

RESPONSES TO DRAFT REPORT: UPDATE ON VITAMIN D (JANUARY 2007)

Member	Comments	Action
GENERAL		
Ann Prentice	<p>I have corrected throughout the use of the plural construction when describing the concentration or intake of a factor in terms of its mean value for a group, a threshold value, % of individuals with a value below a cut-off; correlations between a pair of observations in which many individuals have been studied but each individual contributes only one set of data. I recognise that use of the plural is increasingly common, especially in American literature, but it is to be avoided if possible. When in doubt I mentally substitute with either 'weight' or 'weights' to decide which is correct in each context – it then becomes immediately obvious whether singular or plural is need.</p>	Section amended.
Tony Williams	<p>One point is that I do not think vitamin D exerts any <u>direct</u> effect on the absorption or tubular excretion of phosphorus; I think any such changes are due to the secondary hyperparathyroidism which accompanies vitamin D deficiency. This would be compatible with the view that vitamin D exerts its effect at the molecular level by promoting synthesis of calbindin in sensitive tissues.</p> <p>Another is that we do not mention interactions between vitamin A and D, and these may possibly be important in connection with some of the extra skeletal effects. If so, it makes some of the supplementation studies harder to interpret - depending on the extent of any co-consumption.</p>	<p>Section amended.</p> <p>A paragraph on the interaction between vitamin A and D has been inserted under the section '<i>Vitamin D deficiency</i>'.</p>
Robert Fraser	<p>As far as pregnancy supplementation with Vitamin D is concerned the uncertainty which has caused different recommendations to arise from the COMA Panel and the NIHCE report must be about whether supplementation in pregnancy should be universal or targeted on high risk groups. I understand Alan Jackson's point that in principle a guideline cannot be the subject of a research trial as this puts the cart and the horse the wrong way round. I do query however whether in this particular case we should look again at the short and long term infant outcomes in relation to a randomised trial of Vitamin D supplementation in pregnancy both in the general population and in high risk groups.</p>	Full reference for Brooke 1983 requested. Needs discussion.

	<p>My second point is not related to any expertise I have but eyeballing Figure 2 on page 21 which relates to the proportion of males and females in the NDNS with plasma 25(OH)D concentrations less than 25 nmol/l – it is hard to believe that one is not looking at a physiological phenomenon in respect of the secular change in apparent Vitamin D deficiency. Is it not possible that there is an explanation for this trend with its peak in the 19 to 24 age group in both males and females in the availability of 25 (OH)D substrate related to changes in body composition and bone mineralisation in this age group?</p>	<p>Not actioned as evidence relating to such physiological phenomenon was not available.</p>
<p>Paul Haggarty</p>	<p>If pregnancy is a significant concern with respect the adequacy of vitamin D intakes and there is a strong seasonal variation in vitamin D it should be possible to see seasonal variation in the adverse developmental outcomes of interest. Is there any evidence for this?</p> <p>Also in relation to pregnancy; reference is made to deficiency on the basis of blood metabolites measured at the end of pregnancy. Many nutrient concentrations change significantly during pregnancy therefore it is possible that this may reflect the normal physiological response during pregnancy rather than deficiency; i.e. it may not be appropriate to apply non-pregnant thresholds to blood samples collected in pregnancy. Is there information available on changes in vitamin D during pregnancy.</p> <p>An important conclusion in the report is that; “<i>Almost a third of young women of child bearing age (19- 24 years) appear to have low status and are likely to start pregnancy with low maternal stores. These women will have to be routinely supplemented as recommended by COMA to ensure adequate fetal supply and stores in the newborn</i>”. If the apparently high level of deficiency in 19-24 year olds reflected poor intake of vitamin D it is hard to explain the relatively smooth increase in ‘deficiency’ from age 3 onward till age 19-24, after which it begins to fall again. It certainly peaks in the 19-24 age group but the transition through the ages (or a component of it) could be a natural physiological phenomenon rather than a problem with poor intakes in 19-24 years olds. It could for example be related to developmental changes in fat mass/bone mass/skin surface area.</p> <p>Even apart from food choices and supplement use, a nutritional problem which depends on sunlight exposure/physical activity is likely to track social class. According to NDNS the median plasma 25(OH)D is 28% lower in those receiving benefits. This looks like a</p>	<p>No evidence available.</p> <p>No evidence available.</p> <p>See previous comment by Robert Fraser regarding physiological phenomenon.</p> <p>Paragraph 107 amended to include levels in lower socio-economic groups.</p>

	significant issue of socio-economic inequality but I couldn't find a section on social class in the report or mention of it in the conclusions. I would recommend that such a section be added as this is the group (particularly women of childbearing age) that are likely to provide the key justification for supplementation.	
Anita Thomas	I think somewhere we should mention the proximal myopathy that is a frequent early accompaniment to Vit D deficiency in clinical presentation, and which can occur some to me before the bone disease-this is relevant both in itself and in relation to falls and fractures.	Mentioned in paragraph 74.
SUMMARY		
Tony Williams	Paragraph 1. I think original text an oversimplification; PTH and calcitonin operate together with vitamin D, the main function of which is regulation of calcium balance.	Section amended.
Anita Thomas	Paragraph 2. Is 'ethnic minorities' the correct term these days?	Amended to ' <i>black and ethnic minority groups</i> ' as this conforms to the terms used by DH/NHS.
Ann Prentice	Paragraph 3. I would prefer 'dietary' here rather than 'medicinal' since this does not require prescription by a medical practitioner Paragraph 9. Edited text: 'dietary supplements <u>seem</u> necessary to prevent vitamin deficiency'	Section amended. Sentence amended to make a firm statement, as 'seem' could be interpreted as...
Paul Haggarty	Paragraph 5. Questioned: '...effective UV radiation is lower in the <i>north than the south</i> '	Reference to be included in the text.
INTRODUCTION		
Paul Haggarty	Paragraph 10. The impression given here is that the conclusion of the paper has been decided before the data has been examined. How about something like; "The purpose of this paper is to assess the re-emergence of rickets and the current prevalence of low vitamin D status in the UK"	Not actioned as a formal assessment of the evidence was not undertaken.

Tony Williams	Paragraph 11. I think the intended readership of this paper needs to be made clear in the introduction. Is this an update for SACN - to allow informed judgment on the need for a full risk assessment -or is it for general publication? Unless we are clear about Terms of Reference it may be used for inappropriate purposes once in the public domain.	Sentence amended to include ' <i>..to assess the need for full consideration of the evidence and full risk assessment</i> '
BACKGROUND		
Ann Prentice	Paragraph 12. Referred to as CYP27B1 in the biochemical literature Paragraph 14. There is debate whether adipose tissue acts as a store or a sink for vitamin D	As CYP27B1 is the gene coding for the enzyme, it was not included. Section amended.
ASSESSMENT OF VITAMIN D STATUS		
Ann Prentice	Paragraph 21. Even in frank vitamin D deficiency, 1,25D can be raised (eg early phases of rickets, secondary to TB ie it doesn't automatically decrease at the lowest extreme of nutritional status)	Section amended.
DIETARY SOURCES OF VITAMIN D		
Paul Haggarty	Paragraph 29. Insert ' <i>cod liver oil</i> '	Not included as oily fish was listed.
FACTORS AFFECTING CUTANEOUS SYNTHESIS		
Paul Haggarty	Paragraph 48. Suggested ' <i>In a multilinear regression analysis; vitamin D intake, dwelling, veiling, and parity were independent predictors of hypovitaminosis D</i> ' should be changed to ' <i>In a multiple regression analysis; vitamin D intake, dwelling, veiling, and parity were all significantly related to 25(OH)D concentrations</i> '	Not actioned as we don't know if these are significant. Text amended for clarity.
Tony Williams	Paragraph 50. ' <i>Sunscreens are designed to absorb UV radiation before it enters the skin</i> ' - I think some may work by reflecting it – e.g. titanium oxide compounds?	Sentence amended to read ' <i>..to prevent the entry of UV</i>

	Paragraph 52. Might we say whether there was any measurable benefit associated with the use of sunscreen – e.g. reduction in sunburn? This is relevant to making a judgment about effectiveness and indeed compliance.	<i>radiation...'</i> No measurable benefits were stated in the reference.
FACTORS AFFECTING VITAMIN D STATUS		
Paul Haggarty	Paragraph 59. Need more identification; wild type/mutant etc of the homozygote in the Finnish study (<i>Laaksonen et al, 2002</i>). The word 'phenotypes' could be confusing, are these splice variants, isoforms or something similar?	Not actioned as it would be too much detail for the paper.
EXPOSURE TO SUNSHINE AND SKIN CANCER		
Tony Williams	Paragraph 62. Questioned ' <i>A meeting to discuss the amount of sunlight needed for optimum health in European populations was convened in October 2005. CRUK, together with its advisory group of experts, is currently working on a collaborative position statement (CRUK, 2006)</i> '.	CRUK have not yet issued their position statement.
SAFE UPPER INTAKE LEVELS		
Ann Prentice	<p>This month's AJCN has a useful perspective paper on this from Hathcock, Shaw, Vieth and Heaney, tabulating several studies.</p> <p>Paragraph 67. The combined use with thiazides is also a recognised problem (Hathcock et al AJCN 2007). Also I have heard it said, but have no reference to give you, that vitamin D supplements can also pose a risk to individuals with asymptomatic (normocalcaemic) primary hyperparathyroidism. Maybe one of our clinical colleagues could advise?</p>	<p>Section amended to include the risk assessment by Hathcock et al (2007).</p> <p>Sentence inserted: <i>'Increased risk of hypercalcaemia has also been associated with combined treatment with vitamin D and thiazide and related diuretics (Mehta,</i></p>

		2006)'
REPORTS OF CLINICALLY APPARENT DEFICIENCY		
Ann Prentice	Paragraph 86. <i>'attributed to the cessation of funding for maternal vitamin D supplementation'</i> seems a rather strong statement given the other factors that might be implicated (eg increased avoidance of skin exposure etc), and could be seen as unnecessarily inflammatory. Unless the authors provided evidence, I suggest this is deleted or expanded to include other possibilities.	Sentence amended to read <i>'attributed to the lack of maternal vitamin D supplementation.'</i>
PREVENTION OF DEFICIENCY		
Tony Williams	<p>Paragraph 89. I don't think we should make this comment <i>'(it being known that bottle-fed babies receive an adequate supplement in their formula feeds)'</i> without supporting scientific evidence. It may not be true - see paper In Arch Dis Child by Callaghan 2006{Callaghan, 2006 3359 /id}. In that study 50% of the infants (all of Asian origin) presenting with hypocalcaemic seizures were <i>"receiving formula feeds"</i>. An important point here is that the RNI amounts assume that maternal status has been adequate during pregnancy, whereas many infants from at risk groups will start life with deficiency. This message needs to come through here, as well as in paragraphs 89 and 101. Have added a paragraph to summary (144) suggesting this is specifically mentioned.</p> <p>Paragraph 91. ? state and discuss amount, noting that the only RCT in this group ({Brooke, 1980} employed a dose of 1000i.u. /d which is 2.5x the RNI.</p>	<p>Sentence deleted.</p> <p>Section amended to include the recommendations of Shaw and Pal (2002)</p>
DIETARY INTAKES AND VITAMIN STATUS IN THE UK		
Ann Prentice	Paragraph 103. <i>'vitamin D deficiency'</i> How defined clinically? Or do you mean 25OHD concentration <25nmol/l?	The reference is a BMJ article that does not state how this is defined. Paragraph amended to include <i>'...although the authors do not indicate how this was assessed'</i>

Paul Haggarty	<p>Paragraph 105. Is this really a measure of deficiency? Many nutrient concentrations change significantly during pregnancy therefore it is possible that this may reflect the normal physiological response during pregnancy rather than deficiency; i.e. it may not be appropriate to apply non-pregnant thresholds to blood samples collected in pregnancy. Is there data available on changes in vitamin D during pregnancy.</p> <p>Paragraph 113. If the apparently high level of deficiency in 19-24 year olds reflected poor intake of vitamin D it is hard to explain the relatively smooth transition from age 3 onward. It certainly peaks in the 19-24 age group but the transition through the ages looks more like a natural physiological response than a problem with poor intakes in 19-24 years olds. It could for example be related to developmental changes in fat mass/bone mass/skin surface area.</p>	<p>Same as previous comment by Ann Prentice.</p> <p>Needs discussion.</p>
Ann Prentice	Paragraph 111. Better to quote mean intake relative to RNI	Section amended to include mean intakes from food sources.
VITAMIN D AND DISEASE		
Tony Williams and Paul Haggarty	Paragraph 123. <i>'predicted plasma 25(OH)D concentrations for a cohort of 47,800 men, based on measurements in 1,095 men'</i> - this is not very clear; need to state what predictors were identified.	Section amended for clarity and predictors also included
Tony Williams	Paragraph 128. Possibly comment on the use of supplements in the study	Full text has been requested.
CONCLUSIONS		
Ann Prentice	<p>Paragraph 140. Strictly speaking 25nmol/l was based on an absence of rickets/osteomalacia. There is evidence that for protection against fragility fracture/osteoporosis, a higher threshold is needed. Since bone health includes osteoporosis, it would seem best not to confuse the issue in this paragraph.</p> <p>Paragraph 146. Adipose tissue may store vitamin D, releasing it when needed, or may</p>	<p>Sentence amended – <i>'bone health'</i> replaced with <i>'rickets and osteomalacia'</i></p> <p>Sentence deleted.</p>

	<p>lock it away and so increase requirements – I don't believe we know which yet. So suggest we don't amplify here</p> <p>Paragraph 147. <i>'vitamin D remain necessary to safeguard these groups against deficiency and its adverse effects on bone health'</i> - If we raise the threshold for 25D for other health outcomes then supplements will become even more necessary so suggest we don't confine the last comment to 'bone health'</p>	<p>Sentence amended to read <i>'..vitamin D remain necessary to safeguard these groups against deficiency and its adverse effects on health'</i></p>
Tony Williams	<p>Paragraph 141. <i>'when sufficient evidence has accumulated'</i> - this seems a bit too vague and open-ended to me.</p> <p>Paragraph 147. No RNI set above 3-years of age</p>	<p>Sentence amended.</p> <p>Needs discussion.</p>