COMMENTS ON THE DRAFT SACN REPORT ON VITAMIN D

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I have read the draft of the SACN report on vitamin D with interest, and congratulate the co-authors on their comprehensive account of this challenging, controversial and rapidly evolving subject. I list various comments for consideration by the Panel, some substantial and others more trivial.

1. Information in the reviews by Autier *et al* [Lancet Diabetes Endocrinol 2014, 2, 76] and Theodoratou *et al* (BMJ 2014, 348, g2035) should be included as the most comprehensive, authoritative and balanced meta-analyses of the field.

2. Vitamin D_3 (not D_2 as stated in the Report) is the form found in some plants, such as in the leaves of the *Solanaceae* family [see, for example Japalt & Jakobsen Front Plant Sci 2013, 4, 136]. Vitamin D_2 is the form found in fungi and yeasts, and in plants containing endophytic fungi or with fungal infections.

3. 7-dehydrocholesteraol is found predominantly in the lower layers of the epidermis. Previtamin D is produced from 7-dehydrocholesterol in these same layers following UV-B irradiation, not in the dermis as stated consistently throughout the Report.

4. Section 51. The concept that the serum concentration of 25(OH)D decreases in response to inflammation is very important and merits more explanation and discussion, particularly with regard to the studies on cancer, autoimmunity and infectious diseases.

5. Section 63. To state here that the VDR on macrophages and lymphocytes is not a target for vitamin D action is wrong and is, in fact, stated correctly in section 438.

6. Although data regarding the vitamin D and 25(OH)D content of food are sparse, there are more recent results than in the Ovensen *et al* paper, quoted in section 21. Meat can contain substantial quantities of 25(OH)D and consumers of meat have a higher 25(OH)D status than non-consumers. As vitamin D_3 and 25(OH)D are added to some commercial animal feed stocks, the concentration of these substances in meat could be increasing. The potency factor for 25(OH)D has been estimated as 5 times higher than for vitamin D. Thus further consideration of the contribution of these metabolites in food is required in the Report. For examples, see Taylor *et al* J Nutr 2014, 144, 654 and Heaney & Armas Nutr Rev 2014, 73, 51.
In addition Rice *et al* [Br J Dermatol 2015, 172, 652] have shown that many adults can maintain adequate serum 25(OH)D levels despite negligible exposure to solar UV radiation for several months. Thus further work is required to account for this important finding.

7. Sections 115-117. As stated, it is not clear whether skin pigmentation influences the production of vitamin D following UV irradiation but several key references are missing. There are 12 published studies on this topic of which 7 indicate that vitamin D photosynthesis is reduced in dark-skinned individuals compared with fair-skinned individuals (Clemens *et al* 1982, Matsuoka *et al* 1991, Chen *et al* 2007, Armas *et al* 2007, Farrar *et al* 2011, Farrar *et al* 2013, Libon *et al* 2013) but, in the remaining 5, all but one published prior to 1990 (Stamp

1975, Lo *et al* 1986, Brazerol *et al* 1988, Matsuoka *et al* 1990, Bogh *et al* 2010), skin colour made no difference. It is possible that the spectrum emitted by the UV sources may explain these contradictory findings as, in general, there was a higher proportion of short-wave radiation in the lamps used in the latter group compared with the former group. This could lead to the production of previtamin D in the superficial layers of the epidermis above the melanocyte layer, and therefore not be affected by skin pigmentation [Bjorn J Invest Dermatol 2010, 130, 2848].

8. Section 122. It needs to be added that the vast majority of people do not use sunscreens at the appropriate concentration and do not apply the sunscreen to all exposed areas of skin. A review of all the studies available up till 2009 can be found in Norval & Wulf [Br J Dermatol 2009, 161, 732].

9. Section 126. The recommendation of the WHO INTERSUN Programme regarding "safe" sun exposure should be added which includes the use of the forecast of the local UV Index. It states that no protection is needed when the UV Index is less than 3 but, above this level, you should seek shade during the midday hours, wear protective clothing, a hat and sunscreen.

10. Section 150. The concept that it is more biologically relevant to assess free 25(OH)D in serum rather than total 25(OH)D requires consideration. This is because the unbound form can freely cross the cell membrane to exert its intracellular effects while the form bound the DBP and other proteins cannot. It is possible currently to measure free 25(OH)D accurately as described, for example, in Schwartz *et al* [J Clin Endocrinol Metabol 2014, 99, 1631].

11. The possibility that exposure to UV radiation is likely to have many more effects that the cutaneous production of previtamin D is not addressed in the Report. These could be either protective or detrimental for a range of diseases. This aspect was reviewed by Hart et al [Nat Rev Immunol 2011, 11, 584]. Therefore limited exposure to solar UV radiation could result in the loss of several positive aspects for health, which would not be compensated for by administering vitamin D supplements.

12. Section 688. As pointed out by Brain Diffey in several publications, these timings do not take into account the fact that only one side of the body gets exposed to the sun at any one time. Therefore they require to be doubled.

13. Many of the British population have "sun" holidays, sometimes more than one per year. Data published by the Office for National Statistics show that there were 37.1 million holiday visits abroad in 2013, with Spain accounting for more than 20% of these trips. Being in environments with significantly higher solar UV-B than in the UK contributes significantly, estimated as 30% [Diffey J Cosmet Dermatol 2002, 1, 124], to the annual exposure of individuals to solar UV-B and therefore to raising 25(OH)D status. Such a factor has not been taken into consideration in the model described in the Report.

14. Conclusions. With the contradictory results published thus far, even for some of the positive effects of vitamin D on bone health, together with several of the points outlined above, I am not confident that there is sufficient evidence currently to recommend that the general population of the UK, living "normal" lifestyles, should ingest 10 μg per day vitamin D.