Summary

Calcium and vitamin D are undoubtedly essential nutrients for the human body. The key questions are: What processes can these nutrients affect in terms of desirable health outcomes, and how much of each nutrient is needed to achieve the effect?

During the past 10 years, there has been increasing interest in the possibility of enhanced roles for vitamin D in human health. A number of researchers in the scientific community have suggested relationships between vitamin D intake and health outcomes ranging from cancer prevention to increased immunity; others have suggested possible roles in preventing diabetes or preeclampsia during pregnancy. The media have also taken an interest, and public expectations have been raised. At the same time, physicians have been ordering blood tests that seem to suggest, based on use of criteria that have yet to be validated, that many in our North American population are vitamin D deficient. For calcium, there is concern that some may not be obtaining sufficient amounts given the foods they eat. Calcium has been increasingly added to foods, and calcium supplement use, particularly among older persons, is widespread. There is controversy concerning levels of nutrient intake, and at times the concept that "more is better" emerges. However, for both calcium and vitamin D, there is another underlying question: How much is too much?

Against this backdrop, the Institute of Medicine (IOM) was requested by the U.S. and Canadian governments to conduct a review of data pertaining to calcium and vitamin D requirements and to identify Dietary Reference Intakes (DRIs) based on current scientific evidence about the roles of calcium and vitamin D in human health. The DRIs, as nutrient

reference values, are used by various stakeholders, ranging from those who set national nutrition policy to health practitioners in community settings. Such reference values specify, for normal, healthy persons, an average daily requirement for the nutrient, known as the Estimated Average Requirement (EAR). They also identify levels of intake that are likely to meet the needs of about 97.5 percent of the population (the Recommended Dietary Allowance, or RDA). Further, they include a Tolerable Upper Intake Level (UL) above which the potential for harm increases.

THE COMMITTEE AND ITS CHARGE

The two governments requested that the IOM conduct a study to assess current data and to update as appropriate the DRIs for vitamin D and calcium. The study was to include consideration of chronic disease indicators (e.g., reduction in risk of cancer or diabetes) and other (non-chronic disease) indicators/outcomes, and to assess the ability of each to serve as the basis for specifying adequate intake or excess intake. The final DRI indicators were to be selected based on the strength and quality of the evidence.

To carry out the request, the IOM established an ad hoc consensus committee of 14 scientists. The committee met eight times, held a public workshop and open sessions to gather information and receive input on the nature of the available data, maintained a website that accepted comments and data from stakeholders, conducted a review of existing data, and developed a report that included the specification of DRI values. Committee members had expertise in the areas of vitamin D and calcium or a related topic area, with specific expertise related to pregnancy and reproductive nutrition, pediatrics and infant nutrition, minority health and health disparities, cellular metabolism, toxicology and risk assessment, dermatology, immunology, endocrinology, skeletal health, oncology, cardiovascular health, epidemiology; nutrition monitoring, and biostatistics. Three members of the committee had served on other DRI committees.

DRI CONTEXT FOR COMMITTEE'S WORK

This report marks the first DRI review since the completion of the 1997-2004 DRIs, which in contrast with their predecessors were based on a different approach to respond to expanded uses of the values and newer understandings of the role of nutrients. The DRIs now incorporate the statistical concept of a distribution, including the distributions of requirements and intakes. The major components of the DRIs are shown in Box S-1.

The first DRIs, contained in six volumes, are now used in both the United States and Canada. The governments of these two countries have

BOX S-1
Dietary Reference Intake Components*

Estimated Average Requirement (EAR): Reflects the estimated median requirement and is particularly appropriate for applications related to planning and assessing intakes for groups of persons.

Recommended Dietary Allowance (RDA): Derived from the EAR and meets or exceeds the requirement for 97.5 percent of the population.

Tolerable Upper Intake Level (UL): As intake increases above the UL, the potential risk of adverse effects may increase. The UL is the highest average daily intake that is likely to pose no risk of adverse effects to almost all individuals in the general population.

Adequate Intake (AI): Used when an EAR/RDA cannot be developed; average intake level based on observed or experimental intakes.

*Also, Acceptable Macronutrient Distribution Range (AMDR): An intake range for an energy source associated with reduced risk of chronic disease.

also supported a recent evaluation of the DRI development process, which has informed the approach used to develop this report. The evaluation pointed to the need for enhanced "transparency" about the decisions made, more clarification about uncertainties in the values, and use of a risk assessment framework to organize the scientific assessments. Risk assessment encompasses a series of decision steps and anticipates the need to address uncertainties through documentation and the use of expert judgment.

THE COMMITTEE'S APPROACH AND EXAMINATION OF DATA

To set the stage for its review, the committee gathered background information on the metabolism and physiology of calcium and vitamin D (Chapters 2 and 3). It then identified those relationships that could potentially serve as indicators for establishing nutrient reference values for adequate intakes of the nutrients. To ensure comprehensiveness, the committee included relationships that appeared marginal by standard scientific principles as well as those suggested to be of interest by stakeholders. Box S-2 lists these potential indicators in alphabetical order. The close inter-relationship between calcium and vitamin D often resulted in potential indicators being relevant to both nutrients.

Chapter 4 provides the committee's review of potential indicators,

BOX S-2
Potential Indicators of Health Outcomes for Nutrient Adequacy for Calcium and Vitamin D

Cancer/neoplasms
- All cancers
- Breast cancer
- Colorectal cancer/colon polyps
- Prostate cancer

Cardiovascular diseases and hypertension
Diabetes (type 2) and metabolic syndrome (obesity)
Falls
Immune responses
- Asthma
- Autoimmune disease
  - Diabetes (type 1)
  - Inflammatory bowel and Crohn's disease
  - Multiple sclerosis
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
- Infectious diseases
  - Tuberculosis
  - Influenza/upper respiratory infections

Neuropsychological functioning
- Autism
- Cognitive function
- Depression

Physical performance*
Preeclampsia of pregnancy and other non-skeletal reproductive outcomes
Skeletal health (commonly bone health)
- Serum 25-hydroxyvitamin D, as intermediate
- Parathyroid hormone, as intermediate
- Calcium absorption
- Calcium balance
- Bone mineral content/bone mineral density
- Fracture risk
- Rickets/osteomalacia

*In the discussions related to review of potential indicators, physical performance is considered together with falls.

based on literature identified by the committee and incorporating the systematic evidence-based reviews from the Agency for Healthcare Research and Quality (AHRQ). In sum, with the exception of measures related to bone health, the potential indicators examined are currently not supported by evidence that could be judged either convincing or adequate in terms of cause and effect, or informative regarding dose–response relationships for determining nutrient requirements. Outcomes related to cancer/neoplasms, cardiovascular disease and hypertension, diabetes and metabolic syndrome, falls and physical performance, immune functioning and autoimmune disorders, infections, neuropsychological functioning, and preeclampsia could not be linked reliably with calcium or vitamin D intake and were often conflicting. Although data related to cancer risk and vitamin D are potentially of interest, a relationship between cancer incidence and vitamin D (or calcium) nutriture is not adequately and causally demonstrated at present; indeed, for some cancers, there appears to be an increase in incidence associated with higher serum 25-hydroxyvitamin D (25OHD) concentrations or higher vitamin D intake. The role of vitamin D related to falls and physical performance, cardiovascular disease, autoimmune disorders, and immune functioning has also received considerable attention, and remains unresolved. These potential roles of vitamin D are currently best described as hypotheses of emerging interest, and the conflicting nature of available evidence cannot be used to establish health benefits with any level of confidence. In contrast, the evidence surrounding bone health provides a reasonable and supportable basis to allow this indicator to be used for DRI development.

In making its conclusions about potential indicators other than bone health, the committee noted the observation previously highlighted by others tasked with examining the evolution of evidence for nutrient and disease relationships: that evidence about relationships between specific nutrients and a disease or health outcome remains typically elusive, for a number of reasons. These include the difficulty of isolating the effects of a single nutrient under investigation from the confounding effects of other nutrients and non-nutrient factors; the multi-factorial etiology of the chronic diseases the committee considered; the paucity of data from randomized controlled clinical trials, which typically provide the highest level of scientific evidence relevant for DRI development; and the mixed and inconclusive results from observational studies.

For indicators associated with excess intakes of calcium and vitamin D, a process similar to that for reference values for adequacy was undertaken and potential indicators of excess intake were identified (see Box S-3). The ULs serve as a measure for chronic intake of a free-living, unmonitored population. They are not specified for clinical research; it may be appro-

BOX S-3
Potential Indicators of Adverse Outcomes for Excess Intake of Calcium and Vitamin D

Calcium
- Hypercalcemia
- Hypercalciuria
- Vascular and soft tissue calcification
- Nephrolithiasis (kidney stones)
- Prostate cancer
- Interactions with iron and zinc
- Constipation

Vitamin D
- Intoxication and related hypercalcemia and hypercalciuria
- Serum calcium
- Measures in infants: retarded growth, hypercalcemia
- Emerging evidence for all-cause mortality, cancer, cardiovascular risk, falls and fractures

priate to conduct clinical research with doses exceeding the UL, as long as there is monitoring and the protocol is carefully considered.

KEY CHALLENGES

Beyond the challenge of limited data and the resulting uncertainties, the study faced two additional challenges. The first is that vitamin D, an essential nutrient, is also synthesized in the skin following exposure to sunlight. Thus, the examination of data is complicated by the confounding factors this introduces. Further, vitamin D requirements could not address the level of sun exposure because public health concerns about skin cancer preclude this possibility. There have not been studies to determine whether ultraviolet B (UVB)–induced vitamin D synthesis can occur without increased risk of skin cancer. The best approach was to estimate vitamin D requirements under conditions of minimal sun exposure.

Second, vitamin D when activated functions as a hormone and is regulated by metabolic feedback loops. The intertwining of the effects of vitamin D and calcium represents an extreme case of nutrient–nutrient inter-relationships. Indeed, many studies administered these nutrients together rather than separately. For this reason, distinguishing the health outcomes for one nutrient versus the other was challenging.

THE COMMITTEE'S OUTCOMES

An assumption in developing the DRIs for calcium is that they are predicated on intakes that meet requirements for vitamin D; similarly, DRIs for vitamin D rest on the assumption of intakes that meet requirements for calcium.

Dietary Reference Intakes for Calcium

DRIs for calcium were established as EARs and RDAs except for infants up to 12 months of age for whom AIs were specified. The DRIs for calcium are shown in Table S-1.

TABLE S-1 Calcium Dietary Reference Intakes by Life Stage (amount/day)

Life Stage Group	AI	EAR	RDA	UL
Infants				
0 to 6 mo	200 mg	—	—	1,000 mg
6 to 12 mo	260 mg	—	—	1,500 mg
Children				
1–3 y	—	500 mg	700 mg	2,500 mg
4–8 y	—	800 mg	1,000 mg	2,500 mg
Males				
9–13 y	—	1,100 mg	1,300 mg	3,000 mg
14–18 y	—	1,100 mg	1,300 mg	3,000 mg
19–30 y	—	800 mg	1,000 mg	2,500 mg
31–50 y	—	800 mg	1,000 mg	2,500 mg
51–70 y	—	800 mg	1,000 mg	2,000 mg
> 70 y	—	1,000 mg	1,200 mg	2,000 mg
Females				
9–13 y	—	1,100 mg	1,300 mg	3,000 mg
14–18 y	—	1,100 mg	1,300 mg	3,000 mg
19–30 y	—	800 mg	1,000 mg	2,500 mg
31–50 y	—	800 mg	1,000 mg	2,500 mg
51–70 y	—	1,000 mg	1,200 mg	2,000 mg
> 70 y	—	1,000 mg	1,200 mg	2,000 mg
Pregnancy				
14–18 y	—	1,100 mg	1,300 mg	3,000 mg
19–30 y	—	800 mg	1,000 mg	2,500 mg
31–50 y	—	800 mg	1,000 mg	2,500 mg
Lactation				
14–18 y	—	1,100 mg	1,300 mg	3,000 mg
19–30 y	—	800 mg	1,000 mg	2,500 mg
31–50 y	—	800 mg	1,000 mg	2,500 mg

NOTE: AI = Adequate Intake; EAR = Estimated Average Requirement; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

The EARs and RDAs relied primarily upon calcium balance studies for persons 1 to 50 years of age. The effect of menopause on bone resulted in specifying different EARs and RDAs for women and men 51 to 70 years of age. After the age of 70 years, the effects of aging on bone loss resulted in EARs and RDAs that are the same for men and women. The AIs for infants are based on the calcium content of human milk. There is no evidence that calcium requirements are different for pregnant and lactating females compared with their non-pregnant or non-lactating counterparts.

The ULs for calcium for adults are based on data related to the incidence of kidney stones, largely from work conducted with postmenopausal women who use calcium supplements. Newer data from a feeding study provided evidence of intake levels among infants not associated with elevated calcium excretion, and allowed derivation of a UL for infants. The UL for children and adolescents 9 to 18 years of age gives consideration to the pubertal growth spurt and increases the UL as compared with that for children 1 to 8 years of age.

Dietary Reference Intakes for Vitamin D

DRI values for vitamin D (Table S-2) were established as EARs and RDAs for all life stage groups except infants up to 12 months of age for which an AI was specified. These reference values assume minimal sun exposure.

Measures of serum 25OHD level serve as a reflection of total vitamin D exposure—from food, supplements, and synthesis. Although serum 25OHD level cannot be considered a validated health outcome surrogate, it allowed comparison of intake or exposure with health outcomes. Newer data also allowed the simulation of a requirement distribution based on serum 25OHD concentrations. A level of 40 nmol/L (16 ng/mL) was consistent with the intended nature of an average requirement, in that it reflects the desired level for a population median—it meets the needs of approximately half the population. Moreover, benefit for most in the population is associated with serum 25OHD levels of approximately 50 nmol/L (20 ng/mL), making this level a reasonable estimate for a value akin to "coverage" for nearly all the population. Available data were used to link specified serum levels of 25OHD with total intakes of vitamin D under conditions of minimal sun exposure in order to estimate DRIs.

For children and adolescents 1 to 18 years of age, EARs and RDAs are specified on the basis of serum 25OHD concentrations of 40 and 50 nmol/L (16 and 20 ng/mL), respectively. Likewise this approach was used for young adults and adults from 19 through 50 years of age and was supported by data on osteomalacia. The EAR for persons older than 50 years of age is the same as that for younger adults, as the simulated requirement

TABLE S-2 Vitamin D Dietary Reference Intakes by Life Stage (amount/day)

Life Stage Group	AI	EAR	RDA	UL
Infants				
0 to 6 mo	400 IU (10 µg)	—	—	1,000 IU (25 µg)
6 to 12 mo	400 IU (10 µg)	—	—	1,500 IU (38 µg)
Children				
1–3 y	—	400 IU (10 µg)	600 IU (15 µg)	2,500 IU (63 µg)
4–8 y	—	400 IU (10 µg)	600 IU (15 µg)	3,000 IU (75 µg)
Males				
9–13 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
51–70 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
> 70 y	—	400 IU (10 µg)	800 IU (20 µg)	4,000 IU (100 µg)
Females				
9–13 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
51–70 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
> 70 y	—	400 IU (10 µg)	800 IU (20 µg)	4,000 IU (100 µg)
Pregnancy				
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
Lactation				
14–18 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
19–30 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)
31–50 y	—	400 IU (10 µg)	600 IU (15 µg)	4,000 IU (100 µg)

NOTE: AI = Adequate Intake; EAR = Estimated Average Requirement; IU = International Units; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

distribution suggested no effect due to age. However, there is notable variability around these estimates in the case of bone health for older persons. This suggests that the assumption about the variance associated with coverage for 97.5 percent of the population should be greater for this older group than for the younger group. Therefore, the RDA value for persons older than 70 years of age was increased to a level greater than the two standard deviations used for other groups. In fact, available data provide more information about maximal population coverage than they do about average requirements for these life stage groups. The factors taken into account included changes in bone density and fracture risk. For infants, an AI was established based on evidence that maintaining serum 25OHD levels in the range of 40 to 50 nmol/L (16 to 20 ng/mL) was desirable,

coupled with observational data suggesting that 400 International Units (IU) (10 µg) per day was adequate to maintain this level.

The ULs for vitamin D were especially challenging because available data have focused on very high levels of intake that cause intoxication and little is known about the effects of chronic excess intake at lower levels. The committee examined the existing data and followed an approach that would maximize public health protection. The observation that 10,000 IU (250 µg) of vitamin D per day was not associated with classic toxicity served as the starting point for adults; this value was corrected for uncertainty by taking into consideration emerging data on adverse outcomes (e.g., all-cause mortality), which appeared to present at intakes lower than those associated with classic toxicity and at serum 25OHD concentrations previously considered to be at the high end of physiological values. Possible ethnic/racial differences were taken into account as well. The UL for adults is used for 9 to 18 years olds, but is "scaled down" for children 1 to 8 years of age. Earlier studies remain the best basis for ULs for infants.

DIETARY INTAKE ASSESSMENT

Calcium remains a nutrient of concern given that median calcium intakes from foods in both the United States and Canada are close to the EAR values for most groups. In particular, girls 9 to 18 years of age are falling below desirable intakes when only food sources of calcium are considered, as are women over the age of 50 years. Available data from the United States on the total intake of calcium when dietary supplements are considered suggest that older women have noticeably increased calcium intakes with supplement. For girls, the increase in intake attributable to supplement use is small. No life stage groups exceeded the UL for calcium when foods alone were considered. However, when supplement use was taken into account (United States only), women at the 95th percentile of calcium intake appeared to be at risk for exceeding the UL. The data underscore the possible need to modestly increase calcium intake among older girls; among older women, a high calcium intake from supplements may be concerning.

Although daily median vitamin D intake from foods in both countries for all life stage groups was below the established reference value, these data should be considered in light of the average serum 25OHD concentrations. U.S. serum 25OHD concentrations on average were well above 40 nmol/L (16 ng/mL), the level established as consistent with an intake equivalent to the EAR; in fact, all mean serum 25OHD concentrations were above 50 nmol/L (20 ng/mL). In the case of serum 25OHD concentrations from Canadian surveys, mean serum 25OHD levels for all life stage groups were at or above 60 nmol/L (24 ng/mL). The fact that these values

are higher for the Canadian than for the U.S. population may be in part due to differences in assay methodologies used.

IMPLICATIONS AND SPECIAL CONCERNS

The final risk assessment step is risk characterization, which highlights implications of the DRI outcomes and special concerns including the population segments shown in Box S-4. The nature and extent of the risk associated with these population segments vary.

Uncertainties

On balance, the uncertainties surrounding the DRI values for calcium are less than those for vitamin D because the evidence base is considerably larger for calcium, and the physiology and metabolism of calcium are better understood. The following key issues were identified as introducing uncertainty into DRI values for calcium and vitamin D, as based on bone health outcomes:

- The tendency for study protocols to administer a combination of calcium and vitamin D, reducing the opportunity to ascertain effects of each nutrient independently;
- The lack of data examining the responses and health outcomes

BOX S-4
Population Segments and Conditions of Interest

Adiposity
Persons living at upper latitudes in North America
Persons who experience reduced vitamin D synthesis from sun exposure
- Dark skin (including immigrant groups and exclusively breast-fed infants)
- Use of sunscreen
- Indoor environments and institutionalized older persons

Alternative diets or changes in dietary patterns
- Dairy and animal product exclusion
- Changes in dietary patterns of indigenous Canadian populations

Use of calcium supplements
Oral contraceptive use
Premature infants
Interaction between vitamin D and prescription drugs

from graded doses of calcium or vitamin D intake so as to elucidate dose–response relationships;

- The interaction between calcium and vitamin D to the extent that it would appear that adequate calcium intake greatly diminishes the need for vitamin D relative to bone health outcomes;
- The unique situation in which a nutrient (vitamin D) is physiologically managed by the body as a hormone, introducing a myriad of variables and feedback loops related to its health effects;
- The paucity of data and resulting uncertainty concerning sun exposure, which confounds the interpretation of dose–response data for intakes of vitamin D. This, coupled with the apparent contribution of sun exposure to overall vitamin D nutriture in North American populations, leads to an inability to characterize and integrate sun exposure with dietary intake recommendations as much as may be appropriate, given the concern for skin cancer risk reduction. Thus, for individuals who experience sun exposure, the uncertainty of the DRI is greater than for those who do not;
- The lack of clarity concerning the validity of the serum 25OHD measure as a biomarker of effect;
- The variability surrounding measures of serum 25OHD concentrations owing to different methodologies used;
- The evidence of the non-linear nature of the relationship between serum 25OHD concentrations and total intake of vitamin D, suggesting that lower levels of intake have more impact on serum 25OHD concentrations than previously believed and that higher intakes may have less impact;
- The limited number of long-term clinical trials related to calcium and vitamin D intake and health outcomes; and
- The need to set ULs based on limited data in order to ensure public health protection.

For vitamin D, the challenges introduced by issues of sun exposure are notable. This nutrient is unique in that it functions as a hormone and the body has the capacity to synthesize it. However, concerns about skin cancer risk preclude incorporating the effects of sun exposure in the DRI process. At this time, the only solution is to proceed on the basis of the assumption of minimal sun exposure and set reference values assuming that all of the vitamin D comes from the diet. This is a markedly cautious approach given that the vast majority of North Americans obtain at least some vitamin D from inadvertent or intentional sun exposure. Therefore, the estimated intake data for vitamin D cannot stand alone as a basis for broad public health action. Rather, national policy should consider intake data in the context of measures of serum 25OHD, a well-established biomarker of

total vitamin D exposure (endogenous synthesis and diet including supplements). Although estimates of vitamin D intake appear to be less than needed to meet requirements, the serum 25OHD data available—when coupled with the committee's assessment of serum 25OHD levels consistent with EAR and RDA values—suggest that requirements are being met for most if not all persons in both countries. Moreover, the possibility of risk for subpopulations of concern due to reduced synthesis of vitamin D, such as persons with dark skin or older persons in institutions, is minimized given the assumption of minimal sun exposure as a basis for the DRIs.

CONCLUSIONS ABOUT VITAMIN D DEFICIENCY IN THE UNITED STATES AND CANADA

Serum levels of 25OHD have been used as a measure of adequacy for vitamin D, as they reflect intake from the diet coupled with the amount contributed by cutaneous synthesis. The cut-point levels of serum 25OHD intended to specify deficiency for the purposes of interpreting laboratory analyses and for use in clinical practice are not specifically within the charge to this committee. However, the committee noted with some concern that serum 25OHD cut-points defined as indicative of deficiency for vitamin D have not undergone a systematic, evidence-based development process.

From this committee's perspective, a considerable over-estimation of the levels of vitamin D deficiency in the North American population now exists due to the use by some of cut-points for serum 25OHD levels that greatly exceed the levels identified in this report as consistent with the available data. Early reports specified a serum 25OHD concentration of at least 27.5 nmol/L (11 ng/mL) as an indicator of vitamin D adequacy from birth through 18 years of age, and a concentration of at least 30 nmol/L (12 ng/mL) as an indicator of vitamin D adequacy for adults 19 to 50 years of age. In recent years, others have suggested different cut-points as determinants of deficiency and what has been termed "insufficiency." In the current literature, these include values ranging from less than 50 nmol/L (20 ng/mL) to values above 125 nmol/L (50 ng/mL). Use of higher than appropriate cut-points for serum 25OHD levels would be expected to artificially increase the estimates of the prevalence of vitamin D deficiency.

The specification of cut-points for serum 25OHD levels has serious ramifications not only for the conclusions about vitamin D nutriture and nutrition public policy, but also for clinical practice. At this time, there is no central body that is responsible for establishing such values for clinical use. This committee's review of data suggests that persons are at risk of deficiency relative to bone health at serum 25OHD levels of below 30 nmol/L (12 ng/mL). Some, but not all, persons are potentially at risk for

inadequacy at serum 25OHD levels between 30 and 50 nmol/L (12 and 20 ng/mL). Practically all persons are sufficient at serum 25OHD levels of at least 50 nmol/L (20 ng/mL). Serum 25OHD concentrations above 75 nmol/L (30 ng/mL) are not consistently associated with increased benefit. There may be reason for concern at serum 25OHD levels above 125 nmol/L (50 ng/mL). Given the concern about high levels of serum 25OHD as well as the desirability of avoiding mis-classification of vitamin D deficiency, there is a critical public health and clinical practice need for consensus cut-points for serum 25OHD measures relative to vitamin D deficiency as well as excess. The current lack of evidence-based consensus guidelines is problematic and of concern because individuals with serum 25OHD levels above 50 nmol/L (20 ng/mL) may at times be classified as deficient and treated with high-dose supplements of vitamin D containing many times the levels of intake recommended by this report.

Closing Remarks

At this time, the scientific data available indicate a key role for calcium and vitamin D in skeletal health and provide a sound basis for DRIs. The data do not, however, provide compelling evidence that either nutrient is causally related to extra-skeletal health outcomes or that intakes greater than those established in the DRI process have benefits for health. The last chapter of this report specifies the research needs and reflects an urgent and worthwhile agenda. If carried out, this research will assist greatly in clarifying DRIs for vitamin D and calcium in the future.

DRI

DIETARY REFERENCE INTAKES

Calcium
Vitamin D

Committee to Review Dietary Reference Intakes for Vitamin D and Calcium
Food and Nutrition Board

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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COMMITTEE TO REVIEW DIETARY REFERENCE INTAKES FOR VITAMIN D AND CALCIUM

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Irwin H. Rosenberg**, Friedman School of Nutrition Science and Policy, Tufts University, and **Enriqueta C. Bond**, Burroughs Wellcome Fund (retired). Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

It has been an honor to chair this committee tasked with reviewing Dietary Reference Intake (DRI) values for calcium and vitamin D. In this preface, I would like, first and foremost, to thank those persons without whose help this report would not have been possible. I also would like to comment briefly on the nature of the task we had at hand, and how our committee proceeded, from its first meeting in 2009 to the final stage of its report.

The work of our committee was preceded by three important papers and reports. At a time when interest in vitamin D had reached new heights, and many various claims for benefits were reported, health professionals in the governments of the United States and Canada worked together to address the question: Since the 1997 IOM report on DRIs, including vitamin D, is there sufficient new evidence on this micronutrient to warrant a new DRI study? The publication from this group, "Dietary reference intakes for vitamin D: justification for a review of the 1997 values"[1] concluded that there were sufficient new data to warrant a reevaluation. In funding the DRI review for vitamin D, the sponsors also judged that calcium should be reviewed as well, given its interrelationship with vitamin D. I thank the many individuals from the U.S. and Canadian governments who put into motion the processes that led to this report. Moreover, understanding that

[1]Yetley, E. A., D. Brule, M. C. Cheney, C. D. Davis, K. A. Esslinger, P. W. Fischer, K. E. Friedl, L. S. Greene-Finestone, P. M. Guenther, D. M. Klurfeld, M. R. L'Abbe, K. Y. McMurry, P. E. Starke-Reed and P. R. Trumbo. 2009. Dietary reference intakes for vitamin D: justification for a review of the 1997 values. American Journal of Clinical Nutrition 89(3): 719-27.

a review of the literature would be a tremendous undertaking by itself, this group also commissioned an independent systematic review of the literature on vitamin D and health outcomes for the use of this DRI committee, and intended to update an earlier systematic review on vitamin D and bone health. The systematic review carried out by Dr. Joseph Lau and his colleagues at the Tufts Evidence-based Practice Center, and a preceding systematic review led by Dr. Ann Cranney of the University of Ottawa, both greatly aided the work of the current committee.

In the Statement of Task, the sponsors requested that our report be developed using a risk assessment framework. Such a framework is not one that committee members would naturally have been familiar with at the outset, and some readers of this report may also wonder, "What is that?" The process is discussed and diagrammed in the report in Chapter 1 and referred to throughout. We were greatly helped in adhering to the risk assessment approach by Christine Taylor, Ph.D., Study Director for this DRI study, whose previous background paper, "Framework for DRI Development,"[2] provided us with a much-needed understanding of the uses of risk assessment and the steps in conducting it that we would follow. Chris' insights, as well as her discipline, good humor, and willingness to engage over and over in discussions to obtain a broad understanding and consensus were very much at the heart of the committee's process. I thank her for being the amazing study director she has been. Our committee's work also benefited from the excellent research and support of Ann Yaktine, Ph.D., Heather Del Valle, and Heather Breiner. Linda Meyers, Ph.D., Director, Food and Nutrition Board, kept a watchful eye on our progress and willingly provided guidance as needed. The committee never lacked for exceptionally well-qualified, rigorous, hardworking, professional, and friendly support from the FNB staff, and I sincerely thank each one of them.

It may be of interest to briefly comment on the committee's approach, and how work evolved during its deliberations. The development of IOM reports is a consensus process. Thus, throughout we worked together, dividing specific tasks according to expertise but making sure that discussions proceeded and decisions were always made as a group. During this time, research did not stand still; not a week passed without new publications on these nutrients. We spent a good deal of effort, and staff performed invaluable service for us, in arraying new data, comparing aspects of study design, etc. The committee worked not only at the scheduled committee meetings, but also in a myriad of working groups by conference calls and emails. It was important to keep firmly in mind that DRIs are values meant for im-

[2]Taylor, C. L. 2008. Framework for DRI Development: Components "Known" and Components "To Be Explored." Washington, DC.

proving public health—the health of the *general population* of the United States and Canada. They provide recommendations for adequate and safe daily intakes of nutrients consumed over *many* years, possibly a lifetime, not just for days, weeks, months, or a year. Thus, the need for sound, causal evidence to make the evidence-based recommendations in this report was always at the forefront of our thinking and deliberations. The terms *causality, dose–response, evidence-based, totality of evidence, uncertainty, caveats* were often on the committee minds and prominent in our discussions. On some points, we consulted with experts, whom we thank for generously providing their input in response to our needs, sometimes on quite short notice. New data on the intakes of vitamin D and calcium in the United States and Canada arrived from the Centers for Disease Control and Prevention and Health Canada just as we needed them, and here I would like to thank the persons in these organizations who worked diligently to make these new intake data available for the committee's use. As DRI values evolved, we thought carefully about the implications of these recommendations for practitioners and decision makers in public health and policy who will use this report in their work, and for special populations in both the United States and Canada. Lastly, we considered research recommendations, linking our recommendations to knowledge gaps identified while using the risk assessment framework. This, of course, was a future-directed activity, and we hope that our recommendations will clarify the types of research and resulting new information that will make determining DRIs for calcium and vitamin D easier and more accurate in the future.

Throughout, the committee members worked together with common purpose and always amicably, even when viewpoints differed, and this made working on this study a remarkable experience for all of us. I sincerely thank all the members of the committee for sharing their expertise and greatly enriching the development of this report.

Finally, it is important to acknowledge the many people who assisted the committee with its work and who provided technical input and invaluable perspectives through a variety of venues ranging from white papers to participation in workshops and public information gathering meetings. Foremost, the committee is grateful to Dr. Hector DeLuca, who served as a tireless consultant and generously offered his wisdom and considerable experience to the committee. Many discussions were enriched by his input. Others who provided scientific evaluations and background information for the committee include: Dr. David Bushinsky, Dr. Thomas Carpenter, Dr. Gary Curhan, Dr. Gordon Guyatt, Dr. Craig Langman, Dr. Dwight Towler, and Dr. Susan Whiting. The committee is deeply appreciative of the heroic efforts of those who worked long hours to provide the committee timely national data on calcium and vitamin D intake as well as measures of serum 25-hydroxyvitamin D concentrations, specifically the

National Center for Health Statistics (Mr. Clifford Johnson, Dr. Lester R. Curtin, and Dr. Te-Ching Chen), the U.S. Department of Agriculture (Ms. Alanna Moshfegh and Ms. Joanne Holden), the National Cancer Institute (Dr. Kevin Dodd), and Statistics Canada (Mrs. Jeanine Bustros, Mr. Didier Garriguet, Mr. Christopher Oster, and Miss Dawn Warner). Also, invaluable and illuminating analytical assistance was provided by statisticians at Cornell University, Dr. Francoise Vermeylen and Dr. Shamil Sadigov. Finally, the committee wishes to thank the sponsors of this report for their support and without whom there would not have been the opportunity to carry out this important study.

A. Catharine Ross, *Chair*
Committee to Review Dietary Reference
Intakes for Vitamin D and Calcium

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*Appendixes B through K are not printed in this book, but can be found on the CD at the back of the book or online at http://www.nap.edu.