EXPERT GROUP ON VITAMINS AND MINERALS

COVERING NOTE FOR EVM/01/12/P – REVIEW OF CALCIUM

The attached review of calcium is a revised version of the paper presented to the Expert Group on Vitamins and Minerals at the meeting on 2 April. It has been amended to take into account some of the comments made by Members and to correct a number of minor inaccuracies. A revised version of the review will be presented to the Group at a future meeting. This will include the more extensive amendments suggested by the Group and any new information submitted as a consequence of releasing this paper to the public. If you have any additional information, in particular any new research evidence, that you think is relevant to this review please send it to:

Expert Group on Vitamins and Minerals Secretariat
Room 808C Aviation House
125 Kingsway
London
WC2B 6NH

The following annexes are also attached:

Annex 1 Intakes of calcium from food and supplements

Annex 2 Tables referred to throughout text

Annex 3 Preliminary Risk Assessment

Annex 3 was a preliminary risk assessment the final version of which will be published in the Group's final report. Annex 3 is not therefore being released at this stage.

Expert Group on Vitamins and Minerals Secretariat
May 2001

Calcium

Chemistry and geochemistry

1. Calcium is an alkaline earth metal belonging to Group II of the periodic table. It is a divalent cation with an atomic weight of 40. Calcium shows a single oxidation state of +2.

Natural occurrence

2. Calcium does not exist freely in nature, but occurs abundantly as limestone ($CaCO_3$), gypsum ($CaSO_4.2H_2O$), and fluorite (CaF_2). Many calcium compounds (e.g. fluorspar, calcium carbonate) are very insoluble, although there are exceptions (e.g. calcium chloride and calcium nitrate).

Occurrence in food, food supplements and medicines

Food

3. Foods particularly rich in calcium are milk, cheese, and other dairy products (except butter), green leafy vegetables (except spinach), soybean products, bread and other baked goods made from calcium fortified flour, almonds, brazil nuts and hazel nuts (Anderson *et al.,* 1995; Ensminger *et al.,* 1995). The NDNS of young people aged 15-18 years showed that in those aged 15-18 years 44% of calcium intake came from milk and milk products.

4. Fortified foods such as bread and baked products and some breakfast cereals now contribute significantly more calcium to the diet than they would naturally. Although cereal grains contain low amounts of calcium, they form a large part of the diet. Milling, however, reduces the calcium content by 50%, as much of the calcium content is in the germ and bran. For these reasons, all flour, except wholemeal flour, is required by law to be supplemented with 235-390 mg calcium carbonate per 100g in the UK (The Bread and Flour Regulations 1998).

5. Kellogg's Nutrigrain bars and twists are fortified with 5.40 g/kg calcium. The intention of fortification of these breakfast snacks is to replace the calcium that would be supplied by eating a traditional breakfast cereal with milk. Kellogg's Frosties and Coco-pops, for example, are fortified with calcium and contain 4.53 g/kg.

Drinking water

6. In hard water areas, tap water can form a significant proportion of calcium intake. Water with less than 100 ppm calcium carbonate is considered soft; water with 300 ppm calcium carbonate is considered very hard. People living in hard water areas can typically have an intake of 200 mg/day calcium from water (COMA, 1994).

7. The calcium content of mineral water can also vary widely from < 10 ppm to over 300 ppm (Guillemant *et al.,* 2000).

Food supplements

8. Alfalfa leaf powder (dehydrated) contains 16.4 g/kg calcium. Cod liver oil contains a trace amount of calcium. Carrageenan contains 8.85 g/kg; kelp contains 10.93 g/kg. Torula yeast contains 4.24 g/kg calcium (Ensminger *et al.,* 1995).

9. Supplementary calcium is available over the counter either alone or in combination with other minerals beneficial to bone health (such as vitamin D, magnesium and zinc) or in multivitamins with minerals. Concentrations typically range from 133 mg/tablet, taken once daily, to 800 mg/tablet, taken 3 times per day.

10. Calcium carbonate is a major component of antacids. Concentrations are up to 600 mg/tablet and packets carry a warning to take no more than 12 tablets per 24 hours.

11. Supplementary calcium is available in many different forms. Calcium carbonate contains the highest concentration of elemental calcium (400 mg/g). However, it is of low solubility and poor disintigration, and is therefore less bioavailable than calcium chelates. Calcium chelates

(soluble forms of calcium) include calcium citrate, lactate, glucuronate and calcium citrate malate (CCM). 1g of calcium glucuronate provides only 90 mg calcium, but there is some evidence that chelates of calcium are more effective at reducing bone resorption and promoting bone formation than calcium carbonate (Whiting *et al.,* 1997).

Licensed medicinal products for oral use (data provided by MCA)

12. Calcium is present in many supplement products, but only 20 may be sold in supermarkets and other retail outlets, without the supervision of a pharmacist, to treat conditions needing supplemental calcium. These are generally single nutrient products containing calcium as the carbonate, gluconate or lactate. The highest daily dose authorised is 1.5g calcium. They are used where dietary intake is insufficient as in childhood, pregnancy, lactation and the elderly, in treatment programmes for osteoporosis, osteomalacia and rickets, for malabsorption following gastrectomy and for hyperphosphataemia.

13. Thirty-three calcium supplement products can only be sold in pharmacies (without a doctor's prescription). The recommended daily doses are up to 3 g calcium for the treatment of osteomalacia and up to 1.5 g for other conditions, as shown above. About half of these products also contain vitamin D.

14. Calcium, as calcium carbonate, is also found in many antacids on general sale. A single dose provides up to 0.6 g calcium. Where a maximum dose that may be taken over 24 hours is specified, this generally provides up to 4 g calcium.

Intake and exposure *(UK data)*

Food

15. Intakes of calcium in the UK from food and supplements have been provided (see Annex 1). Average intakes of calcium from food for men were 937 mg/day and for women 726 mg (Gregory *et al*. 1990). Dietary supplements containing calcium (including prescribed products) provided

less than 1% of mean intakes of calcium for all population groups (Annex 1).

Recommended amounts

16. Dietary Reference Values differ for different stages of growth and reproduction and are based on calcium requirements for bone formation and minimised bone resorption, and data for the retention of calcium (COMA, 1994).

17. Based on the absorption efficiency of calcium in breast milk, a Lower Reference Nutrient Intake for infants of 240 mg/day is calculated. However, absorption from infant formula is less (40% as opposed to 66%) and so a Reference Nutrient Intake of 525 mg/day is recommended.

18. The calcium intake required for bone formation and skeletal growth increases from the age of 1 to 10; RNIs of 350, 450 and 550 mg/day are recommended for children of ages 1-3, 4-6 and 7-10 years respectively. For adolescents (11-18 years) RNIs are 800 mg/day for females and 1,000 mg/day for males, due to an increased requirement for calcium at a time of increased skeletal growth.

19. RNIs for adults are based on calcium loss/retention and are 700 mg/day.

20. No extra intake is considered necessary for pregnancy, although during lactation an increase of 550 mg/day over the RNI is recommended.

21. The Committee on Medical Aspects of Food and Nutrition Policy reconsidered the RNIs for calcium in their report Nutrition and Bone Health (DH 1998). They concluded that no change in the existing UK DRVs for calcium was necessary because of insufficient evidence. Additionally recent data do not support the increment for lactation which might not be necessary.

22. In the US, Acceptable Intakes (equivalent to the UK Lower Reference Nutrient Intake) have been calculated, but there are no current Recommended Dietary Allowances due to a lack of evidence of the

average required intake. The current US Acceptable Intakes for calcium are given below (Institute of Medicine, 1997):

Age	***Calcium (mg/day)***
0 – 0.5 years	210
0.5 – 1 year	270
1 – 3 years	500
4 - 8 years	800
9 – 18 years	1300
Adult (19 – 70 years)	1000
Elderly (over 70 years)	1200
Pregnancy and lactation (19 – 50 years)	1000
Pregnancy and lactation (14 - 18 years)	1300

Analysis of tissue levels

23. There are no assays that can directly measure calcium nutritional status. Blood calcium concentrations are tightly regulated and will only be outside the normal range in conditions such as severe malnutrition or hyperparathyroidism (Institute of Medicine, 1997). Therefore proxies have to be used.

24. Bone mineral content (BMC), the concentration of mineral at a specific skeletal site, and bone mineral density (BMD), the bone mineral content per unit area of skeletal site, are indicators of calcium insufficiency and predictors of increased risk of fracture. Change in BMC and BMD are useful indicators of calcium retention in adults; change in BMC is a useful indicator of calcium retention in children.

25. There are several techniques for measuring the amount of calcium in individual bones at different ages, but results from the different methods do not correlate very well (Macrae *et al.,*1993). A recently developed technique, using neutron activation analysis, enables total body calcium to be measured in living persons.

Bioavailability

26. In healthy adults on a normal diet, the bioavailability of calcium is approximately 20-30% (Ensminger *et al* 1995). However, many dietary and physiological factors may affect bioavailablity.

27. Oxalic acid, present in spinach and rhubarb, is the most potent inhibitor of calcium absorption. It reacts with, and precipitates calcium in the gut and thus reduces its bioavailability. Calcium is poorly absorbed from spinach and rhubarb, which are rich in oxalates (Anderson *et al* 1995). Phytic acid, found in cereal brans, also binds to and precipitates calcium, reducing its bioavailability, but generally the inhibition of phytic acid is modest compared to oxalates (Weaver, 1998).

28. Vitamin D deficiency decreases the bioavailability of calcium, as vitamin D induces a calcium binding protein that transports calcium across the intestinal wall.

29. Excess levels of fat intake, particularly of saturated fat, interfere with calcium absorption by combining with calcium to form insoluble soaps that are excreted in the faeces.

30. The body is able to adapt, to some extent, to a low calcium intake or increased calcium requirement, by increasing the absorption of calcium from the small intestine and by reducing renal excretion. In Western countries, where diets are high in calcium, the efficiency of calcium utilisation by the body is reduced compared to countries in which diets are low in calcium.

31. The absorption of calcium supplements, particularly less soluble ones such as calcium carbonate, is greatly increased if they are taken with a meal. This may be due to interactions with food constituents in the small intestine or it may be due to increased gastric secretion in the stomach, as the solubility of calcium is greatly increased at low pH (Allen and Wood, 1994).

Interactions

32. Interactions between calcium and dietary constituents may affect the efficiency of calcium absorption. Phytic acid can reduce calcium absorption by forming an insoluble salt, calcium phytate. Phytates are broken down during fermentation, explaining the higher availability of calcium in leavened compared to unleavened breads (Ensminger *et al.,* 1995). Osteomalacia observed in female Bedouins has been attributed to both a low calcium intake and a diet rich in phytates (Berlyne *et al.,* 1973).

33. Calcium is thought to have an inhibitory effect on iron absorption and data suggests a minimal concentration of calcium is needed to achieve an effect (Hallberg *et al.,* 1992). High calcium diets have also been shown to reduce net zinc absorption and balance (Wood and Zheng, 1997).

34. The phosphate ion can form insoluble complexes with calcium, and therefore potentially decrease calcium bioavailability. It has been suggested that the dietary phosphate:calcium ratio has to be very high (exceeding approximately 3:1) to interfere significantly with calcium availability (Nordin, 1986). However, some studies have shown that phosphorus intake had little or no effect on overall calcium balance (Heaney and Recker, 1982), and that variations in phosphorus intake were not associated with differences in calcium absorption (Heaney, 2000).

35. Calcium binds to fatty acids to form insoluble complexes in the intestinal lumen (Allen, 1982). However, precipitation occurs during malabsorption of fat, and fat intake does not affect calcium balance in healthy adults (Allen and Wood, 1994). Calcium absorption was not affected by changes in dietary fat in rats (Watkins *et al.,* 1992).

Absorption

36. About 25-50% of dietary calcium is absorbed and delivered to the exchangeable calcium pool (Allen, 1998). Most of the calcium in food is in the form of complexes with other dietary constituents, which must be

broken down and the calcium released in a soluble and ionised form before it can be absorbed (Allen, 1982).

37. Calcium crosses the intestinal mucosa by both active and passive transport mechanisms (Allen, 1998). The active transport mechanism is a saturable, transcellular process which involves the calcium-binding protein, calbindin. Calbindin is regulated by the hormonal form of vitamin D (1,25-dihydroxy-vitamin D_3). The passive transport mechanism is a nonsaturable, paracellular process which is not affected by calcium status or parathyroid hormone. Both processes occur throughout the small intestine, although the efficiency of calcium absorption is much greater from the duodenojejunal segments of the intestine than from the ileal segments (Wensel *et al.,* 1969). The mechanism of calcium absorption involves the binding of calcium to a specific protein whose synthesis is stimulated by active forms of vitamin D (Pitkin, 1985). The active metabolite of vitamin D, 1,25-dihydroxyvitamin D_3, has an important role in maintaining calcium homeostasis by mediating calcium absorption into intestinal. There may also be individual genetic influences on calcium absorption as a consequence of Vitamin D receptor polymorphism (Wood and Fleet, 1998).

38. The efficiency of calcium absorption increases when calcium intakes are low and decreases when calcium intakes are high. A low net calcium absorption could be a consequence of a number of factors including: low calcium intake; consumption of diets with low calcium bioavailabilty; increased calcium secretion into the gut; or a low efficiency of true intestinal calcium absorption (Wood, 2000). Differences in calcium balance have been attributed to variation in the efficiency of calcium absorption (Heaney, 2000).

39. Two major factors affect the efficiency of calcium absorption (as identified by Allen, 1998). Firstly, interactions with other dietary constituents can affect calcium absorption. For example, calcium can form complexes with constituents such as proteins, phosphate or oxalate and to be absorbed, calcium needs to be released from these complexes. Secondly, absorption is regulated by physiological factors, including hormones. Compounds enhancing calcium absorption include fibre, lactose, vitamin D. Dietary factors antagonising calcium absorption include vitamin D

deficiency, calcium-phosphorus imbalance, phytic acid, oxalic acid, dietary fibre and excessive fat (Ensminger *et al.,* 1995). Additional specific factors limiting calcium absorption include higher bodyweight, low oestrogen status (Heaney *et al.,* 1989), and decreased intestinal transit time (Barger-Lux *et al.,* 1995).

40. The body can adapt to changes in calcium demand by increasing the absorptive capacity of the gut and regulating renal excretion. Calcium requirements are increased during conditions such as during fracture healing, pregnancy, lactation and in childhood growth.

41. Calcium is also secreted into the intestine, mainly through the bile (Blau *et al,* 1954). The efficiency of reabsorption of bile and digestive juice calcium is controversial (as summarised by Allen, 1982): some authors claim this secreted calcium is reabsorbed to the same extent as dietary calcium (Heaney *et al.,* 1964); however, Rose *et al.* (1965) found it was absorbed less efficiently.

Distribution and metabolism

42. Total body calcium is about 30 mol (1200 g). Of this, 1% is located in the serum, lymph and other fluids and the remaining 99% is located in the bone and teeth. The cellular regulation of calcium concentration is also important. The concentration of ionised calcium in serum is closely regulated to within 10% of approximately 2.5 mmol/l^{-1} (Allen, 1998)

43. The concentration of ionised calcium in the plasma remains remarkably constant (1.2 mmol/l^{-1}) (Macrae *et al.,* 1993). Calcium circulates in the plasma in three forms: bound to plasma proteins (45%); in complexes with citrate, phosphate or bicarbonate (about 10%); and as free calcium ions (about 45%). The free ionised form is the physiologically important one.

44. Distribution of the free ionised calcium is dependent upon interactions between three major hormones (Allen, 1998). Firstly, parathyroid hormone (PTH) is released from the parathyroid gland when there is a fall in calcium concentrations in the extracellular fluid. It functions to restore calcium levels by stimulating resorption of bone to release calcium, increasing

renal reabsorption of calcium and enhancing renal conversion of 25-hydroxy-vitamin D_3 to the active hormonal form, 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). As serum calcium concentration increases, PTH release is inhibited. Secondly, calcitonin is synthesised by the C cells of the thyroid and is secreted in response to an increase in serum calcium levels. The overall effects of calcitonin are to decrease serum calcium levels by inhibiting bone resorption directly and also, by inhibiting the action of other resorptive agents. Thirdly, vitamin D regulates calcium distribution because more of the active metabolite of vitamin D ($1,25(OH)_2D_3$) is formed during calcium deficiency. This gives increased intestinal calcium absorption, increased renal calcium absorption and increased bone turnover. Additionally, other hormones affect calcium metabolism including oestrogen, testosterone, glucocorticoids, thyroid hormones, growth hormone and insulin.

45. Large amounts of calcium are transferred from the mother to the foetus and neonate, during pregnancy and lactation. Maximum calcium accretion during foetal growth occurs during the third trimester. The total calcium accretion rate of the foetus increases from approximately 50 mg/day at 20 weeks gestation to 330 mg/day at 35 weeks (Forbes, 1976). Breastfeeding mothers transfer an average of 200 mg of calcium/day to their infants. There is wide variability in the amount of calcium secreted daily into breast milk, this can be as high as 400 mg/day in some individuals (Prentice 1999).

Excretion

46. In adults of a good nutritional state, excretion tends to equal intestinal absorption. Calcium is excreted mainly in the faeces and also in the urine, and to a lesser extent, sweat. Faecal excretion of calcium is mainly dietary intake that is not absorbed (Ensminger *et al.,* 1995) and the remainder comes from shed epithelial cells and the digestive juices. Urinary calcium excretion varies widely among individuals, ranging anywhere from 100-200 mg/day (Ensminger *et al.,* 1995).

47. High protein diets have been associated with increases in urinary calcium excretion (Kerstetter *et al.,* 1999). Significantly increased urinary calcium

excretion was observed in 7 subjects given a high protein diet (Kerstetter *et al.,* 1998). However, this followed an observation of hypocalciuria in the same subjects. Increased calcium excretion, following raised dietary protein, was also observed in a study involving 27 young female subjects, although the increase was only seen when the diet was supplemented with meat, rather than soy protein (Kaneko *et al.,* 1990).

Function

48. Nordin (1986) summarises the functions of calcium in the body. In the vertebrate skeleton, calcium provides rigidity in the form of calcium phosphate ($Ca_{10}(OH)_2(PO_4)_6$, also known as hydroxyapatite), this mineral is embedded in collagen fibrils. Calcium is also a key component in the maintenance of cell structure. Membrane rigidity, viscosity and permeability are partly dependent on local calcium concentrations.

49. Calcium also plays two important regulatory roles in the body (Macrae *et al.,* 1993). Firstly, a passive role as a cofactor for many enzymes (e.g. lipase) and also as an important component of the blood clotting mechanism. Secondly, an active role as an intracellular signal (Lipkin *et al.,* 1999a). Changes in calcium concentration, in response to a physiological stimulus such as a hormone or neurotransmitter, can give rise to an intracellular signal. This controls events such as cell aggregation, muscle contraction and cell movement, muscle protein degradation, secretion, transformation and cell division (Macrae *et al.,* 1993).

50. Cellular calcium fluxes are important mediators of hormonal effects on target organs and are closely linked with the cyclic adenosine-mono-phosphate system.

51. Calcium demands increase during pregnancy and lactation to meet requirements for foetal growth and breast-milk production.

Deficiency

52. A negative calcium balance occurs in men and non-pregnant/lactating women when net calcium absorption is unable to replace urinary calcium losses (Wood 2000). Calcium absorption is impaired in individuals with conditions of fat malabsorption (e.g. in syndromes such as pancreatic insufficiency, bile duct obstruction, coeliac disease, Crohn's disease and ulcerative colitis) (Sadler *et al.,* 1999).

53. Acute hypocalcaemia is frequently seen following thyroid or parathyroid surgery and is also a complication of acute pancreatitis (Riggs, 1989). Symptoms are numerous and include: seizures, irritability, anxiety, aggression, agitation, confusion, delirium, hallucinations, dementia and psychosis. Tetany is the most common neuromuscular symptom seen in patients with hypocalcaemia.

54. The possible effects of calcium deficiency are numerous and wide-ranging. The most dramatic symptoms of calcium deficiency are manifested in the bones and teeth of all young animal species, including humans. These include stunted growth, poor quality bones and teeth and malformation of bones. For example, a low net calcium absorption in young people can limit the development of optimal peak bone mass (Wood, 2000). The effect of decreased calcium intake on bone health has been investigated in young rats (Gruber *et al.,* 1994). Maternal calcium intake during pregnancy and lactation was normal at 1.01%. At weaning, the offspring were put onto a diet containing 0.5% calcium for 25 days. Significant bone mineral depletion occurred in these animals compared to controls.

55. Osteoporosis occurs when bone resorption exceeds formation. Significantly lower bone mineral densities have been observed in women of economically deprived communities on calcium deficient diets (~ 300 mg/day) compared to women with higher calcium intakes (750 mg/day) (Krishnamachari *et al*., 1975). Increases in bone loss and osteoporotic fracture with age are a consequence of calcium deficiency. This occurs particularly in women. A recent study has indicated that a low fractional calcium absorption efficiency significantly increases the risk of subsequent hip fracture in women, particularly those with low calcium intakes (Ensrud, 2000). A prospective study was conducted investigating the factors

influencing calcium balance on the incidence of hip fractures, over approximately 11 years (Meyer *et al.,* 1997). An elevated risk of fracture was found in women with a high intake of protein from non-dairy animal sources, in the presence of a low calcium intake.

56. Pregnancy and lactation are periods of high calcium requirement. Numerous studies have investigated the relationship between calcium deficiency and various adverse effects seen in pregnancy, lactation and health of offspring. Calcium deficiency has been implicated in increased incidence of gestational hypertension and eclampsia/pre-eclampsia (Sanchez-Ramos *et al.,* 1994, Ito *et al.,* 1994, Lopez-Jaramillo *et al.,* 1997),

57. Animal studies have found that maternal calcium deficiency can cause various effects in offspring including: reduced growth and hypocalcaemia (Rasmussen *et al.,* 1986, Krukowski *et al.,* 1987); spontaneous bone fractures and mortality (Gruber *et al.,* 1994);

Overview of reported beneficial effects

58. Calcium is thought to reduce the hyperproliferation associated with colon carcinogenesis by binding to bile and fatty acids and consequently lowering their toxicity on colonic epithelium (Newmark *et al.,* 1984). Calcium may also have a direct inhibitory action on colonic epithelial cells (Buset *et al*., 1986). Calcium supplementation, at doses of approximately 1250-2000 mg Ca/day, has been shown to reduce colonic and rectal epithelial cell proliferation in subjects at risk from developing colon cancer (Lipkin *et al* 1985, Rozen *et al* 1989, Wargovich *et al* 1992). However, converse results have also been observed (Gregoire et al 1989, Wargovich *et al.,* 1992, Bostick *et al.,* 1995). Of particular interest is a study in which dietary calcium intake was increased using natural food sources (Holt *et al.,* 1998). The trial was a randomised, single-blinded, controlled study involving 70 subjects with a history for adenomatous polyps. The daily calcium intake of the experimental group was increased by approximately 800 mg/day from a baseline intake of 608 mg/day, for a period of 6 or 12 months. For both time periods, supplementation resulted in a significant decrease in the proliferative activity of colonic epithelial cells, and markers of normal cellular differentiation were restored. Animal

data also provides evidence for the beneficial effects of calcium on colorectal cancer (Wargovich *et al.,* 1984, Appleton *et al.,* 1986, Appleton *et al.,* 1987, Wargovich *et al.,* 1991, Newmark *et al.,* 1990, Ranhotra *et al.,* 1999).

59. Evidence from a limited number of studies has suggested that calcium may inhibit the development of breast cancer, particularly in the presence of vitamin D. A retrospective epidemiological study demonstrated a significant inverse relationship between the levels of calcium and magnesium in drinking water and the risk of death from breast cancer in Taiwan (Yang *et al*., 2000). 252 municipalities in Taiwan were studied and adjustments were made for fertility rates and urbanisation. A study by Xue and coworkers (1999) demonstrated that when nutritionally stressed, an increase in dietary calcium (equivalent to approximately 3000 mg/2000 kcal daily human diet) and vitamin D, suppressed hyperproliferation of epithelial cells in the pancreas, prostate and mammary gland. The animals had been fed a nutritionally stressed 'Western style' diet containing reduced levels of calcium and vitamin D, with increased fat content.

60. Epidemiological studies and clinical trials have suggested that dietary calcium may have a significant effect on primary hypertension (in non-pregnant individuals, Hamet *et al.,* 1995). Some studies have also indicated a correlation between calcium intake and decreased blood pressure in children (Gillman *et al.,* 1992).

61. Traditionally, calcium restriction has been recommended to reduce the likelihood of calcium stone formation (Curhan, 1997, Curhan *et al.,* 1997). However, recent evidence suggests that dietary calcium restriction may actually increase the risk.

62. A prospective study was carried out to investigate the relationship between dietary calcium intake and the risk of symptomatic kidney stones (Curhan *et al*., 1993). 45,619 men with no history of kidney stones were followed for 4 years. Dietary calcium intake was inversely associated with the risk of kidney stones.

63. Another study compared the association between dietary and supplemental calcium with the risk of kidney stone formation in women (Curhan *et al.,* 1997). The prospective cohort study followed 91,731 women with no history of kidney stones for a period of 12 years. After adjusting for potential risk factors, it was observed that dietary calcium was inversely associated with the risk for kidney stones. This observation was supported by the results of a smaller study, in which women with renal stones were found to consume almost 250 mg/day less dietary calcium than women without renal stones (Sowers *et al.,* 1998). However, a small increased risk of stone formation with the intake of calcium supplements was observed in the previously described cohort study (Curhan *et al.,* 1997). The authors concluded that this could have been a consequence of the supplements being taken without food, or because they were taken at meals with a low oxalate intake.

64. It has been proposed that by forming insoluble soaps in the colon, supplements of 1.5-2 g calcium daily might limit damage to the colonic mucosa and so reduce the increased rates of cell proliferation caused by free fatty acids and bile arising from a high fat diet (DH 1998). However, several short-term intervention trials in patients with polyps have failed to show conclusive results (DH 1998).

Toxicity

Human toxicity

Acute toxicity

65. Milk-alkali syndrome (MAS) is a rare and potentially life-threatening condition observed in individuals consuming large quantities of calcium and alkali, such as antacid tablets, calcium supplements and milk. The condition can be acute, intermediate (Cope's sydrome) or chronic (Burnett's syndrome) depending on the duration of calcium intake and the symptoms presented. Historically, the majority of patients developing MAS have been middle-aged males ingesting milk and absorbable alkali, but this decreased with the use of modern medication for peptic ulcer disease (Ullian and Linas, 1988). More recently, the syndrome has been observed to occur in predominantly female patients taking calcium-

containing drugs for conditions such as autoimmune disease, organ transplantation, chronic renal failure and osteoporosis (Beall *et al.,* 1995). Orwoll (1982) has reported that the syndrome may be caused by a calcium carbonate intake from as low as 4 g/day.

66. Because the syndrome is rare, its description has been confined to case reports. These are summarised in Table 1.

Subchronic Toxicity

67. Although MAS is usually observed after ingestion of large quantities of antacid tablets, cases have been described of MAS resulting purely from ingestion of large quantities of foods with high calcium content. Wu *et al.* (1996) described two cases of MAS resulting from the chewing of a betelnut paste containing calcium carbonate from oyster shells.

68. 1). A 55-year old man was admitted to hospital with headache and progressive aching soreness of both thighs over the preceding 6 months. The patient was a heavy smoker and chewed a large amount of betelnuts (*Areca catechu)* with an average of 30/day for more than 30 years. Over the past 4 years, he had chewed up to 100 nuts daily. He tended to swallow the saliva mixed with betelnut paste, which is not the common practice of most betelnut chewers, who expectorate the mixture. On admission the patients serum calcium was 3.35 mmol/l. an abdominal X ray showed interstitial calcification of the kidneys and an ultrasonogram showed bilateral nephrocalcinosis. Treatment consisted of rehydration and 40 mg frusemide administered intravenously over 2 days. The patient was also told to reduce his intake of betelnuts to less than 20/day. His serum calcium returned to normal and remained so until 2 months after discharge, but rose again when he increased the consumption of betelnuts. Analysis of the calcium content of each betelnut serving showed an average of 35 mg/betelnut serving.

69. 2). A 63-year old man was admitted to hospital with anorexia and weakness of the limbs from which he had been suffering for 3 months. He had suffered a full sensation of the abdomen and tenesmus 18 months previously and 8 months later he suffered epigastralgia and anorexia. The subject was a heavy smoker and chewed betelnuts, with an average of

50/day for more than 30 years. The betelnuts were also smeared with a special paste (containing calcium) and he liked to swallow most of it. Three months before admission he had dizziness and progressive weakness of the limbs, and he lost his appetite gradually. On admission, serum calcium level was 3.77 mmol/l. An ultrasonogram of the kidneys showed normal sized kidneys with bilateral renal stones. Treatment consisted of rehydration and frusemide. On the eighth day of admission, the patient needed treatment for hypocalcaemia. The patient abstained from betelnut chewing for two months after discharge and he remained normocalcaemic. Analysis of the calcium content of the paste showed more than 50 mg of elemental calcium per betelnut serving.

70. Both cases showed classic MAS symptoms: hypercalcaemia and renal insufficiency. The authors estimated that the patients had ingested 9 g and 6 g of calcium carbonate (3.6 and 2.4 g elemental calcium) per day, respectively. As the authors identify, this is the first report of MAS not caused iatrogenically.

Chronic Toxicity

71. Case studies have also described chronic MAS in humans (see Table 2). Calcification of the lungs and breasts has been seem in some patients with MAS (Abreo *et al.,* 1993). The latter was observed in a 54-year old woman at risk of breast carcinoma who had consumed large quantities of calcium carbonate for several years (see Table 1).

72. MAS has also been observed in patients on chronic haemodialysis receiving calcium carbonate therapy (Slatopolsky *et al.,* 1986). In the study of 20 patients on chronic haemodialysis, the efficacy of calcium carbonate therapy was investigated (mean phosphorus intake was 900 mg/day and a range of 2.5 to 17 g/day (mean 8.5 g/day) in total calcium carbonate administered). A few patients ingesting large amounts of calcium carbonate to control extremely high phosphorus levels developed hypercalcaemia, with serum calcium level reaching 11.5 mg/dl. However, this effect was reversible after discontinuation of calcium carbonate therapy.

73. Yamamoto *et al.* (1982) described the case of reversible hypertension due to calcium overloading in a 37-year old woman. The woman had a 2-month history of hypertension, hypercalcaemia and hypokalaemia. Post-operative hypoparathyroidism occurred after subtotal thyroidectomy (13 years previously) which was treated with intravenous calcium and/or oral calcium lactate in addition to thyroid hormone replacement (taken for 14 years). During this period, the woman complained of numbness and tingling of the perioral area, hands and feet, and occasional symptoms of tetany. The patient began oral treatment with 1α-hydroxycholecalciferol (2-3 μg/day) and calcium lactate (5 g/day). Thereafter, the patient had progressive fatigue, anorexia, constipation, polydipsia, insomnia and nocturia. Hypercalcaemia was diagnosed (serum calcium 13.6 mg/dl). The authors concluded that the 2-month hypercalcaemic period was caused by vitamin D and excessive calcium supplements. They suggest the most probable explanation for the hypertension seen is a direct vasoconstrictor effect of calcium on peripheral blood vessels (calcium infusion when the patient was normocalcaemic, normoreninemic and normotensive produced increases in mean blood pressure and total peripheral resistance).

Neurotoxicity

74. The neurotoxicity seen in patients with hypercalcaemia has been summarised by Riggs (1989). Alterations in mental status are quite common in hypercalcaemia and generally consist of progressive lethargy, confusion and ultimately coma (serum calcium concentrations above 14 mg/dl). These are reversible symptoms and are directly related to the degree of hypercalcaemia. Headache, elevated cerebrospinal fluid protein and, rarely, convulsions, may also occur in patients with hypercalcaemia.

Carcinogenicity

Genotoxicity

75. An increase in the number of micronucleated erythrocytes has been associated with a higher intake of calcium supplements in spleenectomised subjects (Smith *et al.,* 1990). Micronucleated

erythrocytes indicate genotoxic damage and are not selectively removed in individuals lacking splenic activity.

76. Similarly, in a study on 77 spleenectomised subjects, consumption of calcium supplements by older women was statistically associated with higher frequencies of micronucleated cells (MacGregor 1990).

Reproductive Toxicity

77. There is a report of pure calcium carbonate gallstones occurring in a 2-year old child whose mother had ingested calcium supplements during pregnancy (Powell, 1985). A 2-year old Filipino female presented with a 2-day history of cough and fever. Investigations revealed perihilar infiltrates and several small calcified densities in the right upper quandrant on the region of the gallbladder. The patient underwent cholecystectomy and incidental apendectomy and 2 years after surgery remained asymptomatic. Analysis of the gallstones showed they consisted of pure calcium carbonate and further enquiry revealed that the mother had been placed on OS-Cal (a calcium and vitamin D supplement) for leg cramps during the last 4 months of her pregnancy. The authors say that this is the first report of pure calcium carbonate cholelithiasis in association with prenatal supplementation with the calcium salt.

Human supplementation studies

78. It has been suggested the addition of 2000 mg of calcium to the diet of pregnant women may increase the danger of hypercalcuria and renal calculi (Ferris, 1991). Yet populations supplemented with calcium doses of approximately 3000 mg/day showed no significant increase in the incidence of urolithiasis during pregnancy (Levine *et al*., 1997). However, it should be noted that the study excluded women with a history, or high risk for developing renal disease.

79. The meta-analysis displayed a trend in favour of calcium supplementation for a reduction in pre-term delivery, caesarean delivery, and intrauterine or peri-natal death (Bucher *et al.,* 1996a, 1996b). However, calcium supplementation of 2000 g/day in nulliparous women did not prevent adverse perinatal outcomes (Levine *et al.,* 1997). Again, the positive

effects may have been a consequence of supplementation in Ca deficient women.

80. However, a randomised, double-blind controlled clinical trial in pregnant adolescents demonstrated that calcium supplementation had beneficial effects (Villar and Repke,, 1990). Subjects were of 17 years of age or less and both treatment and placebo groups had similar dietary calcium intakes of 1200 mg/day. A reduced incidence of pre-term delivery and low birth weight was observed in the supplemented group receiving 2000 mg elemental calcium/day.

81. A small increased risk of stone formation with the intake of calcium supplements was observed in the previously described cohort study (Curhan *et al.,* 1997). The authors concluded that this could have been a consequence of the supplements being taken without food, or because they were taken at meals with a low oxalate intake.

82. No toxicity was associated with calcium supplementation during a randomised, double-blind, placebo controlled trial on patients with a history of colorectal adenomas (Baron *et al.,* 1999). 930 patients received 3 g of calcium carbonate/day and were examined after 1 and 4 year periods.

Vulnerable groups

83. Patients with malignant neoplasms and hyperparathyroidsim account for 70-80% of cases of hypercalcaemia (Benabe and Martinez-Maldonado, 1987). The neoplasms most commonly associated with hypercalcaemia are breast cancer, lung cancer, and multiple myeloma.

84. Persons at risk from developing milk-alkali syndrome include those using drugs such as thiazide and those with renal failure. These groups should be identified and monitored for alkalosis and hypercalcaemia when using calcium supplements (Whiting *et al*., 1997). This would be particularly important for patients with renal failure who already receive calcium carbonate therapy to control serum phosphorous levels (Slatopolsky *et al*., 1986).

85. Patients with absorptive or renal hypercalcuria, primary hyperparathyroidism and sarcoidosis may have a higher risk of renal stone formation following calcium supplementation (Allen *et al.,* 1994).

86. It has been proposed that there may be an individual hypersensitivity to developing hypercalcaemia (Vanpee *et al.,* 2000). This is because only a limited number of individuals develop the metabolic complications involved in MAS, and excessive calcium intake alone is not enough to induce hypercalcaemia.

87. An overview of patients with adynamic bone and chronic renal failure concluded that these individuals would have more difficulty in handling and buffering calcium loads, and consequently they would have a higher risk of extraosseous calcifications (Cannata, 2000).

Genetic groups

88. No data identified.

Adverse Drug Reactions

89. Suspected adverse reactions to medicinal products are reported to the Committee on Safety of Medicines/Medicines Control Agency. Many factors influence the number of reports received, and in most situations there is considerable “under-reporting” of reactions. Most of the adverse reactions reported for products containing calcium supplements relate to multiconstituent products, and may not, therefore, be directly attributable to calcium. Single constituent calcium supplements are associated with a low number of adverse reactions, including gastrointestinal and skin disorders, but there is no trend or pattern to indicate a particular problem.

Animal toxicity

Acute toxicity

90. Mithofer *et al.* (1995) investigated the effects of induction of acute hypercalcaemia in the rat. Rats were given bolus infusions of $CaCl_2$ (200 mg/kg) and effects were compared with saline-treated control rats. Serum indices (Ca2+ amylase, trypsinogen activation peptide (TAP)) and pancreatic tissue, pancreatic wet/dry weight ratio and histology were undertaken. For dose-response analysis, $CaCl_2$ was injected at a dose of 50-200 mg/kg and serum indices were assayed for 1 hour. The results showed calcium infusion increased serum calcium three-fold after 5 minutes. Within one hour, serum amylase and tissue TAP levels had increased. Macroscopic and microscopic oedema had formed and there was evidence of leucocytic infiltration. Amylase and tissue TAP concentrations remained elevated until 24 hours when serum TAP concentration had increased and focal acinar necrosis had become evident. In conclusion, the authors state acute hypercalaemia induces a dose-dependent morphological alterations characteristic of acute pancreatitis, acute hypermyllasaemia and early ectopic trypsinogen activation.

91. The acute toxicity of a new source of calcium, Biocal™, which is a calcium gluconate stabilised with glycine, was investigated in SD rats (Sarabia *et al.,* 1999). Toxicity studies were carried out with six groups of ten female and six groups of ten male rats, which received increasing doses of 10, 11, 12, 13, 14, and 15 g of Biocal™/kg body weight. The oral LD_{50} value for female rats was 13.5 g/kg and for males it was 13.0 g/kg. These values were higher than those for calcium gluconate (LD_{50} = 10 g/kg) and suggests that Biocal™ can be considered as a promissory calcium compound to be used for dietary supplementation or food fortification.

Sub-Chronic Toxicity

92. The effects of nine commercially available calcium supplements has been investigated in weanling SD rats (Greger *et al.,* 1987). In the first study, rats were fed diets for 20 days containing either: 1) nonfat dry milk; 2) calcium phosphate dibasic; 3) oyster shell calcium; 4) calcium carbonate;

5) calcium lactate; 6) vegetarian amino acid chelated diet. In the second study, rats were fed diets for 27 days containing either: 1) nonfat dry milk; 2) calcium phosphate dibasic; 3) dolomite; 4) oyster shell calcium with magnesium; 5) chelated calcium and magnesium from yeast; 6) calcium carbonate supplemented with iron and vitamins. All diets were formulated to contain about 5 mg Ca/g diet. The results showed that rats fed diet containing calcium phosphate dibasic for 20 days had significantly enlarged kidneys compared to the other treatment groups. The rats fed calcium carbonate and supplemental iron and vitamins for 27 days also had enlarged kidneys. The authors conclude that kidney calcification can be a symptom of magnesium deficiency but that the rats in the study had adequate intakes of magnesium

93. The induction of haemorrhagic syndrome by high dietary levels of calcium has been investigated in growing pigs (Hall *et al.,* 1985). The effects of calcium:phosphate ratio was investigated at three levels of dietary phosphate (3, 6 and 9%). Fortified corn-soybean meal diets with dicalcium phosphate and calcium carbonate as sources of calcium were fed *ad libitum* to growing pigs (initial weight 17 kg). During the 3rd and 4th week of the study, all 8 pigs fed the highest calcium level (2.7%) died. Necropsy showed extensive internal haemorrhage. Clotting time of whole blood and prothrombin time of the plasma were increased in pigs given 1.8 and 2.7% calcium. The addition of 5 mg/kg vitamin K to the diet ameliorated this effect. Increasing the Ca:P ratio reduced growth rate at all levels of phosphate in the diet and increased bone breaking strength at the 6% and 9% phosphate levels. The authors suggested various possible mechanisms for this effect of high dietary calcium, including high calcium may inhibit synthesis, reduce absorption or partially destroy vitamin K in the gut.

94. Zawada *et al.* (1986) investigated the effects of hypercalcaemia on systemic and renal vascular responses in dogs. Twenty mongrel dogs were given 100 mg/kg calcium gluconate and 10,000 IU/kg vitamin D daily in the diet for two weeks (controls did not receive calcium gluconate or vitamin D). Treated animals had hypercalcaemia, a reduced glomerular filtration rate and renal blood flow, and increased fractional excretion of water, sodium, calcium and magnesium. The treated animals also had effects on the vascular system, with lower systolic blood pressure and

stroke volume (probably due to the diuresis) and higher total peripheral resistance. Magnesium levels were also affected, being significantly lower in the treated group. The authors concluded that the effects may be due to the direct effects of increased calcium ions or due to the indirect effects on other vasoactive humoral systems including reductions in magnesium ions.

95. The effects of oral administration of calcium chloride solutions to dairy cows has been investigated through two experiments (Mathieu and Pelletier, 1966). Firstly, two dairy cows, one in lactation and the other dry, were given a solution of 0.1% calcium chloride in tapwater as the sole liquid for 50 days. The concentration of the solution was then increased to 0.2% and this solution was given as the sole liquid for 30 days. Secondly, two cows (again one in lactation and one dry) were offered as the only source of liquid, a 0.3% calcium chloride solution for 45 days. The results from experiment 1 showed that there was no effect of calcium chloride on appetite, body weight and milk production of cows of either experiment. After 80 days, both cows had normal blood parameters (haemoglobin level, haematocrit, total and differential leucocyte counts) and there were no macroscopic signs that could be attributed to ingestion of the salt solution. The cows from experiment 2, however, appeared more thirsty and the presence of mucous traces in the faeces suggested a mild degree of gastrointestinal irritation. However, there was no effect on blood parameters. The authors concluded that calcium chloride poisoning was unlikely anyway because cattle refuse to drink calcium chloride solutions if the concentration exceeds 0.5%.

Chronic Toxicity

96. No data identified.

Carcinogenicity

97. No data identified.

Reproductive toxicity

98. A study in mice investigated the effect of excessive maternal dietary calcium on foetal development. Control animals received 1.2% dietary calcium and the experimental group received an additional 7% calcium as carbonate and lactate in food and water. Treatment started 10 days prior to mating and was continued throughout pregnancy. Foetuses of the treated mothers were found to have significantly decreased weights, and retarded skeletal and dental calcification for the majority of parameters examined. No gross abnormalities were detected (Liebgott *et al*., 1989). However, it was later noted that the rodent diet used contained excessive nutrients (Shackelford *et al.,* 1993).

99. The effect of moderate dietary calcium increases in pregnant rats on foetal development was investigated (Shackelford *et al.,* 1993). The doses were selected to resemble the increases recommended by the 1984 NIH Consensus Development Conference Panel on Osteoporosis, all animals were fed nutritionally adequate diets and received 0.5 (control), 0.75, 1.00 or 1.25% dietary calcium as calcium carbonate. Treatment was for 6 weeks prior to mating, during mating and for the first 20 days of gestation. Foetal bodyweights and lengths remained similar between treatment and control groups. There were no significant increases in external, visceral or skeletal variations of the foetuses, when compared to the control animals.

100. The effect of hypercalcaemia during pregnancy and lactation, on the development of the offspring was investigated (Fairney *et al.,* 1970). Rats were maintained on high calcium diets, containing 3% in diet and an additional 4 g per 100ml drinking water, throughout pregnancy and lactation. In comparison to controls (receiving 0.8% calcium in diet and 1.1 mg per 100 ml water), the offspring of treated rats were born significantly hypocalcaemic and had lower birthweights, lower growth rates, and focal alopecia. These effects were reversible when the pups were weaned onto a normal diet. In one litter from the treated group the liver, heart and kidneys appeared paler than normal, and the kidneys showed focal pyelonephritic scarring. The hypercalcaemic lactating mothers also produced breast-milk with a higher calcium concentration than controls, which may have contributed to the response seen in the offspring.

Mechanisms of toxicity

101. The mechanisms involved in hypercalcaemia, metabolic alkalosis and renal failure have been summarised (Abreo *et al.,* 1993). Acute hypercalcaemia can impair renal function by causing vasoconstriction and consequently decreases both the renal blood flow and glomerular filtration rate. Impaired renal excretion also results from intravascular volume depletion (through vomiting), nephrogenic diabetes insipidus and metabolic alkalosis. Hypercalcaemia increases the absorption of bicarbonate in the proximal tubule. This predisposes the patient to metabolic alkalosis (Vanpee *et al.,* 2000). Bicarbonate absorption is also increased through suppression of PTH (parathyroid hormone). Chronic hypercalcaemia, hyperphosphataemia and metabolic alkalosis promote irreversible renal calcification. An alteration in serum electrolytes can also cause an altered mental state or coma (Riggs 1989).

Regulatory considerations

102. The Recommended Daily Allowance in the Food Labelling Regulations for calcium is 800 mg. In the UK, all flour, except wholemeal flour, is required by law to be supplemented with 235-390 mg calcium carbonate per 100g due to calcium losses during processing (The Bread and Flour Regulations 1998). The Infant Formula and Follow-on Formula Regulations recommend a minimum calcium content of 50 mg per 100kcal. The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations recommend a minimum calcium content of 80 mg/100 kcal for cereals with an added high protein food which are reconstituted with water or other protein-free liquid and 50 mg/100 kcal for rusks and biscuits. The Foods Intended for use in Energy Restricted Diets for Weight Reduction Regulations (1997) recommend that whole diet products should provide 700 mg calcium and meal replacements 210 mg.

Existing recommendations on maximum intake levels

103. The Food and Nutrition Board of the USA National Institutes of Medicine set an upper tolerable daily intake of 2500 mg for toddlers, children adolescents, pregnant and lactating women and adults aged 70 years and over (FNB 1997).

Existing recommendations on maximum supplementation levels

104. Shrimpton (1997) recommended an upper safe level (long term) of 1100mg and upper limit (short term) of 1900mg.

Summary

105. Calcium is an alkaline earth metal with a single oxidation state of +2. It does not exist freely in nature, but occurs abundantly as limestone, gypsum and fluorite. Foods particularly rich in calcium are milk, cheese and other dairy products, green leafy vegetables and soybean products. Some foods are now fortified with calcium, such as bread and baked products and breakfast cereals.

106. Calcium supplements are available over the counter, either alone or in combination with other minerals.

107. Calcium functions to provide the rigidity of the skeleton and teeth, in the form of calcium phosphate (or hydroxyapatite). It is also a key component of cell structure, maintaining membrane rigidity, viscosity and permeability. Calcium also has regulatory roles, as a cofactor for many enzymes (e.g. lipase), as a component of the blood clotting mechanism, and as an intracellular signal.

108. About 25-50% of dietary calcium is absorbed and delivered to the exchangeable calcium pool, crossing the intestinal mucosa by both active and passive transport mechanisms. Many dietary constituents affect calcium absorption including proteins, phosphate, oxalate, fibre and fat.

109. Total body calcium is about 1200 g, of this 1% is located in the serum, lymph and other fluids, and the remaining 99% is located in the bone and teeth. The concentration of free ionised calcium in the plasma remains constant and is regulated by three major hormones, parathyroid hormone, calcitonin and the hormonal form of vitamin D. Excretion of calcium is usually equal to absorption, being mainly excreted in the faeces and urine, and to a lesser extent in the sweat.

110. Calcium interacts with numerous other dietary constituents. These include: phytic acid, which reduces calcium absorption; iron and zinc (calcium reduces absorption of these metals); phosphate, which forms insoluble complexes with calcium; and fatty acids, which also bind calcium forming insoluble complexes in the intestinal lumen.

111. Evidence for the toxicity of calcium to humans is largely restricted to case reports. The majority of these describe milk-alkali syndrome which is a rare and potentially life threatening condition observed in individuals consuming large quantities of calcium and alkali, such as antacid tablets, calcium supplements and milk. However, one report describes the induction of MAS in two people who ingested large quantities of ground oyster shell (giving 9 and 6 g doses of calcium carbonate per day). The condition is usually acute and symptoms include nausea, vomiting, diarrhoea, weakness, hypercalcaemia, metabolic alkalosis, and renal failure. Chronic MAS has been observed in some patients receiving chronic haemodialysis with calcium carbonate. Neurotoxicity is associated with hypercalcaemia.

112. Human supplementation studies have shown 2000 mg calcium of calcium to the diet of pregnant women may increase incidence of hypercalcuria and renal calculi. However, most calcium supplementation studies have found beneficial effects in pregnancy (reduction in pre-term delivery, caesarean delivery, intrauterine or peri-natal death, and low birth weight). An increased risk of stone formation has been observed with calcium supplement, however. Vulnerable groups include those using thiazide drugs and patients with renal failure and primary hyperparathyroidism.

113. Animal studies on the toxicity of calcium are scarce. Acute hypercalcaemia has been induced in rats given infusions of 200 mg/kg calcium carbonate. This led to macro- and microscopic oedema formation and leucocytic infiltration in tissues, acute pancreatitis and acute hypermyllasaemia. Dietary calcium phosphate dibasic for 20 days and calcium carbonate with supplemental iron and vitamins for 27 days (both diets containing 5 mg calcium/g diet) gave rats enlarged kidneys compared to controls. The reproductive toxicity of calcium has been

investigated in mice and rats, with negative effects for calcium doses up to 7% calcium carbonate (throughout mating and pregnancy).

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ANNEX 1 TO EVM/01/12

INTAKES OF CALCIUM FROM FOOD AND SUPPLEMENTS

The data presented on calcium intakes are obtained from dietary surveys of specific population age groups in Britain carried out over the last 15 years[12345]. 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 calcium

Table 1 provides information on the absolute intakes of calcium by the British population, classified by age and sex. Intakes are presented from food sources and also from all sources (ie including supplements) for adults and older people. 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. In addition, intakes of calcium from food and supplements for older people are presented both including and excluding prescribed calcium supplements, for comparison. Although these prescribed preparations were only taken by a small minority of participants within this group, intakes from them were found to have a disproportionate impact on mean daily intakes of calcium.

Average intakes of calcium from food and supplements were lowest for pre-school children, and highest in males aged 85 years and over living in institutions. Mean calcium intakes increased significantly with age for males aged 4 to 18 years and adults aged 16 to 64 years and decreased significantly with age for pre-school children. In addition, young males aged 4

[1] Food and nutrient intakes of British infants. 1986
[2] National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3
[3] National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8
[4] Dietary and Nutritional survey of British adults. 1986/7
[5] National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

to 18 years had a significantly higher mean daily intake of calcium from food sources than girls of the same age. Mean daily intake of calcium for boys in the oldest group (15 to 18 years) was a third higher than for girls of the same age.

Excluding the contribution from supplements, mean and median intakes from food only were below the RNI for young people aged 11 to 18 years, females aged 16 to 34 years and females aged 75 years and over free-living in the community. In addition, median intake of calcium from food sources was below the RNI for females aged 65 to 74 years. When intakes from supplements were included, mean and median intakes for these groups remained below the RNI except for mean intakes of women aged 25 to 34 years. Mean calcium intakes were above the RNI for all other age groups.

Intakes from food and supplements (including prescribed calcium) at the 97.5%ile were about twice the median in all groups.

Table 2 provides information on calcium intakes from food and supplements adjusted for body weight and classified by age and sex. Body weight adjusted calcium intakes are highest in infants and show a trend to decrease with age for children and young people.

Sources of calcium in the diet

Table 3 indicates the contribution made by different types of food to average intakes of calcium 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 calcium in this age group is milk and milk products (44%), of which about two thirds came from milk, followed by cereals and cereal products (28%), of which about half came from bread.

Infants obtained just over half of their calcium intake from milk and milk products, a further fifth from commercial infant foods and about one fifth from infant formulas. Milk and milk products was the major source of calcium for all other age groups (providing about half of total intake from food and 64% for

pre-school children). This was followed by cereals and cereal products (providing about a quarter of total intake from food and 19% and 31% for pre-school children and older people living in institutions respectively). For both pre-school children and young people the data suggests that the contribution of milk to calcium intake decreased with age.

UK legislation requires that calcium carbonate (at not less than 235mg and not more than 390mg per 100g flour) be added as a fortificant to all wheat flour (except wholemeal flour, self-raising flour which has a calcium content of not less than 0.2%, and wheat malt flour). Calcium is often also added voluntarily by manufacturers to other foods such as breakfast cereals, cereal bars and some soft drinks.

Calcium intakes from supplements

Dietary supplements containing calcium (including those prescribed) provided less than 1% of mean intakes of calcium for all population groups. For some groups the effect of supplements providing calcium (including those prescribed) was only apparent at the lower and upper 2.5 percentiles of the distribution. For example, supplements providing calcium increased intakes from food sources alone by 11% at the lower 2.5 percentile for males aged 16 to 24 years. In addition, dietary supplements containing calcium (excluding those prescribed) provided 3% and 2% of intakes of calcium at the upper 2.5 percentile for females aged 65 to 74 years, and 85 years and over respectively free-living in the community. However, this increased to 9% and 10% respectively when prescribed supplements containing calcium were included in the dataset.

Of course, the proportion of intake from supplements is much higher if supplement consumers are considered separately. Table 4 shows the number of consumers of dietary supplements containing calcium in each age group, together with the mean, median and range of intakes of calcium from supplements for those who consumed them. The highest prevalence of calcium supplement use was in older females free-living in the community, taken by about 6% of this group.

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. The range of intakes from supplements was wide with the maximum intake from this source at 1250mg per day.

Diet and Nutrition Surveys Branch
Nutrition Division
Food Standards Agency
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Table 1: Total intakes of Calcium

	Absolute Calcium intake (mg/day)[6]							
Age/sex	*Food Only*				*Food and Supplements*			
	2.5% ile	Mean	Median	97.5%ile	2.5% ile	Mean	Median	97.5%ile
Infants (1986)								
6-12mths/M&F	334	783	767	1433	*	*	*	*
Pre-school children								
1½-2½ yrs/M/F	244	663	639	1305				
2½-3½ yrs/M/F	237	635	598	1294	**	**	**	**
3½-4½ yrs/M	281	625	598	1198				
3½-4½ yrs/F	247	595	584	1099				
Young people (1997/8)								
4-6 yrs/M	249	706	666	1303				
4-6 yrs/F	280	657	635	1243				
7-10 yrs/M	349	741	700	1251				
7-10 yrs/F	279	656	664	1058	**	**	**	**
11-14 yrs/M	299	799	781	1499				
11-14 yrs/F	254	641	630	1200				
15-18 yrs/M	384	878	850	1474				
15-18 yrs/F	258	653	631	1162				
Adults (1986/7)								
16-24 yrs/M	352	894	858	1597	390	899	863	1597
16-24 yrs/F	240	675	656	1220	240	675	656	1220
25-34 yrs/M	379	931	908	1607	379	933	908	1607
25-34 yrs/F	231	699	689	1299	231	700	692	1300
35-49 yrs/M	439	960	956	1683	439	961	959	1686
35-49 yrs/F	328	760	737	1379	328	764	739	1379
50-64 yrs/M	420	949	947	1528	420	952	947	1528
50-64 yrs/F	305	739	731	1131	305	747	732	1167
Older people free-living in the community (1994/5)								
65-74yrs/M	354	852	848	1450	354(354)	853(853)	848(848)	1450(1450)

[6] Data in brackets = intakes from food and supplements, excluding prescribed supplements

65-74yrs/F	341	704	682	1192	341(341)	727(712)	697(683)	1306(1226)
75-84 yrs/M	327	813	807	1434	327(327)	813(813)	807(807)	1434(1434)
75-84 yrs/F	320	680	631	1236	320(320)	687(684)	641(641)	1242(1242)
85 and over/M	373	764	717	1336	373(373)	764(764)	717(717)	1336(1336)
85 and over/F	231	647	619	1272	231(231)	667(656)	621(619)	1420(1294)
Older people living in institutions (1994/5)								
65-84 yrs/M	471	935	899	1566	471(471)	936(936)	899(899)	1566(1566)
65-84 yrs/F	428	900	856	1494	429(428)	902(902)	860(860)	1494(1494)
85 and over/M	539	981	919	1619	539(539)	983(983)	919(919)	1619(1619)
85 and over/F	402	828	799	1381	411(411)	841(835)	804(804)	1381(1381)

* Data unavailable

** Dietary supplements provided negligible calcium for children/young people in this survey

Table 2: Bodyweight adjusted Calcium intake

	Bodyweight adjusted Calcium intake (mg/kg bwt /day)[7]		
Age/sex	*intakes from food and supplements[8]*		
	Mean	Median	97.5%ile
Infants (1986)[9]			
6-12mths/M&F	82.2	79.3	150.1
Pre-school children (1992/3)			
1½-2½ yrs/M&F	54.5	50.7	107.1
2½-3½ yrs/M&F	43.5	40.8	89.1
3½-4½ yrs/M	37.8	35.4	69.9
3½-4½ yrs/F	36.5	35.6	64.3
Young people (1997/8)			
4-6 yrs/M	33.7	32.7	62.2
4-6 yrs/F	32.6	31.1	54.7
7-10 yrs/M	25.0	24.6	46.0
7-10 yrs/F	21.3	20.6	37.1
11-14 yrs/M	17.6	17.4	30.5

[7] Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.
[8] Data includes intakes from prescribed calcium supplements.
[9] Intakes for infants aged 6-12 months are from food only.

11-14 yrs/F	13.7	13.3	26.0
15-18 yrs/M	13.4	13.2	24.5
15-18 yrs/F	11.1	11.0	20.8
Adults (1986/7)			
16-24 yrs/M	13.1	12.7	23.3
16-24 yrs/F	11.4	10.9	23.0
25-34 yrs/M	12.5	11.9	22.6
25-34 yrs/F	11.5	11.3	21.4
35-49 yrs/M	12.7	12.0	21.8
35-49 yrs/F	12.1	11.7	23.0
50-64 yrs/M	12.4	12.3	19.7
50-64 yrs/F	11.7	11.7	18.6
Older people free-living in the community (1994/5)			
65-74 yrs/M	11.1	10.8	20.1
65-74 yrs/F	11.3	10.7	22.4
75-84 yrs/M	11.2	11.0	20.9
75-84 yrs/F	10.9	10.1	20.9
85 and over/M	11.4	10.7	19.3
85 and over/F	11.5	10.7	22.7
Older people living in institutions (1994/5)			
65-84 yrs/M	14.1	13.4	28.5
65-84 yrs/F	15.3	14.1	24.9
85 and over/M	14.7	14.4	24.1
85 and over/F	14.6	13.5	28.4

Table 3[10]: Sources of Calcium in the diet

Food Type	Contribution of food types to average daily intake of Calcium mg/day	% of total
Cereal and cereal products	213	28
- of which bread	*99*	*13*
Milk and milk products	335	44
-of which milk	*215*	*28*
Egg and egg dishes	10	1
Fat spreads	2	<1
Meat and meat products	58	8
Fish and fish dishes	13	2
Vegetables, potatoes and savoury snacks	52	7
Fruits and nuts	6	<1
Sugar, confectionery and preserves	34	4
Beverages	33	4
Miscellaneous	12	2
Total intake from food	**768**	**100**
Intake from dietary supplements	*0*	*0*
Total intake from food and supplements	**768**	**100**

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

Table 4: Calcium intake from supplements[11]

	Consumers of Calcium supplements		Calcium intake from supplements (consumers only) (mg/day)		
Age/sex	*Number*	*%*	*Mean*	*Median*	*Range*
Infants (1986)					
6-12 mths/M&F	*	*	*	*	*
Pre-school children (1992/3)					
1½-4½ yrs/M&F	9	<1	85	70	5 - 324
Young people (1997/8)					
4-6 yrs/M&F	11	3	77	65	0 - 400
7-10 yrs/M&F	8	2	85	73	0 - 180
11-14 yrs/M	4	2	59	30	12 - 115
11-14 yrs/F	4	2	95	71	57 - 152
15-18 yrs/M	3	2	60	48	1 - 95
15-18 yrs/F	2	<1	49	41	19 - 62
Adults (1986/7)					
16-64 yrs/M	21	1	133	60	3 - 822
16-64 yrs/F	36	3	99	66	1 - 500
Older people free-living in the community (1994/5)					
65 and over/M	9	1	87	60	0 - 210
65 and over/F	36	6	311	246	0 - 1250
Older people living in institutions (1994/5)					
65 and over/M	4	2	88	41	25 - 145
65 and over/F	6	3	214	92	56 - 500

* Data unavailable

[11] Data includes intakes from prescribed calcium supplements

ANNEX 2 TO EVM/01/12

Table 1. Acute Human Toxicity of Calcium-Compounds (Case Reports).

Subject	*Symptoms and Duration*	*History*	*Serum Calcium*	*Treatment*	*Ingested*	*Outcome*	*Reference*
60-year old man admitted twice	Nausea, vomiting, anorexia, malaise	Type II diabetes mellitus	11.9 mg/dl on first admission, 15.1 mg/dl on second	Haemodialysis with a dialysate containing 1.25 mmol/L calcium	5 tablets of calcium carbonate (500 mg/tablet) and 2 tablespoons of baking soda daily	Renal function stable at 1.5 years	Abreo *et al.* (1993)
60-year old man	Painful swelling of left leg	Chronic epigastric burning and dyspepsia	13.3 mg/dl on admission	Anticoagulation with heparin and saline diuresis was initiated	36 TUMS™ tablets (containing total of 18 g calcium carbonate (total intake 7.2 g elemental calcium)	Discharged 9 days later	Abreo *et al.* (1993)
54-year old woman	Routine mammogram showed calcification in both breasts. Later diagnosed with breast carcinoma.	Peptic ulcer disease, sigmoid diverticulosis, gout, chronic obstructive pulmonary disease and anxiety neurosis	14.9 mg/dl on admission	Total right mastectomy, hypercalcaemia treated with saline diuresis	1-2 rolls of calcium carbonate tablets (TUMS™) daily for several years. Each tablets contains 500 mg calcium carbonate and 1 roll contain 12-24 tablets. Therefore, intake = 6-12 g calcium carbonate (2.4 - 4.8 g elemental calcium)	Discharged 10 days later. 2 months later, renal function was unchanged and she was normocalcaemic	Abreo *et al.* (1993)
53-year old man	Weakness, sleep	Type 2 diabetes	13.7 mg/dl on	Intravenous saline	Drank 3-4 gallons of whole milk	On discharge,	Abreo *et al.*

	problems, nausea, vomiting, left-sided back pain and depression	mellitus, diabetic neuropathy, coronary artery disease, previous myocardial infarction, hypothyroidism	admission	and loop diuretics. Thyroid medications were readjusted.	each week and ingesting 15 calcium carbonate tablets (Rolaids™) daily, each tablet containing 1000 mg.	serum calcium and phosphorus levels were normal.	(1993)
65-year old man	Nausea, vomiting, confusion and disorientation	Long-standing hypertension (reserpine, enalapril maleate and hydrochlorothiazide treated). Alcohol abuse	13.2 mg/dl on admission	Intravenous saline and loop diuretics. Calcium supplements were discontinued. Required haemodialysis for 3 weeks.	Ingested 2-3 tablets of calcium carbonate (Titralac™) 4-6 times a day for several years (each tablet contains 420 mg calcium carbonate). Also drank 1-1.5 pints of milk daily.	Discharged after 3 weeks of haemodialysis with normal levels of serum calcium and phsophorus.	Abreo *et al.* (1993)
45-year old woman	3 weeks of progressive nausea, malaise and loss of appetite, weight loss and difficulty concentrating	Antiphospholipid syndrome	19.2 mg/dl	Volume replacement and forced diuresis	Antacid tablets (usually 4-6 500 mg tablets per day) for 1 year before admission. 2 weeks before admission, increased intake of calcium carbonate to 6 g or more per day and also took Tylenol Plus™ (500 mg acetaminophen plus 250 mg of	Patient became hypocalcaemic with an elevated PTH after treatment but survived	Beall and Scofield (1995)

					calcium carbonate).		
42-year old woman	2 weeks of epigastric pain, nausea, vomiting, and intermittant headaches	Peptic ulcer disease and bipolar disorder (lithium treated)	Fell to 10.2 mg/dl AFTER treatment	Intravenous saline and H_2 blockers.	Various antacids intermittently until 2 weeks before admission when she began drinking large amounts (>1 qt/day) of milk and ingesting 6-10 g/day of calcium carbonate (TUMS™)	Serum calcium and phosphorus levels returned to normal after treatment	Beall and Scofield (1995)
34-year old women	Admitted for evaluation of fever of unknown origin of 2 years duration. Glucocorticoids had been prescribed 6 months previously.		12.0 mg/dl on admission	Discontinuation of calcium carbonate and increased fluids by mouth	1-2 tablets of calcium carbonate (Tums™) as needed for indigestion and in the month before admission, increased intake to an average of 8-10 tablets daily.	2 years follow-up: no recurrence of hypercalcaemia	Beall and Scofield (1995)
64-year old man	Nausea, vomiting and weakness of 1 week's duration. Confused for 3 days.	Tonsil carcinoma 3 years previously, partial renal failure and alcoholism	14.0 mg/dl on admission	Intravenous saline and loop diuretics	Rennie® taken for 2 weeks before admission at dosage of 10 tablets/day (each tablet containing 680 mg calcium carbonate and 80 mg of magnesium carbonate). This gave a dose of 2.7g/day elemental calcium.	Discharged 14 days after admission and renal function remained stable without recurrence 2 years later	Vanpee *et al.* (2000)

31-year old pregnant women	3-day history of abdominal pain, nausea, vomiting and diarrhoea. Renal insufficiency and pancreatitis diagnosed.	Excessive emesis during previous and existing pregnancy	14.3 mg/dl on admission	Intravenous fluid administration	Large quantities of calcium carbonate, milk and cheese	Stillborn foetus delivered at 37 weeks but this was not linked to the mothers syndrome	Ullian and Linas (1988)
66-year old man	Nausea, anorexia and constipation for 3 weeks. Alkalosis and renal failure diagnosed.	History of ethanol abuse	17.8 mg/dl on admission	Calcium supplementation (for hypocalcaemia which developed after 1st week of admission) and rehydration	Large amounts of laxatives, Tums™ and Rolaids™ daily. Diet had consisted mainly of Ensure™ during the period.	3 weeks after admission, patient died due to upper GI bleed, aspiration pneumonia and sepsis with multi-organ failure	Fiorino (1997)
35-year old woman	Severe fatigue, nausea, constipation. Confusion for last 24 hours.	Anorexia-bulimia (chronic vomiting for 15 years)	16.0 mg/dl on admission	Intravenous infusion of normal saline and cessation of Rolaids and yoghurt consumption	Rolaids preparation containing calcium carbonate and 4 Rolaids tablets, each containing 500 mg calcium carbonate. Also, consumed at least 2 cups of yoghurt (each cup containing 452 mg calcium).	Patient had no further nausea or vomiting in hospital and agreed to cease Rolaids and yoghurt	Muldowney and Mazbar (1996)

					TOTAL = 1,700 mg calcium/daily.	consumption	
56-year old man	Severe indigestion associated with nausea, and occasionally, vomiting. Polyuria and nocturia and more recently, intractable pruritis	Peptic ulcer 10 years previously and not free of indigestion since. 3 years previously he had passed a renal calculus	3.4 mmol/l on admission	Very low calcium diet and intake of antacids stopped	1 litre milk and up to 10 tablets o Rennie (each tablet containing 680 mg calcium carbonate) per day	Within 1 month, serum calcium had returned to normal but renal function was still significantly abnormal	Kallmeyer and Funston (1983).
44-year old woman	2 days of generalised abdominal pain and vomiting	Renal calculi (removed some years previously)	4.0 mmol/l on admission	Acute pancreatitis was diagnosed and both kidneys showed signs of hydronephrosis.	For past 2/3 years she had been taking up to 70 Rennie/week (each tablets containing 680 mg calcium carbonate). Averaging about 4.5 g calcium carbonate/day.	Discharged on lansoprazole (20 mg/day) and on follow up was assymptomatic with normal electrolytes and normocalcaemia	George and Clark (1999)

Table 2. Chronic Human Toxicity.

Subject	*Symptoms and Duration*	*History*	*Serum Calcium*	*Treatment*	*Ingested*	*Outcome*	*Reference*
40-year old woman	Dysuria, urethral pain and micturition for 2 weeks before admission.	Excessive thirst for 8 years and spontaneous twitching of legs and itching of skin for 1 year before admission	11.4 mg/100 ml on admission	Stopped taking Rennies. Treated for urinary infection (tetracycline).	24 Rennie tablets daily for 11 years (each tablet containing 1.1 mg calcium phosphate. Total calcium carbonate intake = 16 g daily	Returned 1 month later, clinically dehydrated. 3 years later she seemed in good health.	Cameron and Spence (1967)
55-year old man	Nausea, malaise, weakness, dizziness, occasional vomiting and nocturia for 5 days	Chronic obstructive pulmonary disease, hypertension, hiatal hernia and renal calculi.	15.8 mg/dl	Oral calcium intake stopped, vigorous hydration with intravenous saline solution and diuresis with intravenous frusemide.	Large quantities of over-the-counter antacids for 30 years but recently increased his daily intake to 50 tablets (each tablet containing 420 mg calcium carbonate). Total calcium intake = 21g/day.	Renal function and calcium levels returned to normal by 3 months after discharge.	Newmark and Nugent (1993)
49-year old man	Unconscious having had 2 grand mal seizures in previous 2 hours.	2 episodes of renal colic and had mild bilateral renal	3.68 mmol/l	Antacids were stopped. Fluid loading undertaken.	For several years taken about 8 g elemental calcium/day in form of 600 ml of milk and 40 Titralac	8 months later the patient remained normocalcaemic	French *et al.* (1986)

	Subsequently gave history of 2 weeks of polyuria, polydipsia and malaise.	scarring			(calcium carbonate 168 mg Ca/tablet)	and milk gastritis was found the only cause for his indigestion	
43-year old man	Elevated serum creatinine (0.46 mmol/l) and serum calcium rose to 4.0 mmol/l over 6 weeks	Persistently elevated serum calcium level (2.65-2.76 mmol/l)	4.0 mmol/l	Saline infusions and frusemide	1 packet of Quick-eze, about 4.2 g of calcium, each day for many years as confectionary.	6 months follow-up = serum calcium had fallen and creatinine level remained normal	French *et al.* (1986)
62-year old woman	Admitted for excision of lipoma – over 9 days developed hypercalcaemia	Chronic pyelonephritis and analgesic abuse.	3.0 mmol/l on admission, rising to 4.0 mmol/l	Advised to stop taking antacids and to reduce her milk intake.	1 pint of milk/day plus 1 packet of Quick-eze tablets for several years. Estimated total daily calcium intake of 5 g.	2 months later she was normocalcaemic	French *et al.* (1986)
71-year old woman	3 weeks of vague abdominal pain, lethargy and malaise	Renal calculi and mild chronic renal failure	3.5 mmol/l	Advised to stop taking antacids. Primary hyperparathyroidism was diagnosed but exploration revealed no abnormailities.	At least 1 half packet of Quick-eze per day for many years and an unknown amount of Hardy's Indigestion Powder	1 week after operation, serum calcium was 2.10 mmol/l	French *et al.* (1986)

ANNEX 2

PRELIMINARY RISK ASSESSMENT

Annex 3 was a preliminary risk assessment the final version of which will be published in the Group's final report. Annex 3 is not therefore being released at this stage.