November 15, 2017

MEMORANDUM

To: Marcia McNutt, President of the National Academy of Sciences and Chair, National Research Council

From: David B. Allison, Dean, The Indiana University School of Public Health-Bloomington
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Cc: Bruce Darling, Executive Officer, National Research Council

Re: Impact on the RDA for vitamin D of mathematical errors in the 2011 IOM report, *Dietary Reference Intakes: Calcium and Vitamin D*

In response to the charge delivered to each of us by Clyde Behney, Executive Director, Health and Medicine Division, please find below the findings of this second panel regarding the impact on Recommended Dietary Allowances (RDAs) of the mathematical errors in the 2011 IOM report, *Dietary Reference Intakes: Calcium and Vitamin D*.

Background

In 2011, the Institute of Medicine[1] published *Dietary Reference Intakes: Calcium and Vitamin D*[i] (hereafter referred to as 'the IOM report'), which determined dietary reference intakes (DRIs) for vitamin D that are used in both the United States and Canada. The IOM report established an Estimated Average Requirement (EAR), an RDA, and a Tolerable Upper Intake Level (UL) for 22 population groups determined by age, gender, and reproductive status (e.g., infants, children, elderly, pregnant women, etc.).

Following the release of the IOM report, concerns were raised in the form of written comments from Dr. Keith A. Baggerly, Professor of Bioinformatics and Computational Biology, MD Anderson Cancer Center, to the leadership of the National Academies of Sciences, Engineering, and Medicine. One issue concerned a potential mathematical error in the analysis of one study used in the discussion of RDAs for four of the twenty-two populations groups considered in the IOM report. This study by Priemel et al. measured bone quality and serum levels of a vitamin D biomarker, serum 25-hydroxyvitamin D (25OHD), in cadavers.[ii] Dr. Baggerly highlighted his concerns and analysis during a presentation at the National

[1] As of March 15, 2016, the Health and Medicine Division continues the consensus studies and convening activities previously undertaken by the Institute of Medicine.

Academy of Sciences' Sackler Colloquium on March 10, 2017.[2] His presentation also included discussion of other statistical aspects of the IOM report that he thought to be in error.

Subsequently, the President of the National Academy of Sciences and chair of the National Research Council, Dr. Marcia McNutt, initiated a 2-phase process to review Dr. Baggerly's concerns. The first phase of the review process was initiated in March 2017, when an independent panel (phase I) was convened and charged to determine whether Dr. Baggerly's assertions regarding specific mathematical and statistical errors he cites in the IOM report were correct. The findings of the panel (discussed below) were reported in a memorandum to Dr. McNutt in May 2017. In June 2017, a second panel (phase II) was convened and charged to advise Dr. McNutt on whether the first panel's findings meaningfully affect the determination of the RDA for vitamin D in the 2011 IOM report.

Findings of the Phase I Panel

The phase I panel examined the use of the data from the study by Priemel and colleagues in the 2011 IOM report and determined that the report presents an incorrect calculation involving the prevalence of vitamin D inadequacy in subjects of this study. The IOM report estimated that the proportion of persons with 25OHD levels at or above 50 nmol/L and a bone mineralization defect—defined as a ratio of osteoid volume to bone volume (OV/BV) above 2%—was 1% and from that concluded that the Priemel study indicated that 50 nmol/L was sufficient for over 97.5% of the population. Instead of a joint probability, the phase I panel concluded that the IOM committee should have calculated a conditional probability.

The phase I panel also examined two other potential statistical issues in the report that were raised by Dr. Baggerly. It concluded that the mixing of standard errors and standard deviations in Table 5-4 does not appear to be an error and the different measures of variance were not stated to have been used to weight the regressions shown in Figures 5-3 and 5-4 of the IOM report. Consequently, this issue is not further discussed by the present panel in this memorandum. The third concern raised by Dr. Baggerly relates to "the variance in the distribution of attained individual serum 25OHD levels conditional on a given age+vitamin D intake level."[iii] The phase I panel found that two sources of variance were ignored, which would have resulted in too narrow of a prediction interval around the mean, but the mean value itself was an unbiased estimate.

Charge to the Phase II Panel and Approach

This phase II panel was charged to advise Dr. McNutt on whether the first panel's findings impact the determination of the RDA for vitamin D in the 2011 report. Specifically, this panel was asked to:

1. Consider the findings of the first independent panel. Given the systematic review and totality of the evidence approach used in the original 2011 report, do the findings of the panel regarding mathematical or statistical errors/concerns have a meaningful impact on the RDA for vitamin D set in the 2011 report?

[2] A video recording of his presentation can be viewed at the following URL: https://youtu.be/y33I8Zb55Rw (accessed November 15, 2017).

2. Consider other more recent determinations of recommended intakes for vitamin D, including 2016 reports from the European Food Safety Authority (EFSA) and the UK Scientific Advisory Committee on Nutrition (SACN). Do these more recent analyses, which were able to draw from a larger evidence base that included individual level data, corroborate the answer to question 1?

Of note, the panel was not charged with reviewing or commenting on whether the methodology used by the IOM committee to set DRIs for vitamin D was optimal, nor was it asked to recalculate RDA values. Furthermore, this panel only considered the mathematical and statistical calculations discussed in the phase I panel report.

In accordance with the scope of its charge as described above, this panel adhered to the following principles as it undertook its deliberations:

- This panel accepted as given the choice of bone health as the only health outcome with sufficient evidence to provide a reasonable and supportable basis for use as an indicator of nutrient adequacy in DRI development for vitamin D. It did not consider whether other outcomes should have been used in the IOM analysis in place of or in addition to bone health.
- This panel accepted as given the IOM study committee's choice of bone health indicators for use in developing the vitamin D RDAs for specific populations. It did not consider whether other bone health indicators should have been used in the IOM analysis.
- This panel accepts that the IOM committee used both mathematical calculations and expert judgment to arrive at the DRIs for vitamin D.

To address its task in a systematic manner, the panel developed and answered a set of questions for the two errors identified in the phase I panel report (see analysis section below). This panel will justify its rationale for its determination of the effect of the errors, but acknowledges that, from a retrospective vantage, it is impossible to say with complete certainty whether and/or how the committee's collective judgment might have changed had the errors not been made.

Analysis by the Phase II Panel:

Prior to evaluating the potential impact of the two errors discussed in the phase I panel report, it is helpful to highlight key aspects of the IOM committee's process that are relevant to the work of this panel. In developing RDAs for vitamin D, the IOM committee employed a risk assessment framework and a process that involved a number of steps incorporating statistical analyses and decisions based on collective expert judgement. Importantly, as discussed on p. 369 of the IOM report, the data available to the committee did not lend themselves to the use of the standard process for DRI development, which is reliant on a normal distribution of requirements—which may not exist for vitamin D given its interactions with calcium—and the ability to determine an average requirement (an EAR). The RDA is usually set at 2 standard deviations above the EAR.[iv]

Based on the availability of data, the committee used 25OHD concentrations—a marker for total vitamin D exposure (diet and endogenous synthesis from sunlight exposure)—to simulate a dose–response

relationship for vitamin D intake and bone health. Evidence across multiple bone health indicators was examined and was used to determine a 25OHD level that would be expected to meet the needs of the majority of the population. The osteomalacia data from Priemel et al. were considered in the context of the target serum 25OHD level. To establish an RDA for some of the life stage populations, the committee then estimated the total intake that would be needed to achieve the desired 25OHD level, assuming minimal sun exposure as a cautious approach. The error in the construction of the confidence intervals pertains to this step in the DRI development process.

Task 1: What impact, if any, do the phase I panel findings regarding statistical errors and other mathematical issues have on RDA values?

I. Analysis of Priemel et al.

Q1.1: To what extent were the osteomalacia data from the study by Priemel et al. used by the IOM committee to develop RDAs?

The analysis of osteomalacia data from the observational study by Priemel et al. was included in the discussion of DRIs for adults 19-50 years of age.[3] The IOM report states on p. 367 that "data from the work of Priemel et al. (2010) have been used by the committee to support a serum 25OHD level of 50 nmol/L as providing coverage for at least 97.5 percent of the population."[i] The language used in the report suggests that the IOM committee considered the Priemel et al. data in the initial process of setting the target 25OHD level, but in a communication to the phase I panel, Dr. A. Catharine Ross, chair of the IOM committee that produced the 2011 report and a member of this phase II panel, clarified that "the study by Priemel et al. was not used to set either the RDA or EAR for vitamin D. These decisions had been reached, based on a review of the totality of literature to this point (a synthesis of more than 1000 articles), well before the Priemel et al. reprint (and dataset from the authors) were obtained, late in the committee's review process. The committee gave these data a look as a way of determining if the already-agreed values were in the appropriate range. The committee deliberated and decided not to conduct statistical modeling using these data because of the extensive limitations of the Priemel report."[v] These limitations include:

- uncertain specificity and potential for misclassification as clinical data were not available to rule out non-vitamin D-related osteomalacia
- the inability to partition data from samples representing a wide age range into age-sex groups used for setting DRIs limited the usefulness of the data set

[3] The Priemel data set includes samples from subjects in their 3rd through 10th decades of life with mean ages of 58.7 (males) and 68.3 (females), indicating these data were also applicable to other older populations considered in the IOM report. However, the data were not coded by age and no age range-specific analyses could be performed. Moreover, the committee relied primarily on RCT data on fracture risk to set RDAs for adults older than 70 years of age.

- use of autopsy samples and postmortem bone staining (the gold standard method of tetracycline labeling could not be used to confirm osteomalacia in deceased subjects and it is not known whether 25OHD levels in the post-mortem samples at the time of blood extraction were equivalent to pre-mortem levels)
- the use of a OV/BV cutoff of 2% as the criterion to define osteomalacia that is not well supported in the literature,[vi] whereas experts in histomorphometric analysis suggest cutoffs ranging from 3 to 5%[vii, viii]
- the lack of dietary data to indicate a deficiency in vitamin D or other nutrients that can affect bone mineralization (e.g., calcium)

The major implication of the Priemel et al. study, in the view of the committee, related to the possibility of a very low EAR for vitamin D, and the indication that calcium may be the driver nutrient for bone health, potentially compensating for low vitamin D levels. Even at serum 25OHD levels lower than 25 nmol/L, more than half of the Priemel et al. study subjects had OV/BV measures below the 2% threshold for bone mineralization defects.

Q1.2: Had the conditional probability intended by the committee been calculated and used as specified in the answer to Q1.1, would the RDAs for men and women 19–30 and 31–50 years of age have been different from those reported in the 2011 IOM report?

The IOM committee's report states that at a serum 25OHD level ≥ 50 nmol/L, 99 percent of the population was protected from deficiency (defined as OV/BV > 2%). However, if the conditional probability had been calculated as described in the phase I panel report, for serum 25OHD ≥ 50 nmol/L, only 91.5% of the Priemel et al. sample (75/82) would have not had the defect. *Given this calculation and OV/BV criterion*, a higher serum 25OHD level would be needed to achieve OV/BV < 2% for at least 97.5% of the sample. However, all other things being equal, if the more widely-used cutoff of < 3–5% OV/BV were used, it might not require a higher serum 25OHD level to achieve an acceptable level for at least 97.5% of the sample.

Although the report considered this observational study in postmortem samples as supporting evidence, these data were not instrumental to setting the DRI values or even the intermediary target serum 25OHD biomarker. The RDA values had been set based on a much larger integrated body of evidence. An apparent congruence of data was observed across several other markers of bone health (calcium absorption, bone mineral density, fracture risk)—no one of which alone would have provided sufficiently strong evidence to serve as a basis for DRI development. In addition, the conceptual model depicted in Figure 5-1 of the IOM report showed a plateau indicating diminishing returns for serum 25OHD levels above 50 nmol/L. This observation and the analysis of randomized controlled trial (RCT) data suggested to the committee that 50 nmol/L was a reasonable RDA-like target for serum 25OHD. Although it may be reasonably argued that serum 25OHD levels between 50 and 75 nmol/L may have conferred some level of additional improvement for some indicators, the exposure–response data did not support such fine resolution and the clinical benefit of such small increases is unclear, given the lack of RCT data showing such benefit.

Moreover, the committee also took into consideration emerging evidence related to all-cause mortality, chronic disease risk, and falls that appeared to suggest that adverse events may occur with serum 25OHD levels as low as 75nmol/L in some subpopulations. Increasing the target serum 25OHD to achieve small increases in beneficial effects for one marker of bone health may thus have resulted in detrimental effects on other outcomes. In the totality of evidence approach used by the committee, with consideration of both beneficial and detrimental effects of intake, 50 nmol/L was determined to be a serum 25OHD level that maximized the beneficial effects of vitamin D for the vast majority of the population while minimizing potential harm.

The precise answer to Question 1.2 is unknowable, as time has passed and the committee no longer exists. However, the phase II panel concurs that calculation of the conditional probability based on the data of Priemel et al. using a 2% OV/BV criterion would likely have resulted in changes to how the osteomalacia data from Priemel et al. were presented in the text (pp. 276, 292, 367, and 388 of the IOM report). However, based on the totality of the evidence discussed above, the low ranking of a cross-sectional design for strength of evidence in the DRI process, and caveats to the use of postmortem data, the panel thinks it unlikely that this result would have changed the determination of the RDA for vitamin D.

II. Relating Dietary Intake of Vitamin D to Serum 25OHD Levels

Q2.1: How were the confidence intervals in Figure 5-4 of the IOM report used in the estimation of vitamin D intake needed to achieve desired 25OHD levels?

To establish an EAR and RDA for those populations for which use of an intermediary serum 25OHD biomarker was needed due to insufficient dose–response data, the committee conducted a regression analysis of the relationship between achieved serum 25OHD concentration and total vitamin D intake. The committee used clinical trial data generated under conditions of limited sun exposure in the regression analysis to minimize the contribution of endogenous synthesis as a precautionary approach. As shown in Table 5-4 of the IOM report, 20 different studies were used in the regression, representing wide ranges of age, study design, and assays used to measure serum 25OHD levels. The confidence intervals shown in Figure 5-4 were calculated to depict uncertainty in the response of serum 25OHD to vitamin D intake and were examined in the DRI development process, but, because of the considerable uncertainty in the simulated dose–response relationship resulting from these recognized and other unknown sources of variation, the committee did not use the confidence intervals in an algorithmic approach for prediction. As indicated on p. 382 of the IOM report, recognizing the uncertainty in the predicted confidence intervals, the committee instead selected the estimated intakes in such a way that they would modestly "overshoot" the targeted serum 25OHD values for the EAR (40 nmol/L) and RDA (50 nmol/L) without approaching levels that emerging evidence (e.g., inverted J- or U-

shaped curves for all-cause mortality, cancer risk, frailty, and other outcomes) suggested could be associated with increased risk of harm for some subpopulations.

Q2.2: Given the totality of evidence approach used by the committee in the 2011 report, did other evidence reviewed by the committee have a modifying effect on the data analyzed and shown in Figure 5-4 of the IOM report?

As stated above, in determining dietary reference intakes, the committee took into account evidence of risk of harm as well as evidence of benefit. These data, which were suggestive of inverted J- or U-shaped curves for all-cause mortality and other outcomes (as presented in Chapter 6 of the 2011 IOM report), informed the UL but also the RDAs. For all-cause mortality, p. 435 of the IOM report states that "increases in risk are suggested at thresholds in the range of 75 to 120 nmol/L for the white population, with lower levels for the black population."[i] In addition, emerging evidence that fracture risk rose in the black population with increasing concentrations of 25OHD was another concern.[ix]

Q2.3: Had all relevant sources of error been appropriately incorporated into the process used to calculate the confidence intervals in Figure 5-4, how would this have affected the estimation of vitamin D intake needed to achieve desired 25OHD levels?

The phase I panel report concludes that two sources of variance were ignored in the construction of the confidence intervals in Figure 5-4—variation in serum 25OHD levels within each age+intake sample group and variation in individual responses around the predicted mean for new individuals in a given age+intake group. As a result, the width of the confidence interval around the mean is underestimated (i.e., "there is greater variation than indicated by the report if the model is used to predict attained levels of serum 25OHD for an individual based on his or her dietary intake"[iii]). Had the RDAs been set solely by using the confidence intervals in an algorithmic way, wider bands would likely have made a difference in the calculation of those RDAs. However, given that an exclusively algorithmic approach was not used by the committee to set the RDA values, this panel believes it is more likely that the error would have had no impact on the committee's determinations of the dietary reference intakes. The paucity of dose–response data did not enable precise predictive analysis and, as stated earlier, the committee sought to balance the potential for benefits and harm. One implication of using a wider confidence interval whose lower bound begins to plateau (slope becomes close to zero; or may not even increase monotonically) at a lower intake level for setting DRIs is that it would require very large vitamin D intakes (beyond those supported by the evidence) to achieve small incremental increases in serum 25OHD. Given the variability in the response of serum 25OHD to vitamin D intake and the fact that endogenous synthesis was not accounted for in the regression model, some individuals would be likely to significantly overshoot the 50 nmol/L target with such an approach, potentially reaching levels associated with adverse effects. Moreover, data from the National Health and Nutrition Examination Survey (NHANES) showed that mean U.S. serum 25OHD levels were already above the 50 nmol/L target (as shown in Tables 7-3 and 7-4 of

the IOM report). In the absence of clear evidence of benefit, it is unlikely that the committee would have specified a higher intake than 600-800 IU/d, given the public health policy implications of the RDA.

Task 2: Do recent determinations of recommended intakes for vitamin D that drew from a larger evidence base, including individual level data, corroborate the conclusions of the panel regarding the meaningful impact on the RDAs set in the 2011 IOM report of the two errors discussed in task 1?

In 2016, two independent reports were released establishing dietary reference values (DRVs) for vitamin D. The Scientific Advisory Committee on Nutrition (SACN)[x] reviewed DRVs for vitamin D in in the United Kingdom (UK) in response to questions on whether previous dietary recommendations were still appropriate given the implications of public messaging to minimize sunlight exposure and wear sunscreen. The European Food Safety Authority (EFSA)[xi] Panel on Dietetic Products, Nutrition and Allergies similarly reviewed DRVs in response to a request from the European Commission.

The SACN and EFSA reports, like the 2011 IOM report, used a risk assessment framework and both used the literature review and conclusions of the IOM report as a starting point for synthesizing the available evidence, but then, independently reviewed and analyzed data published after the IOM report. In reviewing the three reports, the panel noted similarities and differences in methodologies, including musculoskeletal outcomes used for setting DRIs/DRVs, target serum 25OHD levels, types of reference intakes established, and modeling approaches used to relate serum 25OHD targets to recommended vitamin D intakes (the methodologies and recommendations from the three reports are summarized in Table 1 below).

Although reference intakes were similar across the three reports (the SACN set a reference nutrient intake [RNI] of 400 IU/d and the EFSA set an adequate intake [AI] level of 600 IU/D),[4] the panel believes that any conclusions from a direct comparison of reference intakes should consider that there were differences in approaches used to derive those estimates. In addition, the extent to which the conclusions of the IOM report influenced the recommendations of the SACN and EFSA reports is unknown. Such an analysis, however, was beyond the scope of this panel. With regards to task 2 of its charge, the panel did not find the SACN and EFSA reports useful for the purposes of determining whether the errors discussed in the phase I panel report had a meaningful impact on the RDAs set in the 2011 IOM report. Importantly, however, an examination of the SACN and EFSA reports did underscore the fact that, even in 2016, there was no singular methodology for establishing DRIs for vitamin D. In all three reports, there is recognition of the complex biology of vitamin D and its relationship to calcium, and as a result, a significant component of judgment is needed in setting the requirements to ensure there is a comprehensive approach to

[4] An RNI is equivalent to an RDA in that it represents the amount of a nutrient that is likely to meet the needs of 97.5% of the population. In contrast, an AI could be equivalent to or exceed intake levels that would meet the criteria for an RDA.

considering all the data. Still, independent authoritative bodies of scientists with the expertise to independently evaluate the IOM report and assess the RNI or DRV values for their relevant populations have undertaken the process with varied approaches and still reached similar conclusions.

Phase II Panel Conclusions:

The IOM committee that authored the 2011 report faced a number of unique challenges in setting DRIs for vitamin D that precluded use of the standard processes for DRI development. The committee recognized that there was a great deal of uncertainty in the evidence pertaining to the relationship between vitamin D intake and health outcomes. While calling for additional research to address critical knowledge gaps, the committee, nevertheless was able, using its expert judgement, to achieve consensus on dietary reference intakes it felt were reasonable values to recommend for EARs and RDAs. Taking as a given the methodology used by the 2011 IOM committee to set DRIs for vitamin D, it seems unlikely to the panel that the two errors discussed in the phase I panel report would have had a meaningful impact on the committee's recommendations for RDAs. The two more recent reports (2016), by authoritative bodies in the UK and EU,[x,xi] reached substantially similar conclusions regarding DRVs and identical values for the UL. This panel, like the original IOM committee, recognizes that new research is emerging on an ongoing basis and that results from large clinical trials which are already underway are assessing effects of higher vitamin D doses, which may help address knowledge gaps related to dose–response relationships. Following publication of the results of such trials, it may be an apt time for a new committee to be charged with examining not only the updated body of evidence but also opportunities to improve the analytical methodologies employed in the DRI development process.

Table 1: Comparison of IOM, SACN, and EFSA Reports on Reference Intakes for Vitamin D

	IOM (2011)	SACN (2016)	EFSA (2016)
MODEL STRUCTURE			
	Risk (hazard) assessment/reduction	Risk (hazard) assessment/reduction	Risk (hazard) assessment/reduction
BIOMARKERS			
Serum 25OHD	Used as marker of total exposure	Used as marker of total exposure	Used as marker of total exposure
PTH	Not useful for DRI development (PTH levels influenced by multiple factors besides vitamin D)	Not useful for DRV development (PTH levels influenced by multiple factors besides vitamin D)	Not useful for DRV development (PTH levels influenced by multiple factors besides vitamin D)
FINDINGS FOR MUSCULOSKELETAL AND OTHER OUTCOMES (Bold text indicates use in DRI/DRV setting process)			
Rickets (children only)	**With adequate calcium, increased risk at serum 25OHD < 30 nmol/L. Minimal risk for serum 25OHD between 30 and 50 nmol/L.**	**Increased risk when serum 25OHD < 25nmol/L.**	**Evidence of overt rickets at mean serum 25OHD levels < 30nmol/L. No risk of rickets from vitamin D deficiency when serum 25OHD levels ≥ 50 nmol/L.**
Osteomalacia	Discussed Priemel et al. study as check of RDA-type serum 25OHD level already set by committee. Report states EAR-type serum 25OHD level would be very low (close to 0) and ≥ 97.5% population protected at or above 50 nmol/L (20 ng/ml). Using correct calculation, achieving that level of coverage would require a higher serum 25OHD for 2% OV/BV cutoff, but possibly not for higher OV/BV cutoffs (3–5%). RCT data were not available.	**Case reports and cross-sectional studies report osteomalacia at serum 25OHD < 20nmol/L and ≤ 15 nmol/L, respectively. Priemel et al. study not used due to noted limitations. RCT data were not available.**	**In addition to study by Priemel et al. which indicated the risk of osteomalacia is small for serum 25OHD ≥ 50 nmol/L, EFSA considered SACN report findings on osteomalacia data from case reports and cross-sectional studies. In patients with overt osteomalacia, serum 25OHD was below 20 nmol/L. RCT data were not available.**
Bone Mineral Density (BMD)/Bone Mineral Content (BMC)	**Discordance noted between observational studies and RCTs examining relationship between serum 25OHD levels and BMC/BMD in adults. Observational**	Some evidence of beneficial effect of vitamin D supplementation for adults ≥ 50y from RCTs and prospective studies, with one cohort study reporting an association	**Results of observational and intervention studies mixed but some evidence from observational studies suggests that risk of increased BMD/BMC loss**

	studies provide fair evidence to support an association between serum 25OHD and BMC/BMD. Specific circulating concentrations of 25OHD below which bone loss at the hip was increased, ranged from 30-80 nmol/L. RCTs in adults generally did not report associations between serum 25OHD level and BMD and benefit of vitamin D supplementation in calcium replete individuals was not clear.	between serum 25OHD < 50 nmol/L and greater rate of loss in hip BMD. Insufficient data to draw conclusions for adults < 50y. *Not used for DRV development.*	**is higher when serum 25OHD <50 nmol/L.**
Calcium Absorption	**Trend toward maximal calcium absorption noted at serum 25OHD between 30 and 50 nmol/L with no clear evidence of further benefit above 50 nmol/L. Use of 50 nmol/L level provides buffer to account for uncertainty in data and seasonal and dietary variation. Calcium absorption was an important basis for DRI development for vitamin D for adults 19–50y.**	*Not considered or used for DRV development.*	**Fractional calcium absorption shown to be compromised in patients with serum 25OHD levels ≤ 10 nmol/L but no evidence of threshold effect in adults with serum 25OHD concentrations > 30 nmol/L**.
Fracture Risk	**Achieved serum 25OHD levels varied considerably with high vitamin D doses used in RCTs. Some studies suggested 40 nmol/L sufficient to meet bone health requirements for most people but others suggested levels of 50 nmol/L and higher with consistent with bone health.**	Mixed results for adults ≥ 50y but overall evidence does not suggest that vitamin D supplementation decreases fracture risk in this population. Insufficient evidence to draw conclusions for adults < 50y. *Not used for DRV development.*	**Wide variation in serum 25OHD concentration associated with increased fracture risk but majority of studies found an increased fracture risk associated with baseline between < 18 nmol/L and <50 nmol/L. Increased fracture risk also noted in a couple of studies when serum 25OHD exceeded 50 to 75 nmol/L.**

Risk of Falls	RCT data did not support a causal relationship. Cross-sectional studies provided some support for an association between high serum 25OHD and reduced risk for falls but high quality cohort studies were lacking. *Lack of sufficiently strong evidence to support DRI development.*	**Evidence mixed but overall vitamin D supplementation appears to reduce fall risk in adults ≥ 50y, although very high levels may increase risk of falls.**	Study results inconsistent but suggest benefit of vitamin D supplementation for reducing fall risk over a broad range of baseline serum 25OHD levels (23-82 nmol/L). *No target serum 25OHD concentration with regards to risk of falls could be derived.*
Muscle Strength and Function	Physical performance data were considered together with falls. *Lack of sufficiently strong evidence to support DRI development.*	**For adults < 50y, limited evidence suggesting beneficial effect of vitamin D supplementation on muscle strength and function with baseline serum 25OHD < 20 nmol/L and < 30 nmol/L, respectively. Mixed evidence for adults ≥ 50y but overall suggestive of beneficial effect of vitamin D supplementation.**	Evidence was inconsistent. *No target serum 25OHD concentration could be derived from available evidence* (no strong support for an association).
Non-Musculoskeletal Outcomes (e.g., cancer, infection, cardiovascular)	Considered but insufficient data for use in DRI development.	Considered but insufficient data for use in DRV development.	Considered but insufficient data for use in DRV development.
TARGET SERUM 25OHD LEVELS			
	• Given uncertainty of data for adults 19–50y, committee selected 50 nmol/L as serum 25OHD level consistent with coverage of the requirement of nearly all adults in this age range (RDA-like). • Taken together with calcium absorption and BMD, and assuming a normal	• Unable to establish dose–response relationship. • Overall, evidence pointed to increased risk of poor musculoskeletal health between 20-30 nmol/L. • Set 25 nmol/L as "population protective level"—level that all individuals in UK should be above—and	• Found increased risk of adverse musculoskeletal health and pregnancy-related outcomes at serum 25OHD < 50 nmol/L (20 ng/mL). • Set 50 nmol/L as target for all age and gender groups.

	distribution of requirements, serum 25OHD level of 40 nmol/L set as consistent with a median requirement.	used this target to set RNI.	
RELATING SERUM 25OHD TO VITAMIN D INTAKE			
Modeling Method	Regression of ~20 studies (majority RCTs) across all age-groups (curvilinear model). Regression analysis initially conducted separately for 3 different age groups but no effect of age so single combined regression analysis presented in Figure 5-4.	Regression (linear model) using individual-level data from 3 RCTs (Cashman et al., 2008, 2009, 2011 for adults 20-40, adults ≥ 64y, and girls aged 11, respectively).	Metaregression of 35 RCTs with 83 trial arms (curvilinear model). Generated unadjusted and adjusted (for baseline serum 25OHD, latitude, study start year, analytical method used to assess 25OHD, and assessment of compliance) models. Adjusted model used to set AI.
Use of Confidence/ Prediction Intervals	Committee sought to modestly overshoot the targeted 25OHD concentrations because of considerable uncertainty in the simulated dose–response relationship. Report indicates that for both recommended intakes (400 IU/d for EAR and 600 IU/d for RDA), the lower predicted CI for the achieved 25OHD concentration was above the desired level. However, confidence intervals were not used for prediction purposes.	Estimated intakes that maintained serum 25OHD above set cutoffs (including 25 and 50 nmol/L) in 50%, 90%, 95%, and 97.5% of population.	Used lower limit of the 95% prediction interval, which illustrates uncertainty in mean response in a predicted future study, to set AI.
Assumptions	• minimal endogenous vitamin D synthesis from UVB exposure • adequate intake of interacting nutrients (calcium) • normal distribution of requirements	• minimal endogenous vitamin D synthesis from UVB exposure • adequate intake of interacting nutrients (calcium) • normal distribution of requirements	• minimal endogenous vitamin D synthesis from UVB exposure • adequate intake of interacting nutrients (calcium) • normal distribution of requirements

VITAMIN D REFERENCE INTAKES			
	• EAR set to 400 IU/d for all populations. • RDA set to 600 IU/d for people ≤ 70y. • RDA set to 800 IU/d for populations > 70y based on some greater uncertainty (heterogeneity) in this population and some RCT data demonstrating benefit of this higher intake level.	• RNI of 400 IU/d (10 µg/d) from all sources needed to achieve serum 25OHD ≥ 25 nmol/L during winter in 97.5% of the population. • Data not sufficient to set EAR-type value (at lowest vitamin D intake, serum 25OHD in 50th percentile were 34.5 nmol/L.	• Could not derive Average Requirements or Population Reference Intakes so provided Adequate Intakes (AI), which could be equivalent to or exceed intake levels that would meet the criteria for an RDA. • AI for all populations ≥ 1y set to 15 µg/day (600 IU/day).
ADVERSE EFFECTS			
Outcomes	Committee concluded emerging data related to all-cause mortality, chronic disease risk, and falls would appear to suggest that adverse events may occur with serum 25OHD levels of approximately 75 nmol/L or above but hypercalciuria data most reliable and used to set tolerable upper intake levels (UL). RCT of postmenopausal women treated with supplemental vitamin D + calcium had shown higher rate of renal stones.	Considered hypercalciuria, kidney stones, falls and fractures, all-cause mortality. Only hypercalciuria used to set UL.	UL set in 2012 EFSA report based on hypercalciuria. Data on associations with all-cause mortality and cancer risk were inconsistent.
Upper Intake Limit (UL)	4000 IU/d (100ug/d) for ages 9+ years	4000 IU/d (100ug/d) for ages 11+ years	4000 IU/d (100ug/d) for ages 11+ years

Summary of Key Differences: Different musculoskeletal outcomes used for setting DRIs/DRVs with greatest degree of similarity between IOM and EFSA reports; approach to setting target 25OHD level (similar for IOM and EFSA but SACN set population protective level); type of reference intake established (AI for EFSA, IOM only report to set EAR); modeling approach to relate serum 25OHD target to recommended vitamin D intakes (IOM and EFSA used metaregression, SACN used individual data).
Summary of Key Similarities: All three reports used a risk assessment model structure; all used summary analyses of studies (systematic reviews) or expert reports (white papers) to extensively

capture the existing literature; all concluded that bone health was the only outcome that could be used as an indicator of adequacy in the process of DRI/DRV development.

Summary of decisions: Despite differences in methodologies, all reports determined that serum 25OHD concentrations < 50 nmol/L were associated with increased risk (the population protective level was 25 nmol/L as determined by SACN) and reached a recommendation of 400-600 IU/d of vitamin D for adults (IOM set RDA to 800 IU/d for adults >70 y); and all three studies established a UL of 4000 IU/d.

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[iii] Memorandum from the members of the phase I panel to Dr. Marcia McNutt regarding purported errors in the 2011 IOM report, *Dietary Reference Intakes: Calcium and Vitamin D*.

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[v] Communication from A. Catharine Ross to the members of the phase I Panel, David Allison, Bhramar Mukherjee, and Suzanne Murphy.

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