

2nd MEETING

Vitamin D Working Group

7 December 2011, Wellington House, London SE1 8UG

DRAFT MINUTES

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| Chair: | Professor Hilary Powers |
| Members: | Professor Kevin Cashman Professor Roger Francis Professor Tim Key Professor Susan Lanham-New Professor Harry McArdle (am) Dr Ann Prentice Dr Tony Williams |
| Adviser (<i>UV exposure</i>): | Dr John O'Hagan |
| Secretariat: | Dr Alison Tedstone (DH) Ms Mamta Singh (DH) Mr Heiko Stolte (DH) Ms Cath Mulholland (FSA) |
| Observers: | Dr Fiona Comrie (FSA Scotland) Dr Stuart Conney (DH) Ms Rachel Stratton (DH) (for agenda item 5) |

Agenda item 1: Chair's welcome and introduction

1. The Chair welcomed Members to the second meeting of the SACN Working Group (WG) on vitamin D. Apologies of absence were received from Professor Ian Young. Apologies of absence for the afternoon session of the meeting were received from Professor Harry McArdle.

Agenda item 2: Minutes of first meeting on 26 May 2011 and teleconference on 8 September 2011) (SACNvitD/11/min01)

2. There were two sets of Minutes for agreement: those of the first meeting on 26 May 2011 and those of the teleconference on 8 September 2011.

3. Members were invited to comment on the Minutes of the meeting held on 26 May 2011. The following amendments were agreed:
 - (a) paragraph 4, 1st sentence - change '*has*' to '*had*' and delete '*subsequently*';
 - (b) paragraph 9, 2nd sentence - include method for analysis of blood samples;
 - (c) paragraph 14, 1st sentence - change '*requirement*' to '*requirements*';
 - (d) paragraph 29, 1st sentence - insert '*adverse*' before '*effects*';
 - (e) paragraph 31 - replace second '*that*' with '*the*';
 - (f) paragraph 37 - replace '*she*' with '*Ms Mulholland*'.
4. Pending these changes, the Minutes were agreed as a correct record of the meeting on 26 May 2011.
5. Members were then invited to comment on the Minutes of the teleconference on 8 September 2011. The following amendments were agreed:
 - (a) paragraph 10 - insert '*for clarification*' at the beginning of second sentence and transpose second and third sentences;
 - (b) paragraph 18 – insert comma after '*literature*';
 - (c) paragraph 21, 2nd sentence – insert '*understanding of*' before '*vitamin D biology*';
 - (d) include list of the topics (vitamin D and health effects) to be considered by the WG.
6. Pending these changes, the Minutes were agreed as a correct record of the teleconference on 8 September 2011.
7. The Chair reminded Members that, if necessary, the texts of position papers agreed at WG meetings would be revisited by means of teleconference, email, or *ad hoc* meetings.

Agenda Item 3: Overview of how the Institute of Medicine set Dietary Reference Intakes

8. Dr Tedstone explained that this item had been included on the agenda because, prior to reviewing the Dietary Reference Values (DRVs) for vitamin D, Members might find it helpful to be reminded of the approach taken by the Institute of Medicine (IOM) in setting Dietary Reference Intakes (DRIs) for the USA and Canada compared with that used by COMA¹ in setting the DRVs for the UK (DH, 1991²).

¹ Committee on Medical Aspects of Food Policy.

² Department of Health. *Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. Report on Health and Social Subjects, No. 41. London: HMSO, 1991.

9. In the mid 1990s, the Recommended Dietary Allowances in the USA and Recommended Nutrient Intakes in Canada were replaced by the DRIs. The DRIs represented a new approach to setting nutrient values and included four benchmarks: the Estimated Average Requirement (EAR), the Recommended Dietary Allowance (RDA), the Adequate Intake (AI), and the Tolerable Upper Intake Level (UL). The DRIs place more emphasis on the distribution of intakes in healthy populations rather than a single value and are based on optimising health, preventing chronic disease and avoiding excessive consumption of a nutrient. The RDA is roughly equivalent to the Reference Nutrient Intake in the UK, i.e., the amount likely to meet the needs of nearly all (97-98%) of the general healthy population and therefore exceeding the requirements of most of the population. In the USA and Canada, however, greater stress is now placed on the EAR, rather than the RDA, in order to minimise the risk of excessive intakes of a nutrient.
10. In the discussion that followed, the following points were noted:
- the importance of clearly explaining the concept of the DRVs;
 - the functional outcome/s used by the WG as the basis for deriving DRVs for vitamin D;
 - the particular nature of vitamin D, being obtained from a non-food source as well as from food or dietary supplements.
11. Members were reminded that in the IOM report³, the DRIs for vitamin D were based on bone health outcomes. EARs were estimated from a distribution of serum 25-hydroxyvitamin D [25(OH)D] concentrations relating to bone health without taking account of the contribution made from sun exposure. A meta-regression model (using data from 9 RCTs) was used to relate achieved serum 25(OH)D concentration (in winter) [in Ln] to total vitamin D intake and the lower 95% confidence interval of regression equations used to estimate the vitamin D intake needed to maintain serum 25(OH)D concentrations above 40 and 50 nmol/L for the EAR and RDA respectively. This is different to estimating the dietary EAR (to maintain half the individuals in the population at a serum 25(OH)D concentration of 40 or 50 nmol/L) and adding two standard deviations by convention to approximate the RDA.

Agenda Item 4: Vitamin D biology (SACNvitD/11/13)

12. Members were informed that the purpose of the biology chapter was to provide basic background information necessary for understanding some of the complexities of later chapters in the report. It will be amended, when appropriate, as the work of the WG progresses.

³ IOM (Institute of Medicine). 2011. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press.

13. Members were invited to make any general comments on the overall structure and content.
14. It was agreed that the chapter should include:
 - diagrams of the structure of vitamin D₂ and D₃ and some of the metabolic pathways;
 - interactions between vitamin D and other nutrients, in particular vitamin A, vitamin K, calcium, phosphorus, protein and iron;
 - polymorphisms that influence the vitamin D receptor and vitamin D converting enzymes.
15. It was noted that information about effects of developmental changes (physiological/life stage) on vitamin D metabolism had not been included. Members were informed that this information was still to be incorporated.
16. Members discussed units of measurement used for vitamin D intakes and serum/plasma concentrations of vitamin D and its metabolites. Vitamin D intakes are reported in International Units (IU) or micrograms (µg) while serum/plasma concentrations of vitamin D and its metabolites are reported as nanomoles per litre (nmol/L) or nanograms per millilitre (ng/ml). It was agreed to use µg to report dietary intakes and nmol/L to report serum/plasma concentrations and to provide the alternative units (IU for intakes; ng/ml for serum/plasma concentrations) in brackets.
17. It was agreed that references to vitamin D “*in the circulation*” should be avoided and the report should specify whether a study refers to *serum* or *plasma*. It was agreed to refer to *serum* when not describing a particular study.
18. It was agreed to include further background information about the solar spectrum and ultraviolet radiation in the section on cutaneous synthesis.
19. The WG then considered the biology chapter section by section. A number of amendments were agreed.

Agenda Item 5: Relationship between vitamin D exposure and status (SACNvitD/11/14)

20. Before inviting Members to consider the position paper on the relationship between vitamin D exposure and status, the Chair noted the importance of the Committee being clear about its understanding of the term *vitamin D status* since this could refer to exposure or functional adequacy.
21. Historically, the term *status* was equated with the body content of a nutrient. In the literature, however, *vitamin D status* refers only to the amount of 25(OH)D in serum; it does not include vitamin D stored in fat, which might be quickly mobilised. It was agreed that, rather than

examining the relationship between vitamin D exposure and *status*, what is actually being considered in the position paper is the relationship between exposure (diet and sunlight) and *serum 25(OH)D concentration*. It was agreed to make this clear in the report.

22. Members first considered the relationship between vitamin D intake and serum/plasma 25(OH)D concentration. It was agreed that:

- differences in the effectiveness of vitamin D₂ and D₃ in elevating serum 25(OH)D should be considered in more depth in this section rather than in the biology chapter;
- the point regarding the greater effectiveness of dietary 25(OH)D, compared to dietary vitamin D, in raising serum 25(OH)D concentration needs clarification. Data from a recent RCT⁴ have shown that 1 µg of 25(OH)D is about 5 times as effective in raising serum 25(OH)D in winter as 1 µg of vitamin D₃. The content of 25(OH)D in foods of animal origin can play a very important role in contributing to the total vitamin D activity of those foods. While the UK food compositional data take account of the fivefold factor, the US food compositional data do not at present. It was noted that the larger effect, which was maintained 10 to 20 weeks after intake, could be because dietary 25(OH)D does not need to be hydroxylated in the liver and dietary vitamin D might be sequestered in adipose and muscle tissue whereas this is less likely for dietary 25(OH)D.
- although the presence of fat is thought to be required for efficient absorption of vitamin D, a study (Biancuzzo *et al*, 2010⁵) has shown that vitamin D absorption from fortified orange juice is comparable with its absorption from vitamin D capsules. However, it was noted that this was a small study that did not specify if the fortified orange juice was consumed with/without a meal. It is also possible that the vitamin D in the orange juice was enclosed in micelles, which would facilitate absorption. While vitamin D absorption can be impaired in patients with fat malabsorption syndromes (e.g., Crohn's disease), Members agreed that it may be more important to consume vitamin D with a meal rather than with fat.

23. It was noted that the shape of the intake-serum 25(OH)D concentration relationship is linear at intakes below 25-25 µg/day but flattens out at intakes above this amount. It was suggested that it would be helpful to include figure 2 in the paper by Cashman *et al* (2011) (see Annex), which shows how the response of serum 25(OH)D concentration to vitamin D intake varies according to whether a natural logarithmic transformation (curvilinear model) is used or there is no transformation (linear model). The importance of emphasising the variance underlying the

⁴ Cashman KD, Seamans KM, Lucey AJ *et al*. Relative effectiveness of oral 25-hydroxyvitamin D₃ and vitamin D₃ in raising winter-time serum 25-hydroxyvitamin D in older adults (*in press*).

⁵ Biancuzzo RM, Young A, Bibuld D *et al*. Fortification of orange juice with vitamin D₂ or vitamin D₃ is as effective as an oral supplement in maintaining vitamin D status in adults. *Am J Clin Nutr* 2010; 91:1621-6.

different models was noted. The shape of the relationship between intake and serum 25(OH) concentration will be important in determining the vitamin D intake required to achieve a specific serum 25(OH)D concentration.

24. Members were informed of a paper (Tu & Gilthorpe, 2007⁶) suggesting that the finding in some studies, that the serum 25(OH)D response to vitamin D intake is dependent on baseline 25(OH)D concentration (i.e., greater response with initial lower baseline serum 25(OH)D concentration), might be a statistical artifact caused by regression to the mean.
25. The WG then considered the relationship between UVB sunlight exposure and serum 25(OH)D concentration. There is still great uncertainty regarding UVB sunlight exposure and cutaneous vitamin D synthesis because the relationship is complicated by a number of factors.
26. There are two main viewpoints regarding risks associated with sunlight exposure: firstly, that a limited amount of exposure is beneficial in terms of vitamin D synthesis and has no material adverse effect on the risk of cancer; secondly, that any exposure to sunlight is dangerous because of skin cancer risk.
27. It has been suggested that, compared to vitamin D synthesised in the skin, dietary vitamin D is less efficient at maintaining serum 25(OH)D concentrations. It was agreed to consult with Professor David Fraser, an expert on this issue, who may be able to provide further insight.

Agenda Item 6: Appropriate biochemical markers of vitamin D status (SACNvitD/11/15)

28. Members agreed that this section should be amended to '*Appropriate biochemical markers of vitamin D exposure*'. It was noted that a number of factors complicate the use of serum 25(OH)D concentrations as a marker of exposure, including uncertainty regarding how much 25(OH)D is compartmentalised and whether the parent vitamin D or 25(OH)D is stored in adipose tissue and muscle.
29. It was noted that although serum 25(OH)D concentration is a marker of exposure (diet and sun), it continues to be regarded and referred to as a marker of status in many publications.
30. Members noted that *adequate* status refers to adequacy of intake rather than in terms of functional outcomes.
31. Members noted the unsuitability of 1,25 dihydroxyvitamin D [1,25(OH)₂D] as a potential marker of exposure.
32. Findings from a paper by Reid *et al* (2011) (see Annex) suggest that serum concentrations of

⁶ Tu YK, Gilthorpe MS. Revisiting the relation between change and initial value: A review and evaluation. *Statist Med.* 2007; 26:443-457.

25(OH)D are decreased in response to acute inflammation which raises further concerns about the reliability of serum 25(OH)D as a marker of exposure. Decreased serum 25(OH)D concentrations observed in other conditions, such as cancer and diabetes, may simply reflect an underlying inflammatory state. In addition, concentrations of 25(OH)D are decreased during periods of rapid bone growth. It is unclear whether concentrations are lower under these conditions because of physiological changes or because vitamin D supply is inadequate to meet requirements. If the decrease in serum 25(OH)D concentration is caused by physiological changes then this weakens the robustness of 25(OH)D as a marker of exposure.

33. It was agreed to examine serum parathyroid hormone (PTH) concentration as a potential marker of vitamin D status. However, its use may be limited because PTH concentration is affected by a number of factors including age, life stage, race, kidney function and calcium intake. PTH concentration has also been considered as an outcome measure.
34. It was agreed that the emphasis in this section should be on serum 25(OH)D concentration as a marker of exposure but there should be a more comprehensive consideration of all potential markers.
35. Members agreed that even though there are a number of problems with using serum 25(OH)D concentration as a marker of exposure, these are more manageable than problems associated with other markers.

Agenda Item 7: Measurement of vitamin D status (SACNvitD/11/16)

36. Members discussed the main problems associated with the methods used for measuring serum 25(OH)D concentration, which include accuracy and variability. Measurements can vary considerably (15-20%) depending on the type of assay used and across different concentration ranges. There is also lack of agreement between different laboratories using the same methods⁷. It was noted that the Vitamin D External Quality Assurance Scheme (DEQAS) would make a big impact on standardisation. It was agreed to update this section, to include current developments, when the report is near completion.
37. It was agreed to include a consideration of the extent to which pre-analytical variability affects measurements of serum 25(OH)D concentration (e.g., time of day or year blood sample taken).
38. It was noted that the wide variability of 25(OH)D measurements made using different methods and in different laboratories has implications for interpretation of epidemiological studies and

⁷ de la Hunty A, Wallace AM, Gibson S *et al.* UK Food Standards Agency Workshop Consensus Report: the choice of method for measuring 25-hydroxyvitamin D to estimate vitamin D status for the UK National Diet and Nutrition Survey. *Br J Nutr.* 2010; 104:612-619.

trials that have examined the relationship between serum 25(OH)D concentration and health outcomes. Members agreed that this was an important concern that should be highlighted and taken into account when considering the evidence.

Agenda Item 8: Vitamin D and cancer (SACNvitD/11/17)

39. Members considered the position paper on vitamin D and cancer risk, which included results from the most recent meta-analyses together with the results of subsequent papers published after the meta-analyses (see Annex). Papers had been included if they reported data on plasma/serum 25(OH)D or 1,25 (OH)₂D concentration in prospective studies or reported results from randomised controlled trials.
40. It was noted that a number of prospective studies had examined the relationship between serum 25(OH)D and cancer risk and that most information was available on colorectal, breast and prostate cancers. Very little information was available on 1,25 (OH)₂D and cancer risk or from randomised controlled trials.
41. It was noted that results from the observational studies suggest that there is no evidence for an association between serum 25(OH)D and cancer risk, except for colorectal cancer. The association with colorectal cancer risk might be due to a protective effect, reverse causality, or residual confounding by some other factor/s (e.g., obesity).
42. Members agreed it was important to ensure that all the studies examining the association between vitamin D and cancer risk (based on serum 25(OH)D or 1,25 (OH)₂D concentration, or trials) are adequately captured in the SACN report. It was agreed to look again at findings from the IARC report (2008)⁸, the Tufts review (Chung *et al*, 2009⁹) (which informed the IOM report) and the IOM report which updated the findings of the Tufts review and included studies up to 2010.
43. It was agreed that it would be helpful to prepare forest plots of relative risks for prospective studies and to tabulate details of pre- and post-intervention serum 25(OH)D concentrations, where reported, for trials.
44. The limitations in prospective studies that have examined the association between vitamin D and cancer risk were noted. These include categorisation of serum 25(OH)D concentrations (e.g., predefined cut-points, season-specific cut-points) and the concentration of 25(OH)D used in the top categories (≥ 75 or ≥ 100 nmol/L in most prospective studies) which could be in the range of

⁸ International Agency for Research on Cancer (IARC) (2008). Vitamin D and cancer. Lyon: IARC, WHO.

⁹ Chung M, Balk EM, Brendel M *et al*. Vitamin D and calcium: A systematic review of health outcomes. Evidence Report/Technology Assessment, Number 183. AHRQ Publication No. 09-EO15; August 2009.

the putative dose-response relationship where a linear relationship might be observed. Another limitation is the use of only one blood sample because of individual biological variability of serum 25(OH)D concentration.

45. Members agreed that it would be necessary to include a discussion of these points prior to the chapter considering vitamin D and health outcomes.
46. In relation to individual biological variability in serum 25(OH)D over time, two Members agreed to calculate the intra-class correlation coefficient from data available from previous studies they had undertaken and, if possible, to pool the available raw data. Such analysis may be helpful when the WG is considering relationships between serum 25(OH)D and diseases endpoint in longitudinal studies.

Agenda Item 9: AOB

47. The Chair informed Members that she and the secretariat had met with Professor Antony Young, a dermatologist and principal co-ordinator of ICEPURE¹⁰, an EC project involving scientists from six European countries. The project's objective is to determine the beneficial and adverse effects of UVR exposure, including quantification of the relationship between sun exposure and vitamin D status. Professor Young has agreed to share data with the WG when they become available.
48. The Chair informed Members that at a recent conference she had met Professor Lesley Rhodes, a dermatologist with an interest in vitamin D and ultraviolet radiation. Professor Rhodes had offered to forward papers she has written on this subject to the secretariat, for circulation to the WG. Another Member confirmed that Professor Rhodes' expertise would be appropriate to the work of the WG.
49. Members were informed that a review of the evidence on vitamin D has recently been completed in Germany. It was suggested that a representative could be invited to present the findings to the WG. It was agreed to consider this possibility when a report of the findings is available.
50. Members were informed that a number of other European countries are currently reviewing vitamin D requirements.
51. The Chair informed Members that the next WG meeting would be held on 28 March 2012. She reminded those Members responsible for drafting position papers for the next meeting that these would need to be circulated 2 weeks in advance of the meeting. Members were informed that

¹⁰ Impact of climatic and environmental factors on personal ultraviolet radiation exposure and human health.

the secretariat would be sending an email regarding timelines to those members responsible for producing position papers.

52. In relation to the vitamin D research call issued by the Department of Health in November 2011, Dr Alison Tedstone informed Members that, as researchers in the vitamin D field, they would be eligible to apply and that their membership of the vitamin D WG would not be perceived as a conflict of interest.
53. It was agreed to include a declaration of any conflicts of interest as a standing item for future WG meetings.
54. Since there was no other business, the Chair thanked Members for their attendance.

ANNEX

Key references considered by WG prior to 2nd meeting

Relationship between vitamin D exposure and status; appropriate biochemical markers of vitamin D status; measurement of vitamin D status

1. Aloia JF, Patel M, Dimaano R, *et al.* Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *Am J Clin Nutr* 2008; 87:1952-1958.
2. Cashman KD, Fitzgerald AP, Kiely M, Seamans KM. A systematic review and meta-regression analysis of the vitamin D intake-serum 25-hydroxyvitamin D relationship to inform European recommendations. *Br J Nutr* 2011; 106:1638-48.
3. Diffey BL. Modelling the seasonal variability of vitamin D due to sun exposure. *British Journal of Dermatology* 2010; 162:1342-48.
4. Heaney RP, Armas LA, Shary JR, *et al.* 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. *Am J Clin Nutr* 2008; 87:1738-1742.
5. Reid D, Toole BJ, Knox S, *et al.* The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty *Am J Clin Nutr* 2011; 93:1006–11.
6. Seamans KM, Cashman KD. Existing and potentially novel functional markers of vitamin D status: a systematic review. *Am J Clin Nutr* 2009; 89:1997S-2008S.

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7. Abnet CC, Chen Y, Chow WH *et al.* Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172(1):94-106.
8. Gallicchio L, Moore LE, Stevens VL *et al.* Circulating 25-hydroxyvitamin D and risk of kidney cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172(1):47-57.
9. Gandini S, Boniol M, Haukka J *et al.* Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. *Int J Cancer* 2011; 128(6):1414-24.
10. Gilbert R, Martin RM, Beynon R *et al.* Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. *Cancer Causes Control* 2011; 22(3):319-40.
11. Purdue MP, Freedman DM, Gapstur SM *et al.* Circulating 25-hydroxyvitamin D and risk of non-hodgkin lymphoma: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172(1):58-69.
12. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA *et al.* Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172(1):81-93.
13. Yin L, Grandi N, Raum E *et al.* Meta-analysis: Circulating vitamin D and ovarian cancer risk. *Gynecol Oncol* 2011; 121(2):369-75.
14. Zeleniuch-Jacquotte A, Gallicchio L, Hartmuller V *et al.* Circulating 25-hydroxyvitamin D and risk of endometrial cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010; 172(1):36-46.