SACN report response mdf.22.09.2015

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Scientific commentary on the draft SACN Vitamin D report

1. Methodology, terminology and criteria:

Most of the intakes recommended do not meet the requirements for an RNI. The review criteria were not appropriately adapted for vitamin D and are not fit-for-purpose.

The fundamental requirement of an RNI is to 'ensure that needs are met'.
The overall approach taken in the report fails to take into account the particular structural characteristics of the evidence on vitamin D. As a result the recommended intakes and the definition of optimal serum 25(OH)D3 are optimistic in terms of risk reduction. Most of the recommendations leave the UK public at material and unjustifiable risk of avoidable serious ill health and therefore substantially fail to meet the requirements of an RNI.

The aspects of current understanding and evidence on vitamin D which are key to the appropriate derivation of recommendations are unusual but nevertheless quite straightforward:

> Virtually all of the population have for significant times in their lives a vitamin D status substantially below that which would arise from a natural level of exposure of unprotected skin to UVB. Thus *a priori*, in the absence of evidence to the contrary, there is a material possibility that to ensure that 'needs are met' supplementation would be required at intakes which ensure that to a first approximation all subjects at all ages and at all times of the year have a serum 25(OH)D3 status which is at or above the bottom end of the natural-exposure distribution.
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> Unfortunately there is a gross lack of current evidence supporting the determination of the causal relationship between health and interventions at various doses up to those which would reproduce natural-exposure status, e.g. interventions up to circa 4000 IU/d in adults. At this time ample medium term and some long term evidence only exists for interventions up to 400 IU/d. There is much less evidence at doses between 400 and 1000 IU/d. There are virtually no studies whatsoever testing interventions at 2000 IU for medium term or long term outcomes. Furthermore there is a complete lack of published interventions examining the long term consequences of interventions at three critical developmental phases in which vitamin D clearly plays a significant role: firstly the period which covers conception and early development, secondly gestation, and thirdly the period from infancy to early adulthood. Thus current ample interventional evidence only exists for about one tenth of the natural adult dose, and even at this fractional dose the evidence does not cover three of the most important developmental phases in terms of medium or long term outcomes.

The two principle approaches taken in the report are to look at intervention data and to look at disease-specific serum 25(OH)D3 concentrations. Given the huge gaps in the available evidence noted above, these approaches are severely limited. The intervention

analysis in the report fails to recognise and fails make clear that the intervention data only covers a fraction of the natural dose and is lacking coverage of some critical phases altogether. The analysis fails to recognise that therefore it is impossible to come to a valid scientific conclusion that the limited parameters tested demonstrably include those which would produce the optimal reduction in risks of ill-health. Unsurprisingly the report determines that intakes of 400 IU/d, that is the highest dose amply tested, is definitely better than no supplementation at all. Similarly the serum 25(OH)D3 concentration analysis in the report fails to recognise and make clear that the population groups and phases studied are grossly deficient as they fail to include any reference group with lifetime natural-exposure vitamin D status.

The approach actually taken in the report is not to determine the intake which ensures that 'needs are met' as is required for an RNI. Instead the report has determined a serum 25(OH)D3 concentration and vitamin D intake below which the (grossly limited) dataset demonstrates a proven increase in risk of ill health (The 'proof-of-illness' level).

Vitamin D supplementation is not the managed intake of an essentially dietary substances in order to compensate for a deficit in diet. Vitamin D supplementation is the oral intake of a hormone precursor to compensate for a deficit in endogenous synthesis. The working group should have recognised that the application of standard approaches for determining intakes of essentially dietary substances was not appropriate in forming recommendations for vitamin D. In this case the scientific gold standard for fit-for-purpose public health recommendations is to balance the probability-and-severity-weighed risks of deficiency against the probability-and-severity-weighed risks of intervention. As stated above the vitamin D context is one in which on the one hand proof of benefit has only been determined over a very limited range of doses and phases of intervention and where on the other hand there are strong inverse associations with a notable number of illnesses of extreme severity and high incidence. In this case, the correct scientific approach would be to constructively review the biochemical evidence. Such a review would have revealed to the working group that there is a direct relationship between serum 25(OH)D3 concentration and a plethora of immunological cytokine responses, serum 1,25(OH)2D3 concentration during pregnancy (see below), and several indicators of calcium metabolism and bone development. The interpretation of some of these relationships may be open to question However taken as a whole these biochemical indicators clearly indicate that human physiology is abnormal at serum 25(OH)D concentrations below circa 80nmol/L, and is remains normal for a wide range of concentrations above this level. This is consistent with studies which show that 80nmol/L is the bottom end of the range of serum 25(OH)D3 concentrations arising from natural levels of UVB exposure of unprotected skin. In this context the approach which is fit-for purpose is necessarily one which includes a precautionary element with the aim of finding a safe level of intake which goes some way to bridge the gap between the 25nmol/L 'proof-of-illness' threshold and the 80nmol/L biochemical normalization threshold. A vitamin D review at the present time which fails to seriously evaluate this precautionary approach is not fit for purpose.

Failing to extend the analysis in this way may have been a function of the gaps in expertise in the working group. It cannot be appropriate that a UK working group assembled in 2011 to look at vitamin D in the UK failed to include an orthopedic clinician with expertise in pediatric orthopedics and failed to include a clinician specializing in multiple sclerosis. Vitamin D activity is hormonal. It is stunning that the working group did not included a leading endocrinologist**.** Using the narrow criteria described in the report it is not surprising that the working group found 'insufficient evidence' to draw any conclusions in the areas of cancer, type 1 diabetes, multiple

sclerosis and age-related cognitive degeneration. What is surprising, and is scientifically flawed, is to ignore the shortcomings of the evidence and to claim that the level and intakes recommended 'ensure needs are met'. At a minimum there should have been an analysis of the residual risks remaining for the public with intakes at the recommended levels and the results of this analysis should have been included in the report. In contrast the report in its current form reads as if the approach taken has absolutely determined the adequate intake, without material qualification. It would be seriously misleading and unethical for the final report to continue to represent the adult intakes chosen as RNI's and doing so may be subject to legal challenge. The only recommendation which is likely to meet the requirements of an RNI is the intake for infants.

In our view a much wider and more expert discussion should have taken place at the beginning of the review process developing criteria for vitamin D recommendations based on first principles. There should have been no continuation of the misconception that vitamin D deficiency is a dietary deficiency and should be analysed as a dietary deficiency. We would not want to pre-empt the outcome of this discussion but our suggested determinations would be along the lines given at the end of this submission.

2. Recommendations for the non-white and other high-risk groups:

The methodology of determining the needs of the groups at greater risk is flawed and if not corrected the resulting recommendations are discriminatory and irresponsible. The working group should have made a rigorously-determined recommendation specific to these groups, or no recommendation at all.

The report makes the appropriate determination, that vitamin D deficiency rickets is one of the main identifiable and avoidable pathologies of interest in the UK at this time. The benefits of strategies that avoid rickets extend to the large number of unreported cases, and the probably much larger number of less sever but nevertheless important manifestation of vitamin D deficiency. What is not recognised in the report nor taken into account in the decision making is that over 90% of the published cases of rickets in the UK are in the non-white population. Even adjusting for reporting bias, it is clear that the incidence of rickets in the UK is predominantly in the non-white population. A recent report from Glasgow is consistent with an incidence about 100 times higher within the non-white population than in the white population [Ahmed 2011] . One of the essential objectives of the review should have been to ensure that the needs of the non-white population were given rigorous attention with an appropriate recognition of the larger risks of setting intakes which are too low, and therefore greater need for precaution. Clearly the report does not meet these objectives.

First of all the key scientific premise on which the report claims to have addressed the needs of the more at risk groups is fundamentally flawed:
"796. Population groups considered to be at risk of having serum 25(OH)D concentrations < 25 nmol/L include people from ethnic groups with dark skin. The role of skin colour, however, is complicated by behaviours that could also affect serum 25(OH)D concentration (e.g., wearing clothes that cover the skin when outdoors; sun avoidance). Other population groups at risk of having individuals with serum 25(OH)D concentrations < 25 nmol/L include frail and institutionalised people and those not spending substantial time outdoors. An increment added to the RNI was not considered necessary for these *'at risk'* population groups because the recommendation that the RNI is applicable throughout the year is to

take account of individuals with minimal sunshine exposure, including those most at risk. "

The approach of the working group is largely based on two intervention trials of white subjects with the outcome measured at the end of winter [Cashman e.a.]. A key premise was that, as the measurements were made at the end of winter, there was therefore minimal benefit from sunshine exposure. *This interpretation is fundamentally flawed*. Beyond any doubt, the distribution of end-of winter concentrations of the white population in the regions covered by the trials had a large dependency on the end-of summer sunshine-generated stores. For example in a recent study post-menopausal Caucasian women living in Surrey had median winter serum 25(OH)D3 concentrations circa 44nmol/L, about 10 nmol/L higher than their counterparts living in Aberdeen, and Asian post menopausal women living in Surrey had median winter concentrations of circa 23nmol/L. Notably the percentages of each group with levels below 25nmol/L in winter are 9%, 40% and 64% respectively. Beyond doubt, the end of winter vitamin D status white cohorts in the Cashman e.a. studies have benefitted significantly from sunshine, even in the nominally sun-avoiding subgroup, and to conclude otherwise is a serious flaw. Assuming that the determinations made for this white group were valid, such that supplementation at the recommended intake would result in 97.5% of the cohort achieving serum 25(OH)D3 concentrations of >= 25nmol/L, then without doubt, the fraction of the non-white population, even in southern England, who would have serum 25(OH)D3 concentrations of >=25noml/L at the recommended intake will be significantly less than the target 97.5% considered acceptable for the white population. Thus the detailed basis for calculating intakes is fundamentally invalid for the non-white population, and indeed is also invalid for any sub-group of the UK white population living in regions of the UK with a substantially lower UVB availability than that represented by the reference studies.

The second methodological flaw is to fail to take into account the circa two orders of magnitude higher incidence of pathological vitamin D deficiency in the non-white groups in the consideration of risk benefit balance. The appropriate degree of precaution is different in the different population groups. Other things being equal, in the non-white group, the likely outcome of proper risk-benefit assessment, is to go further in avoiding the risk of symptomatic deficiency. In other words the appropriate approach would be to set target serum 25(OH)D3 concentrations and recommended intakes for the non-white group which had a larger precautionary component, purely on the basis that the risks were up to one hundred times higher in this group. We suggest that if the incidence of rickets in the white southern UK population were one hundred times higher than at present, it is highly likely than this working group would have suggested a more cautious approach to setting levels and intakes, and that the target level for serum 25(OH)d3 concentration would have been set with a precautionary increment well above 25nmol/L, and similarly for the recommended daily intake.

It is therefore even more inappropriate for the working group to have made recommendations which actually guarantee that a larger fraction of the most at risk groups will be deficient.

One of the most serious foreseeable consequences of inadequate adult intake will be in deficiency from conception through gestation and at birth. There will also be an increase in the incidence of deficiency in cases where infant supplementation is not reliably started soon after delivery. On the best available UK data (Cockburn 1980) supplementation at the recommended intake will result in *mean* umbilical cord 25(OH)D3 concentrations of less than *20 nmol/L* for winter births of white mothers in Edinburgh. Cockburn 1980 is the most relevant study available. Even allowing for the shortcomings in this study the large trial size and the substantial degree of reported deficiency supports the conclusion that due to the flawed methodology it is likely that with supplementation at the recommended intake an unacceptable fraction of the non-white mothers and their progeny will have serum 25(OH)D3 materially below the target

level during conception, gestation and at birth for pregnancies anywhere in the UK, at any time of year. The working group has thus failed to address the needs of the most at risk groups. In the context of the limited data for non-white subjects, either the working group should have proposed a robustly considered and conservative intake with a precautionary element, or the working group should have determined that it was not in a position to make any recommendation for these groups at all without additional studies. What is totally unacceptable is to take an optimistic musculoskeletal-limited view of the intake required by white people in the middle of the UK in winter, incorrectly conclude that the methodology provides a valid estimate for other groups with substantially lower summer synthesis and present this as an appropriate RNI during pregnancy and gestation for a group with currently a circa 100 fold higher incidence of rickets. The approach taken and the resulting recommendations are irresponsible and discriminatory.

3. Questionable conclusions: The recommended supplementation is near the borderline of futility for the older age group at the same costs as supplementation at levels which are more likely to produce benefit and could be done at essentially zero additional risk.

The working group has recommended an intake of 400 IU/d for adults. As we have explained elsewhere the evidence on which this is based is largely limited to interventions at this level. The critical test that should have been applied and reported, is to determine whether the limited but nevertheless important evidence for interventions at above this level supports the conclusion. The report quotes from a number of meta-analyses. The evidence from our quick review of these meta-analyses, is that daily doses in the range 700 to 1000 IU/d showed greater benefit than doses of 400 IU/d. This is specifically stated in some of the meta-analyses, *and is reported in the draft report*. It appears that in some of the meta-analyses, the 700-1000 IU/d showed a benefit where there was none at 400 IU/d. The working group should have carried out, or should have had commissioned, meta-analyses in older people on falls and breaks which specifically compared daily supplementation at 400 IU to daily supplementation at 700 IU/d to 1000 IU/d. If the trend we have highlighted were confirmed, this would be significant evidence that a supplementary intake of 700-1000 IU was likely to reduce the risk of ill health to a greater extent than an intake of 400 IU, in this key age group. A recommendation is being made in the draft report which would attract the communication and medication costs of supplementing the whole population at a level which is demonstrably near the borderline of futility for the older age group. Adult supplementation at a level such as 1000 IU/d could be done at the identical cost, would be likely to produce greater benefit and would be just as safe.

This data also challenges the adoption of a target of serum 25(OH)D3 concentration of 25 nmol/L. It is unlikely that a material number of subjects supplemented at 400 IU/d in the test groups covered by the meta-analyses would have serum 25(OH)D3 concentrations below 25 nmol/L. Thus if 25 nmol/L were the cut off for benefit, there would be no differential between the outcomes at 400 IU/d and the outcomes at 700-1000 IU/d. The working group is perhaps the only body of its kind in the last five years to set a target minimum serum 25(OH)D3 concentration as low as 25nmol/L. The meta-analyses above are material evidence that the working group may be in error in setting such a low target for minimum serum concentration.

4. Failure to note and address the questions raised by the relationship between the concentrations of serum 25(OH)D3 and serum 1,25(OH)D3 during pregnancy

and the relationship to numerous other bone metabolism or immune system biochemical indicators of sufficiency.

The report states that "There is little correlation between serum concentrations of 25(OH)D and 1,25(OH)2D" [paragraph 43]. The working group seems to have missed , or omitted to report, that there is a very important time when serum 1,25(OH)2D3 concentrations are variable and are strongly correlated with serum 25(OH)D3 concentration. In pregnancy one of the first changes, is that the serum 1,25(OH)D3 concentration typically doubles or triples, to a concentration which would be lethal in a non-pregnant subject. The working assumption has to be that this change in serum 1,25(OH)2D3 concentration has functional importance. The pregnancy serum 1,25(OH)D3 concentration only becomes serum 25(OH)D3 concentration independent at serum 25(OH)D3 concentrations above about 80nmol/L. Therefor unless and until proven otherwise, there is a material risk to having a serum 25(OH)D3 concentration below about 80 nmol/L from pre-conception to delivery. At the minimum serum 25(OH)D3 concentration of 25nmol/L targeted in the report, the median 1,25(OH)2D3 concentration during pregnancy is about one half its 'plateau level' at serum 25(OH)D3 of about 80 nmol/L. Thus there can be no scientific conclusion at the current time that a serum 25(OH)D3 concentration of 25nmol/L is demonstrably sufficient from conception to delivery, either for the mother or the fetus.

5. Example of outline recommendations:

1. We agree with the working group conclusion, that the threshold for 'proof-of-illness', is a serum 25(OH)D3 of circa 25nmol/L.

2. The totality of the evidence adequately demonstrates a threshold for serum 25(OH)D3 concentration for normalization of biochemistry at circa 80nmol/L. Unsurprisingly is the same as the bottom end of the natural-exposure range.

3. The associative and scientific evidence establishes the possibility of substantial ill-health due to low vitamin D status. Together with an absence of proof-of-non-causality this leads to the conclusion that the correct strategy is one which includes a significant precautionary element.

4. On this basis the recommended daily intake for white UK adults should be 1000 IU/d. This supplementary oral intake is one quarter of the estimated natural synthesis rate, and is essentially risk-free in the otherwise healthy population.

5. The target serum 25(OH)D3 concentration, to be achieved in the majority of any significant sub-group, should be at or above 50nmol/L. The expectation is that with adult supplementation of the white sub-group, this serum concentration target will be met by about 80% of the group, at the end of winter. This is below the '97.5%' number used for dietary recommendations, but there is as yet no scientific basis to support the proposition that the 97.5% target is a rational target for minimum vitamin D status.

6. These recommendations should be properly explained and presented - the 50nmol/L is not 'RNI-like' and the 1000 IU/d is not an RNI level. On current best evidence the 'RNI' serum 25(OH)D3 concentration is circa 80nmol/L and the RNI intake for adults is circa 4000IU/d. However, in the absence of direct proof

of benefit, the 50nmol/L concentration is chosen as a common sense interim target, providing a significant safety factor above the 25nmol/L threshold for proof-of-illness. In addition this would achieve a partial but significant normalization of vitamin D impact on other biochemical indicators at a oral dose which is essentially risk free and which is still far below the rate of endogenous synthesis from natural levels of UVB exposure.

7. It should be made clear that there is no suggestion being made that vitamin D supplementation is a 'magic bullet'. Supplementation at above the 'proof-of-illness' level is only an essentially risk-free precaution which will demonstrably go a long way to normalise immunological, calcium and bone pathway biochemical indicators, and to normalise serum 1,25(OH)D3 during pregnancy. The likelihood is that this will go some way to protect the population against the evident risk arising from associations and scientific studies in which a causative role for vitamin D deficiency is plausible and cannot be ruled out at the current time.

8. For the non-white adult population the recommended intake should be 2000 IU/d. This is a dose which is estimated to bring the distribution of serum25(OH)D3 concentrations of the non-white population more into line with the expected distribution of the white population. This recommendation also recognises that there is a greater imperative for a precautionary increment in this group given the estimated two orders of magnitude higher incidence of rickets relative to the incidence in the white population.

9. The recommendations should be presented as interim guidelines, to be reviewed after five years or earlier if mandated by new evidence.

10. In the interim, studies should be commissioned to determine the actual serum 25(OH) response at these intakes in large cohorts. In addition dosing trials should be commissioned in the non-white population, the southern white UK population and the northern white UK population to establish the distribution of 25(OH)D3 responses at higher does , e.g. 2000IU/d in the white populations, and 4000IU/d in the non-white populations. Separate small dosing trials are also needed to properly inform the revision of intakes for each of these sub-groups in the age range 3 to 18 years.

11. Studies should be designed and commissioned to allow a good understanding of the principle health impacts which might become visible over time as these recommendations are taken up.

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