TOX/2014/20

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

SACN Review of vitamin D. Adverse effects of high levels.

Additional information on single dose vitamin D and changes in serum 25(OH)D levels

Introduction and background

1. As members are aware, the Scientific Advisory Committee on Nutrition (SACN) are revising the Dietary Reference Values for vitamin D and the COT have been asked to consider the potential adverse effects of high intakes. This has been discussed in a number of COT papers considered to date.

2. The SACN Working Group have asked COT to comment on whether any recommendations can be made regarding the safety of single, high doses of vitamin D which are sometimes used to improve compliance, particularly in the context of clinical trials and research studies. This request, which was discussed at the February 2014 meeting, was in the light of a paper by Sanders *et al*., 2010 which suggested that a single annual oral dose of 12,500 µg vitamin D was associated with an increase in the risk of falls and fractures.

3. The COT agreed that there was no reason to discount the findings of Sanders *et al*., 2010 although the mechanism was unknown and did not appear to involve hypercalcaemia. Members asked for additional information on the effects of single doses of vitamin D, particularly on the levels of serum 25(OH)D and how these compared to the levels associated with toxicity.

4. Members are asked to consider the available information to establish whether a maximum single dose can be set for vitamin D or for maximum serum 25(OH)D levels, and if not, whether any other guidance can be given.

Absorption, distribution, metabolism and excretion of vitamin D

5. Oral vitamin D is absorbed from the gut along with dietary fat and incorporated into chylomicrons, with a small fraction reaching the liver directly through the portal system. The chylomicrons reach the systemic circulation via the

lymphatics. The chylomicron lipids are hydrolysed in peripheral tissues that express lipoprotein lipase, but particularly adipose tissue. A fraction of the vitamin D contained in the chylomicron is taken up by adipose tissue and sequestered. The vitamin D that has entered the circulation is converted in the liver to 25(OH)D by a CYP enzyme (possibly CYP2R1); there is little or no feedback control of this enzyme (IOM, 2011). At this point 25(OH)D circulates in the serum bound to vitamin D binding protein DBP. When 1,25 dihydroxyvitamin D (1,25()H)D2 or calcitriol -the active form of vitamin D) is required 25(OH)D is hydroxylated in the kidney to 1,25(OH)D2.

6. The US Institute of Medicine (IOM) Food and Nutrition Board (IOM, 2011) stated that increasing intake of vitamin D increases blood levels of 25(OH)D but not necessarily in a linear manner (citing Stamp *et al*., 1977; Clements *et al*., 1987). EFSA (2012) cited Holick, 2006 and stated that the increase was linear into the toxic range (It is unclear what this toxic range is, but the linear dose response may refer to a relationship seen up to a cumulative dose of ≥15,000 µg shown in figure 20.10 of the publication)[1].

Half life

7. The half-life of vitamin D is approximately 2 months (Jones, 2008). Following administration of a single oral dose, peak serum levels of 25(OH)D occur between 15-30 days for vitamin D_3 but occur later for vitamin D_2. The half-life of 25(OH)D in circulation is 15 days. Counts *et al* (1975) reported a case where the half-life of 25(OH)D was 10 days but peritoneal dialysis was used in treatment which may have made clearance more rapid.

25(OH)D levels normal circulating levels and levels associated with toxicity

Normal circulating levels

8. Jones (2008) reported that “normal circulating levels” of 25(OH)D were 25-200 nmol/L. In the UK, data from the NDNS rolling programme up to 2012 reported that mean 25(OH)D levels were 46.1 and 42.5 nmol/L in boys and girls aged 11-18 years respectively and 45.6 and 49.6 nmol/L in men and women respectively.

9. Hollis (2005) stated that in sun-rich environments, where cultural practices permit sun exposure, circulating levels are 135 to 225 nmol/L, suggesting that current circulating levels may not be “normal”. Holick, 2006 further stated that “sun worshippers and life guards” could have serum levels of up to 312 nmol/L 25(OH)D without untoward effect (no further details are provided).

[1] Holick, 2006 is a book chapter which is only partially available on line. The secretariat has not yet had access to the book itself.

10. Hollis (2005) reported that a 10-15 minute whole body exposure to summer sun could generate and release up to 500 µg vitamin D_3 into the circulation.

25(OH)D levels in case reports of vitamin D toxicity

11. The available case report data have been summarised previously (TOX/2014/03) but a simplified form of the table has been attached at Annex A which summarises information from case reports where the final 25(OH)D level is known. It should be noted that these cases involve multiple doses of vitamin D, often over a sustained period.

12. From this table it can be seen that serum 25(OH)D levels tend to be at least 500 nmol/L in cases where toxicity has been described, however, lower levels have been reported in some instances, possibly because the 25(OH)D level has started to decline before vitamin D toxicity was diagnosed and/or the 25(OH)D levels were measured (eg Rizzoli *et al*., 1994; Koul *et al*., 2012). Case reports of poisoning in young children also seem to be associated with lower serum 25(OH)D levels, with values of approximately 300 nmol/L being reported. However it should be noted that there are fewer case reports in this population group

Conclusions on the significance of 25(OH)D levels from regulatory authorities.

IOM view

13. IOM (2011) stated that in the absence of well controlled studies, the serum 25(OH)D level representing the vitamin D toxicity threshold in humans was not readily defined and similarly, the vitamin D intakes required to trigger toxicity symptoms were not precisely known. Moreover even though the physiological changes that occur with vitamin D toxicity were correlated to serum 25(OH)D levels, they may not be precisely aligned and might vary from subject to subject and among sub-populations.

14. IOM further noted that, most reports stated that the toxicity threshold was between 250 and 1000 µg vitamin per day and most do not identify toxicity until serum 25(OH)D levels of 500-600 nmol/L or higher is reached; frank toxicity was been associated with a serum level of 750 nmol/L (IOM cites Jones, 2008 but also its own unpublished commissioned report by DeLuca).

15. In the 2011 IOM review, it was also noted that serum vitamin D concentrations had a reverse J or U shaped dose-response relationship with some endpoints, such as all-cause mortality and the incidence of certain cancers notably pancreatic and prostate cancer, with a flattening of the dose-response curve and a slight increase in the end point being observed at the highest serum 25(OH)D levels. Given this and

taking into account data on African-Americans[2], IOM considered that serum 25(OH)D levels should not exceed 125 nmol/L.

EFSA

16. In the 2012 EFSA NDA panel report, it was noted that when 25(OH)D concentrations were associated with adverse long-term health outcomes. Studies reporting on an association between 25(OH)D concentration and all-cause mortality or cancer were inconsistent. When 25(OH)D concentrations were associated with an increased risk for adverse long-term health outcomes in some studies, there was a wide variation in 25(OH)D levels associated with the adverse effect. It was considered that 25(OH)D concentrations could not be used to characterise the risk for adverse long term health outcomes.

17. The EFSA panel also concluded that the 25(OH) concentrations associated with hypercalcaemia vary over a wide range and that the 25(OH)D concentration in serum or plasma could not be considered a suitable predictor of hypercalcaemia. This conclusion was based on work by Vieth (1999), Jones, 2008 and Hathcock who reported that hypercalcaemia was accompanied by 25(OH)D concentrations of >220, 375-500 or ≥ 700 nmol/L respectively. The review by Vieth (1999) includes the case series reported by Rizzoli *et al*., 1994 where serum 25(OH)D levels of 221, 374, 608, 621, 650, 801 and 1692, nmol/L were reported in seven vitamin D intoxicated patients.

Other authors

18. In a paper arguing that the IOM recommendations on maximum levels were too low, Glade (2012) argued that hypercalcaemia (or hypercalcuria in the absence of hypercalcaemia) required acute vitamin D intakes greater than 1000 µg, and even where acute intakes were higher than this, hypercalcaemia only appeared in otherwise healthy adults when serum 25(OH)D exceeded 750 nmol/L. In particular, a case report from Koutkia *et al* (2001) is noted in which an individual with vitamin D toxicity through supplement use (3900-65100 µg/day for 2 y) had hypercalcaemia which resolved once serum 25(OH)D decreased to less than 750 nmol/L. Glade (2012) also cited one of two cases reported by Kimball and Vieth (2008) where following a sustained intake of vitamin D (200 increasing to 2200 µg/day for 4 years) hypercalcaemia was only observed at serum 25(OH)D of >1100 nmol/L. In a second case from these authors, serum 25(OH)D of 260 nmol/L did not result in hypercalcaemia. Glade (2012) further stated that "normal" circulating levels of serum 25(OH)D were in the range 25-250 nmol/L.

[2] The IOM noted that emerging data suggested that there was a positive association between serum 25(OH)D levels and calcified atherosclerotic plaque in the aorta and carotid arteries of African Americans and that the risk for all-cause mortality among non-Hispanic blacks compared to whites, occurred at lower levels of 25(OH)D. The IOM stated the data were limited and might eventually be explained by factors other than serum 25(OH)D but they were concerning and increased uncertainty.

19. Jones (2008) noted that all the available data on vitamin D intoxication reported that 25(OH)D levels were well above the normal range at 710-1587 nmol/L. Jones endorsed the view of Vieth (1990) that hypercalcaemia only occurred when serum 25(OH)D was consistently greater than 375-500 nmol/L. Animal studies (discussed Jones) suggested that the plasma 25(OH)D levels associated with toxicity were always in excess of 375 nmol/L. Overall, 25(OH)D levels up to 250 nmol/L, the currently considered upper end of the normal range, were safe and left a "broad margin for error" because values significantly higher than this had "never been associated with toxicity".

Single dose studies and changes in 25(OH)D levels

20. The available data from single dose studies of vitamin D have been tabulated in Table 2 of annex A, with a simplified version included as Table 1 below. The different studies measured changes in serum 25(OH)D levels at a range of different time points, and in some cases only presented information on the peak levels in any detail. However, other measures were taken in some investigations and where possible, values have been estimated from the figures included in the reports. Relatively few studies have carried out sequential measurement of 25(OH)D during the first month following exposure.

21. The data suggest that 25(OH)D levels peak at or within 30 days of dosing with vitamin D_3. At the highest dose used (15,000 µg) 25(OH)D levels increased by up to 150 nmol/L from baseline in one study (Cipriani *et al*., 2010), but not in a similar study by the same group. Lower doses resulted in smaller increases above baseline, but the size of 25(OH)D increases were very variable, possibly due to the differences between the populations investigated. D_2 appears to be less effective than D_3 in increasing serum 25(OH)D levels and i.m. rather than oral exposure results in a slower increase in 25(OH)D levels (NB. i.m. data is the annexed table only).

Table 1. Increases in serum 25(OH)D levels following single doses of vitamin D

Dose (µg)	**Population**	**25(OH)D Change from baseline (nmol/L)**	**Time of measurement (day)**	**Reference**
15,000 D_3	48 young people with vitamin D deficiency (25-56y) Italy	+ 153 + 151 + 116	3 15 30	Cipriani *et al*., 2010
15,000 vitamin D_2 or D_3	24 patients with vitamin D deficiency Italy	+ 15.22 + 30.95	30 30	Cipriani *et al*., 2013
12,500	2256 community dwelling women, ≥ 70y Australia	+ 70 + 40	1 mo 3 mo	Sanders *et al*., 2010
12,500 12,500 + 1250/month	19, 22 elderly people (≥ 65 y) hospitalised at time of recruitment, largely independent thereafter. New Zealand	+ 58 + 58 + 20 (estimated from Fig 2)	1 mo 1 mo 3 mo	Bacon *et al.,* 2009
7500	14/group elderly subjects with secondary hyperparathyroidism. Brazil	+ 50 + 37 +30	1 mo 2 mo 3 +mo	Premaor *et al*., 2008
7500 D_2	8/group Elderly women	79.87 62.4	3 7	Romagnoli *et al*., 2008

Dose (µg)	Population	25(OH)D Change from baseline (nmol/L)	Time of measurement (day)	Reference
D_3	Italy	43.28 ± 11.93 25.26 ± 16.85 94.85 104.83 119.38 ± 18.22 70.03 ± 20.8 (mean ± SD) or estimated from figures	30 60 3 7 30 60	
7500	32 outpatients 49 Elderly in-patients (69-94y) New Zealand	+ 35 + 44 inpatients	Various but average of 17 weeks.	Wu *et al*., 2003
3750 given every 3 months or placebo	686 community dwelling women aged >70 y Subset of 40 analysed Australia	+ 37.44 higher than placebo overall	3, 6 and 9 months	Glendenning *et al*., 2010
2500	Elderly people in residential home	+ 62	2 weeks	Weisman *et al*., 1986. Abstract and proceedings[3].
2500	30 subjects (20 aged 61-84y and 10 aged 27-47y) US	+ 37 33 30 27 25	Measured at intervals, peak occurred at day 7, rest of values estimated from figure Day 14 21 30	Ilahi *et al*., 2008

[3] There appear to be 2 references for the same study, one being a conference proceedings.

Dose (µg)	Population	25(OH)D Change from baseline (nmol/L)	Time of measurement (day)	Reference
		15	35 60	
1750	34 pregnant 27 non-pregnant women Bangladesh	32 28	Day 0, 2, 4, 7, and then weekly for up to 10 weeks. Different sampling schedules to minimise burden on volunteers.	Roth *et al*., 2012
1250 of D_2, D_3 or placebo US	10 Healthy male volunteers/group (20-61y)	+ 12 + 17 -	Day 0, 1, 3, 5-7, 14 and 28.	Armas *et al*., 2004

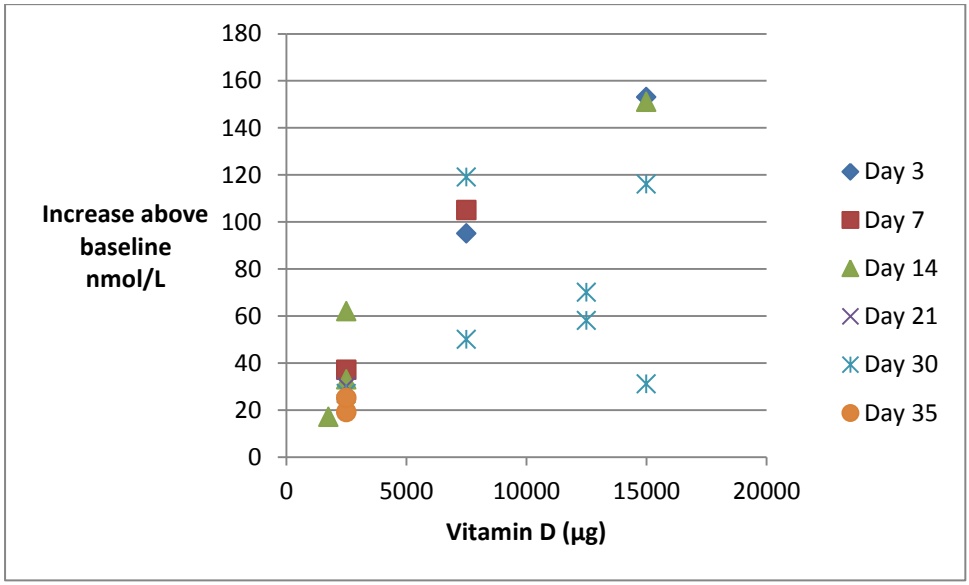
D_2- Ergocalciferol

D_3 Cholecalciferol

22. Some of the data have been plotted as below:

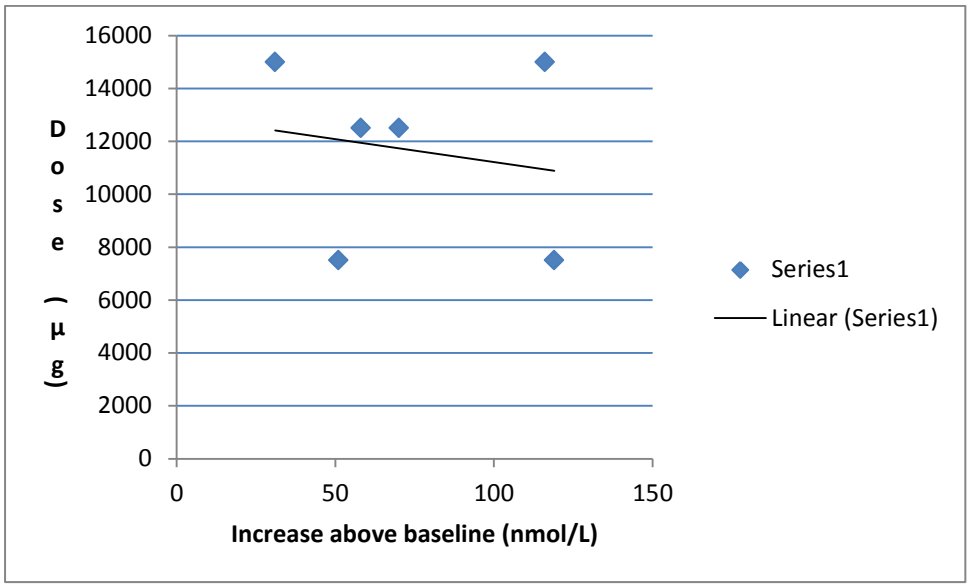
23. Figure 1 shows a plot of the increases in serum 25(OH)D above baseline produced by increasing doses of vitamin D measured at any time point up to 5 weeks post treatment. This would be expected to capture the peak serum levels produced by vitamin D administration. This includes the data from the following studies: Cipriani *et al*., 2010; Cipriani *et al*., 2013; Sanders *et al*., 2010; Bacon *et al*., 2009;Premaor *et al*., 2008; Romagnoli *et al*., 2008; Weisman *et al*., 1986; Khaw *et al*., 1994; Ilahi *et al*., 2008; Roth *et al*., 2012; Armas *et al*., 2004. This plot seems to suggest a dose response is occurring but that it is very variable. The two studies by Cipriani and colleagues report increases of 116 and 30 nmol/L above baseline levels 30 days after dosing with 15000 µg vitamin D_3. The difference in magnitude between the two results is not discussed in the later of the two studies.

Fig 1. Changes in serum 25(OH)D levels following single doses of vitamin D at up to 5 weeks



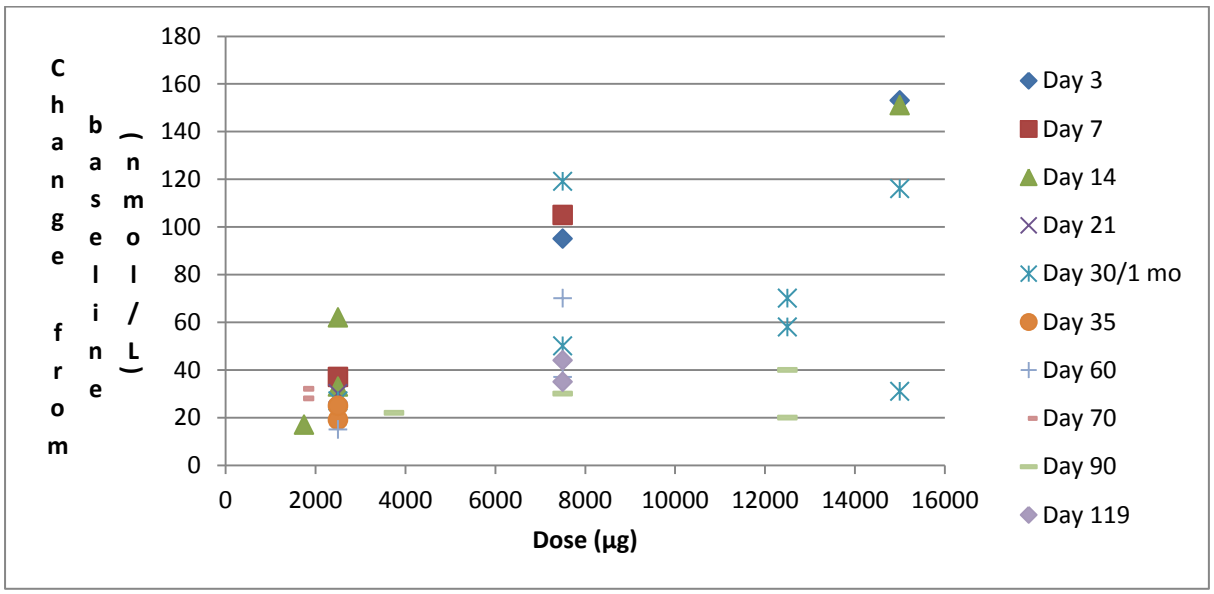
24. Figure 2 shows the increases above baseline produced by increased doses of vitamin D_3 measured on day 30 only. This includes data from six studies: Cipriani *et al*., 2010; Cipriani *et al*., 2013; Sanders *et al*., 2010; Bacon *et al*., 2009;Premaor *et al*., 2008; Romagnoli *et al*., 2008. A dose response, if present at all, is much less obvious in this plot.

Fig 2. Changes in serum 25(OH)D levels following single doses of vitamin D at day 30 only.



25. Figure 3 shows all the available data including measurements up to day 119, separated by time of measurement. Additional data to those in the figures above have been included, these were points which have been estimated from figures in the paper as they were not discussed or reported in the text. Data from Wu *et al*., 2003 and Glendenning *et al*., 2010 are also included.

Fig 3. Changes in serum 25(OH)D levels following single doses of vitamin D up to day 119.



26. Few authors have attempted to calculate or explore dose-response relationships for vitamin D. However, in a study in pregnant and non-pregnant women reported by Roth *et al* it was estimated that, assuming the rise was linear, that the average maximal increase in 25(OH)D would be approximately 17 nmol/L per mg D_3. The occurrence of the maximal mean in the first month was stated to be similar to the findings of other studies in non-pregnant adults (Armas *et al*., 2004, Ilahi *et al*., 2005, Romagnoli *et al*., 2008, Cipriani *et al*., 2010, Bacon *et al*., 2009. Weisman *et al*., 1996, Sanders *et al*., 2010). This was stated to be similar to the previous studies where relevant inferences could be drawn (Armas *et al*., 2004, Ilahi *et al*., 2005, Romagnoli *et al*., 2008, Cipriani *et al*., 2010) indicating Δ Cmax to be 12-16 nmol/L per mg vitamin D_3.

Summary and discussion

27. Oral vitamin D is absorbed from the gut and enters the systemic circulation via the lymphatic system where it is transported to the liver and converted into 25(OH)D. This conversion is subject to little or no feedback control and therefore 25(OH)D accumulates in the circulation. The 25(OH)D remains in circulation until required, when it is hydroxylated in the kidney to 1,25(OH)D2. The half-life of vitamin D is approximately 2 months, the half-life of 25(OH)D in circulation is 15 days..

28. Normal circulating 25(OH)D levels are in the range 25-200 nmol/L and mean levels in the UK range from 42-59 nmol/L. The 25(OH)D levels associated with toxicity are less clear; while levels of at least 400-600 nmol/L 25(OH)D are generally associated with toxicity, lower 25(OH)D levels have also been measured in case reports.

29. The dose response between oral vitamin D intakes and circulating 25(OH)D levels is also highly variable, possible reflecting studies conducted in different population groups as well as individual variation. However, even single doses as high as 15,000 µg vitamin D do not result in mean serum 25(OH)D levels greater than 200 nmol/L. Although some individuals may have higher levels these are unlikely to persist for a sustained period following a single dose.

30. From the available data it appears unlikely that large single doses of vitamin D would elevate serum 25(OH)D levels to those reported in cases of vitamin D toxicity. However, the findings of an increase in falls and fractures as reported by Sanders *et al*., 2010 does not appear to be related to high 25(OH)D levels (or hypercalcaemia) and remains unexplained.

Questions for the committee

31. The committee is asked to consider whether:

a) A maximum level can be set for a single dose of vitamin D, or if not, whether any kind of guidance can be given.

b) A maximum level can be set for serum 25(OH)D, or if not, whether any kind of guidance can be given.

c) They can make any comments with regard to the use of high, single, doses of vitamin D, for example under supervision in human trials?

d) They have any other comments on the data?

Secretariat

May 2014

Glossary

AUC- Area under the curve

1,25(OH)D2 – 1,25-dihydroxyvitamin D

EFSA- European Food Safety Authority

g- gram

25(OH)D - 25-hydroxyvitamin D

i.m.- intra muscular

IOM- Institute of Medicine

µg/day- Micrograms/day

mo-month

NDA- EFSA panel on Dietetic Products, Nutrition and Allergy

NDNS- National Diet and Nutrition Survey

nmol/L- nanomoles/Litre

ng/ml- nanograms/millilitre

SACN- Scientific Advisory Committee on Nutrition

y- years

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Table 1- Case reports of vitamin D intoxication, where serum 25(OH)D was measured.

Population	**Dose/ Exposure µg**	**Duration**	**Serum 25(OH)D nmol/L**	**Symptoms**	**Reference**
Boy 2y	Liquid supplement. 15,000/day	4 days	1175 (peak)	Colic constipation, vomiting lethargy	Barrueto *et al*., 2005
1 child (anephric)			1588		Counts *et al*., 1975*
Female 66y	5 (2 x day). Symptoms started with new pack 200 µg/pill	3 years	696	"severe constitutional symptoms" anaemia	Puig *et al*., 1998
Male 32y	Lab technician working with vitamin D_3 dust	65 days in a 3 y period	1240 (at 1 mo)- still elevated 8 mo after exposure	Polydipsia, anorexia nausea, general malaise	Jibani and Hodges, 1985
Female 58y	Supplements containing 4674 µg per serving	2 months	1171	Fatigue, forgetfulness, constipation, back pain, nausea, vomiting.	Klontz and Acheson, 2007
Male 42y	Supplement powder – variable D_3 content. 3900-65100 µg/day consumed	2 years	1218	Hypercalcaemia	Koutkia *et al*., 2001
Female 70 y	15000/day	3 weeks	1474	Hypercalcaemia not apparent when 25(OH)D declined to 711 nmol/L 9 wks after vitamin D withdrawn.	Lilienfeld Toal *et al*., 1978
Female 49 y	2500	6 years	706, 666	Weight loss, anorexia, pruritis, back pain and bone pain. Hypercalcaemia	Streck *et al*, 1979
7 cases (3 adults, 4 children)	Unknown	Unknown (1 week for 2 adults)	832-1287	Vomiting, anorexia, constipation, polydipsia	Thomson and Johnson, 1986
Family, 2 adults + 11 mo infant	Food cooked in nut oil – Vit D_3 125000 µg /ml	Not stated, (IOM say single	600- 3750	Nausea, vomiting, abdominal pain, weakness and sensory loss. Suffused conjunctivae. Negative calcium	Down *et al.,* 1979

Population	Dose/ Exposure µg	Duration	Serum 25(OH)D nmol/L	Symptoms	Reference
		exposure)		balance suggesting Ca mobilisation from bone. Miscarriage at 10 weeks. 11 years later, all well but persistent nephrocalcinosis in adult male.	
8 patients (7 aged 39-82y, 1 aged 15 mo)	Milk – 118-710 ml/day consumed. D_3 levels ND to 5814 µg /L)	Sporadic excess in milk.	Mean = 293± 435	Weight loss, anorexia, fatigue, weakness, vomiting, constipation	Jacobus *et al*., 1992
2 children 3 mo 7 mo	 - 300		 321 314	Anorexia, diarrhoea, vomiting (IOM) Hypercalcaemia	Jacqz *et al*., 1985*
Males, 63 and 29y	Approximately 1.3 g/ month in table sugar	7 months	3700 and 1555	Right sides flank pain. Conjunctivitis, anorexia, fever, chills, weight loss, thirst, vomiting	Vieth *et al*., 2002
Male, 62 Female, 55	Slow release i.m. preparation 3x 25,000 µg day for 20 days/month	3 months 1.5 months	375 >375	Renal failure, calcification of ileac artery and skeletal muscle	Chiricone *et al*., 2003
11 patients, 8-69 y	Vitamin D concentrate 50,000 µg /g used as cooking oil	Single exposure	847-1652	Abdominal cramps, vomiting, neurological symptoms	Pettifor *et al*., 1995
33 cases (93 controls)	Over-fortified milk- dose unknown	Unknown – could be over 5y in some cases	Mean= 896	Anorexia, weight loss, weakness, fatigue, disorientation, vomiting dehydration, polyuria, constipation. Renal impairment, 2 deaths due to hypercalcaemia.	Blank *et al*., 1995
234 survey respondents	Over-fortified milk- dose unknown	Unclear – assessed by daily intake	32.8, 39.5, 41.3, 44.7 in Qs in increasing intake	Symptom scores and individual symptoms not associated with intakes.	Scanlon *et al*., 1995
6 cases (14-57y) –variety	2.5- 5 mg/day (1 unknown)	2-13 y	533-1203 D_2 and D_3 combined		Selby *et al*., 1995

Population	Dose/ Exposure µg	Duration	Serum 25(OH)D nmol/L	Symptoms	Reference
of indications					
7 cases (50-8 4y) Treated with vitamin D for osteoporosis, osteomalacia or hypoparathyroidism	250-750	Various- 3 wks to 7.2y	710 ± 179 mean (range 221-1692)	Asthenia, weight loss, nausea, polydipsia, polyuria, bradypsychism, sleepiness, pruritus, dizziness, episcleritis Urinary calcium 0.192 ± 0.067 mmol/L	Rizzoli *et al*., 1994
4 cases (all female) 42-77y Patients with osteoporosis or osteomalacia	1250 µg /? 1250 µg/week 1250 µg /day 1250 µg /2 x week	Long term 6 weeks 6 weeks 5 years	Elevated mean 618 range 355-833 in 3 (not measured in 1)	Lethargy, tenderness in some joints, pain, nausea, weakness, confusion, hypertension.	Schwartzman and Franck, 1987
8 cases (15-60y) Female 71y (only case with 25(OH)D	1250 – 5000 µg /day 3750	4 months-10y 2y	 1123	Back ache, sore eyes, nausea, vomiting, anorexia, pruritus, polydipsia. Polyuria. No symptoms in 1 patient.	Davies and Adams, 1978
10 cases (48-75y)	525,000 µg 270,000 µg ? ? 300,000 ? 1,350,000 75000 ? 1,500,000	1-4 months	302 172 200 165 164 283 100 236 176 306	Lassitude, vomiting, polyuria, polydipsia, altered sensorium, anorexia, oliguria. NB. The patients were from an area of India with endemic hypovitaminosis D. 25(OH)D levels seem low, normal range stated to be up to 144 nmol/L	Koul *et al*., 2012

Population	Dose/ Exposure µg	Duration	Serum 25(OH)D nmol/L	Symptoms	Reference

*Abstract only

Table 2. Vitamin D single dose – change in 25(OH)D response

Dose (µg)	Population	Starting mean 25(OH)D nmol/L	25(OH)D after treatment nmol/L[4]	Change ± baseline nmol/L	Measured when?	Comments	Reference
15,000	48 young people with vitamin D deficiency (25-56y) Italy	39 ± 16.22 (mean± SD)	192. 69 ± 76.13 (day 3) 190.94 ± 69.64 (day 15) 155.75 ± 65.15 (day 30) Maximum individual 339 (but baseline ?). (mean± SD)	+ 153 + 151 + 116	3, 15 and 30 d. Sub group followed to 90 d	Serum calcium significantly increased at day 3 but within normal range.	Cipriani *et al*., 2010
15,000 p.o. vitamin D_2 or D_3 i.m. vitamin D_2 or D_3	24 patients with vitamin D deficiency Italy	Not given in main paper.		+ 15.22 (day 30) + 30.95 (day 30) <u>i.m.</u> + 8.23 (day 30) ?[5] 22.71 (day 120) 27.96 (day120)	30, 60, 90 and 120 d.	Oral D_2 peaked at d30 and declined Oral D_3 slower decline, larger AUC. i.m (both forms) slow increase to day 120. AUC $D_2 < D_3$ for i.m. and oral No changes in ionised Ca	Cipriani *et al*., 2013

[4] 25 (OH)D levels peak 2 weeks after the dose, the time point(s) likely to demonstrate the highest level has been used, where extended measurement has occurred.

[5] It is unclear from the paper what the increase above baseline for i.m. D_3 is at day 30

Dose (µg)	Population	Starting mean 25(OH)D nmol/L	25(OH)D after treatment nmol/L[4]	Change ± baseline nmol/L	Measured when?	Comments	Reference
15,000	18 young women with vitamin D deficiency Italy				3, 15 and 30 d.		Cipriani *et al*., 2013 **Waiting for paper**
15,000 i.m.	50 adults (mean age 66.3y) Australia	32 ± 8.4 (mean± SD)	114 ± 35 (4 mo) (mean± SD)		0, 4, 12 mo	No change in serum calcium.	Diamond *et al*., 2005
12,500 or placebo	2256 community dwelling women, ≥ 70y Australia	Median 49 (IQR 40-63) Subset of 137 analysed	Median 120 (1 mo), 90 (3 mo) IQR 105-145, 10-105 (estimated from figure)	+ 70, + 40	1, 3, 12 mo after dosing	No change in placebo 25(OH)D Increase in falls and fractures.	Sanders *et al*., 2010
12,500 12,500 + 1250/month	19, 22 elderly people (≥ 65 y) hospitalised at time of recruitment, largely independent thereafter. New Zealand	58 ± 25 66 ± 41 (mean ± SD)	116 124 At 1 month Maximum individual 220 nmol/L (from 136 nmol/L baseline).	+ 58 + 58	Monthly for 9 months	Peaked at 1 month, declined to a plateau from 3 mo onwards. No effect on serum calcium. Increase higher (71 nmol/L) in deficient, than non-deficient	Bacon *et al.,* 2009

Dose (µg)	Population	Starting mean 25(OH)D nmol/L	25(OH)D after treatment nmol/L[4]	Change ± baseline nmol/L	Measured when?	Comments	Reference
						(50 nmol/L)	
7500 (or 20/day, not presented)	14/group elderly subjects with secondary hyperparathyroidism. Brazil	30.95 ± 16.72 mean ± SD	82 (estimated from figure) at 1 mo	+ 50	0, 1, 2, 3, 6 and 9 mo	Results largely present as % of individuals with serum 25(OH)D > 49.92 Serum calcium not affected.	Premaor *et al*., 2008
7500	8/group Elderly women given D_2 or D_3 –oral Italy	31.45 ± 22.71 33.2 ± 24.71 (mean ± SD)		43.28 ± 11.93 119.38 ± 18.22 At day 30 (mean ± SD)	Day 3, 7, 30, 60	D_2 peaked at day 7 rather than 30 D_2 less effective than D_3	Romagnoli *et al*., 2008
7500	8/group Elderly women given D_2 or D_3 –i.m. Italy	18.22 ± 6.49 24.57 ± 8.99 (mean ± SD)		12.70 ± 11.21 39.71 ± 28.25 At day 30 (mean ± SD)	Day 3, 7, 30, 60	Doses given i.m. - much slower increase, still rising at day 60. D_2 less effective than D_3	Romagnoli *et al*., 2008
7500 D_2 or D_3	Patients with alcoholic cirrhosis	< 25			Day 0, 7, 30, 90	Levels higher in D_3 group	Malham *et al*., 2012 **Waiting for paper**
7500	49 Elderly in-patients (69-94y) New Zealand	17.47 ± 9.98 (mean ± SD)	62.4 ± 27.46 (mean ± SD)	+ 35	Various but average of 17 weeks.	Levels peaked between 13 and 21 days, half life 90 days. Max level 127.3	Wu *et al*., 2003
7500 i.m. D_2	585 elderly men and	141.02 ±		21% increase	1, 4, 8, 13, 13,		Smith *et al*.,

Dose (µg)	Population	Starting mean 25(OH)D nmol/L	25(OH)D after treatment nmol/L[4]	Change ± baseline nmol/L	Measured when?	Comments	Reference
Annual	women >85 y England	59.16[6] Sample of 43 (mean ± SD)		in active group at 4 months. Estimated to be approx. 30 nmol/L	16 mo		2007
3750 given every 3 months or placebo	686 community dwelling women aged >70 y Subset of 40 analysed Australia	165.98 ± 44.43 149.26 ± 51.12 132.79 ± 56.91 150.26 ± 65.65 Placebo at 0, 3, 6, 9 mo (mean ± SD)	162.24 ± 56.66 184.70 ± 53.91 172.47 ± 64.65 186.20 ± 64.4 Treated at 0, 3, 6, 9 mo (mean ± SD)	+ 37.44 higher than placebo overall	3, 6 and 9 months	Baseline levels already high	Glendenning *et al*., 2010
3750 i.m. D_2				Low levels normalised			Heikinheimo *et al*., 1991 **waiting for paper**
2500	Elderly people in residential home	(23.21 ± 2.25)	88.36 ± 5.74 at 2 weeks	+ 62			Weisman *et al*., 1986/? Abstract and proceedings[7].
2500 or placebo	Healthy older people (63-76y)	34.5		+ 19.4 ± 11.6 -2.7 ± 10.8	5 weeks	No changes in serum calcium	Khaw *et al*., 1994.

[6] This seems to be high and was given as 56.5 ± 23.7 ng/ml and converted to nmol/L

[7] There appear to be 2 references for the same study, one being a conference proceedings.

Dose (µg)	Population	Starting mean 25(OH)D nmol/L	25(OH)D after treatment nmol/L[4]	Change ± baseline nmol/L	Measured when?	Comments	Reference
	England			(placebo) (Mean ± SD)			
2500	30 subjects (20 aged 61-84y and 10 aged 27-47y) US	67.64 ± 19.22 (mean ± SD)	104.83 ± 22.71 (mean ± SD)	+ 37	Measured at intervals, peak occurred at day 7	Back to baseline by day 84. Younger subjects had a steeper rise and higher Cmax and larger AUC. No increase in serum Ca 1 SD above mean is 194.94 nmol/L	Ilahi *et al*., 2008
1750	34 pregnant 27 non-pregnant women Bangladesh	39 54		32 28	Day 0, 2, 4, 7, and then weekly for up to 10 weeks. Different sampling schedules to minimise burden on volunteers.	25(OH)D increase slower in pregnant vs non-pregnant women. Variable response but all peaked within 3 weeks. Hypercalcaemia not found.	Roth *et al*., 2012
1250 of D_2, D_3 or placebo	10 Healthy male volunteers/group (20-61y)	79.19 ± 21.13 (all)		+ 12 + 17 -	Day 0, 1, 3, 5-7, 14 and 28.	Similar initial responses but 25(OH)D	Armas *et al*., 2004

Dose (µg)	Population	Starting mean 25(OH)D nmol/L	25(OH)D after treatment nmol/L[4]	Change ± baseline nmol/L	Measured when?	Comments	Reference
US		(mean ± SD)				continued to increase in D_3 peaking at day 14 AUC of D_2 30% of D_3	