

EXPERT GROUP ON VITAMINS AND MINERALS

REVIEW OF VITAMIN D – REVISED VERSION

The attached review of vitamin D is an updated version of the revised paper presented to the Expert Group on Vitamins and Minerals at the meetings in April 2002 and October 2001.

The following annexes are also included:

- Annex 1 Intakes of vitamin D from food and supplements
- Annex 2 Tables summarising the animal and human data
- Annex 3 Summary table of selected nutrition related information and existing guidance on intakes

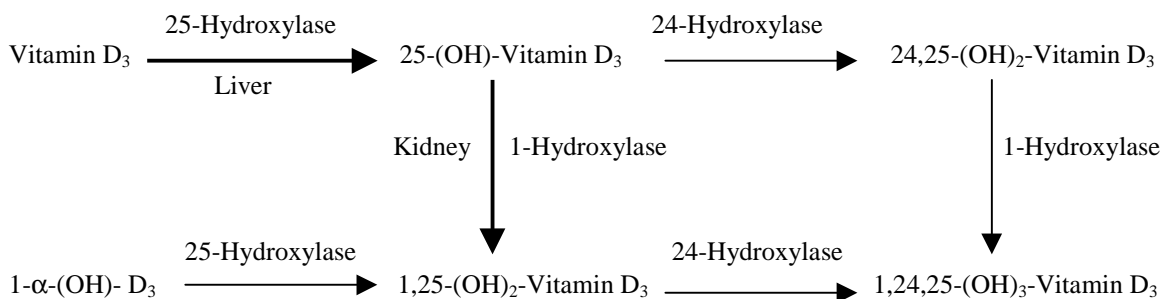
Expert Group on Vitamins and Minerals Secretariat
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Vitamin D

Chemistry

1. The term vitamin D refers to a group of fat-soluble seco-steroid compounds that have in common a conjugated triene system and that exhibit anti-rachitic properties; that is, they prevent the childhood disease rickets, which is characterised by defective bone growth and is caused by long-term deficiency of vitamin D. The two forms of the vitamin that are best known and which are of nutritional significance are ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) (DeLuca and Schnoes, 1976). The active form of vitamin D is 1,25-dihydroxyvitamin D (1,25-(OH)₂D₂) and is formed following sequential hydroxylations in the liver and kidney (see paragraphs 59-60). The structures are given in Fig 1 below.

Fig 1: The pathways of vitamin D₃ metabolism. The most important pathways to the functional hormone are shown with bold arrows



(Adapted from Basu and Dickerson, 1996)

2. Vitamin D₂ (ergocalciferol) is produced synthetically by the UV irradiation of ergosterol, found in plants, fungi and lower life-forms, it is not formed naturally in higher animals. Compared to vitamin D₃, it has an extra methyl group on the 24th carbon and a double bond between the 22nd and 23rd carbon atoms. Vitamin D₂ is metabolised to 25-(OH)-Vitamin D₂ and then to active 1,25-(OH)₂-vitamin D₂ by the same enzyme systems as vitamin D₃ (Koshy, 1982). Two unique metabolites of vitamin D₂ in serum have recently been identified – 24-hydroxyvitamin D₂ and 1,24-dihydroxyvitamin D₂ (Mawer *et al.*, 1998). Vitamin D₂ has long been assumed to have the same biological activity as vitamin D₃ in humans (van den Berg, 1997) and for all practical purposes vitamin D₂ and D₃ are considered to be the same, though a recent study suggests that vitamin D₂ may be approximately 1.7 times less effective than vitamin D₃ at increasing 25-(OH)-vitamin D levels (Trang *et al.*, 1998).

3. Vitamin D concentrations are on occasion quoted in International Units (IU). One µg of vitamin D is equivalent to 40 IU.

Natural occurrence

4. Exposure of the skin to ultraviolet light stimulates the formation of vitamin D₃ (cholecalciferol) from 7-dehydrocholesterol. The naturally occurring vitamin D precursor, 7-dehydrocholesterol, is primarily synthesised in the sebaceous glands, it is first secreted onto the surface of the skin then reabsorbed into the various layers of the epidermis. Absorption of ultraviolet light penetrating the epidermis by 7-dehydrocholesterol results in opening of the B ring of the sterol nucleus and formation of the thermodynamically unstable previtamin D. This previtamin undergoes an isomerisation to form cholecalciferol (Basu and Dickerson, 1996).
5. Increased skin pigment can greatly reduce the UV-mediated synthesis of vitamin D (Clemens *et al.*, 1982).

Occurrence in foods, supplements and medicines

Food and food supplements

6. Relatively few natural foods contain significant amounts of vitamin D. It is not present in detectable amounts in any vegetables, fruits or nuts and only trace amounts exist in non-fatty fish. Analytical surveys of carcass meat, poultry and meat products were carried out in the early-mid 1990s. These surveys found measurable amounts of vitamin D and its metabolites in meats as a result of new analytical methods (see Annex 1). Fatty fish, e.g. herring and mackerel, contain the highest concentrations of vitamin D, with eggs also being a rich source. Vitamin D is to some extent stored in the liver; therefore mammalian liver is also high in vitamin D. The vitamin is stable in foods and on storage; processing and cooking do not appear to affect its activity (National Research Council, 1989; COMA, 1991). Protein bound 25-(OH) vitamin D can be found in milk (discussed by van den Berg, 1997).
7. In addition to the natural sources, in most industrialised countries all processed milk, some powdered milk, margarine, breakfast cereals, bread and chocolate bars have varying amounts of added vitamin D, and are thus significant dietary sources of the vitamin. In the UK, infant formula is fortified with vitamin D at levels between 1 and 2.5 µg/100 kcal. Human milk has a low vitamin D concentration. Both vitamin D₂ and vitamin D₃ are used for food fortification. Food suitable for vegans contains vitamin D₂ only.
8. Vitamin D is present in a number of food supplements, both multivitamin supplements with or without minerals and in fish oil products. The doses generally range from 2.5 to 12.5 µg/day. Both vitamin D₂ and vitamin D₃ are used in dietary supplements.

Licensed medicinal products for oral use

9. Medicinal products containing vitamin D (as cholecalciferol or ergocalciferol) may be sold in supermarkets and other retail outlets, without the supervision of a pharmacist, providing the recommended dose is no greater than 10 µg/day. They are marketed for the prevention and treatment of deficiency, including use in the elderly,

expectant and nursing mothers, children and those on restricted diets. Thirty-eight products, all of which contain one or more additional nutrients, are currently authorised.

10. Vitamin D preparations providing higher doses are only available under the supervision of a pharmacist. Thirty-seven multi-constituent products providing up to 25 micrograms per day are authorised. Indications include the prevention and treatment of deficiency, and use by those on restricted diets or with malabsorption disorders. Combinations with calcium are indicated for use as adjuncts in the treatment of osteoporosis and as supplements in patients with osteomalacia or in pregnant women at risk of deficiency. In addition, three single constituent high potency products (providing up to 5 mg/day) are used in vitamin D deficiency caused by malabsorption and liver disease, hypocalcaemia of hypoparathyroidism and renal osteodystrophy.

Intake and Exposure

11. Intakes of vitamin D in the UK from food and supplements have been provided (see Annex 1). Mean intakes in adults aged 16-64 years from all sources are 3.78 µg/day (males) and 3.09 µg/day (females). High level (97.5 %ile) consumption from all sources can be estimated to be 13 µg/day (males) and 11.4 µg/day (females). The contribution of sunlight to vitamin D exposure is difficult to estimate.

Recommended amounts

12. Establishing a recommended dietary intake for vitamin D is difficult because exposure to sunlight results in the synthesis of vitamin D by the skin. Therefore, adults regularly exposed to sunlight, under appropriate conditions, have no dietary requirement for vitamin D. In adults (18-65 years of age) plasma 25-(OH)-vitamin D normally ranges from 15-35 ng/ml (37.5-87.5 nmol/l) in summer and 8-18 ng/ml (20-45 nmol/l) in winter. The lower level of the normal range for plasma 25-(OH)-vitamin D is 10 ng/ml (25 nmol/l) thus no dietary intake is necessary for individuals leading a normal lifestyle (COMA, 1991). For those confined indoors, a daily intake of 10 µg/day from food is recommended. In the US a substantial proportion of the population is exposed to very little sunlight, especially during certain seasons, so the US Food and Nutrition Board (FNB, 1997) recommend an Adequate Intake¹ of 5 µg/day for individuals aged 0 to 50 years.

13. Several reports question whether human milk contains sufficient vitamin D to prevent rickets in the absence of exposure to sunlight (Finberg, 1981). In infants fed human milk, bone mineral content, total and ionised calcium in serum and serum phosphorus values were all similar to those in infants fed fortified formula, however, serum 25-(OH)-vitamin D levels were lower in the babies fed human milk (Roberts *et al* 1981). In the UK, infants fed formula milk receive approximately 8.5 µg/day, which maintains the plasma 25-(OH)-vitamin D levels at an acceptable 20 ng/ml (50 nmol/l).

¹ An Adequate Intake (AI) is set instead of a Recommended Dietary Allowance if sufficient scientific evidence is not available to calculate an Estimated Average Requirement. It is not known what percentage of the individuals are covered by the AI. It is expected to exceed the average requirements and it should cover the needs of 98% of individuals but it might cover the needs of far fewer.

Therefore, the Reference Nutrient Intake (RNI) for infants aged 0-6 months is 8.5 µg/day and from 7 months to 3 years is 7 µg/day. Breast-fed babies show a seasonal variation in plasma 25-(OH)-vitamin D. For those born in the autumn the serum concentration can decline to very low levels because mother's milk during the winter contains very little vitamin D (COMA, 1991). It was therefore recommended that lactating mothers should receive supplementary vitamin D. In the US, the FNB has recommended an Adequate Intake of 5 µg for infants aged 0-6 months (FNB, 1997).

14. It has not been determined, whether or not there is an increased need for vitamin D during pregnancy. However, since calcium is deposited in the growing foetus, a supplement of 10 µg vitamin D/day is recommended throughout pregnancy in the UK (COMA, 1991). During lactation declines in plasma 25-(OH)-vitamin D values and increased 1,25-(OH)₂D₂ concentrations have been observed, therefore an intake of 10 µg/day is also recommended at this time (COMA, 1991). The FNB in the US concluded that there was no evidence that pregnancy or lactation increases a mother's need for vitamin D (FNB, 1997).

Assessment of tissue levels and vitamin D status

15. Plasma levels of the active form of vitamin D (1,25-(OH)₂D₂) are under homeostatic control, which limits their value as a marker of status (COMA 1998). Consequently the conventional marker of vitamin D status is plasma 25-(OH)-vitamin D. This intermediate is responsive to changes in dietary vitamin D and exposure to sunlight. Plasma 25-(OH)-vitamin D of 25 nmol/l is used as the cut-off point for defining the lower limit of adequacy.

Bioavailability

16. Some evidence exists (Basu and Dickerson, 1996), suggesting that orally administered vitamin D is less effective than biosynthesised vitamin D at raising circulatory levels of 25-(OH)-vitamin D. The more polar hydroxylated metabolites of Vitamin D can be partly absorbed through the portal venous system (van den Berg, 1997). Oral absorption of 25-OH Vitamin D is more efficient and less dependent on bile acids than that of non-hydroxylated derivatives. For example, the absorption of 25-OH-vitamin D is 10 times more efficient than that of vitamin D₃.

17. Absorption of vitamin D from a long chain fatty acid carrier (peanut oil) is more efficient than from medium chain triglycerides (reviewed by van den Berg, 1997). A high fibre diet may increase elimination of vitamin D and iron deficiency may reduce absorption. Absorption of vitamin D₂ from meat (obtained from pigs fed vitamin D₂ supplemented feed) was approximately 60% of that from vitamin D₂ supplements (van den Berg, 1997). Absorption of vitamin D from supplements is thought to range from 55 to 99% (when given in oil to stimulate bile acid release) (van den Berg, 1997).

Interactions

Actinomycin

18. An early observation showed that actinomycin prevented the *in vivo* actions of vitamin D. It is now believed that the mechanism results from depressed protein synthesis upon which the rapid turnover rate of the 1-hydroxylase system of the kidney is dependent. In rats, actinomycin and cyclohexamide inhibit the conversion of 25-(OH)-vitamin D to 1,25-(OH)₂D₂ (Boyle *et al.*, 1971; Gray and DeLuca, 1971).

Lead

19. Lead has been shown to suppress the biosynthesis of vitamin D (Mushak and Crocetti, 1996).

Function

20. 1,25-(OH)₂D₂ the hormonal form of vitamin D regulates calcium and phosphate metabolism by its action on three target tissues, small intestine, bone and kidney. In addition to these major sites of vitamin D action, many other body tissues and cells have receptors for and responses to 1,25-(OH)₂ vitamin D. These include pancreas, pituitary gland, lymphocytes and monocytes. The precise physiological function of vitamin D in these tissues is uncertain, but an anti-proliferative and pro-differentiation action is apparent (FNB, 1997). 1,25-(OH)₂D₃ interacts with a specific receptor protein in its target tissues, the receptor complex is taken up into the nucleus and recycled (DeLuca and Zierold, 1998). The Vitamin D Receptor (VDR) binds to direct repeat response elements called DR-3 in the promoter regions of target genes to stimulate or suppress transcription. The VDR will only bind to the response elements if the retinoid X receptor is also present.

Small Intestine

21. The active form of vitamin D regulates the intestinal absorption of calcium from the diet. Proximal calcium absorption through the enterocyte involves increased luminal permeability, intracellular calcium transport and extrusion through the basolateral membrane into the extracellular fluid (Sahota and Hosking, 1999). Transport is facilitated by two 1,25-(OH)₂D dependent calcium binding proteins, calbindin D9k (CaBP-D_{9k}, the most abundant) and calbindin D28k (CaBP-D_{28k}). In the distal bowel calcium is absorbed both by a 1,25-(OH)₂D mediated carrier process and by passive pericellular diffusion down a concentration gradient. Although mRNA for a range of genes responds to 1,25-(OH)₂ vitamin D in a number of tissues, it is only the transcription of the calbindin genes in the intestine that is dependent on the hormone (Emtage *et al.*, 1973). Thus, it is recognised that the major response of the intestine to vitamin D is an increase in calbindin synthesis, although the function of calbindin is not yet clear. There is some evidence to suggest that it is related to the intestinal transport of calcium.

22. Magnesium absorption through the gut involves both active and passive mechanisms but is much less tightly regulated by 1,25-(OH)₂D than calcium absorption. Transport of inorganic phosphate across the luminal brush border is dependent on the

sodium-phosphate co-transporter; this is the step at which 1,25-(OH)₂D regulated phosphate absorption occurs, but the mechanisms are poorly understood (Sahota and Hosking, 1999).

Kidney

23. The parathyroid hormone (PTH)–vitamin D axis regulates calcium transport in the kidney at the distal convoluted tubule (Sahota and Hosking, 1999). However, approximately 80% of the filtered calcium load is reabsorbed in the proximal convoluted tubules by hormone-independent mechanisms. Calcium and magnesium are driven through the tight junctions between proximal convoluted tubule cells by a concentration gradient caused by the resorption of sodium and water. Whereas in both bone and intestine, calcium and phosphate are co-transported, in the kidney they pass in opposite directions. Calcium resorption at the distal nephron is regulated by 1,25-(OH)₂D₂ and PTH. The mechanisms of the active calcium transcellular transport are similar to those in the enterocyte with 1,25-(OH)₂D₂ stimulating the expression of calcium binding protein. 1,25-(OH)₂D₂ may also stimulate the synthesis of the plasma membrane pump, as well as regulating its activity (Sahota and Hosking, 1999).

24. It has been reported that even in situations of vitamin D deficiency, 99% of the calcium filtered by the kidney is reabsorbed (Hausler and McCain, 1977a). However, reports exist that suggest an effect of 1,25-(OH)₂ vitamin D on stimulation of the renal absorption of calcium (DeLuca and Schnoes, 1976). 1,25-(OH)₂D₃ is able to localise in the nuclei of cells in the distal renal tubules, where it binds to the vitamin D receptor (VDR) (DeLuca and Zierold, 1998). Binding to the VDR is known to be essential to the prevention of rickets and the regulation of calcium and phosphorus.

Bone

25. The mechanical integrity and structure of skeleton is maintained by constant remodelling in response to physiological and pathological stress (Sahota and Hosking, 1999). The replacement of old with new bone is known as remodelling; bone mass is preserved by a balanced process of resorption and replacement.

26. The action of vitamin D on bone is not well defined. Fraser (1981) proposes a role for the 1,25-dihydroxy derivative in bone resorption, possibly in the proliferation of macrophages (Sahota and Hosking, 1999). Bone formation begins with the differentiation of mesenchymal stromal cells to form mature osteoblasts. This is regulated by a number of factors including PTH and 1,25-(OH)₂D. It has been proposed that another metabolite, 24,25-(OH)₂D₃, plays a significant role in normal bone formation (Ornoy *et al.*, 1978). 1,25-(OH)₂D and PTH are also involved in the regulation of the migration of the vesicles containing calcium phosphate from the cell processes of the osteoblast to the zone of mineralisation (Sahota and Hosking, 1999). As this process proceeds some of the osteoblasts are incorporated into bone as osteocytes, while others remain as lining cells covering the trabecular surfaces. However, it appears that there is no direct effect of vitamin D or any of its metabolites on bone mineralisation.

27. When considering the effects of 1,25-(OH)₂ vitamin D on bone it should be noted that bone contains several cell types, which may respond in different ways to 1,25-(OH)₂D. Osteoblasts have receptors for 1,25-(OH)₂D₃, which appears to increase

mineralisation and osteoblast differentiation. In this way, bone formation and hence growth are promoted (Braidman, 1990).

28. To maintain a constant plasma calcium concentration, PTH works in conjunction with vitamin D on the osteoblasts in an unknown and complex mechanism to mobilise calcium, and hence phosphate, from bone (DeLuca and Zeiroid, 1998).

Deficiency

Rickets

29. The disorder due to vitamin D deficiency in children is termed 'rickets', which occurs after prolonged deficiency of vitamin D during periods of bone growth. The disease used to be widespread in city children. The prevalence of rickets was substantially diminished in the UK with the mandatory fortification of margarine and the introduction of modified dried cows' milk powder fortified with vitamin D, together with other factors such as the Clean Air Acts, changes in lifestyle, increasing affluence and longer and more frequent holidays (COMA, 1991b).

30. Late closure of the fontanelle (craniotables) is the earliest sign of rickets. It is detected in infants less than 12 months of age as round unossified areas in the skull. These regions occur on the upper occipital, posterior parietal bones and sometimes in the upper temporal lobe. Beading of the ribs, termed 'rachitic rosary', is an almost consistent sign after 6 months of age. This is caused by the swollen cartilaginous ends of the ribs. The chest may be narrow and rather funnel shaped, described as 'pigeon chest', in severe cases this may interfere with breathing. When the child begins to toddle, putting weight on the legs results in the femur becoming bowed and separation of the knees. Greenstick fractures are common and may often be overlooked, as they result in no further deformity of the already distorted limbs. Severe vitamin D deficiency reduces the growth rate and causes microcephaly, with reduction in brain growth and the eruption of teeth is delayed (Haussler and McCain, 1977b; Basu and Dickerson, 1996). Clinically the child is miserable, apathetic and in pain (COMA, 1998).

31. A low concentration of 25-(OH)-vitamin D is often associated with clinical rickets, but this may be found in individuals without clinical symptoms. Vitamin D-deficient rickets can be completely cured by oral administration of 50-125 µg cholecalciferol/day (Basu and Dickerson, 1996).

Osteomalacia

32. Osteomalacia describes the combination of clinical, biochemical, radiographic and histological abnormalities in adults, which result from severe vitamin D deficiency. The term 'osteomalacia' applies to defective mineralisation of bone. This may be due to either vitamin D deficiency, or impaired vitamin D function. In the UK osteomalacia due to vitamin D deficiency is confined mainly to Asian immigrants and the elderly (see paragraphs 39-42). Secondary deficiency and impaired vitamin D function may occur with gastrointestinal, hepatic and renal disorders. Vitamin D deficient osteomalacia in elderly women often co-exists with osteoporosis and has been attributed to dietary lack of

the vitamin. However, skin synthesis of cholecalciferol during the summer months is probably more important than diet as a source (Lawson *et al.*, 1979).

33. The main clinical features of osteomalacia are skeletal pain and muscle weakness. As the disease progresses, severe pain and body tenderness occurs in the thorax, shoulder, hips, thighs, forearms and feet. Bone density is reduced, as in osteoporosis. However, in contrast to osteoporosis, poor mineralisation is seen more commonly in the peripheral bones than in the vertebrae and pain is less common in the axial skeleton. The most characteristic radiological signs of osteomalacia are pseudofractures, called 'Looser's zones', appearing as translucent bands of decalcification at right angles to the bone surfaces. Fractures are also common. Plasma calcium and phosphate levels are reduced and alkaline phosphatase levels increased. Treatment with vitamin D reverses the clinical signs of osteomalacia and results in healing of fractures (Haussler and McCain, 1977b; Basu and Dickerson, 1996).

Anticonvulsant-induced osteomalacia

34. Studies have shown that long-term treatment with anticonvulsants, especially phenytoin, may induce osteomalacia. Such drugs induce the mixed function oxidase enzyme system in the liver, which acts upon steroids. It has been suggested that such induction may lead to the conversion of cholecalciferol to inactive metabolites (Stamp, 1974). It has also been suggested that such drugs may in some way induce resistance to the vitamin, as unusually large doses (250 µg/ m² body area) are needed for the treatment of anticonvulsant osteomalacia (Hahn and Alvioli, 1975).

Gastrointestinal osteomalacia

35. A substantial proportion of individuals, especially females, develops osteomalacia after partial or total gastrectomy. This form of the disease responds well to treatment with low doses of vitamin D, although there is some evidence that men respond better than women (Basu and Dickerson, 1996). Dietary deficiency or failure to absorb the vitamin may be the cause.

36. Patients with long-term malabsorption, due to cystic fibrosis or gluten-induced enteropathy, are also at risk of developing osteomalacia. Under these conditions it appears that increased destruction of vitamin D, as a result of enhanced activity of hepatic enzymes, is the cause (Shefer *et al.*, 1969).

Osteomalacia and liver/renal disease

37. Osteomalacia may occur in patients with biliary obstruction or hepatocellular damage. There may be decreased absorption of vitamin D and defective production of 25-(OH)-vitamin D as a result of decreased 25-hydroxylase activity.

38. The activity of the 25-hydroxylase enzyme is severely reduced with acquired renal disease, leading to inadequate production of 1,25-(OH)₂D₃. Plasma concentrations of this metabolite remain normal until renal function is so reduced that creatinine clearance has fallen to about 40 ml/min (normal values, 85-125 ml/min). Treatment with either physiological doses of vitamin D or small doses of 1,25-(OH)₂D₃ are equally effective (Basu and Dickerson, 1996).

Groups vulnerable to deficiency

39. The elderly have lower vitamin D levels than younger adults, in part due to an age-related reduction in skin synthesis of vitamin D precursors and a tendency for less exposure to the sun. Elderly people also tend to consume fewer vitamin D fortified dairy products, which may be due to age-related lactase deficiency (Prystowski, 1988). The effect of dietary vitamin D intake has also been shown to decrease with age (Harris *et al.*, 1999). A study on plasma 25-(OH)-vitamin D levels in young (20-35) and old (60-75) men following supplementation with 1,800 IU/day ergocalciferol showed that although plasma 25-(OH)-vitamin D levels increased in both groups, levels increased significantly less in the older group. These results suggest there is decreased absorption, transport or hydroxylation of dietary vitamin D in the elderly. Of the elderly that are institutionalised approximately 37% are vitamin D deficient.

40. Osteomalacia results from severe vitamin D deficiency; lesser deficiencies of vitamin D increase bone turnover by decreasing intestinal calcium absorption and causing secondary hyperparathyroidism. This may increase the risk of fractures in the elderly. Vitamin D levels have been correlated with bone mineral density of the femoral neck (Ooms *et al.*, 1995).

41. Black, Asian and white people all have the same capacity to produce vitamin D₃ via the skin, but greater exposure to sunlight is required in black and Asian people due to the increased amounts of UV radiation-absorbing melanin (Holick, 1987). Black and Asian people living in the United Kingdom and other Northern European and North American countries are therefore at a potentially increased risk of vitamin D deficiency. A study investigating vitamin D deficiency in elderly women found that black women were at a significantly greater risk of deficiency (Semba *et al.*, 2000). Reduced serum levels of 25-(OH)-vitamin D have recently been shown in black African-American women in the United States (Kyriakidou-Himonas *et al.*, 1999), in Asian pre-menopausal women living in Norway (Mazess, 2000) and in Asian infants in the UK (Lawson and Thomas, 1999).

42. Since the early 1960s the highest incidence of rickets in the United Kingdom has been in Asian immigrants (Lawson and Thomas, 1999). This has possibly been exacerbated by a lower consumption of fortified foods due to dietary differences (Singleton and Tucker, 1978). Campaigns to encourage vitamin supplementation have been successful and rickets is now much less common, but cases remain (Wharton, 1999). A recent study of vitamin D levels in 618 Asian toddlers aged 1½ to 2 years showed that 20-34% had a sub-optimal serum 25-(OH)-vitamin D level of ≤ 25 nmol/l, although all were in good health (Lawson and Thomas, 1999).

43. Vegans have a lower dietary intake of vitamin D than omnivores and vegetarians that consume dairy foods. It has been shown that vegans have serum 25-(OH)-vitamin D levels that are below the normal range during winter; this may have a negative long-term effect on bone mass index. Preliminary studies indicate that supplementation with 5 µg/day ergocalciferol for 11 months increases bone mass density in vegans (Outila *et al.*, 2000).

44. People with decreased intestinal absorption of vitamin D, for example following partial gastrectomy, and patients being treated with anti-convulsant drugs are at increased risk of vitamin D deficiency (see paragraphs 34-36 above), as are people with liver, renal

and cardiopulmonary diseases (Compston, 1998). Any people who do not have, or actively avoid, exposure to sunlight due to skin diseases, housebound illnesses, institutionalisation or religious/cultural practises are at increased risk of vitamin D deficiency (Prystowsky, 1988; Compston, 1998; Glerup *et al.*, 2000).

Sunscreen use

45. Sunscreens protect the skin from the harmful effects of overexposure to the sun by absorbing UV-B radiation. However, there is an overlap between the UV absorption spectra of the sunscreen agent *para*-aminobenzoic acid (PABA) and the spectrum required for the synthesis of previtamin D₃. As a result, sunscreen use interferes with the cutaneous production of vitamin D (Matsuoka *et al.*, 1987).

46. Several studies have investigated the effects of chronic sunscreen use on circulating serum levels of 25-(OH)-vitamin D. A study in Illinois, USA showed that serum 25-(OH)-vitamin D levels in 20 chronic users (> 1 year) of PABA were significantly decreased compared to controls matched for age and sun exposure (Matsuoka *et al.*, 1988). In two of the chronic users, serum 25-(OH)-vitamin D levels were < 20 nmol/l, clinically defined as vitamin D deficiency.

47. A study in Barcelona of 24 users of clinically prescribed sun protection factor 15 sunscreens and 19 controls, followed over 2 years, showed that although levels of 25-(OH)-vitamin D were lower in the sunscreen group, this decrease was minor and did not affect bone biological markers or cause secondary hyperparathyroidism (Farrerons *et al.*, 1998).

48. A randomised controlled trial, conducted in Australia, of the daily use during the summer of a broad spectrum sun protection factor 17 sunscreen compared to a placebo cream showed that serum 25-(OH)-vitamin D levels increased significantly by the same amount in both groups. Mean serum levels of 1,25-(OH)₂-vitamin D levels increased significantly only in the placebo group. However, 25-(OH)-vitamin D and 1,25-(OH)₂-vitamin D levels were within the normal reference range in both groups.

49. Sunscreens containing PABA, cinnamates, benzophenones and salicylates all absorb UV in the range 295-300 nm; this is also the optimal wavelength for the photosynthesis of previtamin D₃. Vitamin D photosynthesis is blocked by sunscreens of sun protection factor 8 or higher (Prystowski, 1988). The studies suggest that long term use of sunscreens is unlikely to lead to deficiency in children and young adults who receive adequate levels of vitamin D from a mixture of both sun exposure and the diet. However, the elderly are likely to be at increased risk of vitamin D deficiency with the over-use of sunscreens because they tend to have less exposure to the sun, they have a decreased capacity to photosynthesise vitamin D and they tend to have poor dietary vitamin D intake.

Overview of intakes associated with non-nutritional beneficial effects

50. Vitamin D metabolites have been reported to induce differentiation and/or reduce cell proliferation in a number of malignant and non-malignant cell types. For example, vitamin D has been hypothesised to protect against prostate cancer based on both epidemiologic and laboratory evidence. This is supported by evidence that prostate

epithelial cells possess vitamin D receptors (Clinton and Giovannicci, 1998). It has also been suggested that vitamin D is inversely associated with the risk of colorectal cancer, but few epidemiologic data are available (Martinez and Willett, 1998). Vitamin D has been shown to reduce colorectal epithelial cell proliferation and to induce differentiation. This may be mediated through the vitamin D receptor. However, COMA, in its review of the nutritional aspects of the development of cancer, did not report on a link between vitamin D and prostate or any other cancer (COMA, 1998).

51. There is some evidence that vitamin D supplementation may inhibit or stop the progression of multiple sclerosis (Hayes, 2000). The aetiology of MS is still uncertain but it is known that genetic factors alone are not sufficient to cause MS, that unknown environmental factors are also necessary. Most MS patients suffer from vitamin D deficiency, although there is no evidence that vitamin D deficiency alone causes MS. MS prevalence increases with decreased exposure to the sun, and diets rich in fish, which is rich in vitamin D, may lower MS severity. Studies in Japanese MS patients have shown an association between over representation of the vitamin D receptor gene *b* allele and MS.

52. Graves` disease, an autoimmune thyroid disease, is also determined by both genetic and environmental factors. An association between polymorphism of 2 separate vitamin D receptor genes and Graves` disease has been shown in a Japanese population (Ban *et al.*, 2000).

53. Experiments in animals suggest that vitamin D and its analogues may be of use in treating the autoimmune disease rheumatoid arthritis and in suppressing transplant rejection (DeLuca and Zierold, 1998).

54. Evidence from experiments with interleukin (IL)-10 knockout mice, which develop symptoms similar to human inflammatory bowel disease (IBD), suggests that supplementation with vitamin D may ameliorate the symptoms of IBD (Cantorna *et al.*, 2000). IBD is a chronic inflammatory disorder, primarily of the colon and terminal ileum, of which two forms are known, Crohn`s disease and ulcerative colitis. The cause is thought to be a disorder of the immune system and genetic factors predispose individuals to IBD.

55. It has been proposed that vitamin D supplements may decrease the risk of bone loss and fracture incidence. Ooms *et al.* (1995) found that supplementing older women with 10 µg vitamin D/day significantly reduced their bone loss at the femoral neck. There has only been one randomised placebo-controlled clinical trial of vitamin D supplementation and fracture incidence but this found no difference in fracture incidence in people aged 70 years and over taking 10 µg vitamin D supplement compared with the placebo (Lips *et al.*, 1996).

56. COMA (1998) recommended that the Reference Nutrient Intake of 10 µg/day for people aged 65 years and over should be retained. This would safeguard against vitamin D deficiency and its adverse effect on bone health (COMA, 1998). However, although there is no consensus on what optimum serum 25-(OH)-vitamin D levels are, 80 nmol/l has been suggested as a conservative recommendation (Heaney, 2000), and there is evidence that vitamin D intakes as high as 100 µg/day may be required to achieve this (Vieth *et al.*, 2001). Serum PTH concentration is minimised at levels above 80 nmol/l and

there is evidence that this is beneficial to bone mass density (Sairanen *et al.*, 2000; Pfeifer *et al.*, 2000; Ooms *et al.*, 1995; Kantorovich *et al.*, 2000).

57. It is recognised that 1,25-(OH)₂ vitamin D is a potent anti-proliferative factor in many cells that possess its receptor (Holick, 1995) and it has been suggested that this compound and its analogues could be useful in the treatment of psoriasis.

Absorption and distribution

58. Dietary vitamin D is absorbed through the small intestine in association with lipids and with the aid of bile salts; it is then taken up in the lymph. Vitamin D in the plasma (from either diet or the skin) is bound to a protein synthesised in the liver, vitamin D-binding protein (DBP), for transport to the liver. A portion of all vitamin D reaching the liver is 25-hydroxylated and released into the circulation. Thus, circulating levels of 25-(OH)-vitamin D are proportional to the size of the liver stores. In the plasma 25-(OH)-vitamin D circulates bound to another DBP (α_2 -globulin) (Schoentgen *et al.*, 1986). Vitamin D absorption is not affected by vitamin D status (van den Berg, 1997).

Metabolism and excretion

59. The liver and kidney are the main sites for the metabolic activation of vitamin D₃. Vitamin D₃ is first hydroxylated at the 25-carbon atom by a vitamin D₃-25-hydroxylase enzyme. This reaction requires reduced nicotinamide adenine dinucleotide phosphate (NADPH) and molecular oxygen. The hydroxylase enzyme is present in all species studied (Bhattacharyya and DeLuca, 1974). In the chicken, this enzyme exists in extra-hepatic tissues including the intestine and kidney, but in mammals the liver is the predominant site. The product of this hydroxylation, 25-OHD, also known as calcidiol, is the principle circulating metabolite.

60. Following the initial hydroxylation, 25-OHD is carried from the liver, in plasma bound to an α_2 -globulin and is transported to the kidney, where it undergoes a second hydroxylation before it becomes functional. The second hydroxylation is catalysed by 25-hydroxy-vitamin D₃-1-hydroxylase (1-OH-ase) and produces 1,25-(OH)₂D₂ (calcitriol) (Haussler and McCain, 1977a). This renal enzyme is found in the mitochondria of the proximal convoluted tubules and is rate limiting. It is this dihydroxy metabolite of vitamin D that is believed to stimulate intestinal calcium transport, intestinal phosphate transport, bone calcium mobilisation and other functions attributed to vitamin D (DeLuca, 1974, 1979; Haussler and McCain, 1977a; Fraser, 1981; Koshy, 1982). It prevents rickets, and is at least five times as biologically active as vitamin D₃ or 25-(OH)-vitamin D. It functions at least three times faster than its precursors, in promoting calcium absorption. The rate of conversion to 1,25-(OH)₂D₂ by the kidney is parathyroid hormone (PTH) dependent. PTH is secreted in response to low plasma calcium levels (DeLuca and Zierold, 1998). The metabolism of vitamin D is summarised in Fig 2.

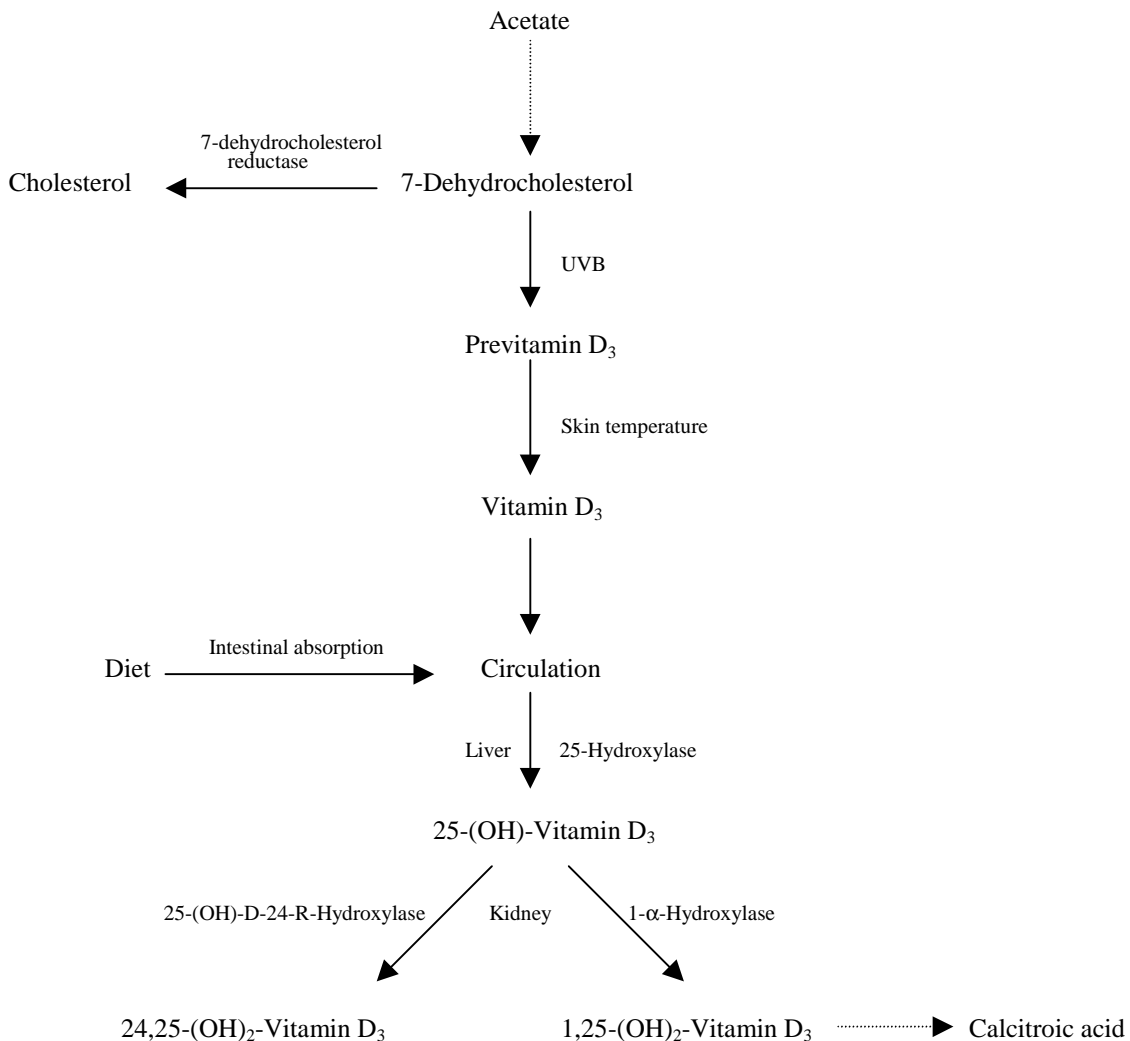
61. Evidence from animal and *in vitro* studies (reviewed by Horlick, 1995) suggest that human decidua and human and rodent placental tissue have the capacity to metabolise 25-OH-vitamin D₃ to 1,25-(OH)₂D₃. 1 α -hydroxylation of 25-(OH)-vitamin D₃ has been demonstrated *in vitro* cell culture systems including neonatal keratinocytes,

chick embryonic calvaria, human bone cells, human osteosarcoma cells and macrophages.

62. Kidney mitochondria contain another enzyme, 25-hydroxy-vitamin D₃-24-hydroxylase (24-OH-ase) which hydroxylates 25-(OH)-vitamin D to form 24,25-(OH)₂D₃. This metabolite is of limited activity and its biological function is uncertain (Basu and Dickerson, 1996). It has been suggested that the 24-hydroxylation is the initial step in the degradation process (FNB, 1997). However, the final degradation product of vitamin D is calcitroic acid, which is excreted in the urine.

63. It appears that there is no direct regulation of 25-hydroxylase activity and that the formation of the hepatic derivative is determined by the vitamin D supply. In contrast, formation of 1,25-(OH)₂D₃ is under homeostatic control, regulated by the supply of calcium and the prevailing 1,25-(OH)₂D₃ concentrations. This is why 1,25-(OH)₂D₃ has come to be considered as a steroid hormone rather than a vitamin (Fraser, 1980).

Fig 2.



Adapted from FNB (1997)

Human toxicity

64. The condition of infantile hypercalcaemia was first described in 1952 from cases in both Switzerland and Great Britain, although it was not immediately associated with vitamin D intake (Stewart *et al.*, 1964). The condition presented as a range of mild and severe clinical symptoms, including failure to thrive and, in the most severe cases, osteosclerosis, mental retardation and death, associated with raised plasma calcium levels. Diagnosed cases rapidly increased in their frequency in Great Britain; in the period 1953-55 there were approximately 100 cases reported. From 1955, suggestions were made that excess vitamin D intake may be a causative factor and in 1957 the Ministry of Health's Joint Subcommittee on Welfare Foods suggested that a substantial reduction should be made in vitamin D allowances (British Paediatric Association, 1964).

65. During and after the Second World War, it had become commonplace in Great Britain for dried milk, cod-liver oil and infant cereals to be fortified with ergocalciferol (vitamin D₂), and to give supplementary concentrated vitamin D to infants (Stewart *et al.*, 1964). Increases in vitamin D intake since the recognition of the aetiology of rickets, improvement in nutrition, and the 'milk in schools' scheme of 1934 had seen a dramatic reduction in the incidence of rickets since its prevalence in the 1920s, and the purpose of the fortification was to ensure that all children received sufficient vitamin D.

66. Devastating metabolic effects of high dietary consumption of vitamin D have since been demonstrated. These are not seen with skin production of the vitamin (Miller and Hayes, 1982). Hypervitaminosis D is generally characterised by an increase in plasma 25-(OH)-vitamin D concentration to approximately 400 to 1250 nmol/l (160 - 500 ng/ml) however, smaller changes have been associated with toxicity (FNB 1997). The effects of excessive vitamin D intake include hypercalcaemia and hypercalciuria (Haussler and McCain, 1977b), leading to deposition of calcium in soft tissues, diffuse demineralisation of bones and irreversible renal and cardiovascular damage. This occurs as a result of vitamin D-mediated increases in calcium absorption and bone resorption. Among the factors that predispose individuals to vitamin D intoxication are increased calcium intake, decreased renal function, diminished oestrogen levels, the existence of sarcoidosis or other vitamin D-hypersensitivity syndromes associated with over-production of 1,25-(OH)₂D₃ (Miller and Hayes, 1982).

67. In most adults, a daily intake in excess of 1.25 mg (50,000 IU) is needed to produce toxicity. This is manifested as muscle weakness, nausea, vomiting, constipation, polyuria, dehydration, polydipsia, hyperlipidaemia, pruritis associated with hypercalcaemia and metastatic calcification of soft tissue and renal calculi or urolithiasis (Hayes and Hagsted, 1973; Davies and Adams, 1978; Patterson, 1980; Miller and Hayes, 1982). The central nervous system may also be involved, a severe depressive illness has been reported with hypervitaminosis D; anorexia, nausea and vomiting have also been reported (FNB, 1997).

68. Hypervitaminosis D has been reported in subjects consuming milk that had been overly fortified (Jacobus *et al.*, 1992). Dietary questionnaires were sent to eight patients who had unexplained hypervitaminosis D. All these patients had elevated serum 25 (OH) vitamin D levels, with 6/8 having elevated serum vitamin D₃ concentrations. Seven of the

eight patients had hypercalcaemia, whilst one of the patients had normocalcaemia but had hypercalcuria. All of the patients drank milk (118-710 ml/day) from a local dairy which contained vitamin D levels ranging from undetectable to 245,840 IU/l (6,100 µg/l). The recommended level for milk fortification in the US is 400 IU/quart (10.55 µg/l).

69. It has been suggested that there is a greater risk of toxicity with vitamin D₂ than with vitamin D₃, due to greater impurity and lack of stability of vitamin D₂ preparations, and because vitamin D₂ has a weaker affinity for vitamin D binding protein than vitamin D₃ (Vieth *et al.*, 2001). However, comparative data of the toxicity of vitamin D₂ and vitamin D₃ in humans are lacking.

70. The recommended UK intake of vitamin D was 800 IU. However, a 1951 survey for the Ministry of Health showed that some children were receiving up to 35,000 IU per day due to supplementation with various vitamin D preparations in addition to fortification of foods (Bransby *et al.*, 1960). From 1957, vitamin D intakes were approximately halved by reducing the concentrations of vitamin D in National cod-liver compound to 400 IU per teaspoon and in National dried milk to 3.2-3.5 IU/g (British Paediatric Association, 1964). A marked decrease in the number of cases of infantile hypercalcaemia was subsequently observed in the early 1960s.

Abnormal sensitivity to vitamin D

71. Bell *et al.* (1964) report on a controlled study in which four patients, in whom sarcoidosis had been confirmed by biopsy, were administered vitamin D, 250 µg (10,000 IU) per day. In all the sarcoidosis patients, but not in the normal controls, an increase in calcium absorption with hypercalciuria was observed with this dose of vitamin D. In three of the patients hypercalcaemia was produced. These patients did not exhibit abnormal circulating levels of 1,25-(OH)₂D₃, thus it is suggested that abnormal calcium metabolism in sarcoidosis is produced not by hypervitaminosis D, but by an abnormal sensitivity to vitamin D. The incidence of hypercalcaemia in patients with sarcoidosis is greater during the summer months, when presumably the production of vitamin D₃ in the skin is enhanced (Taylor *et al.*, 1963).

72. An association between hypercalcaemia and mycobacterium infections, namely tuberculosis was first described by Shai *et al.* (1972). Bradley and Sterling (1978) report on two patients in whom extensive tuberculosis was complicated by hypercalcaemia. Addison's disease (a syndrome caused by inadequate secretion of corticosteroid hormones by the adrenals) may occur in tuberculosis and can be associated with hypercalcaemia but in the two cases reported there was no evidence of Addison's disease. Both patients were on vitamin supplements containing vitamin D and the Kveim test (used for the diagnosis of sarcoidosis) result was positive in both cases. The reason for the increased sensitivity of sarcoidosis patients to vitamin D is unknown but patients with tuberculosis may have a similar hypersensitivity to vitamin D (Bradley and Sterling, 1978).

73. In patients where hypercalcuria and hypercalcaemia are associated with sarcoidosis and other granulomatous conditions including tuberculosis, berylliosis, fungal infection and silicosis, elevated levels of circulating 1,25-(OH)₂-vitamin D are apparent (Horlick, 1995). It was initially thought that this was to do with a defect in the regulation

of renal 25-OH-D-1-hydroxylase. However, it has been suggested that the 1,25-(OH)₂-vitamin D originates from the extra-renal granulomatous tissue.

Vitamin D and heart disease

74. A relationship between vitamin D intake and heart disease has been proposed, however there does not appear to be a correlation between vitamin D and myocardial infarction. An investigation by Linden (1974) suggests a high intake of vitamin D due to the high consumption of fish and fish oil might be the precipitating cause of myocardial infarction in Northern Norway. High mortality rates from myocardial infarction in Northern Norway led to the establishment of the Tromsø Heart Study (THS). Vik *et al.* (1979) present a comparison of data from this study in which plasma 25-(OH)-vitamin D and cholesterol levels from infarction patients are compared with those of age matched controls. No significant correlation between vitamin D status and serum cholesterol concentration was found, thus giving no evidence that the high vitamin D intake or that the vitamin D status of the people of Northern Norway accounts for their higher risk of myocardial infarction.

75. Likewise there does not appear to be a correlation between the serum 25 (OH) vitamin D level and coronary heart disease *per se*. Schmidt-Gayk *et al.* (1977) report that oral intake of vitamin D was higher in patients with myocardial infarction than in randomly selected controls. However, serum 25-(OH)-vitamin D levels from these patients did not differ from controls. In 4 out of 9 elderly persons, measurement of 25-(OH)-vitamin D levels showed vitamin D deficiency, despite high vitamin intake.

76. A comparison has been drawn between intake of vitamin D supplemented foods and incidence of coronary heart disease (Kummerow, 1979). An association has been observed between urolithiasis and heart disease, suggesting that in cases where both exist vitamin D sensitivity or excess may have been the underlying cause (Westlund, 1973). Since some populations that consume less vitamin D supplemented foods have a lower incidence of arterial damage, it is suggested that vitamin D in the diet is an increased risk factor. Animal models have shown vitamin D to increase the smooth muscle necrosis in their arteries (see para 112), but no evidence is provided to indicate such an effect in humans.

Vitamin D and renal disease

77. High intakes of vitamin D override the weak product-inhibited hepatic 25-hydroxylase, leading to high concentration of 25-OHD. This cross reacts with the 1,25(OH)₂D receptor in the bone and intestine leading to an influx of calcium into the extracellular compartment. This is initially balanced by increased renal calcium excretion, but eventually the homeostatic mechanisms of the kidney are overwhelmed and hypercalcaemia ensues (Sarota and Hosking, 1999). In animals, excess vitamin D₃ impairs the responsiveness of renal 1-OH-ase to PTH (Beckman *et al.*, 1995).

78. Urolithiasis may occur after chronic (several years) exposure to modest (25-50 µg/day) dietary supplements of vitamin D, or vitamin D may facilitate renal stone formation in patients with a predisposing cause, such as renal infection or metabolic disease (Taylor, 1972). Maintenance of patients, who absorb calcium poorly (for a variety of reasons) with supplementary vitamin D, often leads to hypercalciuria and the need to

reduce the vitamin D dose. Long-term supplementation with vitamin D of patients without malabsorption eventually increases the absorption of calcium to a point that promotes hypercalciuria, which in turn would promote deposition of calcium in the kidneys (Taylor, 1972). This is a possible mechanism by which the supplements could affect renal stone formation. Patients who have above normal calcium intakes would be especially at risk, as would patients who already have idiopathic hypercalciuria or some other cause of renal stone formation.

79. Nephrocalcinosis and hypercalciuria were identified in ten children (aged 1 to 14 years) all of whom had received intermittent high dose vitamin D prophylaxis. At the time, no vitamin supplementation was being administered and all the children had normal serum 25-(OH)-vitamin D levels; however, all but one child had raised plasma 1,25-(OH)₂D₃ levels (Misselwitz *et al.*, 1990). With intermittent high dose vitamin D prophylaxis, hypercalcaemia of this severity is extremely rare, although approximately one third of infants experience a temporary, but asymptomatic, elevation of serum calcium (Markestad *et al.*, 1987). This response was related to high serum concentration of 25-(OH)-vitamin D and 24,25-(OH)₂D₃, while serum levels of 1,25-(OH)₂D₃ were within normal limits. It is proposed that an exaggerated 1,25-(OH)₂D₃ synthesis in response to vitamin D was an important pathogenic mechanism for the severe hypercalcaemia and subsequent nephrocalcinosis (Misselwitz *et al.*, 1990).

80. In the 1940's several cases of metastatic calcification of soft tissues as a complication of high dosage vitamin D (1,200 – 20,000 IU/day) were reported (Bauer and Freyberg, 1946). Since then only descriptions of a few isolated cases can be found, probably due to the discontinuation of treatment of rheumatoid arthritis with vitamin D. In earlier reports, calcification of soft tissues in overdosage of vitamin D, has been described mainly in the kidneys, bronchi, arteries and periarticular tissue. Renal calcification occurred mainly in the arteries and more rarely in the tubules and glomeruli (Bauer and Freyberg, 1946). Signs of prolonged renal failure (tiredness, vomiting, diarrhoea, polyuria, weight loss and muscle weakness) have been observed in vitamin D intoxication without calcification of renal soft tissue. By withdrawing the vitamin D supplements it is possible to avoid the complication of soft tissue calcification (Irnell, 1969).

81. Vitamin D toxicity appears to be associated with an unbound metabolite (25-(OH)-vitamin D). Whereas it is normally bound to a specific globulin (α_2 -globulin), 25-(OH)-vitamin D becomes linked to albumin when in excess. The albumin bound metabolite may gain access to cells in an uncontrollable manner, damaging cell membranes (Silver *et al.*, 1978; Fainaru and Silver, 1979). In hypervitaminosis D, the metabolite most likely responsible for the toxicity appears to be 25-(OH)-vitamin D, since the circulating levels of 1,25-(OH)₂D₃ are normal or depressed, whereas 25 (OH) vitamin D levels are elevated (up to 30 times greater than normal values) (Counts *et al.*, 1975; Hughes *et al.*, 1976). This hypothesis is further supported by the demonstration that, patients incapable of synthesising 1,25-(OH)₂D₃, can become vitamin D intoxicated (Haussler and McCain, 1977b).

82. Although not as active as 1,25-(OH)₂D₃, 25-(OH)-vitamin D enhances calcium and possibly magnesium absorption across the brush border (Kanis *et al.*, 1976, Sorensen *et al.*, 1976) and facilitates the removal of calcium from bone (Folgelman *et al.*, 1977). In animal experiments vitamin D has been shown to be a potent stimulator of bone

resorption (see paragraph 110). Fogelman *et al.* (1977) report on three patients in whom osteoclastic resorption could be attributable to excess vitamin D, although the relative contribution of the underlying disorder in each case is unclear.

Effects of vitamin D metabolites

83. Synthesis of natural metabolites and analogues of vitamin D has led to treatments for disorders resistant to vitamin D, e.g. treatment of renal failure in patients, who are apparently incapable of biosynthesising the $1,25\text{-(OH)}_2\text{D}_3$ metabolite, with active vitamin D metabolites (Haussler and McCain 1977b, Christiansen *et al.* 1978). Activated by liver hydroxylation at the 25 position, $1\alpha\text{-OHD}$ gives an active metabolite that may itself be toxic to kidney. Reports exist of decreased renal function in patients treated with $1\alpha\text{-OHD}$, already suffering from kidney failure and renal osteodystrophy. These are, however, from clinical observations and should be more adequately controlled and carefully monitored (Feest *et al.*, 1978; Massry and Goldstein, 1979). The long-term administration of $1\alpha,25\text{-(OH)}_2\text{-D}$ in the treatment of hypoparathyroidism, can raise serum $1\alpha,25\text{-(OH)}_2\text{-D}$ levels; this increase is associated with hypercalcaemia and impaired renal function. The increased circulating concentration of $1\alpha,25\text{-(OH)}_2\text{-D}$ and hypercalcaemia are corrected by cessation of treatment and can be prevented by a decrease in the dose (Bell and Stern, 1978).

84. Prolonged hypercalcaemia resulting from therapy with $1\alpha\text{-OHD}$ has been associated with the condition of tumoural calcinosis, an advanced form of periarticular swelling and calcification (Kanis *et al.*, 1976). This calcinosis appears to result from enhanced calcium and phosphate absorption and elevated serum phosphate in association with the hypercalcaemia.

Reproductive toxicity

85. Concern has been expressed that vitamin D, if given to pregnant women, might cause congenital cardiovascular abnormalities (Taussig, 1966). This concern comes from extrapolation of animal data (see paragraphs 116-118) to the human situation. Goodenay and Gordan (1971) monitored 15 women who bore 27 children whilst taking vitamin D treatment for hyperthyroidism. The average maternal vitamin D intake was 2.5 mg (100,000 IU); these doses maintained normal serum calcium concentrations during pregnancy. All pregnancies terminated in live births. None of the children had any of the cardiovascular or craniofacial stigmata associated with infantile hypercalcaemia. It should be noted that these doses did not cause hypercalcaemia in the mother and in this respect differ from the massive doses that caused abnormalities in animals.

Adverse drug reactions

86. Most of the reactions reported to the UK Medicines Control Agency relate to multi-constituent products and may not, therefore, be attributable to vitamin D. A small number of reactions has been reported for single constituent products, but none showed any trends suggestive of an association with vitamin D treatment.

Adverse reactions to supplements

87. Anaemia, in the absence of renal failure, was reported in a 66 year old woman who had consumed vitamin D tablets which inadvertently contained 200 µg (rather than 200 IU – 5 µg) vitamin D (Puig *et al.*, 1998). The duration of consumption is unclear. The authors suggest that vitamin D could directly affect haematopoietic cells or act via high calcium levels, which are known to inhibit erythroid colony formation *in vitro* and erythropoietin production both *in vitro* and *in vivo*.

Human supplementation studies

88. Narang *et al.* (1984) investigated serum calcium levels in healthy subjects aged 21-60 with or without tuberculosis. The diet was supplemented with up to 95 µg vitamin D daily for 3 months. Serum calcium was significantly increased in subjects receiving 60 or 95 µg vitamin D per day. Although the change was significant, only the higher dose increased serum calcium levels above the normal range.

89. Johnson *et al.* (1980) conducted a randomised double-blind study in men aged >65 and women aged >60 who were treated with 2000 IU (50 µg) vitamin D/day for 6 months. Two of the 63 subjects developed hypercalcaemia.

90. Vieth *et al.* (2001) investigated the safety of supplementation with 100 µg/day vitamin D₃ for 2 to 5 months in healthy men and women aged 41 ± 9 years. Urinary calcium concentrations were raised compared to untreated controls but were not reported to be outside the normal range. The number of treated subjects with hypercalciuria was not significantly different to the number of untreated controls with hypercalciuria, although the study was of low statistical power to detect such differences. There was no evidence of hypercalcaemia; mean serum calcium concentrations were inside the normal range (2.2-2.6 mmol/l) in all subjects.

91. Honkanen *et al.* (1990) reported that Finnish women aged 65-72 showed no adverse effects when treated with 45 µg/day vitamin D for 3 months.

92. In a randomised, double-blind, placebo-controlled trial, volunteers aged >70 were given a daily tablet of 10 µg (400 IU) vitamin D₃ for up to 3.5 years (Lips *et al.*, 1996) to investigate whether this reduced the risk of hip or other fractures. 1291 and 1287 subjects received treatment and placebo respectively. Serum 25-(OH)-D levels were increased in the treated group (60 nmol/l) compared to the controls (23 nmol/l). However, there was no difference in fracture incidence between the two groups. No adverse effects were reported.

93. The safety and efficacy of milk fortified with vitamin D₃ and calcium was assessed in a double blind, placebo-controlled trial (McKenna *et al.*, 1995). The fortified milk contained 12 µg vitamin D₃ and 1525 mg calcium/litre compared to 0.3 µg vitamin D₃ and 1270 mg calcium/litre in non-fortified milk and was given to 52 adult volunteers aged 17-54 over the winter. 50 adult controls received non-fortified milk. Milk consumption was not significantly different in the two groups being 65 ± 40 and 64 ± 21 respectively. Fortification significantly reduced the seasonal decline in serum 25-(OH)-D concentrations by >50%. In the treatment group serum 25-(OH)-D declined from 77 ± 35

nmol/l to 62 ± 26 nmol/l, whereas in the controls serum 25-(OH)-D decreased from 85 ± 39 nmol/l to 54 ± 25 nmol/l. No adverse effects were reported.

94. Byrne and colleagues (1995) reviewed eleven papers reporting clinical trials involving a total of 449 elderly subjects receiving 25-(OH)-vitamin D. Of these patients, blood calcium concentrations were measured in 442. Hypercalcaemia was apparent in 3 subjects, in 2 cases the subjects were enrolled in studies using low dose regimes (10-45 µg/day) and predisposing causes were diagnosed in both cases. In the third case, the subjects had received a single dose of 2.5 mg vitamin D. A predisposing cause was not sought. It was concluded that low dose continuous supplementation (10-20 µg/day) was the regimen of choice but that where compliance was poor intermittent high dose supplementation (2.5 mg six-monthly) could be suitable.

95. In a randomised double-blind study (Ooms *et al.*, 1995) 177 elderly women (>70 years) received a dose of 400 IU (10µg) vitamin D₃/day for up to 2 years. A placebo was given to 171 women. The treatment group had significantly increased serum 25-(OH)-D and 1,25-(OH)-D levels and urinary calcium/creatinine ratios and significantly decreased urinary PTH levels. A small increase in bone density was measured at right femoral neck but not at the femoral trochanter or distal radius. One subject in the treatment group reported a rash and dropped out of the study. No other adverse effects were reported. Serum calcium levels were measured; hypercalcaemia was observed in one treated subject after one year who was then excluded from the trial. A predisposing cause was not sought.

96. In a 3 year randomised placebo-controlled study of 17.5 µg/day vitamin D₃ and 500 mg/day calcium supplementation, bone mass density was significantly increased in the supplemented group. No adverse effects were reported. In a follow-up study, in which no supplements were given to the previously supplemented group for two years, these benefits were reversed and bone turnover rates returned to the level they were before supplementation (Dawson-Hughes *et al.*, 2000).

97. No adverse effects were apparent in elderly (>70 years) institutionalised patients given 800 IU (20 µg) vitamin D and 1 g calcium/day for 6 months (Sebert *et al.*, 1996). Prior to the trial, vitamin D deficiency and secondary hyperthyroidism were apparent. These conditions recurred following the end of the trial.

98. Supplementation of healthy postmenopausal 66 year old women for 4 years with 0.5 µg/day 1,25-(OH)₂-vitamin D and adjustment of calcium intake to 800 mg/day resulted in significant increases in bone mineral density compared to a control group. In two of the 14 subjects who completed the study, the 1,25-(OH)₂-vitamin D dose had to be decreased to 0.25 µg/day due to hypercalciuria. In two other subjects hypercalciuria disappeared without the need to reduce 1,25-(OH)₂-vitamin D intake (Sairanen *et al.*, 2000).

99. A study of the effects of vitamin D supplementation in postmenopausal black women with raised serum PTH levels, indicative of secondary hyperparathyroidism, demonstrated that supplementation with 20 µg/day vitamin D₃ (cholecalciferol) for 3 months significantly increased the levels of serum 25-(OH)-vitamin D₃ and decreased the levels of serum PTH (Kyriakidou-Himonas *et al.*, 1999). However, in three out of the

four subjects, the levels of PTH were still above the normal range, suggesting that either longer term supplementation or supplementation with higher concentrations of vitamin D is necessary to treat vitamin D deficiency in this population.

100. Short term supplementation of elderly women, with serum 25-(OH)-vitamin D levels of less than 50 nmol/l with 800 IU/day vitamin D₃ and 1,200 mg/day calcium for 8 weeks, has been shown to decrease body sway and serum PTH levels, and to decrease the incidence of fractures during a 1 year follow-up period, compared to supplementation with calcium only (Pfeifer *et al.*, 2000).

101. Hunter *et al.* (2000) conducted a randomised controlled trial of 800 IU (20 µg) per day vitamin D₃ supplementation in 64 monozygotic twin pairs over two years. No adverse effects were observed, nor was any significant difference in bone mass density.

102. Zamora *et al.* (1999) investigated the effects of supplementation of breast fed infants with 500 or 1000 IU/day vitamin D on bone mineral density and bone mineral concentration in later childhood in pre-pubertal girls (7-9 years). Significantly increased bone mineral density was observed at the femoral neck; significantly increased bone mineral concentration was observed at the femoral neck and trochanter.

Vulnerable Groups

103. Toxicity can occur at levels of vitamin D intake slightly above the normal level (> 25 µg or 1000 IU/day) in certain disease states (see paragraphs 36 – 38), such as sarcoidosis (Bell *et al.*, 1964; MacGregor, 1979), *Mycobacterium* infections (Bradley and Sterling, 1978) and idiopathic hypercalciuria and hypercalcaemia of adults and infants (Seelig, 1969).

104. Infants below six months old are most at risk of hypervitaminosis D, with hypercalcaemia arising from vitamin D intakes of 50 µg/d and mild hypercalcaemia in infants receiving 15 mg vitamin D orally every 3 to 5 months. After six months, COMA recommends that infants fed on formula milk fortified with vitamin D (see paragraph 13) should not receive additional supplementation of vitamin D (COMA, 1991a).

Genetic Variations

105. Vitamin D dependency rickets type II is an autosomal recessive condition characterised by high circulating levels of 1,25-(OH)₂D₃, severe rickets and alopecia. In children with this condition a defect in the vitamin D receptor renders it functionless. Clinically, the children develop normally until about 9 months of age when the rickets develops. Subsequently a wide variety of disorders then develop including unossified areas in the skull, beading of the ribs (pigeon chest), bowed femurs and separated knees and the common occurrence of Greenstick fractures.

106. The vitamin D receptor is located on the human chromosome 12 and is reported to be polymorphic (reviewed by Nakamura, 1997). Depending on whether the gene can be cut by the restriction enzymes Bsm1, Apa 1 or Taq 1, the polymorphisms are classified as either B or b, A or a, T or t respectively the lower case letters indicating lack of cutting sites. In osteoporotic patients of the bb type, a significant increase in lumbar bone mineral

density was obtained after administration of activated vitamin D. However, in patients with the B factor, sensitivity to activated vitamin D was low and the increase in bone density reduced.

Toxicity in animals

107. Daily oral doses of 50,000, 100,000 or 200,000 IU (1.25, 2.5 or 5.0 mg) of ergocalciferol (vitamin D₂) or cholecalciferol (vitamin D₃) in rhesus monkeys indicated that cholecalciferol was significantly more toxic than ergocalciferol in this species. All the animals given cholecalciferol in this study developed hypercalcaemia, died and upon post mortem examination extensive soft tissue mineralisation was observed. Hypercalcaemia occurred in the monkeys treated with ergocalciferol, but the animals survived and comparable soft tissue mineralisation was not evident after sacrifice (Hunt *et al.*, 1972). A feature unique to the lesions produced with the cholecalciferol toxicity, was the deposition of crystals resembling uric acid, with an associated granulomatous reaction.

108. A colony of 558 rhesus monkeys was inadvertently fed a diet high in vitamin D (162,000 IU/animal/day), calcium and phosphorus for a period of almost three months. There was loss of weight, anaemia, elevation of blood urea nitrogen, serum calcium and an increased incidence of diarrhoea and upper respiratory tract infections during the period of acute exposure. Microscopic examination of the tissues of animals that died during the period of exposure, showed characteristic lesions, consisting of mineral deposits, with or without associated inflammation, in kidney, salivary gland and lung. Calcium and iron were present in all of these lesions and phosphorus in most. No attempt was made to measure other minerals that might have been present. The surviving animals examined a year after the high vitamin D diet was terminated, showed few lesions (Kent *et al.*, 1958).

109. Vitamin D intoxication developed in Vietnamese pot-bellied pigs fed commercial swine rations (Wimsatt *et al.*, 1998). The animals had a two week history of anorexia, weight loss, weakness, lethargy, polyuria and polydipsia. Prior to admission to a veterinary hospital, vomiting, tenesmus and tremors developed. Hypercalcaemia and a history incompatible with other sources of hypercalcaemia suggested vitamin D toxicosis. Cholecalciferol concentrations of up to 380, 171 IU/lb were detected; the analyses conducted by different laboratories were very variable suggesting variable mixing of feed and vitamin and mineral premix. The dose is not given but can be estimated to be approximately equivalent to 836 and 376 IU or 21 and 10 µg/kg diet.

110. Pigs fed diets containing optimal calcium and phosphate, received 1,320 (control) or 825,000 IU vitamin D/kg feed (equivalent to approximately 33 or 20,625 µg/kg diet) and were injected with ⁴⁵Ca. These groups were further subdivided, with two pigs in each subgroup and sacrificed 1, 2, 3, 4, 7 and 14 days after treatment. Pigs fed the high level of vitamin D lost weight and anorexia, weakness, rough hair coat and laboured breathing were observed. In the test group, hypercalcaemia began at 12 hours and progressed rapidly after two days. Interpretation of the radioisotope studies indicates that bone was the primary source of the increased plasma calcium, since food intake and therefore calcium absorption from the gut, was depressed. Calcium was released at a rapid rate from prelabelled bone undergoing necrosis. Histopathologic examination of bones from

test pigs showed regressive changes in osteocytes that began within one day of treatment and resulted in osteocytic death. Retardation and arrest of cartilage maturation were also observed (Haschek *et al.*, 1977). This cytotoxic effect of massive doses of vitamin D demonstrated in pigs is probably not representative of a typical case of vitamin D toxicity occurring in humans.

111. At lower levels of vitamin D intake, 1,320, 6,600, 33,000, or 165,000 IU/kg feed (equivalent to 33, 165, 825 or 4125 µg/kg diet) fed to groups of weanling pigs for eight weeks (4 animals per group). In these pigs, the observed hypercalcaemia was thought to result primarily from intestinal absorption of calcium, not from bone necrosis (Chineme *et al.*, 1977). Dystrophic calcification of soft tissue appears to follow cell necrosis and tissue degeneration, as hypercalcaemia *per se* was not always associated with soft tissue calcification in pigs.

112. Degeneration of aortic smooth muscle cells was studied in weanling pigs divided into groups of fourteen and fed basal feed with or without a high fat/cholesterol content. One subgroup of each received 220,000 IU of vitamin D per kg feed, compared to control of 1,430 IU per kg (equivalent to 5,500 and 36 µg/kg feed, respectively). An increased frequency of dead cells, at both three and six months of age, was observed in the groups receiving high vitamin D supplements, on both the high fat and basal diets. No statistically significant difference was demonstrable between the pigs fed the high fat diet, and those fed basal diet alone (Kamio *et al.*, 1977).

113. Of interest is the vitamin D-like toxicity, of spontaneous calcinosis and morbidity occurring among livestock grazing on pastures containing calcinogenic plants (*Solanum malacoxylon* and *Trisetum flavescens*). The former grows mainly in Brazil, whereas the latter produces hypercalcaemia and hyperphosphataemia in livestock grazing in the highlands of Germany. The active component of these plants is thought to be a glycoside derivative of 1,25-(OH)₂D₃ which causes anorexia, weight loss, lameness and spinal deformation, metastatic calcification and ultimately death (Wasserman, 1975; Collins *et al.*, 1977).

114. As with other animals, high doses of vitamin D given to horses results in soft tissue calcification (Breidenbach *et al.*, 1998). However, plasma concentrations of both calcium and inorganic phosphate respond differently compared to other species of domestic animals. Plasma calcium and renal calcium excretion were largely unaffected by the presence of high doses of vitamin D, whereas inorganic phosphate plasma concentrations and renal excretion were substantially increased. The hyperphosphataemia was attributed to mobilisation of phosphate from bone, rather than increased absorption from the diet, though this also occurred. Absorption of calcium from the diet tended to decrease in the presence of high doses of vitamin D.

115. A number of cases of calcinosis were seen in cats during the period 1989-1990 (Morita *et al.*, 1995). Pathological examination of 5 out of 21 animals was performed. Elevated levels of phosphorus, blood urea nitrogen and serum creatinine were determined. Increased density of systemic bones was revealed by X ray analysis and marked calcification was observed in most organs. In the lungs, kidneys and stomach, the calcification was associated with deposition of oxalate crystals. The cats had been fed commercial pet food containing 6,370 IU vitamin D/100 g diet (approximately 1600 µg/kg). The length of feeding varied since the cats were aged 1-9 years and had been fed

the food from “an early age”. The findings were then reproduced experimentally with treated cats being given commercial food supplemented with 15,000 IU (375 µg)/kg bw/day vitamin D₃. Eight out of ten treated cats died following 3-31 days of treatment, clinical symptoms included anorexia, depression, weight loss, vomiting, polydipsia and dehydration. Soft tissue calcification was observed in the treated but not control animals, with the coronary arteries apparently being the most susceptible. In contrast to the natural cases, calcification of the bones and the aorta was not observed in the experimental animals, suggesting that a longer exposure period was necessary for this to occur.

Reproductive toxicity

116. Large doses of vitamin D had a negative influence on foetal viability and induced supravalvular aortic lesions in newborn rabbits (Chan *et al.*, 1979). Throughout pregnancy four groups of four does were given 100,000, 10,000 or 1,000 IU of vitamin D (2,500, 250 or 25 µg) or a placebo daily, by intramuscular injection. Prestudy serum calcium, 25-(OH)-vitamin D and cholesterol levels were not different between control and vitamin D supplemented does. At mid-gestation and term, the vitamin D-dosed does had significantly higher serum calcium, phosphate, 25-(OH)-vitamin D and cholesterol levels than the controls. Two rabbits from the highest dose group developed aortic calcifications. This group also had a significantly higher number of abortions, 6 out of 27 pregnancies, compared to no abortions out of the 27 pregnancies in the control group. There were no significant differences in newborn 25-(OH)-vitamin D and cholesterol levels in the four groups. Supravalvular lesions were found in 2 out of 11 (P<0.05) newborns in the 10,000 IU dose group and 6 out of 20 (P<0.01) newborns in the 100,000 IU dose group, compared with no lesions in the controls. No lesions were found in the 1,000 IU dose group (Chan *et al.*, 1979). These results suggest that high doses of vitamin D during pregnancy affect maternal calcium, phosphate and cholesterol homeostasis and neonatal calcium homeostasis, as well as increasing foetal death. It also suggests vitamin D to be the cause of calcific aortic lesions in the mother and an apparent dose-related development of supravalvular aortic lesions in the newborn.

117. An earlier study in rabbits by Friedman *et al.* (1966) also reported significantly higher serum 25-(OH)-vitamin D and calcium levels, and an increased incidence of aortic lesions in the offspring of mothers that had received 1.5 million units of vitamin D throughout the gestation period. The serum levels of 25-(OH)-vitamin D in the mothers given excess vitamin D and their offspring were 7 and 9 times greater than the control mothers and their offspring, respectively. A total of 14 abnormalities of the aorta were noted in the 34 offspring whose mothers received vitamin D. The thirty five offspring of the mothers on control diet (containing 768 mg vitamin D/lb) showed no abnormalities of the aorta.

118. Ultrastructural studies were conducted on the coronary arteries of six week old piglets. Offspring of sows that had been fed high levels of vitamin D during pregnancy (25 µg vitamin D/lb basal feed, equivalent to 55 µg/kg), had more degenerated smooth muscle cells, without stainable lipid and lipid containing cells, in their coronary arteries, than those from sows fed low doses (3.7 µg/lb basal feed, equivalent to 8 µg/kg) of vitamin D. This suggests that, excess dietary intake of vitamin D by pregnant animals may have potential angiotoxic effects on the coronary arteries of their offspring (Toda *et al.*, 1985).

119. In pregnant rats administered high doses, 320,000 or 480,000 IU vitamin D daily by oral gavage (8,000 or 12,000 µg/day) for 1, 2 or 4 days during gestation, a significant decline in maternal weight, as well as a high rate of morbidity and mortality was observed (Tshibangu *et al.*, 1975). In mothers killed on day 22 of pregnancy, foetal and placental growths were significantly retarded, suggesting an effect, either direct or indirect, by vitamin D or its metabolites. Foetal bone lesions associated with a generalised loss of ossification, placental oedema or calcification, accompanied by a loss of structure of the placenta and degenerative manifestations were observed. A striking alteration in the foetal face was noted in 33-39% of the experimental foetuses, termed by the authors *carnival foetuses*, consisting of the appearance of white nacreous plaques around the eyes and ears (Tshibangu *et al.*, 1975).

120. Similar observations were made in pregnant mice (Zane, 1976). The mice received 50,000 IU (1250 µg) of vitamin D by oral gavage on days 0-3 or 4-7 of gestation. When treatment was given for the first (0-3 days) or second (4-7 days) half of the first trimester it had no discernible influence on maternal weight, foetal weight, implantation rate and survival of the embryo. The incidence of malformed foetuses was similar to that in the control groups when treatment was given for days 0-3. When vitamin D treatment was given in the second half of the first trimester (4-7 days) there was a marked increase in the occurrence of malformed foetuses. The most frequent type of external anomaly was a reduction in the normal size of the cranium (microcephaly). Other anomalies included malformations of the face, palate and skeleton (Zane, 1976).

Carcinogenicity

121. The vitamin D derivative 24R,25-dihydroxyvitamin D₃ reduced the incidence of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)-induced stomach tumours in male Wistar rats (Ikezaki *et al.*, 1996). The authors suggest that the derivative exerts a chemopreventative effect, possibly by influencing calcium pharmacodynamics in the post-initiation phase.

122. Vitamin D depletion increased the number and size of liver foci produced by exposure of rats to the Solt-Farber procedure (exposure to the carcinogens diethylnitrosamine and 2-acetylaminofluorine and partial hepatectomy) compared to control animals (He and Gascon-Barré, 1997).

Genotoxicity

123. No data have been identified

Regulatory Considerations

124. The Infant Formula and Follow-on Formula Regulations 1995 (Amended 1997) specify a maximum vitamin D content of 2.5 µg/100 kcal (0.65 µg/100 kJ) in infant formula and 3 µg/100 kcal (0.75 µg/100 kJ) in follow-on formula. The Processed Cereal-based Foods and Baby Foods Regulations 1997 (Amended 1999) specify a maximum level of 3 µg/100 kcal (0.75 µg/100 kJ) in cereal-based foods for infants. However, vitamin D is not permitted in other baby foods. The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1999 specify that a whole diet

replacement must provide at least 5 µg and a meal replacement 1.5 µg. The Spreadable Fats Regulations (1999) specify that 100 g of margarine must contain not less than 7.05 µg of vitamin D and no more than 8.82 µg.

Recommendations on maximum intake levels

125. COMA (1991a) noted that infants were most at risk of hypervitaminosis D, with mild hypercalcaemia being reported at 50 µg/day and 15 mg every 3-5 months. A joint MAFF/DH (1991) working party identified 50 µg/day as a chronic dose, above which undesirable effects could occur and recommended that no daily dose should exceed one tenth of this level.

126. COMA's Weaning and the Weaning Diet report, 1994 recommended that breastfed infants under six months do not require additional vitamin D supplements provided the mother has adequate vitamin status during pregnancy. From age six months, it is recommended that breastfed infants should be given vitamin D supplements in the form of drops. Infants fed on infant formula do not need additional vitamin D supplementation providing they are consuming more than 500 ml of formula milk daily. Infant formula and follow-on formula is fortified with vitamin D and covered by the Infant formula and follow-on formula regulations.

Recommendations on maximum supplementation levels

127. The UK trade association, the Council for Responsible Nutrition recommends an upper safe level of 10 µg/day (allowing for a contribution from sunlight) for long term supplementation with vitamin D and 50 µg/day for short-term supplementation (CRN, 1999).

Summary

128. Vitamin D refers to a group of fat-soluble seco-steroid compounds that exhibit anti-rachitic properties. The two forms of the vitamin which are of nutritional significance being ergocalciferol (vitamin D₂), the product of ultraviolet-induced conversion of ergosterol in plants, fungi and lower life forms, and cholecalciferol, formed from 7-hydroxycholesterol by penetration of the skin by ultraviolet light (vitamin D₃). Mean intakes of vitamin D from food and supplements are estimated to be 3.78 µg/day (males) and 3.09 µg/day (females). Establishing recommended intakes of vitamin D is difficult due to the contribution made by vitamin D formed by sunlight.

129. Vitamin D is absorbed from the small intestine in the chylomicron fraction and circulated in the body via the lymph. In the liver vitamin D is 25-hydroxylated and released into the circulation bound to α₂-globulin. Additional (1) hydroxylation occurs in the kidney, producing the active form of the vitamin.

130. Vitamin D regulates calcium and phosphate metabolism by its action on three target tissues, small intestine, bone and kidney. In the small intestine it regulates calcium and phosphate uptake. In the kidney the parathyroid hormone-vitamin D axis regulates calcium transport in the renal proximal tubule. Vitamin D is also involved in the maintenance of calcium levels via bone resorption and formation.

131. Prolonged vitamin D deficiency in children results in rickets, the signs of rickets include the late closure of the fontanelle, unossified areas in the skull, beading of the ribs (pigeon chest), bowed femurs and separated knees. In adults, vitamin D deficiency results in osteomalacia, the clinical symptoms of which include skeletal pain and muscle weakness.

132. Excess vitamin D may lead to hypercalcaemia and hypercalcuria; this results in the deposition of calcium in soft tissues, diffuse demineralisation of bones and irreversible renal and cardiovascular toxicity. It has been suggested that excess vitamin D may be linked to heart disease, however, there is little evidence for this. Moderate levels of vitamin D may enhance renal stone formation in individuals that are predisposed to this.

133. A number of supplementation trials have been reported. No adverse effects have been reported at intakes of 10 – 95 µg vitamin D/day. However, increased calcium serum levels were noted in some subjects receiving 60 – 95 µg vitamin D, although the change was significant, generally the increased calcium levels were not outside the normal range.

134. In animals excess vitamin D causes hypercalcaemia, resulting in deposition of calcium in soft tissues and bone demineralisation, anorexia, weight loss, anaemia, and weakness. In studies in monkeys vitamin D₃ was shown to be significantly more toxic than vitamin D₂.

135. Excess vitamin D during gestation in rabbits led to decrease foetal viability, increased number of abortions and induced supravalvular aortic lesions in the offspring. High doses of vitamin D appear to affect maternal calcium, phosphate and cholesterol homeostasis and neonatal calcium homeostasis. In rodents, administration of high levels of vitamin D during gestation results in retarded foetal and placental growth, loss of

ossification of foetal bones and foetal skeletal degeneration, resulting particularly in facial malformations.

136. No *in vivo* or *in vitro* genotoxicity studies have been identified. No adverse effects were seen in the carcinogenicity studies involving vitamin D which were identified.

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ANNEX 1 to EVM/00/11.REVISED AUG2001

INTAKES OF VITAMIN D FROM FOOD AND SUPPLEMENTS

The data presented on vitamin D intakes are obtained from dietary surveys of specific population age groups in Britain carried out over the last 15 years^{2,3,4,5,6}. In each survey food consumption data were collected by means of a dietary record (usually weighed) kept for 4 or 7 consecutive days. Nutrient intakes were calculated using a set of nutrient composition data contemporaneous with the time of the survey. Therefore some apparent differences in intakes between population age groups may be due to changes in the nutrient composition data and reflect changes in the nutrient composition of manufactured foods over time.

Total intakes of vitamin D

Table 1 provides information on the absolute intakes of vitamin D by the British population, classified by age and sex. Mean and median intake, and the upper and lower end of the intake distribution (defined as upper and lower 2.5 percentiles, respectively), are given.

Average intakes of vitamin D from food were lowest for pre-school children, and highest for older people aged 65 years and over. This is due in part due to higher consumption of vitamin D from oily fish in the latter group. Intakes from food sources increased significantly with age for boys aged 4-18 and for girls aged 4-14 years but not for older girls or pre-school children. Average intakes for adults aged 16-64 years, from both food sources alone and from food and supplements increased significantly with age, and were markedly higher for men and women aged 35 years and over compared with younger adults. Average intakes of vitamin D from food sources for those aged 65 years and over decreased with age. Analytical surveys of carcass meat, poultry and meat products were carried out in the early-mid 1990s. These surveys found measurable amounts of vitamin D and its metabolites in meats as a result of new analytical methods⁷. The survey of older people, and of young people aged 4-18 years, incorporated new analytical data for vitamin D in carcass meats. The survey of young people also incorporated new analytical data for vitamin D in poultry and meat products.

None of the average vitamin D intakes from food only, or food and supplements on a population basis, met the RNI which have been set (for infants, pre-school children, and older people aged 65 years and over). Intakes from food and supplements at the 97.5%ile were 2-6 times the median in young people and adults aged 16-85 years and over, and 6-10 times the median in pre-school children.

Table 2 provides information on Vitamin D intakes from food and supplements adjusted for body weight classified by age and sex. This shows a trend to decrease with age for

² Food and nutrient intakes of British infants. 1986

³ National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3

⁴ National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8 (unpublished)

⁵ Dietary and nutritional survey of British adults. 1986/7

⁶ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

⁷ Total vitamin D activity was estimated as the sum of vitamin D₃ (cholecalciferol) and 5 times the amount of hydroxycholecalciferol.

pre-school children, young people and older people free-living in the community, and increase with age for younger adults and older people living in institutions.

Sources of vitamin D in the diet

Cholecalciferol (one of the two main forms of vitamin D) is derived from the action of UV irradiation on 7-dehydrocholesterol in the skin, and for most people in the UK this is the main source of vitamin D. This is determined by exposure to sunlight of the appropriate wavelength (i.e. April-October in England). Adequate summer exposure provides sufficient vitamin D stores throughout winter. Food sources are therefore particularly important for those where exposure to sunlight is compromised by extensive concealment with clothing, or by very limited time spent outdoors, for example (as in housebound older people). The source of vitamin D from the action of sunlight on skin could not be taken into account in the survey results and hence data provided here are for dietary sources of vitamin D only. Table 3 indicates the contribution made by different types of food to average intakes of vitamin D by young people aged 15-18 years. This dataset was collected in 1997 and so most closely reflects current eating habits and fortification practices.

The main food source of vitamin D in this age group is cereal and cereal products (33%), notably breakfast cereals, followed by meat and meat products (22%), then fat spreads (19%). Oily fish (a rich source of vitamin D) provided 11% of vitamin D intake in this age group.

Infants obtained over three quarters of their vitamin D intake from infant formulas supplemented with vitamin D⁸. In young children aged 1½-4½ years, adults aged 16-64 years and older people living in institutions, cereals and cereal products and fat spreads were the major sources of vitamin D. The main source of vitamin D in older people free living in the community was oily fish, which provided approximately a third of their vitamin D intake.

UK legislation requires that vitamin D is added as a fortificant to margarine. Vitamin D is often also added voluntarily by manufacturers to other foods such as reduced and low fat spreads, many breakfast cereals and some yoghurts. The number of foods fortified with vitamin D has increased in the past 20 years and these foods make an increasing contribution to vitamin D intake.⁹

Vitamin D intakes from supplements

For infants and toddlers, dietary supplements containing vitamin D provided 28% and 32% of population average intakes of vitamin D respectively. For the other groups, dietary supplements provided around 1-13% of population average intakes of vitamin D. Of course, the proportion of intake from supplements is much higher if supplement consumers are considered separately.

⁸ This survey of infants predated current advice that cow's milk should not be given as the main drink before 12 months of age. Consequently, current vitamin D intakes from formulas in this group could be higher.

⁹ Department of Health (1998). Report on Health and Social Subjects 49. Nutrition and Bone Health: with particular reference to calcium and vitamin D. London: TSO.

Table 4 shows the number of consumers of dietary supplements containing vitamin D in each age group, together with the median, range and upper level intakes of vitamin D from supplements for those who consumed them. The highest prevalence of vitamin D supplement use was in infant, pre-school, and primary age groups, together with the group of older people, free-living in the community. Over 40% of infants took vitamin supplements containing vitamin D, obtaining 63% of their total intake from this source. At the time of this survey, the Panel on Child Nutrition of COMA¹⁰ recommended supplementation with vitamins A, C and D for all infants from six months up to at least two years and preferably five years. Only a small proportion of older children, adults and older people living in institutions took vitamin D supplements.

The high intakes of vitamin D from supplements in pre-school children was due in part to the use of multivitamin supplements containing vitamin D (such as vitamin A, C and D preparations). For adults, the main source was halibut liver oil. However it should be borne in mind that the data for adults aged 16-64 years was collected in 1986/87 and use of supplements may have changed since then.

Nutrition Surveys Branch
July 2000

¹⁰ Department of Health and Social Security (1988). Present day practice in infant feeding: third report. Report on Health and Social Subjects No 32. London: HMSO.

Table 1: Total intakes of Vitamin D

Age/sex	Absolute Vitamin D intake (µg/day)							
	<i>Food Only</i>				<i>Food and Supplements</i>			
	2.5% ile	Mean	Median	97.5% ile	2.5% ile	Mean	Median	97.5% ile
Infants (1986)								
6-12mths/M&F	0.2	3.5	1.2	14.5	*	5.7	*	*
Pre-school children (1992/3)								
1½-2½ yrs/M&F	0.2	1.2	0.9	4.8	0.2	1.8	1.0	9.4
2½-3½ yrs/M&F	0.2	1.2	1.0	3.5	0.2	1.8	1.2	8.9
3½-4½ yrs/M	0.3	1.4	1.1	4.6	0.3	2.0	1.3	8.5
3½-4½ yrs/F	0.3	1.3	1.1	2.9	0.3	1.9	1.3	10.4
Young people (1997/8)								
4-6 yrs/M	0.7	2.1	1.9	5.3	0.7	2.5	2.1	5.9
4-6 yrs/F	0.5	1.8	1.7	3.7	0.5	2.2	1.8	5.7
7-10 yrs/M	0.7	2.4	2.3	5.0	0.8	2.7	2.5	7.5
7-10 yrs/F	0.5	2.1	1.9	4.3	0.5	2.3	2.0	5.8
11-14 yrs/M	0.8	2.6	2.4	5.7	0.8	2.7	2.5	5.7
11-14 yrs/F	0.6	2.2	2.0	4.7	0.6	2.3	2.0	5.8
15-18 yrs/M	1.0	3.2	2.9	7.6	1.0	3.3	2.9	7.6
15-18 yrs/F	0.5	2.1	1.9	5.4	0.5	2.2	1.9	6.2
Adults (1986/7)								
16-24 yrs/M	0.39	2.81	2.39	8.08	0.39	3.02	2.48	9.82
16-24 yrs/F	0.34	2.10	1.86	5.17	0.34	2.44	1.92	8.60
25-34 yrs/M	0.61	3.16	2.64	9.80	0.61	3.40	2.69	10.36
25-34 yrs/F	0.41	2.30	2.05	6.35	0.41	2.59	2.14	9.90
35-49 yrs/M	0.64	3.71	3.23	11.01	0.64	4.17	3.36	14.00
35-49 yrs/F	0.43	2.61	2.25	7.15	0.44	3.20	2.31	12.59
50-64 yrs/M	0.37	3.80	3.24	10.67	0.37	4.24	3.29	17.86
50-64 yrs/F	0.55	2.82	2.34	7.13	0.55	3.81	2.60	14.60
Older people free-living in the community (1994/5)								
65-74yrs/M	0.87	4.25	3.34	12.77	1.08	4.79	3.61	16.27
65-74yrs/F	0.62	2.96	2.34	8.84	0.69	3.51	2.67	10.44
75-84 yrs/M	0.70	3.81	3.04	10.15	0.72	4.27	3.28	12.28
75-84 yrs/F	0.62	3.03	2.52	10.19	0.73	3.49	2.68	12.45
85 and over/M	0.45	3.18	2.75	8.77	0.45	3.39	2.78	9.17
85 and over/F	0.57	2.31	2.00	6.77	0.57	2.89	2.09	8.21
Older people living in institutions (1994/5)								
65-84 yrs/M	0.81	3.62	3.23	9.28	0.81	3.65	3.23	9.41
65-84 yrs/F	0.99	3.32	2.89	7.47	0.99	3.36	2.93	7.47
85 and over/M	1.02	4.08	3.56	9.72	1.02	4.22	3.56	9.72
85 and over/F	1.00	3.31	2.84	6.92	1.00	3.36	2.90	6.92

*Data unavailable

Table 2: Bodyweight adjusted vitamin D intake

Age/sex	Bodyweight adjusted vitamin D intake ($\mu\text{g}/\text{kg bwt /day}$) ¹¹		
	<i>intakes from food and supplements</i>		
	Mean	Median	97.5% ile
Infants (1986)¹² 6-12mths/M&F	0.37	0.11	1.6
Pre-school children (1992/3) 1½-2½ yrs/M&F	0.16	0.08	0.79
2½-3½ yrs/M&F	0.13	0.08	0.59
3½-4½ yrs/M	0.12	0.08	0.57
3½-4½ yrs/F	0.12	0.08	0.54
Young people (1997/8) 4-6 yrs/M	0.12	0.10	0.28
4-6 yrs/F	0.11	0.09	0.25
7-10 yrs/M	0.09	0.08	0.24
7-10 yrs/F	0.07	0.06	0.18
11-14 yrs/M	0.06	0.05	0.13
11-14 yrs/F	0.05	0.05	0.11
15-18 yrs/M	0.05	0.05	0.11
15-18 yrs/F	0.04	0.03	0.10
Adults (1986/7) 16-24 yrs/M	0.04	0.03	0.13
16-24 yrs/F	0.04	0.03	0.14
25-34 yrs/M	0.05	0.03	0.15
25-34 yrs/F	0.04	0.03	0.16
35-49 yrs/M	0.05	0.04	0.19
35-49 yrs/F	0.05	0.04	0.19
50-64 yrs/M	0.05	0.04	0.22
50-64 yrs/F	0.06	0.04	0.22
Older people free-living in the community (1994/5) 65-74 yrs/M	0.06	0.05	0.23
65-74 yrs/F	0.05	0.04	0.17
75-84 yrs/M	0.06	0.05	0.17
75-84 yrs/F	0.06	0.04	0.22
85 and over/M	0.05	0.04	0.13
85 and over/F	0.05	0.04	0.16
Older people living in institutions (1994/5) 65-84 yrs/M	0.05	0.05	0.13
65-84 yrs/F	0.06	0.05	0.12
85 and over/M	0.06	0.06	0.14
85 and over/F	0.06	0.05	0.16

¹¹ Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.

¹² Intakes for infants aged 6-12 months are from food only.

Table 3: Sources of vitamin D in the diet¹³

Food Type	Contribution of food types to average daily intake of vitamin D	
	ug/day	% of total
Cereal and cereal products	0.9	33
- of which breakfast cereals	0.5	19
Milk and milk products	0.1	4
Egg and egg dishes	0.2	7
Fat spreads	0.5	19
- of which reduced fat spread (polyunsaturated)	0.2	7
- of which reduced fat spread (not polyunsaturated)	0.1	4
- of which low fat spread (polyunsaturated)	0.1	4
- of which soft margarine (not polyunsaturated)	0.1	4
Meat and meat products	0.6	22
Fish and fish dishes	0.3	11
- of which oily fish	0.3	11
Vegetables, potatoes and savoury snacks	<0.1	2
Fruits and nuts	0	0
Sugar, confectionery and preserves	0	0
Beverages	0	0
Miscellaneous	<0.1	1
Total intake from food	2.7*	100*
<i>Intake from dietary supplements</i>	<i>0.1</i>	<i>4</i>
Total intake from food and supplements	2.8	100

* total allowed for rounding

¹³ NDNS: young people aged 4-18 years. 1997/8. 15-18 year group.

Table 4: Vitamin D intake from supplements

<i>Age/sex</i>	Consumers of vitamin D supplements		Vitamin D intake from supplements (consumers only) (µg/day)		
	<i>Number</i>	<i>%</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
<i>Infants (1986)</i> 6-12 mths/M&F	213	44	5.0	*	*
<i>Pre-school children (1992/3)</i> 1½-4½ yrs/M&F	244	15	4.3	3.2	0.4 - 17.1
<i>Young people (1997/8)</i> 4-6 yrs/M&F	56	16	2.2	2.0	0.4 - 10
7-10 yrs/M&F	51	11	2.3	2.1	0.4 - 5.0
11-14 yrs/M	16	7	1.6	1.4	0.4 - 5.0
11-14 yrs/F	9	4	2.5	2.3	0.7 - 5.7
15-18 yrs/M	9	5	2.2	2.0	1.1 - 3.6
15-18 yrs/F	9	4	2.2	0.7	0.4 - 5.0
<i>Adults (1986/7)</i> 16-64 yrs/M	50	5	7.6	8.3	0.3 - 22.3
16-64 yrs/F	105	9	6.0	5.1	0 - 22.5 [#]
<i>Older people free-living in the community (1994/5)</i> 65 and over/M	73	12	4.0	2.5	0.1 - 15
65 and over/F	103	16	3.5	2.5	0 - 15.0 [#]
<i>Older people living in institutions (1994/5)</i> 65 and over/M	4	2	3.4	3.2	0.3 - 6.7
65 and over/F	8	4	1.7	1.1	0.3 - 5.0

* No data available

Values at the bottom of the range are zero due to rounding. Actual figures are 0.03 µg (adults 16-64 yrs/F) and 0.01 µg (65 and over/F).

ANNEX 2 TO EVM/00/11.REVISED AUG2001

Table 1 Summary of animal data

Species	Endpoint/findings	Dose	NOAEL/LOAEL	Duration	Comment	Reference
Rhesus monkey	All animals developed hypercalcaemia, soft tissue mineralisation and deaths seen in D ₃ dosed animals	1.25, 2.5 or 5.0 mg/day of D ₂ or D ₃ <i>p.o.</i>	N/A	16 to 164 days		Hunt <i>et al</i> 1972
Rhesus monkey	Weight loss, anaemia, elevation of blood urea nitrogen and serum calcium. Mineral deposits in kidney, salivary gland and lung		N/A	Approximately 3 months	Accidental exposure to high vitamin D, calcium and phosphorus	Kent <i>et al</i> 1958
Pot-bellied pigs	Weight loss, anorexia, weakness, lethargy, polyuria and polydipsia	10 or 21 µg/kg diet	N/A	2 weeks	Extremely small quantities per kg diet	Wimsatt <i>et al</i> 1998
Pigs	Weight loss, anorexia, weakness, rough coat and laboured breathing. Hyper-calcaemia began at 12 hours	33 or 20,625 µg/kg diet	NOAEL = 33 µg/kg diet	1 – 14 days	Radioisotope studies showed that bone was the primary source of increased plasma calcium	Haschek <i>et al</i> 1977
Pigs	Hypercalcaemia resulting from increased intestinal absorption observed at 165 – 4125 µg/kg dose levels	33, 165, 825 or 4125 µg/kg diet	NOAEL = 33 µg/kg diet LOAEL = 165 µg/kg diet	8 weeks	Hypercalcaemia not always associated with soft tissue calcification	Chineme <i>et al</i> 1977
Weanling pigs	Increased frequency of dead aortic smooth muscle cells in high dose group	36 or 5,500 µg/kg diet	NOAEL = 36 µg/kg diet	3 or 6 months		Kamio <i>et al</i> 1977

Cats	Anorexia, depression, weight loss, vomiting, polydipsia and dehydration	375 µg/kg bw/day D ₃	N/A	1 - 9 years		Morita <i>et al</i> 1995
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Where *p.o* is oral gavage, *i.m.* is intramuscular

Species	Endpoint/findings	Dose	NOAEL/LOAEL	Duration	Comment	Reference
Rabbits	Increased serum calcium, phosphate, 25-(OH)D and cholesterol at mid-term and term. Significant increase in number of abortions at highest dose level. Supra-valvular lesions found in offspring from high and middle dose groups.	25, 250 or 2,500 $\mu\text{g/day}$ <i>i.m.</i>	N/A	Throughout gestation	Suggests vitamin D will effect maternal calcium, phosphate and cholesterol homeostasis and neonatal calcium homeostasis.	Chan <i>et al</i> 1979
Pigs	Offspring of mothers fed high level vitamin D had more degenerated smooth muscle cells in their coronary arteries	8 or 55 $\mu\text{g/kg}$ diet	N/A	Throughout gestation	Excess vitamin D during pregnancy may have potential angiotoxic effects on coronary arteries of offspring	Toda <i>et al</i> 1985
Rats	Significant decline in maternal weight, high rate of morbidity and mortality. Foetal and placental growths retarded, loss of ossification.	8,000 or 12,000 $\mu\text{g/day}$ <i>p.o.</i>	N/A	1, 2 or 4 days during gestation	Striking alteration in foetal face noted in 33–39 % of foetuses, termed by authors <i>carnival foetuses</i> (white nacreous plaques around eyes and ears).	Tshibangu <i>et al</i> 1975
Mice	Significant increase in number of malformed foetuses when treatment given for days 4-7	1250 $\mu\text{g/day}$ <i>p.o.</i>	N/A	Days 0-3 or 4-7 of gestation	Malformation includes reduction in size of cranium, facial, palatial and skeletal malformations	Zane 1976

Table 2 Summary of human data

Study type	Form of vitamin D	Study population	Endpoint/findings	Dose	NOAEL/LOAEL	Duration	Reference
Retrospective	Cholecalciferol	8 patients with hypervitaminosis D, apparently caused by drinking milk excessively fortified with vitamin D	7 of the 8 patients had hypercalcemia, 1 had normocalcaemia but hypercalciuria. Milk, from the same local dairy, was the only common source of vitamin D identified from dietary questionnaires.	0 – 4,331 µg/day (sporadic)	N/A	Unknown	Jacobus 1992
Randomised clinical trial	Cholecalciferol	Age 41 ± 9 years N = 61	Serum calcium levels were not significantly increased in either dose group.	25 and 100 µg/day	NOAEL = 100 µg/day	5 months	Vieth <i>et al</i> 2001
Clinical trial	Not known	Age 21-60 years N = 30	Significant increase in serum calcium levels in groups supplemented with 60 and 95 µg vitamin D daily. However, serum calcium levels remained inside the normal range (< 2.75 mmol/l) in the 60 µg/day group.	0, 10, 20, 30, 60 and 95 µg/day	NOAEL = 60 µg/day	3 months	Narang <i>et al</i> 1984
Randomised double-blind, placebo-controlled clinical trial	Not known	Females > 60 years, males > 65 years N = 63	Significant increase in serum calcium levels. Two of the subjects developed hypercalcaemia (serum calcium > 2.75 mmol/l).	50 µg/day	N/A	6 months	Johnson <i>et al</i> 1980
Randomised clinical trial	Not known	Age 65-72, all female N = 52	Measures of serum calcium, creatinine and calcidiol levels showed no adverse group or individual effects.	45 µg/day (+ 1,558 mg/day calcium)	NOAEL = 45 µg/day	3 months	Honkanen <i>et al</i> 1990

Study type	Form of vitamin D	Study population	Endpoint/findings	Dose	NOAEL/LOAEL	Duration	Reference
Clinical trial	Not known	Age \geq 70 years N = 126	Primarily a study of efficacy of supplementation at correcting a deficiency. No adverse effects reported	20 μ g/day (+ 1,000 mg/day calcium)	NOAEL = 20 μ g/day	6 months	Sebert <i>et al</i> 1996
Clinical trial	Cholecalciferol	Age 60-80 years, all black females	Primarily a study of efficacy of supplementation at correcting secondary hyperparathyroidism. No adverse effects reported	20 μ g/day	NOAEL = 20 μ g/day	3 months	Kyriakidou-Himonas <i>et al</i> 1999
Clinical trial	Cholecalciferol	Age \geq 70 years N = 148	Study designed to investigate effects of supplementation on body sway and secondary hyperparathyroidism. No adverse effects reported	20 μ g/day (+ 1,200 mg calcium)	NOAEL = 20 μ g/day	2 months	Pfeifer <i>et al</i> 2000
Randomised co-twin, placebo-controlled, double-blind clinical trial	Cholecalciferol	Age 47-70 years N = 128 (64 monozygotic twin pairs)	Primarily a study of effect of supplementation at preventing bone loss. No adverse effects reported	20 μ g/day	NOAEL = 20 μ g/day	2 years	Hunter <i>et al</i> 2000
Randomised, double-blind, placebo-controlled clinical trial	Cholecalciferol	Age \geq 65 years N = 389	Primarily a study of effects on bone mineral density. Small but significant increase in serum calcium in treated subjects at end of 3 year period, but levels were not outside normal range. One treated subject withdrawn from study due to hypercalciuria.	17.5 μ g/day (+ 500 mg/day calcium)	NOAEL = 17.5 μ g/day	3 years	Dawson-Hughes <i>et al</i> 1997
Randomised, double-blind, placebo-controlled clinical trial	Cholecalciferol	Age \geq 70 years N = 2578	Primarily a study of supplementation and fracture incidence in the elderly. No adverse effects reported.	10 μ g/day	NOAEL = 10 μ g/day	3.5 years	Lips <i>et al</i> 1996

Study type	Form of vitamin D	Study population	Endpoint/findings	Dose	NOAEL/LOAEL	Duration	Reference
Randomised, double-blind, placebo-controlled clinical trial	Cholecalciferol	Age \geq 70 years N = 248	Hypercalcaemia observed in one treated subject after one year.	10 μ g/day	NOAEL = 10 μ g/day	2 years	Ooms <i>et al</i> 1995
Clinical trial	1,25-dihydroxyvitamin D	Age 66 years, all female	Four patients developed hypercalciuria (urinary calcium excretion $>$ 10 mmol/day). Normocalciuria returned without intervention in 2 subjects and after the dose was reduced to 0.25 μ g/day in the other 2 subjects.	0.5 μ g/day	NOAEL = 0.25 μ g/day	4 years	Sairanen <i>et al</i> 2000

ANNEX 3 TO EVM/00/11.REVISED AUG2001

Vitamin D: Summary table of selected nutrition related information and existing guidance on intakes

Unit of usage	$\mu\text{g/day}$		$\mu\text{g/100 kcal}$	$\mu\text{g/100g}$
	male	female		
<i>UK DRV¹⁴ for adults (19-50+)</i> LRNI EAR RNI	No dietary intake is necessary for individuals living a normal lifestyle. An RNI of 10 $\mu\text{g/day}$ is recommended for pregnant and lactating women, those over 65 years and confined indoors and people who rarely go out of doors or when they do so wear clothes which fully conceal them.			
<i>Mean adult UK dietary intake From food (all sources)</i> Adults (16-64 years) ¹⁵ Adults 65 years and over ¹⁶ free living institutionalised	3.43 (3.78) 4.07 (4.56) 3.79 (3.87)	2.51 (3.09) 2.92 (3.44) 3.31 (3.36)		
EU labelling RDA ¹⁷	5			
Supplemental doses	1.25 – 12.5 $\mu\text{g/unit}$			

¹⁴ Committee on Medical Aspects of Food and Nutrition Policy (1991). Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on Health and Social Subjects 41. London: HMSO.

¹⁵ Dietary and nutritional survey of British adults. 1986/7

¹⁶ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

¹⁷ The Food Labelling Regulations 1996

<p><i>Regulations</i> Infant formula¹⁸ Follow-on formula Cereal-based baby foods¹⁹</p> <p>Weight reduction²⁰ whole daily diet replacement meal replacement Spreadable fats²¹</p>	<p>5 1.5 µg/meal</p>	<p>1 - 2.5 1 - 3 1-3 (vitamin D is not permitted in baby foods)</p>	<p>7.05 – 8.82</p>
<p><i>Maximum total safe daily intake</i> COMA 1991¹</p> <p>EHPM 1997²²</p>	<p>Infants are most at risk of developing hypervitaminosis. There are some reports of hypercalcaemia from 50µg/day and mild hypercalcaemia from 15mg vitamin D orally every 3 to 5 months</p> <p>Upper safe level (long term consumption) – 20µg Upper limit (short term consumption) – 50µg</p>		

¹⁸ The Infant Formula and Follow-on Formula Regulations 1995

¹⁹ The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations 1997.

²⁰ The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997.

²¹ The Margarine Regulations (Statutory Instrument, 1967).

²² Vitamins and Minerals A Scientific Evaluation of the Range of Safe Intakes. European Federation of Health Product Manufacturers 1997.

