

May 15, 2017

MEMORANDUM

To: Marcia K. McNutt, Chair, National Research Council

From: David B. Allison, NAM, Distinguished Professor and Quetelet Endowed Professor, University of Alabama at Birmingham
Bhramar Mukherjee, John D. Kalbfleisch Collegiate Professor of Biostatistics, University of Michigan School of Public Health
Suzanne P. Murphy, NAM, Researcher Emeritus, University of Hawaii Cancer Center

CC: Bruce Darling, Executive Officer, National Research Council

Re: Purported mathematical errors in the 2011 IOM report, *Dietary Reference Intakes: Calcium and Vitamin D*

In response to your memo to each of us dated March 10, 2017, regarding purported mathematical errors in the subject report, below please see the findings of this independent panel. Although the panel was not asked to determine how any such errors would change the RDA value presented in the Report, it is not evident to the panel that the issues pointed to by Dr. Keith Baggerly would have directly impacted the final values of the RDA set in the IOM report.

Background

In 2011, the Institute of Medicine (now the National Academy of Medicine) published *Dietary Reference Intakes: Calcium and Vitamin Dⁱ* (hereafter ‘the Report’). The Report determined dietary reference intakes (DRIs) for Vitamin D that are used in both the US and Canada. The Report set both an Estimated Average Requirement (EAR) and a Recommended Dietary Allowance (RDA) for various population groups determined by age, gender, and reproductive status (for example, infants, children, elderly, pregnant women, etc.).

One question that has been raised since release of the report concerns the analysis of one particular study used in the discussion of RDA for four of the twenty-two populations groups considered in the report. This study measured bone quality and serum levels of a Vitamin D biomarker, 25OHD, in cadavers.ⁱⁱ

The question of a potential mathematical or statistical error in the Report’s consideration of the data from this particular paper was recently raised again in written comments from Dr. Keith A. Baggerly, Professor of Bioinformatics and Computational Biology, M.D. Anderson Cancer Center, to the leadership of the National Academies of Sciences, Engineering, and Medicine.

Subsequent to presenting his written comments to the National Academies leadership, Dr. Baggerly also presented his concerns and analysis at the National Academies Sackler Colloquium on March 10, 2017¹. His presentation repeated the concerns in his written analysis, and broadened them to other statistical aspects of the Report that he thought to be in error.

Origin of this panel

In response to Dr. Baggerly's written comments, the President of the National Academy of Sciences, Dr. Marcia McNutt, convened an independent panel to consider Dr. Baggerly's concerns. In a letter to the members of this panel, Dr. McNutt asked them to "determine whether there is a mathematical error in the IOM report, Dietary Reference Intakes: Calcium and Vitamin D. The question pertains to the estimation of the serum RDA for Vitamin D, presented on pages 275-277 of the report." Pages 275-277 of the Report discuss the data from the above-referenced cadaver study (Priemel et al., 2010).

This Review

This review is limited to determining whether Dr. Baggerly's assertions regarding specific mathematical or statistical errors he cites in the Report are correct. The panel did not review any other mathematical or statistical calculations used in the Report beyond those Dr. Baggerly has asserted are in error.

This panel accepted as given the choice of the Priemel et al. study for use by the IOM study committee. The panel did not review the suitability of this study for use in estimation of the RDA for vitamin D, or whether other studies available in 2011 should have been used in the IOM analysis, either in place of or in addition to the studies chosen by the IOM Committee.

Analysis by this Panel

I. Analysis of Priemel et al.

In examining both the discussion in the Report and Dr. Baggerly's document, this panel concurs that the Report does not answer the intended question in its discussion the Priemel et al. data.

Pages 275-277 of the report consider the Priemel et al. data in the context of the determination of an RDA for Vitamin D. As page 276 states "The question for DRI development is not whether a maximal level (of Vitamin D) provides benefit, but at what level can the vast majority of the population (97.5 percent) expect benefit." Benefit is the avoidance of medical outcomes associated with Vitamin D inadequacy.

The Priemel et al. paper considered bone health, and the ratio of osteoid volume to bone volume (OV/BV) in the cadavers studied was used as a marker of that health. $OV/BV > 2\%$ (0.02) was taken to

¹ A video recording of his presentation can be viewed at the following URL:
<https://youtu.be/y33I8Zb55Rw>.

indicate individuals with inadequate bone health. Attained levels of blood serum 25-hydroxyvitamin D (25OHD) were measured in each individual.²

Based on the statement from page 276 quoted above, it appears that the Report is intended to estimate the lowest level of serum 25OHD in this study for which the prevalence of inadequacy (as measured by $OV/BV > 2\%$) among persons at that level (and also for levels above) is less than or equal to 2.5%. There were 82 people with serum levels at or above a serum 25OHD level of 20 ng/mL, and 7 of those people had $OV/BV > 2\%$.

Instead, the Report discussed among the full sample of 675 people in the study, how many were inadequate *and* had a serum level at or above the proposed RDA. There were 7 people with serum levels at or above a serum 25OHD level of 20 ng/mL (50 nmol/L), and $OV/BV > 2\%$. The prevalence estimate provided in the report divides that number by the total number of individuals in the study ($7/675 = 1\%$). This prevalence estimate is dependent on the size and distribution of the full study sample, not on the actual prevalence of inadequacy among those with intakes at or above the proposed RDA. The Report calculates a joint probability where what was intended was a conditional probability.

In addition, neither of these calculations captures the Report's intent as indicated in the quotation above. Instead, these probabilities reflect the prevalence of inadequacy for intakes at or above 50 nmol/L, not the prevalence *at* 50 nmol/L. Thus, neither of these calculated prevalences from the Priemel data is commensurate with what the Report stated was being calculated.

Put in mathematical terms, the Report discusses estimating the lowest value of τ , that satisfies the following inequality³ :

$$P(OV/BV > 2 \mid \text{serum } 25OHD = \tau) \leq .025. \quad [1]$$

However, the discussion in the Report actually calculates:

$$\hat{P}\left(\frac{OV}{BV} > 2 \cap \text{serum } 25OHD \geq \tau\right), \text{ where } \tau \text{ was set to } 50 \text{ nmol/L.} \quad [2]$$

In a communication to this panel, Dr. Catharine Ross, chair of the IOM committee that produced the Report, said, "The Priemel data were not used to set either the EAR or the RDA for vitamin D." She also notes that, "the proportion the committee estimated by comparing the '7 points' to the entire population was, as pointed out in the panel's analysis, not the right approach with respect to DRI development. Regrettably, the IOM report text did not extensively dissect the limitations to the Priemel

² The Report states "The Priemel et al. (2010) group defined a mineralization defect as a value of greater than or equal to 2 percent for the ratio of osteoid volume (i.e., bone matrix that is not mineralized) to total bone volume, referred to as OV/BV ."

³ Although a minor point, the Report alternates between discussing $OV/BV > 2$ vs $OV/BV \geq 2$ as the indicator of inadequacy. We will use ">" for the remainder of this Panel's report.

et al. dataset ...” She goes on to explain why the committee decided, based on its scientific judgment of the quality of the study, to give the Priemel data a low priority.

Additional Concerns Raised by Dr. Baggerly

Upon reviewing the material presented by Dr. Baggerly at the Sackler Colloquium on March 10, this panel determined to extend its comments beyond the written document submitted by Dr. Baggerly to the National Academies, to a broader set of potential errors raised in that presentation. There are two other potential mathematical errors which he raises; both are related to the conversion of desirable vitamin D serum levels to intake recommendations.

II. Mixing Standard Errors (SEs) and Standard Deviations (SDs)

The second concern is regarding an evidence synthesis across studies that correlate attained serum levels with dietary intake. The data used in this analysis are summarized in Table 5.4 on pages 372-377 of the Report. Dr. Baggerly asserts that four values utilized in the Report as SDs from one study (Schou et al (2003), were in fact SEs, and any inverse variance weighting using the data in the Report in the analysis would not have had the correct weights. However, page 371 of the Report, states that the studies shown in Table 5-4 “needed to report measured serum 25OHD levels with estimates of variance (standard deviation [SD] ,CI, or inter-quartile ranges) ...” Thus , it appears that the IOM Committee recognized that various measures of variance were present in the table. The discussion on pages 380-381 of the Report indicates that Figures 5-3 and 5-4 show the results of a mixed effects meta-regression analysis with study as a random effect, using the mean values reported in Table 5-4. While Dr. Baggerly’s assertion regarding different types of variance in the underlying studies is correct, the mixing of SEs and SDs in the table does not appear to be an error and these measures of variance were not stated to have been used to weight the regressions.

III. Relating dietary intake of Vitamin D to serum 25OHD levels

The third concern relates to prediction of attained serum 25OHD levels based on dietary intake of Vitamin D in specific age-groups. Dr. Baggerly asserts a potential underestimation in the Report of the variance in the distribution of attained individual serum 25OHD levels conditional on a given age+vitamin D intake level. This finally leads to overestimation of the lower limit of the prediction interval for attained serum level of 25OHD for an individual in a given age+intake group.

The Report presents a zero-intercept regression model relating serum levels to log(dietary intake) (Figure 5.4 on page 384 of the Report). The unit of analysis was *mean* serum level for a particular age+intake group. In using this model to estimate the quantiles of the conditional distribution of attained levels in new individuals based on age and dietary intake group, two sources of variance are ignored.

The first source of variance is that the fitted model uses the mean data for each sample group included, rather than individual person attained serum 25OHD levels. The analysis does not account for the

standard deviation of the attained serum levels about their mean in each age+intake group in the observed data. In other words, the present model treats all persons in a given age+intake group as if they had the same serum levels, but there is of course variation within the group that the aggregate/ecological analysis ignores. This is a common issue encountered in meta-regression.

The second source of variance occurs in predicting the attained serum levels for a **new** individual in a given age+intake group using the model in the Report. The variation of the individual responses about the predicted mean curve is not accounted for and the confidence interval for the conditional **mean** attained level for all subjects at that vitamin D intake level is provided instead. Consequently, the values provided for the lower and upper limits in the caption to Figure 5.4 are likely to be incorrect.

The net impact of both these concerns is not on the mean value that was used for the conversion of serum vitamin D levels to vitamin D intake levels, but on the width of the prediction interval around the mean. That is, there is greater variation than indicated by the Report if this model is used to predict attained levels of serum 25OHD for an individual based on his or her dietary intake.

ⁱ Institute of Medicine. *Dietary Reference Intakes: Calcium and Vitamin D*. Washington, DC: National Academies Press, 2011.

ⁱⁱ Priemel et al. *J Bone Miner Res*. 2010 Feb; **25**(2):305-12.