are being devised or food supplied, they should contain nutrients at the level of the PRI (and adequate energy), over a period of time, to ensure negligible risk of deficiency in any person. Most individuals would therefore receive in excess or well in excess of their nutrient needs.

For food labelling purposes

This is discussed in detail in chapter 36 of this report.

Energy recommendations

The above considerations cannot apply to recommendations for energy. PRIs for other nutrients are set at the top end of the distribution of requirements to eliminate any cases of deficiency. The fact that most people will consume more than they need is of relatively little importance and will do no harm. That is not true for energy intakes. These are therefore given as average requirements for a group; they cannot be used for individuals, but are important for catering and food supply programmes.

Acceptable ranges of intakes

For some nutrients known to be essential, the data are inadequate for making recommendations. For these nutrients, an acceptable range of intakes is given, based on observations that individual consumptions within these limits appears satisfactory in that neither deficiency nor signs of excess are seen.

High levels of nutrient intakes

Most individuals aim at a nutrient intake that is not less than the PRI. Many habitually consume more. This may be due to the composition of the customary diet (e.g. a high consumption of meat may lead to a diet rich in protein; a high consumption of fruit and vegetables may produce a diet rich in folate), or to the deliberate consumption of some nutrient-rich foods (e.g. consumption of liver leading to a high intake of iron and vitamin A). Nutrient intakes may also be high due to consumption of dietary supplements or fortified foodstuffs.

Intentional consumption of nutrients considerably above the PRI is not uncommon. This is in part due to the well-publicised claims which have been made that some nutrients have extra health benefits at intakes very much higher than those needed to prevent recognised deficiency signs [6]. The Committee considers the evidence insufficient at present to justify making quantitative recommendations in this regard, but the results of current research are awaited with interest. For most nutrients however, there is little reason to expect any advantage from intakes that are greatly in excess of the PRI.

For most nutrients, the PRI can be exceeded several fold without causing adverse effects and although any additional benefits are unlikely, there is no harm in individuals consuming amounts of these nutrients that are much higher than the PRI.

For some nutrients however, undesirable effects can occur at levels relatively close to the PRI. In some cases, there may be consequences that are not directly harmful, but are undesirable – for example, high intakes of folate may have the effect of masking the effects of vitamin B_{12} deficiency, thus preventing its diagnosis early enough to avoid damage to the nervous system. In a few cases, high amounts of a nutrient are toxic, notably vitamin A after persistent intakes of a little over ten times the PRI. High intakes of these nutrients are likely to cause undesirable effects and should not therefore be encouraged.

This report gives for individual nutrients levels above which there is concern about undesirable or harmful effects. Where there is no hard evidence of adverse effects, then indications are given of intakes that have been reported as producing no apparent adverse effects. However while for many nutrients there is no reason to believe that intakes well above the PRI will be harmful, the Committee counsels caution: for example, vitamin B_6 was thought for a long time to be non-toxic, but recent evidence suggests that intakes above 50 mg per day are potentially toxic.

Age groups reviewed

The main emphasis of this report is placed on values for adults, as the quality of the data on which decisions have to be based is higher than for other groups of the population.

The report deals also with the requirements of children down to six months. For most nutrients the requirements of infants below that age were not considered, as they would be either breast- or formula- fed. The composition of infant formulas is a complex matter raising problems of bioavailability etc. that are better dealt with by a more specialist expert group.

Only for energy and protein have values been given for infants below the age of six months. It seems reasonable to do this because they are based on more solid calculations than are values for other nutrients, they can be calculated for narrower age groups, and the information should be of value for many purposes.

For most nutrients, children have been divided arbitrarily into age groups: 6-11 months, 1-3 years, 4-6 years and 7-10 years. From 11 years onwards, the sexes have been divided into age groups of 11-14 years and 15-17 years. (The convention being used in this report is that, for example, the 1-3 year group covers children from their first birthday to the day before their fourth birthday).

Individuals aged 18 years or more are considered as adults. Adults are broken down further into age groups only for consideration of energy requirements.

Children

Experimental data on the nutrient needs of children are more sparse and in general less reliable than for adults. The Committee considers that information is inadequate to give Average Requirements or Lowest Threshold Intakes for children and is limiting itself to giving Population Reference Intakes. For most nutrients the experimental data are frequently insufficient even for that restricted purpose. Most committees have tackled the problem by interpolating between the values for young adults and those for infants, based on the composition of breast milk. Some committees have based recommendations, usually for minerals, on calculations and assumptions using factorial approaches based on tissue composition, basal losses and the changing size of body compartments.

In this report, where no specific statement has been made, the PRIs for children of one year and over have been derived, in the absence of reliable data, by extrapolation from the PRI of young adults on the basis of energy expenditure. The energy expenditure of a growing child includes the energy cost of growth and the increase in body mass, as well as basal metabolic rate and physical activity. It thus appears to provide a basis on which to estimate the requirement for other nutrients above the maintenance level. For infants 6-11 months, the values are usually derived by interpolation between those known for infants below 6 months, and those calculated for the 1-3 years group.

The PRIs given for children are therefore best estimates, but they are similar to values proposed by committees in a number of countries. They should perhaps be regarded as serviceable values for food labelling and planning purposes, rather than definite statements of need.

The elderly

Because of demographic developments in Europe, more attention now has to be paid to the nutrition of the elderly.

With increasing age, there is usually progressive loss of lean tissue, energy needs tend to decline, and energy intake to fall. The deficiency of some nutrients, seen not infrequently, can arise from a greatly reduced food intake in the elderly. It is

desirable for the elderly to remain active and to keep up their intake with foods of a high nutrient density.

Dietary deficiencies can also occur because of the inability of some old people to care properly for themselves, or because of illness which is the primary cause of malnutrition.

There is no evidence that the nutrient requirements (as distinct from the energy requirements) of the elderly differ from those of middle-aged adults, and except for vitamin D, no different values are given.

Bioavailability

Dietary nutrients have to be absorbed and utilised by the body to exert their physiological effect. The extent to which this occurs is referred to as the bioavailability of the nutrient, usually expressed as a percentage.

For some nutrients the bioavailability is high and does not raise a problem. For others the bioavailability is much lower, and this has been allowed for when making recommendations.

Many factors affect the bioavailability of a nutrient. It may be the chemical form in which it occurs in the diet, for example, folate in the monoglutamate and polyglutamate forms, haem iron and inorganic iron. There may be interactions with other dietary constituents which reduce (or enhance) bioavailability.

The absorptive capacity of the intestine may be limited and may be influenced by systemic factors. It may be dependent on the need for the nutrient in the body; adaptation can occur to change bioavailability.

Because of the many factors influencing it, the bioavailability of a nutrient may vary substantially with circumstances, and it is often poorly predictable. No single value can be given with any reliability, yet in drawing up recommendations it is usually necessary to select one. Some compromise has to be arrived at, usually based on common dietary patterns. The problems are discussed in more detail in the sections on the nutrients where they raise difficulties, notably among the minerals and some of the vitamins.

General considerations

The recommendations are expressed per person per day. This does not mean that those amounts should be taken every day; conceptually they represent the average intake over a period of time.

The values are proposed for groups of healthy people, and may not apply to those with different needs arising from disease, medication or adherence to a special diet.

The values put forward for any one nutrient assume that the requirements for energy and all other nutrients are met.

Research needs

The Committee is acutely aware that there are many gaps in the data it had to use to produce the variety of values presented in this report. Some are mentioned specifically in sections dealing with individual nutrients; others are implicit in that some decisions clearly have had to be made on the basis of inadequate evidence. In the Committee's view this unsatisfactory situation is in part a consequence of the limited amount of nutritional research that has been carried out in the Community and in the world at large. The nutritional needs of the normal healthy individual are commonly classified as a low priority for medical research.

The Committee recommends that the EC reconsider the importance of research on the nutritional needs of the European consumer, to provide more reliable information to serve as the basis for better advice across the wide variety of dietary patterns in Europe.

References

1. Trichopoulou A, Vassilakou T. (1990). Recommended dietary intakes in the European Community member states: an overview. *Eur J Clin Nutr* ; **44** (suppl 2): 51-125.

2. National Reseach Council (1989). *Recommended Dietary Allowances*. 10th Ed. Washington DC: National Academy Press.

3. Health and Welfare, Canada (1990). *Nutrition Recommendations. The Report of the Scientific Review Committee*. Ottawa: Canadian Government Publishing Centre.

4. World Health Organisation (1985). *Energy and Protein Requirements. Report of a joint FAO/WHO/UNU meeting*, Geneva: World Health Organisation. (WHO s

5. Food and Agriculture Organisation (1988). *Requirements of Vitamin A, Iron, Folate and Vitamin B_{12}. Report of a joint FAO/WHO Expert Consultation.* Rome: Food and Agriculture Organisation (FAO Food and Nutrition Series; 23).

6. Gaby SK, Bendich A, Singh VN, Machlin LJ. (1991). *Vitamin Intake and Health. A Scientific Review*. New York: Marcel Dekker.

2. Energy

Definition

Energy requirement has recently been defined [1,2] in terms of the energy expenditure rather than the intake of an individual or group. Previous definitions described requirements on the basis of an assessment of energy intakes but this is now considered unacceptable because intakes may not match the energy demands of the body and the intake may also be incompatible with the long term maintenance of desirable levels of body weight and physical activity. Several EC member countries have now adopted the use of energy expenditure values. In this report energy requirements of adults are therefore defined as the levels of energy intake from food which will balance energy expenditure when individuals have a body size and composition and a level of physical activity which are consistent with long-term good health. The requirement also allows for the maintenance of economically necessary and socially desirable physical activities.

Glossary

BMR: Basal metabolic rate, is the rate of energy used in the postabsorptive state under highly standardised conditions of thermal neutrality, with the individual awake but at complete psychological and physical rest [3].

PAR: Physical activity ratio, is the energy cost of specific tasks, expressed as a ratio of the BMR. The task may include a variety of movements and activities. For example, shopping includes the walking and standing required to choose from shelves, to pay, and carry the purchased goods. PARs are considered on a daily basis, which means that they are not weighted on a weekly or yearly basis.

IEI: Integrated energy index, describes the energy cost of specific occupations as a ratio of the BMR. This value is weighted for the pauses in activity and integrates the cost of various tasks. Thus a domestic helper's IEI specifies the energy spent over the whole work shift, while carrying out the appropriate variety of specific tasks (cooking, ironing, washing etc.) and having a number of interspersed periods of rest.

PAL: Physical activity level integrates on a 24 hours basis the energy spent on all types of activities, i.e. the IEIs specific to various occupations, and the cost of inactive periods such as sleep. Strictly speaking, both IEI and PAL are calculated so that they refer to typical days.

It is possible to calculate average yearly IEIs and PALs, accounting for the average number of hours worked per day, the number of days worked per week, and weeks per year. It is important to distinguish between the two series of values. The yearly weighted averages are expressed as $\overline{IEI}$ and $\overline{PAL}$, and assume that the number of occupational hours correspond to 40 hrs/week for 48 weeks/year.

BMI: Body Mass Index (Quetelet's Index). Body weight (kg) divided by square of body height (m).

Physiology and metabolism

Three major components contribute to the energy expenditure of adults. The first and largest component is the basal metabolic rate, BMR, which is the energy used in maintaining the body in a fasting, relaxed and physically inactive state in a thermoneutral environment. This component usually accounts for 50 - 60 % of the total energy expended. The second component is the energy used in processing and storing the nutrients eaten. This cost usually amounts to about 10 % of the energy ingested but the value depends on the balance of the diet, on individual differences in response and on the extent to which individuals are being underfed or overfed. The third major component is the energy expended in undertaking the variety of physical activities involved in living, working and in social activities.

The BMR of an adult is determined principally by body size, body composition and age. Men have on average more lean tissue than women and it is the lean tissue and the relative sizes of different organs which determine the BMR. The taller and heavier the individual the greater the amount of lean tissue and therefore the higher the BMR. With age there is usually a progressive loss of lean tissue and an increase in body fat. These differences and changes in body composition account for the lower BMR per kg body weight of women than men and for the declining BMR with age even when body weight is taken into account.

The level of physical activity must obviously be considered in detail when assessing the energy needs of an individual or group. Some activities involve the minimum of movement compatible with the individuals' needs at home whereas other activities involve the energy expended at work in a variety of different tasks. Further energy is

expended in discretionary activities which include many useful contributions to the well-being of the individual and society; these can therefore be considered as socially desirable energy costs. There is also increasing recognition that maintaining physical fitness, promoting a sense of well-being by exercise and helping to prevent chronic diseases such as coronary heart disease, osteoporosis and muscle wasting in old age, may involve additional desirable physical activity if the physical cost of occupational work is modest. These additional needs are difficult to quantitate but it is recognised that physical activity is important for health and an allowance may need to be made for these additional exercise costs.

The basis for variation in energy requirements

The energy requirement of an individual is difficult to predict even when account is taken of the sex, age, body size and degree of physical activity. This is because of the substantial differences between individuals in their basal metabolism, in the efficiency with which they store food and in the muscle tone and physical cost of movement. Thus there remains a variation between individuals under standardised conditions with a range of values which extend to ± 15 % of the mean. A group of men or women of the same age and weight who engage in a variety of physical activities may show a range of individual needs which amounts to ± 20 % of the average for the group. It is therefore not possible to predict individual energy needs with any accuracy without special measurements of, for example, the BMR and physical activity patterns.

The traditional approach to deriving nutrient recommended dietary allowances has never been appropriate to estimating energy requirements because a sustained intake of energy either below or above the individual's specific needs has deleterious effects. This is in contrast to the effects of other nutrients where the provision of an ample amount of the nutrient ensures the whole population's needs are covered; individuals who receive more than they need are unlikely to suffer deleterious effects unless the nutrient is taken in very large amounts. It is therefore usual to calculate the average energy needs of a group.

Effects of energy excess

Adults have only a modest ability to dissipate excess dietary energy by altering their metabolic efficiency and thereby increasing their energy expenditure [4]. Weight is readily gained with fat and protein being deposited in adipose and lean tissue respectively. About 30 % of the excess weight gain is lean tissue so the BMR

slowly increases [5,6]. This increase and the energy cost of moving a heavier body during physical activity means that an individual or group eventually comes back into equilibrium at a higher energy intake and expenditure but at the cost of being overweight. The increases in morbidity and mortality associated with excess weight are well documented and include greater risk of arthritis, gallbladder disease, diabetes, coronary heart disease, hypertension, stroke and an increased risk of some cancers [7]. These risks can be avoided if energy intakes and expenditure are matched within a desirable weight range. This has been defined as equivalent to a BMI of about 20-25 [8,9,10]. On a population basis, however, the risk of having individuals who have either chronic energy deficiency with a BMI below 18.5 or overweight with a BMI above 25 is minimised when the median BMI of the population is between 20 and 22. This may therefore be taken as the optimal population BMI range.

Estimation of energy requirement

To estimate energy requirement at the individual or group level it is necessary to establish the habitual level of energy expenditure. This is done in two steps. First the basic expenditure, BMR, is estimated. This can be predicted accurately on a group basis with a standard error of about 2 %, by the set of regressive equations developed for WHO/FAO/UNU [1]. These equations are based on age and weight for males and females separately. Recently new data on BMR of European elderly men and women have been collected so that a more extensive and relevant set of values is now available [11,12]. (See Appendix, Table A.1).

The next step consists in defining the level of activity which the individual or group engages in habitually. This is defined as the physical activity level (PAL) and expressed as a multiple of BMR. This PAL figure integrates in one single value the total energy expended over the whole day. While it is possible to derive the PAL from actual measurement of the energy spent in all the activities during a day, in most cases it is estimated from a knowledge of the type of occupation and recreational activity; these types are then linked to the energy cost of the activity defined as the physical activity ratio (PAR). Thus the total energy cost per minute of each task can be calculated. There are published tables of PARs for various activities and also estimates of the daily PALs of various life styles [13].

The energy cost of different occupations integrated over the working day is also given in specially designed tables which classify the occupations into various activity levels [1,13]. This cost is explained as the integrated energy index (IEI), and integrates the energy costs of a variety of activities carried out in performing a specific task. It is, however, appropriate to reclassify a group's lifestyle if it is apparent that modern living conditions have changed the energy demands. Thus a

domestic helper may be classified as holding a "moderately" active job in some European countries where there are short working weeks and appliances designed to save human energy are available. The same occupation may involve heavy work when performed with little mechanisation and for many hours per day or with more days worked per year in other European countries.

It is now advisable to group daily activities not only in terms of occupation but also to take account of discretionary activities, the latter being further subdivided into socially desirable activities and activity intended for the maintenance of a healthy cardiovascular and muscular system [1]. This health maintenance activity may be totally absent from the life style of modern sedentary populations in Europe. If it is considered desirable, the cost associated with these activities for a given minimum time each day may be provided as an extra energy allowance. This approach implies a prescriptive or normative scheme rather than simply taking the observed patterns of activity and then specifying the energy needs accordingly.

Therefore when attempting to estimate the energy requirement of an individual or group, the following information is needed:

1) age, sex and body weight;

2) type of occupation, the time involved and its energy costs;

3) type of discretionary activity, the time involved and its energy costs;

4) hours of sleep.

The BMR is then calculated from the observed body weight provided the body mass index is between 20 and 25 for an individual. If the body mass index exceeds 25 then a desirable weight should be defined as that corresponding to a BMI of 25. For estimating the BMI of groups, however, a BMI of 22 should be chosen as desirable if the observed average BMI exceeds this value.

The energy cost of the various activities is usually established on the basis of tables of PARs (physical activity ratios), i.e. as a ratio of the cost to BMR. By knowing the time involved in each activity and with the use of tables it is possible to build up a picture of the total 24 hour energy expenditure, which may also be expressed as a ratio of the estimated 24 hr BMR of the individual. This is then the individual's PAL for that day. Experts conversant with the problems of establishing these PAL values are needed in developing this approach to energy requirements since serious errors and misinterpretations are readily made by the untrained analyst.

Simplifying the estimates of energy requirements

The various occupational activities can be grouped, on the basis of their mean IEI, into four major intensity levels. These are set out in Table 2.1 separately for men and women.

These values result from an integration of the energy spent on the actual work and of the interspersed pauses; the heavier the work the longer the pauses. The job specifications of the IEI categories are shown in Table 2.1, but this is meant to provide only general guidance; better definitions may eventually become available.

Table A.2 (Appendix) shows how the differences in body weight and in physical activity levels affect the average daily energy requirements of groups of men and women. There is over a threefold variation in needs. This emphasises the importance of establishing the characteristics of the group whose energy needs are to be met. Therefore, in developing the European average energy requirement, weights and heights and physical activity patterns (as $\overline{IEI}$ and/or as $\overline{PAL}$) within the community are needed. Very little suitable information is available currently, but extensive and representative data are likely to become available as part of current or planned nutritional surveillance surveys.

Developing individual or group requirement values

Table 2.2 provides an example of how the energy requirement of a domestic helper is estimated. She is considered to work in a Southern European country with a relatively low level of mechanisation. She is aged 25 and weighs 60 kg, so that from Table A.1 (Appendix) her BMR can be estimated as 5.8 MJ per day. To illustrate the need to integrate all her activities it is assumed that for two months of the year she also engages in harvesting a crop as part of the regular summer work in the area. In addition she has commitments to maintaining her own household. Three types of activity patterns therefore need to be considered: (a) her regular domestic work combined with her own household duties for three days per week, (b) an average pattern of activity for four week and weekend days when she copes predominantly with her household duties and (c) the two months weekday work picking crops. In this latter period it is assumed that she also works as a domestic for one weekend day to maintain her regular employment. Thus it is possible to obtain three different PAL values to cover the three types of day in the year. By integrating these for the whole year one arrives at an average energy requirement equivalent to 1.69 $\overline{PAL}$ or a total energy need, given her age and weight, of 9.78 MJ (2340 kcal) per day.

Generating an average value for European adult energy requirements

It is useful to determine if possible the average energy requirement of European adults taking into account the known or estimated variations in population structure, in adult weights and heights and the physical activity patterns within the Community.

First estimates of light, moderate and heavy life styles activity levels were specified with or without desirable increments in activity for promoting health and general well-being. These life style $\overline{PAL}$ values, expressed as ratios of the basal metabolic rate, are set out in Table 2.3.

It is more difficult to obtain a suitable estimate of European adult weights. Desirable weights for observed heights were calculated taking a BMI of 22. Actual adult weights and heights were taken from representative national samples or from specific surveys (see data sources in footnote to Table 2.4). These adult body weights and heights were weighted for the total number of adults in each age group in each country, as obtained from Eurostat [14], to obtain estimates of the average weight and height of European men and women of the various age groups. The calculated weights are given in Table 2.4.

Subsequently in this report when standard weights are required for calculating nutrient needs, the value for an adult male is taken as 75 kg, with 62 kg for an adult female, as being the mean actual body weights in the age range 30-59 years.

Energy requirements for each age and sex group were then derived (Table 2.4) by making assumptions about the proportion of men and women of different ages who are involved in different activity levels. These arbitrary assumptions are set out in the footnote to Table 2.4. Table 2.4 also indicates the extent to which the requirements are altered if an allowance is made for physically desirable activities.

Elsewhere in this report, when an average energy intake is required for calculating nutrient needs, the daily value for adult men is taken as 11.3 MJ, and for adult women, 8.5 MJ, from the mean energy requirement of men and women, without any addition being made for desirable physical activity.

In developing these estimates of energy requirements it should be recognised that they are based on extensive data relating to the basal metabolic rate of individuals of different ages but on very limited information on the average and range of physical activity patterns in European adults of different ages. These estimates of requirements may then need to be changed. Social and economic changes will also

alter our estimates. Health promotion is already leading some adults to undertake more physical exercise in their spare time. But automation at work and in the home is tending to reduce the demand for physical activity to an unknown degree. The more generalised introduction of central heating and cooling of offices, factories and homes may also alter behavioural patterns to an unknown extent. These social changes mean that the energy needs of European adults are likely to alter with time. The values presented here are estimates of current European patterns of activity at work and in leisure time. They should therefore be treated with great caution.

Children

Estimating energy requirements from measurements of expenditure is ideal but this is particularly difficult in children because so few measurements have been made. There are coherent, long standing data on the BMR of infants, young children and adolescents but measures of physical activity are few and rarely apply to modern European circumstances, where there seems to have been an appreciable decline in activity patterns over the last 40 years. There are now a few measurements of total energy expenditure by the $^{2}H_{2}{}^{18}O$ method in a selected group of British children but they may well not be representative of the usual pattern in Europe. Reliance must therefore be placed on measures of food intake as well as expenditure data and these need to be related to the European children's growth patterns.

Growth patterns of children in Europe

There has been a substantial number of studies of children's weight and height at different ages but these are rarely conducted on representative populations and no attempt has been made as yet to derive a collated set of data taking into account the size of different European groups and the nature of the sampling and measurement techniques. The Tanner standards [15], based on about 2000 London schoolchildren and on a smaller sample of pre-school children studied repeatedly over many years, were set out in the 1960s. These have been widely used and a British nation-wide survey [16] showed that Tanner's graphs were still a reasonable reflection of British growth patterns in the 1970s. Primary data sources have been obtained from nine European countries, where cross-sectional, mixed longitudinal and longitudinal studies have been published in the 1970s and 1980s. Values from each country have been weighted by the size of the population in each age and sex group and averaged. Plots of the European growth curves are very close to the United States National Center for Health Statistics (NCHS) growth curves. Tables A.3 and A.4 (Appendix) show the mean values for height and weight from 1 month to 17 years of age; they correspond closely with the NCHS values.

Basal metabolic rates of children

These were collected and calculated by Schofield *et al.* [17] for use by the FAO/WHO/UNU Committee. Equations were derived based on age, sex, weight and height to derive the average BMR of boys and girls. These are given in Table A.1 (Appendix). In practice it is simple to use weight alone, although height does reduce the variability of the predicted BMR in children [17].

Physical activity and other thermogenic processes

Unfortunately there are few data on physical activity patterns, energy costs of growth or the thermogenic response to meals in European children of different ages. If these were available it could be possible to build up estimates of the energy used for BMR and these other processes and thereby derive requirement values in the same way as in adults. The pre-adolescent data are sparse and information on adolescents is confined to an unpublished Italian study. Two alternative approaches involve the use of the $^{2}H_{2}{}^{18}O$ method for measuring the total energy expenditure of children or the estimation of requirements from intake data. The $^{2}H_{2}{}^{18}O$ method has recently been introduced into human studies and only lately have some of the theoretical and technical problems associated with its use been evaluated [18]. Nevertheless the recent British report [19] used the data collected by the Cambridge group on 355 healthy infants to illustrate that the energy allowances set out for children by FAO/WHO/UNU [1] were higher than those estimated by adding the estimated energy deposited during growth to the $^{2}H_{2}{}^{18}O$ estimation of total energy expenditure. This new approach used a variety of assumptions which differed from those chosen in the initial validation studies on the $^{2}H_{2}{}^{18}O$ method and it is possible that there might be a small systematic bias in these data.

The FAO/WHO/UNU's [1] allowances for children under 3 years were based on measurements of energy intakes which themselves are subject to error and include assumptions for the digestibility factors for different diets which were derived from adult studies and may not be transferable to children. The FAO/WHO/UNU allowances also included a 5 % increase for a possible underestimate of intakes of energy from breast milk in the first year of life. The same increment was assigned on a prescriptive basis for children in the second and third year. In the values given here for European children this adjustment is not included. The daily energy needs of children decline from 480 kJ/kg at birth to about 360 kJ/kg at 9 months of age because of the very marked fall in the energy need for deposition of new tissue. The total energy cost of synthesizing and storing new tissue amounts to a little over 20 kJ/g weight gain and after the first year of life is always less than 4% of energy needs.

Infants

Breast feeding provides the best nourishment for new born babies and young infants. In these children there is no need to develop energy requirement figures; however it is sometimes useful to have these values for those who are bottle fed. The older data were based on energy-dense milk formulas and energy intakes tended to be 40-50 kJ/kg higher than those now found with infants feeding on new formulas which have a lower solute and energy load. These modern formulas still seem to be consumed in excess of the estimated energy intake of wholly or partially breast-fed babies. This may reflect the greater induction of thermogenic responses by formula feeding or differences in digestibility as well as perhaps the induction of faster growth rates in formula than breast-fed children.

Since estimates of energy requirements are derived in part to help with the artificial feeding of children and in the absence of clear information on the optimal growth rate for long term health, it is sensible for the present to base infant energy requirements on modern formula feeding data. These are set out in Table 2.5. The intake of 400 kJ/kg/d should be ample for growth since new estimates of intake are now tending to be somewhat lower [20]. It is better, however, to err on the side of a slight over-estimate than an underestimate.

In children aged 1-3 years there seems to be increasing evidence that their expenditure is lower than 40 years ago. This may reflect the lower activity or a lower thermoregulatory demand in modern children living indoors at higher environmental temperatures controlled by central heating, or a reduction in physical exertion consequent upon the increasing use of cars.

Children aged 3-9 years

The FAO/WHO/UNU report [1] had to rely on intake data for this age group because physical activity and total energy expenditure data are very limited. Few new studies have been reported since then so it remains appropriate to rely on intake data. In a European context the principal concern in relation to energy is one of overweight and obesity in children rather than of underweight and malnutrition. So the additional 5 % allowance prescribed by FAO/WHO/UNU [1] was not used in deriving the estimates shown in Table 2.6.

Children and adolescents aged 10-18 years

These can more readily be assessed in terms of energy expenditure using a system similar to that applied to adults. Typical time use and energy costs of activities in boys and girls were provided by the FAO/WHO/UNU approach (Table A.5.

Appendix). In different parts of Europe the demand on adolescents will vary substantially with many, perhaps especially in rural areas, contributing to the physical work of the household.

Adjustments for these differing activity patterns can readily be made by reference to Table A.5 (Appendix) and the approach adopted for adults. Table 2.7 summarises the components of energy expenditure and the average energy requirement of adolescents who are moderately active with a physical activity level of about 1.65 for boys and 1.55 for girls, aged 10-13 years. For older adolescents, spending more time in school and related light type activities, calculations are made on the basis of physical activity levels of 1.58 for boys and 1.50 for the girls.

Pregnancy

There have been several detailed European studies of energy metabolism in pregnancy since the FAO/WHO/UNU collation of data in 1981. This has allowed a re-evaluation of the estimates of need. Studies on total energy expenditure in whole body calorimeters [21] have shown considerable variability in the metabolic changes in pregnancy in different women. Analyses of post-prandial thermogenesis have found a more efficient processing of nutrients with a lower metabolic response to meals in pregnant and lactating women [22]. There have also been two major studies in Glasgow and Wageningen as part of an international prospective study of the changes in food intake, energy expenditure and body composition during pregnancy [24]. These European studies are still in progress but sufficient data are available to justify the derivation of values which differ from those given by FAO/WHO/UNU [1].

The original estimates of energy need were based on data collected on the weight gain and body compositional changes in careful studies conducted before and after the war in Scotland. These data and the approach adopted have been used throughout the world for the last 30 years [25]. If a mother gained 12.5 kg and gave birth to a 3.3 kg baby then the total cost of the energy deposited in both maternal and fetal tissues together with the additional cost of maintaining the extra tissue amounted to an extra demand for 80,000 kcal (335 MJ) over the whole of pregnancy [25]. The FAO/WHO/UNU Consultation therefore divided this value by the 250 days after the first month of pregnancy to derive an additional need of about 1.3 MJ per day [1].

The supposed extra energy requirement is not matched by a corresponding increase in measured food intake in the new Glasgow and Wageningen studies. In fact an analysis of 10 studies in Australia, Holland and Britain showed increased intakes of only about 0.42 MJ/d in the third trimester of pregnancy and there was little if any

change before that [19]. The UK proposed an increment of 0.8 MJ/day during the last trimester in view of the conflicting evidence from intake data and estimates based on BMR and tissue compositional changes [19].

The discrepancies in the European data between the estimated need for energy retention in pregnancy and the actual intake amount to 193 MJ in the Glasgow studies and to 264 MJ in Wageningen. This implies an average energy storage of 0.77-1.06 MJ/day [24]. Some of this saving may reflect differences between the pre-pregnancy values for intake and BMR and those used for calculating data which were collected at 10 weeks of pregnancy.

The decline in physical activity in late pregnancy is also difficult to document and may be a mechanism for saving energy.

Variable needs in pregnancy

The estimate of need presupposes that all women are of normal weight and sustain the appropriate weight gain which, in the five country study, amounted to 11.7 kg in Scotland, 10.5 kg in the Netherlands and 7.3-8.9 kg in the other three countries [24]. However new detailed analyses from the US show that both pre-pregnancy weight and weight gain are important indices of birth weight, and perinatal morbidity and mortality.

Provisional weight gain charts related to pre-pregnancy body mass index are now available showing that thin women, e.g. with a BMI below 20, need to gain between 12.5 and 18 kg by 40 weeks of pregnancy and at a rate of 0.5 kg/week during the second and third trimester [5] to reduce the risk to the baby. This compares with a 11.4 to 16 kg gain for most European women with a BMI of 20 to 26 before pregnancy and 7-11.5 kg weight gain for overweight women with BMI > 26. The latest US National Academy report [26] estimates the lowest neonatal and post neonatal mortality rate is achieved when babies are born weighing more than 3.5 kg. Underweight women respond to food supplementation during pregnancy by increasing their own body weight and the birth weight of their children. This implies that the energy requirements of pregnant women should be individually determined and that underweight women should be encouraged to eat more to improve the chance of having a normal weight child. Table 2.8 provides estimates for the additional energy requirements of underweight, normal and overweight European women who may either reduce their physical activity or be forced to maintain their activity patterns, for example because of the demands made by the family and the continuing need to work. Thus thin women require an increase in daily intake of about 1.7 MJ/day from the 10th week of pregnancy unless they become remarkably inactive with a $\overline{PAL}$ of 1.31 (Table 2.8). Clearly overweight and normal weight women who are usually

moderately active can adjust for the extra energy needs by becoming sedentary. There is no direct evidence that such a change occurs, but food intake data suggest that some adjustment has been made in either physical activity or metabolism by the second trimester of pregnancy. On practical grounds therefore, it seems reasonable to halve the supposed extra energy demand, which therefore would be 0.75 MJ/d from the 10th week of pregnancy for normal weight women.

Lactation

The energy requirements for lactation are proportional to the quantity of milk produced. The average energy content of human milk is about 280 kJ/100 ml [1]. Milk output data for Swedish and British women corrected for insensible water losses from the infant being test-weighed reveal that the amount of milk produced increases steadily in the first 3 months of breast feeding. Thereafter output depends on the extent to which weaning foods are introduced. The greater their use the less breast milk the baby drinks. Thus mothers who continue almost exclusively breast feeding to 6 months of age produce 750 ml/d but this can decline rapidly to 300 ml/d with the use of appreciable weaning food.

In calculating energy costs of milk production an assessment of the conversion efficiency of dietary energy to milk energy is needed. This has been traditionally taken as 80 % although in the original calculation [27] this figure was taken as the extreme; the actual value was estimated as 97 %. Recently the issue has been reassessed in Gambian women in a whole body indirect calorimeter [28]. The efficiency was calculated from the energy content of the milk produced and the increment in BMR due to the lactational process. The mean efficiency of milk production was 94.2 % with a milk density of 2.9 kJ/g. Therefore it is now proposed to use an efficiency value of 95 % rather then 80 %. Recent separate studies in Scotland, Sweden and England also found efficiency values of between 97 and 100 %.

Table 2.9 provides new estimates which make use of these allowances and include 2 groups of women who wean their children to varying degrees after 6 months of breast feeding. An allowance is included for the average weight loss of 0.5 kg/month following delivery. From these data it is clear that the energy demands of lactation are substantial compared with those of pregnancy.

References

1. World Health Organisation (1985). *Energy and Protein Requirements. Report of a joint FAO/WHO/UNU meeting*. Geneva: World Health Organisation. (WHO Technical Report Series; 724).

2. National Research Council (1989). *Recommended Dietary Allowances*. 10th Ed. Washington DC: National Academy Press.

3. Schutz Y. (1984). Glossary of energy terms and factors used for calculations of energy metabolism in human studies. In: van Es A J H, ed. *Human energy metabolism: Physical activity and energy expenditure measurements in epidemiological research based upon direct and indirect calorimetry*. EuroNut Report 5.

4. Ravussin E, Schutz Y, Acheson KJ, Dusmet M, Bourquin L, Jéquier E. (1985). Short-term, mixed-diet overfeeding in man: no evidence for "luxuskonsumption". *Am J Physiol*. 249: E470- E477.

5. Forbes GB, Welle SL. (1983). Lean body mass in obesity. *Int J Obesity*, 7: 99-107.

6. Forbes GB, Brown MR, Welle SL, Lipinski BA. (1986). Deliberate overfeeding in women and men: energy cost and composition of the weight gain. *Br J Nutr*, 56: 1-9.

7. World Health Organisation (1990). *Diet, nutrition, and the Prevention of Chronic Diseases. Report of a WHO Study Group*. Geneva: World Health Organisation. (WHO Technical Report Series; 797).

8. Bray GA. (1979). *Obesity in America*. Proc. 2nd Fogarty International Center Conference on Obesity. Report no. 79. Washington: US Department of Health, Education and Welfare.

9. Bray GA. (1985). Complications of Obesity. *Ann Internal Medicine*, 103: 1052-1062.

10. Royal College of Physicians of London (1983). Obesity. *J Roy Coll Phys Lond*, 17 : 5-65.

11. James WPT, Ralph A, Ferro-Luzzi A. (1989). Energy needs of the elderly. A new approach. In: Munro HN, Danford DE, eds. *Human Nutrition: A Comprehensive*

Treatise, Vol.6: Nutrition, Ageing and the Elderly. New York: Plenum Press. 129-151.

12. Ferro-Luzzi A. (1987). *The application of energy costs to activities and overall energy expenditure over 24 hours (including BMR levels) of the elderly.* Report to FAO.

13. James WPT, Schofield EC. (1990). *Human Energy Requirements.* Oxford: Oxford University Press.

14. EUROSTAT: *Annuaire de Statistiques de l'EUROSTAT* (1988). Luxembourg: Office Statistique de la Commission Européene (Publication officieile).

15. Tanner JM, Whitehouse RH, Takaishi M. (1966). Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. *Arch Dis Childh*, **41**: 454-471.

16. Rona RJ, Altman DG. (1977). The National study of health and growth. Standards of attained height, weight and triceps skinfold in English children 5-11 years old. *Ann Hum Biol* , **4**: 501-523.

17. Schofield WN, Schofield C, James WPT. (1985). Basal Metabolic Rate: Review and Prediction. *Hum Nutr Clin Nutr.* **39** (suppl. 1): 1-96.

18. International Dietary Energy Consultative Group (1990). *The doubly-labelled water method for measuring energy expenditure: technical recommendations for human applications.* Prentice A. ed. Vienna: IAEA/IDECG/NAHRES4.

19. Department of Health (1991). *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom.* London: HMSO. (Report on Health and Social Subjects; 41).

20. Whitehead RG, Paul AA. (1988). Diet and growth in healthy infants. *Hong Kong J Pediatr*, **5**: 1-20.

21. Prentice AM, Goldberg GR, Davies HL, Murgatroyd PR, Scott W. (1989). Energy-sparing adaptations in human pregnancy assessed by whole-body calorimetry. *Br J Nutr*, **62**: 5-22.

22. Illingworth PJ, Jung RT, Howe PW, Isles TE. (1987). Reduction in postprandial energy expenditure during pregnancy. *Br Med J*, **294**: 1573-1576

23. Illingworth PJ, Jung RT, Howe PW, Leslie P, Isles TE. (1986). Diminution in energy expenditure during lactation. *Br Med J*, **292**: 437-441.

24. Durnin JVGA. (1987). Energy requirements of pregnancy and integration of the longitudinal data from the five-country study. *Lancet*, ii: 1131-1133.

25. Hytten FE, Leitch I. (1971). *The Physiology of Human Pregnancy*. 2nd ed. Oxford: Blackwell Scientific Publications.

26. National Research Council (1990). *Nutrition during Pregnancy*. Washington: National Academy Press.

27. Thomson AM, Hytten FE, Billewicz WZ. (1970). The energy cost of human lactation. *Br J Nutr*, **24**: 565-572.

28. Frigerio C, Schutz Y, Prentice A, Whitehead R, Jéquier E. (1991). Is human lactation a particularly efficient process? *Eur J Clin Nutr*, **45**: 459-462.

Table 2.1 Classification of occupations into IEI categories*

Light		Moderate		Moderate/Heavy		Heavy	
M	F	M	F	M	F	M	F
1.60	1.60	2.25	1.90	3.0	2.3	3.8	2.8

Housewives Clerical and related workers Administrative and managerial Professional, technical and related workers	Domestic helpers Sales workers Service workers	Agricultural, animal husbandry, forestry and fishery workers Labourers Production and related transport equipment operators	Occupations are as in the moderate/ heavy category but conducted under poorly mechanised conditions

* These IEIs apply under moderately mechanised work conditions. They may need to be shifted towards higher values when dealing with relatively low automation levels. The values for IEI reported in this Table only apply to the part of the day involved in work. The values take account of pauses and intervals in working but they are not weighted to generate an average daily value which includes week-end, summer vacations etc.

Table 2.2 Energy requirements of a female domestic helper in a Southern European country

(age 25 years; weight 60 kg; BMR 5.8 MJ/day)

		Day type 1		Day type 2		Day type 3	
		housewife		domestic labour		agric. labour	
	IEI*	hr	MJ	hr	MJ	hr	MJ
1) In bed	1.0	8	1.93	8	1.93	8	1.93
2) Occupational activities							
a) Household work	2.7	2	1.31	1	0.65	1	0.65
b) Domestic labour	2.8	–	–	8	5.41	–	–
c) Tomato harvesting	3.0	–	–	–	–	8	5.8
3) Discretionary activities							
a) Household maintenance	2.0	2	1.00	–	–	–	–
b) Socially desirable	1.7	4	1.64	2	0.82	2	0.82
c) Cardiovascular and muscular maintenance	6.0	0.25	0.36	–	–	–	–
4) Rest of day	1.4	7.75	2.62	5	1.69	5	1.69
Daily Total PAL (MJ)	–	**1.53**	**(8.86)**	**1.81**	**(10.50)**	**1.88**	**(10.89)**

Integrated $\overline{PAL}$ (MJ) 1.69 (9.78)

Day type 1 = 4 days per week for 10 months (48% of the year)

Day type 2 = 3 days per week for 10 months + 1 day per week for 2 months (38% of the year)

Day type 3 = 5 days per week for 2 months (14% of the year)

* The IEI values used in this Table are higher than the corresponding values in Table 2.1, because the example describes a poorly mechanised situation. The value for cardiovascular and muscular maintenance is a PAR.

Table 2.3 The variety of physical activity levels (in $\overline{PAL}$ and in MJ/d) used in estimating energy requirements in European men and women (actual body weight, see table 2.4).

	Lifestyle Activity Level	Including desirable physical activities		Without desirable physical activities	
		$\overline{PAL}$	MJ/d	$\overline{PAL}$	MJ/d
Men	aged 18-59 years (wt. 74.6 kg)				
	Light	1.55	11.5	1.41	10.5
	Moderate	1.78	13.3	1.70	12.7
	Heavy	2.10	15.6	2.01	15.0
	aged 60-74 years (wt. 73.5 kg)	1.51	10.0	1.40	9.2
	aged≥ 75 years (wt. 73.5 kg)	1.51	9.1	1.33	8.0
Women	aged 18-59 years (wt. 62.1 kg)				
	Light	1.56	9.1	1.42	8.3
	Moderate	1.64	9.5	1.56	9.1
	Heavy	1.82	10.6	1.73	10.1
	aged 60-74 years (wt. 66.1 kg)	1.56	8.5	1.44	7.8
	aged≥ 75 years (wt. 66.1 kg)	1.56	8.3	1.37	7.3

The physical activity levels are based on the 1985 WHO/FAO/UNU report [1] on energy requirements for the men and women under 60 years. An adjustment for estimating $\overline{PAL}$ values without desirable physical activity has been specified by James and Schofield [13] and data on the elderly depend on new assessments of physical activity in these groups as monitored by Ferro-Luzzi [12].

Table 2.4 Desirable and actual average body weights (kg) and normative and actual energy requirements (in MJ/d and as $\overline{PAL}$) for European men and women of various ages.

Age in years		With desirable physical activity		Without desirable physical activity	
	Desirable* body weight (kg)	MJ/d	$\overline{PAL}$	MJ/d	$\overline{PAL}$
Men					
18-29	66.3	12.5	1.77	11.9	1.67
30-59	66.3	11.5	1.66	10.7	1.55
60-74	63.5	9.2	1.51	8.5	1.40
≥ 75	63.5	8.5	1.51	7.5	1.33
Average		**11.4**	**1.67**	**10.7**	**1.56**
Women					
18-29	57.3	9.1	1.63	8.5	1.52
30-59	57.3	8.9	1.60	8.3	1.49
60-74	55.5	7.8	1.56	7.2	1.44
≥ 75	55.5	7.6	1.56	6.7	1.37
Average		**8.7**	**1.60**	**8.3**	**1.48**
	Actual**body weight	MJ/d	$\overline{PAL}$	MJ/d	$\overline{PAL}$
Men					
18-29	74.6	13.4	1.77	12.7	1.67
30-59	74.6	12.1	1.67	11.3	1.56
60-74	73.5	10.0	1.51	9.2	1.40
≥ 75	73.5	9.1	1.51	8.0	1.33
Average		**12.1**	**1.68**	**11.3**	**1.57**
Women					
18-29	62.1	9.6	1.63	9.0	1.52
30-59	62.1	9.2	1.60	8.5	1.49
60-74	66.1	8.5	1.56	7.8	1.44
≥ 75	66.1	8.3	1.56	7.3	1.37
Average		**9.2**	**1.60**	**8.5**	**1.48**

(continues Table 2.4)

* Desirable weight for observed height taking the BMI as 22.

** Weighted median weights of European men and women derived from the studies listed below. Data had to be combined for the whole age ranges 18-59 years and 60 to 75 years because appropriate age groupings were not available. In calculating energy requirements, BMR and activity data appropriate to the specified age groups were applied. The basal metabolic rate values were obtained from Table A.1 (Appendix) and a series of assumptions were made for the proportion of each age group involved at light, moderate and heavy physical activity levels, the cost of these levels being taken as in Table 2.3. It was assumed that for 18-29 year old European men 10 % were engaged in heavy activity, 70 % in moderate and 20 % in light activity levels. For women of the same age 10 % were also considered to engage in heavy activity, 50 % in moderate and 40 % in light activity. For 30-59 years old men and women half were considered to be at moderate activity and the remaining half at light activity levels. All men and women over 60 years were specified as engaged in light activity patterns.

References

for Tables 2.1 to 2.4

The INTERSALT Cooperative Research Group (1989). Special Issue - Intersalt Elliott P. ed. *J Hum Hypert*, 3: 279-408.

Kornitzer M, Bara L. (1989). Clinical and anthropometric data, blood chemistry and nutritional patterns in the Belgian population according to age and sex. For the Belgian interuniversity research on nutrition and health (B.I.R.N.H.) study group. *Acta Cardiologica* , 44: 101-144.

The Copenhagen City Heart Study Group (1989). The Copenhagen City Heart Study Osterbroundersogelsen: A book of tables with data from the first examination (1976-78) and a five year follow up (1981-83). Appleyard M. ed. *Scand J Soc Med* (Suppl. 41), 1-160.

Heitmann BD. (1991). The Danish MONICA-I screening, the 5-year follow up (87/88). Personal communication.

The German National Health Survey of the GCP (German Cardiovascular Disease Prevention Study) (1988). *Eur Heart J*, **9**: 1058-1066.

Monitoraggio CE. Unpublished data from the 1980-1984 National Household Food Consumption Survey in Italy. National Institute of Nutrition. Rome, Italy.

Scaccini C, Sette S, Mariotti S, Verdecchia A, Ferro-Luzzi A. (1992). Nutrient adequacy of dietary intakes of elderly Italians. *Age and Nutrition*, **3**: 41-47.

Blokstra A, Kromhout D. (1991). Risk Factor Monitoring Project (involving both men and women). Personal Communication.

Heffmans MDAF, Kromhout D. Zutphen Study i.e. part of the follow-up to the Seven Country Study on men. Personal communication.

Rolland-Cachera MF, Cole TJ, Sempé M, Tichet J, Rossignol C, Charraud A. (1991). Body Mass Index variations: centiles from birth to 87 years. *Eur J Clin Nutr*, **45**: 13-21.

INSEE. *La taille et le poids des francais. Données Sociales*, 1987: 462-463.

Table 2.5 Estimated average requirements of energy for children aged 0-36 months.

	Average weight (kg)		Intake (kJ/kg body weight)	Estimated energy requirements (kJ/d)	
Age (months)	*Boys*	*Girls*		*Boys*	*Girls*
1	4.0	4.0	480	1900	1900
3	6.0	5.5	420	2500	2300
6	8.0	7.5	400	3200	3000
9	9.0	8.5	400	3600	3400
12	10.0	9.5	400	4000	3800
18	11.5	11.0	400	4600	4400
24	12.5	12.0	400	5000	4800
30	14.0	13.0	400	5600	5200
36	15.0	14.0	400	6000	5600

Taken in part from reference 19. The body weights have been rounded to the nearest 0.5 kg and the estimated energy requirements to the nearest 50 KJ/d

Table 2.6 Estimated average requirements of energy for children aged 3-9 years

	Average weight (kg)		Intake* (kJ/kg)		Estimated energy requirements (kJ/d)	
Age (years)	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*
3.5	15.5	15.0	395	375	6100	5650
4.5	17.5	17.0	375	365	6550	6200
5.5	19.5	19.5	365	350	7100	6800
6.5	22.0	21.5	350	330	7700	7100
7.5	24.5	24.0	330	305	8100	7300
8.5	27.0	27.0	305	275	8250	7400
9.5	30.0	30.5	285	245	8550	7500

* Intake derived from table 23 of reference 1. The body weights have been rounded to the nearest 0.5 kg, and the estimated energy requirements to the nearest 50 KJ/d, with some smoothing of the final values.

Table 2.7 Calculation of basal metabolic rate (BMR), total energy expenditure (TEE) and average requirements of energy of older children and adolescents aged 10-17 years

Age (years)	10.5	11.5	12.5	13.5	14.5	15.5	16.5	17.5
Boys								
Weight (kg)	33.0	36.5	41.0	47.0	55.0	58.0	62.5	64.5
BMR (MJ/day)	5.19	5.45	5.78	6.23	6.67	7.04	7.38	7.52
TEE (MJ/day) *	8.56	8.99	9.54	10.28	10.54	11.12	11.66	11.88
Growth (MJ/day) **	0.17	0.20	0.26	0.35	0.35	0.29	0.26	0.12
Estimated energy requirements (MJ/day)	8.73	9.19	9.80	10.63	10.89	11.41	11.92	12.00
Girls								
Weight (kg)	34.0	37.5	43.0	48.0	50.5	52.5	54.0	54.5
BMR (MJ/day)	4.80	5.00	5.31	5.59	5.73	5.84	5.92	5.95
TEE (MJ/day) *	7.44	7.75	8.23	8.66	8.60	8.76	8.88	8.93
Growth (MJ/day) **	0.20	0.20	0.32	0.29	0.14	0.12	0.09	0.03
Estimated Energy Requirements (MJ/day)	7.64	7.95	8.55	8.95	8.74 ***	8.88	8.97	8.96

* at a $\overline{PAL}$ of 1.65 for boys and 1.58 for girls aged 10-13 years, and 1.55 for boys and 1.50 for girls aged 14-17 years.

** at a cost of 21 kJ per daily weight gain.

*** The small decrease in energy requirement at this stage relates mainly to the fall in the growth rate.

Table 2.8 Assessing pregnancy energy needs in relation to pre-pregnancy weight and desirable weight gain.

Pre-pregnancy BMI	18.5-19.9	20.0-25.9	>25.9
Ideal weight gain (kg)	12.5-18.0	11.4-16.0	7.0-11.5
Estimated extra needs (MJ)			
BMR	175	150	100
Maternal fat store	150	110	60
Other maternal tissue	20	15	10
Fetus	35	35	35
Theoretical total extra need from 10th week of pregnancy	360	310	205
Calculated daily extra demand (MJ) from 10th week	1.7	1.5	1.0
Practical recommendation for extra intake from 10th week (MJ/d)	1.7	0.75	0.5
Pre-pregnancy intake (MJ/d) at moderate activity ($\overline{PAL}$ 1.64)	6.78	10.30	12.50
Activity $\overline{PAL}$ to adjust for tissue storage and metabolism while maintaining pre-pregnancy intake	1.31	1.40	1.51

Calculations based on National Academy of Science assessment [26] of ranges of pre-pregnancy weight and desirable weight gains which on average were assumed to be BMIs of 19, 23 and 28 with weight gains of 15.5, 13.5 and 9 kg. All women were assumed to be 1.65 m and moderately active ($\overline{PAL}$ 1.64 before pregnancy). Values for storage adapted from Durnin [24].

Table 2.9 Additional energy requirements for lactation

Full breast feeding	Milk Volume	Energy Cost	Allowance weight loss	Total extra requirements
Months	*ml/d*	*MJ/d*	*MJ/d*	*MJ/d*
0-1	680	2.00	-0.5	1.5
1-2	780	2.30	-0.5	1.8
2-3	820	2.42	-0.5	1.92
3-6	750	2.21	-0.5	1.71
Weaning Practice from 6 months				
Minor	650	1.92	0	1.92
Substantial	300	0.88	0	0.88

Derived from the UK report [9] but using new value for the efficiency of milk production.

3. Protein

Definition

The physiological requirement for protein of an individual is the lowest level of dietary protein intake that will balance the losses of nitrogen from the body in adults maintaining energy balance at modest levels of physical activity [1].

Physiology of protein metabolism

The body protein amounts to about 12 kg in adult man. The proteins are formed by chains of the 20 amino acids; the structural integrity of the body and its metabolism are wholly dependent on specific proteins. The provision of enough dietary amino acids to maintain these proteins is crucial to survival.

The body's proteins are constantly being synthesized and degraded; in an adult man eating 70g of protein daily the total protein turnover of the body amounts to about 250g protein per day. This in turn means that about 180g protein is being resynthesized without the involvement of new dietary sources of amino acids. The turnover of proteins is controlled, thereby allowing the mass of specific enzymes or structural proteins to be altered. The inflow of amino acids from the cells' cytoplasm into the bloodstream enables the body to reroute the amino acid supply from one organ to another.

The body's proteins contain 96% of the total body nitrogen so a study of nitrogen metabolism usually reflects protein metabolism. Other nitrogenous compounds, e.g., creatine, purine and pyrimidine bases and the porphyrins, are all in part derived from amino acids. Not all the 20 amino acids used to provide these nitrogen-containing compounds can be synthesized in sufficient quantity to meet the body's needs. Nine amino acids are classified as essential because they have to be provided as such in the diet (see Table 3.2). Methionine and phenylalanine are required as such and also as sources of cysteine and tyrosine. Histidine cannot be made in sufficient quantity for children's needs so histidine is also specified as an essential amino acid (and may be required for adults). It is suggested that other amino acids, e.g. glycine, may be needed in the diet to boost amino acid availability when the body's demand exceeds its capacity to synthesize the amino acid. Thus the distinction between essential and some non-essential amino acids is becoming blurred [2].

Protein digestion and amino acid absorption

Dietary proteins are digested by a complex of enzymes secreted by the stomach and pancreas. Amino acids and peptides are released by selective enzymic splitting of the protein chains. Peptides are hydrolysed further by intestinal enzymes so amino acids and small peptides are transferred across the intestinal wall.

The intestine itself is rapidly turning over with protein-rich cells continually sloughing into the lumen. The pancreatic, biliary, and intestinal secretions of proteins, together with sloughed cells, contribute a mass of "endogenous" protein to the intestinal pool. This is thought to amount to about 20-80g or more per day [3,4]. Not all this endogenous protein is readily digestible so the residuum, together with any undigested dietary protein and the proteins incorporated into the bacterial population within the small intestine, will pass into the colon where they are fermented by the bacterial flora. Some of the nitrogen released from fermentation is reabsorbed as ammonia which can be re-used by the liver to synthesize non-essential amino acids. Bacterially produced nutrients including amino acids may also contribute to the body's needs. Thus the assessment of protein digestibility by simply monitoring dietary protein (or N) intake and faecal nitrogen excretion neglects a multiplicity of events within the intestine. The differences between intake and faecal excretion may bear little relationship to the true amino acid supply if considerable amounts of essential amino acids are lost into the colon to be reabsorbed as energy sources such as volatile fatty acids and as ammonia. The true digestibility of dietary proteins in man is therefore uncertain.

Nevertheless, proteins from hen's eggs, cow's milk, meat and fish are usually considered to be 100% absorbed in adults. Protein-containing foods from plant sources are not so readily digested and the true digestibility is more difficult to calculate because of non-protein N-containing compounds in the plant food. The fall in apparent digestibility reflects both an increase in faecal N output, which stems from increased transfer of sloughed cells and protein into the colon, and the additional proliferation of colonic bacteria once a greater supply of undigested polysaccharides enters the colon to provide energy for bacterial proliferation.

Large intakes of fibre-rich foods, especially those containing cereal bran, reduce the apparent digestibility of protein by about 10%. Diets based on coarse whole-grain cereals and vegetables may be given a digestibility value of 85% and those diets based on refined cereals a correction value of 95%.

Amino acid metabolism

Amino acids are transported from the intestine in both the red cells and plasma, and are extracted first by the liver and then by the other tissues. Specific transport systems under hormonal control determine the distribution of amino acids, which themselves not only provide the building blocks for new protein synthesis but may also stimulate an "anabolic drive" of hormonal secretion and tissue responses to amplify the formation of specific proteins [5]. The "anabolic drive" may explain the selective effect of dietary proteins, and particularly those of animal origin rich in essential amino acids, in stimulating the longitudinal growth of children. In addition to protein synthesis individual amino acids are needed for other metabolic functions, including the synthesis of peptide hormones, nucleic acids, neurotransmitters to control brain cell communication, and other hormones.

The use of the amino acids for protein synthesis depends upon the balance of need between the fast and slow turnover proteins [6] and on the controlled changes in synthesis and breakdown occurring in response to dietary changes [7,8]. The amino acid composition of each protein is fixed so the controlled synthesis of a particular array of proteins determines the amino acids needed. If some amino acids are not available in adequate amounts then the synthetic machinery competes for the limiting amino acids and cannot synthesize the whole range of proteins in the intended quantities. Thus amino acid intake may be too limited for the requirements of the growing child or when an adult needs to produce a greater mass of specific proteins, e.g. during pregnancy or lactation or when responding to an infection with the production of antibodies.

Each amino acid has its own pathway for oxidation. They are metabolised and excreted as carbon dioxide, water and as urea formed by the liver. The enzymatic oxidative pathway of each amino acid is controlled in part by the inflow of the amino acid so an excess supply leads to its preferential oxidation. The oxidation of one amino acid may, however, be affected by the inflow of other dietary amino acids so the rate of oxidation of an amino acid may not be solely dependent on its accumulation in the cellular pools of the tissues.

The concept that oxidation reflects an "overflow" of an excess intake has been used to assess amino acid requirements by monitoring the oxidative loss of isotopically labelled carbon or nitrogen in the amino acid at different levels of amino acid intake. The total amount of amino acid catabolized to carbon dioxide and urea is not equivalent to the requirement for absorbed amino acid because of other irretrievable losses. Proteins are lost as hair, in skin and intestinal cells, in bronchial and other secretions and in lactating women as milk protein. New protein formation during growth, pregnancy and early lactation also has to be estimated. Amino acids are also

being lost from the body, as other metabolic non-reutilizeable products such as creatinine and some hormones. It is the total utilisation of each amino acid which determines its turnover ; the requirement is that minimum dietary intake needed to supplement the body's synthesis of the amino acid and meet minimum synthetic and catabolic processes. This approach neglects the potential need for a greater supply than the minimum to stimulate the "anaholic drive" or to sustain protein synthesis rates at a higher "optimum" level than the minimum.

Adults in N balance are assumed to be eating enough protein once an allowance is made for the irretrievable loss of body proteins. Egg or milk protein is used since these proteins are readily digested with a presumed 100 % small intestinal recovery and the protein's amino acid composition is well balanced. The amino acid needs of children and adults are also usually determined by N balance. Faecal and urinary nitrogen output are determined and the net loss of body proteins and amino acids estimated as nitrogen.

If the intake of an essential amino acid falls below the body's needs then the other available amino acids cannot be used to sustain body protein metabolism; they are therefore present in relative excess and have to be oxidised with further urea synthesis and urinary N loss. Thus the N output can be monitored at different carefully defined intakes to find the level which induces the lowest urinary N output. This gives a value for the minimum dietary requirement and includes provision for other losses in skin hair and secretions [9].

Responses to a low protein intake

The body adjusts to a low protein intake by adapting over a period of up to a week during which there is a net loss of body protein amounting to about 1.5% of the total protein mass [10]. The reduced inflow of amino acids into the body fails to meet the body's needs for protein synthesis and amino acids are initially oxidised by the highly active catabolic enzymes, which were set at their prevailing level by the previous protein intake. Protein breakdown continues despite the fall in protein synthesis so there is a net loss of protein. However the amino acid catabolic enzymes begin adjusting within hours so the experimental evolution of isotope from ^{14}C or ^{15}N labelled amino acids is rapidly reduced. As adaptation occurs there is an immediate fall in urinary nitrogen excretion as urea synthesis falls and amino acid catabolism declines. Thus amino acids derived from both the diet and from protein breakdown are conserved and channelled preferentially into protein synthesis; activating enzymes for protein synthesis are stimulated and the enzyme activities involved in the urea cycle and in amino acid catabolism decline [11]. The conservation of the essential amino acids, which is a fundamental feature of the metabolism of

animals, including man, is accentuated. The rates of breakdown of body proteins and of amino acid exchange across cellular membranes are further reduced so internal recycling of amino acids within the body's cells is enhanced. The residual amino acids entering the blood are also preferentially channelled into protein synthesis rather than oxidation. The factors controlling these events are largely unknown.

If no dietary protein is given but energy intake is maintained then urinary N falls even further as the catabolic amino acid enzymes adjust to the complete absence of dietary protein. This obligatory nitrogen loss (ONL) on a protein-free diet reflects the progressive loss of body protein in the faeces, as urea in the urine and as sloughed and secreted proteins. In a series of 11 studies involving more than 200 adults aged 22-77 years from many different countries the observed ONL did not differ greatly (mean, 53 mg N/kg bodyweight /d; range, 41-69 mg) and corresponded to a mean milk protein intake of 0.33 g/kg bodyweight /day [1].

Excessive intakes of protein and amino acids

Excessive protein intake may be associated with health risks, but the level of intake at which a risk is induced and the precise role of protein in the pathophysiological processes remain uncertain. The principal concerns relate to the maintenance of renal function and bone mass. High protein intakes seem to accelerate loss of renal function in some kidney diseases, but whether these effects of dietary protein are relevant to the general population remains uncertain [12]. Similarly the potential for excess dietary protein to mobilise bone calcium and accelerate bone loss needs further study [13].

Animal studies indicate that an unusually high intake of a single amino acid may induce not only a loss of appetite but also secondary metabolic changes in metabolism which are disadvantageous. Recent reports of toxic effects associated with the ingestion of unusual amounts of tryptophan may relate to toxic contaminants but the use of supplements of selected amino acids in individuals on European diets is unwise.

Physiological requirements for protein

Early attempts to estimate protein requirements in adults depended on determining the obligatory nitrogen loss (ONL) of volunteers and then adding each component of the N or protein loss or extra factors. It was assumed that 100% of the milk protein fed was efficiently utilised. In practice the provision of milk protein in amounts

corresponding to the ONL is inadequate to induce N balance because the observed loss of N increases above the ONL value. This is because the input of dietary amino acids necessarily stimulates a modest increase in amino acid oxidation and therefore a 25-50 % rise in urinary N output. The minimum requirement for totally digestible protein of high amino acid quality is therefore greater than the ONL and it is this higher intake to maintain N balance which is taken as the minimum dietary requirement under practical everyday conditions [1]. Measuring N balance is not easy because analytical losses of dietary or urinary nitrogen give the false impression of better N accumulation in the body. Repeated studies with short-term balances measured over about 2 weeks provide estimated mean protein requirements of 0.63 g milk or egg protein per kg bodyweight per day. Longer term balance studies over 1-3 months on 34 adults fed egg or milk protein suggested an average minimum protein requirement of 0.58 g/kg bodyweight/d so the WHO/FAO/UNU Committee [1] chose an average of 0.6 g protein/kg bodyweight/d as a reasonable minimum figure for both adult men and women.

This figure is considered to be the average minimal value of dietary protein compatible with sustained nitrogen balance in health. The intakes needed to achieve N balance have a coefficient of variation of 12.5 %. Thus the minimum on which an individual may sustain N balance can vary from about 0.45 g/kg/d to 0.75 g/kg/d. This upper figure is considered likely to cover the needs of all subjects and has therefore been designated a "safe" protein intake for healthy young adults. The various values for protein intake are included in Table 3.1.

Protein quality and essential amino acid requirements

Table 3.2 provides estimates of the essential amino acid intakes based on the classic studies of Rose [14] as adjusted by FAO/WHO [9]. Rose undertook highly controlled feeding studies on volunteers fed adequate intakes of all the amino acids except the amino acid under test. Therefore the studies were not conducted under physiological conditions and little is known of the potential impact of the concentration of the other amino acids on the catabolism of the tested amino acid.

Several authors have suggested that in adults these estimates of essential amino acid requirements are too low. In short term balance studies, purified amino acid mixtures containing more than the current requirement level have failed to allow balance to occur. From a series of recent experiments on the kinetics of essential amino acid metabolism in which the minimal physiological requirement might be obtained by estimating the obligatory rates of oxidation of essential amino acids, Young *et al* [15] have suggested new requirement values which are about two or three times higher than current requirement figures. However these high estimates have

been challenged [5,16] on methodological and theoretical grounds. The relatively low requirements estimated for adults have been confirmed by a series of nitrogen balance studies on normal volunteers fed normal diets rather than purified amino acid mixtures [17]. There seems to be an appreciable need for non-essential amino acids or N for their synthesis at low protein intakes but detailed studies are still awaited.

Children

The assessment of needs made by the FAO/WHO/UNU Consultation [1] has not been superseded by new information suggesting the need for any changes in the protein requirement of children. The values are based on the amount of high quality egg or milk protein needed for achieving N balance plus the additional need for growth. Table 3.3 shows requirements for children, with a 50% increase being added to the average requirement to take account of the day to day variability in growth. The efficiency of utilisation was assumed to be 70% with all children receiving adequate energy intakes. Breast milk N, although containing appreciable quantities of non-amino N, is extremely well utilised for reasons which are unclear. It is therefore unwise to rely on breast milk data in producing recommendations on protein need for bottle-fed babies. Table 3.3 is derived from the FAO/WHO/UNU report [1] but taking account of European growth patterns. The values all refer to milk protein, which is assumed to be completely absorbed. Digestibility of dietary protein will vary from 80 to 100% of the reference protein depending on the type of diet consumed; cereal diets rich in fibre have digestibility values between 80 and 90%. Adjustments for lower quality protein will need to be made in the manner suggested by FAO/WHO/UNU [1], where the total protein intake is increased to ensure that the intake of each essential amino acid is equivalent to that which would have been obtained from milk protein.

The essential amino acid requirement as a proportion of the protein requirement falls markedly with age from 54% in infants to 14% in adults. The reason for this is not completely explained by the high essential amino acid requirements for growth. Examples of the essential amino acid requirements of children aged about two years and 10-12 years are shown in Table 3.2.

Pregnancy

The extra protein needs in pregnancy are usually based on the FAO/WHO/UNU report [1], these values having been accepted by the National Academy of Sciences [18]. The estimates of protein used are based on the original Hytten and Leitch [19] estimates of body compositional changes and their likely protein content, a total of 925 g accumulated protein being accepted by both groups. It is increasingly recognised however that pregnancy is associated with changes in protein metabolism which may well increase the efficiency of utilisation of amino acids [20,21].

so it may be unwise to consider that the accumulated protein gain has to be superimposed on the normal protein requirement of the non-pregnant woman. Given these uncertainties the recommendation of the US RDA committee to increase protein intakes by 10 g reference protein throughout pregnancy seems appropriate.

Lactation

The need for lactation will depend on the amount of breast milk provided but, with suitable allowances for individual variation, an extra protein intake of 16 g/d in the first 6 months is reasonable, with 12 g being needed for the second six months of breast feeding when the child is beginning to derive additional nutrition from foods.

The elderly

There are no grounds for reducing the figure for the protein requirements of the elderly. Data collated by FAO/WHO/UNU [1] suggest that there may be a somewhat greater need, but a safe adult level of 0.75 g/kg bodyweight/d will provide a higher intake per kg of lean body mass in the elderly because of their having lost lean tissue.

Table 3.1 Levels of intake of high quality protein for achieving nitrogen balance in adults.

(g/kg bodyweight/d)

Average minimum protein Requirement	0.6
Population Reference Intake	0.75
Lowest Threshold Intake	0.45

(expressed as g/d)

	Males	*Females*
Average Requirement	45	37
Population Reference Intake	56	47

(increases, g/d)

Pregnancy		10
Lactation	First 6 months	16
	Second 6 months	12

Table 3.2 Estimates of essential amino acid requirements [1]

(mg/kg bodyweight/d)

	Children about 2 y	*Children 10-12 y*	*Adults*	
Amino acid	Mean requirement	Mean requirement	Mean requirement	Population Reference Intake
Histidine	?	?	[8 - 12]*	[16]*
Isoleucine	31	28	10	13
Leucine	73	42	14	19
Lysine	64	44	12	16
Methionine + Cysteine	27	22	13	17
Phenylalanine + Tyrosine	69	22	14	19
Threonine	37	28	7	9
Tryptophan	12.5	3.3	3.5	5
Valine	38	25	10	13
Total without histidine	**352**	**214**	**84**	**111**

* This figure based on work with children [22] remains uncertain with only limited evidence yet available on the essentiality of histidine for adults.

*Table 3.3 Recommended intakes of protein in children, based on milk protein**

Age**	Bodyweight (kg)	Safe level (g protein/ kg bodyweight/d)	Total intake (g/d)***
4-6 m	7.5	1.86	14.0
7-9 m	9.0	1.65	15.0
10-12 m	10.0	1.48	15.0
1.0-1.5 y	11.0	1.26	14.0
1.5-2.0 y	12.5	1.17	14.5
2-3 y	13.5	1.13	15.5
3-4 y	15.5	1.09	17.0
4-5 y	17.5	1.06	18.5
5-6 y	19.5	1.02	20.0
6-7 y	22.0	1.01	22.0
7-8 y	24.5	1.01	24.5
8-9 y	27.0	1.01	27.5
9-10 y	30.0	0.99	29.5
Males 10 y	33.0	0.99	32.5
11 y	36.5	0.98	36.0
12 y	41.0	1.00	41.0
13 y	47.0	0.97	45.5
14 y	53.0	0.96	51.0
15 y	58.0	0.92	53.5
16 y	62.5	0.90	56.5
17 y	64.5	0.86	55.5
Females 10 y	34.0	1.00	34.0
11 y	37.5	0.98	37.0
12 y	43.0	0.96	41.5
13 y	48.0	0.94	45.0
14 y	50.5	0.90	45.5
15 y	52.5	0.87	45.5
16 y	54.0	0.83	45.0
17 y	54.5	0.80	43.5

* Calculated as in Tables 33 and 34 in FAO/WHO/UNU report [1].

** The midpoint of each age group was used, except for those below 2 years, where the ages taken were 6 months, 9 months, 12 months, 1.5 years (for 1.0-1.5 y) and 2.0 years (for 1.5 to 2.0 y).

*** Rounded to nearest 0.5 g.

References

1. World Health Organisation (1985). *Energy and Protein Requirements. Report of a joint FAO/WHO/UNU meeting*. Geneva: World Health Organisation. (WHO Technical Report Series; 724).

2. Jackson AA. (1983). Amino acids: essential and non essential? *Lancet*, i : 1034-1037.

3. Waterlow JC, Garlick PJ, Millward DJ. (1978). *Protein Turnover in Mammalian Tissues and in the Whole Body*. Amsterdam: North Holland Publishing Co.

4. Bernier JJ, Adrian J, Vidon N. (1988). In: *Les Aliments dans le Tube Digestif de l'Homme*. Paris: Doin, 271-281.

5. Millward DJ, Rivers JPW. (1988). The nutritional role of indispensible amino acids and the metabolic basis for their requirements. *Eur J Clin Nutr*, 42: 367-393.

6. Obled C, Barre P, Millward DJ, Arnal M. (1989). Whole body protein synthesis: study with different amino acids in the rat. *Am J Physiol*, 257: E639-E646.

7. Young VR, Meredith C, Hoerr R, Bier DM, Matthews DE. (1985). Amino acid kinetics in relation to protein and amino acid requirements: the primary importance of amino acid oxidation. In: *Substrate and Energy Metabolism in Man*, Garrow JS, Halliday D, eds. London: John Libbey, 119-134.

8. Arnal M, Obled C, Attaix D, Paturcau-Mirand P, Bonnin D. (1987). Dietary control of protein turnover. *Diabete Metab*, 13: 630-642.

9. World Health Organisation (1973). *Energy and Protein Requirements. Report of a joint FAO/WHO/UNU meeting*. Geneva: World Health Organisation. (WHO Technical Report Series; 522).

10. Rand WM, Young VR, Scrimshaw NS. (1976). Change of urinary nitrogen excretion in response to low-protein diets in adults. *Am J Clin Nutr*, 29: 639-644.

11. Waterlow JC. (1985). What do we mean by adaptation? In: *Nutritional Adaptation in Man*. Blaxter K, Waterlow JC, eds. London: John Libbey, 1-11.

12. Klahr S. (1989). Effects of protein intake on the progression of renal disease. *Ann Rev Nutr*, 9: 87-108.

13. Allen LH, Oddoye EA, Margen S. (1979). Protein-induced hypercalciuria: a longer term study. *Am J Clin Nutr*, 32: 741-749.

14. Rose WC. (1957). The amino acid requirements of adult man. *Nutr Abstr Rev*, 27: 631-647.

15. Young VR, Bier DM, Pellette PL. (1989). A theoretical basis for increasing current estimates of the amino acid requirements in adult man with experimental support. *Am J Clin Nutr*, 50: 80-92.

16. Millward DJ, Jackson AA, Price G, Rivers JPW. (1989). Human amino acid and protein requirements: current dilemmas and uncertainties. *Nutr Res Rev*, 2: 109-132.

17. Inoue G, Komatsu T, Kishi K, Fjita Y. (1988). Amino acid requirements of Japanese young men. In: Blackburn GL, Grant JP, Young VR, eds. *Amino Acids: Metabolism and Medical Applications*. Boston: John Wright, 55-62.

18. National Research Council (1990). *Nutrition during Pregnancy*. Washington: National Academy Press.

19. Hytten FE, Leitch I. (1971). *The Physiology of Human Pregnancy*, 2nd ed. Oxford: Blackwell Scientific Publications.

20. Naismith DJ. (1977). Protein metabolism during pregnancy. In: Philipp EE, Barnes J, Newton M, eds. *Scientific Foundations of Obstetrics and Gynaecology*. 2nd ed. Chicago: Year Book Medical Publishers, 503-511.

21. Jackson AA. (1993). Chronic undernutrition and protein metabolism. *Proc Nutr Soc* (in press).

22. Kopple JD, Swendseid ME. (1981). Effect of histidine intake on plasma and urine histidine levels, nitrogen balance, and N^{τ}-methylhistidine excretion in normal and chronically uremic men. *J Nutr*, 111: 931-942.

4. Essential fatty acids

Physiology and metabolism

Dietary fat is a major source of energy and also provides fat soluble vitamins and essential fatty acids. The properties of dietary fat are primarily determined by the composition of its fatty acids, which may be saturated (no double bonds), monounsaturated (one double bond) or polyunsaturated (2 or more double bonds).

Certain polyunsaturated fatty acids (PUFA) of the n-6 and n-3 series (with the terminal double bond 6 or 3 carbon atoms from the methyl end) cannot be synthesized by man and must be supplied with the diet to avoid deficiency. The major PUFA in vegetable oils, linoleic acid (18:2n-6*), until recently was thought to be the only true essential fatty acid. Linoleic acid can be converted into other n-6 fatty acids, such as dihomo-γ-linolenic acid (20:3n-6) and arachidonic acid (20:4n-6), by consecutive desaturation and chain elongation. These longer chain n-6 fatty acids have an even stronger essential fatty acid activity and specific physiological functions [1,2].

N-6 fatty acids are not interconvertible with n-3 fatty acids, such as α-linolenic (18:3n-3) found in some vegetable oils, and eicosapentaenoic (20:5n-3) and docosahexaenoic acids (22:6n-3) found in marine fish. N-3 fatty acids must be independently supplied in the diet.

Linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3) compete for binding to the same enzyme system, for which α-linolenic acid has a higher affinity. Excessive dietary intakes of α-linolenic acid in relation to linoleic acid may reduce tissue levels of linoleic acid metabolites.

PUFA are indispensable lipid components of cellular and subcellular membranes in all tissues. The extent to which they are incorporated into membranes consequent upon their availability modulates a variety of membrane functions, including membrane fluidity, permeability for metabolic exchange, activity of membrane-bound

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* In the short formula describing fatty acids, the first figure represents the number of carbon atoms, the second figure after a colon represents the number of double bonds, and finally the position of the terminal double bond is indicated (n-x).

enzymes and receptors, electrical and humoral signal transduction, and hence properties of cells and organs [1,2].

Some highly unsaturated fatty acids (20:3n-6, 20:4n-6, 20:5n-3) are also required as precursors for the synthesis of eicosanoids. These biologically active compounds, which include prostaglandins, thromboxanes, prostacyclins and leukotrienes, are regulators of the cardiovascular system, blood coagulation, renal function, inflammation and immune response, and a large variety of other tissue functions.

The quality and quantity of dietary fat intake is related to several risk factors for the occurrence of coronary heart disease. This report however is restricted to the requirements for essential fatty acids and is not concerned with recommendations for the reduction of risk of coronary heart disease.

Levels of deficiency and excess

Clinical signs of linoleic acid (18:2n-6) deficiency, such as growth failure and skin changes, may develop in healthy newborn infants fed a diet with less than 1 % of energy as linoleic acid for 2-3 months [2,3]. In human adults, clinical linoleic acid deficiency has been described only in individuals with chronic disease states or after long-term intravenous feeding. Minimal requirements of linoleic acid for preventing clinical signs of deficiency in healthy adults are not well defined. The occurrence of human α-linolenic acid (18:3n-3) deficiency has been reported [4,5] but the evidence has been questioned [6,7]. Deficiency of n-6 and n-3 very long-chain PUFA (metabolites of linoleic and α-linolenic acids) may occur during the perinatal period [8] but has not been documented in human adults. However, it must be assumed that human adults do require a certain amount of n-3 fatty acids to replace physiological losses (e. g. oxidation and eicosanoid formation, losses with cellular debris).

A large number of infants have been fed formulas with very high amounts of linoleic acid (60 % of total fat) without the occurrence of any apparent short term adverse effects [9]. Nonetheless side effects of very high consumptions of PUFA are conceivable, including formation of potentially toxic lipid peroxides and alterations of immune functions. Diets with a very high ratio of PUFA to saturated fatty acids (P/S-ratio) cause an undesirable decrease of high-density lipoprotein (HDL) cholesterol, while similar absolute PUFA intakes with higher fat intakes and lower P/S-ratios are not associated with this side effect [10,11,12]. High intakes of very long-chain n-3 fatty acids may increase rates of bleeding and apoplectic insults. Therefore, it appears prudent to avoid extremely high dietary intakes of PUFA.

An increased intake of PUFA raises the need for vitamin E to prevent unwanted oxidation. Fortunately foods rich in PUFA tend to contain sufficient vitamin E, but this is not always the case, and may not necessarily be so in preparations of supplements. With high dietary intakes of PUFA it is essential to ensure that the intake of vitamin E is adequate.

Methods of establishing physiological requirements

Adults

Minimal requirements for linoleic acid in human adults are not well established. There are no long-term studies on the amount of linoleic acid required to maintain a stable body pool. In laboratory rats a low dietary intake of linoleic acid leads to an increase of a specific trienoic acid (20:3n-9) and the triene-tetraene ratio (ratio 20:3n-9/20:4n-6). It has been proposed that an increased triene-tetraene ratio may also indicate linoleic acid deficiency in human adults, but there are not enough data to support this assumption or to establish a reliable threshold level of this ratio above which clinical signs of deficiency would appear. Therefore, linoleic acid requirements of healthy adults can only be estimated roughly from the results of feeding studies in infants. As a lower threshold of habitual intake below which deficiency is probable or metabolic integrity is unlikely to be maintained, 0.5 % of dietary energy is suggested. Average physiological requirements are estimated to be 1 % of dietary energy. With a certain margin of safety, a Population Reference Intake of 2 % of dietary energy is proposed.

In addition to n-6 fatty acids, n-3 PUFA (α-linolenic acid and its metabolites) should be supplied to replace physiological losses of endogenous stores. It may be concluded from data on current dietary habits in Europe that an intake of 0.2 % of energy as n-3 PUFA results in no apparent clinical signs and appears to meet average physiological requirements. With a certain margin of safety, a Population Reference Intake of 0.5 % of dietary energy is proposed.

It appears prudent to set upper limits for the dietary intake of PUFA because of potential untoward side effects of excessive consumption, such as lipid peroxidation, immunosuppression and bleeding.

Administration of fish oil providing 1.5 % n-3 PUFA (mainly eicosapentaenoic acid)/d over several months was associated with bleeding problems in adolescents and young adults [13]. Suppression of antiinfective functions of leukocytes occurred in human subjects consuming diets containing 6.3 % of energy as α-linolenic acid [14] or receiving fish oil supplements providing approximately 1.5 % of energy as

eicosapentaenoic plus docosahexaenoic acids [15,16]. Dietary n-3 PUFA usually consist mostly of α-linolenic acid, and only a smaller portion is contributed by its metabolites.

It is recommended that habitual intakes of total n-3 PUFA should not exceed 5 % of energy and intakes of total PUFA (n-6 + n-3) should not exceed 15 % of energy.

Other groups

There is no evidence that essential fatty acid requirements during pregnancy and lactation are different, if they are expressed as percentages of energy intake.

It has been suggested [9] that the dietary essential fatty acid intakes for formula-fed infants should be 4.5 % of energy for n-6 PUFA and approximately 0.5 % of energy for n-3 PUFA and these are now put forward as PRIs for infants 6-11m. Population Reference Intakes for children aged 1-3 years should be 3 % of energy for n-6 PUFA and 0.5 % of energy for n-3 PUFA. Population Reference Intakes for children from 4 years, expressed as percentages of energy intake, should be the same as those for adults.

Summary

Expressed as a percentage of dietary energy

Adults		
	n-6 polyunsaturated fatty acids	**n-3 polyunsaturated fatty acids**
Average Requirement	1	0.2
Population Reference Intake	2	0.5
Lowest Threshold Intake	0.5	0.1
Pregnancy	As for all adults	
Lactation	As for all adults	
Children	**PRI**	
Age	n-6 PUFA	n-3 PUFA
6 - 11 m	4.5	0.5
1 - 3 y	3	0.5
4 - 6 y	2	0.5
7 - 10 y	2	0.5
11 -14 y	2	0.5
15 -17 y	2	0.5

These values can be expressed for average energy expenditures in g PUFA/d.

Adults	*Males*		*Females*	
	n-6 PUFA	n-3 PUFA	n-6 PUFA	n-3 PUFA
Average requirement	3	0.6	2.5	0.5
Population Reference Intake	6	1.5	4.5	1
Pregnancy (from 10th week)			5	1
Lactation			5.5	1

Population Reference Intakes for younger age groups (g PUFA/d)

Age group		n-6 PUFA	n-3 PUFA
	6 - 11 m	4	0.5
	1 - 3 y	4	0.7
	4 - 6 y	4	1
	7 - 10 y	4	1
Males	11-14 y	5	1
	15-17 y	6	1.5
Females	11-14 y	4	1
	15-17 y	5	1

Level above which concern should be expressed about possible development of metabolic abnormalities:

n-3 PUFA	5% of dietary energy
n-3 PUFA + n-6 PUFA	15% of dietary energy

References

1. Yamanaka WK, Clemans GW, Hutchinson ML. (1981). Essential fatty acid deficiency in humans. *Prog Lipid Res*, **19:** 187-215.

2. Koletzko B. (1986). Essentielle Fettsäuren: Bedeutung für Medizin und Ernährung. *Akt Endokrin Stoffw*, **7:** 18-27.

3. Hansen AE, Wiese HF, Boelsche AN, Haggard ME, Adam DJD, Davis H. (1963). Role of linoleic acid in infant nutrition. Clinical and chemical study of 428 infants fed on milk mixtures varying in kind and amount of fat. *Pediatrics*, **31:** 171-192.

4. Holman RT, Johnson SB, Hatch TF. (1982). A case of human linolenic acid deficiency involving neurological abnormalities. *Am J Clin Nutr*, **35:** 617-523.

5. Bjerve KS, Fischer S, Alme K. (1987). Alpha-linolenic acid deficiency in man: effect of ethyl linolenate on plasma and erythrocyte fatty acid composition and biosynthesis of prostanoids. *Am J Clin Nutr*, **46:** 570-576.

6. Koletzko B, Cunnane S. (1988). Human alpha-linolenic acid deficiency. *Am J Clin Nutr*, **47:** 1084-1085.

7. Anderson GJ, Connor WE. (1989). On the demonstration of ω-3 essential-fatty-acid deficiency in humans. *Am J Clin Nutr*, **49:** 585-587.

8. European Society for Paediatric Gastroenterology and Nutrition, Committee on Nutrition (1991). Committee report – Comment on the content and composition of lipids in infant formulas. *Acta Paediatr Scand*, **80:** 887-96.

9. Widdowson EM. (1989). Upper limits of intakes of total fat and polyunsaturated fatty acids in infant formulas. *J Nutr*, **119:** 1814-1817.

10. Bonanome A, Grundy SM. (1988). Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels. *N Engl J Med*, **318:** 1244-1248.

11. Brinton EA, Eisenberg S, Breslow L. (1990). A low-fat diet decreases high-density lipoprotein (HDL) cholesterol levels by decreasing HDL apolipoprotein transport rates. *J Clin Invest*, **85:** 144-51.

12. Mensink RP, Katan MB. (1989). Effect of a diet enriched with monounsaturated or polyunsaturated fatty acids on levels of low-density and high-density lipoprotein cholesterol in healthy women and men. *N Engl J Med*, **321**: 436-441.

13. Clarke JTR, Cullen-Dean G, Regelink E, Chan L, Rose V. (1990). Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. *J Pediatr*, **116**: 139-141.

14. Kelley DS, Branch LB, Love JE, Taylor PC, Rivera YM, Iacono JM. (1991). Dietary α-linolenic acid and immunocompetence in humans. *Am J Clin Nutr*, **53**: 40-46.

15. Lee TH, Hoover RL, Williams JD, Sperling RI, Ravalese J, Spur BW *et al.* (1989). Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on *in vitro* neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med*, **312**: 1217-1224.

16. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JWM *et al.* (1989). The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med*, **320**: 265-271.

5. Vitamin A

Physiology and metabolism

Vitamin A can be obtained in two ways: as preformed vitamin A (retinol) and as carotenoid pigments that can be cleaved in the body to give retinol. Preformed vitamin A (usually in the form of retinyl esters) occurs naturally only in animals. It is also synthesized for fortification of foodstuffs and inclusion in pharmaceutical preparations. Most of the vitamin A in European diets comes as preformed vitamin A, but a substantial contribution is made by carotenoids, mainly from plant foods, and overwhelmingly as β-carotene, although some other carotenoids can also act as provitamins A.

The two contributions have to be added to give the total vitamin A activity. The widely accepted convention is that as they usually come in the diet 6 μg β-carotene and 12 μg other provitamin A carotenoids can be considered to be nutritionally equivalent to 1 μg retinol. The weights of provitamin A carotenoids are converted to the equivalents of retinol and added to the weight of preformed retinol, to express the total vitamin A in terms of retinol equivalents, e.g. an intake of 1800 μg β-carotene plus 600 μg retinol would amount to 300 + 600 = 900 μg retinol equivalents [1]. Retinol equivalents are replacing the older international units (1 international unit = 0.3 μg retinol) as a measure of vitamin A activity, in part because of the problem of adding in the contribution of dietary carotenoids

Provitamin A carotenoids raise a difficult problem of bioavailability. Carotenoids are absorbed better from some foodstuffs and diets than from others and the percentage converted to retinol depends to some extent on how much is ingested in a meal. The vitamin A potency will therefore vary quite substantially according to circumstances [1]. For practical purposes it is necessary to select some value that can be used routinely and the factors mentioned were chosen by an FAO/WHO Expert Group [1]. Taken over a period of time and a variety of foodstuffs, they are a crude but serviceable compromise. They have been used for many years and are internationally accepted; there seems no reason to propose any change.

The conversion of carotenoids to retinol takes place mainly in the intestinal mucosa. The newly formed retinol, along with any preformed retinol in the diet, is esterified in the intestinal mucosa and transported to the liver. The liver is the major organ for storage of reserves of esterified vitamin A. Retinyl esters in the liver are hydrolysed to free retinol, which is put into the plasma on a carrier protein, retinol-binding

protein. The rate of output of retinol from the liver is controlled so as to keep the plasma retinol concentration fairly constant. Dietary vitamin A surplus to immediate requirements is used to build up liver reserves, which can subsequently be drawn upon during any temporary dietary shortage.

Retinol is delivered by retinol-binding protein to the tissues that utilize it. In the eye it serves in its aldehyde form as the light-gathering part of the visual pigments. In other organs it has different functions, being necessary for growth and development and for the normal differentiation of cells; in this role, perhaps in the form of retinoic acid, it appears to react with nuclear receptors to modify gene expression [2].

Levels of deficiency and excess

The reserves of retinyl esters in the liver can be used to maintain the plasma retinol concentration reasonably constant, so normal delivery to target organs can continue. Only when the liver reserves are exhausted does the plasma retinol concentration fall below 20 µg/dl (0.7 µmol/L) and deficiency signs begin to appear. An early indication is impaired adaptation to low-intensity light (night blindness). Other signs show, and in the later stages dryness of the conjunctiva and cornea (xerophthalmia) develops, which can lead to permanent eye damage.

Intakes of vitamin A in excess of needs are used to build up liver reserves of retinyl esters. If however very large amounts of retinol and retinyl esters are ingested, they can overwhelm this liver mechanism and cause liver and bone damage, hair loss, double vision, vomiting, headaches and other abnormalities.

Large single doses (e.g. 300 mg in adults) can cause acute toxicity, but hypervitaminosis A usually arises from chronic ingestion of retinol or retinyl esters, not necessarily in very large amounts (e.g. 15 mg per day) but sufficient over a period of time to build up stocks that exceed the liver's ability to store or destroy them [3]. It has been suggested that even lower daily doses can cause liver damage if taken for long enough [4].

Worst of all, retinol and retinyl esters are highly teratogenic [3], probably as a consequence of the excessive formation of retinoic acid, which modulates gene expression [2] and is a natural morphogen [5]. The lowest intake of retinol (free or esterified) that has teratogenic potential cannot be estimated reliably from the available data. Regular consumption of more than 6,000 µg per day has been associated with birth defects, but the risk seems not to be high unless much larger amounts are taken; chronic intakes of 30,000 µg per day will almost certainly be teratogenic [3].

It is recommended that single doses of retinol and retinyl esters should not exceed 120 mg retinol equivalents, and regular intakes should not exceed 9,000 µg/d for adult men, and 7,500 µg/d for women that are not pregnant or likely to become pregnant [6]. Pregnant women should not take supplementary vitamin A except under medical supervision. Proportionately lower amounts are suggested for children [6].

β-Carotene does not cause hypervitaminosis A because it cannot be converted to retinol sufficiently quickly.

Methods of establishing physiological requirements

As mentioned, vitamin A absorbed in excess of immediate needs is stored in the liver in esterified form. The size of the liver reserve is therefore the best objective measure of vitamin A status, and is commonly used for post-mortem studies.

A biochemical measure that can be easily made in living subjects is the plasma retinol concentration, but this is an insensitive indicator of vitamin A status, for a homoeostatic mechanism maintains the plasma level reasonably constant over quite a wide range of liver reserves. The plasma retinol concentration falls to a potentially hazardous level only in the later stages of deficiency, when other signs are beginning to show.

Most recommendations for the vitamin A requirements of adults have been based on repletion studies with vitamin A-depleted human volunteers. The best known are the so-called Sheffield experiment in UK [7] and a later, and more thorough, American investigation [8,9]. In these studies increasing doses of vitamin A were given to depleted volunteers to cure deficiency signs such as impaired dark adaptation, abnormal electroretinograms, follicular hyperkeratosis and lowered blood haemoglobin and also to restore normal plasma retinol concentrations.

Another approach suggested by Olson [10] defines vitamin A status in terms of an adequate body pool size, conveniently expressed in terms of the liver vitamin A content. Olson proposed as a criterion for vitamin A sufficiency a liver concentration of 20 µg retinol (or the equivalent in the esterified form) per g wet weight liver. This level for vitamin A reserves meets a number of criteria [7].

1. No clinical signs of deficiency have been noted in subjects with this liver concentration.

2. This liver concentration will maintain a steady-state concentration of retinol in the plasma above 20 µg/dl (0.7 µmol/L).

3. This concentration should maintain an adult on a diet containing no vitamin A free from deficiency signs for a period of months.

Translation of physiological requirements into dietary intake

Olson [10] suggested a method of calculating the mean dietary intake needed to maintain a liver retinol concentration of 20 µg/g assuming that the liver reserves represent 90% of the total body vitamin A and the efficiency of storage in the liver of an ingested dose of vitamin A is 50% (reported values 40-90%).

Studies with radioactive vitamin A in eight adult male volunteers [5] gave a mean fractional catabolic rate, i.e. the percentage of total body stores lost per day, of 0.5%. Calculations based on this and the assumptions mentioned gave a mean dietary intake of 6.7 µg retinol per kilogram body weight per day. For a 75 kg man this would be 503 µg/d; for a 62 kg woman, 415 µg/d.

The coefficient of variation for the rates of depletion in these experimental subjects was about 20%, so the mean ± 2SD daily dietary requirement would be 503 µg ± 201 for men and 415 µg ± 166 for women.

Although these calculations rest on a number of assumptions that have to be arbitrary and will not hold in all circumstances, the derived requirements appear consistent with the effects on deficiency signs observed in depletion-repletion studies in human volunteers [7,8,9]. They also provide some indication of what the range of individual requirements might be, even though only eight subjects were investigated. Such calculations have been used as the basis of the latest FAO/WHO [11] and UK [12] recommendations.

Other reviewing bodies have preferred to base their recommendations on repletion studies. Some indeed specifically reject the body pool approach [13,14], in part because of some doubts about the assumptions underlying the calculations, but mainly because it was thought safer to have reserves in the liver higher than 20 µg/g, and to aim for a plasma retinol concentration above 30 µg/dl (1 µmol/L) rather than 20 µg/dl (0.7 µmol/L). Mild deficiency signs have been reported in some American volunteers depleted of vitamin A when plasma concentrations were between 20 and 30 µg/dl (0.7-1.0 µmol/L) [13]. To maintain plasma retinol concentrations over 30 µg/dl a mean daily intake of 900 µg appeared to be needed in adult men; the current US RDA for adult men is set at 1000 µg. For adult women it is 800 µg/d [13].

Repletion studies however tend to overestimate requirements because deficiency signs often take some time to improve when a small curative dose of vitamin A is

given, and there is understandable reluctance to keep subjects on low intakes for prolonged periods.

Both the body pool calculations and the interpretations of the results of repletion experiments are open to criticism not least because both have to be based on a small number of subjects. There are also differences of opinion on what criterion of vitamin A sufficiency should be adopted, notably in terms of the plasma retinol concentration.

Although a homoeostatic mechanism maintains the plasma retinol concentration reasonably constant in an individual, the levels differ between communities. In industrialised countries the values are usually high, e.g. in a recent survey in UK, the mean plasma retinol concentrations for adult men and women were 63 µg/dl (2.2 µmol/L) and 54 µg/dl (1.9 µmol/L) respectively [15]. In other parts of the world much lower concentrations seem compatible with normal function and health. For example, many Thais maintain concentrations below 30 µg/dl (1 µmol/L) even when liver stores are quite high [16].

It is unclear why in prosperous communities high plasma retinol concentrations are normal and why some such subjects when given an A-low diet start to develop deficiency signs at plasma concentrations well above those maintaining health and normal function in other countries. The possibility should be considered that some populations have adapted to a high dietary intake of retinol and their high plasma concentrations are a consequence of that adaptation.

Europeans and North Americans are unlikely to need plasma retinol concentrations higher than are adequate for many other nations. The National Research Council [13] recommended for USA an allowance of 1000 µg/d in order to maintain a plasma retinol concentration of 30 µg/dl (1 µmol/L) in most adult men. Making reasonable assumptions about the coefficient of variation and the consequent range of needs, one would predict, if this recommendation is realistic, that large numbers of men in the world would receive less than the minimum necessary and vitamin A deficiency would be far more widespread than it is. It seems doubtful if it is necessary to maintain a plasma retinol concentration above 30 µg/dl (1 µmol/L) for the whole population.

There seems no need to encourage high consumption of vitamin A in Europe. Intakes appear to be adequate; there is no deficiency. In North America there is some concern about excessive intakes of vitamin A [3]. This Committee [17] has advised women who are or might become pregnant to avoid eating liver because of its high vitamin A content, and has recommended pregnant women not to take supplementary vitamin A in amounts greater than the RDA (here PRI).

In these circumstances it seems better to discourage rather than encourage higher vitamin A intakes. It is proposed that recommendations be based on the body pool procedure as described, i.e. that used by FAO/WHO [8] but with body weights appropriate for Europeans. The rounded off values for adult men and women, expressed in retinol equivalents/d are:

Population Reference Intakes	700 µg (men), 600 µg (women);
Average Requirements	500 µg (men), 400 µg (women);
Lowest Threshold Intakes	300 µg (men), 250 µg (women).

Children

Whereas adult needs for vitamin A seem to be determined largely by the destruction of body stores, children have a requirement for growth, but no good evidence is available for estimating population reference intakes for children.

Most recommendations for formula-fed infants are based on the amounts in breast milk, e.g. the most recent FAO/WHO value of 350 µg retinol equivalents/d [11]. This is likely to be an overestimate as no breast-fed infants ever show signs of A-deficiency, even on intakes of 100-200 µg/d [18,19]. The value of 350 µg retinol equivalents/d is however proposed as the PRI for infants 6-11m.

PRIs for older children are put forward to make a smooth transition from the infant to adult values as shown in the summary. There is little direct evidence to support these values, but they appear unlikely to be underestimates; Reddy [20] has reported that a daily intake of about 300 µg will meet the requirements of pre-school children.

Pregnancy

In pregnancy extra vitamin A is required for the growth of the fetus, for its maintenance, for providing some small reserves for the fetus, and for maternal tissue growth. Much of the requirement for newborn infants seems to be for growth. The fetus grows rapidly during the third trimester, and presumably has needs rising towards those of the newborn.

Recommendations for adult females are intended to maintain a liver concentration of 20 µg retinol equivalents per gram wet weight. Women with such a liver retinol concentration would need an extra supply of retinol to cover the demands of pregnancy. An increment of 100 µg daily throughout pregnancy would enhance

maternal storage to provide adequate vitamin A for the growing fetus in late pregnancy. A PRI of 700 µg retinol equivalents per day is proposed.

Many European women will have intakes of vitamin A higher than that when not pregnant, so their habitual diet will be ample for pregnancy. As mentioned, vitamin A is highly teratogenic, and consumption by pregnant women of more than 6.000 µg per day has been associated with birth defects [3]. Pregnant women on a good diet should not take supplementary vitamin A except under medical advice.

Lactation

If it is assumed that 350 µg retinol is supplied in the milk, the mother needs to have this replaced. The increment proposed throughout lactation is 350 µg retinol equivalents/d.

Summary

(all as µg retinol equivalents/d)

Adults	*Males*	*Females*
Average Requirements	500	400
Population Reference Intake	700	600
Lowest Threshold Intake	300	250

Population Reference Intakes for other groups

Children: Age Group		PRI *(µg retinol equivalents/d)*
	6 - 11 m	350
	1 - 3 y	400
	4 - 6 y	400
	7 - 10 y	500
Males	11 - 14 y	600
	15 - 17 y	700
Females	11 - 14 y	600
	15 - 17 y	600
Lactation		950
Pregnancy		700 (total intake) (Supplements to be taken only under medical advice)

Potentially harmful intakes of retinol (free and esterified)

Single doses should not exceed 120 mg.

Regular intakes should not be greater than the following [15]:

Adults	
Men	9000 µg/d
Women that are not pregnant or likely to become pregnant*	7500 µg/d

Infants	6 - 11 m	900 µg/d
Children	1 - 3 y	1800 µg/d
	4 - 6 y	3000 µg/d
	7 - 10 y	4500 µg/d
	11-17 y	6000 µg/d

Therapeutic doses may exceed these limits, but only under medical supervision.

* Pregnant women should not take supplementary vitamin A except under medical supervision.

References

1. World Health Organisation/Food and Agriculture Organisation. (1967). *Requirements of Vitamin A, Thiamine, Riboflavine and Niacin. Report of a joint FAO/WHO Expert Group*. Geneva: World Health Organization (WHO Technical Report Series; 362).

2. Blomhoff R, Green MH, Berg T, Norum KR. (1990). Transport and storage of vitamin A. *Science*, **250**: 399-404.

3. Hathcock JN, Hattan DG, Jenkins MY, McDonald JT, Sundaresan PR, Wilkening VL. (1990). Evaluation of vitamin A toxicity. *Am J Clin Nutr*, **52**: 183-202.

4. Geubel AP, de Galocsy C, Alves N, Rahier J, Dive C. (1991). Liver damage caused by therapeutic vitamin A administration: estimation of dose-related toxicity in 41 cases. *Gastroenterology*, **100**: 1701-1709.

5. Eichele G. (1990). Pattern formation in vertebrate limbs. *Curr Opin Cell Biol*, **2**: 975-980.

6. Bauernfeind JC. (1980). *The Safe Use of Vitamin A*. International Vitamin A Consultative Group. Washington DC, Nutrition Foundation.

7. Hume EM, Krebs HA. (1949). *Vitamin A Requirement of Human Adults*. London: HMSO. (MRC Special Report Series; 264).

8. Sauberlich HE, Hodges RE, Wallace DL, Kolder H, Canham JE, Hood J, Raica N, Lowry LK. (1974). Vitamin A metabolism and requirements in the human studied with the use of labeled retinol. *Vitam Horm*, **32**: 251-275.

9. Hodges RE, Sauberlich HE, Canham JE, Wallace DL, Rucker RB, Mejia LA, Mohanram M. (1978). Hematopoietic studies in vitamin A deficiency. *Am J Clin Nutr*, **31**: 876-885.

10. Olson JA. (1987). Recommended dietary intakes (RDI) of vitamin A in humans. *Am J Clin Nutr*, **45**: 704-716.

11. Food and Agriculture Organisation. (1988). *Requirements of Vitamin A, Iron, Folate and Vitamin B_{12}. Report of a joint FAO/WHO Expert Consultation.* Rome: Food and Agriculture Organisation. (FAO Food and Nutrition Series; 23).

12. Department of Health. (1991). *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom.* London : HMSO. (Report on health and social subjects; 41)

13. National Research Council. (1989). *Recommended Dietary Allowances*, 10th Ed. Washington DC: National Academy Press.

14. Health and Welfare, Canada. (1990). *Nutrition Recommendations. The Report of the Scientific Review Committee.* Ottawa: Canadian Government Publishing Centre.

15. Gregory J, Foster K, Tyler H, Wiseman M. (1990). *The Dietary and Nutritional Survey of British Adults.* London: HMSO.

16. Suthutvoravoot S, Olson JA. (1974). Plasma and liver concentrations of vitamin A in a normal population of urban Thai. *Am J Clin Nutr*, 27: 883-891.

17. Scientific Committee for Food, Commission of the European Communities (1991). Report on the risks of hypervitaminosis A. Reports of the Scientific Committee for Food, 27th series, 21 June 1991.

18. Belavady B, Gopalan C. (1959). Chemical composition of human milk in poor Indian women. *Ind J Med Res*, 47: 234-245.

19. Butte NF, Calloway DH. (1981). Evaluation of lactational performance of Navajo women. *Am J Clin Nutr*, 34: 2210-2215.

20. Reddy V. (1971). Observations on vitamin A requirement. *Ind J Med Res*, 59 (suppl): 34-37.

6. β-Carotene (and other carotenoids)

β-Carotene is the most abundant member of the carotenoids, a group of pigments of which more than 500 are known. They are widely distributed, particularly in the plant kingdom. In terms of human nutrition, interest in the past concentrated on the function of β-carotene as a precursor of vitamin A. It can be cleaved enzymically to give retinol, mostly in the intestinal mucosa. Some other carotenoids can similarly give rise to retinol, but not so effectively as β-carotene. Most carotenoids have no provitamin A activity and in the past have not usually been considered in human nutrition.

Recently however much interest has been shown in possible functions of β-carotene other than as a provitamin A. It can act as an antioxidant, inactivating certain reactive oxygen species such as singlet oxygen. It can be a chain-breaking antioxidant in a lipid environment, differing from the major fat-soluble antioxidant, vitamin E, in being most effective at the low partial pressures of oxygen found in mammalian tissues [1].

Some of the dietary β-carotene is converted to vitamin A, but some is absorbed intact, and increased dietary intakes are associated with increased plasma concentrations [2].

Carotenoids that are not provitamins A but have a chain of nine or more double bonds would be expected to have essentially the same antioxidant properties. In considering the biological activities of β-carotene other than as a precursor of vitamin A, one should also consider other dietary carotenoids. A number of carotenoids are found in human plasma and tissues, including β-carotene, α-carotene, lycopene, cryptoxanthin and lutein. They may differ in metabolism and rate of uptake by tissues, and thus in biological action [3]. β-carotene (and other carotenoids) can therefore be considered as among the array of antioxidants, including vitamins E and C, which have been implicated in the protection of tissues from disease processes involving free radicals.

Much work with cultured cells, tissue preparations and experimental animals has indicated that β-carotene and other carotenoids may protect against mutagens, decrease malignant transformations, prevent the appearance of tumours and enhance immune responses, among other things [4]. The findings are usually based on either *in vitro* systems or the employment of much larger amounts of carotenoids than in a

normal diet, so their relevance to physiological nutritional requirements in humans is uncertain.

The most persuasive nutritional claim put forward is that a high dietary intake of β-carotene, or carotenoids, confers some protection against cancer. Dietary epidemiological studies have shown fairly consistently that people with a relatively low intake of β-carotene or total carotenoids have a higher risk of cancer, especially lung cancer [5]. There is an inverse correlation between serum β-carotene concentration and risk of cancer [6,7]. While there appears to be an inverse relationship between the consumption of carotenoid-containing fruits and vegetables and the incidence of cancer, there is no proof that β-carotene or carotenoids are the protective factor. Prospective trials of the possible health benefits of β-carotene other than as a provitamin A are in progress. Until the results of these are known, it seems unwarranted to make any recommendation other than to encourage the consumption of vegetables and fruit.

Very high doses of β-carotene may turn the skin yellow, but are not toxic [8].

Summary of proposals

There is as yet insufficient evidence to recommend the consumption of any specific amount of β-carotene, or carotenoids in general, beyond what is needed to supply vitamin A.

References

1. Burton GW. (1989). Antioxidant action of carotenoids. *J Nutr*, **119**: 109-111.

2. Gregory J, Foster K, Tyler H, Wiseman M. (1990). *The Dietary and Nutritional Survey of British Adults*. London: HMSO.

3. Parker RS. (1989). Carotenoids in human blood and tissues. *J Nutr*, **119**: 101-104.

4. Krinsky NI. (1991). Effects of carotenoids in cellular and animal systems. *Am J Clin Nutr*, **53**: 238S-246S.

5. Ziegler RG. (1991). Vegetables, fruits and carotenoids and the risk of cancer. *Am J Clin Nutr*, **53**: 251S-259S.

6. Wald NJ, Thompson SG, Densem JW, Boreham J, Bailey A. (1988). Serum beta-carotene and subsequent risk of cancer: results from the BUPA study. *Br J Cancer*, **57**: 428-433.

7. Stähelin HB, Gey KF, Eichholzer M, Lüdin E, Bernasconi F, Thurneysen J, Brubacher G. (1991). Plasma antioxidant vitamins and subsequent cancer mortality in the 12-year follow-up of the prospective Basel study. *Am J Epidemiol*, **133**: 766-775.

8. Hathcock JN, Hattan DG, Jenkins MY, McDonald JT, Sundaresan PR, Wilkening VL. (1990). Evaluation of vitamin A toxicity. *Am J Clin Nutr*, **52**: 183-202.

7. Thiamin

Physiology and metabolism

The principal metabolic function of thiamin (vitamin B_1) is as the precursor for thiamin diphosphate (thiamin pyrophosphate), which is the coenzyme for a number of reactions involved in carbohydrate and branched-chain amino acid metabolism and central energy-yielding metabolic pathways. In addition thiamin triphosphate has a role in the propagation of nerve impulses in the nervous system [1]. Most thiamin in foods is present as phosphates, mainly thiamin diphosphate. These phosphates are hydrolysed by phosphatases in the intestinal lumen; free thiamin is absorbed in the upper small intestine. The absorption of thiamin is impaired by alcohol. While intestinal mucosal cells take up thiamin normally in the presence of alcohol, there is impaired transport from the cells into the circulation [2]. Some thiamin is phosphorylated to thiamin monophosphate during absorption, or on passage through the liver.

Both free thiamin and thiamin monophosphate circulate at low concentrations in plasma, bound to albumin; they are taken up by tissues, and converted to thiamin diphosphate (and thiamin triphosphate in nerve tissue). At high intakes, when the albumin binding capacity is saturated, the excess (unbound) vitamin is rapidly excreted in the urine. A small amount of thiamin is excreted in the urine unchanged (normally about 3% of a test dose). The major excretory metabolite is thiochrome, although some 20 additional metabolites are excreted in small amounts. There is little storage of thiamin in the body, and metabolic abnormalities develop within a few days of initiating a thiamin-deficient diet.

Deficiency and excess

Thiamin deficiency can result in three distinct syndromes.

(i) Beriberi, a chronic peripheral neuritis, which may or may not be associated with heart failure and oedema.

(ii) Acute pernicious (fulminating) beriberi, in which heart failure and life-threatening metabolic acidosis predominate, with little or no evidence of peripheral neuritis.

(iii) Central nervous system disturbances, Wernicke's encephalopathy with Korsakoff's psychosis. This is most commonly associated with alcoholism and narcotic abuse.

In general, an acute deficiency is involved in the central nervous system lesions of the Wernicke-Korsakoff syndrome, and a relatively high energy intake is a predisposing factor. Beriberi is more commonly associated with a more prolonged, less severe, deficiency, together with a generally low food intake. A higher intake of carbohydrate and physical activity predispose to the development of heart failure and oedema.

The intestinal absorption of thiamin is readily saturated, and no more than about 2.5 mg can be absorbed in a single dose. Thiamin in the bloodstream which is not bound to plasma proteins is rapidly excreted in the urine [8]. There is no evidence of toxicity of thiamin taken by mouth, at intakes of up to 500 mg/day (for 1 month).

Requirements

Adults

Because the principal metabolic role of thiamin is in energy-yielding metabolism, and especially in carbohydrate metabolism, the requirement is related to energy intake. Saturation of the red cell enzyme transketolase with its coenzyme, thiamin diphosphate, provides a convenient means of assessing the adequacy of body reserves of thiamin. This is generally expressed as the transketolase activation coefficient – the ratio of enzyme activity with added thiamin diphosphate/ that without added coenzyme.

Clinical signs of deficiency are seen in subjects receiving less than 30 µg/MJ, so this is obviously an inadequate intake. In a long-term feeding study, an intake of 45 µg/MJ led to a progressive decline in urinary excretion, falling to 15 µg/24h after 20 months. There were no clinical signs of deficiency, but after 30 months there was an impairment in the metabolism of a test dose of glucose [3,4]. This intake is therefore marginally inadequate.

In depletion / repletion studies, intakes of about 50 µg/MJ are adequate to maintain urinary excretion above 15 µg/day. The average requirement for the maintenance of a normal erythrocyte transketolase activation coefficient is 72 µg/MJ [5,6]. Allowing for individual variation, this gives a PRI of 100 µg/MJ. For people on energy intakes of less than 8 MJ/d, thiamin requirements may not be related directly to energy intake. For them a PRI of 0.8 mg/d is suggested.

Maximum activity of erythrocyte transketolase and complete saturation of the enzyme with its coenzyme require an intake of 140-190 µg/MJ [7]. There is no evidence that this confers any benefit, or is a desirable aim.

Other age groups

There is no evidence that thiamin requirements of women differ from those of men, other than as affected by energy expenditure, or that children, adolescents or the elderly have different requirements /MJ energy intake.

Pregnancy and lactation

In pregnancy and during lactation thiamin requirements/MJ energy intake are unchanged. The thiamin produced in the milk should be covered by the extra amount accompanying the increased energy intake.

Summary

The requirement for thiamin depends on the utilisation of energy-yielding substrates. It therefore increases with the energy expenditure.

Average requirement	72 µg/MJ
Population Reference Intake	100 µg/MJ
Lowest Threshold Intake	50 µg/MJ

These can be expressed for average energy expenditure in mg thiamin/d.

Adults	*Males*	*Females*
Average requirement	0.8	0.6
Population Reference Intake	1.1	0.9
Lowest Threshold Intake	0.6	0.4
Pregnancy		1.0 *
Lactation		1.1

* From 10th week of pregnancy

Population Reference Intakes for younger age groups

Age Group		PRI (mg/d)
	6 - 11 m	0.3
	1 - 3 y	0.5
	4 - 6 y	0.7
	7 - 10 y	0.8
Males	11 - 14 y	1.0
	15 - 17 y	1.2
Females	11 - 14 y	0.9
	15 - 17 y	0.9

References

1. Bender DA. (1984). B Vitamins in the nervous system. *Neurochem Int*, 6: 297-321.

2. Hoyumpa AM, Nichols SG, Wilson FA, Schenker S. (1977). Effect of ethanol on intestinal (Na,K)ATPase and intestinal thiamine transport in rats. *J Lab Clin Med*, 90: 1086-1095.

3. Horwitt MK, Liebert E, Kreisler O, Wittman P. (1948). Investigation of human requirements for B-complex vitamins. *Bulletin of the National Research Council* No 116, National Academy of Sciences, Washington DC.

4. Horwitt MK, Kreisler O. (1949). The determination of early thiamine-deficient states by estimation of blood lactic and pyruvic acids after glucose administration and exercise. *J Nutr*, 37: 411-427.

5. Sauberlich HE, Herman YF, Stevens CO, Herman RH. (1979). Thiamin requirement of the adult human. *Am J Clin Nutr*, 32: 2237-2248.

6. Williams RD, Mason HL, Wilder RM. (1943). The minimum daily requirement of thiamine of man. *J Nutr*, 25: 71-97.

7. Brin M. (1964). Erythrocyte as a biopsy tissue for functional evaluation of thiamine adequacy. *JAMA*, 187: 762-766.

8. Morrison AB, Campbell JA. (1960). Vitamin absorption studies 1. Factors influencing the excretion of oral test doses of thiamine and riboflavin by human subjects. *J Nutr*, 72: 435-440.

8. Riboflavin

Physiology and metabolism

Riboflavin is the precursor for the synthesis of two coenzymes, riboflavin phosphate (flavin mononucleotide, FMN) and flavin adenine dinucleotide (FAD), and covalently bound flavin prosthetic groups in enzymes. These function in a variety of enzymes catalysing oxidation and reduction reactions and electron transport; riboflavin is thus involved in a wide variety of metabolic pathways, including the biosynthesis and catabolism of amino acids, fatty acids and carbohydrates.

Apart from milk and eggs, which contain a relatively large amount of riboflavin bound to specific binding proteins, most of the riboflavin in foods is as riboflavin phosphate and FAD bound to enzymes. After release by digestion of the enzyme proteins, the coenzymes are hydrolysed in the intestinal lumen by phosphatases. The resultant free riboflavin is absorbed in the upper small intestine by an active process.

Riboflavin is transported in plasma both as the free vitamin and as coenzymes, largely bound to plasma proteins. There is rapid excretion from tissues of any riboflavin which is not bound to enzymes, and hence functionally active. Riboflavin and riboflavin phosphate which are not bound to plasma proteins are rapidly excreted by the kidneys, both by simple filtration and by active secretion into the urine. Active resorption of riboflavin from the urine is saturated at normal plasma concentrations of the vitamin, and so is mainly important in deficiency, acting to conserve the vitamin.

About 25% of the urinary excretion of riboflavin is as the unchanged vitamin; the remainder is excreted as a variety of metabolites. There is little or no storage of riboflavin in the body; any surplus intake is rapidly excreted. Once intake is adequate to meet requirements, the urinary excretion of the vitamin reflects intake until the capacity for intestinal absorption is exceeded. There is very efficient conservation of tissue riboflavin in deficiency; as the vitamin is released by protein breakdown, it is re-used in the synthesis of new enzymes. Only that relatively small proportion which is covalently bound to enzyme proteins cannot be re-utilised [1].

Deficiency and excess

Riboflavin deficiency is characterised by lesions of the margin of the lips (cheilosis) and corners of the mouth (angular stomatitis), a painful desquamation of the tongue,

so that it is red, dry and atrophic, and a seborrhoeic dermatitis, with filiform excrescences. There may also be conjunctivitis, with vascularisation of the cornea and opacity of the lens, leading to the development of cataract. On a global scale, riboflavin deficiency is common, yet never seems to be fatal, since there is very efficient conservation and reutilization of riboflavin in tissues when the dietary intake is inadequate.

Riboflavin deficiency can also result in secondary deficiency of iron, leading to anaemia; iron absorption is impaired in deficiency, and the utilisation of iron reserves also requires riboflavin. Similarly, riboflavin deficiency can result in impaired formation of the active metabolite of vitamin B_6, and can thus lead to secondary vitamin B_6 deficiency, and can also impair the metabolism of tryptophan, so leading to development of the tryptophan-niacin deficiency disease pellagra [2].

Inadequate riboflavin intake can be demonstrated biochemically by measuring the erythrocyte glutathione reductase (EGR) activation coefficient. EGR is an enzyme which has FAD as a coenzyme; addition of FAD *in vitro* increases its activity. The size of the activation coefficient is inversely related to riboflavin status.

Riboflavin has a low solubility in water, and there is only a limited capacity for absorption. There is also rapid excretion of any riboflavin not bound to enzymes. This means that there is little or no accumulation or storage of the vitamin in the body, and there is no evidence of any toxicity of riboflavin taken by mouth. There is some concern about the safety of high doses of riboflavin given to infants undergoing phototherapy for neonatal hyperbilirubinaemia.

Requirements

Adult males

A number of studies of subjects maintained on controlled intakes of riboflavin over several months, conducted in the 1940s and 1950s, defined the requirements of male adults

Long-term studies of subjects maintained on controlled intakes of riboflavin show that 0.55 mg/d is inadequate to prevent signs of deficiency. Intakes of 0.7 mg/d do not result in deficiency signs over 41 weeks, while in 22 subjects maintained on 0.75-0.85 mg/d, deficiency signs were seen in only one. Epidemiological studies show that clinical signs of deficiency are apparent in subjects whose habitual intake is between 0.5-0.8 mg/d, but not at higher intakes [3,4].

It is thus apparent that a riboflavin intake of 0.55 mg/d is inadequate, and intakes between 0.55-0.8 mg/d are marginally adequate. In subjects maintained on graded intakes of riboflavin from 0.55-3.55 mg/d, there is a clear inflection in the relationship between intake and excretion, with a considerable increase in the excretion of the vitamin as intake is increased from 1.1 to 1.6 mg/d. At intakes of 1.1 mg/d and below, only 2-7 % of a test dose is excreted over 4h, and basal excretion is below 100 µg/24h. At intakes above 1.6 mg/d, 23-37 % of the test dose is recovered in the urine over 4h, and basal excretion begins to increase with intake [4].

There is no information on the excretion of riboflavin at intakes between 1.1 and 1.6 mg/d. Nevertheless, it is clear that intakes below 1.1 mg/d may be adequate to prevent the development of deficiency signs, but do not fill tissue reserves, while intakes above 1.6 mg/d are more than is required, so the excess is excreted. By interpolation, the 'critical intake' at which excretion increases sharply is 1.3 mg/d, and this is taken as the average requirement for adult males [5].

There have been no detailed studies of riboflavin requirements of adults in which the EGR activation coefficient has been used as an index of status. In one report an intake of 0.53 mg/d resulted in a significant elevation of the activation coefficient in 6 weeks, showing that this level of intake is inadequate to prevent the depletion of body reserves and the development of biochemical deficiency [5].

Because of its central role in energy metabolism, it has been conventional to express riboflavin requirements on the basis of energy intake. However, flavoproteins are also involved in a large number of other reactions, so riboflavin requirements are not related only to energy expenditure. The recommendations here are therefore not being given in terms of energy.

The average requirement of adult males is being taken as 1.3 mg/d, as mentioned above. In the urinary excretion studies 1.6 mg/d appeared to be adequate for all adult males, and this is given as the PRI.

Deficiency is highly probable on intakes of less than 0.6 mg/d, and this is taken as the Lowest Threshold Intake.

Adult females

Although not conclusive, there is a fair amount of indirect evidence that the daily amounts of riboflavin required by women are lower than for men. One would expect this *a priori*, and other reviewing bodies have reached this conclusion. The recommendations for adult women are therefore reduced in amounts per day below those of men, roughly in line with body weight. The Average Requirement for women is therefore given as 1.1 mg/d, with a Population Reference Intake of 1.3 mg/d. The

Lowest Threshold Intake is not reduced below 0.6 mg/d, in the absence of any information that it would be safe to do so in women.

Children

These are no good data on the riboflavin requirements of children. The PRIs given are derived from those of young adults on the basis of energy expenditure.

The PRI for infants 6-11 m is based on the finding that Gambian infants in their first 12 months receive 0.2 mg/d, and have a raised EGR activation coefficient. Increasing their intake to 0.4 mg/d restored the EGR activation coefficient satisfactorily [6].

Pregnancy and lactation

Pregnancy is associated with an increased EGR activation coefficient, and in populations where riboflavin intake is marginal clinical signs of deficiency are seen in pregnant women as parturition approaches. *Post partum* the deficiency resolves, despite continued low intake of the vitamin, and secretion of considerable amounts into the milk. While modest supplements during pregnancy prevent the development of deficiency signs, relatively large amounts (about 2.5 mg /d) are required to maintain the EGR activation coefficient within the range seen in non-pregnant women [2]. EGR activation coefficient data are therefore not being used in making a recommendation for pregnancy.

The demand for increased tissue synthesis by the fetus and the mother is estimated as 0.3 mg/d, making the PRI for pregnancy 1.6 mg/d.

The riboflavin content of breast milk varies considerably, being strongly influenced by the mother's recent intake. An increment of 0.4 mg/d is proposed during lactation, to meet the increased metabolic burden and provide an adequate amount in the milk, giving a PRI of 1.7 mg/d.

The elderly

There is no evidence that the riboflavin requirements of the elderly are greater than for younger people.

Summary

(amounts as mg/d)

Adults	*Males*	*Females*
Average Requirement	1.3	1.1
Population Reference Intake	1.6	1.3
Lowest Threshold Intake	0.6	0.6

Population Reference Intakes for other groups

	Age Group	PRI (mg/d)
	6 - 11 m	0.4
	1 - 3 y	0.8
	4 - 6 y	1.0
	7 - 10 y	1.2
Males	11-14 y	1.4
	15-17 y	1.6
Females	11-14 y	1.2
	15-17 y	1.3
	Pregnancy	1.6
	Lactation	1.7

References

1. Bender DA. (1992). *Nutritional Biochemistry of the Vitamins*. Cambridge: Cambridge University Press, 156-181.

2. Bates CJ. (1987). Human riboflavin requirements and metabolic consequences of deficiency in man and animals. *World Rev Nutr Diet*, 50: 215-265.

3. Bro-Rasmussen F. (1958). The riboflavin requirement of animals and man and associated metabolic relations. *Nutr Abstr Rev*, 28: 1-23, 369-386.

4. Horwitt MK, Harvey CC, Hills OW, Liebert E. (1950). Correlation of urinary excretion of riboflavin with dietary intake and symptoms of ariboflavinosis. *J Nutr*, 41: 247-264.

5. Van der Beek EJ, van Dokkum W, Schrijver J, Wedel M, Gaillard AWK, Wesstra A, van de Weerd H, Hermus RJJ. (1988). Thiamin, riboflavin and vitamins B_6 and C: impact of combined restricted intake on functional performance in man. *Am J Clin Nutr*, 48: 14151-1462.

6. Bates CJ, Prentice AM, Paul AA, Prentice A, Sutcliffe BA, Whitehead RG. (1982). Riboflavin status in infants born in rural Gambia, and the effect of a weaning food supplement. *Trans R Soc Trop Med Hyg*, 76: 253-258.

9. Niacin

Physiology and metabolism

Two related compounds, nicotinic acid and nicotinamide, have the biological activity of niacin. Niacin is not strictly a vitamin, and there is no absolute requirement for a source of preformed nicotinic acid or nicotinamide in the diet; nicotinamide can be synthesised from the essential amino acid tryptophan. Requirements for tryptophan and niacin must therefore be considered together, and are generally expressed as 'niacin equivalents' – the sum of preformed niacin plus that provided by endogenous synthesis from tryptophan.

The metabolic function of niacin is as the precursor of the nicotinamide nucleotide coenzymes, NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate), which are involved in a wide variety of oxidation and reduction reactions.

In addition to its role in such reactions, NAD is the source of ADP-ribose for the DNA repair mechanism which is activated by a variety of DNA-breaking mutagens and other toxins. Much of the nicotinamide released by this poly-(ADP)-ribosyl transfer reaction is metabolised further and excreted, so it is likely that heavy exposure to such toxins will increase niacin requirements. There is little evidence that this is nutritionally significant, although toxins have been implicated in the actiology of pellagra in people whose intake of tryptophan and niacin is marginal.

Most of the dietary preformed niacin is present in foods as the nicotinamide nucleotide coenzymes. These are hydrolysed by intestinal enzymes, and the resultant nicotinamide is absorbed either unchanged or as nicotinic acid after deamidation. The niacin in cereals is largely present as a glycoside of nicotinic acid, niacytin. A small proportion of this is hydrolysed by gastric acid, and more free niacin may be liberated in cooking, but 90% of the apparent niacin content of cereals cannot be utilised, and hence is biologically unavailable. The preformed niacin of cereals is usually ignored in calculating intakes.

Tissues can take up either nicotinic acid or nicotinamide from the circulation, and utilise them for the synthesis of the nicotinamide nucleotide coenzymes. The liver has only a very limited capacity for niacin uptake, and functions mainly to release nicotinamide and nicotinic acid synthesised from tryptophan, into the circulation for use by other tissues.

Tryptophan which is not required for net new protein synthesis or the synthesis of specialised metabolites (i.e. both 'surplus' tryptophan derived from the diet and that released by the turnover of tissue proteins) is oxidised in the liver. This is the fate of about 99% of the total dietary intake of tryptophan of an adult in nitrogen balance [1].

The oxidative pathway of tryptophan metabolism leads either to complete oxidation or to the synthesis of the nicotinamide ring of the coenzymes. Therefore, the amount of nicotinamide coenzymes formed from tryptophan changes with the amount of tryptophan available. At normal intakes of tryptophan, about 60 mg dietary tryptophan is equivalent to 1 mg preformed niacin, although there is considerable variation around this figure. The ratio of 60 mg tryptophan equivalent to 1 mg preformed niacin is an over-estimate of the mean requirement, including a 'safety margin' to cover individual variation [2,3]. By convention, the total niacin equivalence of a diet is taken to be the sum of preformed niacin (neglecting that in cereals) plus 1/60 of the tryptophan content.

Nicotinamide arising from the breakdown of the coenzymes which is not required for the synthesis of new coenzyme, and surplus nicotinamide from the diet, are mainly converted to N^1-methyl nicotinamide in the liver. N^1-Methyl nicotinamide may be either excreted unchanged or may undergo further metabolism to methyl pyridone carboxamide before excretion.

Deficiency and excess

An inadequate intake of both tryptophan and preformed niacin leads to the development of the deficiency disease pellagra. Diseases involving impairment of the oxidative metabolism of tryptophan, drugs which inhibit enzymes in the pathway or deficiency of riboflavin and vitamin B_6, both of which are required for the synthesis of nicotinamide nucleotides from tryptophan, can also result in the development of pellagra.

Pellagra is characterised by a photosensitive dermatitis resembling severe sunburn, normally restricted to areas of the skin directly exposed to the sun, although physical pressure on the knees and elbows, and abrasion by clothes around the wrists and ankles, can lead to similar skin lesions in deficient subjects. Advanced pellagra also involves a characteristic depressive psychosis or dementia. The psychosis may also develop in the absence of skin lesions in subjects not exposed to sunlight. Untreated pellagra is fatal because of the severe impairment of nicotinamide nucleotide-requiring reactions in energy metabolism.

Nicotinic acid in modest doses causes a marked vasodilatation, with flushing, burning and itching of the skin. Very large single doses of nicotinic acid may cause sufficient vasodilatation to lead to hypotension; after the administration of 3-6 g of nicotinic acid daily for several days the effect wears off. Nicotinamide does not have this effect.

Doses of nicotinic acid, but not nicotinamide, of 3-6 g/day have a modest, but potentially useful, hypocholesterolaemic and hypolipidaemic effect. At this level of intake there is evidence of liver damage and even clinical liver dysfunction. Use of sustained release preparations of nicotinic acid providing more modest intakes of the vitamin (500 mg/day) may also result in liver damage as a result of prolonged high concentrations in blood and tissues [6].

Requirements

Adults

The only data available on which to base estimates of niacin requirements are the results of depletion-repletion studies in which the amount of preformed niacin or tryptophan required to restore 'normal' excretion of N^1-methyl nicotinamide and methyl pyridone carboxamide was determined [2,3].

In subjects receiving 1 mg niacin equivalents /MJ, the urinary excretion of N^1-methyl nicotinamide fell to the upper limit of that seen in pellagrins, although none of the subjects showed clinical signs of deficiency. Adequate excretion of N^1-methyl nicotinamide is seen in subjects receiving 1.3 mg niacin equivalents /MJ. Allowing for individual variation, the Population Reference Intake is based on 1.6 mg niacin equivalents /MJ energy expenditure.

For people on low energy diets, niacin will be required for the metabolism of tissue reserves of metabolic fuels. It is possible that the requirement for those habitually on intakes below 8 MJ/d also may not be covered by 1.6 mg niacin equivalents /MJ. For such groups a PRI of 13 mg niacin equivalents /d is suggested.

It is likely that there is no requirement for any preformed niacin in the diet under normal conditions, and that endogenous synthesis from tryptophan will meet requirements. Average protein intakes in the EC are about 15% of energy intake. On the assumption that dietary protein provides 14 mg tryptophan /g (a conservative estimate), this represents 2 mg niacin equivalents /MJ energy intake from dietary tryptophan, greater than the Population Reference Intake without any preformed dietary niacin.

Other age groups

There is no evidence that any other group of the population has a requirement for niacin different from that for adult men, other than on the basis of energy expenditure.

Pregnancy and lactation

The hormonal changes associated with pregnancy increase the efficiency of the synthesis of nicotinamide nucleotides from tryptophan. There is thus no increased requirement for niacin in pregnancy. In lactation the Population Reference Intake is for 2 mg niacin equivalents /d above that calculated on the basis of energy intake to allow for the vitamin secreted in milk.

Summary

There is no absolute requirement for preformed niacin in the diet, since endogenous synthesis from normal intakes of tryptophan is more than adequate to meet requirements. There is a requirement for an adequate intake of tryptophan plus niacin, apart from the requirement for tryptophan as an essential amino acid for the maintenance of nitrogen balance. Population Reference Intakes are based on the ratio of 60 mg dietary tryptophan equivalent to 1 mg preformed niacin (i.e. total niacin equivalents = preformed niacin + 1/60 x tryptophan), and assume that intakes of riboflavin and vitamin B_6 are adequate.

Average Requirement	1.3 mg niacin equivalents /MJ
Population Reference Intake	1.6 mg niacin equivalents /MJ
Lowest Threshold Intake	1.0 mg niacin equivalents /MJ

These can be expressed for average energy expenditures as mg niacin equivalents/d.

Adults	*Males*	*Females*
Average Requirement	15	13
Population Reference Intake	18	14
Lowest Threshold Intake	11	9
Pregnancy		14
Lactation		16
Harmful effects	>500 mg/day as preformed nicotinic acid	

Population Reference Intakes for younger age groups

Age Group		PRI (mg niacin equivalents /d)
	6 - 11 m	5
	1 - 3 y	9
	4 - 6 y	11
	7 -10 y	13
Males	11-14 y	15
	15-17 y	18
Females	11-14 y	14
	15-17 y	14

References

1. Bender DA, Bender AE. (1986). Niacin and tryptophan metabolism: the biochemical basis of niacin requirements and recommendations. *Nutr Abstr Rev (Ser A)*, **56**: 695-719.

2. Horwitt MK, Harvey CC, Rothwell WS, Cutler JL, Haffron D. (1956). Tryptophan-niacin relationships in man. *J Nutr*, **60** (supplement 1): 1-43.

3. Kelsay JL. (1969). A compendium of nutritional status and dietary evaluation studies in the United States 1957-1967. *J Nutr*, **99** (supplement 1): 119-166.

4. Winter SL, Boyer JL. (1973). Hepatic toxicity from large doses of vitamin B_3 (nicotinamide). *N Engl J Med*, **289**: 1180-1182.

10. Vitamin B_6

Physiology and metabolism

Six different chemical forms of vitamin B_6 occur in foods: pyridoxine, pyridoxal, pyridoxamine and their phosphates. They are readily interconvertible in the body, giving rise to the metabolically active coenzyme pyridoxal phosphate.

The principal metabolic function of pyridoxal phosphate is as the coenzyme in reactions of amino acids. It is also required for the enzyme glycogen phosphorylase in muscle and liver, and in the metabolism of polyunsaturated fatty acids and phospholipids, and has a role in the function of steroid hormones, acting to release hormone-receptor complexes from tight nuclear binding, and so terminate the actions of the hormone [1,2].

The phosphate forms of vitamin B_6 are dephosphorylated in the intestinal lumen; pyridoxine, pyridoxal and pyridoxamine are all taken up from the small intestine by an energy-dependent process. The various vitamers are readily converted to pyridoxal phosphate in tissues. Pyridoxal phosphate which is not bound to enzymes in tissues is oxidised to 4-pyridoxic acid, the major metabolite of the vitamin excreted in the urine.

A proportion of the vitamin B_6 in plant foods is biologically unavailable, because it is present as pyridoxine glycosides which are not hydrolysed by intestinal enzymes. While the glycosides may be absorbed, they are not used in the body, but are excreted unchanged in the urine.

Some 80% of the body's vitamin B_6 is associated with the enzyme glycogen phosphorylase in muscle. As glycogen reserves are depleted in prolonged fasting, so the vitamin is released from muscle, and made available for the synthesis of glucose from amino acids in the liver. However, muscle pyridoxal phosphate is not released in vitamin B_6 deficiency, so the muscle reserves cannot be regarded as storage of the vitamin.

Deficiency and excess

Gross clinical deficiency of vitamin B_6 is extremely rare; the vitamin is widely distributed in foods, and intestinal flora synthesise relatively large amounts, some of which may be available.

Much of our knowledge of human deficiency comes from an 'outbreak' in the early 1950s, resulting from an infant milk preparation which had undergone severe heating in manufacture, leading to the formation of a biologically inactive complex between pyridoxal (and pyridoxal phosphate) and lysine in proteins. In addition to abnormalities of the metabolism of tryptophan, methionine and other amino acids, the affected infants convulsed. They responded to supplements of vitamin B_6 [3].

Intakes of vitamin B_6 in excess of 500 mg/day are associated with the development of peripheral sensory neuropathy, which is only partially reversible on return to more appropriate intakes [4]. Similar symptoms have been reported in subjects taking doses of 50-500 mg /day. Intakes of more than 50 mg /day must therefore be regarded as potentially harmful [5].

Requirements

Adults

Although 80% of the body's vitamin B_6 is in muscle, this pool turns over relatively slowly, and requirements are closely related to protein intake. Attempts to estimate requirements by measurement of the turnover of body pools have not yielded useful results, and current estimates are based on changes in tryptophan and methionine metabolism, and the decline in blood concentrations of vitamin B_6 during experimental depletion / repletion studies.

Biochemical indices of vitamin B_6 status decline more rapidly in subjects receiving high protein intakes (80-160g /day) than in those receiving low intakes of protein (30-50g /day). Similarly, restoration of indices of vitamin B_6 nutritional status during repletion occurs faster in subjects receiving lower intakes of protein [6,7,8,9]. Such studies suggest that the average vitamin B_6 requirement is 13 µg/g dietary protein. Allowing for individual variation gives a Population Reference Intake of 15 µg vitamin B_6/g dietary protein, and suggests a Lower Threshold Intake of 11 µg/g protein, although there is no experimental evidence to support this lower figure.

The relationship with protein intake may not be valid at low intakes of protein, or under conditions of restricted food intake, when amino acids will be catabolised for energy-yielding metabolism.

High-oestrogen oral contraceptives cause changes in tryptophan metabolism which have been widely interpreted as indicating vitamin B_6 depletion. However, relatively large intakes of the vitamin are required to normalise tryptophan metabolism in women taking oral contraceptives, and other indices of vitamin B_6 nutritional status are generally unaffected by contraceptives. It seems most likely that the derangement of tryptophan metabolism is due to direct effects of oestrogens or their metabolites on tryptophan metabolism. There is no evidence for an increased requirement for vitamin B_6 in women using oral contraceptives [2].

Children

There is no evidence that children have a requirement for vitamin B_6 different from that for adults, i.e. a Population Reference Intake of 15 µg/g dietary protein. It is reasonable to assume that children in the EC have a diet similar to that of adults, providing some 15% of energy from protein.

Pregnancy

Plasma concentrations of pyridoxal phosphate fall markedly and progressively through pregnancy, although erythrocyte transaminase activation coefficients and excretion of 4-pyridoxic acid are normal. The drop of plasma pyridoxal phosphate appears to be a consequence of the preferential uptake of the vitamin by the fetus, and a normal feature of pregnancy. Supplements of 2.5-4 mg/day are required to maintain the plasma concentration of pyridoxal phosphate at the pre-pregnancy level [10]. This is considered neither necessary or desirable, and the same PRI is proposed for pregnancy as in non-pregnant women – 15 µg/g dietary protein. On the extra protein intake recommended during pregnancy, this will result in an increase in the amount of dietary vitamin B_6.

Lactation

There is no evidence that vitamin B_6 metabolism is changed by lactation, and there appears to be no reason for changing the recommendation from that for non-lactating women – 15 µg /g dietary protein. This will provide vitamin B_6 at a higher level than is secreted in milk, and the extra protein intake recommended during lactation will result in an increase in the amount of dietary vitamin B_6.

The elderly

There is a fall in the plasma concentration of pyridoxal phosphate with increasing age, but erythrocyte transaminase activation coefficients do not show a similar change. There is some evidence of age-related changes in the metabolism of the vitamin [8], but there are no good grounds for believing that ageing increases the vitamin B_6 requirement beyond that for younger adults.

Summary

Vitamin B_6 requirements (expressed in weight of pyridoxine) vary with protein intake in all groups.

Average Requirement	13 µg /g protein intake
Population Reference Intake	15 µg /g protein intake

Average protein intakes in the EC are 15% of energy intake. On this basis, and using average energy requirements, vitamin B_6 requirements of adults can be expressed in mg/d.

Adults	*Males*	*Females*
Average Requirement	1.3	1.0
Population Reference Intake	1.5	1.3

Population Reference Intakes for other groups

Age Group		PRI (mg/d)
	6 - 11 m	0.4
	1 - 3 y	0.7
	4 - 6 y	0.9
	7 - 10 y	1.1
Males	11-14 y	1.3
	15-17 y	1.5
Females	11-14 y	1.1
	15-17 y	1.1
	Pregnancy	1.3*
	Lactation	1.4*

* Based on protein increments in pregnancy and lactation.

High intakes

Intakes greater than 500 mg/d are associated with neurological damage and intakes of more than 50 mg/d are potentially harmful in adults.

References

1. Bender DA. (1989). Vitamin B_6 requirements and recommendations. *Eur J Clin Nutr*, **43**: 289-309.

2. Bender DA. (1987). Oestrogens and vitamin B_6 – actions and interactions. *World Rev Nutr Diet*, **51**: 140-188.

3. Coursin DB. (1954). Convulsive seizures in infants with pyridoxine-deficient diet. *JAMA*, **154**: 406-408.

4. Schaumburg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ. (1983). Sensory neuropathy from pyridoxine abuse, a new megavitamin syndrome. *N Engl J Med*, **309**: 445-448.

5. Dalton K, Dalton MJT. (1987). Characteristics of pyridoxine overdose neuropathy syndrome. *Acta Neurol Scand*, **76**: 8-11.

6. Canham JE, Baker EM, Harding RS, Sauberlich HE, Plough IC. (1969). Dietary protein – its relationship to vitamin B_6 requirements and function. *Ann N Y Acad Sci*, **166**: 16-29.

7. Kelsay J, Miller LT, Linkswiler H. (1968). Effect of protein intake on the excretion of quinolinic acid and niacin metabolites by men during vitamin B_6 depletion. *J Nutr*, **94**: 27-31.

8. Kelsay J, Baysal A, Linkswiler H. (1968). Effect of vitamin B_6 depletion on the pyridoxal, pyridoxamine and pyridoxine content of the blood and urine of men. *J Nutr*, **94**: 490-494.

9. Miller LT, Linkswiler H. (1967). Effect of protein intake on the development of abnormal tryptophan metabolism by men during vitamin B_6 depletion. *J Nutr*, **93**: 53-59.

10. Lee CM, Leklem JE. (1985). Differences in vitamin B_6 status indicator responses between young and middle-aged women fed constant diets with two levels of vitamin B_6. *Am J Clin Nutr*, **42**: 226-234.

11. Folate

Physiology and metabolism

Metabolic functions

Folate is the general name given to compounds with nutritional properties similar to those of folic acid (pteroylglutamic acid). Besides folic acid itself, with one glutamate residue, there are other forms with a varying number of extra glutamates attached. Reduced derivatives of these participate in enzymic reactions providing single carbon units for DNA and RNA biosynthesis and methylation reactions [1].

Absorption and metabolism

The enzymatic interconversions in which the folate cofactors participate involve eight forms of the vitamin. Many of these are easily oxidised, some to forms that can subsequently be reduced and which are thus nutritionally active, others to catabolized products which are inactive [2]. The extent to which these oxidations occur will have a profound effect upon the folate ultimately available from the diet. This in turn will depend upon not only the forms of the cofactor predominating in a particular food but also the length and conditions of storage, the presence or absence of natural or added antioxidants etc. All natural folates exist as polyglutamyl conjugates. These extra glutamates may get removed either during storage and processing of food or by conjugases that are present in the human intestine. At physiological concentrations only folates containing a single glutamyl residue are absorbed into the circulation, usually after conversion to the 5-methyltetrahydro form. Human cells depend principally upon the uptake of this circulating 5-methyltetrahydrofolate for their supply of the vitamin.

The folate content of the diet is usually estimated by microbiological methods which may underestimate the true content of folate in food by as much as 20%-30%. Some foods but not others contain factors that inhibit the intestinal folate deconjugation enzymes thus decreasing absorption [3]. The degree of inhibition varies considerably from food to food, with some foods, for example beans, giving 20% inhibition while values as great as 80% are found for orange juice. There is also a solid body of evidence that polyglutamyl forms of folate are less well absorbed than monoglutamates even in the absence of such inhibitors. Straight comparisons of folic acid containing one glutamyl residue with the corresponding heptaglutamyl form have

indicated the latter to be some 58-79% as available as the former. However, an important new approach has recently been introduced, namely the comparison of various folate forms labelled differently with deuterium, which found that folate hexaglutamate was only 50% as available as the monoglutamate when given in pure forms at physiological concentrations [4]. This value indicates an even lower availability of polyglutamyl forms than previously expected. Thus there are three areas where calculations based on mean requirement must be adjusted to get mean dietary requirement. There is probably an underestimation of the amount of folate in food. Inhibition of intestinal conjugase would decrease the availability of folate polyglutamates. Finally even in the absence of such inhibitors folate polyglutamates are probably only 50% as available as the corresponding monoglutamates, upon which some of the mean requirement calculations are based. Factors one and two work in the opposite directions and may cancel each other out, leaving a 50% overall adjustment as being an acceptable correction factor.

Deficiency and excess

Folate deficiency decreases DNA and RNA biosynthesis, and manifests itself most obviously in cell types that turn over rapidly, such as in the bone marrow, thus causing anaemia.

5-Methyltetrahydrofolate is involved in providing, via methionine, methyl groups for many methylation reactions; these systems will fail however only in severe prolonged folate deficiency.

A "pseudo folate-deficient" state is seen in B_{12} deficiency, because cells fail to handle folate normally, resulting in the signs of folate deficiency. There is however no dietary deficiency of folate; the condition is cured by vitamin B_{12}. The haematological picture can however be improved by high intakes of folic acid itself, which is particularly effective in this role. Large doses of folic acid, which is the synthetic form in supplements, can therefore prevent the timely diagnosis of vitamin B_{12} deficiency, allowing the neuropathy which also occurs to proceed undiagnosed, only to emerge at a much more advanced stage when its effects are largely irreversible.

High levels of folic acid around 5.0 mg per day have been used in pregnancy for periods of several months without any apparent ill effects. Thus in normal subjects levels of up to 5.0 mg per day would seem to be well tolerated [1]. There is evidence that high levels of folic acid increase fit frequency in epileptics [5]. There is also the certainty that such high levels taken on a daily basis would mask the emergence of vitamin B_{12} deficiency. At lower levels of 100-200 µg of folic acid per day this masking would be less likely. Since a part of the neurological damage in B_{12}

deficiency is largely irreversible, it is serious if allowed to go undiagnosed and untreated. Vegans and the elderly, being at increased risk of vitamin B_{12} deficiency, should avoid large daily intakes of folic acid supplements. However folic acid supplements of around 400 µg per day are in widespread use, particularly in the United States, and it is claimed that there is no evidence of their masking pernicious anaemia at that level [6].

Physiological and dietary requirements

Adults

Folate status can be measured from the concentration of folate in serum, but the level of folate in the red blood cells gives a much closer estimate of tissue stores [1]. Red cell folate values above 150 µg/L are an indication of sufficiency [1]. However there is no clear borderline separating the normal population from those with clinical signs of deficiency [1]. Approaches using depletion of folate [8,9] and considerations of folate catabolism [10] suggest daily requirements of 50-100 µg.

The level of oral folic acid required to treat folate deficiency in an adult man has been reported as 50 µg/d. A study of a group of normal volunteers found higher amounts were needed – 75 µg/d [12]. A limited study on three normal women showed that on a daily intake of 50 µg folic acid their red cell folate remained in the normal range but respectively fell or rose at levels of 25 or 100 µg/d [13]. A different study on four women indicated that their plasma levels were stabilized by 80 µg pure folic acid and 20 µg dietary folate daily [14].

From these studies with folic acid, the mean requirement for an adult is taken to be 70 µg/d. As discussed above, one would expect this to be twice as available as food folate. The mean dietary requirement of folate would therefore be 140 µg/d.

Dietary recommendations for folate have often been supported by values for the intakes of folate observed in individuals and groups that clearly receive adequate amounts of the vitamin. It is probably unwise to rely on this approach as the values obtained for food folates may be substantial underestimates because of the uncertainties of the analytical procedures.

Children

In a study of infants between 2 and 11 months 3.6 µg folic acid per kg body weight per day appeared to maintain plasma levels [15]. Infants between 6 and 11 months of age are likely to receive a mixture of folic acid and food folate, so a Population Reference Intake of 50 µg/d is proposed.

In the absence of specific information, values for children have been derived from those for adults on the basis of energy expenditure.

Pregnancy

Folate deficiency in the later stages of pregnancy in women not ingesting extra folate is extremely common. Various studies have shown one quarter to one half would have clear signs of deficiency [1]. Red cell folate drops during pregnancy and while part of this drop may be due to haemodilution some of it is certainly due to the mother's being unable to meet the extra demand for folate made by the fetus from her stores by normal dietary intake. Studies have shown this drop in RBC (red blood cell) folate could be prevented by a supplement of 100 µg folic acid daily [16,17]. Since these studies were carried out on women on good diets this level is really a minimum. To allow for the problems of bioavailability discussed above, a dietary increment of 200 µg of folate per day should be sought. Recent work on the increase of folate catabolism in pregnancy indicates that this amount is not generous [10].

Neural tube defects

There is now good evidence that daily periconceptual folic acid supplementation may have a protective effect on the occurrence of the congenital abnormalities, spina bifida and anencephalus, collectively called neural tube defects (NTDs) [18]. While some of these studies [19] involved the use of very high levels of folic acid, it seems probable that amounts around 400 µg per day confer equal protection with a lesser risk of side effects [20]. Even at this lower level one cannot completely exclude the risk involved in taking a greater than normal amount of a vitamin in early pregnancy. However as far as toxicity to the mother is concerned there are only two established causes for concern, which have been mentioned already. Women taking antiepileptic drugs should be aware that it has been suggested that taking folic acid supplements of much above 400 µg may cause loss of control of their epilepsy. Taking extra folic acid, if one is also vitamin B_{12} deficient, results in the masking or exacerbation of neurological disease associated with such deficiency. However vitamin B_{12} deficiency is extremely rare in women of less than 40 to 50. Should women, particularly when nearing the end of their child-bearing years, plan to take folic acid

supplements for periods of months, they should have possible vitamin B_{12} deficiency excluded by a simple blood test.

While it is possible that improved dietary intake of folate may confer protection from NTDs it is difficult to achieve intakes of 400 µg per day because of the low density of folate in food and the lower availability of the natural forms of the vitamin than of the folic acid used in supplements. Fortified foods containing folic acid in the more available form may provide an alternative for women who do not wish to take tablets.

It should be emphasised that the neural tube is formed between three and four weeks after conception, at which point many women who are pregnant are not aware of the fact. It is thus recommended that women wishing to attempt to achieve protection using folic acid should ensure that its intake is commenced before conception, so as to ensure adequate levels at the critical time. While there is no direct evidence on the issue, the ingestion of folic acid post conception may be of benefit up to the time of closure of the neural tube, i.e. four weeks. Thus women who suspect that they may be at an early stage of an unplanned pregnancy, e.g. by observing a missed period, may wish also to take folic acid even at this later and far less certain stage.

Lactation

Earlier studies suggested that milk contains about 50 µg per litre [21]. It now seems more likely that with better methods of estimation this value should be doubled [22]. Assuming a daily output of 750 ml, loss could thus be between 37 and 75 µg per day. To allow for bioavailability and taking the higher value one arrives at an increment of 150 µg per day to compensate for normal lactation.

The elderly

A significant body of evidence [23] indicates that the elderly have no increased requirement for folate. As mentioned previously, they should avoid large intakes of folate supplements.

Summary

Values expressed in terms of mixed dietary folates (calculated for a relative molecular mass of 441), assuming a bioavailability about half that of pure folic acid (monoglutamate form), per day.

Adults	
Average Dietary Requirement	140 µg
Population Reference Intake (mean requirement + 2 SD, assuming a coefficient of variation of 20%)	200 µg*
Lowest Threshold Intake (mean requirement - 2 SD)	85 µg
Pregnancy	400 µg*
Lactation	350 µg

Population Reference Intakes for other groups

Age Group	PRI
6 - 11m	50 µg
1 - 3y	100 µg
4 - 6y	130 µg
7 - 10y	150 µg
11-14y	180 µg
15-17y	200 µg

* Neural tube defects have been shown to be prevented in offspring by periconceptual ingestion of 400 µg folic acid per day in the form of supplements.

References

1. Chanarin I. (1979). *The Megaloblastic Anaemias*. 2nd ed. Oxford: Blackwell Scientific Publications.

2. Scott JM, Weir DG. (1976). Folate composition, synthesis and function in natural materials. *Clin Haematol*, **5**: 547-568.

3. Bhandari SD, Gregory JF. (1990). Inhibition by selected food components of human and porcine intestinal pteroylpolyglutamate hydrolase activity. *Am J Clin Nutr*, **51**: 87-94.

4. Gregory JF, Bhandari SD, Bailey LB, Toth JP, Baumgartner TG, Cerda JJ. (1991). Relative bioavailability of deuterium-labelled monoglutamyl and hexaglutamyl folates in human subjects. *Am J Clin Nutr*, **53**: 736-740.

5. Reynolds EH. (1967). Effects of folic acid on the mental state and fit-frequency of drug-treated epileptic patients. *Lancet*, **i**: 1086-1088.

6. Moss AJ, Levy AS, Kim I *et al.* (1989). *Use of Vitamin and Mineral Supplements in the United States; Current Users, Types of Products and Nutrients*. Hyattsville, MD: National Center for Health Statistics (Advance data n° 174).

7. Hoffbrand AV, Newcombe BFA, Mollin DL. (1966). Method of assay of red cell folate activity and the value of the assay as a test for folate deficiency. *J Clin Pathol*, **19**: 17-28.

8. Herbert V. (1962). Experimental nutritional folate deficiency in man. *Trans Assoc Am Physicians*, **75**: 307-320.

9. Gailani SD, Carey RW, Holland JF, O'Malley JA. (1970). Studies on folate deficiency in patients with neoplastic diseases. *Cancer Res*, **30**: 327-333.

10. McPartlin J, Halligan A, Scott JM, Darling M, Weir DG. (1993). Accelerated folate breakdown in pregnancy. *Lancet*, **341**: 148-149

11. Zalusky R, Herbert V. (1961). Megaloblastic anemia in scurvy with response to 50 micrograms of folic acid daily. *N Eng J Med*, **265**: 1033-1038.

12. Banerjee DK, Maitra A, Basu AK, Chatterjee JB. (1975). Minimal daily requirement of folic acid in normal Indian subjects. *Indian J Med Res*, **63**: 45-53.

13. Herbert V, Cuneen M, Jaskiel L, Kapff M. (1962). Minimal daily adult folate requirement. *Arch Intern Med*, **110**: 649-652.

14. Sauberlich HE, Kretsch MJ, Skala JH, Johnson HL, Taylor PC. (1987). Folate requirement and metabolism in non pregnant women. *Am J Clin Nutr*, **46**: 1016-1028.

15. Asfour R, Wahbeh M, Waslien CI, Guindi S, Darby WJ. (1977). Folacin requirement of children III. Normal infants. *Am J Clin Nutr*, **30**: 1098-1105.

16. Hansen H, Rybo G. (1967). Folic acid dosage in prophylactic treatment during pregnancy. *Acta Obst Gyn Scand*, **46** (suppl. 7): 107-112.

17. Chanarin I, Rothman D, Ward A, Perry J. (1968). Folate status and requirement during pregnancy. *Br Med J*, **2**: 390-394.

18. Scott JM, Kirke PM, Weir DG. (1990). The role of nutrition in neural tube defects. *Ann Rev Nutr*, **10**: 277-295.

19. MRC Vitamin Study Research Group. (1991). Prevention of neural tube defects: Results of the Medical Research Council Vitamin Study. *Lancet*, **338**: 131-137.

20. Smithells RW, Sheppard S, Wild J, Schorah CJ. (1989). Prevention of neural tube defect recurrence in Yorkshire: final report. *Lancet*, **ii**: 498-499.

21. Ek J. (1983). Plasma, red cell and breast milk folacin concentrations in lactating women. *Am J Clin Nutr*, **38**: 929-935.

22. O'Connor D, Tamura T, Picciano MF. (1991). Pteroylpolyglutamates in human milk. *Am J Clin Nutr*, **53**: 930-934.

23. Suter PM, Russell RM. (1987). Vitamin requirements of the elderly. *Am J Clin Nutr*, **45**: 501-512.

12. Vitamin B_{12}

Physiology and metabolism

Metabolic functions

The term vitamin B_{12} covers the two forms active in the body – 5'-deoxyadenosyl-cobalamin and methylcobalamin – and a number of other cobalt-containing corrinoids which by being converted to the active forms have the same nutritional effect.

Two enzymes in man have a requirement for vitamin B_{12} [1]. Methionine synthase uses methylcobalamin and is involved in the channelling of carbon units from amino acids such as serine to remethylate homocysteine to methionine. This remethylation is necessary because all tissues use methionine as a source of methyl groups and as a consequence generate significant amounts of homocysteine which needs to be remethylated. Methylmalonyl CoA mutase, which uses 5'-deoxyadenosyl-cobalamin, is necessary in the metabolism of propionyl CoA, which arises either from the catabolism of certain amino acids or the oxidation of odd-chain fatty acids.

Absorption

Dietary vitamin B_{12} is bound by a glycoprotein called "intrinsic factor" secreted by the parietal cells of the stomach. The resultant intrinsic factor – vitamin B_{12} complexes pass to the ileum where they are absorbed. About three quarters of an oral dose of 0.5 µg is absorbed while the amount absorbed from 1.0 µg is half [1]. Intrinsic factor-mediated absorption seems to have an upper limit of about 1.5 µg per meal irrespective of how much vitamin B_{12} is presented to it.

Excretion

It has been calculated that the biliary secretion of vitamin B_{12} is around 0.5 µg per day [1]. Perhaps less than 20 % or 0.1 µg of this is lost through non-reabsorption [2].

Vitamin B_{12} is very well stored. Its half-life in humans has been measured in a number of studies as being of more than one year to almost four years [3].

Deficiency

Vitamin B_{12} levels in most diets appear to be adequate, the exception being strict vegetarian or vegan diets. As will be discussed later, individuals or communities on such diets have well documented lower than normal blood levels of vitamin B_{12} and some studies show biochemical evidence of deficiency. This is easily understood since plant food does not contain any vitamin B_{12} unless contaminated with microorganisms [3]. Individuals among the elderly and the poor may also have an increased risk of deficiency where their diet is low in animal produce.

By far the biggest cause of vitamin B_{12} deficiency is impairment of absorption [4]. This arises most often from destruction of the parietal cells of the stomach by autoantibodies, resulting in diminution or absence of secretion of intrinsic factor. Autoantibodies are also frequently produced against intrinsic factor itself, some of which render it incapable of binding vitamin B_{12}, with more rarely other antibodies permitting binding of vitamin B_{12} but preventing uptake of the complex by the ileum [1]. These three autoimmune conditions are called pernicious anaemia (PA).

Deficiency, when it occurs, has two general consequences: arrest of cell replication and neurological damage [1]. The former manifests itself clinically in the more rapidly dividing cells such as those of the marrow, the immune system, the skin and the gastrointestinal tract. Anaemia is the most obvious clinical sign. Appropriate treatment with the vitamin completely reverses all the effects on cell replication. The neurological lesion presents first as paraesthesia with a tingling sensation in the fingers and/or toes with or without numbness. Untreated, this will progress to a peripheral neuropathy and ataxia and an overt demyelination of the spinal cord called sub-acute combined degeneration. Psychiatric manifestations such as confusion, depression, agitation and delusions may also be present. Treatment with vitamin B_{12} appears to completely redress the latter manifestations. The peripheral neuropathy will also improve but the demyelination of spinal cord is essentially irreversible.

It is now widely accepted that, as described originally in the 5-methyl-tetrahydrofolate trap hypothesis [5], the arrest of cell division seen in vitamin B_{12} deficiency results from an impairment in the proper utilisation of the folate cofactors involved in the synthesis of DNA and RNA in replicating cells. One of these cofactors, 5-methyltetrahydrofolate, requires to be demethylated by vitamin B_{12}-dependent methionine synthase for its further metabolism. In the absence of vitamin B_{12} the other cellular folates needed to synthesise DNA and RNA become metabolically trapped in this form resulting in a 'pseudo' folate deficiency

in such cells, which causes an anaemia identical to that seen in simple folate deficiency.

The neurological lesion is thought to be due to the inability to utilize 5-methyltetrahydrofolate to remethylate homocysteine to methionine [6,7]. The latter supplies methyl groups for the synthesis of proteins and lipids in myelin and other nerve structures.

Higher and undesirable intakes

Daily ingestion of high amounts of vitamin B_{12}, of even one or two orders of magnitude above normal dietary levels, does not cause any obvious side effects even over a prolonged period. However, nutritionally inactive vitamin B_{12} analogues can be found in some vitamin preparations and increasing their intake may not be without risk. A daily intake greater than 200 µg should be discouraged.

Requirements

Criteria of vitamin B_{12} nutritional adequacy

A number of methods have been used to assess vitamin B_{12} status or to detect its deficiency.

The serum concentration of the vitamin can be determined; the results vary somewhat according to the procedure used, but most laboratories would regard concentrations of less than 100 ng/L as indicating deficiency, 100-150 ng/L as possibly deficient, with values above 150 ng/L being taken as normal [1,8]. These ranges cannot however be regarded as wholly reliable as there is some overlapping.

In B_{12} deficiency, the methylmalonic acid concentrations in urine and plasma might be expected to increase. The recent availability of methods sensitive enough to estimate methylmalonate in plasma has revealed a very good correlation between raised methylmalonate concentration and the presence of clinical disease, but there can be some overlap with the reference range [9].

Traditionally the presence of a macrocytic anaemia has been considered to be the most usual way of picking up subjects with vitamin B_{12} deficiency. However very

deficient subjects can sometimes have normal concentrations of haemoglobin and no increase in mean corpuscular volume [10].

While they are difficult to perform, neurological assessments, preferably using newer methods such as evoked response studies, are really the only way of determining the presence or absence of neurological damage due to vitamin B_{12} deficiency.

Individually these tests may not be wholly reliable but the use of two or more gives useful information in the B_{12} status of individuals and groups that can be used to make recommendations on B_{12} intake.

Adults

A number of approaches have been used to calculate requirements.

Studies have been made on the response of patients with pernicious anaemia, who have no contribution from dietary vitamin B_{12}, to daily parenteral doses. They indicate that 0.3 µg/d is not quite adequate [11] but 0.5 µg/d is [12,13]. These patients however will secrete some B_{12} in the bile which will not be reabsorbed and so will be lost from the enterohepatic circulation. Dietary values for normal subjects would therefore need to be adjusted downwards for that reason, but also upwards to allow for incomplete absorption from the diet. If it could be said that these would balance out, one might expect a daily intake of 0.3 µg vitamin B12 to be too little and 0.5 µg to be adequate on the evidence of these studies using mainly haematological criteria.

The amount of B_{12} in the diet of strict vegetarians has been investigated. Studies on sizeable populations indicated that while a mean intake of 0.26 µg/d might provide inadequate stores, no deficiency was detected [14]. Similar studies indicated that smaller groups got by on intakes ranging from 0.3 to 0.5 µg/d [15,16]. This work depended mainly on abnormal haematological findings to detect abnormal states. While some studies assessed neurological function, this is not easy to do and perhaps subtle changes that were present might not have emerged. While earlier studies that related intake to well being did not look for biochemical evidence of deficiency, from subsequent studies on similar strict vegetarian groups it seems very likely that biochemical deficiency, as detected by elevated urine methylmalonic acid levels, exists on diets containing these low levels of vitamin B_{12} [17,18]. It appears that biochemical deficiency would exist with a risk of eventual neurological dysfunction on intakes less than 0.5 µg/d.

Two studies have been based on vitamin turnover. They made a number of assumptions about various factors and came up with mean daily requirements of between 0.25 and 1.0 µg/d [19] and of 1.3 µg/d [20].

At levels of 0.5 µg/d that are likely to be consumed by subjects on strict vegetarian diets, there is no evidence of haematological or neurological dysfunction, but there is biochemical abnormality. Interpretation of many of the studies of the type cited above depends very heavily either on the absence of apparent clinical problems in populations or upon the apparent adequacy of the treatment. These studies regarded the absence of haematological abnormalities as being an assurance of general health, and it is difficult to rule out neurological damage because it is so much more difficult to assess [21]. Examination of the early literature makes it clear that many people with apparently normal haematology were developing irreversible neurological damage. More recent studies suggest that this circumstance is much more common than is usually appreciated.

It therefore seems prudent to put forward a mean requirement towards the high end of the scale: 1.0 µg/d.

Pregnancy

There seems to be no risk of signs of clinical deficiency developing in a pregnant woman, even on a diet low in vitamin B_{12}. The major cause for concern is the effect of such low intakes on the developing embryo and on progeny that are subsequently breast-fed. It is clear that children of strict vegetarian mothers who were subsequently breast-fed, and then went on to vegetarian diets themselves, are at serious risk not just of biochemical evidence of deficiency as indicated by elevated methylmalonic acid but also of decreased growth rates [18]. Such low status has been shown to lead to overt signs of neurological damage, which in time would become irreversible [22]. There thus seems no doubt that women on strict vegetarian diets should be encouraged to increase their intake of vitamin B_{12} during pregnancy and that this advice should, as a precaution, be extended to all women. Unlike folate, there is no evidence for a high rate of turnover of vitamin B_{12} in pregnancy. However to allow for transfer of some of the vitamin to the fetus, an additional 0.2 µg/d is recommended.

Lactation

During lactation, loss of the vitamin in milk depends to a large extent upon the mother's vitamin B_{12} status [23]. It is difficult to assess how much if any of this loss needs to be reinstated in women who have normal stores. However if the values in milk fall below about 0.37 µg per day, evidence of biochemical deficiency begins

to be seen in breast-fed infants [17] (who probably had very inadequate stores of vitamin B_{12} to begin with). It would thus seem prudent to try to replace at least 0.37 µg per day. If one estimates that about three quarters of a dose is absorbed at this level, this requires an increment of 0.5 µg/d during lactation.

Children

Infants born to women with a diet very low in B_{12}, and thus with very poor stores of the vitamin, needed 0.37 µg/d to cure biochemical deficiency as evidenced by methylmalonic acid excretion [17]. A PRI for infants 6-11 months is set at 0.5 µg/d.

In the absence of specific studies, values for children have been calculated from those for adults on the basis of energy expenditure.

The elderly

There appears to be no increased requirement for vitamin B_{12} with age [24]. While a decrease in vitamin B_{12} status as measured by serum levels has been reported in some studies as age advanced, it is almost certainly due to an increased prevalence of malabsorption due either to the autoimmune disease pernicious anaemia or to atropic gastritis [25].

Summary

(amounts in µg/d, based on a relative molecular mass of 1355)

Adults	**Average Dietary Requirement**	1.0
	Population Reference Intake (Mean requirement + 2SD, assuming a coefficient of variation in this case of 20%)	1.4
	Lowest Threshold Intake (Mean requirement - 2SD)	0.6
Pregnancy	Plus	0.2
Lactation	Plus	0.5

Population Reference Intakes for other age groups

(amounts in µg/d, based on a relative molecular mass of 1355)

6 - 11 m	0.5
1 - 3 y	0.7
4 - 6 y	0.9
7 - 10 y	1.0
11 - 14 y	1.3
15 - 17 y	1.4

References

1. Chanarin I. (1979). *The Megaloblastic Anaemias*. 2nd ed. Oxford: Blackwell Scientific Publications.

2. Reizenstein P, Ek G, Matthews CME. (1966). Vitamin B_{12} kinetics in man. Implications on total-body-B_{12}-determinations, human requirements and normal and pathological cellular B_{12} uptake. *Phys Med Biol*, **11**: 295-306.

3. Hall CA. (1964). Long-term excretion of Co^{57}-vitamin B_{12} and turnover within the plasma. *Am J Clin Nutr*, **14**: 156-162.

4. Kolhouse JF, Allen RH. (1977). Absorption, plasma transport and cellular retention of cobalamin analogues in the rabbit. Evidence for the existence of multiple mechanisms that prevent the absorption and tissue dissemination of naturally occurring cobalamin analogues. *J Clin Invest*, **60**: 1381-1392.

5. Herbert V, Zalusky R. (1962). Interrelationship of vitamin B_{12} and folic acid metabolism: folic acid clearance studies. *J Clin Invest*, **41**: 1263-1276.

6. Scott JM, Dinn JJ, Wilson P, Weir DG. (1981). Pathogenesis of subacute combined degeneration: a result of methyl group deficiency. *Lancet*, **ii**: 334-337.

7. Weir DG, Keating S, Molloy A, McPartlin J, Kennedy S, Blanchflower J, Kennedy DG, Rice D, Scott JM. (1988). Methylation deficiency causes vitamin B_{12}-associated neuropathy in the pig. *J Neurochem*, **51**: 1949-1952.

8. Lindenbaum J, Savage DG, Stabler SP, Allen RH. (1990). Diagnosis of cobalamin deficiency. II. Relative sensitivities of serum cobalamin, methylmalonic acid and total homocysteine concentrations. *Am J Hematol*, **34**: 99-107.

9. Stabler SP, Marcell PD, Podell ER, Allen RH, Lindenbaum J. (1986). Assay of methylmalonic acid in the serum of patients with cobalamin deficiency using capillary gas chromatography - mass spectrometry. *J Clin Invest*, **77**: 1606-1612.

10. Lindenbaum J, Healton EB, Savage DG, Brust JCM, Garrett TJ, Podell ER *et al.* (1988). Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Eng J Med*, **318**: 1720-1728.

11. Baker SJ, Mathan VI. (1981). Evidence regarding the minimal daily requirement of dietary vitamin B_{12}. *Am J Clin Nutr*, **34:** 2423-2433.

12. Darby WJ, Bridgfort EB, Le Brocquy J. (1958). Vitamin B_{12} requirements of adult man. *Am J Med*, **25:** 726-732.

13. Adams JF, Hume R, Kennedy EH, Pirrie TG, Whitelaw JW, White AM. (1968). Metabolic responses to low doses of cyanocobalamin in patients with megaloblastic anaemia. *Br J Nutr*, **22:** 575-582.

14. Armstrong BK, Davis RE, Nicol DJ, van Merwyk AJ, Larwood CJ. (1974). Hematological, vitamin B_{12} and folate studies on Seventh-day Adventist vegetarians. *Am J Clin Nutr*, **27:** 712-718.

15. Jathar VS, Inamdar-Deshmukh AB, Rege DV, Satoskar RS. (1975). Vitamin B_{12} and vegetarianism in India. *Acta Haematol*, **53:** 90-97.

16. Abdulla M, Andersson I, Asp NG, Berthelsen K, Birkhed D, Dencker I *et al.* (1981). Nutrient intake and health status of vegans. Chemical analyses of diets using the duplicate portion sampling technique. *Am J Clin Nutr*, **34:** 2464-2477.

17. Specker BL, Black A, Allen L, Morrow F. (1990). Vitamin B_{12}: low milk concentrations are related to low serum concentrations in vegetarian women and to methylmalonic aciduria in their infants. *Am J Clin Nutr*, **52:** 1073-1076.

18. Miller DR, Specker BL, Ho ML, Norman EJ. (1991). Vitamin B_{12} status in a macrobiotic community. *Am J Clin Nutr*, **53:** 524-529.

19. Anderson BB. (1965). Investigations into the Euglena method of assay of vitamin B_{12}: the results obtained in human serum and liver using an improved method of assay. Ph.D. Thesis. University of London.

20. Herbert V. (1987). Recommended dietary intakes (RDI). of vitamin B_{12} in humans. *Am J Clin Nutr*, **45:** 671-678.

21. Kamaze DS, Carmel R. (1990). Neurologic and evoked potential abnormalities in subtle cobalamin deficiency states, including deficiency without anaemia and with normal absorption of free cobalamin. *Arch Neurol*, **47:** 1008-1012.

22. Kühne T, Bubl R, Baumgartner R. (1991). Maternal vegan diet causing a serious infantile neurological disorder due to vitamin B_{12} deficiency. *Eur J Pediatr*, **150:** 205-208.

23. Bates CJ, Prentice A. (1988). Vitamins, minerals and essential elements. In: Bennett PN ed. *Drugs and Human Lactation*. Amsterdam: Elsevier: 433-493.

24. Suter PM, Russell RM. (1987). Vitamin requirements of the elderly. *Am J Clin Nutr*, **45**: 501-512.

25. Siurala M, Isokoski M, Varis K, Kekki M. (1968). Prevalence of gastritis in a rural population. *Scand J Gastroenterol*, **3**: 211-223.

13. Pantothenic acid

Physiology and metabolism

Pantothenic acid is required for the synthesis of coenzyme A (CoA), which is required in the metabolism of carbohydrates, amino acids and fatty acids and the synthesis of steroids and other metabolites, and for the synthesis of the prosthetic group of acyl carrier protein required for fatty acid synthesis. It thus has a central role in a wide variety of metabolic pathways [1].

About 85% of dietary pantothenic acid is as CoA or phosphopantotheine. In the intestine these undergo hydrolysis to pantothenic acid, which is absorbed by diffusion throughout the small intestine.

All tissues are capable of forming CoA and the prosthetic group of acyl carrier protein from pantothenic acid. This synthesis requires the amino acid cysteine, and deficiency of the sulphur amino acids, methionine and cysteine, can result in impaired synthesis and hence secondary functional pantothenic acid deficiency. Phosphopantotheine, arising from the catabolism of CoA and acyl carrier protein, can be reused for CoA synthesis and new synthesis of acyl carrier protein. Phosphopantotheine which is not re-utilised is dephosphorylated, and the resultant pantotheine is cleaved to pantothenic acid and cysteamine.

Pantothenic acid is well conserved in the body; over a week after administration of tracer doses of [^{14}C] pantothenic acid only some 38% of the dose is recovered in the urine, all as the free vitamin. There is no information on body reserves of pantothenic acid.

Deficiency

Pantothenic acid is widely distributed in foods, and it is possible that intestinal bacterial synthesis also makes a contribution to intake. Deficiency has not been unequivocally reported in human beings except in specific depletion studies, which have frequently also used the antagonist methyl pantothenic acid.

Prisoners of war in the Far East, who were severely malnourished, showed, among other signs and symptoms of vitamin deficiency diseases, a new condition of paraesthesia and severe pain in the feet and toes, which was called the 'burning foot'

syndrome or nutritional melalgia. Although it was attributed to pantothenic acid deficiency, no specific trials of pantothenic acid were carried out; rather the subjects were given yeast extract and other rich sources of all vitamins as part of an urgent programme of nutritional rehabilitation.

Experimental pantothenic acid depletion, normally together with the administration of the antagonist methyl pantothenic acid, results in neuromotor disorders, including paraesthesia of the hands and feet, hyperactive deep tendon reflexes and muscle weakness, as well as mental depression, gastrointestinal complaints and metabolic abnormalities which can be attributed to changes in lipid metabolism [2].

Requirements

From the limited studies which have been performed it is not possible to establish requirements for pantothenic acid. Average intakes in adults are about 4-7 mg/d, but individuals consume 3-12 mg/d. Such intakes are obviously adequate to prevent deficiency; much higher amounts are harmless. There is no evidence on which to base estimates of changed pantothenic acid requirements in pregnancy or lactation.

Summary

Average intakes of pantothenic acid are adequate to meet requirements. There is no information on intakes below which deficiency is likely, nor adequate evidence to determine Population Reference Intakes.

The acceptable range of intakes in adults is the observed range 3 - 12 mg/d.

References

1. Bender DA. (1992). *Nutritional Biochemistry of the Vitamins*. Cambridge: Cambridge University Press. 341-360.

2. Fry PC, Fox HM, Tao HG. (1976). Metabolic responses to a pantothenic acid deficient diet in humans. *J Nutr Sci Vitaminol (Tokyo)*, **22**: 339-346.

14. Biotin

Physiology and metabolism

Biotin functions as the coenzyme transferring carbon dioxide in four reactions: pyruvate carboxylase, a key step in gluconeogenesis; acetyl CoA carboxylase, the first step of fatty acid synthesis; and in propionyl CoA and methylcrotonyl CoA carboxylases [1].

Most biotin in foods is present as biocytin, covalently bound to enzymes. This is released on proteolysis, and hydrolysed by biotinidase in the pancreatic juice and intestinal mucosal secretions to yield the free vitamin. The extent to which bound biotin in foods is biologically available is not known. Biotin is absorbed from the upper intestinal tract by active transport, although there is also some active uptake from the large intestine. Intestinal bacteria synthesise relatively large amounts of biotin, and it is assumed that this contributes to the host's nutrition. Biotin circulates in the bloodstream both free and tightly bound to a serum glycoprotein. Both free and protein-bound biotin are taken up by tissues. In tissues biotin is incorporated covalently into biotin-dependent enzymes, and on catabolism of these enzymes, the biocytin is hydrolysed by a specific peptidase, biotinidase, permitting reutilisation.

Biotin may be excreted either unchanged or as the oxidation production bis-norbiotin. As a result of both resorption of the vitamin from urine and the protein binding of plasma biotin, which reduces excretion, there is very efficient conservation of biotin. This, together with the recycling of biotin released by the catabolism of enzymes, may be as important as intestinal bacterial synthesis of the vitamin in explaining the scarcity of biotin deficiency. There is no information on body reserves of biotin.

Deficiency

Biotin deficiency due to simple inadequacy of intake is unknown except in patients receiving total parenteral nutrition.

The activities of biotin-dependent enzymes fall in deficiency. This results in impaired gluconeogenesis, with accumulation of lactate, pyruvate and alanine, and impaired lipogenesis, with accumulation of acetyl CoA, resulting in ketosis. There is also an impairment of protein synthesis. Abnormal organic acids are excreted in deficiency [2].

The few early reports of human biotin deficiency are all of people who consumed large amounts of uncooked eggs, and therefore had a high intake of the protein avidin, which binds biotin and renders it unavailable. They developed a fine scaly dermatitis and hair loss. Provision of biotin supplements of between 200–1000 µg/day resulted in cure of the skin lesions, and regrowth of hair, despite continuing the abnormal diet providing large amounts of avidin. Unfortunately, there seem to have been no studies of provision of modest doses of biotin to such patients, and none in which their high intake of uncooked eggs was either replaced by an equivalent intake of cooked eggs (in which avidin has been denatured by heat, and the yolks of which are a good source of biotin) or continued unchanged, so there is no information from these case reports of the amounts of biotin which are required for normal health.

In experimental studies of biotin depletion, diets providing up to 30% of energy intake from raw egg white have been used. The subjects developed glossitis, anorexia, nausea, hallucinations, depression and somnolence, as well as a fine scaly desquamating dermatitis. Injection of 150 µg biotin daily reversed all the clinical signs. Again there have been no studies of graded intakes of biotin in such experiments [3,4].

Similar signs of biotin deficiency have been observed in patients receiving total parenteral nutrition for prolonged periods, e.g. after resection of the gut. The signs resolve following the provision of biotin, but there have been no studies of the amounts required; curative intakes have ranged between 60 and 200 µg/day [5].

Requirements

There is little information concerning human biotin requirements, and no evidence on which to base recommendations. Average intakes of biotin in the EC are around 28-42 µg /day, but individuals may consume between 15 and 100 µg/d. Such intakes are obviously adequate to prevent deficiency. There is no evidence of adverse effects from high intakes of biotin.

There is no information on which to base estimates on additional requirements in pregnancy or lactation.

Summary

Average intakes of biotin are adequate to meet requirements. There is no information on intakes below which deficiency is likely, nor adequate evidence to determine the Population Reference Intakes.

The acceptable range of intakes for adults is the observed range 15-100 µg /day.

References

1. Hommes FA. (1986). Biotin. *World Rev Nutr Diet*. **48**: 34-84.

2. Bitsch R, Toth-Dersi A, Hoetzel D. (1985). Biotin deficiency and biotin supply. *Ann N Y Acad Sci*., **447**: 133-139.

3. Oppel TW. (1942). Studies of biotin metabolism in man. *Am J Med Sci* , **204**: 856-875.

4. Sydenstricker VP, Singal SA, Briggs AP, DeVaughn NM, Isbell H. (1942). Observations on the "Egg White Injury" in man and its cure with a biotin concentrate. *JAMA*, **118**: 1199-1200.

5. Mock DM, Baswell DL, Baker H, Holman RT, Sweetman L. (1985). Biotin deficiency complicating parenteral alimentation: diagnosis, metabolic repercussions and treatment. *J Pediatr*, **106**: 762-769.

15. Vitamin C

Physiology and metabolism

Vitamin C (L-ascorbic acid) is involved in numerous metabolic reactions in ways not yet fully understood [1,2]. The most specifically defined biochemical function is as a cofactor in hydroxylations using molecular oxygen, notably of proline to hydroxyproline, as in the biosynthesis of collagen. Ascorbic acid participates in this and other reactions as a reducing agent. It reduces Fe(III) to Fe(II), which helps in improving the absorption of non-haem iron. It reduces superoxide radicals to hydrogen peroxide, and effectively quenches singlet oxygen, which is the basis of its ability to inhibit many destructive photo-dynamic effects, e.g. in the eye, and other beneficial effects of vitamin C in the human body have been ascribed to its antioxidative capacity.

Ascorbic acid is one of the main water soluble chain-breaking antioxidants in biological systems [3]. Much attention is now being paid to the role of vitamin C in the antioxidant defences of the body, but insufficient evidence is currently available to enable the antioxidant status of the body to be used as the basis of calculating vitamin C requirements.

At low doses, absorption of vitamin C may be almost complete, but over the range of usual intake in food (30-180 mg/d), 80 to 90 % is absorbed. When ingested in amounts higher than 100 mg/d, it is mainly excreted as such, while the percentage of gastrointestinal absorption decreases with the oral dose of vitamin C to values as low as 16 % [4].

Total body stores of ascorbic acid in adult man may reach levels up to 3 g at daily intakes exceeding 200 mg. The average body pool of vitamin C of healthy male subjects consuming a self-selected diet with a daily ingestion of 60-100 mg of ascorbate is around 1500 mg, i.e. about 20 mg/kg body weight [5].

Levels of deficiency and excess

Frank vitamin C deficiency appears in the adult as scurvy, in the child as Moeller-Barlow disease, which has somewhat different signs.

Scurvy affects primarily the mesenchymal tissues. Because collagen formation is impaired, wound healing is delayed. The deficient formation of intercellular substance and collagen leads to increased fragility of the capillaries and to bleeding in the skin, mucous membranes, internal organs and muscles.

In childhood scurvy, the bone tissue is most obviously involved, especially in the breast cage and the stressed epiphyseal cartilage of the extremities. The disease can occur in artificially nourished infants after the 6th month of life, when the transplacentally transferred reserves of the vitamin have been exhausted.

Clinical signs of scurvy appear in adult men on a daily intake of less than 10 mg/d, when the total body pool falls below 300 mg [6], and are associated with plasma (or serum) and whole blood vitamin C values of less than 2 mg/L (11 µmol/L plasma) and 3 mg/L (17 µmol/L blood); leukocyte levels of less than 2 µg/10^8 cells (85 µmol/L) are observed.

A lesser degree of hypovitaminosis C can manifest itself in "prescorbutic" symptoms such as weakness, lassitude, fatigue, increased susceptibility to infections, and perhaps to other disease conditions [2]. Behavioural abnormalities, delayed recovery from surgical procedures, weight loss and deficient immune system responses have been reported.

A common feature of vitamin C deficiency is anaemia, due to impaired iron and perhaps folic acid metabolism.

Reports that high intakes may be beneficial have led some individuals to take large doses of vitamin C. The only adverse effects consistently reported in apparently healthy subjects are transient gastrointestinal disturbances. These can occur after ingestion of as little as 1 g, but seem to be caused by the acidity rather than the ascorbic acid *per se* because the symptoms can be largely avoided by taking the vitamin as a buffered salt. Ill effects of higher doses have occasionally been reported, e.g. an increased urinary excretion of oxalate with a resulting higher risk of kidney stones in patients with defects of oxalate metabolism, but in general intakes up to 10 g/d seem not to be unsafe for healthy individuals [7].

Methods for establishing physiological requirements

Vitamin C status can be evaluated from signs of clinical deficiency (such as follicular hyperkeratosis, swollen or bleeding gums, petechial haemorrhages, and joint pain), or from its concentration in plasma, blood or leukocytes. It has also been estimated from isotopic studies of body stores [2].

The Sheffield experiment on the vitamin C requirements of human adults [8] and the later Iowa study [6] indicated that a daily amount of 6.5-10 mg ascorbic acid is sufficient to prevent or to cure signs of scurvy. The ultimate lowest physiological requirement of adults is presumably in that range.

It is generally assumed that the amount of vitamin C required for optimal functioning of metabolic processes within the body is higher than the amount to prevent classical signs of scurvy. However, the optimal tissue levels of vitamin C for these processes are not known. Blood levels of vitamin C are often considered, although these levels have their limitations. Plasma concentrations above 5 mg/L (28 µmol/L) are taken as indicating an acceptable supply. Such levels are reached at vitamin C intakes from about 30 mg per day. Vitamin C levels rise rapidly with increasing daily intake and reach a plateau of 12-15 mg/L (68-85 µmol/L) at intakes far above 80 mg per day [9]. The strong relation between plasma vitamin C and recent oral intake limits the value of the plasma level as a reliable indicator of vitamin C adequacy.

The ascorbic acid level in leukocytes approximately reflects that in the tissues. However, it may not be a reliable index of vitamin C status as the vitamin rapidly moves from plasma into cells, e.g. during infections [10].

A priori, the best means of determining vitamin C requirement would seem to be determination of the total body pool and its fractional rate of loss or catabolism. The appropriate intake would be that needed to replace losses and thus maintain the body pool, taking into account the bioavailability of vitamin C from the diet.

Translation of physiological requirements into dietary intake

Clinical signs of scurvy appear in adult males when the total body pool of vitamin C falls below 300 mg [6]. It is desirable to have vitamin C in amounts more generous than just to prevent the appearance of scurvy, and psychological abnormalities have been reported in men with body pools below 600 mg. There is no convincing evidence of extra benefits from a pool in excess of 600 mg, but a pool of 900 mg would provide reserves for periods of low intake or temporary higher needs, e.g. stress.

For a wide range of body pool sizes (12-1700 mg) and vitamin C intakes up to 60 mg/day, the mean first-order rate of urinary excretion of vitamin C and its metabolites in adult men has been calculated as 2.7 ± 0.5 % of the body pool per day [11].

During the depletion periods of the Iowa experiments [12], the body pool was catabolized at a rate of 2.9 ± 0.6 % per day. One can derive from this a daily intake of

vitamin C in adult men by assuming a body pool of 900 mg and an absorption efficiency of 85%. In this way the Average Requirement (AR) for an adult man is calculated as:

900 x 2.9/100 x 100/85 = 30.7 mg/d, which can be rounded off to 30 mg/d.

The Population Reference Intake (PRI) for adult men would be

900 x (2.9 + 1.2)/100 x 100/85 = 43.4 mg/d, which can be rounded off to 45 mg/d.

It is difficult to estimate a Lowest Threshold Intake (LTI) for vitamin C. It can be argued that it should be the amount that will certainly prevent scurvy – somewhat less than 10 mg/d in adult men – but many would consider that a too restricted view of the nutritional importance of the vitamin. Maintenance of an adequate body pool has been used as the basis for calculating the AR and PRI; a similar approach can be employed for estimating the LTI.

It would be unreasonable to calculate a LTI to maintain a body pool size of 900 mg, as failure to do so is unlikely to be harmful. However, it can be derived for a body pool of 600 mg as

600 x (2.9 - 1.2)/100 x 100/85 = 12 mg/d.

Women probably have a smaller body pool than men, and might therefore be expected to have a lower requirement. No comparable turnover studies have been carried out on women, however, and in a depletion experiment the plasma vitamin C concentration was reported to fall more rapidly in females than in males [13]. It therefore seems prudent to make the same recommendations for non-pregnant, non-lactating women as for men.

Requirements of other groups of the population

Children

Little information is available beyond that 7 mg/d is sufficient to prevent scorbutic signs in infants [14]. The amount of vitamin C in breast milk seems to reflect maternal dietary intake, not the infant's needs, and in Europe and USA intake may range down to 23 mg/d, while apparently satisfying all the needs of the infant [2,11,14,15].

The PRI for infants 6-12 months is therefore set, somewhat arbitrarily, at 20 mg/d, i.e. about three times higher than amounts known to prevent scurvy.

The PRIs of older children are increased gradually to those for adults.

Pregnancy

Plasma and leukocyte vitamin C drop during pregnancy [14]. It is not known whether this drop represents a normal physiological adjustment (haemodilution) or indicates an increased requirement. It is assumed that the requirement of vitamin C during pregnancy is somewhat higher than that of non-pregnant women but by not more than 10 mg/d. This increase would allow for the 50 % higher plasma levels and probably higher cell concentration of vitamin C in the fetus and the higher catabolic rate of the fetus.

Lactation

Lactating women should have a vitamin C intake which compensates for at least 20 mg vitamin C excreted in breast milk. On the assumption of a 85 % bioavailability, the dietary intake of lactating women should be 25 mg/d higher than non-lactating women for the entire lactating period.

The elderly

Conflicting results have been reported on the changes of blood levels of vitamin C as a result of ageing. It seems, however, that in the absence of pathological conditions that may influence vitamin C metabolism (e.g. digestion or absorption) or renal functioning, the vitamin C requirement of the elderly do not deviate from those of other adults [13].

Other factors affecting vitamin C requirement

There are indications that smoking and some other factors and conditions may influence the vitamin C requirement.

Smoking decreases the absorption and blood level of vitamin C and increases its catabolism. In heavy smokers (routinely more than 20 cigarettes per day) with a vitamin C intake of 60 mg/day, the mean absorption efficiency has been reported as 9 % lower and the mean half-life significantly reduced (by about 60 %) as compared with non-smokers [16]. A direct relationship has been demonstrated between the number of cigarettes smoked per day and levels of vitamin C. The daily turnover of vitamin C of heavy smokers would be about 40 % higher than that of non-smokers [16].

The function of ascorbic acid in the absorption of non-haem iron has been mentioned already. The section of this report dealing with iron discusses the difficulty some women have in obtaining an adequate supply of iron. The bioavailability of dietary non-haem iron can be substantially improved if the meal contains 25 mg or more ascorbic acid.

Some circumstances enhance the requirement for vitamin C, e.g. high physical activity, mental stress, alcoholism, drugs, and a number of pathological states, e.g. diabetes [14]. Unfortunately, the effects of all these factors have not been quantified and results of studies are not concordant. Therefore, the optimal intake of vitamin C in such stress conditions is not known.

Higher recommendations

There is a school of thought which believes that human requirements for vitamin C are considerably higher than the PRIs discussed above, e.g. more than 1 g/d. However, this is based on extrapolations to man from observations in animals that many consider unjustified. Intakes in excess of about 80-100 mg/d lead to a quantitative increase in urinary excretion of unmetabolised vitamin C, indicating that at this level tissue reserves are saturated. It is difficult to justify a requirement in excess of tissue storage capacity.

It is hoped that in the near future more information will become available on the quantitative role of vitamin C in the body's defences against free radicals and on epidemiological evidence that appears to link higher vitamin C intakes with a lower level of some diseases [1,2,9,17].

Summary

Adults	mg/d
Average Requirement	30
Population Reference Intake	45
Lowest Threshold Intake	12

Population Reference Intakes of other groups

Age Group	PRI (mg/d)
6-11 m	20
1-3 y	25
4-6 y	25
7-10 y	30
11-14 y	35
15-17 y	40
Pregnancy	55
Lactation	70

References

1. Padh H. (1991). Vitamin C: newer insights into its biochemical functions. *Nutr Rev*, **49**: 65-70.

2. Friedrich W. (1988). *Vitamins*. Berlin: de Gruyter, 931-1001.

3. Frei B, England L, Ames BN. (1989). Ascorbate is an outstanding antioxidant in human plasma. *Proc Nat Acad Sci USA*, **86**: 6377-6381.

4. Melethil L, Mason WD, Chiang CJ. (1986). Dose-dependent absorption and excretion of vitamin C in humans. *Int J Pharmaceutics*, **31**: 83-89.

5. Kallner A. (1987). Requirement for vitamin C based on metabolic studies. *Ann NY Acad Sci*, **498**: 418-423.

6. Baker EM, Hodges RE, Hood J, Sauberlich HE, March SC. (1969). Metabolism of ascorbic 1-^{14}C acid in experimental human scurvy. *Am J Clin Nutr*, **22**: 549-558.

7. Flodin NW. (1988). *Pharmacology of Micronutrients*. New York: Wiley, 201-244.

8. Bartley W, Krebs HA, O'Brien JRP. (1953). *Vitamin C Requirement of Human Adults*. London: HMSO. (MRC Special Report Series; 280).

9. Basu TK, Schorah CJ. (1982). *Vitamin C in Health and Disease*. London: Croom Helm.

10. Lee W, Davis KA, Retmer RL, Labbe RF. (1988). Ascorbic acid status: biochemical and clinical considerations. *Am J Clin Nutr*, **48**: 286-290.

11. Olson JA, Hodges RE. (1987). Recommended dietary intakes (RDI) of vitamin C in humans. *Am J Clin Nutr*, **45**: 693-703.

12. Baker EM, Hodges RE, Hood J, Sauberlich HE, March SC, Canham JE. (1971) Metabolism of ^{14}C- and ^{3}H-labelled L-ascorbic acid in human scurvy. *Am J Clin Nutr*, **24**: 444-454

13. Blanchard J. (1991). Depletion and repletion kinetics of vitamin C in humans. *J. Nutr*, **121**: 170-176.

14. Irwin MI, Hutchins BK. (1976). A conspectus of research on vitamin C requirements in man. *J Nutr*, **106:** 821-879.

15. Van Zoeren-Grobben D, Schrijver J, Van den Berg H, Berger HM. (1987). Human milk vitamin content after pasteurisation, storage, or tube feeding. *Arch Dis Childh*, **62:** 161-165.

16. Kallner A, Hartmann D, Hornig DH. (1981). On the requirements of ascorbic acid in man: steady-state turnover and body pool in smokers. *Am J Clin Nutr*, **34:** 1347-1355.

17. Gaby SK, Singh VN. (1991). Vitamin C. In: Gaby SK, Bendich A, Singh VN, Machlin LJ. eds. *Vitamin Intake and Health. A Scientific Review*. New-York: Marcel Dekker, 103-161.

16. Vitamin D

Physiology and metabolism

The two major forms of vitamin D are the secosteroids cholecalciferol (vitamin D_3), derived from cholesterol and of animal origin, and ergocalciferol (vitamin D_2), derived from the plant sterol, ergosterol. Since vitamins D_2 and D_3 have roughly the same activity in man, the term vitamin D will be used here to refer to both D_2 and D_3. Amounts of vitamin D are usually expressed in terms of weight, but the older International Unit (IU) is still in use (1 IU = 0.025 µg vitamin D).

Sources

Vitamin D is not strictly a vitamin as most of it is formed in the body by the action of sunlight converting 7-dehydrocholesterol in the skin to previtamin D_3 [1]. This endogenous synthesis depends on the thickness and pigmentation of the skin and on the quality (290-315 nm) and intensity of the ultraviolet irradiation; the lowest UVB radiation that produces a significant increase in serum vitamin D_3 is 18 mJ/cm^2 in untanned white subjects [2]. As in North America [2,3], this threshold level may not be reached in Northern Europe for a large part of the year. For example in Paris (48°N) only between late spring and early autumn is there sufficient UVB solar radiation to produce vitamin D. Even so, the amount produced during that limited season appears to be adequate to cover the needs of healthy adults living at latitudes between 35°N and 60°N, provided that the time in sunlight (10-15 min/d) and the amount of skin exposed (30%) to optimal UV irradiation are sufficient [3,4] and that atmospheric pollution is not excessive [5]. Vitamin D synthesis also depends on the age of the subject, being decreased in elderly people [3].

The diet is a much less important source of vitamin D. Only a few foods (fatty fish, eggs, butter, liver and certain types of meat) contain significant amounts of the vitamin and average daily intakes are too small to influence vitamin D status significantly, unless fortified food products are eaten regularly, e.g. margarine, milk, cereals. Dietary practices, such as vegetarianism [6], macrobiotic diets [7], or just low calcium intakes [8], may decrease the availability of exogenous vitamin D or increase its catabolism.

Metabolism

In the blood vitamin D is bound to a specific vitamin D-binding protein, DBP, and is transported to the liver, where it undergoes a first hydroxylation into 25-hydroxyvitamin D (25-(OH)D). This formation of 25-(OH)D in the liver is not tightly regulated and after inadvertent administration of excessive doses of vitamin D circulating levels of this metabolite increase up a hundred fold higher than those found in healthy populations. In its turn 25-(OH)D is transported, bound to the same DBP, to the renal proximal tubule, where it is converted into 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2D$) [9].

The renal proximal tubule is the major contributor to the circulating pool of $1,25\text{-}(OH)_2D$ in healthy non-pregnant subjects, 0.3-1 µg/d being formed [10]. During pregnancy, the fetoplacental unit is a second major source of the circulating $1,25\text{-}(OH)_2D$. Unlike its precursor, 25-(OH)D, the circulating levels of $1,25\text{-}(OH)_2D$ are not influenced by vitamin D status except in situations of severe vitamin D deficiency. In contrast, the synthesis of $25\text{-}(OH)_2D$ is tightly feedback regulated by $1,25\text{-}(OH)_2D$ itself and depends mainly upon the calcium and phosphate needs of the body [9,11,12].

Actions

$1,25\text{-}(OH)_2D$ is the form of vitamin D responsible for calcium and phosphate absorption from the intestine, and for various actions on bone, kidneys, parathyroid glands and muscle, leading to the maintenance of phosphate homoeostasis in the extracellular fluid, to an increase in the extracellular concentration of calcium and to adequate mineralization of the skeleton [11,12]. In addition, $1,25\text{-}(OH)_2D$ may be directly involved in a variety of different processes unrelated to calcium and phosphate homoeostasis, but the physiological relevance, if any, of these latter actions remains to be evaluated.

Deficiency and excess

The early signs of vitamin D deficiency are infraclinical: decreased serum concentrations of calcium and phosphate, resulting from depressed absorption of calcium and phosphate from the intestine, secondary hyperparathyroidism and increased serum alkaline phosphatase activity. Hypocalcemic convulsions may occur at this stage. Later signs are inadequate skeletal mineralization (rickets or osteomalacia), bone pains, severe bone deformities, and alterations in muscle metabolism and respiratory function.

Signs of acute and chronic vitamin D intoxication include nausea, diarrhoea, polyuria, weight loss, hypercalcaemia, hypercalciuria, and eventually nephrocalcinosis, decreased renal function, or calcification of soft tissues. Signs of vitamin D intoxication have been found after prolonged administration of 250-1250 µg/d [13], although short term administration (7 weeks) of 250 µg/d to healthy adults had no detectable effects on the serum and urinary calcium and phosphate concentrations, and did not increase 25-(OH)D concentrations above levels spontaneously reached after daily total body exposure to UV irradiation [14].

Hypercalcaemia has been shown to occur occasionally in infant populations receiving periodic administration of very high doses of vitamin D (15 mg, every 6 months) as a prophylaxis against rickets, and 25-(OH)D levels in the blood of these infants reach values similar to those found in patients with obvious vitamin D intoxication [1,5].

It was claimed that prolonged daily intakes of 100 µg/d by infants increased the incidence of hypercalcaemia [16], but no reliable assessments of vitamin D intake could be made at that time. Doses of 50 µg/d do not appear to be harmful to infants as they do not affect statural growth [17].

Requirements

Assessment of vitamin D status

The most reliable marker of vitamin D status is the circulating level of 25-(OH)D. Healthy adults who do not expose themselves to sunshine, or live in countries with only a short season of useful UV irradiation, may have 25-(OH)D values as low as 6-8 ng/ml (15-20 nmol/L). Subclinical signs of vitamin D deficiency have been found in some of these otherwise healthy adults with 25-(OH)D levels below 10 ng/ml. At the other end of the scale, 25-(OH)D levels as high as 80 ng/ml (200 nmol/L) are found in healthy adults living in tropical countries or in southern Europe after prolonged sunbathing. Patients with clear signs of vitamin D intoxication usually have 25-(OH)D levels above 100 ng/ml. Thus a desirable range for 25-(OH)D could be 10-40 ng/ml (25-100 nmol/L). The vitamin D requirement is therefore being considered as that necessary to maintain circulating 25-(OH)D concentrations in that range.

Dietary recommendations

The problem in trying to give a dietary requirement for vitamin D is that many individuals maintain their circulating 25-(OH)D concentrations in the desirable range by endogenous synthesis of vitamin D, and so need none in the diet.

Those that do not produce sufficient vitamin D by endogenous synthesis need some dietary supply. The intake necessary will depend on the shortfall of exposure to effective UV radiation and perhaps on inadequacy of calcium and phosphate intakes. There will thus be considerable variation between different geographical regions in Europe (latitude, climate and air pollution) and perhaps between social and ethnic groups in a given geographical region (calcium and phosphate intake, exposure to sunlight).

In such circumstances, precise recommendations are hard to give; for some groups it would be pointless to try to do so, notably for adults, where most have no dietary requirement.

In all groups of the population however some individuals will need some dietary vitamin D, and a range of values is suggested that would meet the needs of all members of the group, even those with minimal endogenous production of vitamin D.

Some population groups may have difficulty in obtaining their needs by endogenous synthesis, either because of inadequate exposure to sunlight (e.g. the elderly) or of a physiologically raised requirement (e.g. in pregnancy and lactation) or both (e.g. very young children). Substantial numbers in these groups will need dietary vitamin D, and there is a sizeable risk of an individual becoming deficient. In these groups, as a matter of prudence, a minimum value for intake is given, i.e. it is recommended that all members of the group receive that amount. In practice this will call for the consumption of supplements or fortified foodstuffs.

Adults

On the basis of their 25-(OH)D levels, dietary intakes of vitamin D do not appear essential for healthy adults, adequately supplied with calcium and phosphate, unless they are confined indoors [4].

No information is available on the effects of dietary vitamin D on 25-(OH)D levels of non-pregnant younger adults, but from studies on elderly people [18,19], it appears that daily intakes of 10 µg/d would bring 25-(OH)D concentrations into the desired range, even if endogenous synthesis were minimal.

It is suggested that the requirements of all adults would met by dietary intakes of 0-10 µg/d.

Children

There is a substantial incidence of rickets in infants not given vitamin D supplements. Studies on the 25-(OH)D levels of infants supplemented or not supplemented with vitamin D confirm that infants have a high requirement [20,21].

In order to maintain circulating 25-(OH)D levels in the desired range it is recommended that the dietary intake of infants 6-11m should not be less than 10 µg/d. It is possible that the requirement may be higher in some infants, perhaps up to 25 µg/d [21].

Infants and children are vulnerable to vitamin D deficiency because calcium is being laid down in bone at a high rate. As children in the 1-3 y group may not get adequate exposure to sunlight it is recommended that their intake should not be less than 10 µg.

Older children still have a high requirement for vitamin D, and adolescents, who have to reach adult bone mass at a time of accelerated skeletal growth, have a particularly high requirement for calcium and thus for vitamin D. Most children of 4 years and over and most adolescents should however get enough exposure to sunlight to make adequate amounts themselves.

Those belonging to social or ethnic groups with insufficient exposure to the sun, or on not wholly satisfactory diets, are at risk of vitamin D deficiency, and attention should be paid to adolescents in northern Europe. The ranges of dietary vitamin D are 0-10 µg/d for 4-10 y and 0-15 µg/d for 11-17 y.

Pregnancy and lactation

Pregnant and lactating women have higher requirements for vitamin D than do non-pregnant women along with their need for high amounts of calcium and phosphate for the mineralization of the growing skeleton of the fetus and infant; lactating women also have to provide vitamin D in the milk. Numerous studies on 25-(OH)D levels have shown that customary exposure to sunlight in Europe may be insufficient to cover the needs for vitamin D, especially during the last trimester of pregnancy, and notably at the end of the winter. The ensuing vitamin D deficiency will affect not only the mother but also the newborn, whose vitamin D reserves are very dependent on those of the mother. To maintain 25-(OH)D levels, 10 µg/d is recommended [22,23].

The elderly and institutionalized individuals

Because of lack of exposure to sunlight, and the decline with age of the ability to synthesize vitamin D_3, elderly and institutionalized people are prone to develop D deficiency. To maintain circulating 25-(OH)D values between 10 and 20 ng/ml, elderly and institutionalized people should receive 10 µg/d [18,19].

Summary

Requirements

A range of values up from zero indicates that all members of the group should be able to produce adequate vitamin D for themselves by exposure to sunlight, and most will, with no need for a dietary supply. The higher end of the range is the estimated dietary requirement of an individual with minimal endogenous synthesis.

In other groups a single value indicates that it is prudent for the whole group to be supplemented to avoid occurrence of vitamin D deficiency.

Age group	PRI (µg/d)
6 - 11 m	10-25
1 - 3 y	10
4 - 6 y	0-10
7 - 10 y	0-10
11-14 y	0-15
15-17 y	0-15
18-64 y	0-10
65 + y	10
Pregnancy	10
Lactation	10

Higher intakes

Intakes of 250 µg/d have been reported as harmful [13]; the lowest level at which ill effects appear is not known. Intakes of 50 µg/d appear safe [17]. There seems no benefit to be obtained by healthy individuals from higher regular intakes. It would be prudent not to exceed 50 µg/d in habitual intake.

References

1. Webb AR, Holick MF. (1988). The role of sunlight in the cutaneous production of vitamin D_3. *Ann Rev Nutr*, 8: 375-399.

2. Matsuoka LY, Wortsman J, Haddad JG, Hollis BW. (1989). *In vivo* threshold for cutaneous synthesis of vitamin D_3. *J Lab Clin Med*, 114: 301-305.

3. Holick MF. (1986). Vitamin D requirements for the elderly. *Clin Nutr*, 5:121-129.

4. Markestad T, Elzouki AY. (1991). Vitamin D-deficiency rickets in northern Europe and Libya. In: Glorieux F, ed. *Rickets*. Nestlé Nutrition Workshop Series, 21. New York: Raven Press 203-213.

5. Loomis WF. (1970). Rickets. *Scientific Amer*, 223 (6):76-91.

6. Henderson JB, Dunnigan MG, McIntosh WB, Motaal AA, Hole D. (1990). Asian osteomalacia is determined by dietary factors when exposure to ultraviolet radiation is restricted: a risk factor model . *Q J Med*, 76: 923-933.

7. Dagnelie PC, Vergote FJVRA, van Staveren WA, van Den Berg H, Dingjan PG, Hautvast JGAJ. (1990). High prevalence of rickets in infants on macrobiotic diets. *Am J Clin Nutr*, 51:202-208.

8. Clements MR, Johnson L, Fraser DR. (1987). A new mechanism for induced vitamin D deficiency in calcium deprivation. *Nature*, 327:62-65.

9. Fraser DR. (1980). Regulation of the metabolism of vitamin D. *Physiol Rev*, 60: 551-613.

10. Gray RW, Caldas AE, Wilz DR, Lemann J, Smith GA, DeLuca HF. (1978). Metabolism and excretion of ^{3}H-1,25-$(OH)_2$-vitamin D_3 in healthy adults. *J Clin Endocrinol Metab*, 46:756-765.

11. Kumar R. (1986). The metabolism and mechanism of action of 1,25-dihydroxyvitamin D_3. *Kidney Int*, 30:793-803.

12. Reichel H, Koeffler HP, Norman AW. (1989). The role of the vitamin D endocrine system in health and disease. *N Engl J Med*, 320:980-991.

13. Anning ST, Dawson J, Dolby DE, Ingram JT. (1948). The toxic effect of calciferol. *Q J Med*, 17:203-228.

14. Berlin T, Emtestam L, Björkhem I. (1986). Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3. *Scand J Clin Lab Invest*, 46: 723-729.

15. Markestadt T, Hesse V, Siebenhuner M, Jahreis G, Aksnes L, Plenert W, Aarskog D. (1987). Intermittent high-dose vitamin D prophylaxis during infancy: effect on vitamin D metabolites, calcium and phosphorus. *Am J Clin Nutr*, 46: 652-658.

16. Fraser D, Kidd BSL, Kooh SW, Paunier L. (1966). A new look at infantile hypercalcemia. *Pediatr Clin North Am*, 13: 503-525.

17. Fomon SJ, Younoszai MK, Thomas LN. (1966). Influence of vitamin D on linear growth of normal full-term infants. *J Nutr*, 88:345-350.

18. MacLennan WJ, Hamilton JC. (1977). Vitamin D supplements and 25-hydroxyvitamin D concentrations in the elderly. *Br Med J*, 2:859-861.

19. Toss G, Larsson L, Lindgren S. (1983). Serum levels of 25-hydroxyvitamin D in adults and elderly humans after a prophylactic dose of vitamin D_2. *Scand J Clin Lab Invest*, 43:329-332.

20. Poskitt EME, Cole TJ, Lawson DEM. (1979). Diet, sunlight and 25-hydroxyvitamin D in healthy children and adults. *Br Med J*, 1:221-223.

21. Garabédian M, Zeghoud F, Rossignol C. (1991). Les besoins en vitamine D du nourrisson vivant en France. In: Journées Parisiennes de Pédiatrie. Médecine-Sciences, Flammarion, Paris, 51-57.

22. Cockburn F, Belton NR, Purvis RJ, Giles MM, Brown JK, Turner TL *et al.* (1980). Maternal vitamin D intake and mineral metabolism in mothers and their new-born infants. *Br Med J*, 281:11-14.

23. Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. (1981). Bone mineral content and 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *J Pediatr*, 98:696-701.

17. Vitamin E

Physiology

Vitamin E activity is manifested by two series of compounds. The more important are the tocopherols; the tocotrienols, differing in the degree of saturation of the phytyl side chain, are less potent biologically and provide only a little of the vitamin E activity of the diet. Within each series are four compounds (designated α, β, γ and δ) differing in the number and position of the methyl groups on the chromanol ring. Synthetic α-tocopherol is a mixture of isomers. The multiple forms differ in vitamin E potency, the most active being the natural isomer RRR-α-tocopherol, which accounts for about 90% of the vitamin E present in human tissues. The vitamin E activity of all is now conventionally summed in terms of the equivalent value of RRR-α-tocopherol [1] (1 mg α-tocopherol equivalent = 1.5 international units).

The biological action of vitamin E results principally and perhaps entirely from its antioxidant properties; it prevents propagation of the oxidation of unsaturated fatty acids by trapping free radicals. This is believed to be the basic function of vitamin E in animal tissues, where tocopherol is found in cellular membranes associated with polyunsaturated fatty acids (PUFA) in phospholipids. In vitamin E deficiency, the oxidation of PUFA leads to structural and functional damage to cellular membranes.

Levels of deficiency and excess

Most diets are an adequate source of vitamin E, and consequently for many years no clearly defined deficiency syndrome could be described in man, and no clinical signs of deficiency are ever seen in individuals without other metabolic defects. Children and adults unable to absorb or utilise vitamin E adequately can develop a characteristic and progressive neurological syndrome involving the central and peripheral nervous system, retina and skeletal muscles, after a period of years during which the plasma tocopherol concentration has been extremely low. Appropriate treatment with vitamin E can prevent this if given sufficiently early.

A specific syndrome comprising haemolytic anaemia, thrombocytosis and oedema has been reported in premature infants, but the introduction of milk formulas containing adequate vitamin E has resulted in its virtual disappearance.

Over the years there have been many claims that vitamin E in quantities much larger than those needed to prevent any detectable deficiency may have beneficial effects on various disease processes or in promoting better general health. Most have not gained wide acceptance. Currently however there is much interest in a postulated role of antioxidants in preventing pathological processes in which free radicals have been implicated; particular attention has been paid to vitamin E as it can act as a free-radical scavenger. It has been suggested that a generous intake of vitamin E might protect against, among other things, cancer, atherosclerosis, coronary heart disease, cataracts, arthritis, ageing and air pollutants [2]. For example, an inverse relationship has been reported between plasma vitamin E concentration and coronary heart disease [3,4].

Because of the numerous reports of the beneficial effects of high doses, it is not uncommon for individuals to consume large amounts of vitamin E. There have been a number of double blind trials to investigate high doses of vitamin E up to 3,200 mg/d. Few adverse effects were reported and none consistently but above 2,000 mg α-tocopherol equivalents per day some subjects showed intestinal disorders (diarrhoea and cramps) [5].

Methods of establishing physiological requirements

Since clinical vitamin E deficiency due to an inadequate supply in the diet does not exist, some other marker of E status is necessary, and a commonly used one is the plasma tocopherol concentration. This however changes with the concentration of serum lipids; as they rise tocopherol appears to partition out of cellular membranes into the circulation. The tocopherol concentration is therefore best expressed as the serum tocopherol: total lipid ratio, but the serum tocopherol:cholesterol ratio is almost as good, and is more convenient to measure [6].

The major function of vitamin E is believed to be the protection of cellular membrane lipids from oxidation and a widely employed test for this is to expose red cells *in vitro* to oxidizing agents such as dilute solutions of hydrogen peroxide. Below a plasma tocopherol concentration of 0.5 mg/dl (11.6 μmol/L; tocopherol:cholesterol ratio 2.25 μmol/mmol), the erythrocytes tend to haemolyse. A substantial decrease below this concentration is necessary to reduce red cell survival time *in vivo* [7]. Nevertheless a plasma tocopherol concentration of 0.5 mg/dl (11.6 μmol/L) or, better, a serum tocopherol: cholesterol ratio of 2.25 μmol/mmol, is taken as an indication of biochemical abnormality, and it is considered undesirable to have tocopherol concentrations fall below that.

In favourable circumstances the plasma tocopherol concentration can be maintained above that on not very large intakes of vitamin E – for some adult males, on not much above 3 mg α-tocopherol equivalents per day, provided they have a low intake of PUFA [8].

The requirement for vitamin E is determined to a large extent by the PUFA content of the tissues, which is influenced by the PUFA content of the diet. Numerous experiments have shown that increasing the PUFA content of a diet low in vitamin E has adverse effects on E status [8,9] and if there are very large amounts of PUFA, substantial quantities of extra vitamin E are needed to restore the plasma tocopherol concentration to an adequate level [9].

Translation of these physiological requirements into dietary intakes

A major problem in making recommendations arises from the fact that E requirements are influenced by the PUFA intake. There are wide variations in PUFA consumption; the intakes of individuals are not normally distributed but are skewed with some quite high values. In a recent study of adult men in UK [10] the 97.5 centile intake of n-6 PUFA was 29 g per day. The amount of vitamin E required for such an intake of PUFA would be high. To give such a value as the PRI would have the undesirable effect of indicating to people with a much lower, but adequate, intake of PUFA that they ought to take substantially more vitamin E when they had no need to do so.

However, widely differing intakes of PUFA are normally not a problem in practical vitamin E nutrition. Foods rich in PUFA tend to contain large amounts of vitamin E, so high intakes of PUFA are usually accompanied by comparably high intakes of vitamin E. This is not always the case with all individual foodstuffs, but taken over a mixed diet, the generalization seems to hold.

The difficulty in making recommendations about dietary intake of vitamin E is that there is no good evidence that dietary vitamin E deficiency exists, in part because vitamin E is widely distributed in common foodstuffs, and accompanies the PUFA that raise requirements. A recent demonstration of this was in a survey in UK [10]. Of 1,763 adult subjects only 11 (0.6%) had serum tocopherol:cholesterol ratios below 2.25 μmol/mmol.

There are various responses to this problem. One is to declare that, as virtually all diets are adequate with respect to vitamin E, recommendations are unnecessary except for infant formulas.

A second approach is to decide that since the diet as consumed is clearly adequate with respect to vitamin E, the recommendation should be based on current intakes. In prosperous societies, however, most people seem to ingest more vitamin E than they need to maintain apparent biochemical normality. In the recent survey of British adults [10], of which over 99% had acceptable serum tocopherol:cholesterol ratios, seven-day weighed dietary records (excluding vitamin supplements) showed that the 2.5 and 97.5 centile intakes of a group of 1,087 males were 3.5 and 19.5 mg α-tocopherol equivalents per day, and of a group of 1,110 females 2.5 and 15.2 mg per day.

Another apparently more logical approach is to make dietary recommendations for vitamin E in terms of the dietary PUFA intake. There is however no general agreement about what the ratio mg α-tocopherol equivalents:g PUFA should be, but about 0.4 seems adequate in a normal American diet [11,12]. Furthermore there is evidence that even on a very low intake of PUFA, a substantial amount of vitamin E is still needed [9].

Suggestions have been made that intakes of vitamin E in amounts much larger than normally considered essential would raise plasma α-tocopherol concentrations and have health benefits. The evidence for this is as yet insufficiently convincing, and there is even less certainty on what the effective daily amounts might be.

The claim should be kept under review as the results of more work, including, it is hoped, intervention trials, are published. Should it prove true, the problem could arise of distinguishing between true nutrient needs and the use of nutrients as prophylactic drugs [13].

Children and infants (6-11m)

A diet containing 0.4 mg α-tocopherol equivalents per g PUFA seems adequate for children. It is reasonable to assume that as in adults there is some basic requirement for vitamin E on a diet very low in PUFA, but there is no information about what the amount might be. In practice, there seems no cause for concern, as there is no evidence of E deficiency in metabolically normal children.

Infant formulae always contain adequate amounts of vitamin E.

Pregnancy and lactation

Since vitamin E deficiency has never been reported during pregnancy and lactation, even on quite low intakes [14], no recommendations for supplementation are made.

Summary of proposals

1. As the vitamin E requirement depends on the dietary PUFA intake, and dietary PUFA intakes vary greatly between individuals, it is inexpedient to set a single PRI value that would meet the known nutrient needs of practically all healthy persons as this would be misleadingly far too large for most of the group.

2. Similarly there seems little merit in giving an average requirement.

3. A requirement for vitamin E can be defined in terms of dietary PUFA intake. Vitamin E requirement (mg α-tocopherol equivalents) = 0.4 x (g dietary PUFA). There is no evidence that this level would be inadequate for anyone, provided the value did not fall below 4 mg/d for adult men and 3 mg/d for adult women (because of their smaller body size, women would have less PUFA in their tissues needing protection).

4. Large doses are usually harmless, but should not exceed 2,000 mg α-tocopherol equivalents per day.

5. Claims that very generous intakes of vitamin E have beneficial effects on health are not being taken into account in making the present recommendations.

References

1. Diplock AT. (1985). Vitamin E. In: Diplock AT, ed. *Fat-Soluble Vitamins, Their Biochemistry and Applications*, London: Heinemann, 154-224.

2. Packer L. (1991). Protective role of vitamin E in biological systems. *Am J Clin Nutr*, 53: 1050S-1055S.

3. Gey KF. (1990). The antioxidant hypothesis of cardiovascular disease: epidemiology and mechanisms. *Biochem Soc Trans*, 18: 1041-1045.

4. Riemersma RA, Wood DA, Macintyre CCA, Elton RA, Gey KF, Oliver MF. (1991). Risk of angina pectoris and plasma concentrations of vitamins A, C and E and carotene. *Lancet*, 337: 1-5.

5. Bendich A, Machlin LJ. (1988). Safety of oral intake of vitamin E. *Am J Clin Nutr*, 48: 612-619.

6. Thurnham DI, Davies JA, Crump BJ, Situnayake RD, Davis M. (1986). The use of different lipids to express serum tocopherol : lipid ratios for the measurement of vitamin E status. *Ann Clin Biochem*, 23: 514-520.

7. Horwitt MK. (1980). Interpretation of human requirements for vitamin E. In: Machlin LJ, ed. *Vitamin E, A Comprehensive Treatise*, New York : Marcel Dekker, 621-636.

8. Bunnell RH, De Ritter E, Rubin SH. (1975). Effect of feeding polyunsaturated fatty acids with a low vitamin E diet on blood levels of tocopherol in men performing hard physical labor. *Am J Clin Nutr*, 28: 706-711.

9. Horwitt, M.K. (1974). Status of human requirements for vitamin E. *Am J Clin Nutr*, 27: 1182-1193.

10. Gregory J, Foster K, Tyler H, Wiseman M. (1990). *The Dietary and Nutritional Survey of British Adults*. London: HMSO.

11. Bieri JG, Evans RP. (1973). Tocopherols and fatty acids in American diets: the recommended allowance for vitamin E. *J Am Dietet Assoc*, 62: 147-151.

12. Witting LA, Lee L. (1975). Dietary levels of vitamin E and polyunsaturated fatty acids and plasma vitamin E. *Am J Clin Nutr*, 28: 571-576.

13. Draper HH. (1988). Nutrients as nutrients and nutrients as prophylactic drugs. *J Nutr*, 118: 1420-1421.

14. Black AE, Wiles SJ, Paul AA. (1986). The nutrient intakes of pregnant and lactating mothers of good socio-economic status in Cambridge, UK: some implications for recommended daily allowances of minor nutrients. *Br J Nutr*, 56: 59-72

18. Vitamin K

Physiology

Vitamin K activity is shown by a number of compounds containing the 2-methyl-1,4-naphthoquinone structure. They include phylloquinone (the major dietary source), which occurs in plants, and the menaquinones, synthesized by bacteria [1].

Knowledge of the physiology of vitamin K has lagged behind that of the other fat-soluble vitamins mainly because of the difficulty of quantifying the various forms. The best dietary sources are green leafy vegetables. Much smaller but nevertheless significant amounts are found in other foodstuffs of both plant and animal origin [1]. It is uncertain to what extent the intestinal bacteria contribute vitamin K to the body [2,3,4].

Vitamin K is reasonably well absorbed from the small intestine, but only poorly from the colon. Like all fat-soluble vitamins its absorption in substantial amounts depends upon normal production of bile acids and pancreatic enzymes. It is enhanced by dietary fat. In malabsorption syndromes uptake from the diet is very poor [1].

There is little storage of vitamin K in the body and there appears to be a fairly rapid turnover, so a continual supply is necessary in the diet.

Vitamin K operates as an essential cofactor for a carboxylase enzyme catalysing the posttranslational carboxylation of specific glutamyl residues in some proteins to the γ-carboxyglutamic form [2]. The best known such proteins are prothrombin and at least five other proteins involved in blood clotting. More recent work has shown that a number of other proteins containing γ-carboxyglutamic acid require vitamin K for their biosynthesis, notably osteocalcin in bone [3].

Deficiency and excess

Vitamin K deficiency results in a bleeding syndrome consequent upon a lack of clotting factors. No deficiency signs have been reported as a result of inadequate production of other vitamin K-dependent proteins.

Clinical features may range from mild bruising to severe life-threatening haemorrhage. Deficiency can occur in infants, who are born with low reserves and no gut flora, as breast milk is not a good source of the vitamin.

Clinical vitamin K deficiency is never seen after the first few months of life, except as a consequence of disease states, e.g. malabsorption, the use of vitamin K antagonists as anticoagulant drugs, long-term treatment with some antibiotics, parenteral nutrition without vitamin K [4].

No adverse signs have ever been reported from large oral doses of vitamin K [5]. Menadione, a synthetic water-soluble compound with vitamin K activity, may induce haemolytic anaemia, hyperbilirubinaemia and kernicterus in the newborn; these are not manifestations of hypervitaminosis K, but are side effects of an unphysiological form [5].

Requirements

It is not easy to estimate human requirements because of the difficulty of inducing vitamin K deficiency in normal subjects. Vitamin K status has usually been assessed from the plasma concentration of prothrombin, measured from the clotting time in standardized conditions (prothrombin time). New more sensitive procedures are now being used to measure decreased activity of vitamin K-dependent clotting factors, lowered serum concentration of vitamin K and decreased urinary excretion of γ-carboxyglutamic acid [6].

In one experiment young healthy subjects consumed a diet, from which foods rich in vitamin K had been removed, to give approximately 50 µg phylloquinone/d. Blood clotting appeared normal, but there were signs that prothrombin biosynthesis was not optimal, and there was a decrease in γ-carboxyglutamic acid excretion. Supplements of 50 µg phylloquinone/d restored these indices to normal [7].

These findings are consistent with earlier work indicating that the requirement for dietary vitamin K is about 1 µg per kg body weight per day [2,7].

Considering the difficulty of inducing vitamin K deficiency in healthy subjects, the problem of monitoring vitamin K status sensitively and reliably, the uncertainty of how much might be supplied by intestinal bacteria and the lack of accurate values for the amount of dietary K just sufficient to maintain normal function, the Committee decided to make no recommendation for vitamin K. An intake of 1 µg per kg body weight per day appears adequate and would be provided by a normal mixed diet.

References

1. Suttie JW. (1985). Vitamin K. In: Diplock AT, ed. *Fat-Soluble Vitamins, Their Biochemistry and Applications*. London: Heinemann. 225-311.

2. Suttie JW. (1987). Recent advances in hepatic vitamin K metabolism and function. *Hepatology*, 7 : 367-376.

3. Shearer MJ. (1990). Vitamin K and vitamin K-dependent proteins. *Br J Haematol*, 75. 156-162.

4. Carlin A, Walker WA. (1991). Rapid development of vitamin K deficiency in an adolescent boy receiving total parenteral nutrition following bone marrow transplantation. *Nutr Rev*, 49 : 179-183.

5. Miller DR, Hayes KC. (1982). Vitamin excess and toxicity. In: Hathcock JN, ed. *Nutritional Toxicology*, vol. 1. New York: Academic Press. 81-133.

6. Sadowski JA, Bacon DS, Head S, Davidson KW, Ganter CM, Haroon Y, Shephard DC. (1988). The application of methods used for the evaluation of vitamin K nutritional status in human and animal studies. In: Suttie JW, ed. *Current Advances in Vitamin K Research*. New York: Elsevier. 453-463.

7. Suttie JW, Mummah-Schendel LL, Shah DV, Lyle BJ, Greger H. (1988). Vitamin K deficiency from dietary vitamin K restriction in humans. *Am J Clin Nutr*, 47: 475-480.

19. Calcium

Physiology

The adult male contains approximately 1.2 kg calcium (i.e. 1.5-2 % of the body weight), about 99 % of which is in the skeleton and the teeth; the residual 1 % is distributed between soft tissues (0.6 %) and the extracellular fluid (ECF) (0.06 %) including plasma (0.03 %). The intracellular concentration of calcium ranges from 15 mmol/kg in muscle and platelets to as little as 0.02 mmol/kg in erythrocytes. Plasma and ECF calcium concentrations are 2.0-2.5 mmol/L; of this approximately 10 % is complexed with citrate, phosphate, bicarbonate, and 45 % is bound to circulating proteins of which 80-90 % is bound to albumin. About 45 % is present as free calcium ions – this is the functionally active pool, and it is far in excess of the intracellular activity of free calcium, which is only about 0.1 µmol/L [1,2].

Calcium in bone has a structural function as a component of calcium hydroxyapatite, the principal bone mineral, which is complexed within the glycosaminoglycan ground substance and collagen fibres of the organic matrix.

Calcium has an important regulatory role; the thousand fold gradient between extra- and intra-cellular ionic calcium concentrations is fundamental to cellular signal transduction and amplification. An induced influx of calcium triggers and activates a variety of cellular physical and metabolic events such as enzyme activation, muscle contraction, neurotransmission, vesicular secretion, cellular aggregation, transformation and cell division.

Although some calcium is absorbed in the distal bowel most is taken up in the proximal intestine via a carrier-mediated pathway and by diffusion which may be paracellular. The former involves a calcium-binding protein which transfers the element across the enterocyte to the baso-lateral membrane where it is extruded by Ca-Mg ATPase. When calcium requirements are increased, circulating concentrations of calcitriol (1,25-dihydroxycholecalciferol) increase, upregulating the carrier-dependent absorption of calcium.

Within the intestinal lumen dietary components such as phytate, oxalate, alginate, uronate, phosphate, and unabsorbed lipids may bind calcium and reduce its absorption. On the other hand the luminal availability and absorption of the element is enhanced by lactose, phosphatidic acid, amino acids, sucrose, and increased intraluminal pH [3].

Calcium excretion occurs via both the gastrointestinal tract and the kidneys. The urinary content of calcium is related closely to the dietary intake of the element. Up to 97 % of the calcium entering the renal glomerular filtrate can be reabsorbed. The remaining 3 % may represent an 'obligatory' urinary loss of calcium which is considered as a significant determinant of calcium requirements. Urinary calcium loss rises with increasing intakes of sodium and protein; however the latter effect may be offset by the accompanying high phosphorus intakes in the protein sources.

Calcium homoeostasis controls and protects the metabolically vital plasma pool of ionised calcium by simultaneously modifying its absorption, renal excretion and turnover in the mobilisable pool in bone. The principal regulators of these processes are parathyroid hormone, calcitonin, and calcitriol [4].

The secretion of parathyroid hormone is increased in response to low plasma ionised calcium concentrations and, possibly, low plasma magnesium concentrations. Initially this increased secretion is effected by increased cellular production of the hormone itself but with chronic hypocalcaemia parathyroid hyperplasia sustains the increased secretion of hormone. Parathyroid hormone increases renal excretion of phosphate and retention of calcium. It also stimulates the 1 α-hydroxylation of calcidiol (25-OH cholecalciferol) to calcitriol; thereby having an indirect effect on the intestinal absorption of calcium. Parathyroid hormone may also have a direct effect on the enterocyte. The hormone increases bone turnover and the release of calcium from the freely exchangeable calcium pools. It does this first via the surface osteocytes and in the long term by increasing the number of basic multicellular units (BMU) which mediate and coordinate bone turnover.

Calcitriol stimulates intestinal calcium uptake by increasing the enterocytic production of calcium-binding protein. It also induces the maturation of osteoblasts thereby stimulating calcification of bone matrix, whilst simultaneously blocking bone resorption by inhibiting parathyroid hormone production. Calcitonin is secreted by the thyroid C cells in response to high plasma ionised calcium activity, which it reduces by increasing the renal excretion of calcium and reducing osteoclastic activity.

Other hormones including the female sex hormones, mineralocorticoids, the thyroid hormones, and parathyroid hormone-related protein have a direct or indirect effect via the BMU on skeletal mineralisation and calcium metabolism but the precise mechanisms are not clear.

Deficiency and excess

Acute calcium deficiency arising from dietary origin is rare, the exception being young infants fed infant formulas with an inappropriately low calcium:phosphorus ratio. The features are muscular weakness and tetany resulting from reduced ECF ionised calcium activity. Thus features of calcium deficiency are commonly seen in severe systemic alkalosis in which ionised calcium levels are reduced.

Chronic calcium deficiency causes a reduction in bone density in children and may contribute to an increased fracture rate; it is debatable whether or not it causes growth retardation in children. Similarly the role and importance of an inadequate calcium intake in the pathogenesis of osteoporosis is not clear. Adequate bone formation depends on many nutrients and similarly the aetiology of osteoporosis is probably multifactorial [4]. It is uncertain that current calcium intakes play a major role in the pathogenesis of osteoporosis [5,6]. Although calcium supplements (1 g calcium/d) slow the loss of bone density in established post-menopausal osteoporosis, this needs to be further evaluated in the context of the similar, or possibly extra, benefits which can be achieved by exercise, vitamin D or hormone replacement therapy [7,8,9,10,11,12] or by changes in lifestyle and calcium intakes in earlier life.

Calcium excess arising from dietary intake is rare because of the effectiveness of the homoeostatic mechanisms. In healthy individuals, intakes of 2.5 g (62.5 mmol) are tolerated. At intakes above this, as may occur with ingestion of supplements of calcium (and sometimes of vitamin D) or of antacids, there is a risk of renal stones, hypercalcaemia and impaired renal function.

Requirements

Adults

Since plasma ionised calcium activity is maintained by mobilisation of skeletal calcium stores, as well as by increased net intestinal absorption and renal conservation of the element, if the dietary intake of calcium is inadequate the plasma ionised calcium can be maintained for a long time at the expense of the skeletal pool. The approximately thousand fold bigger size of this endogenous resource of calcium compared with ingested amounts (500-1000 mg daily) makes it difficult to establish reliable conditions under which obligatory losses of calcium can be gauged against dietary intakes. Although metabolic balances have been used to analyse the adequacy of calcium requirements, experience has shown that few studies allowed

sufficient time for systemic and intestinal adaptation to altered dietary intakes to occur or measured simultaneously the systemic hormonal homoeostatic adaptation. The prolonged studies of Malm [9] suggest that with time adult men can adapt to a calcium intake of 400 mg/d, but most metabolic studies have used intakes in excess of this and extrapolation of the data is limited also by the variable bioavailability arising from the various diets used.

Bone density or the incidence of osteoporosis were not considered suitable measurements for determining calcium requirements because they are both subject to many physical, genetic and nutritional influences [4,5].

Requirements have been estimated on the assumption that the principal determinant is the obligatory loss of the element via skin, faeces and urine, with additional estimated increments for skeletal growth and consolidation. In adults the needs for bone growth are minimal even though some 10 % of bone consolidation occurs during the third decade. No reliable data are available on losses via sweat and the integuments although these may not be negligible [6]. A level of such nonfaecal losses including 'obligatory urinary loss' has been taken as 160 mg/d. Assuming conservatively an absorptive efficiency of 30 % this translates to an average requirement of 530 mg/d (rounded to 550 mg/d) which with a 2SD distribution comes to 700 mg/d as a PRI with the LTI being set at 400 mg/d. [This may be a generous recommendation, and at an alternative, and not unlikely, absorptive efficiency of 40 % the average 'systemic need' would be met by an intake of 400 mg (+2SD = 520 mg)].

An upper limit of intake of 2.5 g/d is advised.

Children

Between the ages of 1 and 10, the average daily calcium retention needed for skeletal growth has been estimated to rise from 70 to 150 mg/d [13]. The PRIs given are based on the assumption that there is a net absorption of 35% of dietary calcium, with 30% (considered as equivalent to 2SD) being added to the calculated amount to allow for individual variation.

In the absence of reliable information, the PRI for 6-11 months old infants was taken as the same as for 1-3 year olds.

PRIs for adolescents are raised above those for adults to reflect the increased requirements for skeletal development. They are derived from a mean retention of 250 mg/d in girls and 300 mg/d in boys, assuming net absorption of 40% of dietary calcium, again with 30% being added to cover individual variation.

Pregnancy

There appears to be no spontaneous increase in calcium consumption by pregnant women. The physiological way of obtaining the calcium required for fetal growth includes an increased efficiency of dietary absorption and the mobilization of calcium from maternal bone [14]. There seems to be no need to increase the dietary calcium intake during pregnancy.

Lactation

The calcium required in the milk is normally obtained from the spontaneous increase of food intake by lactating women. On the assumption of an absorption efficiency of 40%, plus an allowance for 2SD, an extra 500 mg/d is proposed for lactating women.

Summary

Adults	mg/d
Average Requirement	550
Population Reference Intake	700
Lowest Threshold Intake	400

Population Reference Intakes of other groups

Age Group		PRI (mg/d)
	6-11 m	400
	1-3 y	400
	4-6 y	450
	7-10 y	550
Males	11-14 y	1000
	15-17 y	1000
Females	11-14 y	800
	15-17 y	800
	Pregnancy	700
	Lactation	1200

References

1. British Nutrition Foundation (1989). *Report of Task Force on Calcium*. London: British Nutrition Foundation.

2. Nordin BEC. (1988). *Calcium in Human Biology*. London: Springer Verlag.

3. Spencer H, Kramer L. (1986). The calcium requirement and factors causing calcium loss. *Fed Proc*, **45**: 2758-2762.

4. Raisz LC. (1988). Local and systemic factors in the pathogenesis of osteoporosis. *N Engl J Med*, **318**: 818- 828.

5. Kanis J, Passmore R. (1989). Calcium supplementation of the diet not justified by present evidence. *Br Med J*, **298**: 137-140 and 205-208.

6. Nordin BEC, Heaney RP. (1990). Calcium supplementation of the diet: justified by present evidence. *Br Med J*, **300**: 1056-1060.

7. Nilas L, Christiansen C, Rødbro P. (1984) Calcium supplementation and postmenopausal bone loss. *Br Med J*, **289**: 1103-1106.

8. Riis B, Thomsen K, Christiansen C. (1987). Does calcium supplementation prevent postmenopausal bone loss? *N Engl J Med*, **316**: 173-177.

9. Malm OJ. (1958). Calcium requirement and adaptation in adult men. *Scand J Clin Lab Invest*, 10 (suppl 36): 1-290.

10. Prince RL, Smith M, Dick IM, Price RL, Webb PG, Henderson NK, Harris MN. (1991). Prevention of postmenopausal osteoporosis; a comparative study of exercise, calcium supplementation, and hormone-replacement therapy. *N Engl J Med*, **325**: 1189-1195.

11. Tilyard MW, Spears GFS, Thomson J, Dovey S. (1992). Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med*, **326**: 357-362.

12. Chesnut CH. (1992). Osteoporosis and its treatment. *N Engl J Med*, **326**: 406-407.

13. Leitch I, Aitken FC. (1959). The estimation of calcium requirement: a re-examination. *Nutr Abst Rev*, **29**: 393-411.

14. Purdie DW. (1989). Bone mineral metabolism and reproduction. *Contemporary Reviews in Obstetrics and Gynaecology*, **1**: 214-221.

20. Magnesium

Physiology

The adult male contains 20-28 g magnesium; 60-65 % of this is in the skeleton; only about 1 % is in the extracellular fluid, and is distributed similarly to calcium in the plasma; the rest is intracellular where its activity concentration is tightly regulated [1]. Magnesium is essential for mineralisation and skeletal development and for the maintenance of the transmembrane electrical potentials in nerves and muscle. It also serves as a cofactor for the phosphorylated purine nucleotides and hence all related enzyme activities. It is involved in the structure and replication of nucleic acids, and the ribosomal binding of mRNA. Thus magnesium is vital for the regulation of cellular metabolism and the synthesis of proteins.

Magnesium is absorbed by a carrier-mediated mechanism and by a non-specific diffusional process [2]. Reported intakes range from 132 to 350 mg for women and 157 to 595 mg for men with respective means of 234 and 310 mg [3]; in the UK dietary survey corresponding means of 237 mg (9.8 mmol) and 323 mg (13.3 mmol) were recorded [4]. At such intakes there is great variability in the efficiency of absorption and retention: average net absorptions of 21 % and 27 % have been reported in men and women respectively [5]. Absorption of magnesium is adaptive; at intakes in excess of 2 g/d the element is poorly absorbed. Phytate, calcium phosphate and long chain triacylglycerols may impair the intestinal absorption of magnesium but since there is very little evidence of magnesium deficiency arising from the diet, there is very little definitive information on factors influencing its bioavailability. Systemic homoeostasis of magnesium is achieved primarily through renal excretion; at low dietary intakes there is increased absorption and renal conservation of the element.

The endocrine control of magnesium homoeostasis and metabolism is understood poorly. The parathyroid hormone responds to acute changes in extracellular (serum) concentrations of magnesium in the same way as it does to alterations in ionised calcium activity; thus, in response to a sudden drop in serum magnesium, the production of parathyroid hormone increases, thereby enhancing both the renal conservation of the element and its release from the skeletal pool [1].

Deficiency and excess

Current dietary intakes of magnesium are adequate but systemic magnesium deficiency can result from other conditions such as intestinal and pancreatic malabsorption syndromes, the use of diuretic drugs and increased requirements arising from rapid tissue synthesis, e.g. during recovery from malnutrition, for which as an intracellular cation the element is essential.

Deficiency is manifested by altered metabolism of calcium, sodium and potassium, which is reflected in altered function of skeletal and cardiac muscle, muscle weakness, and fits. Tetany may develop with a resistant hypocalcaemia arising from reduced secretion of parathyroid hormone and end organ hyporesponsiveness.

Large intakes (e.g. 3-5 g of the element) induce intestinal secretion and diarrhoea. Since renal excretion of excess magnesium is so efficient, such ingestions usually have minimal direct systemic effects, but systemic excess, such as may arise from large intakes of magnesium salts by individuals with renal insufficiency or from intravenous administration, can cause central nervous system depression, with muscular paralysis and death [6].

Requirements

Adults

Magnesium is ubiquitous in the diet; both plants and meats are good dietary sources. Early balance studies suggested that adult requirements may be as high as 700 mg/d [7] but interpretation of these is difficult because of analytical difficulties and the long time needed to achieve equilibrium [8]. Additionally the improved efficiency, on restricted intakes, of both intestinal absorption [9] and increased renal conservation of magnesium make it difficult in the absence of more definitive studies to propose any PRI with confidence. One study [10] has suggested that normal adults can achieve positive balance on 3 mg/kg/d over a 6-9 day period. Evaluation of the variance of such balance data suggests that intakes of 3.4 mg/kg would be associated reliably with a net balance [11]. Actual requirements may well be below this; and, in the absence of better physiological data with which to establish reliable reference intakes, an acceptable range of intakes of 150-500 mg /d is proposed on the basis of observed intakes.

This range of intakes will also cover pregnancy and lactation.

Children

The difficulties in proposing a reliable PRI for adults are more pronounced in children, for whom data are even more scarce. If however some guidance is required, rough estimates can be made by calculating average requirements for groups on the basis of body weights. Factors can be used ranging from 7 mg/kg body weight/d at 6-11 months (slightly higher than the intake from breast milk at 6 months) to 4.2 mg/kg body weight/d at 15-17 years (slightly higher than the 3.4 mg/kg/d which appears adequate for adults). An extra 30% is added to allow for individual variations in growth. The quasi - PRIs thus calculated are (mg/d): 6-11 months, 80; 1-3 years, 85; 4-6 years, 120; 7-10 years, 200; 11-14 years, 280; 15-17 years, 300. These guesses should be treated with caution. The amounts would certainly be adequate, and it is highly likely that they are over-generous, but the data are too sparse to support good estimates.

Summary

Acceptable Range of Intakes for Adults: 150-500 mg/d.

References

1. Shils ME. (1988). Magnesium in Health and Disease. *Ann Rev Nutr*, **8**: 429-460.

2. Milla PJ, Aggett PJ, Wolff OH, Harries JT. (1979). Studies in primary hypomagnesaemia: evidence for a defective carrier-mediated small intestinal transport of magnesium. *Gut*, **20**: 1028-1033.

3. Joint Nutrition Monitoring Evaluation Committee. Nutrition Monitoring in the United States. (1986). *DHHS Publication* 86-1255, Washington DC: US Government Printing Office, 356.

4. Gregory J, Foster K, Tyler H, Wiseman M. (1990). *The Dietary and Nutritional Survey of British Adults*. London: HMSO.

5. Lakshmanan FL, Rao RB, Kim WW, Kelsay JL. (1984). Magnesium intakes, balances and blood levels of adults consuming self-selected diets. *Am J Clin Nutr*, **40**: 1380-1389.

6. Mordes JP, Wacker WEC. (1977). Excess magnesium. *Pharmacol Rev*, **29**: 273-300.

7. Seelig MS. (1982). Magnesium requirements in human nutrition. *J Med Soc New Jersey*, **70**: 849-854.

8. Marshall DH, Nordin BEC, Speed R. (1976). Calcium, phosphorus and magnesium requirement. *Proc Nutr Soc*, **35**: 163-173.

9. Schwartz R, Spencer H, Welsh JJ. (1984). Magnesium absorption in human subjects from leafy vegetables intrinsically labelled with stable ^{26}Mg. *Am J Clin Nutr*; **39**: 571-576.

10. Jones JE, Manalo R, Flink EB. (1967). Magnesium requirements in adults. *Am J Clin Nutr*, **20**: 632-635.

11. Health and Welfare, Canada. (1990). *Nutrition Recommendations. The Report of the Scientific Review Committee*. Ottawa: Canadian Government Publishing Centre.

21. Phosphorus

Physiology

Between 80 and 85 % (600-900 g) of phosphorus exists as phosphate in the calcium salt hydroxyapatite in the skeleton. The residue is in soft tissues as phosphate, mainly as a component of proteins, phospholipids and nucleic acids; 5-20 mmol (0.2-0.6 g) is present intracellularly in a large variety of phosphorylated compounds (e.g. adenosine triphosphate (ATP), guanosine triphosphate, etc.) which are needed for metabolic energy transfer and storage processes, enzyme activation and control. Furthermore via the interconversion of HPO_4^{2-} and $H_2PO_4^-$ phosphorus contributes to extracellular and intracellular acid-base regulation.

Absorption occurs throughout the gut. At least 60 % of dietary phosphorus is absorbed; at least one carrier-mediated process and diffusional component is involved. The former mechanism is stimulated by calcitriol. Within the intestinal lumen complexes of phosphorus with minerals and amino acids may limit its uptake by the gut mucosa. Plasma inorganic phosphate concentration is normally 0.8-1.4 mmol/L. Homoeostasis is achieved by urinary excretion, and there is a prompt increase of urinary phosphate in response to increased dietary intake [1].

Deficiency and excess

Hypophosphataemia with intracellular depletion of phosphate is associated with muscle weakness and altered tissue oxygen tension, perhaps arising from defective synthesis of ATP and impaired delivery of oxygen to tissues as a consequence of depletion of red cell 2,3-diphosphoglycerate content. Prolonged moderate hypophosphataemia leads to osteomalacia. Excessive dietary intake is rare because renal excretion is efficient. In diseases prolonged hyperphosphataemia can result in abnormal calcification of soft tissues and acute hyperphosphataemia increases calcium binding and can precipitate features of hypocalcaemia including tetany. Although adults can tolerate varying Ca:P ratios in their diets without gross disturbances of their metabolism of calcium, infants cannot. A Ca:P molar ratio of 0.9-1.7 in diets for infants is considered safe.

Requirements

It is suggested that phosphorus intakes should correspond on a molar basis with those for calcium and rounded values are proposed accordingly.

Summary

Adults	mg/d
Average Requirement	400
Population Reference Intake	550
Lowest Threshold Intake	300

Population Reference Intakes of other groups

Age Group		PRI (mg/d)
	6-11 m	300
	1-3 y	300
	4-6 y	350
	7-10 y	450
Males	11-14 y	775
	15-17 y	775
Females	11-14 y	625
	15-17 y	625
	Pregnancy	550
	Lactation	950

References

1. Berner YN, Shike M. (1988). Consequences of phosphate imbalance. *Ann Rev Nutr.* **8**: 121-148.

2. Marshall DH, Nordin BEC. Speed R. (1976). Calcium, phosphorus and magnesium requirement. *Proc Nutr Soc*, **35**: 163-173.

22. Sodium

Physiology [1,2]

Sodium is the principal cation in extracellular fluid. Its physiological roles include the maintenance of (i) extracellular fluid volume (ECF), which is related closely to total body sodium content, (ii) extracellular fluid oncotic pressure, (iii) acid base balance, (iv) electrophysiological phenomena in muscle, neuromuscular and nerve impulse transmission, and (v) generation of transmembrane gradients essential for the energy-dependent carrier-mediated uptake of nutrients and substrates by cells, including hepatocytes and those in the intestinal mucosa and renal tubules.

A typical adult male has a total body sodium of 4 mol (92 g); of this 0.5 mol (11.5 g) is in the intracellular fluid at an activity concentration of 2 mmol/L (46 mg/L), and 1.5 mol (34.5 g) is sequestered in bone. About 2 mol (46 g) is in the ECF at a concentration of 135-145 mmol/L (3.1-3.3 g/L).

Net intestinal absorption of sodium occurs in the distal small intestine and colon: its concentration in the ECF is maintained by the kidneys. Daily 25 mol (575 g) sodium enters the glomerular filtrate; since daily dietary intakes (say 50-150 mmol; 1.15-3.45 g) represent only 0.2-0.6 % of this amount, almost all of this filtered sodium must be reabsorbed to maintain sodium homoeostasis.

Renal sodium reabsorption is highly efficient and adaptable. Regulation of the sodium content of the ECF is closely related to the systemic control of the ECF volume. If the body sodium burden is increased, water is also retained and ECF volume increases: conversely, if the body sodium burden falls the ECF volume decreases. The overall regulation of these changes is unclear [1]. Changes in ECF volume are detected by sensors of pressure and distension which are located in the cardiac atria and right ventricle, the pulmonary vasculature, the carotid arteries and the aortic arch. From these sensors afferent nerve pathways end in the medulla and hypothalamus. When ECF or blood volume falls retention is stimulated, sympathetic nervous activity increases, stimulating the nerves supplying the afferent renal arterioles to induce vasoconstriction and thereby producing a redistribution of renal blood flow which, by reducing glomerular filtration, increases sodium and water retention.

Additionally, sympathetic nervous stimulation of the juxtaglomerular apparatus increases production of renin. This in turn leads to an increase in circulating

angiotensin II, adrenal medullary secretion of noradrenaline and adrenaline, and pituitary release of adrenocorticotrophin (ACTH) and antidiuretic hormone (ADH). ACTH and angiotensin II induce adrenal cortical secretion of aldosterone and other mineralocorticoids which stimulate sodium retention and potassium loss by the kidneys and the distal bowel. Increased secretion of antidiuretic hormone promotes sodium reabsorption from the renal distal tubules and probably the colon.

Renal sodium excretion is increased by factors which include specific natriuretic hormone, and vasodilators, parathyroid hormone, prostaglandins and kinins. The adult kidney can regulate sodium excretion at between 0.5 and 30 % of its filtered load. Under normal circumstances virtually all dietary sodium is absorbed and daily urinary loss matches this amount closely after allowance is made for that which may be lost in sweat.

Deficiency and excess

The role of higher sodium intakes in the pathogenesis of hypertension has generated much interest [3,4,5,6,7,8]. However other factors, such as low intakes of potassium (see chapter 23), little physical activity, mental stress, alcohol consumption, smoking and high body mass index, are contributory to the development of hypertension [4,5]. Indeed obesity is associated with an increased sensitivity to sodium-induced hypertension [9]. It has been suggested that absence of these adverse factors, rather than lower sodium intakes alone, is responsible for the lower blood pressures observed in economically less developed communities compared with those seen in developed societies. Nevertheless, after allowance is made for such confounders, a relationship still exists between urinary sodium excretion (assumed to be a marker of intake) and increasing blood pressure with age [4]. A recent meta-analysis of studies of the relationship between sodium intake and blood pressure strongly implies that the causal association has been underestimated [6,7]. When published epidemiological studies and clinical trials in economically advanced and non-advanced populations were analysed separately to minimise the socio-economic variables mentioned, there was apparent for both types of community, and amongst individuals within such communities, an association between sodium intake, and increasing systolic and diastolic blood pressures. This relationship was continuous, i.e. there was no threshold of sodium intake below which the effect did not exist: it affected all age groups and it increased progressively with age. This reanalysis then applied the regression equations of blood pressure against sodium intake derived from the initial pooled study to calculate for each age group the potential falls in blood pressure which would result from reductions in sodium intakes [8]. Since the major source of sodium in the diet is salt these predictions were compared with

observed falls in blood pressure arising from intervention trials of reductions of salt intake on blood pressure. For trials lasting five weeks or longer the predicted and observed reductions matched closely. From this it was deduced that dietary salt reduction would have an appreciable effect on reducing mortality from ischaemic heart disease and stroke [8].

Requirements

Adults

The determination of a meaningful PRI and Average Requirement for sodium intake is difficult and a range of intakes is proposed for adults.

Healthy adults maintain a sodium balance on intakes as low as 3-20 mmol/d (69-460 mg/d), and some healthy populations have customary daily intakes of less than 40 mmol (920 mg), possibly even as low as 10 mmol/d (230 mg/d) [3,4,6]. The latter intake requires maximal adaptation to conserve sodium: to allow for changes in physical activity and climate it is thought prudent to set a lower intake at 25 mmol/d (575 mg/d).

On the basis of current evidence intakes in excess of 200 mmol (4.6 g) sodium daily would be associated with a significant risk of high blood pressure, especially in older people [6,7,8]; ideally intakes should be lower than this to reduce or prevent hypertension and the attendant risk of cardiovascular and cerebrovascular disease in the population in general. On the basis of the recent analyses, it is proposed that an upper limit of 150 mmol/d (3.5 g/d) be set.

Children

The evidence is insufficient to give any recommendations for children.

Summary

Adults:

Acceptable Range of Intakes	575-3500 mg/d
	(25-150 mmol/d)

References

1. Simpson FO. (1988). Sodium intake, body sodium and sodium excretion. *Lancet*, ii: 25-29.

2. Luft FC. (1990). Sodium, chloride and potassium. In: Brown M, ed. *Present Knowledge in Nutrition*. 6th ed. Washington DC: International Life Sciences Institute Nutrition Foundation, 233-240.

3. Glieberman L. (1973). Blood pressure and dietary salt in human populations. *Ecol Fd Nutr*, **2**: 143-156.

4. Intersalt Cooperative Research Group. (1988). Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Br Med J*, **297**: 319-328.

5. Swales JD. (1988). Salt saga continued. *Br Med J*, **297**: 307-308.

6. Law MR, Frost CD, Wald NJ. (1991). By how much does dietary salt reduction lower blood pressure? I- Analysis of observational data among populations. *Br Med J*, **302**: 811-815.

7. Frost CD, Law MR, Wald NH. (1991). By how much does dietary salt reduction lower blood pressure? II- Analysis of observational data within populations. *Br Med J*, **302**: 815-818.

8. Law MR, Frost CD, Wald NJ. (1991). By how much does dietary salt reduction lower blood pressure? III- Analysis of data from trials of salt reduction. *Br Med J*, **302**: 819-824.

9. Rocchini AP, Key J, Bondie D, Chico R, Moorehead C, Katch V, Martin M. (1989). The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med*. **321**: 580-585.

10. Rose G. (1986). Desirability of changing potassium intake in the community. In: Whelton PK, Whelton AK, Walker WG, eds. *Potassium in Cardiovascular and Renal Disease*. New York: Marcel Dekker, 411-416.

23. Potassium

Physiology

Potassium is predominantly an intracellular cation. This compartmentalisation is maintained by the energy-dependent cellular uptake of the element and simultaneous excretion of sodium by the cell membrane bound enzyme Na-K ATPase. This process is fundamental to the cellular uptake of molecules against electrochemical and concentration gradients, to the electro-physiology of nerves and muscle, and to acid-base regulation [1,2,3].

An adult male contains approximately 40-50 mmol (1.6-2 g)/kg body weight, on which basis a 75 kg adult would contain 3000-3750 mmol (117-147 g) potassium. At least 95 % of this is intracellular at an activity concentration of 150 mmol (5.9 g)/L, the remainder is in the ECF at a concentration of 3.5-5.5 mmol (137-215 mg)/L. The total body potassium reflects lean tissue mass and consequently varies with muscularity.

The systemic homoeostasis of potassium is understood imperfectly. Over 90 % of dietary potassium is absorbed in the proximal small intestine, possibly by a combination of diffusional mechanisms and solvent drag. The body content is regulated by the renal glomerular filtration and tubular secretion but up to 10 % of the daily loss of potassium can occur via the distal ileum and colon; additionally a small amount is lost in sweat. The glomerular filtration of potassium is approximately 3 % of that for sodium, and amounts to only about 680 mmol (26.5 g)/d; however, renal tubular secretion of the element, which is regulated predominantly by aldosterone and other mineralocorticoids, is highly efficient and the kidney is able to excrete potassium considerably in excess of its filtered load. As long as renal function is normal, on habitual dietary intakes it is almost impossible to induce potassium excess. An additional but usually less important regulation of ECF and plasma potassium excess is achieved by the capacity of cells induced by glucose and insulin to take up the element.

Deficiency and excess

Potassium deficiency arising from inadequate dietary intake is unlikely because of the ubiquity of potassium in all foodstuffs. Potassium deficiency alters the

electrophysiological phenomena of cell membranes. This causes weakness of skeletal muscles and the effect on cardiac muscle is reflected by electrocardiographic changes characteristic of impaired polarisation, which may lead to arrhythmia and cardiac arrest. Similar functional changes in intestinal muscle cause intestinal ileus. Mental depression and confusion can also develop.

The reported intakes of potassium by Western populations are 40-150 mmol (1.65-9 g)/d [4]. An inverse correlation exists between increased blood pressure and urinary potassium excretion or urinary Na:K excretion ratios [4]. An adequate potassium intake is needed to achieve effective homoeostasis of sodium. Young normotensive men on a potassium intake of 10 mmol/d (390 mg/d) were less able to excrete an imposed sodium excess than when they had a potassium intake of 90 mmol (3.5 g)/d [5]; simultaneously their blood pressure increased. In the Intersalt study urinary potassium excretion, an assumed indicator of potassium intake, was negatively related to blood pressure as was the urinary Na:K concentration ratio [4]. Increasing potassium intakes to levels achievable with customary diets [i.e. 65 and 100 mmol/d (2.5 and 3.9 g/d)] reduced blood pressure in normotensive and hypertensive individuals and increased urinary sodium loss [6,7]. This effect of potassium on blood pressure is supported by a recent meta-analysis of published reports [8]. It has been calculated that an increase in potassium intakes from 60 to 80 mmol/d (2.3 to 3.1 g/d) could induce a fall of 4 mmHg systolic blood pressure and that this could possibly achieve a 25 % reduction in deaths related to hypertension [6].

Requirements

Adults

Renal and faecal losses each amount to about 10 mmol (390 mg)/d and there are also integumental losses. However, an intake of 40 mmol/d (1.6 g/d) is needed to avoid low plasma potassium concentrations and loss of total body potassium [9] and on this basis a lower intake of 40 mmol/d (1.6 g/d) is suggested.

An Average Requirement is not set. On the basis of the evidence cited earlier, a PRI of 80 mmol/d (3.1 g/d), which would also cover pregnancy and lactation, is proposed.

This intake could be reliably achieved by an appropriate intake of vegetables, fruit and derived juices, rather than by the use of potassium salts as substitutes for sodium chloride [10], because such measures if pursued indiscriminately could result in intakes at which toxicity might develop in individuals with undetected renal insufficiency and abnormal retention of potassium. Intakes above 450 mmol (17.5g)/d induce symptomatic hyperkalaemia in some otherwise normal individuals and can

thus be used as a threshold for acute toxicity, but such intakes are highly unlikely to arise from usual diets. However, for chronic intakes, intakes above 150 mmol (5.9 g)/d could be dangerous for individuals with undetected renal dysfunction [10]. Additionally, since there is no apparent benefit of exceeding an intake of 150 mmol (5.9 g)/d, this is proposed as an upper safe level of intake.

Children

The basal losses of children are not known reliably. Urinary excretion has been reported as 0.7-2.3 mmol (27-90 mg)/d. The amount needed for growth and lean tissue synthesis has been taken as 50 mmol (2 g)/kg. With these and other factors to allow for faecal losses (which are higher in children) and for integumental losses, PRIs for ages up to 17 were estimated factorially.

Summary

Adults	mg/d	mmol/d
Population Reference Intake	3100	80
Lowest Threshold Intake	1600	40

Population Reference Intakes of other groups

Age Group		*mg/d*	*mmol/d*
	6-11 m	800	20
	1-3 y	800	20
	4-6 y	1100	28
	7-10 y	2000	50
Males	11-14 y	3100	80
	15-17 y	3100	80
Females	11-14 y	3100	80
	15-17 y	3100	80
	Pregnancy	3100	80
	Lactation	3100	80

References

1. Pitts RF. (1968). *Physiology of the Kidney and Body Fluids*. 2nd ed. Chicago: Year Book Medical Publishers.

2. Patrick J. (1977). Assessment of body potassium stores. *Kidney Int*, **11**: 476-490.

3. Luft FC. (1990). Sodium, chloride and potassium. In: Brown M, ed. *Present Knowledge in Nutrition* 6th Ed. Washington DC: International Life Sciences Institute Nutrition Foundation, 233-240.

4. Intersalt Cooperative Research Group (1988). Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *Br Med J*, **297**: 319-328.

5. Krishna GG, Miller E, Kapoor S. (1989). Increased blood pressure during potassium depletion in normotensive men. *N Engl J Med*, **320**: 1177-1182.

6. Rose G. (1986). Desirability of changing potassium intake in the community. In: Whelton PK, Whelton AK, Walker WG, eds. *Potassium in Cardiovascular and Renal Disease*. New York: Marcel Dekker, 411-416.

7. Matlou SM, Isles CG, Higgs A, Milne FJ, Murray GD, Schultz E, Starke IF. (1986). Potassium supplementation in Blacks with mild to moderate essential hypertension. *J Hyperten*, **4**: 61-64.

8. Cappuccio FP, MacGregor GA. (1991). Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hyperten*, **9**: 465-473.

9. Sebastian A, McSherry E, Morris RC. (1971). Renal potassium wasting in renal tubular acidosis (RTA): its occurrence in types 1 and 2 RTA despite sustained correction of systemic acidosis. *J Clin Invest*, **50**: 667-678.

10. Swales JD. (1991). Salt substitutes and potassium intake. *Br Med J*, **303**: 1084-1085.

24. Chloride

Physiology

Chloride is the major extracellular and intracellular counter anion to sodium and potassium; 70 % is in the ECF, and the remainder is in the intracellular space, connective tissue and bone [1,2]. Total body chloride in adult men is about 33 mmol (1.2 g) /kg body weight. Plasma chloride is maintained at 95-107 mmol/L (3.4-3.8 g/L); its concentration in interstitial fluid is slightly higher, whereas the intracellular concentration of chloride has been varyingly reported between 4 and 25 mmol/L. Chloride is absorbed passively in the proximal small intestine, where it follows the electrochemical gradient created by transport of the major cationic electrolytes. Intestinal secretion of chloride occurs proximally but the anion is conserved distally by uptake in exchange for bicarbonate. Dietary chloride deficiency has been described only once, in healthy infants who were fed an infant formula which, accidentally, provided less than 2 mmol/L [3]. It has been suggested that chloride may interact with sodium in inducing hypertension [4,5].

Requirements

Daily chloride intake is derived principally from sodium chloride. Since the dietary intake and systemic metabolism of chloride match closely, and are dependent on sodium, it is suggested that in the absence of more definitive information the requirements of chloride should match those for sodium.

References

1. Pitts RF. (1968). *Physiology of the Kidney and Body Fluids.* 2nd ed. Chicago: Year Book Medical Publishers.

2. Luft FC. (1990). Sodium, chloride and potassium. In: Brown M, ed. *Present Knowledge in Nutrition* 6th ed. Washington DC: International Life Sciences Institute Nutrition Foundation, 233-240.

3. Rodriguez-Soriano J, Vallo A, Castillo G, Oliveros R, Cea JM, Balzategui MJ. (1983). Biochemical features of dietary chloride deficiency syndrome: a comparative study of 30 cases. *J Pediatr.* **103:** 209-214.

4. Kurtz TW, Al-Bander HA, Morris RC. (1987). 'Salt-Sensitive' essential hypertension in men. Is the sodium ion alone important? *N Engl J Med.* **317:** 1043-1048.

5. Weinberger MH. (1987). Sodium chloride and blood pressure. *N Engl J Med.* 317: 1084-1086.

25. Iron

Physiology and metabolism

Iron is present in all cells in the body and has several vital functions: as a carrier of oxygen to the tissues from the lungs, in electron transport in cells and as an integral part of important enzymes.

The main part (>65%) of the iron in the body is present in the red cells as haemoglobin. In average adult men and women, approaching 3 mg and 2 mg iron respectively is in the form of haemoglobin. Myoglobin, the oxygen reserve in muscle, amounts to about 10% of the body iron. Iron is the functional portion of the cytochromes, essential for harnessing the energy of metabolized foodstuffs, and it is present in enzymes which play other key roles, for example, as signal-controlling substances, in some neurotransmittor systems in the brain such as the dopamine and serotonin systems. The amount of iron in cytochromes and enzymes is small.

The body has three unique mechanisms for maintaining iron balance and preventing iron deficiency and iron overload.

1. Storage of iron. Ferritin is a protein adapted for the reversible storage of iron. Iron stores are especially important for women to meet the excessive iron demands in the last trimester of pregnancy. The amount of stored iron is about 500-700 mg in 25-30 year old men. In women the amounts are much less. In most European countries at least 20-30% of women in the fertile ages have no iron stores at all.

2. Reutilization of iron. Iron is not lost from the body with urine or faeces but only with losses of cells, including bleeding. Iron is required to cover such losses and to supply the body with the needs for growth, including pregnancy.

3. Regulation of iron absorption. The body tries to maintain iron balance not by regulating the losses of iron but by controlling the absorption of dietary iron. This control is not perfect but still of great importance for the prevention of iron deficiency and excess [1].

Deficiency

When less iron is absorbed than is needed to cover iron losses and demands for growth and pregnancy, body iron stores, if present, are first depleted. When the stores are exhausted the supply of iron to various tissues is compromised. Iron deficiency can thus be defined as a state with an absence of iron stores. This state can be recognized clinically by the absence of stainable reticular iron in bone-marrow smears or more conveniently by a low serum ferritin (e.g. ≤15 g/L). The insufficient supply of iron to tissues depresses erythropoiesis. The haemoglobin level is reduced and at a certain point falls below the lower normal limit of the population. This is the rather arbitrary definition of iron-deficiency anaemia.

During the depletion of iron stores the absorption of iron increases, but if losses are high this compensatory mechanism may not be sufficient to guarantee an adequate delivery of iron for the formation of haemoglobin and enzymes.

A number of adverse effects of iron deficiency are known in man [2]. It was observed by early investigators that iron deficiency impaired physical endurance and work capacity. In recent years other functional defects have been demonstrated, such as disturbances in normal thermoregulation and impairment of certain key steps in the immune response. Great interest today is focused on the relationship between mild iron deficiency and various brain functions, such as learning. Iron is present in key enzymes in several neurotransmittor systems in the brain, for example, the dopamine and serotonin systems. Only 10% of the iron content of the brain is present at birth, 50% at the age of 10 and it continues to increase up to the age of 20-30 years. Studies in both children and animals strongly suggest that some of the brain symptoms are not reversible by iron treatment, even though all other signs of iron deficiency disappear. Emphasis should therefore be put on prevention rather than on treatment of iron deficiency [3-6].

Iron deficiency is probably the most frequent deficiency disorder in the world and the main remaining nutritional deficiency in Europe. In European countries the prevalence of iron deficiency as indicated by absence of iron stores is especially high in menstruating women and teenagers (about 20-30%). The prevalence of detectable anaemia due to iron deficiency is however much lower in these groups (around 2-8%).

Excess

The very effective regulation of iron absorption prevents overload of the tissues by iron from a normal diet, except in individuals with genetic defects as in idiopathic haemochromatosis.

Side effects of iron supplements

All iron compounds used therapeutically have side effects. The most disturbing side effects (epigastric pain, nausea and diarrhoea) are dose related and more severe if tablets are not taken with food. Other side effects such as constipation occur in some subjects but are independent of dose. Effects may be seen in adults with doses as low as 30 mg of elemental iron but most subjects tolerate well single doses of 100 mg.

Acute accidental iron intoxication is mainly seen in children who have mistaken iron tablets for sweets. The lowest known lethal dose in infants is 650 mg ferrous iron.

Physiological requirements (absorbed requirements)

Iron is needed to cover the basal losses of iron in cells shed from the body, to replace that lost by menstruation and to provide the amounts required for growth, including pregnancy.

The basal iron losses with cells from the exterior and interior surfaces of the body amount to 14 µg/kg body weight/d and are thus little over 1 mg/d in an average man and about 0.9 mg/d in an average woman [7] (see Table 25.1). The evidence suggests that these losses may have an interindividual variation of 15% (coefficient of variation). Sweat iron losses amount to only about 23 µg iron per litre of sweat and are thus so small that they can be disregarded [8].

Adult men and postmenopausal women

In healthy adult men and postmenopausal women, recommendations are derived from the basal iron losses. For an average adult man, the mean basal losses can be taken as 1.05 mg/d. The mean + 2SD would be 1.37 mg, which can be rounded off to give 1.4 mg/d. For an average postmenopausal woman, the corresponding figures will be 0.87 mg/d and 1.1 mg/d (Table 25.1).

Menstruating women

For women in the fertile age period the iron required to cover losses from menstruation has to be added. Menstrual iron losses vary markedly between women but are very constant in an individual woman. The magnitude of the menstrual losses is strongly genetically controlled and studies made in different countries report very similar figures for average menstrual losses when related to body size. An extensive study on menstrual blood losses in women at different ages was made in Sweden [9] (before contraceptive methods known to markedly influence the menstrual blood losses were introduced). The observed blood losses were transformed to iron losses by "multiplying" them by the distribution of the haemoglobin values in healthy women with optimal values. This is done by a mathematical-statistical process of convolution. The total iron requirements and their variation in menstruating women are then obtained by "adding" basal iron losses and their variation to the observed variation in menstrual iron losses by a further convolution step.

By this means the values in Table 25.1 were calculated. Table 25.2 shows the percentage of a population of menstruating women whose requirements are satisfied by various amounts of absorbed iron [10]. The 90th and 95th centile values of total absorbed iron requirements are 2.37 and 2.94 mg respectively.

Pregnancy and lactation

Pregnant women need iron to replace the basal iron losses during pregnancy (about 240 mg), to provide for the fetus and placenta (about 350 mg), and for the expansion of the red cell mass of the mother (about 450 mg). In total these requirements have been estimated as 1,040 mg [11]. The average blood loss at delivery corresponds to 250 mg iron. About 200 mg of the iron used for the expansion of the red cell mass is thus retained by the mother in her iron stores at delivery.

In the first trimester the iron requirement of the fetus is negligible. The total iron requirements of the mother are thus limited to the basal iron losses, about 0.9 mg/d. In the latter half of pregnancy iron requirements increase continuously and considerably, especially in the third trimester when the daily iron requirements reach the range 8-10 mg/d. Iron absorption is reduced in the first trimester but increases during the later half of pregnancy. In this period the iron requirements, however, are so great that, in spite of the increase in absorption, even on a diet with a good bioavailability there will be a deficit of about 400-500 mg iron. The physiological solution for covering the high iron requirements in pregnancy is to use iron from stores. The problem, however, is that very few women, if any, have iron stores of

this magnitude. Therefore, daily iron supplements are recommended in the latter half of pregnancy [12]. Since diet alone cannot cover the iron requirements in most women, in their recent report [13] FAO/WHO refrained from giving a value for a recommended dietary intake during pregnancy.

Breast milk contains 0.15-0.3 mg iron/d. As menstruation is usually absent during lactation the total iron requirements in a lactating woman are considerably less than in an average non-pregnant, menstruating women.

Adolescent girls

Menstrual iron losses in teenage girls are about the same as in adult women [10]. Thus in menstruating teenage girls the requirements for growth and their variation have to be added to the requirements of adult menstruating women. This addition has also to be made using the same mathematical convolution process. There is a marked variation in growth rate in girls. The coefficient of variation of the change in body weight in the age range 13-16 years is about ± 19%. In the present calculations, the figures 0.36 ± 0.054 mg (mean ± SD) have been used as the daily amount of iron needed for growth [14]. This corresponds to the situation in 15-16 year old girls. In younger teenagers the growth requirements are higher (> 0.5 mg/d) but basal losses are then slightly lower. Moreover, some of the younger teenage girls have not started to menstruate. The growth figures used are based on a longitudinal study on the development of children [14] and on calculations of iron requirements for growth in the recent FAO/WHO report [13].

Table 25.2 shows the percentages of teenage girls whose needs are satisfied by various amounts of absorbed iron [10]. The 90th and 95th centile values for these girls are 2.54 and 3.10 mg/d respectively.

Adolescent boys

During the age period 12 to 16 years boys gain an average of 5.5 kg/year [14]. At the peak year of their growth spurt the average weight gain is about 10 kg. At about the same time, in response to sexual maturation, their haemoglobin concentration increases between 5-10 g/L per year. The 95th percentile value for total iron requirements may thus be considerably higher at the peak growth rate than the value given in Table 25.1. It should also be noted in Table 25.1 that the median iron requirement in adolescent males is as high as in adult menstruating women.

Children

Iron requirements in term infants are negligible for the first 4-6 months of life since there is a physiological redistribution of iron from the large red cell mass at birth to stores. This excess iron covers the needs for growth including expansion of the blood volume during this period. In the following months, however, the requirements are very considerable and amount to about 0.7 mg/d during the remaining part of the first year. This figure is very high in relation to body weight and energy intake.

The bioavailability of iron in weaning foods consumed during the age period 6-11 m is usually lower than that of iron in the adult diet because of an often high content of inhibitors of iron absorption such as milk and phytate in infant cereals and a low content of enhancers of iron absorption such as meat and ascorbic acid. The figure given for bioavailability in Table 25.1 (10%) may thus have a considerable variation. Moreover the bioavailability of iron used to fortify infant foods is usually unknown.

As shown in table 25.1 iron requirements are high in children especially in relation to their usual energy requirements and in periods of rapid growth. It is thus important that the bioavailable nutrient density for iron [15] is high in the diets of children.

Dietary iron requirements

Two main factors need to be considered in the translation of absorbed (physiological) iron requirements into dietary iron requirements: body iron status and composition of the diet.

Iron status and iron absorption

The absorption of iron from the diet is influenced by the iron status of the body: the greater the body's need for iron, the higher the percentage of a given dose taken up [16]. How this regulation mechanism works is unknown, but it is located in the intestinal mucosal cell. There is however an upper limit to this adaptation.

Dietary iron requirements must therefore be given for a certain iron status, and the calculations made here are based on the bioavailability of dietary iron at the borderline between normality and iron deficiency. The values given represent the amounts of iron needed to be absorbed to prevent an insufficient supply to tissues in the body, including the erythron, i.e. to maintain optimal haemoglobin values, but not iron stores.

Factors influencing dietary iron absorption

There are two kinds of iron in the diet with different absorption mechanisms: haem and non-haem iron [17]. Haem iron in meat and meat products amounts to about 1-2 mg/d in most EC countries and about 25% of haem iron present in meat is absorbed. This absorption is almost independent of meal composition and iron status.

Non-haem iron (in bread and other cereal products, vegetables and fruits) constitutes about 90% of the dietary iron intake. The dietary absorption of non-haem iron, however, is very dependent on iron status and the balance between several dietary factors influencing absorption. Some substances enhance the absorption of non-haem iron (e.g. ascorbic acid, meat, fish) and others inhibit it (e.g. phytate, calcium and iron-binding phenolic compounds). There is thus a marked variation in the absorption of iron from different meals depending on the meal composition.

Bioavailability of dietary iron

The bioavailability of iron from the diet as a whole needs to be known in order to translate absorbed iron requirements into dietary requirements. Direct information is limited as long-term chemical balance studies on different diets would be required. Indirectly, however, it is possible to estimate the bioavailability of iron in the whole diet using results obtained in different studies.

In a recent paper attempts were made using indirect methods to estimate the bioavailability of dietary iron in USA and different countries in Europe [10]. The calculations were made for iron-replete subjects with no iron stores. The estimated upper limit was about 15% of the intake of available iron and the figures were very similar in all studies after corrections were made for unavailable fractions of fortification iron [18]. This figure may represent "an average European diet" – rather varied, and containing meat, fish, bread, vegetables, fruits, etc. Diets with a very high meat intake (>250 g/d) may have a slightly higher bioavailability, possibly amounting to 17%, whereas diets with little red meat (<50 g/d) and little fruit and vegetables with meals, or having a high phytate content due to a high consumption of cereal fibre (wholemeal bread, crispbread) may have a lower bioavailability, possibly down to 10% or even less. The bioavailability of iron in some vegetarian diets with a low content of ascorbic acid is thus probably much lower (5-10%). It is important to be aware of the multitude of factors influencing the bioavailability of iron and that there may be segments of most populations having diets with a rather poor bioavailability. On the other hand, for the European population at large, the error will not be great if a single figure of 15% is selected as a basis for the calculations of dietary requirements from the physiological requirements.

The present figure for bioavailability of iron from the whole diet (15%) should be considered as the upper borderline value associated with maintenance of health (i.e. absence of iron stores but normal haemoglobin values). Correction should be made for dietary fortification iron that is only partially soluble in the gastrointestinal tract. For example, only about 15% of reduced iron, often used for fortification of flour, is potentially available [18]. It can then be estimated that 15% of this fraction will finally be absorbed.

Values proposed

The values given in Table 25.1 are the intakes needed to cover the requirements of 95% of the various population groups, based on a bioavailability of 15%.

Menstruating women, both adults and teenagers, have a very skewed distribution of their iron requirements. A PRI based on the 95th centile would be unrealistically high for the great majority of women, so Table 25.1 gives the requirements of the 90th and 95th centiles of menstruating women.

Table 25.2 gives the physiological requirements and dietary intakes needed to cover centiles of the population of menstruating women from the 50th to the 95th.

Strategies to improve iron nutrition

Modification of dietary composition

Iron nutrition can be improved by various modifications of the diet. A higher intake of foods enhancing iron absorption or a lower intake of foods inhibiting absorption (see earlier) will increase the bioavailability of the dietary iron.

An increased intake of lean meat will not only provide more well-absorbed haem iron but also enhance the absorption of non-haem iron. The latter can also be achieved by increasing the intake of ascorbic acid-rich foods, especially if the usual intake of ascorbic acid is low.

Iron supplementation

The iron balance situation for most women is critical during pregnancy. With the present type of diet and present low-energy life-style about 500 mg iron would be needed in iron stores of mothers to cover iron requirements during pregnancy. About 25-30% have no iron stores; the average store is about 150 mg; less than 5% reach an amount of 400 mg and none the critical amount of 500 mg. This is the background

for the FAO/WHO recommendation [13] that all pregnant women should be given iron supplements during the latter half of pregnancy.

Iron fortification

The marked skewness of the distribution of iron requirements in menstruating women implies that a considerable fraction of them are at risk of developing iron deficiency. Personal assessment of individual menstrual losses is unreliable and women with physiological but heavy losses usually consider themselves as quite healthy and their losses as normal. They would not seek medical advice and thus cannot be simply reached and given iron supplementation. Iron fortification is then a measure that must be seriously considered, especially as the life style of many individuals results in their having low energy needs, and thus reduced food consumption, resulting in a lowered iron intake.

References

1. Bothwell TH, Charlton RW, Cook JD, Finch CA. (1979). *Iron Metabolism in Man.* Blackwell Scientific Publications. Oxford.

2. Scrimshaw NS. (1984). Functional consequences of iron deficiency in human populations. *J Nutr Sci Vitaminol*, **30:** 47-63.

3. Dallman PR. (1986). Biochemical basis for the manifestations of iron deficiency. *Ann Rev Nutr*, **6:**13 - 40.

4. Lozoff B. (1988). Behavioral alterations in iron deficiency. *Adv Pediatr*, **35:** 331-59.

5. Walter T, Kovalskys J, Stekel A. (1983). Effect of mild iron deficiency on infant mental developmental scores. *J Pediatr*, **102:** 519-22.

6. Youdim MBH. (1988). *Brain Iron: Neurochemical and Behavioural Aspects.* London: Taylor & Francis, 89-114.

7. Green R, Charlton R, Seftel H, Bothwell T, Mayet F, Adams B *et al.* (1968). Body iron excretion in man. A collaborative study. *Am. J. Med*, **45:** 336-53.

8. Brune M, Magnusson B, Persson H, Hallberg L. (1986). Iron losses in sweat. *Am. J. Clin. Nutr*, **43:** 438-43.

9. Hallberg L, Högdahl A-M, Nilsson L, Rybo G. (1966). Menstrual blood loss - a population study. Variation at different ages and attempts to define normality. *Acta Obstet Gynaecol Scand*, **45:** 320-51.

10. Hallberg L, Rossander-Hultén L. (1991). Iron requirements in menstruating women. *Am J Clin Nutr*, **54:** 1047-58.

11. Hallberg L. (1988). Iron balance in pregnancy. In Berger H, ed. *Vitamins and Minerals in Pregnancy and Lactation.* Raven Press, New York, 115-126.

12. DeMaeyer EM, Dallman P, Gurney JM, Hallberg L, Sood SK, Srikantia SG. (1989). Preventing and controlling iron deficiency anaemia through primary health care. World Health Organization, Geneva.

13. Food and Agriculture Organization. (1988). *Requirements of Vitamin A, Iron, Folate, and Vitamin B_{12}. Report of a joint FAO/WHO Expert Consultation*. Rome: Food and Agriculture Organization. (FAO Food and Nutrition Series, 23).

14. Karlberg P, Taranger J. Engström I, Lichtenstein H, Svennberg-Redegren I. (1976). The somatic development of children in a Swedish urban community. A prospective longitudinal study. *Acta Paediat Scand*, Suppl **258.**

15. Hallberg L. (1981). Bioavailable nutrient density: a new concept applied in the interpretation of food iron absorption data. *Am J Clin Nutr*, **34:** 2242-7.

16. Rybo E, Bengtsson C, Hallberg L. (1985). The relative importance of various laboratory measurements in the diagnosis of iron deficiency. *Scand J Haematol*, Suppl **43:** 57-75.

17. Hallberg L. (1981). Bioavailability of dietary iron in man. *Ann Rev Nutr*, **1:**123-47.

18. Hallberg L, Brune M, Rossander L. (1986). Low bioavailability of carbonyl iron in man: studies on iron fortification of wheat flour. *Am J Clin Nutr*, **43:**59-67

Table 25.1 Absorbed and dietary iron requirements [a].

Age	Mean body weight	Growth requirements	Basal losses	Menstrual losses		Total requirements		Dietary iron requirements (assuming bioavailability 15%)			
								mg/d (rounded to nearest mg/d in brackets)			
								90th centile		95th centile	
years	kg	mg/d	Median mg/d	Median mg/d	95th per. mg/d	Median mg/d	95thper. mg/d				
0.5-1	9	0.55	0.17			0.72	0.93			[6.2] b	(6)
1 - 3	13.5	0.27	0.19			0.46	0.58			3.9	(4)
4 - 6	19.5	0.23	0.27			0.50	0.63			4.2	(4)
7 - 10	29	0.32	0.39			0.71	0.89			5.9	(6)
Males 11 - 14	44.5	0.55	0.62			1.17	1.46			9.7	(10)
15 - 17	62	0.60	0.90			1.50	1.88			12.5	(13)
18+	75		1.05			1.05	1.37			9.1	(9)
Females 11 - 14 [d]	45	0.55	0.65			1.20	1.40			9.3	(9)
11-14	45	0.55	0.65	0.48 [c]	1.90 [c]	1.68	3.27	18	(18)	21.8	(22)
15 - 17	54	0.35	0.79	0.48 [c]	1.90 [c]	1.62	3.10	16.9	(17)	20.7	(21)
18+	62		0.87	0.48 [c]	1.90 [c]	1.46	2.94	15.8	(16)	19.6	(20)
Post-menopausal women	62		0.87			0.87	1.13			7.5	(8)
Lactating women	62		1.15			1.15	1.50			10	(10)

a. Partly based on an FAO/WHO report [13] and partly on new calculations of the distribution of iron requirements in menstruating women [10]. Because of the very skewed distribution of iron requirements in these women, dietary iron requirements are calculated for two levels of coverage, 90% and 95%, in these groups.

b. Bioavailability of dietary iron during this period is greatly varying and on average lower than 15%. With a 10% bioavailability, for example, dietary iron requirements will be 9.3 mg.

c. Effect of the normal variation in Hb concentration not included in this figure.

d. Non-menstruating

Table 25.2 *The percentages of populations of menstruating adult women and girls aged 15-17 years whose needs will be satisfied by various amounts of absorbed iron, and the dietary intakes that would be necessary to provide these amounts, assuming 15% bioavailability.*

Probability of adequacy	Absorbed iron requirements (mg/d)		Dietary iron intake (mg/d)	
%	Adult women	Adolescents	Adult women	Adolescents
50	1.46	1.62	9.7	10.8
55	1.51	1.68	10.1	11.2
60	1.58	1.75	10.5	11.7
65	1.65	1.81	11	12.1
70	1.74	1.90	11.6	12.7
75	1.83	2.00	12.2	13.3
80	1.96	2.12	13.2	14.1
85	2.12	2.29	14.1	15.3
90	2.37	2.54	15.8	16.9
95	2.94	3.10	19.6	20.7

26. Zinc

Physiology

Zinc is ubiquitous in the body. It has essential structural, regulatory or catalytic roles in many enzymes [1,2]; additionally it maintains the configuration of a number of non-enzymic proteins such as pre-secretory granules of insulin, some mammalian gene transcription proteins [3], and thymulin; it facilitates hormone and receptor binding at membrane and nuclear levels, and it may maintain integrity of biomembranes. Consequently zinc participates in gene expression and in the mechanisms and control of major metabolic pathways involving proteins, carbohydrates, nucleic acids and lipids.

An adult human contains about 2 g zinc of which 60 % and 30 % are in skeletal muscle and bone respectively, and 4-6 % is present in skin [2,4]. Zinc turnover in these tissues is slow and these depots do not provide a reliable source of zinc at times of deprivation. Since zinc is essential for the synthesis of lean tissue, it is whilst this is occurring that it may become a limiting nutrient. Although some zinc may be available in short term zinc deprivation from a mobile hepatic pool it is generally assumed that the body has no specific zinc reserve and is dependent on a regular dietary supply of the element .

Zinc is absorbed throughout the intestine. Proximal intestinal absorption is efficient, but since it has a large enteropancreatic circulation, net intestinal absorption of the metal is achieved by the distal small intestine. Relatively small amounts of zinc are lost in the urine. Homoeostasis at low and customary intakes is achieved by adjustments in net intestinal absorption and to a lesser extent by renal conservation [4,5]. With inappropriately high zinc intakes the systemic burden of the element is limited by its sequestration in the enterocyte by a cysteine-rich protein, metallothionein [2,4]. The amount of zinc lost in desquamated skin and shed hair and in sweat varies with preceding intakes.

Deficiency and excess

The classic features of severe zinc deficiency comprise the tetrad of neuropsychiatric disturbances, acrodermatitis and alopecia, diarrhoea, and increased susceptibility to infections as a manifestation of defective immune mechanisms (in particular cell-

mediated immunity). These features by and large represent the dependence on zinc of tissues with a high turnover [2,6]. However, there is currently an increasing interest in the occurrence in some children in Western communities, as well as in the Middle East, of a mild zinc deficiency syndrome manifest as zinc-responsive growth retardation [7,8].

Gross acute zinc toxicity has been described following the drinking of water which has been stored in galvanised containers or the use of such water for renal dialysis. Symptoms include nausea, vomiting, fever and are apparent after acute ingestion of 2 g or more of the element [2]. Of more general concern are the effects of supra-physiological intakes of zinc. Prolonged intakes of 75-300 mg/d have been associated with impaired copper utilisation, producing features such as microcytic anaemia and neutropenia, but even short term intakes of about 50 mg zinc daily interfere with the metabolism of both iron and copper [9]. It is not known if long-term adaptation of the metabolism of these metals would compensate for such interactions with zinc, however it would be unwise to exceed a daily zinc intake of 30 mg in adults.

Requirements

Adults

The assessment of zinc requirements in adults has been based on factorial analyses using measurements of basal losses during periods of extended deprivation, the turnover of radio-labelled endogenous zinc pools, and inference from observations in patients receiving total parenteral nutrition. None is ideal but all indicate that systemic supplies of 2-3 mg/d are adequate to avoid disturbed metabolism of other nutrients, and to support optimum nitrogen and carbohydrate metabolism.

In studies of human volunteers adapted to very low daily intakes of zinc (0.2-0.3 mg/d), faecal and urinary loss of the element falls to 1.4 and 0.9 mg/d in men and women respectively; it is probable that integumental (principally dermal) loss would fall similarly [10]. Allowing for losses of zinc in semen and menstruation, it has been estimated that basal losses are around 2.2 and 1.63 mg/d in men and women respectively [11]. Absorptive efficiency varies with intake [5,10]; at the levels being considered here, a value of 30% can be assumed, giving Average Requirements of 7.3 and 5.4 mg/d which can be rounded to 7.5 and 5.5 mg/d. Assuming a normal population distribution, Population Reference Intakes of 9.5 and 7 mg/d can be derived with Lowest Threshold Intakes at 5 and 4 mg/d for men and women respectively.

In reality requirements may be lower; in adult males zinc balance can be maintained on intakes of 5.5 mg/d but, since on a prolonged intake of 3.4 mg/d negative balances ensue, the above figures would seem prudent and practical on the basis of present evidence.

Children

Better information not being available, requirements have been calculated factorially [12].

In children 6-11 m, average faecal, sweat and urinary losses are estimated to amount to about 0.1 mg/kg body weight/d, and a growth increment has been based on a lean tissue zinc content of 30 mg/kg. Absorption of dietary zinc is taken as 30%, giving an average requirement, and 30% is added for individual variation to give the PRI.

For children from 1 year of age onwards, similar calculations have been made, interpolating values for basal losses between these for adults and infants, plus increments for growth, assuming 30% absorption. The values given are probably on the generous side.

Pregnancy

The extra zinc accumulated during the last trimester amounts to about 0.8 mg [13]. It is possible that there is more efficient absorption, but even so it might be thought that there would be a need for a raised dietary intake in late pregnancy. In reality this appears not to be so; pregnant women do not increase their customary intake, and there is no benefit from zinc supplements [14]. Healthy women seem to be able to adapt metabolically to transfer an adequate amount of zinc to the fetus. No additional recommendation is therefore made for pregnancy.

Lactation

It is possible that the absorption of dietary zinc may increase during lactation, but there is no good evidence that it does. An extra dietary intake of 5 mg/d is proposed to cover the amount of zinc produced in the milk.

Summary

(mg/d)

Adults	Males	Females
Average Requirement	7.5	5.5
Population Reference Intake	9.5	7
Lowest Threshold Intake	5	4

Population Reference Intakes of other groups (mg/d)

	Age Group	PRI
	6-11 m	4
	1-3 y	4
	4-6 y	6
	7-10 y	7
Males	11-14 y	9
	15-17 y	9
Females	11-14 y	9
	15-17 y	7
	Pregnancy	7
	Lactation	12

References

1. Vallee B, Galdes A. (1984). The metallobiochemistry of zinc enzymes. *Advanc Enzymol Relat Areas Mol Biol*, 56, 283-430.

2. Hambridge KM, Casey CE, Krebs NF. (1986). Zinc. In: Mertz W, ed. *Trace elements in Human and Animal Nutrition*. 5th ed. Vol 2. New York: Academic Press, 1-137.

3. Struhl K. (1989). Helix-turn-helix, zinc-finger and leucine-zipper motifs for eukaryotic transcriptional regulatory proteins. *Trends Biochem Sci*, 14: 137-140.

4. Jackson MJ. (1989). Physiology of zinc: general aspects. In: Mills CF, ed. *Zinc in Human Biology*. London: Springer Verlag, 1-14.

5. Taylor CM, Bacon JR, Aggett PJ, Bremner I. (1991). Homeostatic regulation of zinc absorption and endogenous losses in zinc-deprived men. *Am J Clin Nutr*, 53: 755-763.

6. Aggett PJ. (1989). Severe zinc deficiency. In: Mills CF, ed. *Zinc in Human Biology*. London: Springer Verlag, 259-279.

7. Anonymous. (1989). Does zinc supplementation improve growth in children who fail to thrive? *Nutr Rev*, 47: 356- 358.

8. Gibson RS, Vanderkooy PDS, MacDonald AC, Goldman A, Ryan BA, Berry M. (1989). A growth limiting, mild zinc-deficiency syndrome in some Southern Ontario boys with low height percentiles. *Am J Clin Nutr*, 49: 1266- 1273.

9. Yadrick MK, Kenney MA, Winterfeldt EA. (1989). Iron, copper and zinc status: response to supplementation with zinc or zinc and iron in adult females. *Am J Clin Nutr*, 49: 145-150.

10. Milne DB, Canfield WK, Mahalko JR, Sandstead HH. (1983). Effect of dietary zinc on whole body surface loss of zinc: impact on estimation of zinc retention by balance method. *Am J Clin Nutr*, 38:181-186.

11. King JC, Turnlund JR. (1989). Human zinc requirements. In: Mills CF, ed. *Zinc in Human Biology*. London: Springer Verlag, 335-350.

12. Hambridge KM. (1991). Zinc in the nutrition of children. In: Chandra R, ed. *Trace Elements in Children*. New York: Raven Press, 65-77.

13. Aggett PJ. (1989). Extra zinc in pregnancy. *Contemp Rev Obstet Gynaecol*, 181-189.

14. Mahomed K, James DK, Golding J, McCabe R. (1989). Zinc supplementation during pregnancy: a double blind randomized controlled trial. *Br Med J*, **299**: 826-830.

27. Copper

Physiology

The two oxidation states of copper enable it to participate in electron-transferring (oxidase) enzyme activities such as cytochrome oxidase, Cu/Zn superoxide dismutase, thioloxidase, and amine oxidases/ monophenol monooxygenases, e.g. DOPA oxidase and lysyl oxidase. Thus it is essential for cellular energy metabolism, the production of connective tissue and synthesis of neuroactive peptides (catecholamines and enkephalins) [1,2,3].

The total body copper in adults is 50-120 mg of which approximately 15 %, 10 % and 40 % are located in liver, brain and muscle respectively. In plasma (copper content 10-25 µmol/L) 90-95 % of copper is bound to caeruloplasmin, the remainder is bound to albumin, transcuprein and free amino acids.

The precise function of caeruloplasmin is unknown. It may participate in the peripheral distribution of copper as may transcuprein and free amino acids. Additionally caeruloplasmin has numerous oxidase activities, substrates for which include biogenic amines, adrenaline, serotonin, ascorbate, and sulphydryl groups, and its oxidation of Fe(II) to Fe(III) and Mn(II) to Mn(III) may be essential for the binding of these metals to transferrin. It may also serve as a plasma free radical scavenger.

Intestinal uptake and transfer of copper occur predominantly in the small intestine, where, as with other trace metals, it is probably presented to the mucosa bound to low molecular weight ligands. Intestinal absorptive efficiencies of between 35 and 70% have been reported.

Systemic homoeostasis of copper is achieved by adjustment of biliary excretion; 0.5-1.5 mg of the element is lost by this route daily. Intestinal adaptation also contributes and with high copper intakes an intestinal block of copper absorption mediated by metallothionein may occur [4].

Deficiency and excess

The features of severe copper deficiency can be related to loss of specific cuproenzyme activities [5]. The typical syndrome of copper deficiency has occurred in

preterm infants, in normal term infants who have been inappropriately fed on unmodified cow milk, in children recovering from malnutrition and in adults and children receiving parenteral nutrition. Features of copper deficiency in infants and young children include neutropenia, leucopenia and skeletal abnormalities, and increased susceptibility to respiratory and other infections [6]. Anaemia may develop if deficiency is prolonged and severe.

The occurrence of dietary copper deficiency in adults is far less well documented. Some systematic studies of copper deprivation have excited interest that low intakes may contribute to cardiovascular diseases [7,8]. These defects include impaired cardiac function and dysrhythmias perhaps secondary to defective metabolism of catecholamines and enkephalins [3]; such defects and the contribution of "sub-optimal" copper intake to atherogenesis need further metabolic evaluation.

Copper toxicity arises from deliberate ingestion of copper salts, or accidentally from contamination of drinks. In acute toxicity the gastrointestinal tract is affected, variable degrees of intravascular haemolysis, heptocellular necrosis and renal tubular failure result and death may ensue [1,9].

With chronic exposure copper accumulates in the liver and toxicity is insidious. Eventually hepatic necrosis or cirrhosis with liver failure develops. Some infants and young children, at least, are vulnerable to high intakes arising from the use of copper containers and conduits [9].

Copper taken as copper sulphate induces nausea at intakes of 10 mg and intakes above this are increasingly emetic [1]. However when consumed with foods the element is better tolerated and it has been suggested that intakes of 10 to 35 mg/d could be tolerated. These suggestions, however, have not been verified and for the moment an upper limit of 10 mg/d is proposed.

Requirements

There are limited data on which human copper requirements can be based. A review of published balance studies suggests that balances can be achieved at intakes around 1.2 mg copper daily (CF Mills, personal communication). Copper-responsive clinical and biochemical defects have been seen in adults on experimental intakes of 0.7-1.0 mg/d for four weeks or more. However it is possible that some of these abnormalities may have arisen from the nature of the experimental diets [7], and another study using more customary, although still experimental, diets found no deterioration of current indices of copper supply in men on intakes of 0.79 mg/d for 42 days [11]. This suggests that 0.8 mg Cu/d is an adequate intake although actual

requirements may be lower. For example, for adults on parenteral nutrition 0.3 mg/d is adequate [12]; at an absorbability of 50 % this could correspond to a dietary intake of 0.6 mg/d. Such evidence suggests that an Average Requirement of 0.8 mg/d could be set with a LTI of 0.6 mg/d and, with an allowance for possible storage requirements, a PRI of 1.1 mg/d. Dietary intakes are generally 1.0-1.5 mg daily.

Children

Requirements for infants 6-11 months have been calculated on the basis of a tissue content of 1.38 µg/g [13], and an adjustment to allow for a possible loss of endogenous copper [14]. An absorption of 50% is assumed, to give a PRI of 36 µg/kg/d. PRIs were calculated from the interpolated values of 30 µg/kg/d at 1-6 years, 24 µg/kg/d at 7-10 years, and 18 µg/kg/d at 15-17 years.

Pregnancy

The estimated requirements for the products of conception are 0.033, 0.063 and 0.148 mg/d for the first, second and third trimesters respectively [15]. It is considered that these can probably be met by metabolic adjustment by the mother, so no increment is proposed for pregnancy.

Lactation

If 750 ml milk is produced with a copper content of 0.22 mg/L [16], and absorption is 50%, an increase of 0.33 mg/d would be required in the diet to support lactation.

Summary

Adults	mg/d
Average Requirement	0.8
Population Reference Intake	1.1
Lowest Threshold Intake	0.6

Population Reference Intakes of other groups

Age Group		PRI (mg/d)
	6-11m	0.3
	1-3 y	0.4
	4-6 y	0.6
	7-10 y	0.7
Males	11-14 y	0.8
	15-17 y	1.0
Females	11-14 y	0.8
	15-17 y	1.0
	Pregnancy	1.1
	Lactation	1.4

References

1. Mason KE. (1979). A conspectus of research on copper metabolism and requirements of man. *J Nutr*, **109**: 1979-2066.

2. Prohaska JR. (1988). Biochemical functions of copper in animals. In: Prasad A, ed. *Essential and Toxic Trace Elements in Human Health and Disease*. New York: Alan R Liss, 105-124.

3. Bhathena SJ, Recant L, Voyles NR, Timmers KI, Reiser S, Smith JC, Powell AS. (1986). Decreased plasma enkephalins in copper deficiency in man. *Am J Clin Nutr*, **43**: 42-46.

4. Cousins RJ. (1985). Absorption, transport and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. *Physiol Rev*, **65**: 238-309.

5. Danks DM. (1988). Copper deficiency in humans. *Ann Rev Nutr*, **8**: 235-257.

6. Castillo-Durán C, Fisberg M, Valenzuela A, Egaña JI, Uauy R. (1983). Controlled trial of copper supplementation during the recovery from marasmus. *Am J Clin Nutr*, **37**: 898- 903.

7. Reiser S, Smith JC, Mertz W, Holbrook JT, Scholfield DJ, Powell AS *et al.* (1985). Indices of copper status in humans consuming a typical American diet containing either fructose or starch. *Am J Clin Nutr*, **42**: 242-251.

8. Klevay LM, Inman L, Johnson LK, Lawler M, Mahalko JR, Milne DB *et al.* (1984). Increased cholesterol in plasma in a young man during experimental copper depletion. *Metabolism*, **33**: 1112-1118.

9. Spitalny KC, Brondum J, Vogt RL, Sargent HE, Kappel S. (1984). Drinking-water-induced copper intoxication in a Vermont family. *Pediatrics*, **74**: 1103-1106.

10. Müller-Höcker J, Meyer U, Wiebecke B, Hübner G, Eifer R, Kellner M, Schramel P. (1988). Copper storage disease of the liver and chronic dietary copper intoxication in two further German infants mimicking Indian Childhood Cirrhosis. *Pathol Res Pract*, **183**: 39-45.

11. Turnlund JR, Keyes WR, Anderson HL, Acord LL. (1989). Copper absorption and retention in young men at three levels of dietary copper by use of the stable isotope ^{65}Cu. *Am J Clin Nutr*, **49**: 870-878.

12. Shike M, Roulet M, Kurian, Whitewell J, Stewart S, Jeejeebhoy KN. (1981). Copper metabolism and requirements in total parenteral nutrition. *Gastroenterol*, **81**: 290-97.

13. Widdowson EM, Dickerson JWT. (1964). Chemical composition of the body. In: Comar C, Bronner F, eds. *Mineral Metabolism: An Advanced Treatise*. Vol.2, New York: Academic Press, 1-247.

14. Zlotkin SH, Buchanan BE. (1983). Meeting zinc and copper intake requirements in the parenterally-fed preterm and full-term infant. *J Pediatr*, **103**: 441-446.

15. Shaw JCL. (1980). Trace elements in the fetus and young infant. II Copper, manganese, selenium and chromium. *Am J Dis Child*, **134**: 74-81.

16. Casey CE, Neville MC, Hambridge KM. (1989). Studies in human lactation: secretion of zinc, copper and manganese in human milk. *Am J Clin Nutr*, **49**: 773-785.

28. Selenium

Physiology

The total body content of selenium (3-30 mg) varies according to the geochemical environment and dietary intakes. Selenium is an integral part of the enzyme glutathione peroxidase (GSHpx), one of the mechanisms whereby intracellular structures are protected against oxidative damage [1]. Less than 2 % of selenium in plasma exists as glutathione peroxidase. Most is associated with α- and β-globulins, and with glycoproteins amongst which one, selenoprotein P, may be involved specifically with selenium transport [2].

Selenium deficiency (in animal models) has been associated with defective microsomal oxidation of xenobiotics and rat hepatic microsomal type 1 iodothyronine 5'-dejodinase is a seleno-enzyme [3,4]. Other selenoproteins have been isolated from mammalian tissues. One may be essential for normal morphology of mammalian sperm [5] but the roles of the others have not yet been identified. Additionally cellular immune functions are disturbed by selenium deficiency [6].

Selenium is present in foods mainly as selenomethionine and selenocysteine. Selenoamino acids are probably absorbed by energy-dependent and sodium co-transport mechanisms similar to their sulphur analogues. Although the bioavailability of inorganic selenium is less than that of organic forms, this is probably of little practical significance because all usual dietary forms are absorbed quite efficiently [1,7].

The pool of selenomethionine in protein is subject to factors influencing methionine metabolism, and its constituent selenium is not necessarily available for selenium-dependent processes. For example, when methionine intake is limiting, selenomethionine is incorporated into methionine sites even if there is a concomitant selenium deficiency. However if the methionine supply is adequate, selenium released from degraded selenomethionine is available to the active selenium pool. The biologically active pool of selenium depends on selenocysteine, which can be synthesised endogenously.

Homoeostasis of organic selenium is achieved by adaptations in urinary excretion, and to a lesser extent intestinal absorption. Systemically selenoamino acids can be

degraded to yield amino acid residues and selenite. Excess selenium is successively reduced to methylated and other derivatives, which are excreted in the urine.

Deficiency and excess

In man the most striking selenium-responsive syndrome is that of Keshan disease, a selenium-responsive cardiomyopathy which affects predominantly children, adolescents and young women in China. Other factors probably contribute to the pathogenesis of Keshan disease, but related cardiomyopathies have been observed in patients on total parenteral nutrition. Less severe deficiencies, involving skeletal myopathy with increased plasma creatine kinase activities, macrocytosis and lightening of skin and hair pigmentation, have been documented. An increased degree of haemolytic sensitivity of red cells *in vitro* to peroxide, as evidence of significantly reduced GSHpx activity, may be the only detectable feature.

At excessive intakes of selenium a volatile dimethylated compound $[(CH_3)_2 Se]$ is formed, which when lost via expired air gives a characteristic garlic odour. Dietary intakes of 3.2-6.7 mg/d cause severe selenosis, encompassing an erythematous, bullous dermatitis, dystrophic nails, alopecia and neurological abnormalities involving parasthesia, paralysis and hemiplegia [9].

Requirements

Adults

Customary adult daily intakes of selenium vary between 20 and 300 µg/d. In China dietary intakes range from 11-5000 µg/d, at which extremes deficiency and toxicity syndromes occur.

In New Zealand and Finland habitual intakes of 15-40 µg/d have not been associated with selenium-responsive disease although whole blood GSHpx activity was below its possible peak activity, which occurs with whole blood selenium concentrations about 100 µg/L [7,8]. In China populations with intakes of selenium of less than 12 µg/d experience Keshan disease, and those with intakes of 19 µg or more do not [9,10]. If allowance is made for the smaller size of individuals in China, 20 µg/d can be proposed as the European LTI [11]. Studies based on the saturation of GSHpx activity suggest that an Average Requirement would be about 40 µg/d [10], which would give a PRI of 55 µg/d.

Disturbed metabolism of selenium occurs at intakes above 750 µg/d and early features of nail dystrophy have been described at intakes of 900 µg/d [12]. Since the intake beyond which there is no discernible benefit is much lower than this, it is suggested that the maximum safe intake from all sources should be 450 µg/d.

Children

No extensive investigations have been made on selenium requirements in children. Blood concentrations at 1 year of age are about 80% of those of adults, increase to adult values by 3 years, and then remain fairly constant [13]. The PRIs have been calculated from adult values, on the basis of body weight, and should cover the relatively much smaller requirements for growth (0.2 ng/g weight gain).

Pregnancy and lactation

Adaptive changes in the metabolism of selenium occur during pregnancy [14], so no recommendation is made for any extra increment.

To maintain the selenium concentration in infants' serum at about 70 ng/ml, a daily intake from breast milk of about 8-10 ng/ml is necessary [15]. In the absence of more specific information, the extra requirement during lactation has been calculated on the basis of 60% absorption from the diet, and milk with a selenium content of 12 ng/ml, to give an increment of 15 µg.

Summary

Adults	µg/d
Average Requirement	40
Population Reference Intake	55
Lowest Threshold Intake	20
Maximum safe intake	450

Population Reference Intakes of other groups

Age Group	PRI (µg/d)
6 - 11 m	8
1 - 3 y	10
4 - 6 y	15
7 - 10 y	25
11-14 y	35
15-17 y	45
Pregnancy	55
Lactation	70

References

1. Levander OA. (1987). A global view of human selenium nutrition. *Ann Rev Nutr*, 7: 227-250.

2. Motchnik PA, Tappel AL. (1990). Multiple selenocysteine content of selenoprotein P in rats. *J Inorg Biochem*, **40**: 265-269.

3. Arthur JR, Nicol F, Beckett GJ. (1990). Hepatic iodothyronine 5'-deiodinase: the role of selenium. *Biochem J.*, **272**: 537-540.

4. Behne D, Kyriakopoulos A, Meinhold H, Köhrle J. (1990). Identification of type I iodothyronine 5'-deiodinase as a selenoenzyme. *Biochem Biophys Res Commun*, **173**: 1143-1149.

5. Watanabe T, Endo A. (1991). Effects of selenium deficiency on sperm morphology and spermatocyte chromosomes in mice. *Mutat Res*, **262**: 93-99.

6. Dhur A, Galan P, Hercberg S. (1990). Relationship between selenium, immunity and resistance against infection. *Comp Biochem Physiol*. **96**: 271-280.

7. Robinson MF. (1988). The New Zealand selenium experience. *Am J Clin Nutr*, **48**: 521-534.

8. Casey CE. (1988). Selenophilia. *Proc Nutr Soc*, **47**: 55- 62.

9. Yang G, Wang S, Zhou R, Sun S. (1983). Endemic selenium intoxication of humans in China. *Am J Clin Nutr*, **37**: 872-881.

10. Yang GA, Zhu LZ, Liu SJ *et al.* (1987). Human selenium requirements in China. In: Combs GF, Spallholz JE, Levander OA, Oldfield JE, eds. *Selenium in Biology and Medicine*. New York: Nostrand Rheinhold/AVI, 589-607.

11. Yang G, Ge K, Chen J, Chen X. (1988). Selenium-related endemic diseases and the daily selenium requirement of humans. *Wld Rev Nutr Diet*, 55: 98-152.

12. Yang G, Yin S, Zhou L *et al.* (1989). Studies of safe maximal dietary Se intake in a seleniferous area in China. Part II. Relation between Se intake and the manifestation

of clinical signs and certain biochemical alterations in blood and urine. *J Trace Elem Electrolytes Health Dis*, **3**: 123-130.

13. Ward KP, Arthur JR, Russell G, Aggett PJ. (1984). Blood selenium content and glutathione peroxidase activity in children with cystic fibrosis, coeliac desease, asthma and epilepsy. *Eur J Pediatr*, **142**: 21-24.

14. Swanson CA, Reamer DC, Veillon C, King JC, Levander OA. (1983). Quantitative and qualitative aspects of selenium utilization in pregnant and nonpregnant women: an application of stable isotope methodology. *Am J Clin Nutr*, **38**: 169-180.

15. Smith AM, Picciano MF, Milner JA. (1982). Selenium intakes and status of human milk and formula fed infants. *Am J Clin Nutr*, **35**: 521-526.

29. Iodine

Physiology [1]

Iodine is a constituent of thyroxine (T4) and tri-iodothyronine (T3). Adequate circulating levels of these thyroid hormones are necessary for optimum cellular metabolism, normal growth and development.

Both inorganic and organic iodine are absorbed efficiently by the small intestine. Extracellular fluid contains 10-15 µg iodide/L. The total size of the iodide pool is approximately 250-350 µg, but its precise mass varies with iodide intake, which, in the absence of specific dietary or exogenous supplementation, corresponds closely to the amount of element entering the local food chain from the immediate geochemical environment. Thus populations living on heavily leached soils, which are often, but not exclusively, mountainous areas are at particular risk of sub-optimal iodine intakes. Plasma inorganic iodide is loosely bound to protein. It is cleared principally by the thyroid and kidneys but other tissues such as the gastrointestinal mucosa, mammary and salivary glands, and ovaries can also concentrate the element.

Over 75 % of the 10-20 mg iodine present in the normal adult is found in the thyroid gland. Iodide is taken up into the thyroid actively by a sodium-dependent carrier-mediated pathway which is stimulated by thyroid stimulating hormone. The iodide is then rapidly oxidised by thyroperoxidase, and 'organified' by iodination of tyrosyl residues in thyroglobulin. Pairs of the resultant iodotyrosines link to form iodothyronines. The major excretory route of iodide is via the urine, and daily urinary excretion of the element is often used as a convenient index of intake. Goitrogenic cyanoglucosides in brassicas, cassava, maize, sweet potatoes, lima beans and bamboo shoots interfere with the organification of iodide by the thyroid [1,2].

Decreased circulatory levels of T3 lead to a loss of the inhibitory feed back on the release of hypothalamic thyrotrophin releasing hormone, the increased secretion of which increases the secretion of pituitary thyroid stimulating hormone, which stimulates the uptake of iodide by the gland and can lead to thyroid hyperplasia and goitre.

Deficiency and excess

Iodine Deficiency Diseases (IDD) may be widespread in Europe [3,4]. The spectrum of IDD is extensive and subtle, as are their impact on socio-economic development [5,6].

Maternal iodine deficiency causes infertility, increased incidence of abortions and stillbirths, increased perinatal and neonatal mortality, congenital abnormalities including neurological and myxoedematous cretinism, and, less obviously, degrees of psychomotor retardation evident in later childhood resulting from intrauterine iodine deficiency. In older children and adults IDD include impaired mental function, hypothyroidism with goitre and growth retardation.

High iodine intakes cause toxic nodular goitre and hyperthyroidism. Such toxicity is rare in normal populations or individuals with an intake of less than 5 mg/d but those with pre-existent iodine deficiency may be susceptible to developing toxic nodular goitre, hyperthyroidism, and thyroid cancer at intakes below this [7], and transient hyperthyroidism has been observed in previously deficient individuals on intakes of 150-200 µg/d [8]. The incidence of such complications diminishes with time as the overall iodine supply of the population is improved and the number of people previously exposed to iodine deficiency diminishes. Intakes of 1-2 mg/d appear to be safe [9] but intakes above 10 mg/d in the form of seaweed have been associated with an increased incidence of iodine goitre [10].

Requirements

Adults

Most adults can maintain iodine balance and normal thyroid function on intakes between 40 and 100 µg iodine/d. A plateau concentration of iodide in the thyroid gland is achieved at an iodine intake of 100 µg/d, and increasing intakes to 300 or 500 µg daily has no further effect on this or on reducing the incidence of goitre [11]. An Average Requirement of 100 µg is proposed and a PRI of 130 µg/d. (A daily intake of up to 200 µg is being advised by a current WHO initiative designed to eradicate iodine deficiency disorders). For the LTI 70 µg/d is proposed, as an intake below which thyroid adaptation may become inadequate with a risk of dysfunction or sub-optimal operation [6,7,12].

Children

PRIs for younger age groups have been calculated from adult values, on the basis of energy requirements.

Pregnancy and lactation

Provided the normal prepregnancy iodine intake is adequate, there is no evidence that an increased dietary intake is needed during pregnancy, so no increment is recommended.

Lactating women on a normal plane of iodine nutrition produce iodine in their milk in amounts more than sufficient for the infant. In order to replace these losses, a PRI of 160 µg/d is suggested during lactation. The increase is based on the needs of the infant rather than the amount actually produced in the milk.

Summary

Adults	µg/d
Average Requirement	100
Population Reference Intake	130
Lowest Threshold Intake	70

Population Reference Intakes of other groups

Age Group	PRI (µg/d)
6 - 11 m	50
1 - 3 y	70
4 - 6 y	90
7 - 10 y	100
11 - 14 y	120
15 - 17 y	130
Pregnancy	130
Lactation	160

References

1. Ingbar SH. (1985). The thyroid gland. In: Wilson JD, Foster DW, eds. *Williams Textbook of Endocrinology*, 7th ed. Philadelphia: Saunders, 682-815.

2. Gaitan E. (1988). Goitrogens. *Ballieres Clinics Endocrinol Metabol*, **2**: 683-702.

3. Subcommittee for the Study of Endemic and Iodine Deficiency of the European Thyroid Association. (1985). Goitre and iodine deficiency in Europe. *Lancet*, **i**: 1289-1292.

4. Delange F, Heidemann P, Bourdoux P, Larsson A, Vigneri R, Klett M *et al.* (1986). Regional variations of iodine nutrition and thyroid function during the neonatal period in Europe. *Biol Neonate*, **49**: 322-330.

5. Hetzel BS. (1983). Iodine deficiency disorders and their eradication. *Lancet*, **ii**: 1126-1129.

6. Stanbury JB, Ermans AM, Hetzel BS, Pretell EA, Querido A. (1974). Endemic goitre and cretinism: public health significance and prevention. *WHO Chronicle*, **28**: 220-228.

7. Phillips DI, Nelson M, Barker DJP, Morris JA, Wood TJ. (1988). Iodine in milk and incidence of thyrotoxicosis in England. *Clin Endocrinol*, **28**: 61-66.

8. Livadas DP, Koutras DA. (1977). The toxic effects of small iodine supplements in patients with autonomous thyroid nodules. *Clin Endocrinol*, **7**: 121-127.

9. Freund G, Thomas WC, Bird ED, Kinman RN, Black AP. (1966). Effect of iodinated water supplies on thyroid function. *J Clin Endocrinol Metab*, **26**: 619-624.

10. Suzuki H, Higuchi T, Saura K, Ohtaki S, Horiuchi Y. (1965). 'Endemic coast goitre' in Hokkaido, Japan. *Acta Endocrinol*, **50**: 161-176.

11. Moulopoulu DS, Koutras DA, Mantzos J *et al.* (1988). Iodine intake and thyroid function in normal individuals. In: Nagataki S, Torizuka K, eds. *The Thyroid*. New York: Elsevier, 283-286.

12. Lamberg BA. (1986). Endemic goitre in Finland and changes during 30 years of iodine prophylaxis. *Endocrinol Exp*, **20**: 35-47.

30. Manganese

Physiology

Manganese is a component of arginase, pyruvate carboxylase and mitochondrial superoxide dismutase. It participates also in various hydrolase, kinase, decarboxylase, and phosphotransferase activities. The intestinal absorption of manganese occurs throughout the length of the small intestine. Mucosal uptake appears to be mediated by two types of mucosal binding, one which is saturable with a finite capacity and one which is non-saturable. The efficiency of manganese absorption in adults is low (approximately 10 %) but there is some evidence of improvement at low intakes. High levels of dietary calcium, phosphorus, and phytate impair the intestinal uptake of the element but are probably of limited significance because as yet no well documented case of human manganese deficiency has been reported.

Systemic homoeostasis of manganese is maintained principally by hepato-biliary excretion. Urinary manganese falls with reduced intake and rises with increased intake, suggesting a role of the kidney [1].

Deficiency and excess

Although it is difficult to characterise the precise biochemical mechanisms that have failed, manganese-deprived animals display numerous reproducible phenomena. These include growth retardation, impaired cartilage formation and defective endochondrial osteogenesis in fetuses leading to impaired development of the skeleton and otoliths (with resultant ataxia); impaired glucose tolerance and insulin secretion; reduced gluconeogenic response to glucagon and adrenaline; hypocholesterolaemia; hepatic and renal accumulation of lipids and ultra-structural abnormalities in cellular and sub-cellular membranes and convulsions [1].

Evidence of manganese deficiency in man is poor [2]. Interest in possible manganese deprivation in humans has been stimulated by reports of manganese-responsive carbohydrate intolerance, and reduced manganese concentration in the hair of some mothers whose babies had congenital abnormalities and in the blood or hair of children with skeletal abnormalities, osteoporosis, and non-traumatic epilepsy.

Men fed a low manganese diet (10 µg/d) developed an evanescent skin rash and hypocholesterolaemia; however neither feature responded unequivocally to manganese repletion [3].

Manganese toxicity of dietary origin has not been well documented. Mineworkers in Chile exposed to manganese ore dust developed, possibly as a result of inhalation rather than ingestion, 'Manganic Madness' manifested by psychosis, hallucinations, and extrapyramidal damage with features of Parkinsonism [1].

Requirements

Manganese is particularly abundant in vegetable-based diets and beverages such as tea and it would seem that current population intake is adequate [2]. Most intakes are around 2-3 mg/d, but some reach 8.3 mg/d [1,3]. No manganese-responsive problems were seen in young men on an intake of 0.1 mg [4] and a basal requirement of 0.74 mg daily has been derived from other balance studies [5]. Thus the finding of some negative balances on dietary intakes between 1.21 and 2.89 mg/d could represent homoeostasis [5]. In the absence of more information an LTI of 0.75 mg daily could perhaps be set, but it is considered preferable to give a safe and adequate range of 1-10 mg/d.

Summary

Acceptable Range of Intakes	1-10 mg/d

References

1. Hurley LS, Keen CL. (1987). Manganese. In Mertz W ed. *Trace Elements in Human and Animal Nutrition*. 5th ed.Vol 1. San Diego: Academic Press, 185-223.

2. Anonymous. (1988). Manganese deficiency in humans: fact or fiction? *Nutr Rev*. **46**: 348-352.

3. Friedman BJ, Freeland-Graves JH, Bales CW, Behmardi F, Shorey-Kutschke RL, Willis RA *et al.* (1987). Manganese balance and clinical observations in young men fed a manganese-deficient diet. *J Nutr*, **117**: 133-143.

4. Wenlock RW, Buss DH, Dixon E J. (1979). Trace nutrients. 2. Manganese in British Food. *Br J Nutr*, **41**: 253- 261.

5. Freeland-Graves JH, Behmardi F, Bales CW, Dougherty V, Lin P-H, Crosby JB, Trickett PC. (1988). Metabolic balance of manganese in young men consuming diets containing five levels of dietary manganese. *J Nutr*, **118**: 764-773.

31. Molybdenum

Physiology

Molybdenum has several oxidation states. The redox potential between Mo(V) and Mo(VI) is appropriate for electron exchange with flavinmononucleotides and this is exploited biochemically in the activities of sulphite oxidase, xanthine oxidase and aldehyde dehydrogenase, for which molybdate (Mo_4^{2-}) linked with a pterin is a cofactor. Intestinal absorption of dietary molybdenum is highly efficient (approximately 80 %). The element is metabolised as an anion (molybdate) and systemic homoeostatic excretion is attained by renal excretion [1,2].

Molybdenum deficiency in man has occurred with prolonged parenteral feeding [3], and in a fatal autosomal recessive syndrome affecting infants in whom the hepatic synthesis of the molybdenum-pterin cofactor is probably defective [2]. With both conditions the metabolism of sulphur amino acids and nucleotides was impaired, and neurological and encephalopathies developed. The inborn error of metabolism presents in neonates: they have abnormal faeces, feeding difficulties, and severe neurological and developmental abnormalities leading to encephalopathy and death.

Requirements

Molybdenum-responsive defects have been observed in adults fed about 50µg daily [4]. Reported dietary intakes in adults are 44-460 µg/d in USA, 48-96 µg/d in New Zealand, 44-260 µg/d in Sweden and mean intakes of 128 and 120 µg/d in the United Kingdom and Finland respectively [1]. A requirement cannot be established reliably, and, in the absence of evidence to the contrary, current intakes appear to be adequate and safe.

References

1. Mills CF, Davis GK. (1987). Molybdenum. In: Mertz W, ed. *Trace Elements in Human and Animal Nutrition*. 5th ed. Vol 1. San Diego: Academic Press, 429- 463.

2. Rajagopalan KV. (1988). Molybdenum: an essential trace element in human nutrition. *Ann Rev Nutr*, 8: 401- 427.

3. Abumrad NN, Schneider AJ, Steel D, Rogers LS. (1981). Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. *Am J Clin Nutr*, 34: 2551-2559.

4. Chiang G, Swendseid ME, Turnlund J. (1989). Studies of biochemical markers indicating molybdenum status in humans. *FASEB J*, 3: A 1073.

32. Chromium

Physiology

The precise biological role of chromium has not been established [1,2]. It is thought that chromium facilitates the activity of insulin, possibly by optimising the number of membrane insulin receptors or their interaction with insulin or both. It is reported to have been beneficial in the management of both hyperglycaemic and hypoglycaemic responses to glucose loads. However, its use in the management of patients with diabetes mellitus has produced inconsistent results and this has created scepticism about the essentiality of chromium [3]. The element may also have a role in the metabolism of lipids and of nucleic acids. It has been suggested that some of these effects may arise from a non-specific effect on phosphoglucomutase [3].

Chromium (III) absorption is low at 0.5 to 2.0 % of dietary intake. Organic chromium is absorbed more efficiently but its bioavailability is low since it is excreted rapidly in the urine.

Deficiency and excess

Chromium deficiency has been reported in adults and in a child who had received prolonged parenteral nutrition. The features involved an insulin-resistant hyperglycaemia, elevated serum lipids, weight loss, ataxia, peripheral neuropathy, and encephalopathy. The adult patients responded to intravenous chromium chloride ($CrCl_3$), but the response in the child was less conclusive [3,4].

Trivalent chromium has a low level of toxicity but hexavalent chromium is more toxic. In experimental animals intakes of 50 μg/g diet cause renal and hepatic necrosis and growth retardation.

Requirements

Since data on the essentiality and metabolism of chromium are so sparse the Committee is unable to specify any requirements.

References

1. Stoecker BJ. (1990). Chromium. In: Brown M, ed. *Present Knowledge in Nutrition* 6th ed. Washington DC: International Life Sciences Institute Nutrition Foundation, 287-293.

2. Offenbacher EG, Pi-Sunyer FX. (1988). Chromium in human nutrition. *Ann Rev Nutr*, **8:** 543-563.

3. Anonymous. (1988). Is chromium essential for humans? *Nutr Rev*, **46:** 17-20.

4. Brown RO, Forloines-Lynn S, Cross RE, Heizer WD. (1986). Chromium deficiency after long-term total parenteral nutrition. *Digest Dis Sci*, **31:** 661-664.

33. Fluoride

Physiology

The essentiality of fluoride is debatable but since epidemiological studies have demonstrated in children an inverse relationship between the incidence of dental caries and their calculated intakes of fluoride, the element has been accepted as being beneficial to dental health [1,2]. Both topical and systemic fluoride replace hydroxyl moieties in enamel to form calcium fluoroapatite, which is less soluble in acid than is calcium hydroxyapatite, thus increasing resistance to demineralisation and improving mineralisation. Additionally, fluoride may have an antimicrobial effect on cariogenic oral microflora [2]. Ninety-five percent of systemic fluoride is in the skeleton and teeth. The concentration in bone increases with age and it has been suggested, but not proven conclusively, that fluoride may have a role in both the mineralisation of bone and the maintenance of peak bone mass [1].

Systemic homoeostasis of fluoride is achieved by the kidneys [3].

Deficiency and excess

Apart from an increased risk of susceptibility to dental caries, there are no well documented effects arising from low intakes of fluoride. On the other hand fluoride excess (fluorosis) is endemic in many parts of the world. An early feature of this is patchy demineralisation (mottling) of the tooth enamel, more usually of the permanent dentition. In terms of intake, this affects populations with intakes approximating 0.1 mg/kg/d [4]. This problem occurs in 10 % of children in areas with a water supply containing 1 mg (50 mol) fluoride/kg. Chronic exposure to high intakes (10-25 mg/d, resulting for example from consuming water supplies containing 15 mg/kg) results in a sclerotic calcification of bones, ligaments, tendons and interosseous membranes. This manifests as debilitating musculo-skeletal deformities which have been noted particularly in India, East Africa, the Persian Gulf and China [5]. However, the overall intake of fluoride, rather than the concentration in water is crucial in the pathogenesis of this syndrome and early skeletal features of fluorosis have been detected in populations from arid zones with water supplies containing less than 15 mg/kg.

Requirements

There does not appear to be a specific physiological requirement for fluoride and no specific recommendations have been made. Acute toxicity and perhaps death have been reported in adults exposed to intakes of 0.5 to 2.6 g/d [6].

References

1 Schamschula RG, Barnes DE. (1981). Fluoride and health: dental caries, osteoporosis and cardiovascular disease. *Ann Rev Nutr*, **1**: 427-435.

2. DePaola PF, Kashket S. (1983). Prevention of dental caries. In: Shupe JL, Peterson HB, Leone NC, eds. *Fluorides: Effects on Vegetation, Animals and Humans*. Salt Lake City: Paragon Press, 199-211.

3. Spencer H, Lewin I, Wiatrowski E, Samachson I. (1970). Fluoride metabolism in man. *JAMA*, **49**: 807-813.

4. Leverett DH. (1982). Fluorides and the changing prevalence of dental caries. *Science*, **217**: 26-30.

5. Krishnamachari KAVR. (1986). Skeletal fluorosis in humans: a review of recent progress in the understanding of the disease. *Prog Food Nutr Sci*, **10**: 279-314.

6. Waldbott GL. (1981). Mass intoxication from accidental overfluoridation of drinking water. *Clin Toxicol*, **18**: 531-541.

34. Other minerals

Sulphur occurs extensively throughout the body and although a human deficiency syndrome has not been demonstrated, there is no doubt that it is essential. The sulphate anion is a component of proteoglycans (e.g. keratan sulphate, chondroitin sulphate and dermatan sulphate) which are vital constituents of the extracellular matrix [1], and it is a substrate for the detoxification of various xenobiotics and their excretion as sulphate conjugates [2]. The sulphate for these functions is derived by the endogenous oxidation of the sulphur in the amino acids methionine and cysteine. Thus there does not appear to be any requirement for dietary sulphate.

Silicon may well be needed for the normal development of the skeleton and connective tissue and there does appear to be a differential distribution of the element in the body, with high concentrations in the lungs, tendons, trachea and aorta. Silica is absorbed poorly but silicic acid is taken up well by the intestine. However the significance of these observations is understood imperfectly, as are the human requirements for silicon [3].

Some studies in animal models suggest that **cadmium** [4], **lithium** [5], **lead** [6] and **nickel** [7] may be essential, but the current data are not sufficiently conclusive to justify setting any recommended intakes. Similarly, evidence supporting the essentiality of **arsenic, boron** and **vanadium** has yet to be substantiated.

References

1. Muir H. (1990). The coming of age of proteoglycans. *Biochem Soc Trans*, **18:** 787-789.

2. Williams RT. (1959). *Detoxication Mechanisms: The Metabolism and Detoxication of Drugs, Toxic Substances and other Organic Compounds*. 2nd ed. London: Chapman and Hall.

3. Carlisle EM. (1986). Silicon. In Mertz W, ed. *Trace Elements in Human and Animal Nutrition*. 5th ed. Vol 2. Orlando: Academic Press, 373-390.

4. Kostial K. (1986). Cadmium. In Mertz W, ed. *Trace Elements in Human and Animal Nutrition*, 5th ed. Vol 2. Orlando: Academic Press, 319-345.

5. Mertz W. (1986). Lithium. In Mertz W, ed. *Trace Elements in Human and Animal Nutrition*, 5th ed. Vol 2. New York: Academic Press, 391-397.

6. Nielsen FH. (1984). Ultra-trace elements in nutrition. *Ann Rev Nutr*, 4: 21-41.

7. Nielsen FH. (1984). Fluoride, vanadium, nickel, arsenic and silicon in total parenteral nutrition. *Bull N Y Acad Med*, **60:** 177-195.

35. Other substances sometimes considered to be of nutritional importance

Certain nutrients are known to be dietary essentials for some higher animals, notably choline, taurine, carnitine and inositol.

It has been suggested that newborn humans may have insufficient biosynthetic capacity to produce their full requirement of carnitine, taurine and choline. Any possibility of this is usually allowed for in the make up of infant formulas.

There is no indication of any need for the compounds mentioned to be supplied in the diet of healthy individuals above the age of six months.

Many specific growth factors are known to be required in cell or tissue cultures, e.g. ubiquinone (coenzyme Q), lipoic acid, nerve growth factor, p-aminobenzoic acid. There is no need for them in human diets as they can be synthesized in the body in adequate amounts.

Over the years there have been many reports of benefits to be derived from the consumption of a wide variety of organic compounds that can occur in foodstuffs, e.g. amygdalin (laetrile), pangamic acid, bioflavonoids, chlorophyll, orotic acid. There is no persuasive evidence of any need for such compounds in the diet.

36. Values for nutrition labelling

The Committee has also been asked to advise on a set of nutrient values which should be used for nutrition labelling purposes. The nutrient content of a food could then be expressed as a percentage of these values as required by the Council Directive 90/496/CEE on nutrition labelling. Having derived general recommendations on scientific grounds the Committee then had to decide on two issues, namely (i) the choice of the value for nutrition labelling in itself, and (ii) whether different values should be recommended for different groups of the population.

Choice of a value for nutrition labelling purposes

The Committee recognises that choosing a value for nutrition labelling purposes involves more than strictly scientific considerations: issues related to policy have to be taken into account.

This report sets out a range of reference values for each nutrient, and the Committee needed to assess whether only one of these values should be used consistently throughout the labelling process. The Committee also considered the merit of setting an entirely different single value which in some way encompassed the needs of the whole European population with its varying national, age and sex structure. To choose a single value for labelling seemed sensible from a practical point of view, and general consumer understanding was also an important issue, on which there is surprisingly little information. The consumers need some simple, coherent, understandable and meaningful reference point, should they wish to choose a diet to meet their own perceived needs. Consumer organisations and health educators support universal, unambiguous labelling. With continuing education and a suitable labelling format, an increasing proportion of the population is expected to use nutrition labelling in making choices in food purchasing.

It must be remembered that the value for nutrition labelling will not be used by professionals, dieticians or policy makers for assessing the adequacy of the population's diet or by those responsible for ensuring that specific population groups (e.g. armed forces, schoolchildren taking school meals and those in hospitals, etc.) receive an adequate nutrient supply.

Nutrition labelling may be of use to the consumer in two respects: (i) providing information which would enable consumers to compare different products; (ii) providing information to enable consumers to assess the usefulness of a food in the overall diet and thus to compose a diet suitable for their individual needs.

In the first case, the choice of reference value will not affect the comparison of different products. Further, products can be compared on the basis of absolute value perhaps more effectively. However, it is recognised that there is confusion about the use of different units, e.g. μg, mg, g and nutrient equivalents. The use of absolute units alone would also fail to provide a perspective on the different quantitative needs for the various nutrients. When consumers try to compose their diets on the basis of products providing nutritional information as a percentage of a reference value or when they try to evaluate the contribution of such products to their daily nutrient intake the reference value chosen for nutrition labelling acquires importance.

The Committee believes that the proportion of the population using nutrition labelling reference values to compose their daily diet is at present small, although the media may use the values to construct 'model diets'. Labelling values are more likely to be used by the consumer as a guide as to which key foods make important or useful contributions to overall needs. Further, it is highly unlikely that diets will be composed entirely of labelled products which are consumed as purchased.

Use of the PRI for nutrition labelling

Traditionally, nutrient information has been presented on the label in relation to a recommended daily amount which usually corresponds to the PRI in this report i.e. point c on Figure 1.1. Many would advocate that this should continue. If the importance of a product as a contributor to the daily intake of nutrients is to be judged, the reference value for nutrition labelling should cover the needs of as great a proportion of the population as possible. On this view the reference value for nutrition labelling should be the PRI for adult men, except for iron for which the PRI for adult women should be selected.

If consumers were striving to reach 100% of the PRI then an adequate nutrient intake for the vast majority of the population would be ensured. Supporters of the male PRI as the reference value recognise that this would lead to excess nutrient intake by a substantial proportion of the population, and that those unable to reach it would be tempted to take dietary supplements. They feel however that this is acceptable and preferable to the reverse situation, i.e. a proportion of the population possibly not covering their needs if a value lower than the PRI were chosen as the reference for nutrition labelling.

Further, this body of opinion believes that opting for a high set of reference values, i.e. the male PRIs, will ultimately lead to an upward trend in food quality due to the manufacturers' efforts to enhance nutrient value, for example, through better processing, nutrient restoration or fortification. There is a risk however that they may do this only to improve 'label cosmetics'. The primary aim of reference values for nutrition labelling is not to serve as a reference to adjust the composition of specific foods but manufacturers may use them in that way.

Use of the Average Requirement for nutrition labelling

An opposing opinion argues that the use of a reference value as high as the adult male PRI is not appropriate for nutrition labelling. It is more than the needs of most men, and women and children are substantially misled about their requirements. It makes most peoples' diets appear inadequate when they are not. Despite repeated clear statements that the PRI is a value designed to meet very high individual requirements, the consumer, the media and even some professionals continue to consider anyone eating less to be deficient.

The use of the adult male PRI for food labelling could lead to a fall in confidence in some traditional foods by making them appear to be of low nutritional value. In some cases nutritional information could not be given, because nutrients would not be present in amounts reaching 15% of the reference value per 100g, a condition for labelling in the Community directive.

Thus the use of the adult male PRI as the basis of nutrition labelling could mislead consumers, cause them unnecessary anxiety, encourage them to try to cover their needs from sources other than their normal diet and result in unnecessary fortification of foods by manufacturers.

An alternative proposal is to use an average value i.e. point b in the Fig 1.1, which should be of more use to consumers than one taken from the end of the range of requirements.

If only one value can be used for labelling purposes, which should be chosen? An overall weighted average value could be calculated for Europe, taking account of the total population structure. It would however be inappropriately low and lead to unwarranted complacency in adult men. A more suitable average value to choose for nutrition labelling would be the average requirement for adult men, except for iron, for which the average requirement for adult women would be selected.

Serviceability of the two proposed values

Table 36.1 gives data on selected micronutrient intakes by women in the EC. The intakes by women have been shown because women do most of the shopping and they also tend to be more interested than men in nutrition. They are thus more likely to read and use nutrition labelling to design or evaluate their own and their family's diets.

Table 36.2 shows that the average EC female diet normally contains less than the male PRI of several vitamins and minerals, although it does provide more than the male AR, which is also close to the female PRI. So if nutrition labelling is based on men's PRI, and women use it to obtain a good diet (or more likely, the media try to design "healthy" diets or discuss normal people's intakes) they may find that it is difficult for themselves and their children to reach these official targets. Yet there is no evidence of thiamin or riboflavin deficiency in Europe, and little or none of deficiencies in the other nutrients shown, with the exception of iron where heavy menstrual losses can contribute to anaemia, as outlined in chapter 25.

In table 36.3, the average nutritional value of a number of basic foods is compared with ARs and PRIs. This table shows that a number of basic foods barely contain 15% of the PRI per 100 g, but are important sources for most people because of the amounts eaten. Although it is not shown in this table, beef, with an average iron content of 2 mg/100 g, would provide per 100 g only 12.5% of the PRI for women. If the PRI for women were used as the labelling reference value, beef could not be labelled as a source of iron, even though it is one of the best.

Conclusion

The Committee has explored a number of options and has sought to identify a strategy which would best meet the aims set out in the Council Directive 90/496/CEE on nutrition labelling.

The Committee accepted that for practical purposes a single reference value had to be chosen, and recognized that the use of any single reference value would unavoidably give a potentially misleading message to some of the population. The Committee aimed to select the single value that would be of widest benefit.

The consumer seems to understand the term "average requirement" as implying varying individual needs, so the choice of the word "average" for use on the label may be more appropriate in informational terms than the currently used term of RDA.

Inspection of the range of derived reference values shows that the average nutrient requirement of adult men is sufficiently similar to the PRI of women to allow a rational approach to be developed. The clear exception is iron, which is dealt with below. The Committee therefore favours the use of the Average Requirement for adult males as the nutrition labelling value, which would cover the needs of the majority of the population. This strategy therefore covers the PRI of most groups and misleads the least number of consumers.

The chapter on iron makes it clear that iron needs vary remarkably within the population because of the additional needs of women of reproductive age. It is difficult therefore to maintain the same rationale set out above unless a special allowance is made for women who would be in real danger of deficiency if they simply chose foods corresponding to the male average requirement of 7 mg/day. The Committee therefore proposes that the iron content of foods should be given two labelling reference values. The average male requirement is proposed, together with a figure that meets the needs of more than 80% of menstruating women. The two values should be used simultaneously on the label, together with an explanatory asterisk. In the case of vitamin D, a value of 5 µg is proposed for nutrition labelling purposes, being the midpoint of adult requirements. Table 36.4 shows the Committee's proposed values for nutrition labelling purposes.

The Committee has discussed a large number of nutrients, many of them not currently permitted by Community legislation to be used in food labelling. The Committee does not consider that all the nutrients discussed in this report should appear on food labels. Values can be derived only for those nutrients for which an Average Requirement for men is given (apart from iron). An exception to this is for vitamin D, where no AR has been established, but a labelling value is recommended because of documented deficiencies.

The Committee considered its recommendations in accordance with the Council Directive 90/496/CEE, which calls for the amount of nutrient to be given per 100 g or 100 ml of foodstuff. The Committee also gave some thought to the suggestion that nutrition labelling should be in terms of the energy content rather than weight or volume. Nevertheless, as a method of nutrition labelling, it would not be so serviceable for the consumer to whom this information is directed.

Special needs of infants and young children

The Committee is aware that current Community legislation provides for the declaration of a single percentage value for the different products. This approach has the very important merit of practicality and simplicity. The Committee would

however like to point out that this presents a problem for products intended solely for the nutritional use of infants and young children, whose needs are very different from those of adults.

Since these foods are most unlikely to be eaten by other population groups, the Committee is proposing an additional set of reference values which could serve for the nutrition labelling of foods intended for the particular nutritional use of infants and young children. These are given in table 36.5. They are based on the PRIs for children aged between 6 months and 3 years, i.e. they should cover the needs of all children under the age of 4.

Table 36.1 Mean daily intake of selected micronutrients by women in the EC from national dietary surveys.

	Britain	Denmark	Ireland	Netherlands	Belgium	Germany	Portugal	EC average
Thiamin (mg)	1.3	1.1	1.2	1.0	1.1	1.1	1.8	1.2
Riboflavin (mg)	1.6	2.0	1.7	1.5	1.2	1.3	1.1	1.5
Vitamin B_6 (mg)	1.6	1.2	1.4	1.3	1.3	1.4	1.8	1.4
Iron (mg)	10.0	13.0	10.6	11.4	13.0	12.1	12.0	11.7
Zinc (mg)	8.2	—	9.2	—	—	9.3	7.6	8.6

Source: Nutriscan EC Food and Nutrition Intake Atlas

Note: Data for Italy and Spain are at the household level and have not therefore been included

Table 36.2 A comparison of the average EC female intake of selected micronutrients against male Average Requirements (AR), male Population Reference Intakes (PRI) and female Population Reference Intakes (PRI).

	Average EC female intake	Male AR	Intake as % of male AR	Male PRI	Intake as % of male PRI	Female PRI	Intake as % of female PRI
Thiamin (mg)	1.2	0.8	150	1.1	109	0.9	133
Riboflavin (mg)	1.5	1.3	115	1.6	94	1.3	115
Vitamin B_6 (mg)	1.4	1.3	108	1.5	93	1.1	127
Iron (mg)	11.7	7	167	9	130	16 *	73
Zinc (mg)	8.6	7.5	114	9.5	90	7	123

* The intake meeting the requirements of 90% of women of reproductive age

Table 36.3 Average content of selected nutrients for a number of basic foods

Food	Nutrient	Amount per 100g of food	% of male AR	% of male PRI
Raw potato	vitamin C	9 mg	30	20
	folate	35 µg	25	17
Baked potato	vitamin C	8 mg	27	18
White bread	thiamin	0.21 mg	26	19
Spaghetti, boiled	niacin	0.5 mg	3	3
Milk	calcium	115 mg	21	16
	riboflavin	0.17 mg	13	11

Table 36.4 Reference values for nutrition labelling for all foods (except those for the particular nutritional use of infants and young children)

Nutrient		Labelling reference value
Vitamin A	(µg)	500
Vitamin D	(µg)	5
Vitamin C	(mg)	30
Thiamin	(mg)	0.8
Riboflavin	(mg)	1.3
Niacin equivalents	(mg)	15
Vitamin B_6	(mg)	1.3
Folate	(µg)	140
Vitamin B_{12}	(µg)	1.0
Calcium	(mg)	550
Iron	(mg)	7 for men 14 for women
Zinc	(mg)	7.5
Iodine	(µg)	100
Selenium	(µg)	40
Copper	(mg)	0.8

Table 36.5 Reference values for nutrition labelling for foods intended solely for infants and young children

Nutrient		Labelling reference value
Vitamin A	(µg)	400
Vitamin D	(µg)	10
Vitamin C	(mg)	25
Thiamin	(mg)	0.5
Riboflavin	(mg)	0.8
Niacin equivalents	(mg)	9
Vitamin B_6	(mg)	0.7
Folate	(µg)	100
Vitamin B_{12}	(µg)	0.7
Calcium	(mg)	400
Iron	(mg)	6
Zinc	(mg)	4
Iodine	(µg)	70
Selenium	(µg)	10
Copper	(mg)	0.4

37. Summary of proposals

The main proposals of the Committee are summarized in three tables

Table 37.1 gives Average Requirements, Population Reference Intakes and Lowest Threshold Intakes for adults.

Table 37.2 gives for all groups the Population Reference Intakes expressed in the manner chosen by the Committee.

For those nutrients for which the recommendations are in terms of energy, protein intake or body weight, **Table 37.3** gives examples expressed in weight per day.

Table 37.1 Multiple values proposed for adults

(Amounts per day, unless given in other terms. If that for women is different from that for men, it is given in parentheses)

Nutrient	Average Requirement	Population Reference Intake	Lowest Threshold Intake
Protein (g)	0.6/kg body wt	0.75/kg body wt	0.45/kg body wt
Vitamin A (μg)	500 (400)	700 (600)	300 (250)
Thiamin (μg)	72/MJ	100/MJ	50/MJ
Riboflavin (mg)	1.3 (1.1)	1.6 (1.3)	0.6
Niacin (mg niacin equivalents)	1.3/MJ	1.6/MJ	1.0/MJ
Vitamin B_6 (μg)	13/g protein	15/g protein	-
Folate (μg)	140	200	85
Vitamin B_{12} (μg)	1.0	1.4	0.6
Vitamin C (mg)	30	45	12

Nutrient	Average Requirement	Population Reference Intake	Lowest Threshold Intake
Vitamin E (mg α-tocopherol equivalents)		0.4/g PUFA*	4 (3)/d regardless of PUFA* intakes
n-6 PUFA* (as percentage of dietary energy)	1	2	0.5
n-3 PUFA* (as percentage of dietary energy)	0.2	0.5	0.1
Calcium (mg)	550	700	400
Phosphorus (mg)	400	550	300
Potassium (mg)	-	3100	1600
Iron (mg)	7 (10, 6 [a])	9 (16 [b], 8 [a])	5 (7, 4 [a])
Zinc (mg)	7.5 (5.5)	9.5 (7)	5 (4)
Copper (mg)	0.8	1.1	0.6
Selenium (µg)	40	55	20
Iodine (µg)	100	130	70

For the following, acceptable ranges of intake are given

Pantothenic acid (mg)	3-12
Biotin (µg)	15-100
Vitamin D (µg)	0-10
Sodium (g)	0.575-3.5
Magnesium (mg)	150-500
Manganese (mg)	1-10

* PUFA: Polyunsaturated fatty acids

[a] Postmenopausal women

[b] PRI to cover 90% of women

Table 37.2 Population Reference Intakes

Age group	Protein	n-6 PUFA [a]	n-3 PUFA [a]	Vitamin A	Thiamin	Ribo-flavin	Niacin	Vitamin B_6	Folate	Vitamin B_{12}	Vitamin C
	(g/kg body weight/d)	% of dietary energy	% of dietary energy	(µg/d)	(µg/MJ)	(mg/d)	(mg/MJ)	(µg/g protein)	(µg/d)	(µg/d)	(mg/d)
6 - 11 m	1.6	4.5	0.5	350	100	0.4	1.6	15	50	0.5	20
1 - 3 y	1.1	3	0.5	400	100	0.8	1.6	15	100	0.7	25
4 - 6 y	1.0	2	0.5	400	100	1.0	1.6	15	130	0.9	25
7 - 10 y	1.0	2	0.5	500	100	1.2	1.6	15	150	1.0	30
Males											
11-14 y	1.0	2	0.5	600	100	1.4	1.6	15	180	1.3	35
15-17 y	0.9	2	0.5	700	100	1.6	1.6	15	200	1.4	40
18+ y	0.75	2	0.5	700	100	1.6	1.6	15	200	1.4	45
Females											
11-14 y	0.95	2	0.5	600	100	1.2	1.6	15	180	1.3	35
15-17 y	0.85	2	0.5	600	100	1.3	1.6	15	200	1.4	40
18+ y	0.75	2	0.5	600	100	1.3	1.6	15	200 [b]	1.4	45
Pregnancy	0.75 (+10 g/d)	2	0.5	700	100	1.6	1.6	15	400	1.6	55
Lactation	0.75 (+16 g/d)	2	0.5	950	100	1.7	1.6 (+2 mg/d)	15	350	1.9	70

[a] Polyunsaturated fatty acids.

[b] Neural tube defects have been shown to be prevented in offspring by periconceptual ingestion of 400 µg folic acid per day in the form of supplements.

Table 37.2 Population Reference Intakes (continued)

Age group	Calcium	Phosphorus	Potassium	Iron	Zinc	Copper	Selenium	Iodine
	(mg/d)	(mg/d)	(mg/d)	(mg/d)	(mg/d)	(mg/d)	(µg/d)	(µg/d)
6 - 11 m	400	300	800	6	4	0.3	8	50
1 - 3 y	400	300	800	4	4	0.4	10	70
4 - 6 y	450	350	1100	4	6	0.6	15	90
7 - 10 y	550	450	2000	6	7	0.7	25	100
Males								
11-14 y	1000	775	3100	10	9	0.8	35	120
15-17 y	1000	775	3100	13	9	1.0	45	130
18+ y	700	550	3100	9	9.5	1.1	55	130
Females								
11-14 y	800	625	3100	22* 18**	9	0.8	35	120
15-17 y	800	625	3100	21* 17**	7	1.0	45	130
18+ y	700	550	3100	20* 16** 8***	7	1.1	55	130
Pregnancy	700	550	3100	****	7	1.1	55	130
Lactation	1200	950	3100	10	12	1.4	70	160

* To cover 95% of population

** To cover 90% of population

*** Post-menopausal

**** Supplements necessary

Table 37.3 Daily intakes of those nutrients for which the recommendations are given in relation to body weight, energy or protein intakes [a]

Age group	Protein	n-6 PUFA[b]	n-3 PUFA[b]	Thiamin	Niacin	Vitamin B_6
	(g)	(g)	(g)	(mg)	(mg)	(mg)
6 - 11 m	15	4	0.5	0.3	5	0.4
1 -3 y	15	4	0.7	0.5	9	0.7
4 - 6 y	20	4	1	0.7	11	0.9
7 - 10 y	29	4	1	0.8	13	1.1
Males						
11-14 y	44	5	1	1.0	15	1.3
15-17 y	55	6	1.5	1.2	18	1.5
18+y (PRI)	56	6	1.5	1.1	18	1.5
(AR)	45	3	0.6	0.8	15	1.3
Females						
11-14 y	42	4	1	0.9	14	1.1
15-17 y	46	5	1	0.9	14	1.1
18+y (PRI)	47	4.5	1	0.9	14	1.1
(AR)	37	2.5	0.5	0.6	11	1.0
Pregnancy	57	5[c]	1	1.0[c]	14	1.3[d]
Lactation	63	5.5	1	1.1	16	1.4[d]

a Population Reference Intakes (PRI) except where indicated as Average Requirements (AR), (calculated as mean group intake x PRI or AR)

b Polyunsaturated Fatty Acids

c From 10th week of pregnancy

d Based on protein increments in pregnancy and lactation.

Appendix

Table A.1 Equations for predicting the average basal metabolic rate (BMR) from body weight (W), expressed in kg, and for children and adolescents, from body weight and height (H expressed in m) (BMR expressed in MJ per day)

Age in years	BMR (from weight)	BMR (from weight and height)
Males < 3	0.249 W - 0.13	0.0007 W + 6.35 H - 2.58
3-9	0.095 W + 2.11	0.082 W + 0.55 H + 1.74
10-17	0.074 W + 2.75	0.068 W + 0.57 H + 2.16
18-29	0.064 W + 2.84	
30-59	0.0485 W + 3.67	
60-74	0.0499 W + 2.93	
≥ 75	0.035 W + 3.43	
Females < 3	0.244 W - 0.13	0.068 W + 4.28 H - 1.73
3-9	0.085 W + 2.03	0.071 W + 0.68 H + 1.55
10-17	0.056 W + 2.90	0.035 W + 1.95 H + 0.84
18-29	0.0615 W + 2.08	
30-59	0.0364 W + 3.47	
60-74	0.0386 W + 2.88	
≥ 75	0.0410 W + 2.61	

These values are taken from the WHO/FAO/UNU report on energy and protein requirements [1] and Schofield *et al.* [2] except for the data on the two older groups where selected data, taken from Schofield *et al.* [2] and used in the report, have been amplified by new and more extensive data collected on Scottish elderly men and from both elderly men and women in Italy.

Table A.2 Estimated Energy Requirements (MJ/d) for groups of men and women at various ages, weights and activity levels

		Physical Activity Level ($\overline{PAL}$)								
Body weight (kg)	BMR (MJ/d)	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2
Men 18-29 yr										
60	6.7	9.3	10.0	10.7	11.4	12.0	12.7	13.4	14.1	14.7
65	7.0	9.8	10.5	11.2	11.9	12.6	13.3	14.0	14.7	15.4
70	7.3	10.2	11.0	11.7	12.5	13.2	13.9	14.6	15.4	16.1
75	7.6	10.7	11.5	12.2	13.0	13.7	14.5	15.2	16.0	16.8
80	8.0	11.2	12.0	12.8	13.6	14.4	15.2	16.0	16.8	17.6
Men 30-59 yr										
60	6.6	9.2	9.9	10.6	11.2	11.9	12.5	13.2	13.9	14.5
65	6.8	9.5	10.2	10.8	11.5	12.2	12.9	13.5	14.2	14.9
70	7.1	10.0	10.7	11.4	12.1	12.8	13.5	14.2	14.9	15.6
75	7.3	10.2	10.9	11.6	12.4	13.1	13.8	14.5	15.3	16.0
80	7.6	10.6	11.4	12.2	12.9	13.7	14.4	15.2	16.0	16.7
Men 60-74 yr										
60	5.9	8.3	8.9	9.4	10.0	10.6	11.2	11.8	12.4	13.0
65	6.2	8.7	9.3	9.9	10.5	11.2	11.8	12.4	13.0	13.6
70	6.4	9.0	9.6	10.2	10.9	11.5	12.2	12.8	13.4	14.1
75	6.7	9.4	10.1	10.7	11.4	12.1	12.7	13.4	14.1	14.7
80	6.9	9.7	10.4	11.0	11.7	12.4	13.1	13.8	14.5	15.2
Men ≥75 yr										
60	5.5	7.7	8.3	8.8	9.4	9.9	10.5	11.0	11.6	12.1
65	5.7	8.0	8.6	9.1	9.7	10.3	10.8	11.4	12.0	12.5
70	5.9	8.3	8.9	9.4	10.0	10.6	11.2	11.8	12.4	13.0
75	6.1	8.5	9.2	9.8	10.4	11.0	11.6	12.2	12.8	13.4
80	6.2	8.7	9.3	9.9	10.5	11.2	11.8	12.4	13.0	13.6

(continues Table A.2)

Physical Activity Level (PAL)

Body weight (kg)	BMR (MJ/d)	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2
Women 18-29 yr										
45	4.8	6.8	7.2	7.7	8.2	8.7	9.2	9.7	10.2	10.6
50	5.1	7.2	7.7	8.2	8.7	9.2	9.7	10.3	10.8	11.3
55	5.5	7.7	8.3	8.8	9.4	9.9	10.4	11.0	11.6	12.1
60	5.8	8.1	8.7	9.2	9.8	10.4	11.0	11.5	12.1	12.7
65	6.1	8.5	9.1	9.7	10.3	10.9	11.5	12.1	12.7	13.3
70	6.4	8.9	9.6	10.2	10.8	11.5	12.2	12.8	13.4	14.0
Women 30-59 yr										
45	5.1	7.1	7.7	8.2	8.7	9.2	9.7	10.2	10.7	11.2
50	5.3	7.4	8.0	8.5	9.0	9.5	10.1	10.6	11.1	11.7
55	5.5	7.7	8.3	8.8	9.4	9.9	10.5	11.0	11.6	12.1
60	5.7	8.0	8.6	9.1	9.7	10.3	10.8	11.4	12.0	12.5
65	5.8	8.1	8.7	9.3	9.9	10.4	11.0	11.6	12.2	12.8
70	6.0	8.4	9.0	9.6	10.2	10.8	11.4	12.0	12.6	13.2
Women 60-74 yr										
45	4.6	6.4	6.9	7.4	7.8	8.3	8.7	9.2	9.7	10.1
50	4.8	6.7	7.2	7.7	8.2	8.6	9.1	9.6	10.1	10.6
55	5.0	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5	11.0
60	5.2	7.3	7.8	8.3	8.8	9.4	9.9	10.4	10.9	11.4
65	5.4	7.6	8.1	8.6	9.2	9.7	10.3	10.8	11.3	11.9
70	5.6	7.8	8.4	9.0	9.5	10.1	10.6	11.2	11.8	12.3
Women ≥75 yr										
45	4.5	6.3	6.8	7.2	7.7	8.1	8.6	9.0	9.5	9.9
50	4.7	6.6	7.1	7.5	8.0	8.5	8.9	9.4	9.9	10.3
55	4.9	6.9	7.4	7.8	8.3	8.8	9.3	9.8	10.3	10.8
60	5.1	7.1	7.7	8.2	8.3	9.2	9.7	10.2	10.7	11.2
65	5.3	7.4	8.0	8.5	8.7	9.5	10.1	10.6	11.1	11.7
70	5.5	7.7	8.3	8.8	9.4	9.9	10.5	11.0	11.6	12.1

Table A.3 Mean body weights (kg) of European children [1]

Age		Males	Females	Males & Females
years	months			
-	1	4.0	4.0	4.0
-	3	6.0	5.5	6.0
-	6	8.0	7.5	7.5
-	9	9.0	8.5	9.0
1	0	10.0	9.5	10.0
1	6	11.5	11.0	11.0
2	0	12.5	12.0	12.5
2	6	14.0	13.0	13.5
3	0	15.0	14.0	14.5
3	6	15.5	15.0	15.5
4	6	17.5	17.0	17.5
5	6	19.5	19.5	19.5
6	6	22.0	21.5	22.0
7	6	24.5	24.0	24.5
8	6	27.0	27.0	27.0
9	6	30.0	30.5	30.0
10	6	33.0	34.0	33.5
11	6	36.5	37.5	37.0
12	6	41.0	43.0	42.0
13	6	47.0	48.0	47.5
14	6	53.0	50.5	51.5
15	6	58.0	52.5	55.5
16	6	62.5	54.0	58.0
17	6	64.5	54.5	59.5

[1] Values, rounded to nearest 0.5 kg, obtained by pooling national data sets from Italy, Denmark, France, Spain, UK, The Netherlands, Germany, Belgium and Greece, weighted on the basis of each country's population at any given age. Luxemburg, Ireland, Portugal not included.

Table A.4 Mean height (cm) of European children [1]

Age		Males	Females	Males & Females
years	months			
-	1	53.0	52.5	53.0
-	3	60.0	59.0	59.5
-	6	67.5	66.0	66.5
-	9	71.5	70.0	70.5
1	0	75.5	74.0	75.0
1	6	82.0	80.5	81.5
2	0	87.5	86.0	86.5
2	6	92.0	90.5	91.0
3	0	96.0	95.0	95.5
3	6	99.0	98.0	98.5
4	6	106.5	105.5	106.0
5	6	112.5	111.5	112.0
6	6	119.0	118.0	118.5
7	6	124.5	123.5	124.0
8	6	130.5	129.0	129.5
9	6	135.5	135.0	135.0
10	6	140.5	140.5	140.5
11	6	145.5	146.5	146.0
12	6	150.5	153.0	151.5
13	6	158.0	157.5	158.0
14	6	166.0	160.5	163.0
15	6	171.0	162.0	166.5
16	6	174.0	162.5	168.0
17	6	175.5	163.0	169.0

1 Values, rounded to nearest 0.5 cm, obtained by pooling national data sets from Italy, Denmark, France, Spain, UK, The Netherlands, Germany, Belgium and Greece, weighted on the basis of each country's population at any given age. Luxemburg, Ireland, Portugal not included.

Table A.5 Estimated time use and energy cost of activities in older children and adolescents aged 10-17 years

Activity			Energy Cost (as ratio of BMR)			
	Hours		Boys		Girls	
	age yrs 10-13	age yrs 14-17	age yrs 10-13	age yrs 14-17	age yrs 10-13	age yrs 14-17
Bed	9	8	1.0		1.0	
School	5	6	1.6		1.5	
Light	4.5	7	1.6		1.5	
Moderate	5	2.5	2.5		2.2	
High	0.5	0.5	6.0		6.0	
Total	**24**	**24**				
PAL			1.65	1.58	1.55	1.50

Based on FAO/WHO/UNU values [3]

References

1. World Health Organisation. (1985). *Energy and Protein Requirements. Report of a joint FAO/WHO/UNU meeting*. Geneva: World Health Organisation (WHO Technical Report Series: 724).

2. Schofield WN, Schofield C, James WPT. (1985). Basal Metabolic Rate: Review and Prediction. *Hum Nutr Clin Nutr*, **39** (Suppl 1): 1-96.

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The present report deals with 'Nutrient and energy intakes for the European Community' (opinion expressed on 11 December 1992).