Response to SACN report

2nd Page Background pt 2: Current UK government advice is that no dietary intake of vitamin D is necessary for individuals living a 'normal lifestyle'. Only certain groups of the population, who are at risk of vitamin D deficiency, are advised to take a daily supplement: pregnant and breastfeeding women (10 µg), infants and children aged under 4 years (7-8.5 µg); adults over 65 years (10 µg); those with limited exposure to the sun (e.g., if they cover their skin for cultural reasons or are housebound) (10 µg) and people of Asian origin (10 µg). The DRVs for vitamin D were reviewed and endorsed by COMA in 1998.

Pt 2 makes no mention of African's having a greater requirement for sun to maintain an adequate Vitamin D

5th page One IU of vitamin D is defined by the World Health Organization (WHO) (1950) as the activity produced by 0.025 µg of crystalline vitamin D3 (1 µg = 40 IU).

Serum concentrations of circulating vitamin D and its metabolites are expressed as nanomoles per litre (nmol/L) or nanograms per millilitre (ng/ml); 2.5 nmol/L is equivalent to 1 ng/ml.

***11th page no mention of cathelolithicin in para 66 non-genomic actions except see Lipps 2006

13th page section 78 >375 nmol/L toxic from hypercalcaemia when Drug overdose studies but UVB production switches off long before oral dose effects

***14th page section 86 no mention of lasting deformities such as knock knees, bow legs and pigeon toes which are an endemic sign in areas of London with high concentration of Asian and African and poor people of all races without access to regular sunshine by owning weekend country cottages

14th page section 87 fail to mention muscle weakness and lethargy with bone pain as symptom in adolescents

15th page section 90 no mention of Vitain D deficiency during pregnancy and Scizophreniis and MS

16th page section 96 UVB is only 5% of UV exposure

16th page section 98 70% daily solar UVB between 10.30 and 14.30

***17th page section 99 Synthesis of vitamin D is the only established benefit of solar UV exposure.No discussion of Nitric oxide and blood pressure

17th page section 104 incomprehensible

17th page section 105 no mention of DNA repair time and reduced melanoma with 2days outdoor activity

18th page section 116 participants with various skin tones (n=72), who had 90% of their skin exposed to UVB light (20-80 mJ/cm2) 3 times a week for 4 weeks, reported that 80% of the variation in treatment response was explained by UVB dose and skin tone (Armas et al, 2007). Farrar et al (2011) examined the effect of a controlled dose of UVR exposure (3x/week for 6 weeks) in individuals of South Asian ethnicity (n=15; aged 20-60 y; skin type V) exposing about 35% skin surface area. The study was conducted in January-February when ambient UVB is negligible in the UK to avoid confounding by lifestyle factors. Effects were compared with those of white-skinned individuals (n=109; age, 20-60y) who had been treated with the identical UVradiation exposure in a previous study (Rhodes et al, 2010). The mean increase in serum 25(OH)D concentration was 11 nmol/L in South Asian individuals compared with 26 nmol/L in white-skinned individuals ($p<0.0001$).

20th page section 123/124 Few studies have compared the effect of UVR with vitamin D supplementation on serum 25(OH)D concentration. One randomised trial compared the effect of full body narrow band solar range UVB (311 nm) (3x week) for 6 weeks with a daily dose of vitamin D3 (40 µg/1600 IU) in participants (n=73) with serum 25(OH)D concentrations ≤ 25 nmol/L (Bogh et al, 2012). A greater increase in mean serum 25(OH)D concentration was found in the UVB treated group (from 19·2 to 75.0 nmol/L) compared with the vitamin D3 supplemented group (from 23·3 to 60·6 nmol/L) ($p=0.02$). 124. Similar findings were reported in a 4-week study (Ala-Houhala et al, 2012) in which participants (n=63) with serum 25(OH)D concentration < 75 nmol/L were randomised to receive narrow band solar radiation exposures (3x week) with vitamin D3 supplements (20 µg/d; 800 IU). Mean (SD) baseline serum 25(OH)D concentration of participants was 53 (±10.4) nmol/L. Narrow band UVB was more effective than supplements, with

increases of 41.0 and 20.2 nmol/L respectively. The difference between the two treatments was significant at 2 weeks ($p = 0{\cdot}033$) and 4 weeks ($p < 0{\cdot}001$).

20/21st page section 125/126 Current recommendations regarding sun exposure 125. NHS Choices advice on safe sun exposure17 follows that from Cancer Research UK's Sunsmart18 : • Spend time in the shade between 11am and 3pm. • Make sure you never burn. • Aim to cover up with a T-shirt, hat and sunglasses. • Remember to take extra care with children. • Then use factor 15+ sunscreen. 126. The British Photodermatological Group (British Association of Dermatology) is similar to the above (i.e., avoid sunlight exposure between about 11am and 3 pm or seek shade and wear appropriately protective clothing if sunlight exposure between these times is unavoidable). However, it advises liberal use of SPF sunscreen of SPF 30 or more shortly before exposure and then again every couple of hours or so (and after 17 http://www.nhs.uk/Livewell/skin/Pages/Sunsafe.aspx 18 http://www.cancerresearchuk.org/about-cancer/causes-of-cancer/sun-uv-and-cancer/ways-to-enjoy-the-sun-safely 21 swimming or exercise). It warns that failure to apply sunscreen correctly will result in much reduced protection (often less than a third of the protection stated) and that sunscreens should not be used to stay outside longer or to avoid more reliable protective measures such as clothing and shade.

24th page section 128 Vitamin D in adipose tissue, muscle and liver (& brain) is unknown. This is important because vitamin D taken up by peripheral tissues that express lipoprotein lipase, especially adipose tissue and skeletal muscle may have differential availability ??Need post mortem or intra-operative samples

24th page section 131 1,25(OH)2D is homeostatically regulated; concentrations are not directly regulated by vitamin D intake but by other factors (such as serum PTH); even in the presence of severe vitamin D deficiency, 1,25(OH)2D concentration may be normal or even elevated as a result of upregulation of the CYP27B1 enzyme; serum 25(OH)D concentration is about a thousand-fold higher than 1,25(OH)2D concentration and its half-life is about 2-3 weeks compared to that of serum 1,25(OH)2D, which is less than 4 hours

25th page section 133 However, the extent to which serum 25(OH)D concentration serves as a biomarker of effect is not clearly established; i.e., whether serum 25(OH)D concentrations relate to health outcomes via a causal pathway and can serve as predictors of such health outcomes (IOM, 2011). OR ARE JUST A SURROGATE MARKER OF SUN PLUS DIETARY EXPOSURE

25TH PAGE SECTION 134 For example, a study of patients who underwent elective knee arthroplasty has raised concerns about the reliability of serum 25(OH)D concentration as status marker in the face of significant systemic inflammatory insult (Reid et al, 2011). By day 2 post-operatively there was a large increase in C-reactive protein (CRP)19 concentrations and a significant decrease in plasma 25(OH)D concentration of ~40%. CRP, 25(OH)D, and calculated free 25(OH)D (i.e., 25(OH)D not associated with DBP or albumin) had not returned to preoperative concentrations by 5 days post-operatively and, even at 3 months, 25(OH)D and free 25(OH)D concentrations remained significantly lower (20% and 30%). Mechanisms for the decrease in plasma 25(OH)D concentration were not evident.

25th page section 135 The study by Reid et al (2011) therefore raises an important question in relation to reverse causality: low serum 25(OH)D concentration may be a consequence of diseases with an inflammatory component and not the cause or evidence (??or consumption at sites of major macrophage activation).

25th page section 138 As serum 25(OH)D concentrations increase, serum PTH falls. For this reason, the threshold concentration above which there is no further suppression of PTH has been suggested as a biochemical marker for distinguishing adequate vitamin D status from inadequacy/insufficiency; however, this is much debated (IOM, 2011; Holick et al, 2011). While circulating PTH concentration can be indicative of clinical vitamin D deficiency, its use as a marker of vitamin D status is hindered by a number of uncertainties, such as the 19 C-reactive protein (CRP) is an acute phase protein produced by the liver; plasma/serum concentrations rise in response to inflammation. 26 nature of the 25(OH)D–PTH relationship, and concentrations of PTH which may have adverse effects on bone health (IOM, 2011). In addition, serum PTH concentration varies widely within and among individuals and appears to be dependent upon age, race, ethnicity, body composition, renal function, as well as dietary intake of calcium and phosphorus

26th page section 142 Accurate assessment of habitual vitamin D intake (including both vitamin D and 25(OH)D in foods) can be hindered by lack of up-to-date and accurate food composition databases for vitamin D. In addition to optimising analysis of raw foods or commodities, consistent monitoring of the levels of vitamin D (and correct identification of the vitamers D2 and D3) added to manufactured foods including supplements is also required to maintain currency of the databases (Cashman & Kiely, 2011). Another difficulty is that there are few naturally rich sources of vitamin D and these are consumed relatively infrequently; this means their consumption could be missed by some dietary assessment methods (e.g., food diaries recording all food consumed over a few days or week) if they were not consumed in the recording period. ( ??Or if the animals consumed were all reared indoors or consumed shortly after birth in winter )

26th page section 150 Mass spectotroscopy's potential advantages compared to antiobody techniques also include high specificity, high sensitivity, and better reproducibility (< 10%). The consensus among analysts is that LC-MS/MS assays will become the 'gold standard' for assay performance in the future (de la Hunty et al, 2010; IOM, 2011).

29th page section 164 Exploratory meta-regression analyses of RCT data, 16 trials in adults (Cranney et al, 2007) and 36 trials in children and adults (Seamans & Cashman, 2009) reported that for each additional 1 μg (40 IU) of vitamin D consumed, serum 25(OH)D concentrations increased by 0.64 and 0.53 nmol/L, respectively

30th page section 165 An analysis of 64 vitamin D RCTs (Aloia et al, 2008) showed that the slope response of serum 25(OH)D concentration to increasing doses of oral vitamin D flattens off at a dose of 35 μg/d (1400 IU).

31st page Section 169 a 4-arm RCT (placebo, 25, 50, or 100 μg/d vitamin D3 for 3months) Ng et al (2014) estimated that 41 μg/d of vitamin D was required to maintain winter 25(OH)D concentrations > 50 nmol/L in 97.5% of African American men and women (n=292; age, 30-80 y). This is almost twice the amount (15-20 μg/d) established by the IOM based on data from RCTs with white people

31st page section 175 Laboratory studies that have investigated the relationship between UVR exposure and vitamin D synthesis have typically used UVB phototherapy sources which also contain non-solar UVB radiation (< 295 nm) that is also very effective at vitamin D production. It is, therefore, difficult to make comparisons with solar UVR. A study that compared doses of natural solar UVR (April-September) with doses of artificial UVB radiation of hands and face reported a significant increase in serum 25(OH)D concentration with UVB from artificial sources but not with sunlight (Datta et al, 2012). It was estimated that UVB from a phototherapy source was at least 8 times more effective (in terms of erythemally equivalent exposure) than solar UVB.

32nd page section 180/181 Holick (2001, 2004) has suggested that exposure of approximately 25% of body surface, 2-3 times per week, to 1/4 MED in spring to autumn is equivalent to an oral dose of 25 μg (1000 IU) vitamin D. For the UK, in people with skin types I to IV, this corresponds to exposure times of around 5-15 minutes in midsummer and 15-60 minutes in mid-March and mid-September (Webb & Engelsen, 2006). Many solar recommendations to achieve and maintain serum 25(OH)D at specific concentrations are based on this guideline; however, it is difficult to extrapolate it to solar UVB exposure since it was derived from full body exposure to doses of artificial UVR radiation containing non-solar UVB. 181. Diffey (2010) developed a mathematical model to estimate changes in serum 25(OH)D concentration from sun exposure throughout the year using data and calculations for synthesis and decay of serum 25(OH)D concentration following a specific sun exposure and accounting for various factors (including time outside, month, available UV radiation in the UK, % skin exposure). The results from this model suggest that 10-20 minutes of daily sun exposure during summer months in the UK may achieve a maximum increase of 5- 10 nmol/L in serum 25(OH)D concentration.

36th page section 192 Another important factor for consideration in observational studies is that people with a higher serum 25(OH)D concentration tend to be healthier than those with lower concentrations because of greater exposure to sunlight as a result of greater outdoor physical activity and/or a healthier diet and/or prophylactic use of supplements

36th page section 193 Serum 25(OH)D concentration may also decrease in response to acute inflammation which raises further concerns about its reliability as a marker of exposure since a low serum 25(OH)D concentration may simply reflect an underlying inflammatory state. (Problems relating to measurement of serum 25(OH)D concentration are considered in more detail in chapter 4.)

44th page section 250 A study in India (Kumar et al, 2011) investigated the effect of vitamin D3 supplementation (35 µg/1400 IU/wk for 6 months) on growth (secondary outcome24) in low birth-weight term infants (n=2070; age ≤ 48 hours). After 6 months, the Mean serum 25(OH)D concentration was 55 nmol/L in the supplemented group and 36 nmol/L in the placebo group. Vitamin D supplementation significantly increased z scores at 6 months for weight (p=0.026), length (p=0.014) and arm circumference (p = 0.033) and significantly reduced the proportion of children with stunted growth (p=0.018).

47th page section 269 Ward et al (2010) examined the effect of vitamin D2 supplementation (4 doses of 3750 µg/150,000 IU over 1 year) on muscle function in adolescent girls (n=69; age, 12-14 years; 88% of south Asian origin). Mean (±SD) baseline serum 25(OH)D concentration increased significantly in the intervention group (18.1±8.0 to 56±8.9 nmol/L) but not in the control group (17.9±7.4 to 15.7±6.6 nmol/L). Efficiency of movement increased significantly (by 5%; p=0.02) in the intervention group. An interaction was also found between baseline serum 25(OH)D concentration and jump velocity in the intervention group (p=0.02) with greater change in those with lower concentrations. There were no improvements in muscle force or power.

48th page section 276 Tomlinson et al (2014) investigated the effect of vitamin D supplementation on muscle strength in adults (< 40 y) in a systematic review and meta-analysis of 6 RCTs and 1 controlled trial (n=310; mean age 24 y). Three studies also administered calcium; in 2 studies both control and vitamin D groups were required to take calcium; in the 3rd study, participants were randomised to receive placebo, calcium, vitamin D3 or vitamin D3 and calcium. Mean baseline serum 25(OH)D concentration of participants (reported in 5 studies) was 30.8 nmol/L. Overall, vitamin D supplementation significantly improved upper (p=0.005) and lower (p=0.04) limb muscle strength.

56th page section 325-7 . Three meta-analyses of RCTs reported a beneficial effect of vitamin D supplementation on muscle strength and function in adults > 50 years with mean baseline serum 25(OH)D concentration of 24-66 nmol/L, < 30 nmol/L and < 25 nmol/L; however the latter was based on 2 studies in hospitalised patients in Japan and may not be applicable to the general population in the UK. 326. Three subsequent RCTs were largely unsupportive of an effect of vitamin D supplementation on muscle strength. 327. Out of 7 cohort studies, 5 found an association between serum 25(OH)D concentration and muscle strength and function in people with baseline serum 25(OH)D concentration < 50 nmol/L; however, cut-offs were predefined in most studies.

63rd page section 363 An RCT (Wagner et al, 2013a) not included in the Harvey et al (2014) review, of pregnant women (n=257; 12-16 weeks gestation) supplemented daily with vitamin D3 (50 µg/2000 IU or 100 µg/4000 IU) reported no differences in birth weight, gestation or neonatal health. A combined analysis of the RCTs (n=759) by Wagner et al (2013a) and Hollis et al (2011) also found no differences in birth weight, gestation or neonatal health (Wagner et al, 2013b). Data on birth length were not provided.

65th page section 379 The Southampton Women's Survey (SWS), a prospective cohort study, did not find any associations between maternal serum 25(OH)D concentration in pregnancy and any tests of cognitive performance or psychological health to the age of 9 y (Gale et al, 2008). In another prospective cohort study in Western Australia, no associations were found between maternal serum 25(OH)D concentration and offspring psychological health at ages 2, 5, 8, 10, 14, and 17 years although there was a significant association between low serum 25(OH)D concentration in pregnancy and offspring language delay at the ages of 5 and 10 years (Whitehouse et al, 2012). Risk was approximately doubled in mothers with serum 25(OH)D concentration < 46 nmol/L in pregnancy compared to those with concentrations > 70 nmol/L

68th page section 401 Stolzenberg-Solomon et al (2010) reported a significant increase in pancreatic cancer risk associatedwith higher (≥ 100 nmol/L) compared to lower (< 25 nmol/L) serum 25(OH)D concentration.

69th page sections 402-4 Summary - Cancer 402. RCTs have not shown an effect of vitamin D supplements on overall cancer risk. 403. Observational studies indicate an inverse association between serum 25(OH)D concentration and colorectal cancer risk. This might be due to a protective effect, reverse causality, or residual confounding by other factors such as obesity, physical activity and smoking. 404. There is no strong evidence of associations between serum 25(OH)D concentration and risk of cancer at other sites. Although studies of skin cancer suggest risk may be increased in individuals with a relatively high serum 25(OH)D concentration this might be because a high serum 25(OH)D concentration is a marker of high sun exposure

73rd page section 424-8 Summary - CVD 424. Intervention studies have generally considered CVD risk as a secondary outcome; these studies, therefore, need to be interpreted with caution. 425. Out of 3 systematic reviews assessing the effect of vitamin D supplementation on CVD outcomes, 2 reported no significant effect and 1 reported an increased CVD risk with vitamin D plus calcium. 426. Prospective cohort studies, overall, report an inverse association between serum 25(OH)D concentration and CVD risk. Increased risk in these studies was reported at serum 25(OH)D concentrations ranging between < 25 nmol/L and 60 nmol/L. 427. Meta-analyses of intervention studies on vitamin D supplementation and hypertension are inconsistent. 428. Observational studies (cohort and cross-sectional) report an inverse association between serum 25(OH)D concentration and hypertension

75th page section 435-6 Summary - mortality 435. Evidence from a systematic review of 56 randomised trials shows that vitamin D supplementation in combination with calcium reduces mortality risk but, overall, vitamin D supplementation alone does not affect total mortality. 436. Evidence from 2 meta-analyses of observational studies indicate an inverse association between serum 25(OH)D concentration and mortality. This might be due to a protective effect of vitamin D on mortality risk, reverse causality, or residual confounding by other factors such as obesity, physical activity and smoking.

78th page section 456 An RCT in Denmark assessed the effect of oral vitamin D3 treatment on clinical relapse in patients (n=94) with Crohn's disease in remission. Patients were randomised to receive either vitamin D3 (30 µg/1200 IU per day) or placebo for 12 months. The serum 25(OH)D concentration of patients in the vitamin D treatment group increased from mean (SD) 69±31 nmol/L to 96±27 nmol after 3 months ($p< 0.001$). The relapse rate was lower in the vitamin D3 treated group compared with the placebo group (13% compared to 29%; $p=0.06$).

80th page sections 465-70 Summary – Autoimmune disease 465. A large systematic review (219 intervention, prospective and cross-sectional studies) reported that vitamin D supplementation has little effect on risk of developing auto-immune disease. 466. There is a paucity of RCTs on the effect of vitamin D supplementation on development of specific autoimmune diseases. One RCT reported no effect of vitamin D supplementation during pregnancy on childhood wheezing. 467. Evidence from cohort studies on maternal serum 25(OH)D concentration and development of asthma in the offspring is inconsistent. A systematic review of observational studies reported that conflicting results make it difficult to establish any clear relationship. Findings from 4 subsequent cohort studies are inconsistent. 468. Findings from cohort studies of atopic disorders are inconsistent. 469. Evidence to link vitamin D and MS is largely observational and inconsistent. Genetic studies suggest associations between the ApaI and FokI VDR polymorphisms and MS risk but the role of CYP27B1 in the development of MS is unclear. 470. Data are lacking on the relationship between vitamin D and type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis and SLE.

83rd page section 486-88 Intervention studies 486. A systematic review and meta-analysis of 11 RCTs (n=5660; mean age, 16 y) for prevention of RTIs (Bergman et al, 2013), reported that vitamin D supplementation significantly reduced the risk of RTI (OR, 0.64; 95% CI, 0.49-0.84; $p=0.001$) however there was evidence of significant heterogeneity between studies (p

84th page Sections 496-500 Summary – Infectious disease 496. The majority of evidence in this area relates to use of vitamin D as a therapeutic agent in patients with pre-existing disease and whether vitamin D can reduce severity or progression of the disease. Findings from such studies are not applicable to the general population. 497. Evidence on vitamin D and infection is inconsistent and mainly observational. RCTs do not generally show a beneficial effect of vitamin D supplementation on autoimmune disease risk. 498. No RCTs on the effect of vitamin D supplementation for prevention of TB could be identified. Observational studies report a positive association between serum 25(OH)D concentration and TB risk. Studies examining associations between VDR gene polymorphisms and susceptibility to TB are inconclusive. 499. Out of 2 systematic reviews/meta-analyses of RCTs on the effect of vitamin D supplementation on RTIs, 1 reported beneficial effects of vitamin D supplementation in reducing RTI risk while the other reported conflicting results. Findings from cohort studies are generally supportive of an inverse association between serum 25(OH)D concentration and RTIs with serum 25(OH)D concentrations ranging between < 25 and < 50 nmol/L

associated with increased risk for developing RTIs. 500. No studies could be identified on vitamin D and risk of developing COPD.

86th page section 508. A systematic review and meta-analysis (Spedding, 2014) identified 15 RCTs on the effect of vitamin D in depression. The authors reported wide variation in study methodology and diversity in study populations. Many of the studies were in patients and 6 RCTs did not report baseline serum 25(OH)D concentration. Vitamin D supplemental doses varied from 10-460 µg/d (400-18,400 IU) across the 15 trials. Eight out of the 15 studies were classified as having flawed study designs that limited their ability to demonstrate a change in the serum 25(OH)D concentration of the intervention group53. Of the 7 studies considered to be without flawed study design, 6 showed an improvement in depression with vitamin D supplementation; 6 of the 9 flawed studies had a null result. Only 2 studies were included in a meta-analysis of studies without flaws as they used the same depression measure54 which showed a significant improvement in depression (0.78; 95% CI, 0.24-1.27). Two studies were also included in the meta-analysis of flawed studies (due to the diverse outcome variables used in the other studies) which showed a significant negative effect of vitamin D supplementation (-1.1; 95% CI, -0.7 to -1.5)

87th page sections 517-9 Summary – Neuropsychological functioning 517. Evidence linking vitamin D to cognition and to depression is supported mainly by cross-sectional data which report an association between lower 25(OH)D concentration and poor cognitive function. This finding might be due to reverse causation since changes in cognition and depression may alter diet and/or behaviour in a way which would reduce serum 25(OH)D concentration. Beneficial effects of vitamin D on cognition or depression are not currently supported by robust clinical trials. 518. Evidence relating vitamin to autism is very limited and mainly ecological. 519. No intervention trials have examined the relationship between vitamin D and schizophrenia. Evidence linking vitamin D to schizophrenia is mainly ecological. Cross-sectional and case-control studies report that serum 25(OH)D concentration < 50 nmol/L is associated with increased schizophrenia risk; however, 1 case-control study found that serum 25(OH)D concentration < 20 nmol/L and > 50 nmol/L is associated with increased schizophrenia risk.

89th page sections 526-9 Summary – Oral health 526. Evidence from RCTs on effects of vitamin D supplementation on oral health is lacking. 527. Cross-sectional data show a positive association between serum 25(OH)D concentration and measures of oral health. One cohort study found an inverse association between serum 25(OH)D concentration and tooth loss. 528. Evidence from genetic studies suggests that associations between vitamin D and periodontal disease is influenced by changes in host immunity rather than through effects on calcium metabolism

93-94th pages Sections 548-60 Selection of health outcomes to inform the setting of DRVs for vitamin D 548. Evidence for a relationship between vitamin D and a range of musculoskeletal and non musculo-skeletal health outcomes was reviewed in order to assess whether any might be used to inform the setting of DRVs for vitamin D. The health outcomes examined were those considered to be of public health importance. 549. The evidence on vitamin D and musculoskeletal health was considered to be suggestive of beneficial effects of vitamin D on: a. rickets in infants and children; b. osteomalacia in all adult age groups; c. falling in adults > 50 years; d. muscle strength and function in young people and adults. 550. These musculoskeletal health outcomes were therefore selected as the basis for setting the DRVs for vitamin D. 551. Data on vitamin D and any non-musculoskeletal health outcome were considered to be insufficient at this time to inform the setting of DRVs for vitamin D. 552. Since serum 25(OH)D concentration reflects exposure to vitamin D from both sunlight and diet, the next step was to determine if it was possible to identify a distribution of serum 25(OH)D requirements for the selected musculoskeletal health outcomes or, if this was not possible, a threshold serum 25(OH)D concentration below which the risk of these musculoskeletal health outcomes is increased. The current lower limit used to indicate increased risk of deficiency is a serum 25(OH)D threshold concentration of 25 nmol/L (DH, 1998). Concentrations below this are associated with increased risk of rickets and osteomalacia. 553. Serum 25(OH)D concentrations in the studies on musculoskeletal health outcomes judged to be suggestive of beneficial effects of vitamin D (rickets, osteomalacia, falls, muscle strength & function) were considered further to assess whether a distribution or threshold serum 25(OH)D concentration associated with beneficial effects could be identified. • Rickets - Rickets was present at individual and mean serum 25(OH)D concentrations < 25 nmol/L in the majority of studies considered. • Osteomalacia – Based on the limited evidence (mainly case reports) individual serum 25(OH)D concentrations were < 20 nmol/L in case reports. In 2 cross-sectional studies, mean concentration was < 15 nmol/L in one and individual concentrations were < 7.5 nmol/L in the other. • Falls – The evidence is mixed but, on balance, is suggestive of beneficial effects of vitamin D

supplementation in reducing fall risk in adults > 50 years with mean baseline serum 25(OH)D concentrations over a range of values. There is also evidence of an adverse effect of an annual high dose (12,500 µg/500,000 IU) • Muscle strength and function - Overall, the evidence suggests that vitamin D supplementation may improve muscle function in adolescents and adults < 50 years with a mean serum 25(OH)D concentration < 30 nmol/L and in adults > 50 years with mean baseline serum 25(OH)D concentrations over a range of values. 94 554. With the exception of case reports, the studies considered only provided mean/median serum 25(OH)D concentrations of participants. It was not possible, therefore, to establish a distribution of serum 25(OH)D concentrations associated with the selected musculoskeletal health outcomes. 555. Overall, there was wide variability in the mean and individual serum 25(OH)D concentrations associated with increased risk of rickets, osteomalacia, falls and improvement in muscle strength and function together with many uncertainties in the data, including the use of predefined cutoffs; however, risk appears to increase at serum 25(OH)D concentrations below 20-30 nmol/L. 556. An additional complexity in the interpretation of the data is the high inter-assay and inter-laboratory variation in serum 25(OH)D concentration measurements (see chapter 4). Since a range of assay methods were utilised to measure serum 25(OH)D concentration in the different studies on musculoskeletal health, it is difficult to make comparisons between studies on the serum 25(OH)D concentration associated with increased risk. Since the data do not allow differentiation between a serum 25(OH)D threshold concentration of 20 vs 25 vs 30 nmol/L, the current threshold of 25 nmol/L (DH, 1998) is retained. This threshold serum 25(OH)D concentration is not diagnostic of disease but indicative of increased risk of poor musculoskeletal health. 557. A serum 25(OH)D concentration of 25 nmol/L indicates the concentration below which the risk of poor musculoskeletal health is increased at a population level and therefore represents a 'population protective' concentration. It does not refer to the mean target serum 25(OH)D concentration for a particular life-stage group but rather the serum 25(OH)D concentration that the majority (97.5%) of individuals should reach or be above (all year round) in terms of protecting musculoskeletal health. 558. Since it was not possible to identify the serum 25(OH)D concentration below which risk of poor musculoskeletal health is increased during pregnancy and lactation because of insufficient or inadequate evidence, the 'population protective' concentration of 25 nmol/L was extended to these groups. 559. A serum 25(OH)D concentration of 25 nmol/L is therefore selected as the basis for establishing the Reference Nutrient Intake for vitamin D; i.e., the mean vitamin D intake required to achieve a serum 25(OH)D concentration ≥ 25 nmol/L, throughout the year, by the majority (97.5%) of the population. The mean vitamin D intake refers to the mean or average intake over a period of time (e.g., one week) and takes account of day to day variations in vitamin D intake. 560. The vitamin D intake and the summer sunshine exposure required to achieve a serum 25(OH)D target concentration of ≥ 25 nmol/L is considered in chapter 9.

100th page sections 603-606 Summary & conclusions 603. Acute and chronic exposure to excess vitamin D intake can result in hypercalcaemia, demineralisation of bone, soft tissue calcification and renal damage. It is the most appropriate endpoint on which to base TULs for vitamin D since adverse effects that might occur at lower doses, through other mechanisms, have not been reliably established. 604. TULs for vitamin D, of 100 µg/d (4,000 IU) for adults and children aged 11-17 y, 50 µg/d (2000 IU) for children aged 1-10 y, and 25 µg/d (1,000 IU) for infants, as recommended by EFSA, are considered appropriate. The TULs do not distinguish between total and supplementary vitamin D intake since dietary intakes of vitamin D are make only a small contribution to total exposures at the TULs. 605. The TULs proposed may not provide adequate protection for individuals with medical disorders that pre-dispose to hypercalcaemia. These include normocalcaemic hyperparathyroidism, granulomatous diseases (e.g., sarcoidosis and tuberculosis) and genetic pre-disposition (e.g., IIH). 606. Doses of 7500 µg (300,000 IU) at intervals of 3 months or longer would not be expected to cause adverse effects in adults but there is greater uncertainty about the effects of larger doses, which might cause hypercalcaemia in some individuals. There are insufficient data to specify a safe upper limit for single doses in children but the limited information that is available suggests that toxicity could occur in infants at doses ≥ 15,000 µg (600,000 IU).

103rd page section 620 TABLE 1- Vitamin D content of dietary sources of vitamin D Food Mean vitamin D content (µg/ 100g) Fish Herring (grilled) 16.1 Salmon (farmed, grilled) 7.8 Salmon (farmed, steamed) 9.3 Salmon (pink, canned in brine, drained) 13.6 Salmon (cold & hot smoked) 8.9-11 Mackeral (grilled) 8.5 Mackeral (smoked) 8.2 Sardines (grilled) 5.1 Sardines (canned in brine, drained) 3.3 Tuna (baked) 3.1 Tuna (canned in brine, drained) 1.1 Eggs Eggs (whole, boiled) 3.2 Eggs (yolk, boiled) 12.6 Meat Beef (rump steak, fried) 0.7 Fortified foods Bran flakes 4.6 Cornflakes 4.7 Rice cereal 4.6 Fat spreads (reduced fat 62-75% polyunsaturated) 7.5 Taken from The Composition of Foods, 7th edition (Finglas et al, 2015)

107th page section 661 Serum 25(OH)D concentration by ethnicity 661. The HSE (2010) analysed serum 25(OH)D concentration by ethnicity (categorised as White, Mixed, Asian, Black and other). Mean serum 25(OH)D concentration was highest in white adults (16 years +): 45.8 nmol/L compared to 20.5 nmol/L for Asian adults and 27.7 nmol/L for black adults. The sample size was too small for mixed and other ethnic groups.

113 section 688. An estimate of sun exposure area and duration to achieve the ≥ 80.5 nmol/L was also performed within the modelling. It was estimated that with 35% skin area exposed (equivalent to wearing modest shorts/skirt and T-shirt) at around noon (12:00-13:00) from March to September, the daily exposure time to reach the end of summer (September) target serum 25(OH)D concentration would be 9 minutes for skin types I-IV (white) and 25 minutes for skin type V (south Asian ethnicity). These exposure durations would not be expected to exceed the sunburn thresholds for skin types I-V. ***or 31 vs 90 mins over a 2 day weekend***

***119th ppage section 720-7*** Summary & conclusions 720. The RNI for vitamin D proposed for the UK population is based on protection of musculoskeletal health. 721. A threshold serum 25(OH)D concentration of 25 nmol/L was used as the criterion for establishing the RNI for vitamin D. This concentration represents a 'population protective' level; i.e., the concentration below which risk of poor musculoskeletal health is increased and above which the risk is decreased at a population level. The RNI was developed to ensure that the majority (97.5%) of the population has a serum 25(OH)D concentration > 25 nmol/L all year round. 722. Sunlight UVB exposure could not be taken into account in setting the RNI because it is not possible to quantify the contribution it made to serum 25(OH)D concentrations within the general population. 723. The process of translating the target serum 25(OH)D concentration of ≥ 25 nmol/L into an RNI for vitamin D was based on RCTs carried out during winter when UVB radiation is absent or minimal. 724. An RNI of 10 µg/d of vitamin D, applicable throughout the year, is proposed for the UK population aged 4 years and above. The RNI assumes minimal sunshine exposure. 725. The RNI of 10 µg/d also includes at risk population groups (frail older adults, individuals wearing concealing clothing; those not spending substantial time outdoors; people from ethnic groups with darker skin). 726. A Safe Intake range of 8.5-10 µg/d is proposed for infants aged 0-11 months, including those who are exclusively breast-fed (from birth). The proposed Safe Intake for exclusively breast-fed infants is a change to previous advice. 727. A Safe Intake of 10 µg/d is proposed for children aged 1 to < 4 years.

130th page sections 799-806. Recommendations 799. Serum 25(OH)D concentration is an indicator of exposure to vitamin D (i.e., from the diet and skin synthesis). In order to protect musculoskeletal health, it is recommended that the serum 25(OH)D concentration of individuals in the UK should not fall below 25 nmol/L at any time of the year. 800. In the UK, population groups at increased risk of having a serum 25(OH)D concentration < 25 nmol/L are those with minimal sunshine exposure as a result of not spending substantial time outdoors (e.g., frail and institutionalised people) or due to the habitual wearing of clothing that covers most of the skin while outdoors. 801. It is not possible to make a recommendation regarding the amount of sunlight exposure that would be required during the summer to maintain serum 25(OH)D concentration ≥ 25 nmol/L in 97.5% of the population during winter because of the number of factors that affect endogenous vitamin D production. 802. A Reference Nutrient Intake (RNI) for vitamin D of 10 µg/d is therefore proposed for the UK population aged 4 years and over. This is the amount needed for 97.5% of the population to maintain a serum 25(OH)D concentration of 25 nmol/L when UVB sunshine exposure is minimal. 803. The RNI of 10 µg/d proposed for the whole UK population includes individuals from minority ethnic groups with darker skin. 804. It is proposed that the RNI is applicable throughout the year, as a precautionary measure, to cover population groups in the UK identified to be at risk of minimal sunshine exposure as well as unidentified individuals in the population with minimal sunshine exposure who would be at risk of 25(OH)D concentrations < 25 nmol/L in summer. 805. Data are insufficient to set RNIs for infants and children aged 0-3 years. As a precaution, a 'Safe Intake' of vitamin D is therefore proposed for these ages: in the range 8.5-10 µg/d for ages 0 to < 1 year (including exclusively breast fed infants); and 10 µg/d for ages 1 to < 4 years. 806. Since it is difficult to achieve the RNI/Safe Intake from natural food sources alone, it is recommended that consideration is given to strategies for the UK population to achieve the RNI of 10 µg/d for those aged 4 years and older and for younger children to achieve a Safe Intake in the range 8.5-10 µg/d at ages 0 to < 1 year and 10 µg/d at ages 1 to < 4 years.