Egenvårdspoolen

Karlstad, Sweden 8th of September 2022

EGENVÅRDSPOOLENs Comment on the TRIS notification number 2022/0395/S on the Swedish draft measure amending the current Swedish Food Agency Regulation (LIVSFS 2003:9) on food supplements Dnr 2018/02027.

Dear EC Commission,

We are appalled to see this notification and we cannot but trust that the EC Commission will do its uttermost to stop it from becoming law in Sweden. This notification lacks both the correct up-to-date scientific grounds required when setting national limits to vitamins and minerals, but most of all it also lacks the correct legal grounds required in its present form.

Egenvårdspoolen AB founded in 2007, is a manufacturer and supplier of functional nutritional food supplements. We have 1200+ nutritional/self-care therapists in our distribution network. Many of these therapists routinely also test Vitamin D levels on their clients or recommend them to test their vitamin D levels with their regular doctor. There has not been one single incident of vitamin D toxicity from the Vitamin D supplements that we have sold to these therapists during our 15 year history.

The EC Commission needs to understand that in Sweden there are approximately 9500-10 000 nutritional therapists who will be affected severely if these low levels of iodine (200mcg) and Vitamin D (80mcg) are allowed to become law. These are non-medical practitioners who work with health promotion in the Swedish Population.

As far as we understand it current EU law (Directive 2002/46) which the court also upholds in its judgement (Noria Distribution SARL, Judgement of 27 April 2017, C-672-15, EU:C:2017:310) demands that national authorities have to take into account the latest most recent international scientific opinions in order to justify any levels to be established in local regulations.

The EFSA opinion used by the Swedish Food Agency on Iodine only has literature search data with studies up until 2001. For vitamin D the opinion is from 2012.

Hence, as these are not up to date they cannot ALONE be used as baseline for setting restrictive iodine and vitamin D levels.

Hence we present as attachments with this comment (from a later date then EFSAs opinion's) the following:

1) Expert Scientific Opinion from 2015 by Professor Michael F Holick) on Vitamin D supporting the safety of the dosage 125µg (5000iu) for all year round, also urging Sweden not to ban Vitamin D 125µg (5000iu) products.
2) The Swedish Food Supplement Industry & Nutritional Therapists Safety basis for Vitamins and Minerals: **Vitamin and Minerals Safety Handbook**, Council for Responsible Nutrition (CRN) (now 3rd edition 2014, 4th is on its way).

This guiding work with comprehensive risk assessments of all vitamins and minerals for the food supplement industry is carried out primarily by the industry's global expert body Council for Responsible Nutrition (CRN) in collaboration with the International Alliance for Dietary Food Supplement Associations (IADSA). CRN's risk assessment basis published by IADSA and CRN, is followed and supported by 50+ different national federations/associations and over 20,000 companies globally. https://www.iadsa.org/vitamin-and-mineral-safety-handbook-3rd-edition

Attached in this comment is an extract from their 2014 risk assessment for Vitamin D and Iodine which concludes that based on current scientific data the UL for Vitamin D is 250mcg (10 000iu) and iodine 500 µg/day for food supplements. This data cannot be ignored and should be taken into account by the Swedish Food Agency and the Commission.

Finally, the proposal for this new national maximum limits on iodine and Vitamin D would, from a gender perspective, be a complete disaster and strongly push back gender equality in Sweden. The industry has had a strong over-representation of women for a long time. Close to 90% of small businesses in the health sector are run by women. The proposal would risk knocking out hundreds of small businesses run by women, where the sale of nutritional food supplements is a crucial part of the company's survival.

Best Regards

Pekka Nylund

CEO

Egenvårdspoolen AB. Pumpgatan 2 A, 652 21 Karlstad.

Phone: +46 54-15 25 88

E-mail: info@egenvardspoolen.se

Michael F. Holick, Ph.D., M.D.

715 Albany Street, M-1013
Boston, MA 02118
Tel: 617-638-4545
Fax: 617-638-8882
Email: mfholick@bu.edu

BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Professor of Medicine, Physiology and Biophysics

Director of the General Clinical Research Center

Director of the Vitamin D, Skin and Bone Research Laboratory

Director, Biologic Effects of Light Research Center

BOSTON MEDICAL CENTER

Director, Bone Healthcare Clinic

July 31, 2015

To whom this may concern:

My name is Michael F Holick. I am currently professor of Medicine, Physiology and Biophysics, emeritus chief of this section of Endocrinology, Diabetes and Nutrition, Director of the Bone Health Clinic and Director of the Vitamin D, Skin and Bone Research Laboratory at Boston University Medical Center. I received my PhD in Biochemistry and my M.D. degree both from the University of Wisconsin. I conducted my residency in internal medicine at the Massachusetts General Hospital. I am board certified in internal medicine and grandfathered board certified in endocrinology. I have served on and continued to serve on several NIH study sections and chaired NASA's research committee on human health and performance. I serve on several editorial boards including the *American Journal for Bone and Mineral Research* and the *Journal of Clinical Endocrinology and Metabolism*, I am an associate editor for the journal *Dermato-Endocrinology* and am editor and chief for the *Journal of Clinical Laboratory*. I have been conducting basic, clinical and translational research in the fields of vitamin D and bone metabolism for more than 40 years. . I wrote the review on Vitamin D Deficiency for the New England Journal of Medicine (Holick, M.F. Vitamin D Deficiency. New Engl. J. Med. 2007. 357:266-81) and alerted health care professionals worldwide about the unrecognized vitamin D deficiency and

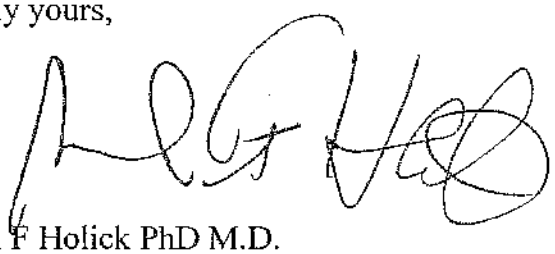
rickets epidemic in the review Resurrection of Vitamin D Deficiency Rickets in the Journal of Clinical Investigation 2006. (Holick, M.F. Resurrection of vitamin D deficiency and rickets. J Clin Invest. 2006. 116(8):2062-2072) I have published over 500 manuscripts in well-respected peer-reviewed journals and more than 250 reviews and book chapters. I served as the chair for the Endocrine Society's Clinical Practice Guidelines Committee for Vitamin D that published recommendations for how to treat and prevent vitamin D deficiency in children and adults. I have received numerous awards for my research activities including The Linus Pauling Prize in Human Nutrition, The Linus Pauling Functional Medicine Award, The General Clinical Research Centers Program Award for Excellence in Clinical Research from the National Institutes of Health, and the Louis Avioli Award from the American Society for Bone and Mineral Research just to name a few. I was recognized by Thompson Reuters as one of the most influential scientific minds for 2014.

This letter is in response to a request of the appellant in the legal proceedings regarding sales bans on vitamin D 5000 IUs. In collaboration with Dr. Heaney we conducted a study in healthy adults and gave them 10,000 IUs daily for 5 months and demonstrated no untoward toxicity. A recent study that I participated in Canada revealed that healthy adults taking up to 20,000 IUs daily for more than a year did not raised their blood level of 25-hydroxyvitamin D above 250 nmol per liter (100 ng/ML) which is considered to be the safe upper limit for this blood test. I routinely treat my patients with 50,000 IUs of vitamin D once a week for 2 months to treat vitamin D deficiency. This is equivalent to 6600 IUs daily. The Endocrine Society's Practice Guidelines Committee which I chaired recommends for healthy adults 1500-2000 IUs daily. However for obese patients they require 2-3 times more i.e. 3000-4500 IUs (2X) and for morbidly obese 4500-6000 IUs daily (3X). The Endocrine Society's Practice Guidelines Committee recommended that the safe upper limit of vitamin D for adults is 10,000 IUs daily based on the review of the literature.

I would encourage you not to ban the sales of 5000 IU of Vitamin D. In the northern hemisphere people cannot make enough vitamin D from the sun for at least 6 months of the year. To maintain normal vitamin D levels and for optimal health, supplements may be necessary. For a normal weight healthy adult 5000 IUs a day is perfectly safe for long term use all year round. For those who are obese 6000-10,000 IUs may be required.

If you have any questions please feel free to contact me.

Sincerely yours,



Michael F Holick PhD M.D.

The Swedish Food Supplement Industry & Nutritional Therapists Safety basis for Vitamins and Minerals

Risk assessment basis

CRN and IADSA

In matters of risks with vitamins and minerals, as in many other cases concerning food toxicology, the basis is international cooperation. Carrying out risk assessments of vitamins and minerals is generally a very extensive work that requires extremely large and broad competence as well as large financial resources. All individual Swedish companies, of course, carry out local risk assessments when necessary, especially when new studies show whether any clear side effects or risks have emerged. The guiding work of making large comprehensive risk assessments of all vitamins and minerals is therefore carried out above all by the global expert body for the industry *Council for Responsible Nutrition* (CRN) in collaboration with the *International Alliance for Dietary Food Supplement Associations* (IADSA). These evaluations are usually updated as new relevant data becomes available. IADSA's and CRN's risk assessment *Vitamin and Minerals Safety* is now in its third edition (1:1997, 2:2004, 3:2014). Work on the fourth edition has begun, but the publication date has not yet been specified. The food supplement industry follows these guiding risk assessment closely, almost as if it were a law book and adjusts its range doses if and when IADSA and CRN is changes its dosage recommendations for individual vitamins and minerals. CRN's risk assessment basis The *Vitamin and Minerals Safety Handbook* published by IADSA and CRN is followed and supported by 52 different national associations and over 20,000 dietary supplement companies globally.

Vitamins and Minerals Safety Handbook

Swedish food supplement companies, like many other European companies in other EU countries as well as globally (USA, Canada, Asia, India), use this risk evaluation in assessments of specific cases or individual products before they are released on the market. Producers of food supplements who do not follow IADSA and CRN's risk assessment *Vitamins and Minerals Safety Handbook* and who release higher doses than what IADSA and CRN have deemed safe, are not considered to be serious actors. It is not uncommon for online stores with the motto "the more the better". Among these internet shops you sometimes find doping-classified or drug-classified products (without registration). These stores are often found outside Sweden's borders but within the EU. The manufacturers are normally never members of any local or international trade association. We believe that this unserious group of companies, which is a clear minority, should not, however, be confused with the serious Swedish producers who make up an industry-leading majority.

In addition to making risk assessments, the CRN (Council for Responsible Nutrition) in the USA has done surveys for 22 years in a row. In one survey, published in September 2019, it was found that vitamins and minerals continue to be the most common category of food supplements, with 76% of Americans having taken this type of product in the past 12 months. https://www.nutraingredients.com/Article/2019/09/30/Dietary-supplement-use-more-popular-than-ever-CRN-study . The final analysis of the survey suggests that Americans trust the safety of food supplements.

Should IADSA and CRN's *Vitamin and Minerals Safety Handbook* have somehow missed important information, the United States is the country most likely in the world to sue manufacturers or organizations for the slightest little sign of side effect that could be attributed to a product. The fact is, however, that the doses that now are questioned in Sweden has been available in every single health food store in the USA, Canada and Great Britain as well as most other EU countries for over 50 years without any reports of serious side effects of the kind now hypothetically emphasized by The Swedish Food Agency. It is therefore particularly important that the Swedish Food Agency takes into account that the product dosages that the Swedish food supplement industry uses today are safe, which is not only supported by available and current scientific studies but also because these product dosages have been used for a long time globally.

EFSA, NASEM (IOM) and EVM

The food supplement industry often keeps itself more up-to-date on the latest research on safe product doses than EFSA, NASEM (IOM) and EVM do, whose work sometimes seems to be almost static, where a group is put together for individual project work and whose work is then rarely updated. For example, EFSA's 2006 report on recommended UL values only included studies up to the year 2000. The exception with EFSA was that in 2012 they updated the risk assessment for vitamin D for adults, infants and children in 2012 due to a large amount of research showing that higher doses were needed and were safe. It may be interesting to know that the UL value for vitamin D of 50 µg (2000iu) which was based on studies up to 2002 but was first published in EFSA's report from 2006, in 2012 had to be shockingly increased by 200 percent to 100 µg (2012).

The industry predicts that EFSA will probably raise its UL value for Vitamin D in adults in the near future to at least 250 µg (10 000iu) when the research that took place between 2012 and today finally catches up with EFSA again.

The UK EVM risk assessment was carried out as a one-off project in 2003 and has not been updated since then. The NASEM (IOM) in the US is extremely careful when doing their risk assessments and their criteria for including studies is much stricter than both EFSA and EVM. The NASEM (IOM) conclusions on many nutrients are often published as an entire book per nutrient. Which can be compared to EFSA's report, which sometimes bundles everything together in one single paper. This gives the NASEM (IOM's) conclusions a special weight and a decisive importance for the food supplement industry. The industry often adheres to NASEM (IOM's) conclusions, although IADSA and CRN's risk assessment naturally takes into account all conclusions from EFSA and EVM as well. NASEM (IOM) is the world's largest and oldest risk assessment institute, which has existed for over 75 years. However, of course they partly have the same problem as for EFSA and EVM, i.e. NASEM (IOM) rarely updates its works once they have been published. The exception here is potassium, where recently NASEM (IOM) published its work with a new risk assessment around potassium and sodium. This is appreciated by the food supplement industry and industry recommendations will likely change shortly.

HEALTH CANADA

The Canadian health care agency (Health Canada) differs a little from the rest of the world in that they make updates a little more regularly to their safety monographs. Health Canada is also incredibly up-to-date with the research and they are constantly adjusting their supplemental text instructions (extended information) for vitamins and minerals, linked to new studies where some forms of specific nutrients have been shown to be more harmful (usually the synthetic ones) than others (usually the natural). They updated their monograph in September 2018. Hence, the industry often also looks at Health Canada's conclusions regarding UL values and recommendations regarding additional labeling and extended information.

This will probably also soon lead to a new cross-industry review, which will then become the basis for an industry revision of appropriate information texts on the products. That the Canadian health care agency Health Canada is a credible source, can undeniably be confirmed by the fact that the Swedish Medicines Agency on August 16, 2012, wrote a mutually valid information exchange agreement with them for the time being. This was done through Health Canada's two branches *Health Products and Food Branch* (HPFB) and *Health Environments and Consumer Safety Branch* (HECSB). The agreement facilitates cooperation and collaboration on security issues and other important critical health information. As an example, it can be the exchange of product safety information that could result in regulatory action that needs to be taken simultaneously in Canada and Europe. This form of joint global safety work is something that the Swedish food supplement industry appreciates and advocates.

About the Council for Responsible Nutrition (CRN)

CRN and CRN-I

Founded in 1973, the Council for Responsible Nutrition (CRN), https://www.crnusa.org/ , is a Washington- based and US-leading industry organization. They represent 120+ dietary supplement manufacturers, ingredient suppliers and companies that provide services to these manufacturers and suppliers. In addition to CRN meeting a variety of federal and state regulations surrounding dietary supplements within manufacturing, marketing, quality control and safety, their manufacturer and supplier members also endorse additional voluntary safety guidelines as well as CRN's Code of Ethics.

CRN also has an international organization called the Council for Responsible Nutrition International (CRN-I) https://www.crn-i.org/. CRN-I also works to promote a healthy diet and food safety policy based on science and proven experience. CRN-I's mission is to provide scientific and research-based information to regulators, companies, staff and the media regarding the safety of dietary supplements. CRN-I always holds its symposia in Germany in direct connection with the CCNFSDU conference of the Codex Alimentarius Commission (The Codex Committee on Nutrition and Foods for Special Dietary), which WHO is also involved in. Through a clear presence in Europe, CRN-I can ensure that they can always be up to date with current EU legislation and follow developments of important food and nutrition issues within the EU.

Scientific symposia

CRN-I holds annual science symposia in Germany. In 2018, the symposium was about *Nutrition interventions for healthy aging across the lifespan.* A summary of the symposium is available here https://link.springer.com/article/10.1007/s00394-019-02027-z. It was published in the European Journal of Nutrition.

In October 2019, CRN held a conference in Ireland together with the Federation of European Nutrition Societies (FENS) See https://www.crn-i.org/web/fens-2019-session/ The theme was *From Lifespan to Healthspan: The Role of Nutrition in Healthy Aging.* This is an area that the Swedish Food Agency has also raised in recent years.

On 28 November 2019, the theme of the symposium is: *Roundtable on measuring health promotion. Translating science into policy.* At this symposium of CRN, speakers include from WHO, Dr. Faten Ben Abdelaziz from WHO Dept of Health Promotion, Geneva and Dr Susan Wopereis from TNO was invited to speak. TNO is Europe's oldest risk assessment institute. These representatives from WHO and TNO will hold lectures for delegates from all over the world, where also national food authorities often participate (https://www.crn-i.org/web/2019-dusseldorf/At this CRN-I symposium, CRN-I will present presentations from prominent experts on different ways to scientifically measure health promotion (eng. *health promotion),* as the industry has also noticed that it is an important topic placed within the 2030 agenda for sustainable development of the UN s general assembly (eng. *2030 Agenda for Sustainable Development).* We also welcome the Swedish Food Agency to visit these science symposia where the industry examines the latest research and where they also want to connect the research to more for the planet "sustainable" business. Several Swedish industry suppliers are in the process of conducting a complete review of the entire production chain precisely to promote, among other things, more environmental and sustainable business. See, for example https://www.greatearth.se/hallbarhet where displays its Sustainability report *From product to breakfast table* clearly shows how a company self-critically examines what they are good at, what they are worse at and above all how the company can improve.

That CRN is well recognized internationally can also be confirmed by the fact that high-ranking government officials often visit CRN's international scientific symposia both as speakers and participants. In 2015, a major scientific symposium was held in Kronberg Im Tanaus, Germany. There Ann L. Yaktine (Ph.D., MS, RD) who is the US Director of the Food and Nutrition Board (FNB), *Institute of Medicine (IOM) from Washington, DC* visited and lectured Ann L. Yaktine from IOM was very clear that UL values can never or should be considered as NOAELS or LOAELS, which unfortunately several European authorities seem inclined to do (directly or indirectly) when they want to legislate maximum values. CRN Symposium 2015, had its entire work published in the European Journal of Nutrition where

CRN together with IOM stood as joint authors. Lupton JR, Blumberg JB, L'Abbe M, LeDoux M, Rice HB, von Schacky C, Yaktine A, Griffiths JC. *Nutrient reference value: non-communicable disease endpoints - a conference report.* Eur J Nutr. 2016 Mar;55 Suppl 1:S1-10. https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC4819601/. For ten years in a row, CRN's symposia have been published in globally recognized scientific journals. In the Appendix to this document there is a selection of them.

About CRN's internationally used risk assessment *"Vitamin and mineral Safety"*

Globally most recognized safety documentation

CRN's risk assessment document *Vitamin and Minerals Safety* is the most globally recognized safety documentation and guidance document on safe levels of vitamins and minerals in dietary supplementsavailable. The authors are recognized nutritional toxicologists who consider the results of all major riskassessment institutes around the world (SCF/EFSA, UK EKM, IOM and others). As they also closely follow the international research on nutrients, they regularly adjust their UL recommendations based on the results of the most reliable, new scientific studies that are published on an ongoing basis. Thereis no other organization or authority in the world that presents as up-to-date information on micronutrients as CRN does.

CRN's internationally established and used risk assessment *Vitamin and mineral Safety* has also beencited and referred to by EFSA. The fact that CRN is a trade organization can perhaps lead to some authorities becoming doubtful about the "scientific weight" in CRN's risk assessment and safety documentation. However, the internationally highly regarded and highly regarded American researcherand nutritional toxicologist, Professor John N Hathcock, former senior scientist at the US Food and Drug Administration (FDA), is the lead editor for all three CRN documents. It implies a scientific weight.In addition, CRN's *Vitamin and mineral Safety* is cited and used by EFSA.
The main global trade association of national trade associations, which organizes dietary supplement manufacturers and dietary supplement companies around the world is called the International Alliancefor Dietary Food Supplement Associations (IADSA): http://www.iadsa.org/. All the major pan-Europeanindustry associations are members of IADSA, EHPM (European Federation of Associations of Health Product Manufacturers) and FSE (Food Supplements Europe), of which the Swedish branch organization Svensk Egenvård is a member. IADSA advocates CRN's risk assessment *Vitamin and Mineral Safety* as a governing document for all its members. IADSA supports CRN's risk assessment and always publishes the latest version on its website: https://www.iadsa.org/vitamin-and-mineral-safety-handbook 3rd-edition

Vitamin and Mineral Safety 3rd Edition

Council for Responsible Nutrition
The Science Behind the Supplements

IADSA
International Alliance of Dietary/
Food Supplement Associations

Nutrition scientists and public health policy experts from all parts of the globe are concerned about nutrient deficiencies, but in well-nourished societies there are questions regarding potential harm from over-ingesting nutrients at high and potentially toxic levels. In 1997, the Council for Responsible Nutrition (CRN) addressed the latter by developing science-based recommendations that would acknowledge the highest allowable concentrations for vitamins and minerals based on proven and accepted risk assessment principles, rather than relying on politicized proposals based on recommended daily intakes (RDIs or RDAs) or nutrient reference values (NRVs). This science-based method for Tolerable Upper Intake Levels (ULs) for supplemental sources of vitamins and minerals gained wide interest and acceptance by regulators and scientists internationally. Now in its third edition, "Vitamin and Mineral Safety" is a highly respected and trusted technical resource for dietary supplement and dietary ingredient manufacturers, as well as scientific bodies and regulatory policy makers worldwide. CRN and IADSA are partnering on this project to further corroborate the need for scientifically-based information on how much is too much and to disseminate that science to make appropriate recommendations.

The IADSA Scientific Council would like to thank CRN for this important contribution to further understanding of the safety of vitamins and minerals. This will be a key reference point for policy makers and scientists across the world.

Vitamin and Mineral Safety 3rd Edition

By John N. Hathcock, Ph.D.
with a foreword by James C. Griffiths, Ph.D.

Edited by:
Douglas MacKay, N.D.
Andrea Wong, Ph.D.

Authored/edited by CRN

Council for Responsible Nutrition
The Science Behind the Supplements

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Foreword

In this age of concern for not getting enough essential nutrients, i.e., vitamins and minerals, one might ask what is the utility in providing guidance on the safe upper levels? Other than calories, which many members of Western societies are over- ingesting at toxic levels, morbidity and mortality data do not seem to indicate an epidemic of vitamin and mineral toxicities. In fact, for most people, even in well-fed societies, the greater concern is nutrient deficiency. However, the popularity and usefulness of the previous two editions of "*Vitamin and Mineral Safety*" handbook, authored by John N. Hathcock, Ph.D., for the Council for Responsible Nutrition (CRN) seem to corroborate the need for scientifically-based information on how much is too much. The CRN "upper levels for supplements (ULS)," as well as the key studies and dose levels that are used to derive these values, continue to be requested and cited by scientific organizations and regulators alike. Further, the assumptions, models and data being used by regulatory authorities, including the U.S. Institute of Medicine (IOM) Food and Nutrition Board (FNB) "tolerable upper intake level (UL)," the European Commission Scientific Committee on Food (EC SCF) UL and the U.K. Expert Group on Vitamins and Minerals (UK EVM) "guidance level (GL)," make the current edition of this handbook a continued trusted resource in the international arena.

The argument has been made that Western populations may be over-consuming vitamins and minerals, since much of our basic foodstuffs are fortified, often at levels that equal or approach the current "recommended dietary allowances (RDAs)" or "nutrient reference values (NRVs)." When one adds to that one or more of the plethora of designer or tailored products appealing to the sports-minded, the sensitive demographic, the consumer picking up the latest trend, or the impulse point-of-sale promotion, then the levels of vitamin and mineral consumption may reach levels equal to some of the higher tolerable levels of nutrients that are proposed for specific sub- populations. Addition of a multi-vitamin/mineral on top of this background ingestion does lend credence to the need to have some reliable, nutrient-appropriate, scientific risk assessments for safety.

When one talks of vitamin and mineral toxicity, it is important to note that from a safety perspective there exist "tolerable upper limits" (ULs) which, after a thorough review of the underlying safety information, attempt to put a numerical value on the maximum amount a person could consume without negative effects, based solely on good science. RDAs and NRVs attempt to delineate the amount of a specific nutrient a person should consume at a minimum to derive the expected benefit afforded by such a nutrient, i.e., just enough…but not too much.

Because of the variability associated with the continuum of human consumers, i.e., intakes that are affected by gender, age, idiosyncratic sensitivities, physiological compromises, diets, and a multitude of other mitigating factors (nutritional as well as lifestyle), recommendations for normal intakes are complex and not a one-size-fits-all. This inability to provide the exact quantitative knowledge of what individuals should eat in order to maintain health makes this handbook's approach to providing guidance on the upper levels a plausible and useful reference. It is up

to national, and in the case of Codex, multi-national, regulatory and standard-setting bodies to evaluate the safety data, and the efficacy data, and to set daily intake recommendations in line with the needs of their populations.

This current edition, the 3rd, has the same previously evaluated fourteen vitamins, four minerals, and ten trace elements, albeit re-examined with the addition of appropriate new references as needed. The Introduction describes the CRN Safety Methodology, the Nutrient-Appropriate Scientific Risk-Assessments, the IOM FNB Tolerable Upper Limit Method, the EC SCF UL Values and Proposal for Setting Maximal Amounts ofVitamins and Minerals in Supplements, the UK EVM Risk Assessments, and the overall CRN Approach to Supplement Safety—and these have remained intact from the 2nd edition, as has the comparison of scientifically-based risk assessment methodologies versus the RDA-based upper limit approach. In most cases, there is a wide range of safe intakes between the RDAs (or NRVs) and Upper Levels, giving consumers the ability to achieve levels within these ranges without concern for safety risks. This new edition, currently being updated chapter by chapter, provides updated research and calculations where appropriate, but continues to demonstrate that the question of over-nutrification is a very different analysis than one identifying levels of deficiency.

Methodology

Introduction

Vitamins and minerals are essential for life and health. Supplemental intakes of several nutrients provide clearly established benefits for many people, most obviously for those in specific age and gender groups. Dietary supplements are commonly used in pursuit of these benefits, as well as to provide "nutritional insurance" to those who do not know whether they are consuming recommended amounts of vitamins and minerals. For those consuming supplements for health benefits, it is important to have information about the upper levels of these nutrients that may be safely consumed.

Risk assessment is the accepted approach to evaluate the safety of any substance. The methodologies for risk assessment have been in development for decades and are accepted by the U.S.'s Institute of Medicine (IOM), the European Food Safety Authority (EFSA), and many other authoritative institutions and organizations as well as a large number of national governments.

The first step in risk assessment is to decide which type of data and what sources are relevant to the assessment. For vitamins and minerals, data from both animals and humans are available. In each of these datasets, the most reliable type of data is for overt clinical endpoints rather than for surrogate biochemical markers. Each data source has advantages and disadvantages. Animal data have the advantage of quite extensive and robust datasets and the disadvantage of requiring very uncertain and problematic extrapolation for application to humans. Human data are in many ways the exact opposite—the disadvantage is that types and amounts of human data are quite limited for many nutrients, but the advantage is that little or no extrapolation is needed for decisions that are relevant for humans.

In general, risk assessments for noncarcinogens can be separated into two main types: (1) those that depend on threshold dose-response concepts (the threshold approach) and (2) those that construct probability estimates (the benchmark dose approach). Carcinogenicity is usually treated as a nonthreshold event and for the most part will not be further considered in this document. Risk assessments that use the no observed adverse effect level (NOAEL) or the lowest observed adverse effect level (LOAEL) identify intakes that are either below (NOAEL) or just above (LOAEL) the threshold for adverse effects. The quantitative methodology for risk assessment for unknown effects of nutrients with no observed adverse effects at any intake will be discussed later in this chapter.

Studies of vitamin and mineral safety based on animal data generally use the threshold approach. In contrast, studies of drug, pesticide, and environmental chemical safety often use the benchmark dose (BMD) approach to identify an intake that produces adverse effects in some specified percentage (often 10 percent) of a population. This method constructs a probability basis for evaluating the safety of the substance being tested, but it requires an extensive database that

involves administration of (or exposure to) a range of levels of the test substance at least up to those that produce adverse effects in 10 percent of the population. Such data are almost never available for human subjects, and it would be unethical to perform the experiments to obtain such data.

This third edition of the *Vitamin and Mineral Safety* handbook is based almost exclusively on human data. This methodology is based on the premise, supported by observation, that no matter how robust and extensive an animal dataset may be, the extrapolation to humans carries a very large uncertainty. This document flows from that decision and relies almost entirely on studies using human data only.

During the last several decades, the tolerable upper intake level (UL) has become internationally accepted as the best approach for nutrient safety evaluations. To this end, several international organizations and numerous government agencies have developed or accepted recommendations on UL values. These UL values may be expressed in terms of total dietary intake, supplementary amounts, or both. The UL values have been accepted by the Codex Alimentarius Commission (a food standards organization jointly formed by the UN and the World Health Organization) venture as the only valid basis for regulatory maximum limits on the contents of vitamins and minerals included in supplement products, and the adoption of this approach by Codex is leading many national governments to do likewise. The UL assumes a threshold for adverse effects and is calculated from either a NOAEL or LOAEL.

The Institute of Medicine (IOM), the European Commission's Scientific Committee on Food (EC SCF) and its successor EFSA, the UK's Expert Group on Vitamins and Minerals (EVM), industry groups, and peer-reviewed publications have all reviewed and published risk assessments for one or several of the vitamins and minerals (including trace elements). Regulatory strategies to specify maximums or other guidelines for vitamins and minerals in supplements have been or are being considered by the governments of several countries as well as by the EC, the Association of South East Asian Nations (ASEAN), and the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU). The Codex guidelines are recognized by the World Trade Organization (WTO) as being the most authoritative view on vitamin and mineral safety and therefore have special implications for international trade. The Codex guideline is a method, approved by the Codex Alimentarius Commission, but no quantitative values have yet been identified.

The UL method as defined and implemented by the IOM is an extension of the earlier quantitative methods used in risk assessment for other substances, such as food additives and environmental chemicals. Because of the authoritative character of the IOM publications, the UL risk assessment method for nutrients has gathered widespread support and adoption by other organizations such as the EC SCF/EFSA and the EVM, with some slight modifications. All current UL methods emphasize the concept of nutrient-appropriate, quantitative risk assessment, but disparities in the selection and interpretation of available scientific literature on safety and the approach to handling uncertainty have led to sometimes large differences in the values for various nutrients. The safety evaluation method used in this document utilizes the basic features of these methods but emphasizes the direct evaluation of supplemental intakes, rather than total intakes, when feasible.

Intake Level: Definitions and Applications

There are several types of intake levels used in the literature on vitamin and mineral safety. This section reviews the definitions and differences between two of the most common ones.

Tolerable Upper Intake Level (UL)

In its report on nutrient risk assessment, the IOM states the following:

> "The *Tolerable Upper Intake Level* (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population."

For most nutrients, the UL is defined to apply to the total nutrient intake from all sources, including food, fortified foods, water, and supplements. For a few nutrients, the UL values identified apply only to supplemental sources. For example, the UL for magnesium is based on the amount needed to cause diarrhea or unacceptably loose bowels. This effect is most likely when the magnesium is consumed in a single bolus dose, and therefore the UL applies only to magnesium consumed as supplemental to the normal diet. In addition, bolus dose magnesium compounds are sometimes used as a nonprescription drug (laxative), and the UL could be used as an indicator of the dose likely needed to begin to achieve this effect.

The IOM's interpretation of this definition led them to not establish UL values for nutrients with no established adverse effects, such as vitamin B_1, vitamin B_2, vitamin B_{12}, biotin, pantothenic acid, and trivalent chromium. This interpretation was based on the premise that risk communication would adequately explain why there was no UL value for some nutrients; therefore, in these examples, a UL value would not be useful. Similar decisions have been made by EC SCF/EFSA.

Without defining the procedure or giving it a name, the EVM established guidance levels (GLs) for nutrients without sufficient evidence of adverse effects to establish a safe upper level (SUL), their approximate equivalent to the UL. The EVM expressed less confidence in the numerical values described as GLs compared with those characterized as SUL (equivalent to UL) values. Nonetheless, the interpretation and proposed use of the GL were the same as for the SUL (UL).

A major issue in setting an UL value is determining the size of the uncertainty factor (UF), or safety factor, to apply to the NOAEL or LOAEL. In some instances, credence is given to any hint whatsoever that a risk might occur at an intake below the recognized NOAEL. This point is illustrated in considerable detail in the 2010 IOM publication on vitamin D, as will be described in the Vitamin D chapter of this document.

Highest Observed Intake (HOI) Level

The highest observed intake (HOI) level was established by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) to supply guidelines for those nutrients for which there is no established UL by the IOM or SCF/EFSA. The FAO and WHO adopted the highest observed intake (HOI) under this guideline and definition:

> "The *Highest Observed Intake* is derived only when no adverse health effects have been identified. It is the highest level of intake observed or administered as reported within (a) study(ies) of acceptable quality."

Under these guidelines, a complete risk assessment for nutrients will include the identification of UL values for those nutrients with observed adverse effects and HOI values for those with no known adverse effects. The procedures for UL and HOI are identical—both are risk assessments. If evaluation of the data shows risk, a UL can be set; if no risk is found in the data analysis, an HOI can be identified as the highest intake level with adequate data to establish that adverse effects do not occur at intakes up to that level.

In the previous edition of this document, a concept equivalent to the HOI was termed the observed safe level (OSL). This term was suggested to the FAO/WHO committee but they ultimately adopted the HOI terminology. The basic concepts of the HOI and OSL are identical. Due to the sanction of the HOI term by the FAO/WHO and further adoption in the Codex guideline on nutrient risk analysis (Codex Alimentarius Commission 2010), CRN will use the HOI term in this document.

Sources of Nutrients

To assess the safety of a nutrient, all significant sources of intake must be considered, but this is more important for some nutrients than for others. The relative importance of each source depends on several factors, including the difference between the UL value and either the recommended intake, such as the recommended dietary allowance (RDA), or the typical intakes from commonly consumed foods, as well as the chronic or acute nature of the adverse effect that is the basis of the UL.

For example, an intake equal to the UL for calcium is difficult but can be reached with consistent consumption of multiple servings (but not a single serving) of dairy foods. Moreover, excessive intakes of calcium for short periods do not lead to any acute toxicity, and acute high intakes are not known to lead to chronic adverse effects. Therefore, intakes of calcium that temporarily exceed the UL probably do no harm. In addition, calcium is a *macro*-mineral needed in relatively large amounts (approximately 1 g per day), and therefore a supplement that exceeded the UL (2,000 mg) would be noticeably large (bulky). In safety evaluations of dietary calcium, all sources should be considered: foods, fortified foods, and dietary supplements. In addition, the consumer should be aware that some nonprescription antacids have calcium carbonate as their active ingredient, but these are not known to cause any harm with short-term use.

In contrast to calcium, the UL for vitamin A (preformed vitamin A as retinol or one of its esters) can be exceeded by consistent intakes of liver or other organ meats. Furthermore, retinol is a *micro*-nutrient and the UL is only 3 mg; thus, an excessive intake could be contained in a physically small tablet or capsule. An additional factor is that adverse effects of vitamin A can be chronic (e.g., birth defects after a pregnant woman consumes far too much at a critical early stage). In safety evaluations of vitamin A, all sources of retinol must be considered, but vitamin A activity from

high intakes of carotenes seems not to produce adverse levels of vitamin A. The safety of beta-carotene itself will be discussed separately from vitamin A.

Vitamin B_{12} has no known adverse effects, and the RDA and intakes from foods are in the low microgram range. In contrast, the proposed HOI is 2,000 ∝g. The HOI value could be considered to apply to supplements only, with food supplying amounts that are trivial in a safety evaluation.

Methodologies for Determining Safety Levels: A Comparison

The methodology described in this document and the quantitative values identified are intended to assist in interpreting reports of adverse effects, making a quantitative approach to nutrient safety issues, and establishing policies that will help ensure consumer safety without inappropriate and unneeded restrictions based on current concepts of "nutrient need" or the composition of the most common foods. These scientific concepts and analyses are valid in any country or population with a few adjustments, such as those for nutrient intake levels related to specific local or national dietary composition and patterns. The quantitative values identified for most nutrients have sufficient margins of safety that few adjustments should be necessary. Specifically, the UL definition includes the phrase "almost all individuals in the general population" and therefore it should be valid to apply the UL values to populations with large differences in average body weight.

Some governments and agencies base their safety recommendations on the RDA of the vitamins and minerals under consideration. The sections below review the limitations of using RDA for supplements and the appropriateness of the risk assessment approach.

The Limitations of RDA-Based Methods

Recently some governments have used the RDA to set upper limits for vitamins and minerals in supplement products and have applied drug regulations on products with amounts of nutrients higher than the RDA. Although the RDA may appear to be a convenient marker, there are several problems with using the RDA in this way.

First, RDA-based limits have no scientific validity for identifying supplement safety. The RDA is not defined or identified to describe safety or represent a safety limit for either total or supplemental intake. Risk assessment is the only scientifically valid approach toward identifying supplement maximums. The Codex Alimentarius Commission, for example, has declared that maximums for nutrients in foods offered into international trade must be based primarily on risk assessment.

Second, the application of RDA-based limits to supplements leads to inconsistency in allowable ULs among products. Some countries have applied drug regulations on products with amounts of nutrients higher than the RDA. These regulations are much more stringent than regulations on conventional foods, some of which also contain many multiples of the RDA of certain vitamins. For example, the natural amounts of vitamin B_{12} in conventional foods such as liver and some shellfish can approach 100 ∝g per 100 g serving. The adult RDA for this vitamin is commonly set at approximately 2 to 2.5 ∝g. Thus, these ordinary, conventional foods may contain upward of

40 to 50 multiples of the RDA of vitamin B_{12}. Since there is no known toxicity of oral vitamin B_{12} in humans, RDA-based upper limits serve no useful purpose.

Third, RDA values, or equivalent values such as the population reference intake (PRI), are set on a very similar basis from one country to another, as they represent the consensus of scientific opinion on the nutrient quantities necessary to assure the performance of recognized and essential physiological functions. Thus, the RDA values are geared toward avoiding classical nutrient deficiency signs and symptoms or meeting some nutrient storage level deemed acceptable. Although this approach may be appropriate for helping undernourished populations identify and reach minimum levels, the data and methodology used to establish RDAs or their equivalents is not applicable to establishing safe upper levels.

Fourth, RDA-based limits are not possible for nutrients without established RDA values. For example, no RDA has been set for lutein, lycopene, boron, and many other important substances with nutritive value. These substances have beneficial effects, but the available evidence has not been judged appropriate to identify the RDA. Again, risk assessment is the appropriate methodology to identify safety limits for these important nutrients.

Fifth, drug-based regulations are not appropriate for food items for which Codex Alimentarius has established a standard or guideline. Codex is recognized by the WTO as presumptive international authority on food issues, and WTO agreements require that applied regulatory measures be no more restrictive than necessary to protect the health of consumers. The existence of a Codex guideline is direct evidence that drug-based regulations would be more restrictive than necessary.

Finally, arbitrary limits at or near the RDA may preclude certain benefits of some nutrients. There are currently many documented benefits of nutrient quantities above the RDA. For example, in 2010 the IOM updated the vitamin D RDA, which was based entirely on the skeletal effects. Although there is strong evidence to support several other beneficial effects of this vitamin, the IOM judged the evidence insufficient to serve as the basis for an RDA value. Several of the other functions, such as neuromuscular activities, require greater amounts of vitamin D than needed for the skeletal effects. Therefore, an upper limit based on the RDA might preclude these additional potential benefits. Likewise folic acid, vitamin B_6, and vitamin B_{12} are known to help control plasma homocysteine concentrations. Homocysteine is not yet accepted as a recognized risk factor for heart disease, but there is an ever-increasing body of scientific evidence to support this conclusion. Supplementation with these three vitamins helps to control plasma concentrations of homocysteine and is likely to prove to reduce the risk of heart disease.

All of these facts point to the inappropriateness of using RDA-based limits for supplements. Labeling, not limits, can address proper usage by providing information on contents in the package, noting any benefits related to the RDA or any other measure of benefit and drawing attention to limits imposed on a safety basis, as identified by risk assessment.

The Risk Assessment Method

As indicated earlier, risk assessment is the accepted approach to evaluate the safety of substances. The methodologies for risk assessment are well established and are accepted by the IOM, EFSA, and many other authoritative institutions and organizations. The sections below address some of the recent developments and variations in risk assessment methodologies.

Nutrient Appropriateness.

An important refinement of the risk assessment method is the concept of nutrient-appropriate methods. Before the advent and widespread adoption of the UL, the term *nutrient-appropriate* was used to describe risk assessment for vitamins and minerals. This terminology indicated that not all risk assessment methods are appropriate for the task. Certain risk assessment methods use default UF (sometimes called safety factors) that, although generally considered acceptable for identifying safe intakes of food additives and environmental contaminants, are unacceptably large for application in risk assessment of vitamins and minerals. Application of these factors can lead to identification of "safety limits" that are below the recommended intakes of some nutrients for certain age-gender groups. For example, the acceptable daily intake (ADI) and the reference dose (RfD) used by the U.S. Environmental Protection Agency (EPA) involve arbitrary UFs that calculate zinc safety limits below the RDA for some populations. The benchmark dose is a probability estimate that has not been shown to be useful for human data on vitamins and minerals.

Hazard Identification.

Hazard identification identifies a hazard related to excess consumption of a vitamin or mineral, using the guidelines and procedures described in the UL method. Hazard is preferably determined from human data, but animal data can be used when necessary. Biochemical or other indirect indicators should be judged to represent a hazard only if they are surrogate markers for pathological conditions. If no hazard can be identified, the additional steps in the UL method can be used to identify an HOI value. The criteria for causality should be applied, including the strength of the association, consistency of the association, specificity of the association, dose-response relationship, temporal relationship, biological plausibility, and overall coherence. If a nutrient has more than a single adverse effect, the hazard occurring at the lowest intake is the *critical effect* for this risk assessment to set a UL through the following steps. If no critical effect can be identified, the following steps allow identification of a HOI value. The Codex Alimentarius Commission uses the term *hazard* to refer to a chemical or physical agent even though the scientific publications they reference use the term *hazard* to mean an unacceptably adverse effect that is used as the basis of a policy standard or guideline. This difference in definitions should not cause a problem if it is recognized and taken into account.

Dose-Response Assessment.

This process identifies a NOAEL, from human data if possible. Alternately, if the data are appropriate but do not support a NOAEL, a LOAEL may be established. Animal data are used only if appropriate human data are not available and also to guide the search for a hazard that might be identified in the human data. The uncertainties in the data are assessed and a numerical UF is assigned. It applies to the overall database and the specific data used to establish the NOAEL or LOAEL. Reasonable judgment must be applied to avoid a choice of UF that represents a worst

possible but exceedingly unlikely case. If a LOAEL is used, the UF must be greater than unity (1.0) and should be appropriate for the conversion to a NOAEL. If the NOAEL or LOAEL is identified from animal data, an appropriate UF is assigned to the extrapolation to UL values for humans. If no adverse effects are known, these procedures can be used to identify an HOI.

Deriving the UL through Risk Assessment.

The UL of a vitamin or mineral may be calculated through risk assessment in the following way:

UL = NOAEL | UF (or UL = LOAEL | UF).

If the HOI is based on sparse data, a similar procedure may be used to adjust for uncertainty in that value; however, if the total dataset is extensive (e.g., vitamin B_{12}), the absence of any adverse effect at any intake supports the argument that no correction for uncertainty is needed (i.e., the UF should be 1.0). For all nutrients with large datasets that include multiple clinical trials involving administration of a range of doses, the uncertainties may be addressed by arranging the data in decreasing order of intake and then selecting downward until confidence in the data is sufficient to justify the selection of a NOAEL or HOI with a UF of 1.0. The vitamin D chapter provides such an example.

European Commission Methodology

The Scientific Committee on Food (SCF) was established in 1974 to provide the European Commission with scientific advice on food safety. In 2002, this mandate was transferred to the newly created European Food Safety Authority (EFSA). EFSA provides independent scientific advice and communication on existing and emerging risks.

The SCF/EFSA has published UL values for several vitamins and minerals, using a methodology similar to that developed by the IOM and first published in 1997. The EC's Food Supplements Directive requires the identification of maximum amounts for supplements from risk assessments that at least nominally are derived from total intakes from all sources. No method for deriving the supplement maximums had been published by the EC as of the writing of this book. However, the approach specified in the directive would include the following steps.

Step 1

Step 1 comprises (1) use of the SCF/EFSA UL values identified through a UL method almost identical to the one developed by the IOM and (2) consideration of intakes from other dietary sources.

Step 2

Step 2 takes into "due account" population reference intakes (presumably the RDA or equivalent). However, no method for identifying or applying this due account had been published by the EC as of the writing of this book. Two industry associations have proposed that the RDA could be used along with the ULs and intakes from food sources to calculate a population safety index that separates the nutrients into three categories that demand different levels of regulation and monitoring.

CRN suggests that the population reference intakes referred to in step 2 could also be used to ensure that the risk assessment and identification of other intakes are not excessively conservative, thereby producing a UL and a supplement maximum below the RDA.

The EC proposal would seem to need to identify maximums for supplements plus fortified foods as the differences between the UL and the intakes from other sources. That is, the supplement maximum would be the UL minus the expected intake from conventional foods. The EC has not yet proposed how it will allot the difference between the UL and unfortified intakes into fractions for supplementation and increased fortification, or for the variations in expected intake from one country to another or from one dietary pattern to another. It has been reported that the EC is working on establishing dietary "supplement maximums" by using risk assessments done by EFSA, but has not done so for any of the nutrients. These values with corresponding analysis will be added in future editions when this information becomes available.

EVM Methodology

The risk assessments in the EVM report on vitamin and mineral safety are based on the UL method developed by the IOM, but they assigned the term *safe upper level* (SUL) to the values derived by this method. The EVM stated that for most nutrients, the databases were not sufficient to set an SUL; therefore, a guidance level (GL) was identified. Nonetheless, this GL was often derived and used for overall safety evaluation and discussion of policy options in the same manner as a SUL value. In contrast to CRN's views, the EVM used animal data to identify some SUL values entirely on the basis of high-quality animal data, despite the great uncertainty inherent in quantitative extrapolation from animals to humans.

For a few nutrients, the EVM report takes an additional step toward risk management recommendations for supplements. A safety value based on supplemental intake effects could be logically used to identify maximum contents of products marketed and regulated as supplements. Indeed, most of the SUL and GL values identified by EVM were based on supplemental intakes. In these cases, the EVM uses data on typical intakes from foods along with the supplemental SUL or GL to calculate these values for total intakes. In addition, the EVM explicitly states that it assumes daily consumption throughout the adult lifetime (age 16 years to death), whereas the IOM and SCF/EFSA are not explicit on this issue for all nutrients.

Methodologies for Determining Supplement Safety: A Summary

The premise of this handbook is that the safety evaluation for dietary supplements is best determined on a case-by-case basis through nutrient-appropriate risk assessment, and not as arbitrary multiples of the RDA. Scientific assessments used to identify adequate intake levels (RDAs or their equivalents) are not well suited to identifying hazards. Nutrient-appropriate risk assessment incorporates internationally recognized methodology and is grounded in sound toxicological principles.

Nutrient-appropriate risk assessment requires the safety evaluation to depend on identification of a hazard causally related to excessive intake, assessment of the dose- response relationship for the identified hazard, consideration of uncertainty, and, finally, derivation of a supplementation level that is not only safe but also includes a reasonable margin of safety.

In the identification of a hazard related to excessive consumption of a nutrient, care must be taken to distinguish between effects that represent a genuine hazard and those that are merely a nuisance. For example, the minor gastrointestinal distress that can occur when supplements are taken on an empty stomach should not be considered equivalent to the risk of a serious consequence, such as liver toxicity. Similarly, the dermal "flushing" that can be produced by nicotinic acid is a definite nuisance but does not produce any known pathology. Nonetheless, the IOM, EC SCF/EFSA, and EVM used flushing as the critical effect to establish UL or equivalent values. (For more details, see the Niacin chapter.)

Direct Safety Evaluation of Supplemental Intakes

If appropriate data on supplemental intakes of a specific vitamin or mineral are available, the safety may be determined by risk assessment directly on those data, as illustrated by the EVM report. If the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). For some nutrients, the NOAEL or HOI data are related to the use of supplemental amounts of the vitamin or mineral, above and beyond the amounts contributed by the diet; therefore, such data do not require any additional consideration of amounts contributed by consumption of conventional foods.

The expected intakes of most nutrients from conventional foods do not invalidate this approach for two primary reasons: either (1) intakes are small in comparison with the UL or HOI (e.g., for vitamin B_{12}) or (2) the evidence for the safety of supplemental amounts was developed under conditions in which the amount of the nutrient consumed from conventional foods was well known (e.g., in the case of selenium). These considerations are taken into account in each section on the specific nutrients.

Indirect or Difference Method for Supplement Safety

If appropriate data on supplemental intakes of a vitamin or mineral are not available, a difference procedure, similar to that identified by the EC, may be used. The difference method involves the following:

- Determination of the UL or HOI for total intake from all sources.
- Identification of the usual intakes from conventional foods from appropriate food intake surveys and food composition tables, taking consumption of fortified foods into account. There is considerable controversy about the selection and management of the intake data. Which source of data is appropriate? What percentile of intake should be considered?
- Calculation of the UL for supplements as a difference. This method still leaves an unresolved dispute about how to allocate this difference between supplementation and fortification and how to account for differences in dietary patterns and composition.

Characteristics of CRN's Safety Methodology

The CRN approach as described above includes the basic elements of both the IOM and FAO/WHO methods. For some nutrients, the CRN and EVM methods are the same; for others, CRN and the EVM use different approaches. CRN's principal points of departure from all three of these approaches include the following:

- CRN gives preference to data on effects of *supplemental* intakes, rather than total intakes, thereby eliminating any need to correct for intakes from conventional foods.
- CRN gives stronger preference to use of human data over animal data, thereby avoiding the uncertainties involved in extrapolation between species.
- CRN gives stronger preference to clinical trial data from human studies, if available, but also uses epidemiologic data.
- CRN gives stronger preference to identifying NOAEL values than to LOAEL values, thereby eliminating the uncertainty related to extrapolation downward from the LOAEL.
- CRN considers only effects that represent a true hazard (i.e., risk of impaired health) rather than nuisance effects.
- CRN preferentially uses direct evidence of adverse effects, if available, rather than biochemical markers or other indirect indicators.
- CRN utilizes history of use data, if necessary, to identify an HOI and UL when adverse effects in humans have not been identified for a nutrient. This approach relies on previous human experience when consistent with the scientific evidence that for some nutrients includes an indication of a high order of safety.
- CRN conservatively selects human NOAEL values that justify selection of an UF of 1.0, thereby eliminating the need to select a specific numerical value.
- CRN recognizes that supplement use is an independent choice for the consumer and does not impose increased intake on anyone who does not select it. This contrasts with food fortification programs that require the consumer to carefully scrutinize labels in an effort to obtain or avoid increased intake of nutrients.

References. Codex Alimentarius Commission. 2010. *Procedural Manual of the Codex Alimentarius Commission.* 19th ed. Rome: World Health Organization.

Vitamin D

Introduction

Vitamin D is required in quantities smaller than any other fat-soluble vitamin. The major forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D has been described as a pro-hormone or sunshine-dependent vitamin. Some dietary vitamin D_2 comes from plants, but the largest contribution to dietary intake of vitamin D is the vitamin D_3 in fish liver oils, eggs, milk, and liver. Milk is commonly fortified with 10 µg (400 IU) of vitamin D_3 per quart. Extremely high potency (40,000 to 50,000 IU) products—sold as prescription or sometimes over the counter—often consist of vitamin D_2. Most vitamin D dietary supplements contain vitamin D_3. The conversion of international units to metric weights is extremely simple for both vitamin D_2 and D_3: 1 µg equals 40 IU; 0.025 µg equals 1 IU.

Vitamin D_3 (or D_2) from endogenous production, foods, or vitamin supplements is inert and must undergo two hydroxylation reactions in the body for activation. The first occurs in the liver and the second in the kidneys. The first hydroxylation produces 25-hydroxy vitamin D (25[OH] D) and the second produces the active hormone 1,25-dihydroxy vitamin D (1,25-di[OH]D). Because the plasma half-life of the active form 1,25-di(OH)D is short (approximately 15 hours), the best indicator of vitamin D status is 25-(OH)D (plasma half-life of 15 days or so). Because of these pharmacokinetics, most vitamin D in plasma is present as 25(OH)D, also called calcidiol, and its concentration has become the standard index of vitamin D status. 1,25-di(OH)D (calcitriol), the activated vitamin, regulates intestinal absorption and plasma concentration of calcium. As calcitriol, vitamin D is fundamentally involved in the formation of bone, and so its deficiency can lead to rickets in children or osteoporotic changes in adults.

Bioavailability

Although it can be synthesized in the body with sufficient exposure to sunlight or another ultraviolet (UV) light source, most people are not exposed to such UV light in consistent and sufficient quantities. No extra vitamin D is required when skin exposure to UV light is ample; but without such exposure, a person is completely dependent on ingested vitamin D. The UV component of sunlight converts internally produced 7- dehydrocholesterol naturally present in the skin to cholecalciferol (vitamin D_3) (Life Sciences Research Office [LSRO] 1978; Holick 1999).

Although adequate UV light exposure can provide sufficient vitamin D, many elderly persons have limited sunlight exposure, inadequate dietary sources, and a decreased ability to activate vitamin D, making them susceptible to vitamin D deficiency (Gloth et al. 1995; Holick 1999). Elderly people are likely to have substantially increased needs for dietary vitamin D because of their decreased mobility and exposure to sun and decreased activation in the liver and kidneys.

Thus, the nutritional need for dietary vitamin D depends on the biosynthesis in the skin, which in turn is influenced by time of exposure to sunlight, season (sun intensity and clothing), latitude, skin pigmentation, and the use of sunscreens.

Safety Considerations

The formation of vitamin D in the skin is slowed once dietary vitamin D intakes are sufficient and blood levels of the activated forms are high. Therefore, excess exposure to sunlight does not lead to vitamin D toxicity (Holick 1999; Hathcock et al. 2007).

Dietary vitamin D can, however, produce toxic effects when consumed in very large quantities, especially over an extended period of time. Studies have shown that subjects with abnormally high levels of vitamin D intake can suffer from a wide range of signs and symptoms, from dehydration to permanent mineral deposits in soft tissues, including muscle, heart, kidney, and cartilage. Continued intake of toxic levels can have severe and persistent adverse consequences. The widespread occurrence of vitamin D overdoses in British children just after World War II, caused by consumption of excessively fortified milk, led health professionals to be extremely conservative in estimating safe levels for vitamin D.

Prolonged intake of excess vitamin D may lead to predictable increases in plasma 25- hydroxy vitamin D concentrations (Institute of Medicine [IOM] 2011), and the increase is directly proportional to the vitamin D dose (Barger-Lux et al. 1998). Treatment with vitamin D or 25-hydroxy vitamin D does not generally increase the serum concentrations of the active metabolite (calcitriol, 1-alpha, 25-dihydroxycholecalciferol, or 1,25- dihydroxy vitamin D) (Barger-Lux et al. 1998). Nonetheless, excess vitamin D can have toxic effects, perhaps because of the increases in blood concentrations of 25-hydroxy vitamin D, a form that can overstimulate intestinal absorption of calcium and cause excessive calcium mobilization from bone and hypercalcemia (Norman 1996; Holick 1999). Although the IOM considers hypercalcemia to be the critical effect in vitamin D toxicity, no clinical trials have used levels sufficiently high to produce such high blood levels of calcium. All such evidence comes from reports of anecdotal cases of accidental massive overdoses.

The amount of daily vitamin D ingestion needed to produce adverse effects varies widely. In most adults, daily intake in excess of 50,000 IU (1.25 mg) is needed to produce toxicity (Miller and Hayes 1982). Clinical trials in the last decade or so have found no hypercalcemia in subjects in subject taking 10,000 IU (250 µg) in long-term clinical trials. In certain disease conditions such as sarcoidosis, mycobacterium infections such as tuberculosis, or idiopathic hypercalcemia, toxicity can occur at levels of vitamin D intake lower than those in healthy persons. A causal relationship between excess vitamin D intake and hypercalcemia is unlikely, although people with idiopathic hypercalcemia may be subject to adverse effects of vitamin D at lower intakes than are comfortably tolerated by healthy individuals (Expert Group on Vitamins and Minerals [EVM] 2003).

Body size matters. One study has found that in children of unspecified body weight (probably between 10 and 30 kg), the amount of dietary vitamin D causing adverse effects may be as low

as 2,000 to 4,000 IU (50 to 100 µg) per day. In full-term infants, adverse effects are reported to occur with intakes as low as 1,800 IU (45 µg) per day (Chesney 1989), but no adverse effects occurred in a 6-month study of infants given 1,600 IU per day (Fomon et al. 1966). Numerous reports confirm a variety of adverse effects at very high intakes when vitamin D is used as a drug, whether administered parenterally or in activated forms (Nanji 1985; Goldman and Wheeler 1987; Schwartzman and Franck 1987; Allen and Shah 1992; Boulard et al. 1994; Oymak et al. 1994; Matsukawa et al. 1995). These circumstances do not relate to the usual oral intakes of vitamin D from foods or dietary supplements, and such reports provide no useful information about the safety of dietary sources of vitamin D.

Official Reviews

Expert Group on Vitamins and Minerals (EVM 2003)

The UK's EVM did not find the data sufficiently compelling to identify a NOAEL or a LOAEL. Instead, it set a guidance level of 25 µg, based on studies by Vieth et al. (2001) at 100 µg and Johnson et al. (1980) at 50 µg. The EVM concluded that long-term use of supplements of 25 µg is "well tolerated," but did not establish a safe upper limit.

IOM (2011)

The IOM has established a UL of 100 µg (4,000 IU) vitamin D, based on downward extrapolation from the NOAEL of 250 µg (10,000 IU), as derived from multiple clinical trials in a risk assessment using UL methodology (Hathcock et al. 2007). To take into account uncertainties from emerging data regarding all-cause mortality, chronic disease risk, and falls at serum 25(OH)D levels of approximately 75 to 125 nmol per L, the IOM considered the findings of Heaney et al. (2003) in establishing a UL. In this study, intakes of 5,000 IU vitamin D per day for 160 days resulted in serum 25(OH)D levels that did not exceed 150 nmol per L and serum calcium levels within normal ranges. The UL was set at 20 percent below 5,000 IU (i.e., 4,000 IU) because of the uncertainties surrounding the data and the reliance on one study. The IOM intended "not to determine that certain levels of intake definitively cause harm, but rather to decide whether the emerging data were sufficiently compelling to warrant caution relative to vitamin D intakes."

The IOM approach, however, did not take into account the ample caution built into the NOAEL and the UL method in the peer-reviewed literature (Hathcock et al. 2007). In addition, the IOM examined the data related to several endpoints but based their UL of 4,000 IU on only one of several different adjustments of the data on all-cause mortality in several different age, gender, and disease groups (Visser et al. 2006).

For example, Figure 6-1 of the IOM report graphs the hazard ratio of all-cause mortality against serum 25(OH)D (nmol per L), with adjustments for various health and age factors. All risk curves are high when vitamin D status is low and progress downward to low points as vitamin D status increases. Although the two right side points are equal, there is no hint of a reverse J-shape to the curves—and thus no indication that that vitamin D status up to 82 nmol per L causes any harm.

Figure 6-2 plots relative risk of death in elderly people against baseline serum 25(OH)D, graphed with four different adjustments for factors that could influence health. Only Model 4 shows definite increases in risk as serum 25(OH)D reaches 75+ nmol per L. This model adjusts the data for gender, age, education, chronic disease, serum creatinine concentration, and lifestyle variables including smoking status, alcohol consumption, and physical activity; it adjusts for all these plus frailty indications including physical activity, low serum albumin concentration, and low serum total cholesterol concentration.

Figure 6-3 displays the results of adjustment to the data similar to that in Figure 6-2's Model 4, and there is no increase in risk with serum 25(OH)D concentrations up to 80.3+. There was no discussion of the likelihood of a random "significant" effect when more than 20 adjustments are made to the primary data.

EFSA (2012)

EFSA considered that a daily vitamin D dose of 250 µg per day reflects a NOAEL, based on two studies in which doses of 234 to 275 µg vitamin D3 per day for 8 weeks to approximately 5 months did not result in hypercalcemia in healthy young men (Barger-Lux et al. 1998; Heaney et al. 2003). A UF of 2.5 was applied to account for the variation in the sensitivity of the population to potential adverse effects of long-term vitamin D exposure, the short duration of the studies, as well as the small number and characteristics (healthy young men with minimal sun exposure) of the individuals studied. The UL was therefore estimated to be 100 µg per day.

CRN Recommendations

The traditional—but not data-based—conservatism of vitamin D recommendations is rapidly being corrected to evidence-based assessments. These assessments indicate that larger amounts are now considered safe for most persons.

The data by Heaney and coworkers (2003) indicate that the NOAEL for vitamin D is at least 250 µg (10,000 IU). Thus, from the available data, the LOAEL is greater than 250 µg per day in relation to its hypercalcemic effects. The IOM and EVM estimate vitamin D intakes from all nonsupplement sources to be in the range of 360 IU (9 µg) or less. Many dietary supplements that include vitamin D contain 10 µg (labeled in the U.S. as 400 IU) or less, although some recent formulations contain 600 to 800 IU. There are no reports of adverse effects at these levels of intake. It is noteworthy that hypercalcemia has never been observed in a causal relationship to vitamin D in a randomized clinical trial. All the evidence for vitamin D causing hypercalcemia comes from anecdotal reports of accidental or misinformed consumption of much higher amounts.

With recent clinical trial data in mind, the CRN UL for supplements is identified as 250 µg (10,000 IU), based on the absence of adverse effects at this level of supplementation in clinical trials of sufficient size and duration and under a variety of conditions (Hathcock et al. 2007; IOM 2011). Having confidence in the safety of the 250 µg intake level, CRN does not consider this NOAEL µg

to need adjustment by application of a UF (i.e., a UF of 1.0 is applied). Thus, CRN sets the UL for supplements at 250 µg (10,000 IU).

Quantitative Summary for Vitamin D

CRN UL, supplemental intake	250 µg (10,000 IU)/day
IOM UL, total intake	100 µg (4,000 IU)/day
EFSA UL, total intake	100 µg (4,000 IU)/day
EC supplement maximum	Not determined
EVM, guidance level, supplemental intake	25 µg (1,000 IU)/day

References

Allen SH, Shah JH. 1992. Calcinosis and metastatic calcification due to vitamin D intoxication. *Hormone Res.* 37:68–77.

Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. 1998. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporosis Int.* 8:222–230.

Boulard JC, Hanslik T, Alterescu R, Baglin A. 1994. Hypercalcémie symptomatique après association vitamine D diurétiques thiazidiques: 2 observations chez des femmes dosés [letter]. *La Presse Medicale.* 22:96.

Chesney RW. 1989. Vitamin D: can an upper limit be defined? *J Nutr.* 119:1825–1828.

European Commission, Scientific Committee on Food (EC SCF). 2002. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin E. European Commission, SCF/CS/NUT/UPPERLEV/31 Final Report. Brussels.

European Food Safety Authority (EFSA). 2012. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); scientific opinion on the tolerable upper intake level of vitamin D. *EFSA J.* 10(7):2813.

Expert Group on Vitamins and Minerals (EVM), Committee on Toxicity. 2003. *Safe Upper Levels for Vitamins and Minerals.* London: Food Standards Agency Publications.

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

Gloth FM, Gundberg CM, Hollis BW, Haddad JG, Tobin JD. 1995. Vitamin D deficiency in homebound elderly persons. *JAMA.* 274:1638–1646.

Goldman JM, Wheeler MF. 1987. Vitamin D-induced hypercalcemia [letter]. *Am J Med.* 82:1277.

Hathcock JN, Shao A, Vieth R, Heaney R. 2007. Risk assessment for vitamin D. *Am J Clin Nutr.* 85:6–18.

Heaney RP, Davies KM, Chen TC, et al. 2003. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr.* 77: 204–210.

Holick MF. 1999. Vitamin D. In: Shils ME, Olson JA, Shike M, eds. *Modern Nutrition in Health and Disease.* 8th ed. Philadelphia: Lea and Febiger; 8–25.

Institute of Medicine (IOM). 2011. *Dietary Reference Intakes: Calcium, Vitamin D.* Washington, DC: National Academies Press.

Johnson KR, Jobber J, Stonawski BJ. 1980. Prophylactic vitamin D in the elderly. *Age and Ageing.* 9:121– 127.

Life Sciences Research Office (LSRO), SCOGS: Select Committee on GRAS Substances. 1978. *Evaluation of the Health Aspects of Vitamin D2 and Vitamin D3 as Food Ingredients.* Washington, DC: Federation of American Societies for Experimental Biology (FASEB).

Matsukawa Y, Ikeda E, Hayama T, Nishinarita S, Sawada S, Horie T. 1995. Ectopic calcinosis possibly due to lot (OH) vitamin D_3 in a patient with systemic lupus erythematosus. *Clin Exp Rheumatol.* 13:91–94.

Miller DR, Hayes KC. 1982. Vitamin excess and toxicity. In: Hathcock JN, ed. *Nutritional Toxicology.* Vol. 1. New York: Academic Press; 81–133.

Nanji AA. 1985. Symptomatic hypercalcaemia precipitated by magnesium therapy. *Postgraduate Med J.* 61:47–48.

Norman AW. 1996. Vitamin D. In: Zeigler EE Jr, Filer LJ. *Present Knowledge in Nutrition.* 7th ed. Washington, DC: ILSI Press; 120–129.

Oymak O, Akpolat T, Arik N, Yasavul C, Turgan Q, Caglar S. 1994. Hyperammonemic encephalopathy due to vitamin D induced hypercalcemia in a uremic patient [letter]. *Nephron.* 66:369.

Schwartzman MS, Franck WA. 1987. Vitamin D toxicity complicating the treatment of senile, postmenopausal, and glucocorticoid-induced osteoporosis. *Am J Med.* 82:224–230.

Vieth R, Chan P, MacFarlane GD. 2001. Efficacy and safety of vitamin D_3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr.* 73:288–294.

Visser M, Deeg DJH, Puts MTE, Seidell JC, Lips P. 2006. Low serum concentrations of 25- hydroxyvitamin D in older persons and the risk of nursing home admission. *Am J Clin Nutr.* 84:616–622.

Iodine

Introduction

Iodine is an essential element for animals because it is a constituent of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) (Stanbury 1996; Hetzel and Clugston 1999; Institute of Medicine [IOM] 2001; European Commission, Scientific Committee on Food [EC SCF] 2002). Both iodine deficiency and excess have adverse consequences for the thyroid gland. Iodine deficiency not only results in a syndrome known as iodine deficiency disorder (IDD) but can also, in extreme cases, ultimately result in goiter, the overt manifestation of thyroid gland enlargement stimulated by deficiency of the thyroid hormones. This hormone deficiency leads to many adverse effects in addition to gland enlargement, including congenital and developmental defects, poor growth, and mental retardation. Excess iodine—as well as iodine deficiency—can lead to thyroid dysfunction and elevated thyroid stimulating hormone (TSH) levels (Laurenberg et al. 1998).

Iodine occurs in the atmosphere—by evaporation of seawater and industrial sources (EC SCF 2002). Iodine levels in foods and total diets are dependent on geochemical, soil, and cultural conditions. The major natural food sources of iodine are marine fish, shellfish, marine algae, and sea salt. Milk and dairy products contain relatively high amounts derived from iodinated cattle feed supplements and iodine-containing sterilization products.

In mountainous tropical countries, iodine intakes are higher near the coast and lower in high regions where rain has leached much of the iodine from the soil (EC SCF 2002).

Safety Considerations

Except for rare instances of hypersensitivity to iodine, humans are remarkably tolerant of high intakes of iodine (Stanbury 1996; EC SCF 2002). Although toxic effects are not observed in humans until daily intakes have exceeded 10,000 µg, intakes of 2,000 µg should be regarded as excessive and potentially harmful (Hetzel and Clugston 1999). Residents of coastal regions in some areas of Japan have chronic daily intakes of iodine as high as 50,000 to 80,000 µg. Persons who have not been conditioned by iodine deficiency can maintain normal thyroid size and function when they are consuming several milligrams of dietary iodine per day, but previous deficiency can cause hypersensitivity (Hetzel and Clugston 1999). In such situations, hyperthyroidism and iodine-induced thyroiditis may occur when intakes exceed approximately 200 to 300 µg per day. Healthy adults are much less sensitive to excess iodine.

Official Reviews

IOM (2001)

The IOM concluded that elevated TSH levels associated with high levels of iodine intake constituted the critical indicator for adverse effects of excess iodine in a healthy adult population. For normal persons who have not been conditioned to iodine deficiency, the IOM identified an LOAEL of 1,700 µg per day. A UL of 1,100 µg of iodine from all sources was derived by applying a UF of 1.5 to the LOAEL. The IOM concluded that the adult iodine intake in the U.S. is usually 240 to 300 µg per day from foods plus another 140 µg from dietary supplements.

EC SCF (2002)

The EC SCF utilized iodine intakes of 1,700 and 1,800 µg to establish a UL value, but selected a default UF of 3 to derive a UL of 600 µg per day. The report concluded that dietary intakes are unlikely to exceed 500 µg per day, since the 97.5 percentile intake in European men is 434 µg per day.

Expert Group on Vitamins and Minerals (EVM 2003)

The UK's EVM, deciding that neither human nor animal data were sufficient to set a UL value, set a guidance level instead. From several clinical studies of supplemental iodine (Gardner et al. 1988; Paul et al. 1988; Chow et al. 1991), it was concluded that 500 µg of supplemental iodine "would not be expected to have any significant adverse effects in adults." The EVM identified 430 µg as the 97th percentile intake by adults. This led to establishment of guidance levels of 500 µg for supplemental iodine and 930 µg for total intake from all sources. Notably, the EVM did not cite the article by Laurenberg and coworkers (1998) that was relied upon by the IOM and the EC SCF in their calculations.

CRN Recommendations

CRN identifies its NOAEL for iodine as 500 µg per day for supplements and 1,000 µg for total intake. These values are based on the absence of adverse effects in healthy adults given 500 µg of supplement. Although the experimental subjects consumed diets of unknown composition (Gardner et al. 1988; Paul et al. 1988; Chow et al. 1991), their dietary intake of iodine almost certainly did not exceed 500 µg. The NOAEL for supplemental iodine is justified as the CRN UL because adverse effects occur only at 1,700 µg or higher total intake (the LOAEL identified by the IOM and EC SCF) and because dietary intakes almost certainly will not exceed 500 µg.

Quantitative Summary for Iodine

CRN UL, supplemental intake	500 µg/day
IOM UL, total intake	1,100 µg/day
EC SCF UL, total intake	600 µg/day
EC supplement maximum	Not determined
EVM, guidance level	500 µg/day supplemental; 930 µg/day total intake

References

Chow CC, Phillips DIW, Lazarus JH, et al. 1991. Effect of low dose iodide supplementation on thyroid function in potentially susceptible subjects: Are dietary iodide levels in Britain acceptable? Clin Endocrinol. 34:416–423.

European Commission, Scientific Committee on Food (EC SCF). 2002. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Iodine. European Commission, SCF/CS/NUT/UPPLEV/26 Final Report. Brussels.

Expert Group on Vitamins and Minerals (EVM), Committee on Toxicity. 2003. Safe Upper Levels for Vitamins and Minerals. London: Food Standards Agency Publications.

Gardner DF, Centor RM, Utiger RD. 1988. Effects of low dose oral iodide supplementation on thyroid function in normal men. Clin Endocrinol. 28:283–288.

Hetzel BS, Clugston GA. 1999. Iodine. In: Shils ME, Olson JA, Shike M, eds. Modern Nutrition in Health and Disease. 9th ed. Philadelphia: Lea and Febiger; 253–264.

Institute of Medicine (IOM). 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press.

Laurenberg P, Pedersen KM, Hreidarsson A, Sigfusson N, Iversen E, Knudsen PR. 1998. Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. J Clin Endocrinol Metab. 83:765–769.

Paul T, Meyers B, Witorsch RJ, et al. 1988. The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism. 37:121–124.

Stanbury JB. 1996. Iodine deficiency and iodine deficiency disorders. In: Ziegler EE, Filer LJ, eds. Present Knowledge of Nutrition. 7th ed. Washington, DC: ILSI Press; 378–383.

Acronyms, Abbreviations, Measurements and International Comparison Charts

List of Acronyms and Abbreviations

ADI	acceptable daily intake
AI	acceptable intake
alpha-TE	alpha-tocopherol equivalent
ANS	EFSA Panel on Food Additives and Nutrient Sources Added to Food
AREDS	Age-Related Eye Disease Study
ASEAN	Association of South East Asian Nations
ATBC	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study
BMD	benchmark dose
CARET Study	Carotenoid and Retinol Efficacy Trial
CCNFSDU	Codex Committee on Nutrition and Foods for Special Dietary Uses
CDC	Centers for Disease Control
CHAOS	Cambridge Heart Antioxidant Study
DFE	dietary folate equivalent
DRI	dietary reference intake
EC SCF	European Commission's Scientific Committee on Food
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
EVM	Expert Group on Vitamins and Minerals
FAO	Food and Agriculture Organization of the UN
FASEB	Federation of American Societies for Experimental Biology
FDA	U.S. Food and Drug Administration

FNB	Food and Nutrition Board of the Institute of Medicine
FSA	UK Food Standards Agency
GL	guidance level
HHS	U.S. Department of Health and Human Services
HOI	highest observed intake
HOPE	Heart Outcomes Prevention Evaluation Study
IOM	Institute of Medicine
IRIS	Integrated Risk Information System
IU	international unit
IVACG	International Vitamin A Consultative Group
LOAEL	lowest-observed adverse-effect level
LSRO	Life Sciences Research Office
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NIH	National Institutes of Health
NOAEL	no-observed adverse-effect level
NTP	National Toxicology Program
OSL	observed safe level
PHS	Physicians' Health Study
PRI	population reference intake
PSA	prostate specific antigen
RAE	retinal activity equivalent
RDA	recommended daily allowance
REACT	Roche European American Cataract Trial
RfD	reference dose

RNI	recommended nutrient intake (UK)
SCOGS	Select Committee on GRAS Substances
SOD	superoxide dismutase
SUL	safe upper level
UF	upper level or tolerable upper intake level
UL	upper level or tolerable upper intake level
ULS	upper level for supplements
WAVE	Women‘s Angiographic Vitamin and Estrogen Trial
WHI	Women‘s Health Initiative
WHO	World Health Organization

Units of Measure

µg	microgram
g	gram
kg	kilogram
mg	milligram
ml	milliliter

IADSA

International Alliance of Dietary/
Food Supplement Associations

Council for Responsible Nutrition

1828 L Street, NW
Suite 510
Washington, DC 20036-5114

Telephone: (202) 204-7700
Email: webmaster@crnusa.org
Website: www.crnusa.org

Gridiron Building
One Pancras Square
London, NC1 4AG
United Kingdom

iadsa.org

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INTERNATIONAL

10-YEAR REPORT

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Active participant in CCNFSDU:
CRN-I is a recognized NGO observer at the Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU), actively participating in physical and electronic working groups and providing written and oral expert testimony at Codex meetings. CRN-I is on record for bringing scientifically-grounded considerations on essential nutrients and bioactives.

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