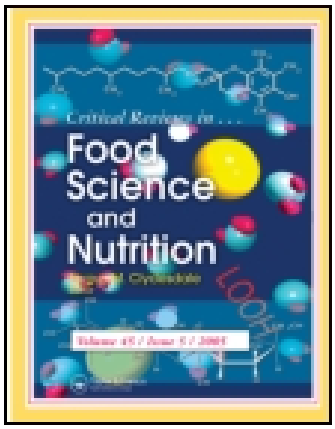

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EURRECA—Estimating Vitamin D Requirements for Deriving Dietary Reference Values

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The time course of the EURRECA from 2008 to 2012, overlapped considerably with the timeframe of the process undertaken by the North American Institute of Medicine (IOM) to revise dietary reference intakes for vitamin D and calcium (published November 2010). Therefore the aims of the vitamin D-related activities in EURRECA were formulated to address knowledge requirements that would complement the activities undertaken by the IOM and provide additional resources for risk assessors and risk management agencies charged with the task of setting dietary reference values for vitamin D. A total of three systematic reviews were carried out. The first, which pre-dated the IOM review process, identified and evaluated existing and novel biomarkers of vitamin D status and confirmed that circulating 25-hydroxyvitamin D (25(OH)D) concentrations is a robust and reliable marker of vitamin D status. The second systematic review conducted a meta-analysis of the dose-response of serum 25(OH)D to vitamin D intake from randomized controlled trials (RCT) among adults to explore the most appropriate model of the vitamin D intake-serum 25(OH)D) relationship to estimate requirements. The third review also carried out a meta-analysis to evaluate evidence of efficacy from RCT using foods fortified with vitamin D, and found they increased circulating 25(OH)D concentrations in a dose-dependent manner but identified a need for stronger data on the efficacy of vitamin D-fortified food on deficiency prevention and potential health outcomes, including adverse effects. Finally, narrative reviews provided estimates of the prevalence of inadequate intakes of vitamin D in adults and children from international dietary surveys, as well as a compilation of research requirements for vitamin D to inform current and future assessments of vitamin D requirements.

[Supplementary materials are available for this article. Go to the publisher's onilne edition of *Critical Reviews in Food Science* and *Nutrion* for the following free supplemental files: Additional text, tables, and figures.]

Keywords Vitamin D requirements, dietary reference values, research gaps, risk assessment framework, EURRECA

BACKGROUND

The major source of vitamin D in humans is cutaneous synthesis of cholecalciferol in the presence of ultraviolet B (UVB) radiation (280–315 nm). However, there are several environmental factors that impede year-round synthesis, such as latitude and prevailing weather conditions, which determine availability of UVB of sufficient intensity to stimulate the conversion of 7-dehydrocholesterol in the skin to precholecalciferol. Personal characteristics, such as skin pigmentation, age, attire, sunscreen, working environment, physical activity, and sun exposure behavior can also prevent or impede vitamin D synthesis. Thus, substantial portions of the world's population, including all who reside at latitudes greater than $\sim 40^{\circ}$, rely on body stores and dietary sources to maintain adequate vitamin D status all year round. Given that body stores are dependent on sun exposure, the importance of vitamin D intake to overall vitamin D status is a corollary of UVB sunshine deficit (Holick, 2008).

Vitamin D status is currently best defined by circulating concentrations of 25-hydroxyvitamin D (25(OH)D), which reflect exposure from both cutaneous synthesis, dietary intake and mobilization of tissue stores, although the relative contributions of each of these sources is unknown and likely to vary considerably according to environmental factors and personal characteristics. These multiple sources of variation create a uniquely complex set of considerations within which dietary requirements for vitamin D must be framed. Further layers of complexity from the

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metabolic interactions between calcium, vitamin D, and phosphate arise as intakes of one impact on requirements for the other. There are fundamental gaps in our understanding of the relationships between circulating 25(OH)D concentrations and health outcomes, which, with the possible exception of indicators of skeletal health, are poorly defined. In certain life-stage groups, e.g., infants, there is very little information on typical circulating 25(OH)D concentrations and associations with dietary intakes of vitamin D. Notwithstanding these complexities and knowledge deficits, among others, several authoritative agencies have either recently completed (North American Institute of Medicine (IOM)) or are undergoing (UK Scientific Advisory Committee on Nutrition (SACN)), Nordic Council of Ministers (NORDEN), European Food Safety Authority (EFSA)) the process of defining dietary reference values (DRVs) for vitamin D.

INTERNATIONAL CONTEXT FOR VITAMIN D ACTIVITIES WITHIN EURRECA

The time course of the EURRECA which ran from 2008 to 2012, overlapped considerably with the timeframe of the process undertaken by the IOM to revise dietary reference intakes (DRIs) for vitamin D and calcium, which were published at the end of 2010 (Institute of Medicine, 2011). Therefore, the aims of the vitamin D-related activities in EURRECA were formulated to address knowledge requirements identified by the NoE, which would complement rather than overlap with the activities undertaken by the IOM.

Following a 10-year period of review of the process of developing DRIs, documented across several reports (Institute of Medicine, 2006; Institute of Medicine, 2007; Institute of Medicine, 2008; Taylor, 2008), the IOM committee approached the task of revising DRIs for calcium and vitamin D using the risk assessment framework, summarized in a recent review [(Cashman and Kiely, 2011); see Fig. 1]. Risk analysis is a process for managing situations where public health monitoring and interventions are expected or needed by analyzing and controlling the risks that may be experienced by a population. The terminology used in risk assessment, such as hazard identification and hazard characterization and even the concept of "risk" in association with nutrient intakes is unfamiliar to nutrition scientists and practitioners (Institute of Medicine, 2007; Institute of Medicine, 2008; Taylor, 2008). However, nutritionists are mindful that nutrient intakes, unlike substances such as drugs or chemical toxicants where there is zero to minimal background exposure, can pose a dual risk, due either to consumption at a level too low to deliver benefit (deficient), or sufficiently high to pose the threat of an adverse effect (toxic). Widespread adoption of the risk assessment framework would encourage international collaboration and potential harmonization of recommended dietary intakes and could potentially include the major authorities as well as expertise from smaller or less developed countries that would not be able to undertake the process independently (Institute of Medicine, 2008). Application of the framework by the IOM expert committee to establishing the Estimated Average Requirement (EAR) for vitamin D and calcium ensured independence and transparency in decision-making, facilitated objectivity throughout the process, and offered flexibility to allow the committee to make scientific judgments when decisions had to be taken on the basis of limited or incomplete data. By ensuring accountability, the framework enables the scientific community to proceed and continue to build knowledge from the point where the expert committee finalized its program of work.

In response to the European Commission [Question No EFSA-Q-2008-463], the EFSA panel on Dietetic products, Nutrition, and Allergies (NDA) published a scientific opinion dealing with the general principles for development and application of DRVs and outlined a process that broadly tracks the risk assessment framework employed by the IOM (EFSA, 2010). The EURRECA NoE, on behalf all EU member states, had originally proposed and used a step-by-step flowchart to further define the process for setting micronutrient requirements, which also broadly follows the risk assessment framework, as outlined in Fig. 1, but also includes additional steps prior to the beginning and leading on from the reporting step, which is where the risk assessment framework stops and risk management takes over. These additional steps include the method of defining the issue in question, which is sometimes but not always defined on behalf of the expert group charged with the task, and translating the scientific outcomes into policy, which is sometimes but not always within the risk management remit. EURRECA has more recently evolved this original flow-chart to a set of stages and activities which replace the original nine Steps in Fig. 1 (Dhonukshe-Rutten et al., 2013; van 't Veer et al., 2013).

The purpose of this review is to provide a summary of the vitamin D-related activities within the EURRECA NoE, which were undertaken in awareness of the scope and magnitude of the concurrent IOM process and with a view to providing additional resources for risk assessors and risk management agencies charged with the task of setting DRVs for vitamin D. Summaries of specific activities are presented in the context of the EURRECA stages and activities, with reference to the corresponding steps in the risk assessment framework.

ACTIVITY 1. DEFINING THE NUTRITION-RELATED HEALTH PROBLEM: WHY VITAMIN D?

In response to growing public concern and uncertainty, the US and Canadian governments requested the IOM to assess the current data on health outcomes associated with calcium and vitamin D and update the DRIs for both nutrients. During the period between 1997, when the last DRIs for calcium and vitamin D were published (Institute of Medicine, 1997), and 2010, when it revised the DRIs for calcium and vitamin D (Institute of Medicine, 2011), the research output in the field

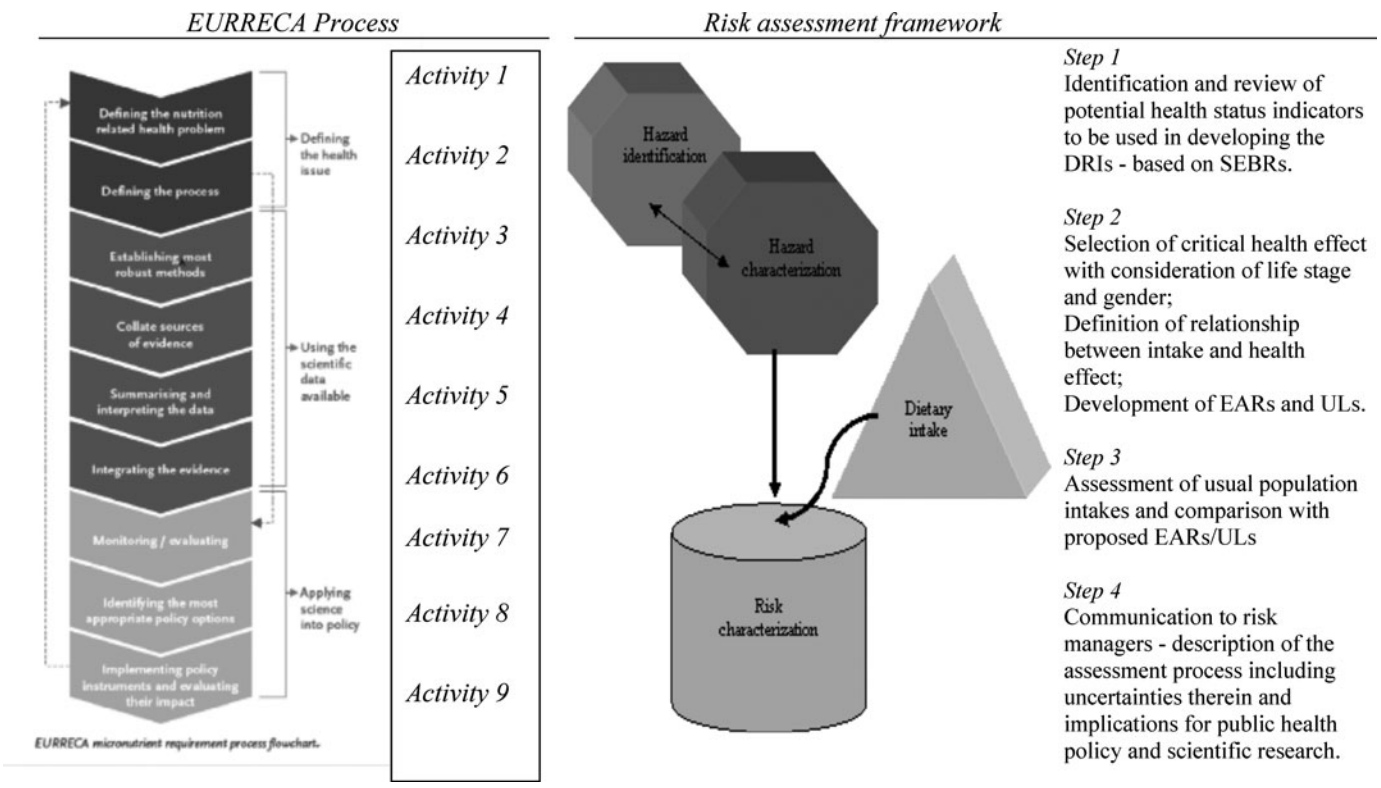

Figure 1 Summary of the risk assessment framework used by the IOM committee for calcium and vitamin D as it maps to the EURRECA process for setting micronutrient requirements (modified from 2,6,7, and www.EURRECA.org).

of vitamin D increased exponentially, yielding a considerable body of data to inform the IOM DRI re-evaluation.

In Europe, the UK DRVs were established in 1991, and the EC DRVs in 1993. The UK DRVs were re-evaluated in 1998 (UK Department of Health, 1998), but were unchanged. In 2010, the SACN agreed to review the data on vitamin D because a substantial amount of evidence has subsequently become available even since their position statement "Update on Vitamin D" in 2007 (Scientific Advisory Committee on Nutrition SACN, 2007), which concluded that there was insufficient evidence, at that time, to amend the existing vitamin D DRV. This exercise is ongoing at present. In 2008, the European Commission requested the EFSA to re-evaluate the 1993 DRVs for micronutrients and it prioritized a number of these including vitamin D. This too is ongoing.

ACTIVITY 2. DEFINING THE PROCESS

The process of establishing DRVs varies by country but the risk assessment framework approach is becoming widely adopted as the ideal approach. The process has been described in detail (Institute of Medicine, 2007; Institute of Medicine, 2008; Taylor, 2008; Institute of Medicine, 2011) and summarized with respect to the approach taken by the IOM expert committee to vitamin D and calcium both in the report (Institute of Medicine, 2006) and on behalf of EURRECA (Cashman and Kiely, 2011). In brief, the risk assessment framework used by the DRI committee on vitamin D and calcium was organized across four steps, summarized in Fig. 1:

Risk assessment framework Step 1: Hazard identification: use of systematic evidence-based reviews (SEBR) to identify, describe and rate potential indicators (including clinical outcomes, biomarkers of effect, functional outcomes and biomarkers of exposure) to be used in developing the DRIs for vitamin D and calcium and to select the critical indicators.

Risk assessment framework Step 2: Hazard characterization: specification of the DRIs on the basis of clarifying the relationship of the nutrient exposure and the reference level of the critical indicator(s), taking into consideration gender, life stage and vulnerable groups.

Risk assessment framework Step 3: Intake assessment: comparison of the EAR and Tolerable Upper Intake Level (UL) values specified in *Risk assessment frameworkStep 2* to habitual population intake data.

Risk assessment framework Step 4: Risk characterization: reporting of each aspect of the approach used, outcomes, decisions, special concerns and uncertainties relevant to risk managers and regulatory bodies charged with public health policy and scientists.

Once reporting is completed, the committee rests and risk management agencies implement the DRIs by reforming public

health policy and implementing education programs as well as addressing research recommendations based on the knowledge gaps and data requirements identified in the report.

The process outlined in the EFSA principles document (EFSA, 2010) describes the background and terms of reference for the expert panel and the general principles for development and application of DRVs, including terminology and definitions, conceptual frameworks, types of data to be used, and application of the data to the assessment of risk of nutrient (in)adequacy.

ACTIVITY 3. ESTABLISHING MOST ROBUST METHODS

In the time running up to the IOM re-evaluation of the DRI for vitamin D and calcium, some investigators had proposed that use of biomarkers or functional end points (such as parathyroid hormone (PTH), calcium absorption, bone resorption, and bone mineral density (BMD)) to more clearly define adequacy of circulating 25(OH)D levels with respect to calcium homeostasis (Heaney, 2004; Weaver and Fleet, 2004; Hollis, 2005; Whiting and Calvo, 2005). It had been suggested that 25(OH)D alone was inadequate to define dietary requirements for vitamin D because optimal levels for health are unknown, so dietary requirements should be on the basis of functional outcome measures (Weaver and Fleet, 2004). Within the EURRECA project we performed a systematic review in 2009 aimed at assessing the usefulness of existing (serum/plasma 25(OH)D and to a lesser extent PTH) and novel functional markers of vitamin D status (calcium absorption, bone turnover, and BMD) in healthy humans as potentially useful in defining dietary requirements (Seamans and Cashman, 2009). In brief, electronic searches were run (on Medline, EMBASE and Cochrane CENTRAL) from inception to 25 September 2007, using a structured search strategy agreed within the EURRECA project. Details of this strategy are published elsewhere (Seamans and Cashman, 2009). Studies to be included were randomized controlled trials (RCTs) of vitamin D (+/− calcium) supplementation in apparently healthy humans, fulfilling predefined inclusion characteristics: (a) vitamin D_3 or $D_2 \leq 50$ μg/d [2000 IU; 1 μg = 40 IU]) administered orally alone or with calcium; (b) reported serum/plasma 25(OH)D following supplementation in at least one intervention group and one control group; (c) no other nutrients (besides calcium), hormones, or pharmaceutical agents co-administered; (d) six weeks minimum duration. To assess calcium absorption, these criteria were relaxed (as otherwise there were insufficient studies). These studies did not have to be RCTs or be of at least six week's duration. Data collection and data synthesis protocols, defined within the EURRECA for the micronutrient status systematic reviews (Hooper et al., 2009), were followed. In total, 2363 titles and abstracts were screened, and 40 studies (36 RCTs and 4 before/after studies [calcium absorption]) were included and of the 36 RCTs, 32 provided extractable data on serum/plasma 25(OH)D data, 16 provided extractable data on serum/plasma PTH data, 6 on bone turnover marker data, and 6 on BMD data.

In summary, the systematic review found that vitamin D supplementation significantly raised circulating 25(OH)D in all but one RCT (see Supplemental Fig. 1). Thus, increased intake of vitamin D lead to significantly increased circulating 25(OH)D irrespective of age-group or gender. There was a high degree of heterogeneity in the response of 25(OH)D to supplementation across the various RCTs but this was not unexpected in light if the variable population groups, doses and supplementation form of vitamin D used in the RCTs. The response of other potential markers of vitamin D status to increased vitamin D status showed more inconsistent responses:

- Vitamin D supplementation (without calcium) significantly reduced circulating PTH, but this was not apparent in the presence of calcium supplementation.
- There was a suggestion that whole body or lumbar spine BMD may be a useful biomarker in older people but not in adolescents.
- Bone turnover markers were not useful biomarkers of vitamin D status.
- The four before/after studies suggested that intestinal calcium absorption may respond to vitamin D status.

Thus, while circulating 25(OH)D was found to be a robust and reliable marker of increased vitamin D status, further research is needed to clarify which population subgroups show responses of PTH, BMD, and/or calcium absorption in response to changes in vitamin D status. While acknowledging some limitations of its use for derivation of DRI for vitamin D (see below under *Identification of research gaps to inform future DRI panels*), the IOM committee chose to use serum 25(OH)D as a functional indicator of vitamin D status on the basis of the evidence in the two Agency for Healthcare Research and Quality (AHRQ) SEBRs (Cranney et al., 2007; Chung et al., 2009). In relation to measurement of serum 25(OH)D, there is a need for its standardization (Institute of Medicine, 2011). Currently, different assays for the determination of serum 25(OH)D levels are in use and they provide disparate results (Binkley et al., 2004; Institute of Medicine, 2011). While the performance has been a concern of analysts and clinicians in the vitamin D field for some time, the role of standard reference materials for 25(OH)D from the National Institute of Standards and Technology (NIST) in the USA and interlaboratory collaboration and quality assurance schemes (such as DEQAS in the UK [www.deqas.org/] and the Vitamin D Standardization Program from the US [www. http://ods.od.nih.gov/pubs/20110302VitDStandardizationFedRegNotice.pdf]) is an important aspect of overcoming the challenges that the assay methodologies present.

ACTIVITY 4. COLLATE SOURCES OF EVIDENCE

This activity links closely to the *Hazard identification* step of the risk assessment framework, whereby SEBR were used

to identify, describe, and rate potential indicators (including clinical outcomes, biomarkers of effect, functional outcomes, and biomarkers of exposure) to be used in developing the DRIs for vitamin D and calcium and to select the critical indicators.

While exploring relationships between nutrient intake—nutrient status—health outcome was a core activity with the EURRECA project, in the case of vitamin D a strategic decision made early on in the project once the NoE became aware of the IOM's planned work in the area of vitamin D, was to not duplicate effort and particularly with a fraction of the resources. Two AHRQ SEBRs were commissioned as part of the preparation for the IOM vitamin D and calcium DRI exercise from the Ottawa (Cranney et al., 2007) and Tufts (Chung et al., 2009) evidence-based practice centers in 2007 and 2009, respectively. The purpose of AHRQ-Ottawa, requested by the Office of Dietary Supplements, National Institutes of Health (NIH-ODS) and conducted by the University of Ottawa Evidence-Based Practice Center was to review and synthesize the published literature on five key questions:

1. Are specific circulating concentrations of 25(OH)D associated with bone health outcomes in:
   a. Children: rickets, BMD, bone mineral content (BMC), fractures, or PTH?
   b. Women of reproductive age (including pregnant and lactating women): BMD, calcaneal ultrasound, fractures, PTH?
   c. Elderly men and postmenopausal women: BMD, fractures, falls?
2. Do food fortification, sun exposure, and/or vitamin D supplementation affect circulating concentrations of 25(OH)D?
3. What is the evidence regarding the effect of supplemental doses of vitamin D on bone mineral density and fracture or fall risk and does this vary with age groups, ethnicity, body mass index, or geography?
4. Is there a level of sunlight exposure that is sufficient to maintain adequate vitamin D levels but does not increase the risk of nonmelanoma or melanoma skin cancer?
5. Does intake of vitamin D above current reference intakes lead to toxicities (e.g., hypercalcaemia, hypercalciuria, and calcification of soft tissue or major organs)?

The review focused on electronic searches of the medical literature to identify publications addressing the aforementioned questions. Out of 9150 citations, 112 RCTs, 19 prospective cohorts, 30 case-control studies, and 6 before-after studies were systematically reviewed, and each was rated on quality and used to assess the strength of evidence for each outcome. The report in its entirety, including appendices and evidence tables, can be accessed and viewed at http://archive.ahrq.gov/downloads/pub/evidence/pdf/vitamind/vitad.pdf.

The purpose of the AHRQ-Tufts SEBR, also requested by the NIH-ODS and the Public Health Agency of Canada, Health Canada, and the Food and Drug Administration and conducted by the Tufts Evidence-Based Practice Center, was to answer key scientific questions on how dietary vitamin D and calcium intake effect health (bone but also nonskeletal) outcomes. The key questions addressed in AHRQ-Tufts are as follows:

1. What is the effect of vitamin D, calcium, or combined vitamin D and calcium intakes on clinical outcomes, including growth, cardiovascular diseases, body weight outcomes, cancer, immune function, pregnancy or birth outcomes, mortality, fracture, renal outcomes, and soft tissue calcification?
2. What is the effect of vitamin D, calcium, or combined vitamin D and calcium intakes on surrogate or intermediate outcomes, such as hypertension, blood pressure, and bone mineral density?
3. What is the association between serum 25(OH)D concentrations or calcium balance and clinical outcomes?
4. What is the effect of vitamin D or combined vitamin D and calcium intakes on serum 25(OH)D concentrations?
5. What is the association between serum 25(OH)D concentrations and surrogate or intermediate outcomes?

The AHRQ-Tufts review focused on electronic searches of the medical literature (1969–April 2009) to identify publications addressing the aforementioned questions. One hundred and sixty-five primary articles and 11 systematic reviews that incorporated more than 200 additional primary articles were systematically reviewed, and each was rated on quality and used to assess the strength of evidence for each outcome. The report in its entirety, including appendices and evidence tables, can be accessed and viewed at http://www.ahrq.gov/clinic/tp/vitadcaltp.htm.

The IOM committee used these SEBRs to identify, describe, and rate potential indicators (including clinical outcomes, biomarkers of effect, functional outcomes, and biomarkers of exposure) to be used in developing the DRIs for vitamin D and calcium and to select the critical indicators.

ACTIVITY 5. SUMMARIZING AND INTERPRETING THE DATA AND ACTIVITY 6. INTEGRATING THE EVIDENCE

These activities link closely to the *Hazard characterization* step of the risk assessment framework, in which there is the specification of the DRIs on the basis of clarifying the relationship of the nutrient exposure and the reference level of the critical indicator(s), taking into consideration gender, life stage, and vulnerable groups.

Devising nutrient recommendations for population intakes relies on scientific analysis and judgment of data that exist within a specified timeframe and is an iterative process. The amount of research data generated since 1997 advanced the knowledge base in vitamin D to the extent that for the first time the DRI committee had sufficient evidence on which to base EARs. Taking indicators of bone health, including rickets and osteomalacia, bone mineral density and calcium absorption, for which

there was sufficient evidence to provide a *reasonable and supportable basis* for DRI development, the committee proposed a serum 25(OH)D level of 40 nmol/L as the median value above which approximately half the population might meet its vitamin D requirement (and below which half might not; which the committee called the EAR-like concentration) and 50 nmol/L as its estimate of the serum 25(OH)D level that would meet the requirement of nearly all (i.e., 97.5%) "normal healthy persons" (which the committee called the Recommended Dietary Allowance (RDA)-like concentration) (Institute of Medicine, 2011). Data from randomized placebo-controlled studies that reported the dose-response of serum 25(OH)D to total intake of vitamin D in northern latitudes in Europe and Antarctica during their respective winter seasons and in conditions of minimal UVB radiation enabled the committee to specify DRI for vitamin D. The EAR for all persons above 12 months is 10 μg/d (400 IU) and the RDA is 15 μg/d (600 IU) up to the age of 70 years, and 20 μg/d (800 IU) thereafter. In the absence of sufficient data to define reference intervals, an Adequate Intake (AI) value for infants up to 12 months of 10 μg/d was indicated. The UL was revised upwards to 100 μg/d (4000 IU) in persons over the age of 9 years, with lower levels for younger children down to 25 μg/d (1000 IU) in infants up to 6 months.

The DRI committee, however, highlighted that the regression analysis used to define the dose–response relationship had several assumptions and/or uncertainties, which may have implications for its DRI estimates: lack of age effect on the response of serum/plasma 25(OH)D to total vitamin D intake, large inter-study variance, and uncertainties surrounding the predicted confidence intervals (CIs) of the vitamin D intake-status relationship.

To inform the current re-evaluations of vitamin D requirements in Europe, within the EURRECA project we conducted a systematic review of vitamin D intake-status, in which we aimed to identify relevant RCTs with vitamin D in children/adolescents, adults, and older adults and then apply metaregression to the extracted data, as well as using individual data from four recent vitamin D RCTs in Northern European adolescents, adults, and elderly (Cashman et al., 2008; Cashman et al., 2009; Cashman et al., 2011b) during winter, to test the appropriateness of some of the assumptions used and outcomes of the IOM committee's regression analysis of the vitamin D intake-status relationship (Cashman et al., 2011a).

The methodology we used in the meta-analyses and metaregression followed the general methodology used in the EURRECA series of systematic reviews in relation to markers of nutrient status (Hooper et al., 2009) and in our recent systematic review of existing and potentially novel functional markers of vitamin D status (Seamans and Cashman, 2009) described in Activity 3. The review included an updated structured search on Ovid MEDLINE from our previous review, rigorous inclusion/exclusion criteria, data extraction, meta-analysis, and metaregression (using different model constructs). In particular, priority was given to data from winter-based RCTs at $>49.5^{\circ}$; 12 of these were identified, in comparison with 9 by the IOM.

The DRI committee used a collection of bone health outcome (calcium absorption, bone mineral density, risk of rickets and osteomalacia) to define the EAR-like serum 25(OH)D concentration (40 nmol/L) to which 30% was added to set 50 nmol/L as concentration covering the needs of nearly all in the population. It is possible that European agencies briefed with the task of re-evaluation of DRVs for vitamin D may decide to use a serum 25(OH)D target concentration other than 50 nmol/L. For example, should an European agency decide to use risk of rickets or osteomalacia as the health outcome used to establish their RDA or equivalent DRV in preference to the more holistic approach used by the DRI, they may well use 30 or 40 nmol/L (Institute of Medicine, 2011) as the target concentration upon which to base their intake requirement value. The IOM DRI committee fit a curvilinear relationship between vitamin D intake-serum 25(OH)D (using a natural logarithm) and this was done with a target serum 25(OH)D concentration of 50 nmol/L in mind. Our review showed that if one uses 40 nmol/L as the target concentration, the RDA would be only 111 IU/d. This is because the curvilinear fit has a very rapid drop in serum 25(OH)D with decreasing vitamin D intake. Others, including ourselves (Seamans and Cashman, 2009), have reported serum 25(OH)D response estimates to vitamin D supplementation from RCTs based on a linear analysis (Heaney et al., 2003; Cranney et al., 2007). Therefore, in our review, for comparative purposes we also explored the impact of using a linear relationship between vitamin D intake and serum 25(OH)D. Inputting an intake of 600 IU/d (the RDA) in the predictive regression equation, the predicted serum 25(OH)D concentration was 52 nmol/L—similar to that from the curvilinear model. The vitamin D intake required to achieve a serum 25(OH)D concentration of 40 nmol/L was predicted to be 200 IU/d compared to the 111 IU/d (see Fig. 2). Clearly the shape of the relationship has an important bearing on the predicted RDA estimates for vitamin D.

The DRI committee draw attention to differences in the response of serum 25(OH)D depending on whether the dose was above or below 1000 IU/d within the studies they considered—a steeper rise in serum 25(OH)D levels when vitamin D dosing was less than 1000 IU/d, whereas a slower, more flattened response was evident when doses of 1,000 IU/d or higher were administered, regardless of baseline intakes or serum 25(OH)D levels (Institute of Medicine, 2011). It was this apparent nonlinear response of serum 25(OH)D above baseline levels to doses of vitamin D for all age-groups, which lead them to use the curvilinear Ln model (Institute of Medicine, 2011). Aloia et al. (2008) recently showed using a spline-fit approach to the response slope estimates from 64 RCTs that the response slope becomes constant at a dose of 35 μg/d (1400 IU/d). The choice of whether a curvilinear (which accounts for blunted response of serum 25(OH)D at intakes above 1000–1400 IU/d) versus linear fit (intakes up to 1000–1400 IU/d) in this relationship should be informed by habitual intakes of vitamin D in the population(s) in the region for which the DRV are being established. For Europe, intakes of vitamin D at the top of the distribution are less than

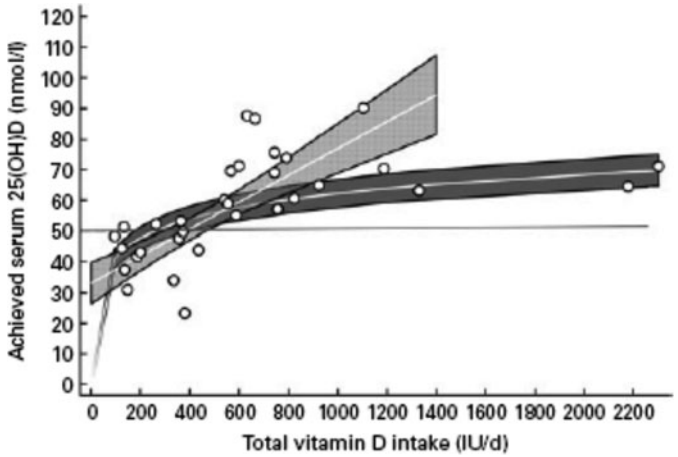

Figure 2 Response of serum 25-hydroxyvitamin D (25(OH)D) level to total intake of vitamin D in northern latitudes in Europe (>49·5°N) and Antarctica (78°S) during their respective winter seasons, when effective sun exposure for endogenous vitamin D synthesis is minimal. Mean responses (white lines) with 95% CI using a weighted linear metaregression model following either a natural logarithmic transformation (dark gray shading, curvilinear model) or no transformation (pale gray shading, linear model) of total vitamin D intake data. The maximum total intake data point in the linear model was 1400 IU/d. A line is plotted at 50 nmol/L serum 25(OH)D for illustrative purposes. [See (Cashman et al., 2011a) for full details.]

600 IU/d (Flynn et al., 2009); therefore, use of a model which provides a range up to 1000 IU vitamin D/d seems appropriate and could be a linear model.

An additional consideration highlighted by this EURRECA review was the fact that the IOM regression model used CIs in its meta-regression analyses to provide some estimate of the variability around the fitted response line, but did not provide any estimate of the variability between individuals in terms of dietary intake of vitamin D needed to achieve a serum 25(OH)D concentration (i.e., an estimate of the range). The use of the lower limit CI in the metaregression analysis gives 95% surety that the average serum 25(OH)D level in the adult population is above 50 nmol/L at an intake of 544 IU/d, whereas our previous findings from our RCTs, which built in variability on the fitted regression line, also took account of inter-individual variability on intake required to reach a chosen serum 25(OH)D cut-off. When we performed a meta-regression analyses which included the 95% range (and thus variability between individuals), the dietary estimate for vitamin D was about 1000 IU/d to maintain serum 25(OH)D above 50 nmol/L for 97.5% of adults and older adults which agreed well with our experimental data from RCT (Cashman et al., 2008; Cashman et al., 2009).

While the relation of serum 25(OH)D to vitamin D intake is critical to the establishment of dietary requirements, the model used to describe this relationship needs to be considered carefully and be appropriate to the purpose of setting new recommendations for vitamin D. In particular, the model should reflect the typical range of vitamin D intakes in the population(s) for which the dietary requirements are being established.

ACTIVITY 7. MONITORING/EVALUATING

This activity links closely to the *Intake assessment* step of the risk assessment framework, in which the EAR (and UL) values specified in *Hazard characterization* are compared with habitual population intake data. We provided an updated summary of vitamin D intakes and sources in adults and children, focusing on data from North America and Europe, to evaluate the evidence that intakes of vitamin D are inadequate and to explore the impact of various strategies to increase intakes (Kiely and Black, 2012). Foods containing naturally occurring vitamin D are limited and many are not consumed on a regular basis. Natural sources include oily fish, meat, dairy, egg yolk and mushrooms. Depending on legislation, some foods are fortified with vitamin D, including milk, yoghurt, spreads, cheese, juices, breads, and breakfast cereal. In addition, vitamin D is available as a dietary supplement, either as vitamin D_2 or vitamin D_3.

Bailey and colleagues at the NIH-ODS described vitamin D intake from foods and supplements from the National Health and Nutrition Examination Survey (NHANES 2005–2006) (Bailey et al., 2010). The rate of use of vitamin D-containing supplements varied from 21% in young women to >40% in older adults. Mean daily vitamin D intake from food alone ranged from 3.6 μg in women aged 19–30 years to 5.6 μg in men over 70 years; intake from all sources ranged from $\sim$ 6 to 11 μg/d. Less than 7% of adults over the age of 51 years had an intake greater than 10 μg/d (the AI for vitamin D in 51–70 year olds at the time) from food; this was <1% in older women. However, when dietary supplements were included, the prevalence of meeting the AI increased in all age groups. Notwithstanding that 49% of them took supplemental vitamin D, adults $\geq$71 years were at highest risk of not meeting their AI and 77% had average intakes < 15 μg/d. Further analysis in the United States' population examined contributions of micronutrients to usual intakes derived from all sources (naturally occurring, fortified and dietary supplements) based on NHANES 2003–2006 data (Fulgoni, III et al., 2011). The median vitamin D intake among adults was 1.8 μg/d from naturally occurring sources (base diet). When fortified foods were included, the median increased to 3.9 μg, and to 5.8 μg when dietary supplements were included. Mean intakes were higher than the median values, indicating the skewed distribution of vitamin D intakes, particularly when contributions from fortified and supplemental sources are considered. The prevalence of inadequate intakes, determined by the percentage of the EAR of <10 μg/d, was 68% overall when intakes were calculated from all sources including supplements. Exclusion of supplemental vitamin D and fortified foods increased the prevalence of not meeting the EAR to 100%.

In Canada, vitamin D intakes from food sources were calculated from data reported in the 2004 Canadian Community Health Survey Cycle 2.2 (CCHS 2.2) (Vatanparast et al., 2010). Median intakes ranged from 3.5 to 4.5 μg in women and 5.3 to 5.7 μg in men. In adults aged 51–70 years, 80% of men and 92% of women had intakes below the EAR and 95% of adults over 70 years failed to meet the EAR for vitamin D of 15 μg/d from

foods. Fortified milk products and meat contributed 49 and 31% of dietary vitamin D, respectively. Ultimately, despite mandatory fortification of milk, the majority of Canadians consumed less than the EAR for vitamin D. The authors encouraged increasing the range of foods to which vitamin D can be lawfully added and wider practice of voluntary fortification.

Food consumption surveys throughout Europe have consistently reported low vitamin D intakes in the UK (Whitton et al., 2011; Department of Health, 2012), Ireland (Hill et al., 2004), Denmark (Tetens et al., 2011), France (Dufour et al., 2010), and Finland (Hirvonen et al., 2007; Pietinen et al., 2010). Data from the first year of the rolling program of the UK National Diet and Nutrition Survey (NDNS 2008–2009) showed a median daily vitamin D intake of 2.8 μg in men and 2.3 μg in women from food sources (including fortified foods) (Whitton et al., 2011). Intakes were slightly lower among males than previous NDNS data and similar in females. Intakes from supplements were not included in the paper by Whitton et al. (2011) but are included in the summary report by the UK Department of Health (2012), which merged data from the 2008–2009 and 2009–2010 rolling surveys: median intakes ranged from 2.1 μg in women below 65 years to 3.2 μg in men over 65 years.

The mean daily intake of vitamin D from food sources only in Irish adults from the North/South Ireland Food Consumption Survey was estimated at 3.2 μg (Hill et al., 2004). Despite a low prevalence of consumption of vitamin D-containing supplements at 15%, the contribution from supplements increased the overall mean intake to 4.2 μg/d. Vitamin D-containing supplement users had intakes of 7.1 μg/d. Similar intakes were reported among Danish men and women aged 18–49 years who used supplements, at 7.8 and 7.6 μd/d, respectively, compared with 2.7 and 2.0 μg/d in nonusers (Tetens et al., 2011). Intakes from food only in supplement users were 2.8 and 2.1 μg/d in men and women, respectively, indicating that differences in vitamin D intakes between users and nonusers were attributable to the contribution from supplements and not to any differences in dietary habits. This point is worth noting: intakes of vitamin D, unlike many other nutrients, are not necessarily higher in those who have a healthier diet per se, but are likely to be higher in those who make a conscious effort to eat healthily due to the use of dietary supplements, which is seen as a health-promoting behavior. The report by Tetens and colleagues (2011) showed that Danish adults who reported a stronger "intention to eat healthy" were more likely to be users of dietary supplements.

In an analysis of the second French Individual and National Study on Food Consumption (2006–2007), Dufour et al. (2010) assessed the safety of various mathematical models developed to propose maximum safe levels of nutrient addition to fortified foods and dietary supplements. They reported median vitamin D intakes from food sources (excluding fortification) of 2.1 μg/d among adults aged 18–79 years. In Finland, fortification of butter/spreads and milk products has been widespread since 2003. Using FINDIET 2002, Hirvonen et al. (2007) reported median intakes of almost 5 μg/d in men and women from all sources, and recommended a refined fortification model to increase intakes. In the meantime, the updated FINDIET 2007 reported average intakes of 5.2 and 7.1 μg/d among men and women, respectively, suggesting that the fortification policy implemented in 2003 produced a slight increase in mean vitamin D intakes, at least in men (Pietinen et al., 2010).

Jenab et al. (2009) described vitamin D intakes among 35–74 year old adults in 10 countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Mean daily vitamin D intakes from food sources only were 5.5 and 3.6 μg/d among men and women with a pronounced North-South gradient. In a further investigation of the geographical variation in nutrient intakes, Freisling et al. (2010) observed lowest vitamin D intakes in Italy and highest in Sweden and Norway, with most other countries within ~25% of the EPIC mean (reported here as 4.8 and 3.3 μg/d in men and women, respectively). As part of EURRECA, nutrient intake data were obtained from the European Nutrition and Health Report II, and summarized according to participating countries (Vinas et al., 2011). Intakes of vitamin D among men were lowest in Spain (<2 μg), between 3 and 4 μg in most other countries (UK, Germany, Denmark, Ireland, Netherlands, Italy, Portugal) and 6, 7, and 11 μg/d in Sweden, Finland and Norway, respectively. Intakes among women were lower in almost all countries. Similarly with most micronutrients, reported intakes of vitamin D in national surveys and large cohort studies (notably EPIC, which uses a standardized dietary assessment method and food composition database) vary according to country-specific fortification practices, sex, and age.

Children

The report by Bailey et al. (2010) also described vitamin D intakes from food and supplements in boys and girls in different age groups using NHANES 2003–2006 data. Mean vitamin D intakes in boys aged 4–18 years were 5.7–6.4 μg from food and 6.9–9.3 μg from all sources. In girls of the same age, intakes ranged from 3.8–5.5 μg from food and 5–7.9 μg/d from all sources. The highest prevalence (80%) of meeting the AI of 5 μg at that time was among boys aged 4–8 years and the lowest prevalence (32%) was among girls aged 14–18 years. Prevalence of D-containing supplement use ranged from 16% in 14–18 year old boys to 43% in 4–8 year olds and from 27% of 14–18 year old girls to 34% of 1–8 year olds. Further analysis of the same survey (Fulgoni, III et al., 2011), which disaggregated the contribution from the base diet, fortification, and supplements, showed that in all children and adolescents aged 2–18 years ($n = 7250$), mean intake of vitamin D from naturally occurring foods was 1.7 μg/d, which increased to 6.1 μg when fortification was included and to 8.3 μg when supplements were added. The percentage of 2–18 year olds with usual intakes below the EAR of 10 μg was 100% from the base diet, decreasing to 87% when fortified foods were included and further to 73% with the addition of the contribution from supplements.

The Canadian CCHS 2.2 reported vitamin D intakes from food sources only in children (Vatanparast et al., 2010) that

were very similar to adults. Boys and girls aged 1–8 years had mean intakes of 6.2 μg/d and more than 60% were achieving >5 μg. Boys aged 9–18 years had higher intakes (7.3 μg/d) than all other sex and age groups. Reflecting the vitamin D food fortification policy in Canada, where milk and margarine are fortified on a mandatory basis, milk products contributed 75% of dietary vitamin D intake in children aged 1–8 years. Based on food records from four consecutive days, data from the NDNS rolling program (Whitton et al., 2011; Department of Health, 2012) showed that the mean daily vitamin D intake from food sources in the UK was between 1.9 and 2.4 μg in boys and girls aged 4–18 years. When supplements were included, intakes in boys increased to 2.7 and 2.5 μg in ages 4–10 years and 11–18 years, respectively, and intakes in girls increased to 2.4 and 2.2 μg in ages 4–10 and 11–18 years, respectively.

Verkaik-Kloosterman et al. (2011) estimated habitual vitamin D intake from food and supplements among young children using data from the Dutch food consumption survey. From food sources only, mean vitamin D intake was 1.8 and 2 μg/d in 2–3 and 4–6 year olds, respectively. Vitamin D intakes in users of dietary supplements were 5.6 μg/d in 2–3 year olds and 3.7 μg/d in 4–6 year olds. Similarly with the trends observed in adults in Denmark (Tetens et al., 2011), vitamin D intakes from food sources only were comparable between users and nonusers of dietary supplements. Total vitamin D intakes were below the EAR of 10 μg/d in almost everyone, with the exception of ~5% of supplement users. Similar data were reported in Flemish preschoolers (Huybrechts et al., 2011): mean (95% CI) intakes of vitamin D from food only were 2.0 (1.8, 2.2) μg/d in 2.5 to 6.5 year olds. Intakes of vitamin D decreased with age and only 4% of 2–3 year olds and 1% of children 4–6 years had intakes of vitamin D at the EAR of 10μg/d from food.

The European Nutrition and Health Report (Elmadfa et al., 2009) summarized vitamin D intake in children and teens from a variety of sources. Data showed an interval of intakes from 1.2–6.5 μg in children and teenagers aged 4–14 years, depending on country, sex, and age group. Highest intakes of vitamin D in children were reported in the Nordic countries, where children between 10 and 14 years had intakes of 5.1–6.8 μg/d. In adolescents aged 15–18 years in Denmark, Germany, Italy, Norway, Poland, Slovenia, Spain, and the Netherlands, mean intakes ranged from 1.5 μg/d in Spanish girls to 7.5 μg/d in Norwegian boys, respectively. Intakes were <5 μg/d among adolescents of all ages in every participating country except for Norwegian boys and girls and Polish boys. Vitamin D intakes from food sources reported by the CSIRO in Australian children (CSIRO, 2008) were 2.8–4 μg/d, with the lowest intakes in girls and the highest in adolescent boys. In Ireland, the national food surveys in children (NCFS) (Irish Universities Nutrition Alliance, 2012b) and teens (NTFS) (Irish Universities Nutrition Alliance, 2012a) reported mean vitamin D intakes from food sources of 1.5 μg in children aged 5–12 years and 2.4 and 1.8 μg in boys and girls aged 13–17 years, respectively. Almost all (98%) children and teens had intakes below the EAR of 10 μg/d, and although supplement users had higher intakes of vitamin D, at 6–7 μg/d, 90% of users had inadequate intakes.

Data from European national dietary and food consumption surveys use various methods of data collection, analysis, and reporting, making meaningful comparison problematic. Nonetheless, with regard to vitamin D, it appears from these data that the main source of variation in intake estimates across the population >2 years is the contribution from nutritional supplements. Surveys that do not include supplemental vitamin D omit the largest source of vitamin D in supplement users, which accounts for up to 50% of the adult population and a variable percentage of children depending on age; the prevalence of supplement use decreases in older children (Irish Universities Nutrition Alliance, 2012b). This has implications for assessing the public health significance of low vitamin D intakes if intake estimates are derived from food sources only, as higher total intakes increase circulating 25(OH)D concentrations. In an analysis of the role of vitamin D-containing supplements in increasing the prevalence of Canadians meeting DRI thresholds of circulating 25(OH)D concentrations of 30, 40, and 50 nmol/L (Institute of Medicine, 2011), Whiting et al. (2011) reported that supplement users aged 6–79 years, who represented 31% of the population surveyed during the 2007–2009 Canadian Health Measures Survey-Cycle I, had not only higher 25(OH)D concentrations than nonusers but also a much lower prevalence of serum 25(OH)D <50 nmol/L (19 vs. 37%). The data summarized here show that the current availability of vitamin D in the food supply (excluding the contribution from supplements, which is a matter of personal choice) is insufficient to reduce the prevalence of the population with intakes of vitamin D from food sources below the EAR of 10 μg/d.

In summary, our analysis showed that usual vitamin D intakes are higher in the US and Canada than most of Europe, with the exception of the Nordic countries. Intakes of vitamin D in national surveys are typically below 5 μg/d in most European countries and vary according to country-specific fortification practices, sex, and age. While great strides have been made in providing nationally representative intake data on vitamin D, more data as well as a consistent approach to data reporting would be helpful. As the main source of variation is the contribution from nutritional supplements, usual vitamin D intake estimates need to capture data on the contributions from fortified and supplemental sources as well as the base diet. In addition, reliable data on the practice and impact of discretionary fortification on the part of food manufacturers is lacking. These issues are also highly relevant to Europe, particularly given the varying national policies with regard to mandatory and voluntary nutrient fortification across member states. A challenge encountered with fortifying several foods, is that the food composition databases are hard-pressed to keep step with innovations. Access to current and accurate food composition data is a requirement for the estimation of vitamin D intakes. More comprehensive coverage of the vitamin D content, including D_3, D_2, and 25(OH)D, of staple foods is needed. Investment in the provision of quality food composition data for vitamin D is

necessary to support assessment of vitamin D intakes in national surveys and research in nutrition and health.

ACTIVITY 8. IDENTIFYING POLICY OPTIONS AND ACTIVITY 9. EVALUATING POLICY IMPLEMENTATION

This activity links closely to the *Risk characterization:* step of the risk assessment framework, which is essentially the reporting step of the framework where the committee details each aspect of the approach used, outcomes, decisions, special concerns, and uncertainties relevant to risk managers and regulatory bodies charged with public health policy and scientists. Once reporting is completed, the committee rests and risk management agencies implement the DRIs by reforming public health policy and implementing education programs as well as addressing research recommendations based on the knowledge gaps and data requirements identified in the report.

On the basis of the shortfall between the current dietary supply of vitamin D and updated DRIs, we explored potential policy options on behalf of EURRECA. While supplements are an effective method for individuals to increase their intake, food fortification represents the best opportunity to increase the vitamin D supply to the population. Well-designed sustainable fortification strategies, which use a range of foods to accommodate diversity, have potential to increase vitamin D intakes across the population distribution and minimize the prevalence of low serum 25(OH)D. During the First and Second World Wars, fortification of food became widespread in order to prevent micronutrient deficiencies and to address nutrient losses during food processing. During this time, it became common practice to add a number of nutrients to foods, including iodine to salt; vitamins A and D to margarine; vitamin D to milk; and thiamine, riboflavin, niacin, and iron to flour (Mejia, 1994). Fortification of food with vitamin D began in response to the development of rickets in children in industrialized countries. In 1932, soon after the structure of vitamin D_2 was determined, vitamin D fortification of milk began in the United States at a level of 400 IU/quart (1 quart = 0.95 L) (Mertz, 1997). In the United Kingdom, fortification of margarine with vitamin D first became mandatory at the start of World War II, at a level of 8 μg/100 g, to match the nutritional profile of butter (Richardson, 1990). However, the fortification process was poorly monitored and, when over-fortification of some milk products shortly after World War II led to vitamin D intoxication in young children, the practice largely ceased (British Pediatric Association, 1956).

In the modern food industry and regulatory context, the likelihood of excessive intakes due to food fortification is relatively low. Liberal fortification practices have been in place in a number of countries for many years, with no reported adverse health effects (Meltzer et al., 2003). Currently, fortification practices vary between countries and may be applied voluntarily by manufacturers or implemented by national legislation. In order to harmonize voluntary food fortification practices throughout EU member states, and to provide consumer protection, a regulation governing the addition of vitamins and minerals was proposed by the European Commission (Commission of the European Communities, 2012), which does not affect existing national rules regarding compulsory fortification. Micronutrients may be added to foods for the purpose of restoring the nutrients lost during processing; for producing a substitute food that resembles a common food in appearance and nutritive value; or for the purpose of enriching a food in order to provide a nutritional or physiological effect.

In the UK and Ireland, a significant number of foods are fortified on a voluntary basis. Hannon et al. (2007) reported that fortified foods contributed 11% of total vitamin D intake in Irish women aged 18–64 y, increasing the median daily intake by 23%, with no concomitant risk of excessive intakes of vitamin D. The Finnish experience over the past 10 years is exemplary with respect to implementation and evaluation of vitamin D fortification policies. In 2003, the government initiated regulations for the optional vitamin D_3 fortification of milks and yoghurt (0.5 μg/100 g) and margarine and spreads (10 μg/100 g) (Tylavsky et al., 2006). The resulting increase in daily vitamin D intakes in 100 adolescents (12–17 years) was 3.3 in 12–14 year olds and 1.7 in 15–17 year olds (Tylavsky et al., 2006). Serum 25(OH)D was measured immediately prior to implementation of the fortification policy and one year later 196 Finnish men in the Defense Forces (18–28 years) (Laaksi et al., 2006). After fortification, mean 25(OH)D during the winter months increased by 50% and the prevalence of serum 25(OH)D <40 nmol/L decreased from 78% in January 2003 to 35% in January 2004. The prevalence of serum 25(OH)D<25 nmol/L decreased from 19 to 5% in the same year. After fortification, 5% of participants had 25(OH)D>100 nmol/L (101–111 nmol/L); however, no clinical signs of toxicity were seen. Vitamin D intakes increased from 2.1 to 4.5μg/d and serum 25(OH)D increased from 54.7 to 64.9 nmol/L in 4-year old children during winter months, before (n = 82) and after (n = 36) fortification (Piirainen et al., 2007). Lehtonen-Veromaa et al. (2008) found a modest increase in intakes (from 4 to 5.4 μg/d) adolescent girls due to the fortification policy, but no change in serum 25(OH)D, probably due to low dairy consumption among adolescent girls.

The problem of fortifying a single staple, for example milk, or focusing on a commodity sector such as dairy, is that it does not increase the vitamin D supply in nonconsumers. For example, Babu & Calvo (2010) suggested that fortification of wheat flour might be more efficacious in alleviating vitamin D deficiency in countries such as India and Jordan, where pasteurised milk is not widely consumed. Van Horn et al. (2011) showed that African-American girls relied more heavily on meat and beans as a source of vitamin D than white girls, emphasizing the need to account for diversity in food consumption patterns when developing fortification strategies.

O'Donnell et al. (2008) carried out a systematic review to assess the efficacy of food fortification on serum 25(OH)D concentrations from RCT using vitamin D fortified foods and found evidence for benefit of fortification. On behalf of EURRECA,

we updated a previous systematic review to evaluate current evidence from randomized controlled intervention studies in community-dwelling adults on the effect of fortified foods on 25(OH)D levels (Black et al., 2012). Ovid MEDLINE, PubMed, CINAHL, Embase, and Cochrane Central Register of Controlled Trials were searched for randomized controlled intervention studies with vitamin D-fortified foods in free-living adults and data on circulating 25(OH)D. Two reviewers independently screened 441 papers for eligibility and extracted relevant data. Meta-analysis of the absolute mean change in circulating 25(OH)D concentrations was conducted using a random effects model. Sixteen studies from 15 publications were included, of which 14 showed a significant effect of fortified foods on 25(OH)D levels [see Supplemental Fig. 2]. Heterogeneity was high ($P \leq 0.0001$, $I^2 = 89\%$) and was partly explained by dose, latitude (range 3 to 60°) and baseline 25(OH)D (range 24.0 to 83.6 nmol/L). When combined in a random effects analysis ($n = 1513$; 767 treated, 746 controls), a mean individual intake of ~11 μg/d (440 IU/d) from fortified foods (range 3 to 25 μg/d) increased 25(OH)D by 19.4 nmol/L (95% CI = 13.90, 24.90), corresponding to a 1.2 nmol/L (95% CI = 0.72, 1.68) increase in 25(OH)D for each 1 μg ingested. In conclusion, our analysis showed that foods fortified with vitamin D increase circulating 25(OH)D concentrations in a dose-dependent manner. However, there is a need for stronger data on the effect of vitamin D-fortified food on circulating serum 25(OH)D, deficiency prevention, and potential health benefits. Careful consideration must be given to the range of products used for fortification and amount of vitamin D used in each, to optimize effectiveness and minimize risk of excessive intakes. This can only be achieved by modeling usual food consumption intakes in representative populations and evaluating potential fortification initiatives by carrying out high quality food-based randomized controlled studies in the community that measure the impact on serum 25(OH)D in the population to achieve efficacy without compromising safety.

Identification of Research Gaps to Inform Future DRI Panels

The IOM expert committee on vitamin D and calcium found an overall lack of causal evidence from intervention studies for the task of identifying health outcome indicators (Institute of Medicine, 2011). This was especially true for nonskeletal outcomes for vitamin D, but also true for skeletal outcomes, particularly in certain life-stage groups. The extensive data evaluation and analysis undertaken by the IOM committee, facilitated largely by the outcomes of the two AHRQ SEBRs, placed a focus upon the vitamin D research conducted to date and has provided a valuable opportunity to reflect and identify data requirements to meet the needs of planned and ongoing revisions of recommended nutrient intakes by several authoritative agencies, including the EFSA, SACN, and NORDEN, among others, as well as future revisions of the IOM DRIs.

As part of its DRI report on vitamin D and calcium, the IOM committee highlighted a number of data requirements and research gaps, which impinged in their derivation of DRI for vitamin D. These gaps were evident in the hazard identification and hazard characterization steps of the risk assessment framework (Activities 3–7 in the EURRECA Process). For example, the SEBRs found that (a) most vitamin D studies were conducted using older persons or postmenopausal women, (b) some available data suggested the possibility of ethnic differences in relation to bone health and nutrient interactions, but this suggestion could not be further clarified, (c) very few studies were designed to explore the effects of calcium and vitamin D independently, and (d) very limited data were available on adverse health effects (Institute of Medicine, 2011). These information gaps presented challenges in synthesizing evidence for calcium and vitamin D separately and in combination. Further, lack of clarity concerning the physiology and metabolism of vitamin D was problematic as was the ability to judge the effects of vitamin D as a nutrient given its role as a pro-hormone. Each of these gaps is expanded in the DRI report and the interested reader is referred to Chapter 9 of the IOM Report. These research gaps and others, which may track more to Risk Management (Activities 8–9 of the *EURRECA* process), have been overviewed and highlighted in a EURRECA review on *Towards prevention of vitamin D deficiency and beyond - knowledge gaps and research needs in vitamin D nutrition and public health* (Cashman and Kiely, 2011). Supplemental Table 1briefly outlines the main gaps as they related to the steps of the Risk Assessment Framework (and *EURRECA* process) and within some steps are divided into research topics.

In conclusion, this overview has mapped the procedure outlined by EURRECA for estimating micronutrient requirements to the risk assessment framework adopted by the IOM expert committee for vitamin D and calcium. We have traced the vitamin D-related EURRECA activities along the steps in both frameworks and summarized the results obtained, as well as outlining research requirements necessary to progress the next iteration of vitamin D requirement assessments.

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ABBREVIATIONS

25(OH)D = 25-hydroxyvitamin D
AHRQ = Agency for Healthcare Research and Quality

AI = Adequate intake
BMC = Bone mineral content
BMD = Bone mineral density
CIs = Confidence intervals
DRI = Dietary reference intake
DRV = Dietary reference values
EAR = Estimated average requirement
EFSA = European Food Safety Authority
EPIC = European Prospective Investigation into Cancer and Nutrition
IOM = Institute of Medicine
IU = International units
NDA = Dietetic products, nutrition, and allergies
NDNS = National Diet and Nutrition Survey
NHANES = National Health and Nutrition Examination Survey
NIH = National Institutes of Health
NoE = Network of Excellence
NORDEN = Nordic Council of Ministers
ODS = Office of Dietary Supplements
PTH = Parathyroid hormone
RCT = Randomized controlled trials
RDA = Recommended dietary allowance
SACN = Scientific Advisory Committee on Nutrition
SEBRs = Systematic evidence-based reviews
UL = Tolerable upper intake level
UVB = Ultraviolet B

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