Problems With the Serum RDA for Vitamin D

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1. Statement of the Problem

We think the serum RDA of 20 ng/mL for vitamin D (serum 25(OH)D) set in the 2011 IOM report[1] is too low due to a mathematical error.

Using the same raw data (from Priemel et al, 2010[2]), we get an estimate of roughly 30 ng/mL. Parallel estimates Alicia Carraquiry has derived with data on intact serum parathyroid hormone (iPTH) give an estimate of 28 ng/mL, again much closer to 30 than 20. Given the logarithmic nature of the dose response curve for vitamin D, increasing the target serum level by 50% may require increasing the recommended intake in IU by several times this factor.

We give details of our observations below. Specifically, we

- examine how the IOM report describes estimating the RDA using data from Priemel et al
- load the raw Priemel et al data for analysis
- discuss how the Priemel et al data could be used to estimate the RDA, and then look at how it was used

- outline a back-of-the-envelope approximation for what we see the Priemel et al data suggesting for the RDA
- note how this estimation of the RDA also affects the EAR, as the former was used in deriving the latter
- note how concerns about the method of estimation used were raised in 2011
- discuss some related implications

The data and code used in preparing this report are attached.

We would be happy to discuss any of the points raised.

2. How the IOM Report Describes Estimating the RDA

The IOM report relies strongly on data from Priemel et al (2010), in which samples from 675 autopsy cases were used to examine the relationship between serum 25(OH)D levels (which are stable enough to be measured shortly after death) and bone health (the biological outcome of primary interest). If the ratio of unmineralized osteoid volume (OV) to total bone volume (BV) is less than 2%, requirements are said to have been met. The report uses this estimation to estimate the RDA as follows.

IOM p275ff:

> 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. The authors pointed out that, based on their findings, no subject experienced the defect at serum 25OHD levels of 75 nmol/L. That is, 100 percent of the population could be considered "covered" by a serum 25OHD concentration of 75 nmol/L. However, this conclusion from Priemel et al. (2010) over-states the levels of 25OHD in serum consistent with population coverage akin to an RDA. The question for DRI development is not whether a maximal level provides benefit, but at what level can the vast majority of the population (97.5 percent) expect benefit. The committee, therefore, examined the data provided in Panel D of Figure 4 (osteoid volume versus 25OHD scatterplot) from Priemel et al. (2010) in detail. Determination of the number of cases with serum 25OHD levels above 50 nmol/L and above 40 nmol/L was of interest. The number of data points above 50 nmol/L was counted by inspection of the data. At a serum 25OHD level of 50 nmol/L, there were seven data points reflecting persons who failed to achieve the prescribed bone mineralization (OV/BV $>$ 2 percent). This suggested that a serum 25OHD level of 50 nmol/L met the needs of 99 percent of the persons in the study (that is, only 7 of 675 surpassed the measure). In fact, the analysis suggested that 97.5 percent of the population met the measure at a serum 25OHD level of approximately 45 nmol/L; however, as it could not be precisely calculated from the graphic, 50 nmol/L was selected to err on the side of caution. Thus, more than 97.5 percent of the cohort was protected from the defect (OV/BV of $>=$ 2 percent) at a serum 25OHD concentration of 50 nmol/L.

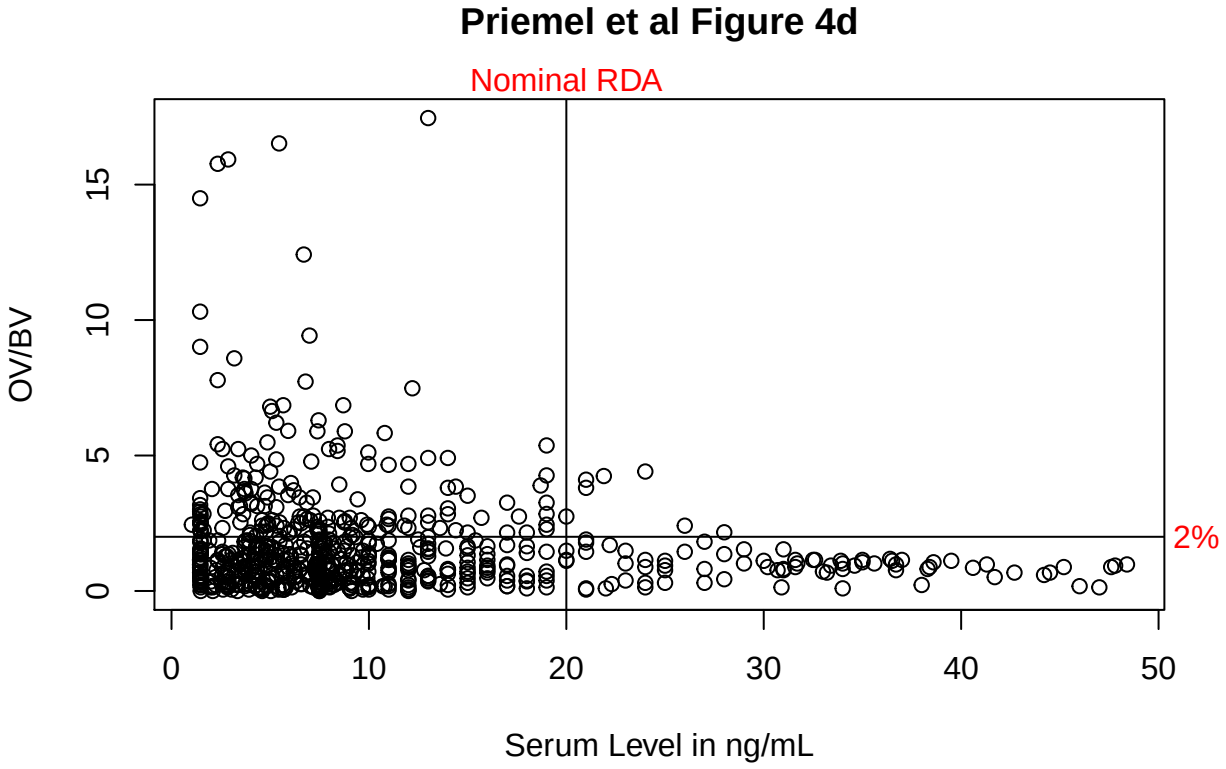
3. The Priemel et al Data

The IOM report describes visual inspection of Priemel et al's Figure 4d. It is actually possible to reconstruct the full dataset used for this Figure. Details of the reconstruction can be provided if desired, but they basically involve parsing the higher resolution version of the figure used in Maxmen 2011[3] for the observation coordinates. For now, we simply load the data for examination.

```
priemel <- read.csv("../../Priemel/Reports/priemelDataReconstruction.csv")
```

Plotting the data gives our reconstruction of Priemel et al's Figure 4d, with the requirement threshold and nominal RDA indicated.

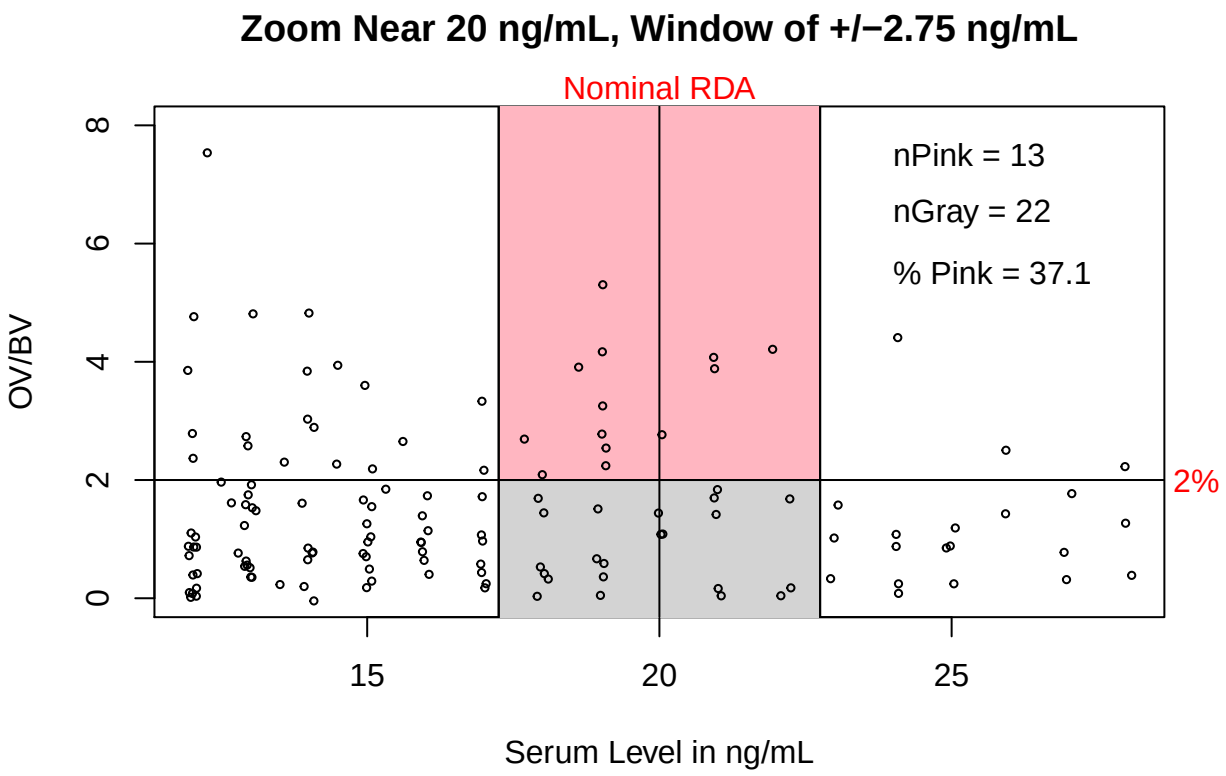
```r
plot(priemel$SerumLevelInNgPerMl,
     priemel$OV.BV,
     xlab = "Serum Level in ng/mL",
     ylab = "OV/BV",
     main = "Priemel et al Figure 4d")
abline(h = 2, v = 20)
mtext(" 2%", side = 4, at = 2, col = "red", las = 2)
mtext("Nominal RDA", side = 3, at = 20, col = "red")
```



3. How the Priemel et al Data Could Be and Were Used to Estimate the RDA

3.1 Local Windowing Around 20 ng/mL

First, we zoom in on the region around 20 ng/mL, jittering the points slightly for display. If 20 ng/mL is the right value for the serum RDA, and we had a huge amount of data, then of the individuals with serum levels very close to 20, just about 2.5% of them should have OV/BV values above 2% and thus not have their requirements met.



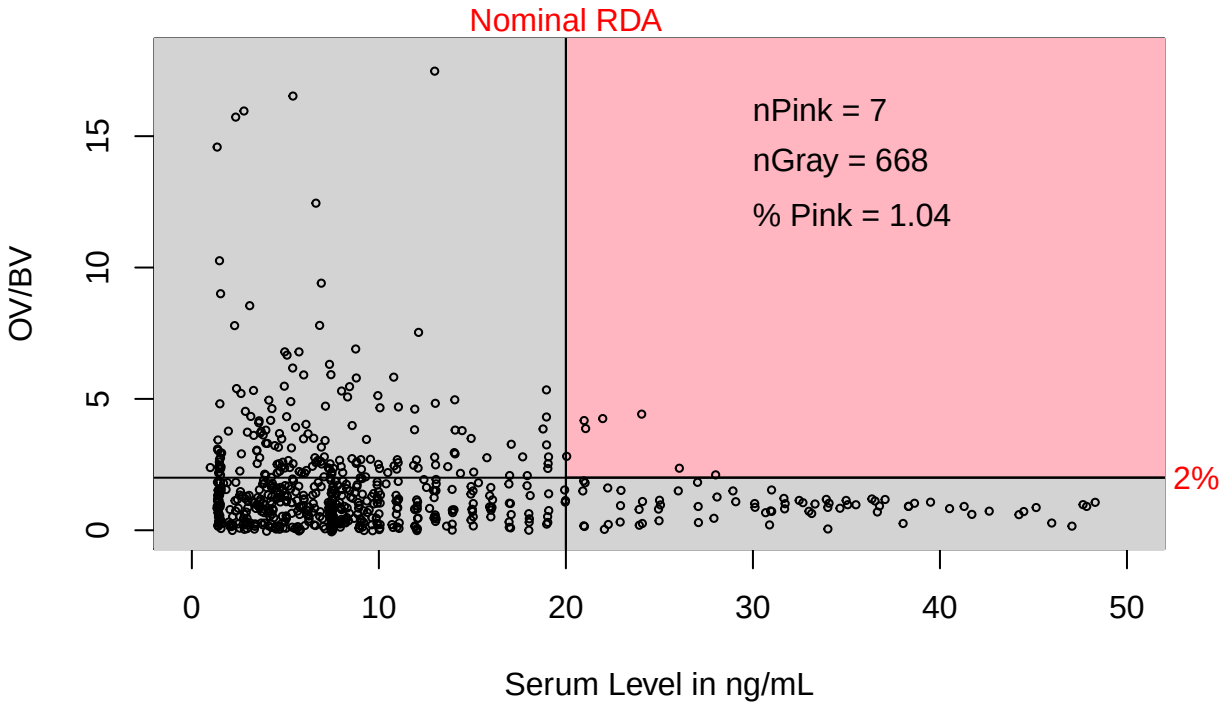
Using a window of +/- 2.75 ng/mL about the nominal RDA, we have data on 35 people. The 13 in the pink shaded region are not having their requirements met. The 22 in the gray shaded region are having their requirements met. Thus, 13/35, or 37.1%, do not have their requirements met. While we are admittedly not yet in the realm of very large numbers, this fraction is far larger than the 2.5% we want.

While we could expand the window we're using (say to +/- 5 ng/mL, or more),

- the more we expand it the more we run the risk of being "close enough" for the OV/BV ratio to be about the same, and
- visual inspection suggests we still won't get anywhere close to 2.5%.

3.2 How the Data Were Used

To see why our answers are so different from those in the IOM report, let's redraw Figure 4d to indicate the pink and gray regions associated with the rule used there.



Here,

- the gray region extends to the left of the pink region
- the gray region includes OV/BV values above 2%

Both of these can lead to very odd results with thought experiments.

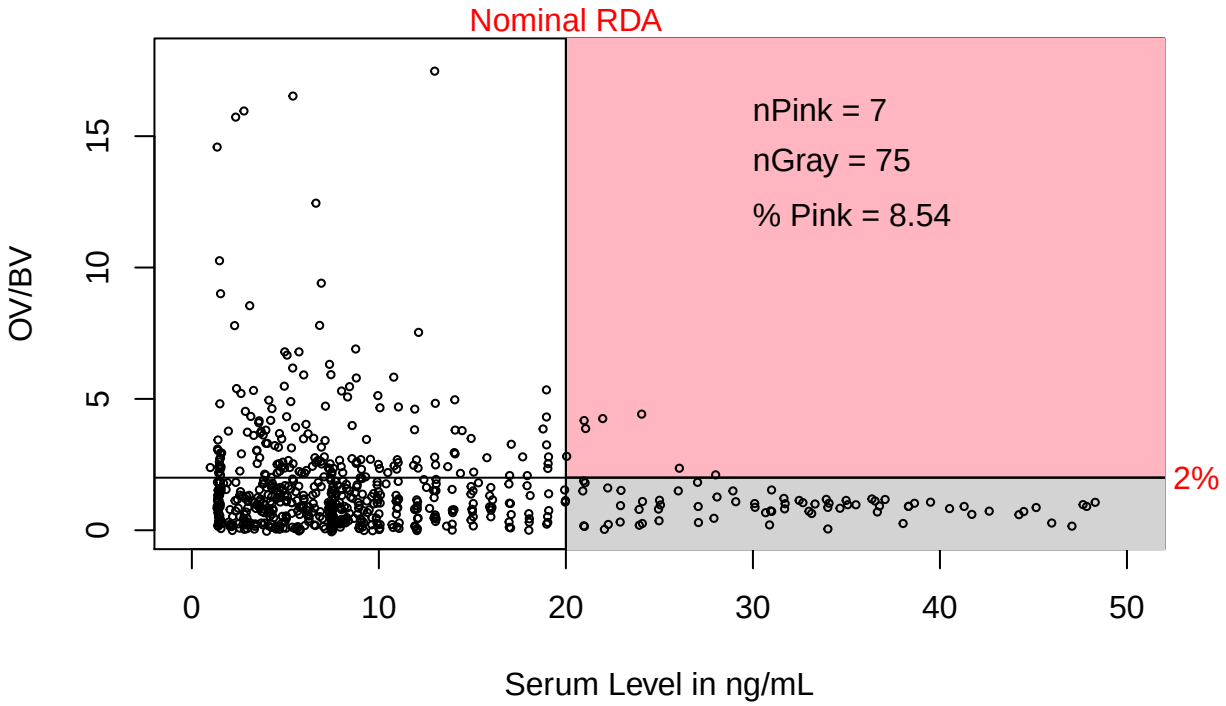
For example, say we now obtain data from another 10000 patients, all of whom had serum levels in the 2-4 ng/mL range (far below what's needed for good health). It's not clear that the likely response rates at these serum levels should be that informative about rates near 20 ng/mL, but adding these not only does affect things, it drives this estimate of the RDA down even further. There are 45 patients in the intial cohort with OV/BV values above 2% and serum levels at or above 10 ng/mL; adding 10000 in the 2-4 ng/mL range thus means the this estimate of the RDA would go below 10 ng/mL, as 45/10000 is less than 1%.

As another hypothetical, let's say we add data on another 1000 patients with values in the 18-20 ng/mL range, and that the fraction of these patients not having their requirements met is about 35% (close to the binned estimate near 20 we saw above). This information, instead of raising the estimate of requirements not being met at 20 closer to 35%, actually drops the estimate of this proportion even further.

3.3 Restricting Attention to Serum Values of 20 or More

Now let's consider what happens if we get rid of the gray region to the left of the pink region.

Figure 4d With Regions Above 20 Shown



This produces a valid estimate of the fraction of patients in an interval not having their requirements met, but

- the fraction is still above 2.5%
- the region is "centered" around 35 ng/mL
- the region isn't local enough

Adding lots more patients with serum levels between 30 and 40 ng/mL and assuming they all have their requirements met doesn't alter the fact that the failure rate near 20 ng/mL is still too high.

4. Our Approximation to the RDA

Since we think 20 is too low, what would we suggest?

One approximation is to view the problem as one of estimating the probability requirements will not be met as a function of serum level. Estimating p as a function of x is a common task for logistic regression. We restrict attention to patients with serum levels of 20 ng/mL and higher, in part because nobody's arguing we should go below this level.

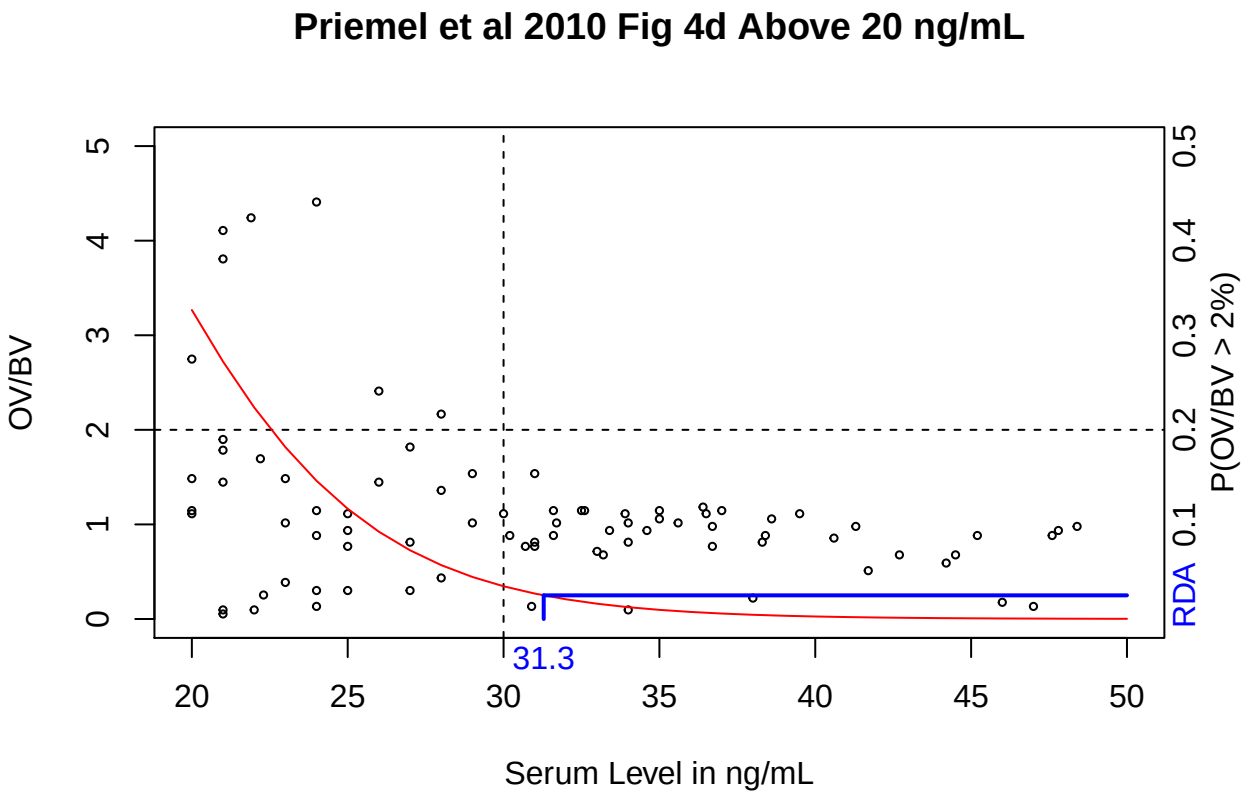
```
highSerum <- priemel$SerumLevelInNgPerMl >= 20

osteoidModel <-
  glm((priemel[highSerum, "OV.BV"] > 2) ~
        priemel[highSerum, "SerumLevelInNgPerMl"],
      family="binomial")

## Use the coefficients of the fitted model to estimate where
## p = 0.025 by looking at where the model hits logit(p) = log(p/(1-p))
```

```
serumRDA <-
  (log(0.025/0.975) -
     osteoidModel$coefficients["(Intercept)"])/
  osteoidModel$coefficients["priemel[highSerum, \"SerumLevelInNgPerMl\"]"]
## This gives 31.29 as the serum RDA
```

Plotting the data and the superimposed curve shows an estimate of around 31.3.



This estimate is in keeping with a subjective assessment on our part that a "plateau" in behavior is reached around 30; the OV/BV values are visually lower and less variable. This was part of what led Priemel et al themselves to argue that 30 ng/mL should be the target level.

We are not arguing that this fit of 31.3 is the "absolute best of all possible fits". We are arguing that a reasonable back of the envelope calculation shows the Priemel et al data suggest an RDA close to 30, not 20.

5. The RDA was Used to Derive the EAR

Per p369ff of the IOM report

> The standard model specifies, based on the assumption of a normal distribution for requirements, that the average or median requirement (i.e., the EAR) is used to calculate the RDA. This unanticipated situation is primarily evident for adults for whom it is not possible to estimate the level of 25OHD in serum at which 50 percent of the population is at increased risk of osteomalacia. Rather, in this case, the data allow a better estimation of the serum 25OHD level that likely covers most persons in the population. ... For adults, the evidence that most are covered by a serum 25OHD level of 50 nmol/L is used as the starting point, and a value of 40 nmol/L is estimated as the targeted level for a median dietary requirement.

I.e., the estimated RDA of 50 nmol/L (20 ng/mL) was used as a starting point, and the EAR of 40 nmol/L (16 ng/mL) was subsequently derived.

The report text on p366-8 does mention several factors which were considered in setting the EAR. However, the committee's summary of these combined effects on p369 states

> Overall, when the data are examined for an EAR-type of serum 25OHD concentration—that is, a median type of value, a level above which approximately half the population might meet requirements and below which one-half might not—the data do not specifically provide such information, although this value can be concluded to lie between 30 and 50 nmol/L for all age groups.

The upper limit of this range, 50 nmol/L, is their estimate of the RDA; this text immediately precedes the citation from the previous section noting how the committee started at the RDA and worked down.

Replacing the 50 used here with 75 (30 ng/mL), the "median type of value" would move the EAR from 40 nmol/L (16 ng/mL) to 52.5 nmol/L (21 ng/mL) – the revised EAR would exceed the RDA value initially used.

The fact that this ordering of estimation (RDA before EAR) was used was not apparent in the IOM's response to other concerns in 2015 http://www.nationalacademies.org/hmd/Global/News%20Announcements/How-the-RDA-for-Vitamin-D-Was-Determined.aspx

> The Recommended Dietary Allowance (RDA), by definition, meets the requirements of 97.5 percent of the population. It is set from an Estimated Average Requirement (EAR) that represents an intake amount that will meet the needs of about 50 percent of the population.

6. Earlier Reports of This Problem

We are not the first to worry about this issue of estimation.

Concerns about the method used in the IOM report to estimate the RDA were the subject of a news feature in Nature in 2011 (Maxmen 2011[3]) in which committee members JoAnn Manson and Cliff Rosen were cited. Michael Amling (senior author of the Priemel et al study was among those raising concerns). Per the feature:

> In response to Amling's charge that the IOM made a mathematical mistake, Rosen maintains that the method the IOM used to calculate 1% risk is standard procedure for dietary recommendations.

This problem was also alluded to in less detail by Holick et al 2012[4] (p1153 and Figure 1) and by Heaney et al 2011[5].

7. Implications

First and foremost, if the serum RDA is as far off as we believe, the public health implications are large. The associated recommended intakes will not suffice to meet the requirements of the vast majority of the population. Just as an illustration, using the dose response curve given in the report (p.384), serum level in nmol/L = 9.9 log(intake), a target serum level of 75 nmol/L suggests an intake of exp(75/9.9) = 1950 IU/day, far in excess of the current recommendation of 600. Other estimates could be used, but they would all point to a higher intake.

Similarly, using a lower EAR obscures the magnitude of the public health issue. Manson et al 2016[6] recently argued that vitamin D deficiency was not pandemic. Based on data from NHANES, Taylor et al 2015[7]

(Figure 1) show roughly 15% of the US population is below an EAR of 16 ng/mL. That fraction is close to 50% if an EAR of 21 ng/mL is used. Both also voice concerns about the dangers of targeting getting most of the population to a serum level of 20 ng/mL (the nominal RDA) because that would unacceptably raise risks that some fraction of the population would then exceed the UL of 50 ng/mL http://www.nationalacademies.org/hmd/Global/News%20Announcements/How-the-RDA-for-Vitamin-D-Was-Determined.aspx. But 20 is actually below the EAR, so we view the risks to bone health as being at least as large.

To the extent that the values for the EAR and RDA were used in choosing the scaling factor for moving from the NOAEL to the UL, estimation of the latter may need to be reviewed as well.

Many institutions use the RDAs for setting their own guidelines, so the range for further downstream effects is large.

8. Conclusions

As noted in the introduction, we are happy to discuss any of the points raised here in more detail.

At present, however, we cannot see how the current recommendations can stand.

9. References

1. Institute of Medicine. Dietary reference intakes: calcium and vitamin D. Washington, DC: National Academies Press, 2011.

2. Priemel et al. J Bone Miner Res. 2010 Feb;25(2):305-12. doi: 10.1359/jbmr.090728.

3. Maxmen, A. Nutrition advice: The vitamin D-lemma. Published online 6 July 2011. Nature 475, 23-25 (2011). doi: 10.1038/475023a.

4. Holick et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30. doi: 10.1210/jc.2011-0385.

5. Heaney et al. The IOM Report on Vitamin D Misleads. J Clin Endocrinol Metab. 2011, e-letter commenting on Ross et al re "What Clinicians Need to Know" http://press.endocrine.org/doi/10.1210/jc.2010-2704.

6. Manson et al. Vitamin D Deficiency — Is There Really a Pandemic? N Engl J Med 2016; 375:1817-1820. November 10, 2016. doi: 10.1056/NEJMp1608005.

7. Taylor et al. Use of Folate-Based and Other Fortification Scenarios Illustrates Different Shifts for Tails of the Distribution of Serum 25-Hydroxyvitamin D Concentrations. J Nutr. 2015 Jul;145(7):1623-9. doi: 10.3945/jn.115.211185. Epub 2015 May 13.