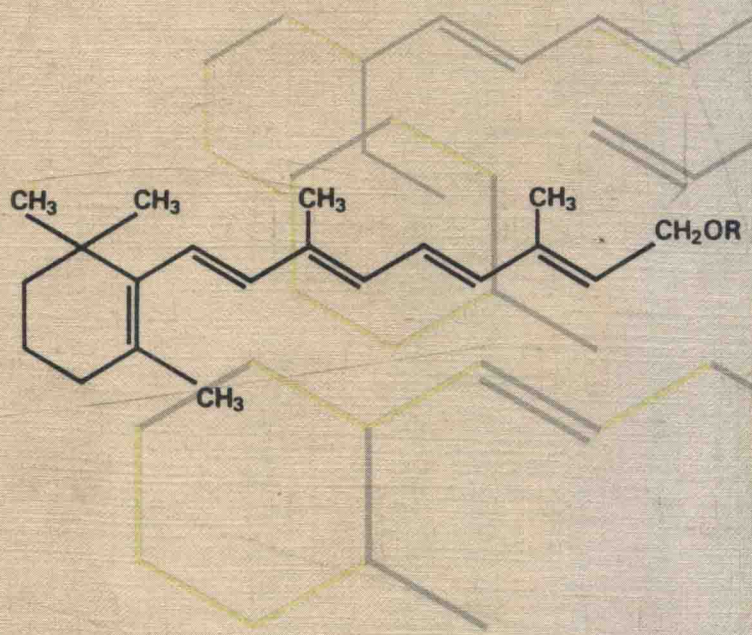
No. 55
Bibliotheca Nutritio et Dieta
Editors: P. Walter, J.C. Somogyi

Functions of Vitamins beyond Recommended Dietary Allowances

Editors
P. Walter
D. Hornig
U. Moser



KARGER

Functions of Vitamins beyond Recommended Dietary Allowances

Volume Editors *P. Walter*, Basel
D. Hornig, Basel
U. Moser, Basel

34 figures and 26 tables, 2001

KARGER

Basel · Freiburg · Paris · London · New York ·
New Delhi · Bangkok · Singapore · Tokyo · Sydney

Paul Walter
Biochemisches Institut
Vesalianum, Universität Basel
Vesalgasse 1
CH–4051 Basel (Switzerland)

Ulrich K. Moser
F. Hoffmann-La Roche Ltd
Vitamins and Fine Chemicals Division
CH–4070 Basel (Switzerland)

Dietrich Hornig
F. Hoffmann-La Roche Ltd
Vitamins and Fine Chemicals Division
CH–4070 Basel (Switzerland)

Library of Congress Cataloging-in-Publication Data

European Academy of Nutritional Sciences. Workshop (1997 : Nice, France)
Functions of vitamins beyond recommended dietary allowances/
volume editors, P. Walter, D. Hornig, U. Moser.
p. ; cm. – (Bibliotheca nutritio et dieta; no. 55)
Includes bibliographical references and index.
ISBN 3805570732 (hard cover : alk. paper)
1. Vitamins in human nutrition – Congresses. I. Walter, Paul, 1933– . II. Hornig, D.H.
III. Moser, U. (Ulrich), 1946– . IV. Title. V. Series.
[DNLM: 1. Vitamins – physiology – Congresses. 2. Nutrition Policy – Congresses. QU
160 E89f 2001]
TX341.B5 no. 55
[QP771]
613.2'86–dc21 00–043435

Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and Index Medicus.

www.karger.com
Printed in Switzerland on acid-free paper by Reinhardt Druck, Basel
ISSN 0067–8198
ISBN 3–8055–7073–2

Functions of Vitamins beyond Recommended Dietary Allowances

Bibliotheca Nutritio et Dieta

No. 55

KARGER
Basel · Freiburg · Paris · London · New York ·
New Delhi · Bangkok · Singapore · Tokyo · Sydney

Preface

More and more has become known on new properties and functions of various nutrients in our food. Of particular interest are functions of single or combinations of vitamins which seem to be involved in the improvement of immune function and in the risk reduction of chronic diseases such as cardiovascular diseases, cancer, and also neurological disorders like Alzheimer disease. The about 50 experts of the workshop that was held under the auspices of the European Academy of Nutritional Sciences in October 1997 discussed the progress in this area in great detail. In the summary discussions, which are also part of this book, the questions were raised for which of the vitamins recommendations can be formulated or if the necessary evidence is still missing and what the estimated time scale for obtaining this knowledge will be. Since not only scientists but also the consumers are very much interested in this development especially concerning the reduction of the risk of chronic diseases it was also discussed how the consumer should be informed on the progress science is making.

This volume of 'Bibliotheca Nutritio et Dieta' is the last one both under my editorship and the present name. Starting with No. 56, the series will change its name to 'Forum of Nutrition', with Professor I. Elmadfa from Vienna as the new editor and myself as co-editor.

Paul Walter

Contents

Walter P, Hornig D, Moser U (eds): Functions of Vitamins beyond Recommended Dietary Allowances. Bibl Nutr Dieta. Basel, Karger, 2001, No 55, pp 1–3

A Conceptual Approach for Scientifically Based Guidelines

P. Walter [a], *D. Hornig* [b], *U. Moser* [b]

[a] Swiss Vitamin Institute and Department of Biochemistry, University of Basel,
[b] F. Hoffmann-La Roche Ltd, Vitamins and Fine Chemicals Division, Basel, Switzerland

This book will review the scientific evidence for vitamin intake based on functions beyond the classical deficiencies. The objective is to elaborate guidelines for vitamin intake in individuals to cover new functions for these nutrients. Of particular interest are functions of single or of combinations of vitamins which may contribute to the prevention or risk reduction of chronic disease.

It is generally accepted that the basic needs of vitamins are covered by the intake equivalent to the Recommended Dietary Allowances (RDAs) which were originally established mainly to prevent deficiencies. RDAs are defined as 'the levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged to be adequate to meet the known nutritional needs of practically all healthy persons'. What is meant by 'practically all healthy persons'? The individual requirements for each nutrient are conventionally assumed to have gaussian distribution. The RDA value is set as the mean requirement of the group plus 2 standard deviations, i.e. covering at least 97.5% of the population. RDAs are often misinterpreted because they are regarded as the lowest acceptable intake for each individual which is of course not true since most of the individuals may actually meet their requirements at a lower value. Furthermore, in most cases, RDAs include a factor relevant to each nutrient to account for the variation in turnover rates and body pools.

It is important to realize that even the more recently re-evaluated RDAs are still based essentially on the vitamin requirements to prevent the classical deficiencies (see for instance SCF report on 'Nutrient and Energy Intake for

the European Community', 1992, and the report of the Department of Health (UK) on 'Dietary Reference Values for Food Energy and Nutrients for the United Kingdom', 1991). However, more and more scientific evidence is accumulating that several vitamins exhibit additional function each with a different requirement that is usually somewhat higher than the one for the prevention of the respective classical vitamin deficiency. Such functions include e.g. the radical scavenging effect of various antioxidant vitamins, the role of folate in the prevention of neural tube defect, and the effects of folate, vitamins B_6 and B_{12} in the regulation of the homocysteine concentration in blood. It is the goal of this workshop to substantiate the relations between the scientific evidence for selected functions and the respective vitamin intake.

Some functions apparently require not only one but several vitamins due to observed synergistic interactions. A typical example is the established synergism between the antioxidant vitamins C, E and β-carotene as radical scavengers. Therefore, the workshop will also consider other potential synergistic actions of vitamins.

The prevailing opinion is that a so-called balanced diet provides all essential nutrients in adequate amounts (RDAs). However, the intake necessary to cover additional functions adequately may not be achieved with such a balanced diet unless special measures are taken to adapt the dietary behaviour specifically. Guidelines advising a much higher intake of fruits and vegetables (5–7 servings per day) have already been established to help in the reduction of risk for certain diseases such as some types of cancer, coronary heart disease and maybe also the degeneration of mental functions (e.g. Parkinson and Alzheimer disease). Such a diet includes several vitamins at considerably higher amounts than the respective RDAs, e.g. about 200 mg vitamin C, 20–30 IU vitamin E, 6 mg β-carotene and also several of the B vitamins such as folate and vitamin B_6. It is quite likely that these increased intakes of vitamins together with other nutrients may play an important role for the beneficial effect of such a diet rich in fruit and vegetables.

But even when these special guidelines are followed it may not be possible to adequately cover particular additional needs for some of the vitamins. The most typical example is the prevention of neural tube defect by folate. Thus it may be necessary to take special measures to adequately cover these additional needs.

Today, individuals are very much concerned about their personal contribution to well-being and 'optimal' health in later life. Guidelines advising what to eat according to the latest established scientific information on vitamins and other nutrients to reduce the risk for certain diseases are in demand by a broad segment of the population. Since knowledge accumulates rapidly, such guidelines should be reassessed frequently to incorporate new scientific data,

and competent organizations such as academies or other professional associations could be responsible to establish them. These could now and even more so in the future contribute to lower public health costs by contributing to the reduction of the incidence of costly chronic diseases.

Since many of the leading experts attended the workshop it was decided to publish not only the lectures but also summaries of the discussions in the working groups. For the topics of each session, one working group was formed. They were asked to include in their discussions and summaries the following four questions: (1) Do we have sufficient evidence to make recommendations for increasing the current allowance of vitamins to beneficially effect certain functions? (2) What knowledge is missing before new vitamin recommendations for optimal function can be developed? (3) How long will it take to obtain the missing knowledge? (4) How should our current knowledge be communicated to the consumer?

Finally it should be mentioned that like the previous workshop on 'The Scientific Basis for Vitamin Intake in Human Nutrition' [1], this meeting was also organized in the name of the European Academy of Nutritional Sciences and was held in October 1997. The contents of this book represent a continuation of the discussions held in the previous volume.

Reference

1 Walter P (ed): The Scientific Basis for Vitamin Intake in Human Nutrition. Bibl Nutr Dieta. Basel, Karger, 1995, vol 52.

Prof. Paul Walter, Swiss Vitamin Institute and Department of Biochemistry,
University of Basel, Vesalgasse 1, CH–4051 Basel (Switzerland)
E-Mail paul.walter@unibas.ch

Walter P, Hornig D, Moser U (eds): Functions of Vitamins beyond Recommended Dietary Allowances. Bibl Nutr Dieta. Basel, Karger, 2001, No 55, pp 4–13

Dietary Reference Intakes: A New Approach to Setting Nutrition Standards in the USA and Canada

Allison A. Yates

Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, Washington, D.C., USA

It is a great pleasure to be here to discuss the progress to date on the Dietary Reference Intake initiative. This presentation covers three areas: (1) the present status of vitamin recommendations in the United States and Canada, (2) what the ideas are for setting upper safe levels, and (3) the time scale for everything that is planned.

Development of the Framework

Since 1992, the Food and Nutrition Board (FNB) in the United States has been undergoing an extensive review of (1) the process for developing nutrient-based dietary recommendations and reference intakes and (2) the uses made of quantitative estimates of intakes. When the previous meeting of the EANS was held in 1994 [1], the FNB had just issued a comment paper entitled 'How Should the Recommended Dietary Allowances be Revised?' [2]. It put forward a framework for developing dietary allowances and other quantitative reference intakes patterned to a large extent on the previous Dietary Reference Values of the United Kingdom [3], in which four reference values were given: a lower intake at which a high probability of deficiency existed, an estimated average requirement, a recommended intake, and an upper safe level of intake.

The definition of an RDA has remained somewhat the same for many years [4], and has not changed in the new framework as described here. The ideal criteria for establishing a recommended intake is to select a healthy, representative sample of the population, determine the average requirements

of that group; assess the range of individual variability, and calculate an allowance to cover needs. The new term, Dietary Reference Intakes (or DRIs), is a collective term that includes four nutrient-based dietary reference values. The values are the Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), Adequate Intake (AI), and Tolerable Upper Intake Level (UL). As is evident, some of these are similar, but in total these do not parallel the Dietary Reference Values of the United Kingdom [3]. In addition, a key concept included in the comment paper [2] was that the recommended intakes would not necessarily be restricted to being developed based on criteria related to prevention of nutrient deficiency diseases, but also to levels of intake which were expected to decrease risk of chronic disease *where the data were conclusive.*

Based on comments received to that initial proposal, adjustments were made in the proposed framework, as described in this discussion; but of significance is the continued inclusion of basing recommended intakes on risk of all diseases or chronic conditions, rather than focusing only on deficiency diseases.

Also of importance in the development of this new framework was the subsequent recognition by the FNB, based on an earlier report of the FNB on using recommended intakes to assess nutrient adequacy [5], that RDAs would not refer to population goals, but would be more accurately goals for individuals. This is in keeping with both the growing understanding of the influence of the variability of intakes in evaluating population intakes, and a better understanding that in estimating average requirements, it is an estimate for an individual. Given the concerns as discussed in the 1994 EANS Workshop [1] with regard to the growing body of evidence indicating the role of nutrients and other substances in food on long-term health, mounting interest developed on the part of federal agencies in the United States and Canada to provide funding to undertake the development of new dietary allowances which would apply the new framework to one group of nutrients, as a trial/test of the model (fig. 1).

With the involvement of the Health Protection Branch of Health Canada, the US Department of Health and Human Services agencies (Office of Undersecretary for Health, the Food and Drug Administration, and the National Heart, Lung and Blood Institute at NIH), and the US Department of Agriculture contracted with the FNB to initiate the project. In December 1995, the National Academy of Sciences appointed a standing committee to oversee this process. The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes currently has ten members, one of whom is from Canada. It is hoped that the government of Mexico can also participate in future portions of the process.

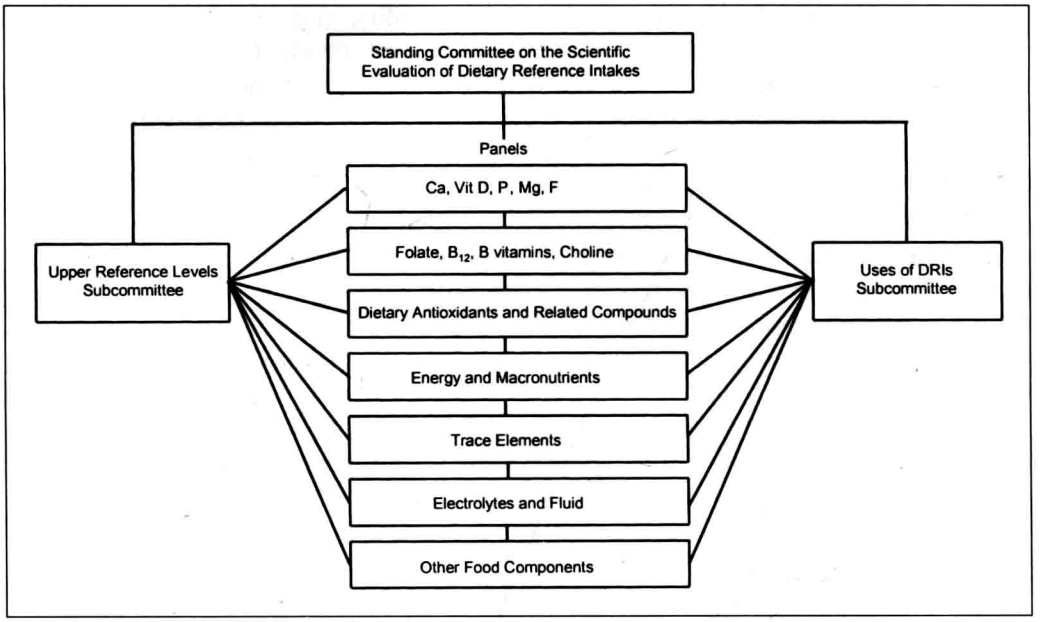


Fig. 1. Dietary Reference Intakes.

Initiation of the DRI Process

The first panel, the Panel on Calcium and Related Nutrients, was formed in early 1996. Their charge was to evaluate the scientific literature and establish, where adequate data was available, estimated average requirements for subgroups varying in age and gender, determine the variability of such requirements, and then develop recommended dietary allowances of levels of intake which would be the minimal amounts necessary to maintain approximately 98% of individuals in a population subgroup at the criterion of adequacy. The first group of nutrients so evaluated included calcium, phosphorus, magnesium, vitamin D, and fluoride [6].

Simultaneously with this effort, the Subcommittee on Upper Reference Levels was appointed. Their charge was to develop a model of risk assessment for nutrients, using standard risk assessment methodology, but adapted to the fact that nutrients are required for normal metabolism and thus are not contaminants, for which it is expected that one would want to have as low a level in the diet as possible. They were to apply the model to develop upper levels of intake of the five nutrients included in this first group that, when consumed chronically, would not result in adverse effects in more sensitive members of the population subgroup.

What are the Dietary Reference Intakes?

The overall framework has been titled *Dietary Reference Intakes*. DRIs are a set of reference values that can be used for planning and assessing diets for healthy populations and for many other purposes. They expand upon and replace the RDAs, which have been published since 1941 by the National Academy of Sciences [4], and are intended to replace the Recommended Nutrient Intakes developed in Canada [7]. As mentioned earlier, DRIs encompass the EAR, RDA, AI and UL.

Estimated Average Requirement

The EAR is the nutrient value that is estimated to meet the requirement defined by a specified indicator of adequacy in 50% of the individuals in a life stage and gender group. At this level of intake, the remaining 50% of the specified group would not have their nutrient needs met. For some life stage or gender groups, data may have to be extrapolated to estimate this value. In deriving the EARs, contemporary concepts of the reduction of disease risk are among the factors considered, rather than basing reference values solely upon the prevention of nutrient deficiencies. The EAR is used in setting the RDA, and it may be used as one factor for assessing the adequacy of intakes of groups and for planning adequate intakes by groups.

Recommended Dietary Allowance

The RDA is the daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98%) individuals in the life stage and gender group. The RDA applies to individuals, not to groups. The EAR serves as the foundation for setting the RDA. If the standard deviation (SD) of the EAR is available, the RDA is set at 2 SDs above the EAR:

$$RDA = EAR + 2\,SD_{EAR}.$$

If data about variability in requirements are insufficient to calculate a standard deviation, a coefficient of variation (CV_{EAR}) of 10% is assumed, and the resulting equation for the RDA is:

$$RDA = EAR + 2(EAR \times 0.1)$$
$$RDA = EAR \times (1.2).$$

If data are sufficient only to set an AI (see discussion following) for a nutrient for a specific life stage group, no RDA will be set.

Adequate Intake

If sufficient scientific evidence is not available to calculate an EAR, a value called an AI is used instead. The AI is based on observed or experimentally

determined approximations of a nutrient intake, by a defined population or subgroup, that appear to sustain a defined nutritional state, such as normal circulating nutrient values or growth. In the case of young infants, for whom human milk is the recommended sole source of food for the first 4–6 months of life, the AI is based on the daily nutrient intake supplied by human milk for healthy, full-term infants who are exclusively breast-fed.

The AI may be expected to exceed the EAR and possibly the RDA for the same specified endpoints of nutritional adequacy. The AI value depends upon the indicator of nutritional adequacy, the dietary characteristics of the group used to derive it, and the database and methods used to estimate it. Therefore, the excess of an AI, relative to a true EAR, is likely to differ among nutrients, population groups, and distinct sociocultural settings. In the absence of definitive data on which to base an EAR and RDA, the AI may be used as a goal for nutrient intake of individuals.

It should be emphasized that the AI as defined above is different from both the RDA and from the WHO 'lower limit of the population mean intake range for nutritional sufficiency', which are each based on a determined EAR [8].

In the first report issued on calcium, phosphorus, magnesium, vitamin D and fluoride, AIs rather than EARs and RDAs have been proposed for all nutrients for infants to the age of 1 year, and for calcium, vitamin D, and fluoride for all other life stages.

Vitamin D, an Example of a Case Where an AI is the Recommended Intake (table 1). For vitamin D, as an example, the AI is the intake value that appears to be needed to maintain, in a defined group of individuals with limited and uncertain sun exposure and stores, circulating serum 25-OH-vitamin D concentrations above a defined amount [6]. Here the rationale for an AI rather than EAR was that methods are not available to determine the extent to which stores are being used, or that sun exposure is providing additional sources. The cutoff for serum 25-OH-vitamin D was the concentration below which vitamin D deficiency rickets or osteomalacia occurs in some individuals. The intake value was rounded to the nearest 50 IU in micrograms, and then doubled as a safety factor to cover the needs of all, regardless of exposure to the sun.

Indicator of Nutrient Adequacy

Since the publication of the last version of the Recommended Dietary Allowances in the United States [4], the Canadian Recommended Nutrient Intakes [7], and the report on *Diet and Health* [9], the research base related to the role of diet in chronic disease has expanded sufficiently to permit moving beyond deficiency indicators to other indicators with broader functional significance. Examples of such indicators are those related to decreasing the