

## EXPERT GROUP ON VITAMINS AND MINERALS

### 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 2001. New information has been incorporated into the review to take account of some of the comments made by Members and to correct a number of minor inaccuracies. This additional information has not affected the outcome of the risk assessment.

- Annex 1 Intakes of calcium from food and supplements
- Annex 2 Tables referred to throughout text
- 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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## 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 ( $\text{CaCO}_3$ ), gypsum ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ), and fluorite ( $\text{CaF}_2$ ). 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, fortified foods, 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 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 100 g in the UK.
5. Some breakfast bars are fortified with 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. Some breakfast cereals are also fortified with calcium.

#### *Drinking water*

6. Calcium from drinking water is well absorbed and in hard water areas, tap water can form a significant proportion of calcium intake. Very hard water, such as that found in the Cotswolds, can contain 300 mg calcium per litre. Water with less than 100 mg/l calcium carbonate is considered soft and in some areas, such as Lancashire, the water supply contains little or no calcium. A study of calcium intake in adolescents living in South Northumberland, where the water supply

contains 300 mg/l, showed that 8% of their non-milk beverage derived calcium intake was from water. However, intake from water is generally hard to determine because water used in the manufacture of purchased drinks (i.e. canned drinks, bottled waters) may come from a source local to their manufacture or may be de-ionised (COMA, 1998).

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

#### *Fortified foods*

8. Calcium lactate-citrate complexes are used to fortify carbonated and non-carbonated waters, clear juices and low pH beverages stable at refrigeration, room and high temperatures with calcium (Sher *et al.*, 2001). Levels of 500-1000 mg calcium lactate have also been used in the fortification of beverages, this would provide calcium levels of 1200 ppm.

#### *Food supplements*

9. 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).
10. Supplementary calcium is available over the counter either alone or in combination with other minerals considered to be 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 (OTC, 2001).
11. 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.
12. 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 disintegration, and is therefore thought to be less bioavailable than calcium chelates. Calcium chelates (soluble forms of calcium) include calcium citrate, lactate, glucuronate and calcium citrate malate (CCM). 1 g of calcium glucuronate, for example, provides only 90 mg calcium, but there is some evidence that chelates of calcium are more bioavailable than calcium carbonate (Whiting *et al.*, 1997) (see paras 34-35).

#### *Licensed medicinal products for oral use*

13. 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 1.5 g 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.

14. Thirty-three calcium supplement products can only be sold in pharmacies. 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.
15. 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**

#### *Food*

16. 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).
17. Average calcium intakes in the U.S. were found to be falling. Females were more likely to be deficient in calcium than males throughout most of their life. The recommended intake of 1300 mg/day approximates to the 90<sup>th</sup> percentile for girls in the USA.

### **Recommended amounts**

18. 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).
19. 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 (RNI) of 525 mg/day is recommended.
20. The calcium intake required for bone formation and skeletal growth increases from the age of 1 to 10 years; 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 1000 mg/day for males, due to an increased requirement for calcium at a time of increased skeletal growth.
21. RNIs for adults are based on calcium loss/retention and are 700 mg/day.
22. No extra intake is considered necessary for pregnancy, although during lactation an increase of 550 mg/day over the RNI is recommended.

23. 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 there was insufficient evidence for a change in the existing UK DRVs for calcium. Additionally, it was noted that recent data suggest that the increment for lactation might not be necessary.
24. 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):

<i>Age</i>	<i>Calcium (mg/day)</i>
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**

25. 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.
26. 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.
27. 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**

28. 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 bioavailability.

29. 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 calcium absorption by phytic acid is modest compared to the inhibition by oxalates (Weaver, 1998).
30. Vitamin D deficiency decreases the bioavailability of calcium, as vitamin D induces a calcium binding protein that transports calcium across the intestinal wall.
31. 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.
32. 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.
33. 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).
34. A number of studies have compared the bioavailabilities of the two most common forms of calcium supplement, calcium carbonate and calcium citrate, with variable results. For example, Heller *et al.*, (2000) conducted a randomised cross-over study of bioavailability of a single dose of supplements containing calcium citrate and calcium carbonate and found that there was a 41% greater increase in urinary calcium and a 94% higher area under the curve for serum calcium with calcium citrate than with calcium carbonate; Nicar and Pak (1985) found that urinary calcium levels were 20-66% higher when 1000 mg calcium citrate was given to 14 subjects than when calcium carbonate was given; but Heaney *et al.*, (2001) found no significant difference between the two forms of calcium. A meta-analysis of such studies showed that calcium citrate was 22 to 27% more bioavailable than calcium carbonate, regardless of whether the supplement was taken with meals or on an empty stomach (Sakhae *et al.*, 1999).
35. The table below shows the solubilities and absorptions of calcium carbonate, calcium citrate and a highly soluble form of calcium supplement - calcium citrate malate (Patrick *et al.*, 1999):

<i>Supplement</i>	<i>Solubility (mM/l)</i>	<i>Fractional absorption (with food)</i>	<i>Fractional absorption (without food)</i>
Calcium carbonate	0.14	0.296 ± 0.054	0.235 ± 0.123
Calcium citrate	7.3	N/A	0.242 ± 0.049
Calcium citrate malate	80	0.363 ± 0.076	N/A

### Interactions

36. 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).
37. 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). Zinc, magnesium and fluoride may compete with calcium for common absorption sites (Spencer and Kramer, 1987).
38. The phosphate ion can form insoluble complexes with calcium, and therefore potentially decrease calcium bioavailability at high intakes. 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). This is likely to be because phosphorus decreases urinary calcium excretion (Spencer *et al.*, 1964).
39. Aluminium-containing antacids, when used for long periods of time, can cause calcium loss. This is due to inhibition of phosphorus absorption, caused by the aluminium complexing with the phosphorus, which increases calcium excretion (Spencer and Kramer, 1987).
40. Calcium binds to fatty acids to form insoluble complexes in the intestinal lumen (Allen, 1982). However, 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).

41. Caffeine has been shown to increase urinary and faecal excretion of calcium. The effect on calcium balance was shown to be -0.006 g/day per 50% increase in caffeine intake, in a study of 170 premenopausal women (age 36 to 45 years) (Heaney and Recker, 1982).
42. Calcium excretion is linked to sodium excretion in the proximal tubule and so increased sodium intake, and therefore excretion, increases calcium excretion. The relationship between sodium and calcium excretion at low calcium intakes is weaker because raised parathyroid hormone (PTH) levels increase calcium resorption in the distal renal tubule (Institute of Medicine, 1997).
43. Calcium is postulated to interact with lead, either by reducing absorption by precipitating or binding lead in the gut, by competing with lead for transport sites or by altering the affinity of target tissues for lead, and calcium supplementation has been recommended to reduce lead absorption in children (reviewed by Ballew and Bowman, 2001). Serum lead levels rise in women during pregnancy as a result of bone resorption. Studies of calcium intake in pregnant women and serum lead concentrations have shown an association between calcium intakes of >2000 mg/day and decreased serum lead concentrations (Johnson, 2001).

### **Absorption**

44. 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).
45. 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<sub>3</sub>). 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<sub>3</sub>, has an important role in maintaining calcium homeostasis by mediating calcium absorption into intestine. There may also be individual genetic influences on calcium absorption as a consequence of Vitamin D receptor polymorphism (Wood and Fleet, 1998).
46. 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 bioavailability; 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).

47. 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).
48. 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.
49. 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**

50. 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 (Allen, 1998).
51. The concentration of ionised calcium in the plasma remains remarkably constant (1.2 mmol/l) (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.
52. Distribution of the free ionised calcium is dependent upon interactions between three major hormones (Allen, 1998). Firstly, 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<sub>3</sub> to the active hormonal form, 1,25-dihydroxy-vitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>). 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 ( $1,25(\text{OH})_2\text{D}_3$ ) is formed during calcium deficiency. This results in 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.

53. Large amounts of calcium are transferred from the mother to the fetus and neonate, during pregnancy and lactation. Maximum calcium accretion during fetal growth occurs during the third trimester. The total calcium accretion rate of the fetus 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

54. In adults of a good nutritional state, excretion tends to equal intestinal absorption. Absorbed calcium is excreted mainly in the urine, and to a lesser extent, sweat. Faecal calcium excretion consists of unabsorbed dietary calcium (Ensminger *et al.*, 1995) with the remaining component coming 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).
55. 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

56. Nordin (1986) summarised the functions of calcium in the body. In the vertebrate skeleton, calcium provides rigidity in the form of calcium phosphate ( $\text{Ca}_{10}(\text{OH})_2(\text{PO}_4)_6$ , 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.
57. 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).

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

### Deficiency

59. A negative calcium balance occurs 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).
60. 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.
61. 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 1.0%. 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.
62. Osteoporosis occurs when bone resorption exceeds formation. Significantly lower bone mineral densities have been observed in women on calcium deficient diets (~300 mg/day, due to deprivation) than in 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.
63. 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).

64. 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);
65. Laskey and Pretice (1997) studied bone mineral density in 12 women during 3 months of lactation. A significant decrease in bone mineral density was shown during lactation but these changes were reversed following the end of lactation.

### Overview of reported beneficial effects

#### *Cancer*

66. Calcium supplementation has been associated with decreased colon cell proliferation rates and incidence of colon cancer or recurrence of colon cancer in high risk groups. Studies using tritiated thymidine uptake to measure the rate of colon cell proliferation in biopsies from subjects taking calcium supplements have shown that doses of approximately 1250 - 2000 mg Ca/day, have reduced colonic and rectal epithelial cell proliferation in subjects at risk from developing colon cancer (i.e. persons with a history of adenomatous polyps or who were first-degree relatives of people who had had colorectal cancer) (Lipkin *et al.*, 1985, Rozen *et al.*, 1989, Wargovich *et al.*, 1992). However, not all studies have shown this effect (Gregoire *et al.*, 1989, Alberts *et al.*, 1997, Weisberger *et al.*, 1996). A randomised, double-blind study of treatment with placebo, 1000 mg/day calcium or 2000 mg/day calcium and effects on cell proliferation and patterns of cell proliferation, as shown by rectal biopsies at 1, 2 and 6 months, showed no significant effect of calcium supplementation on the rate of cell proliferation, but the distribution of proliferating cells appeared to be normalised in the calcium supplementation groups (Bostick *et al.*, 1995).
67. 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 of 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.
68. Bonithon-Kopp *et al.*, (2000) conducted a prospective, cohort study to investigate the effect of supplementation with 2000 mg elemental calcium per day on the recurrence of colorectal adenoma in patients with a history of colorectal adenomas. At the end of a three year supplementation period, participants underwent colonoscopy. Adenoma recurrence (at least one adenoma discovered) was found in 28 of the 176 patients taking calcium, compared to 36 out of 178 patients in the placebo group. The odds ratio for adenoma recurrence, adjusted for

age, sex, adenoma history, number and location of adenomas was 0.66 (95% confidence interval, 0.38-1.17) for supplementation with calcium. The results showed a small but not significant decrease in the risk of adenoma recurrence for participants taking 2000 mg/day calcium. Several other studies have supported this finding (Baron *et al.*, 1999, Martinez *et al.*, 1996, Whelan *et al.*, 1999). However, a 14-17 year prospective cohort study of 8006 men of Japanese ancestry showed no association between dietary calcium intake (as assessed by 24 hour dietary recall) and risk of colon cancer (Heilbrun *et al.*, 1986).

69. Epidemiological evidence in humans also suggests that high calcium intakes could have a protective effect associated with a reduced risk of colorectal cancer. Weaver (2000).
70. Data from animal studies are conflicting, with some providing evidence for the beneficial effects of calcium in reducing the incidence of experimentally-induced 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).
71. 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). 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).
72. A study of differential expression of the calcium-binding protein, S100A6, identified four isoforms of this protein, and showed a significant increase in isoform I and a significant decrease in isoform IV in malignant tissue (Stulík *et al.*, 2000). The significance of this is not yet clear, though S100A6 is thought to have some involvement in the regulation of cell growth and proliferation.
73. 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.
74. A study by Xue and coworkers (1999) demonstrated that increased dietary calcium (equivalent to approximately 3000 mg/2000 kcal daily human diet) and vitamin D suppressed hyperproliferation of the epithelial cells in the pancreas, prostate and mammary gland in nutritionally stressed mice. The animals had been fed a nutritionally stressed 'Western style' diet containing reduced levels of calcium and vitamin D, with increased fat content.

*Hypertension*

75. 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).

*Kidney stones*

76. 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.
77. 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.
78. 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.

**Toxicity***Human toxicity**Acute/subchronic toxicity*

79. 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. It is characterised by hypercalcemia, alkalosis and renal impairment. The condition can be acute, intermediate (Cope's syndrome) or chronic (Burnett's syndrome) depending on the duration and magnitude of calcium and alkali intake. 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.

80. Because the syndrome is rare, its description has been confined to case reports. Case-reports of acute and subchronic toxicity are summarised in Table 1.

#### *Chronic Toxicity*

81. Although MAS has usually been 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.
82. Case 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 patient's 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.
83. Case 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.
84. Both of the above 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.

85. Case studies describing chronic toxicity in humans are summarised in Table 2. Calcification of the lungs and breasts has been seen 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.
86. Hypercalcemia has 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, equivalent to 2.88 mmol/l. The normal range for serum calcium concentration is 2.2-2.6 mol/l. However, this effect was reversible after discontinuation of calcium carbonate therapy.
87. 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  $1\alpha$ -hydroxycholecalciferol (2-3  $\mu$ g/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 suggested that the most probable explanation for the hypertension seen was 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*

88. 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.

*Reproductive Toxicity*

89. 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 quadrant on the region of the gallbladder. The patient underwent cholecystectomy and incidental appendectomy 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 noted this was the first report of pure calcium carbonate cholelithiasis in association with prenatal supplementation with the calcium salt.

*Carcinogenicity*

90. No data have been identified in addition to the suggested beneficial effects of calcium discussed earlier in this paper (see paragraphs 66-74)

*Genotoxicity*

91. An increase in the number of micronucleated erythrocytes has been associated with a higher intake of calcium supplements in splenectomised subjects (Smith *et al.*, 1990). Micronucleated erythrocytes indicate genotoxic damage and are not selectively removed in individuals lacking splenic activity.
92. Similarly, in a study on 77 splenectomised subjects, consumption of calcium supplements by older women was statistically associated with higher frequencies of micronucleated cells (MacGregor, 1990).

**Human supplementation studies**

93. It has been suggested the addition 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) and no other adverse effects were reported. However, it should be noted that the study excluded women with a history, or high risk for developing renal disease.
94. The meta-analysis displayed a trend in favour of calcium supplementation for a reduction in pre-term delivery, caesarean delivery, and intrauterine or perinatal death (Bucher *et al.*, 1996a, 1996b). However, calcium supplementation of 2000 mg/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 calcium deficient women.

95. A randomised, double-blind placebo-controlled clinical trial in pregnant adolescents demonstrated that calcium supplementation had beneficial effects (Villar and Repke, 1990). Subjects were 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.
96. 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.
97. Numerous clinical trials have been reported in which patients with a history of adenomatous colon polyps have been supplemented with calcium (see also paragraphs 66-68). These mainly consist of double-blind placebo-controlled studies, with patients receiving between 250 mg and 2.0 g of elemental calcium per day (usually in the form of calcium carbonate), over periods ranging from 4 weeks to 4 years. These have been summarised in Table 3. Few adverse effects in individuals participating in such trials are reported as a consequence of ingestion of calcium at these levels. However, in many reports it is unclear whether the patients were asked about side effects.
98. No signs of toxicity (or treatment related medical symptoms) were 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 (equivalent to 1200 mg elemental calcium per day) and were examined after 1 and 4 year periods.
99. In a study by Hofstad and colleagues (1998) in which patients received 1.6 g/day elemental calcium or placebo for 18 months, five patients in the treatment group experienced constipation compared to the one of the controls. Diarrhoea was reported in 5 calcium and 7 placebo subjects and bloating (8 patients) was equally distributed between groups.
100. Calcium tablets were well tolerated by participants in an intervention study reported by Kleiberger *et al.*, (1993). No mention of side effects was made when individuals were specifically asked about them. Individuals received 1.5 g calcium/day (as calcium carbonate) for twelve weeks.
101. In the study by Bonithon-Kopp *et al.*, (2000), patients received 2 g calcium/day (as calcium carbonate) or placebo for 3 years. The total number of patients reporting side effects were 26/176, 19/198 and 12/178 in the calcium, fibre and control groups, respectively. Major side effects (severe abdominal pain or diarrhoea) were also reported to be higher in the calcium group (6/176) compared to the control (3/178) or fibre (3/198) groups. Compliance was also poorer in the calcium group.

### **Vulnerable groups**

102. 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).
103. 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).
104. 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.
105. 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 Variations*

106. No data identified.

#### **Adverse Drug Reactions**

107. 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*

108. Mithofer *et al.*, (1995) investigated the effects of induction of acute hypercalcaemia in the rat. Rats were given bolus infusions of CaCl<sub>2</sub> (200 mg/kg) and effects were compared with saline-treated control rats. Serum indices (Ca<sup>2+</sup> amylase, trypsinogen activation peptide (TAP)) and pancreatic wet/dry weight ratio and pancreatic tissue histology were undertaken. For dose-response analysis, CaCl<sub>2</sub> 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 hypercalcaemia induced a dose-dependent morphological alterations characteristic of acute pancreatitis, acute hyperamylasaemia and early ectopic trypsinogen activation.

109. 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 groups of ten female and male rats, which received doses of 10, 11, 12, 13, 14, and 15 g of Biocal™/kg body weight. The oral LD<sub>50</sub> value for female rats was 13.5 g/kg and for males it was 13.0 g/kg. The authors noted that these values were higher than those for calcium gluconate (LD<sub>50</sub> = 10 g/kg) and suggested that Biocal™ could be considered as a promissory calcium compound to be used for dietary supplementation or food fortification.

#### *Sub-Chronic Toxicity*

110. 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: 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 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.
111. 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 3<sup>rd</sup> and 4<sup>th</sup> 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.

112. 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.
113. 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*

114. No data identified.

#### *Carcinogenicity*

115. No data identified.

#### *Reproductive toxicity*

116. A study in mice investigated the effect of excessive maternal dietary calcium on fetal 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. Fetuses 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 (Lieb Gott and Srebro low, 1989).

117. The effect of moderately increased dietary calcium on fetal development was investigated in pregnant rats (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. Fetal bodyweights and lengths remained similar between treatment and control groups. There were no significant increases in external, visceral or skeletal variations of the fetuses, when compared to the control animals.
118. The effect of maternal 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 birth weights, 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**

119. 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**

120. 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 100 g 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 100 kcal. 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**

121. 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**

122. Shrimpton (1997) concluded that supplementary daily intakes of 1500 mg/day were safe. The Council for Responsible Nutrition, a UK trade association recommended an upper safe level of 1500 mg for long term supplementation and an upper safe level for short term supplementation of 1900 mg (CRN, 1999).

### **Summary**

123. 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.
124. Calcium supplements are available over the counter, either alone or in combination with other minerals.
125. 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.
126. 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.
127. 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.

128. 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.
129. 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.
130. Some human supplementation studies have shown that addition of 2000 mg calcium to the diet of pregnant women may increase the 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.
131. 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 hyperamylasaemia. 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.REVISED JAN 2002

## 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<sup>1,2,3,4,5</sup>. 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 (i.e. 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 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.

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<sup>1</sup> Food and nutrient intakes of British infants. 1986

<sup>2</sup> National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3

<sup>3</sup> National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8

<sup>4</sup> Dietary and Nutritional survey of British adults. 1986/7

<sup>5</sup> National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

Intakes from food and supplements (including prescribed calcium) at the 97.5<sup>th</sup> percentile 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 235 mg and not more than 390 mg per 100 g 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.

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 were 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 1250 mg per day.

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

Age/sex	Absolute Calcium intake (mg/day) <sup>6</sup>							
	Food Only				Food and Supplements			
	2.5% ile	Mean	Median	97.5%ile	2.5% ile	Mean	Median	97.5%ile
<b>Infants (1986)</b> 6-12mths/M&F	334	783	767	1433	*	*	*	*
<b>Pre-school children</b> 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				
<b>Young people (1997/8)</b> 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				
<b>Adults (1986/7)</b> 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
<b>Older people free-living in the community (1994/5)</b> 65-74yrs/M	354	852	848	1450	354(354)	853(853)	848(848)	1450(1450)
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)
<b>Older people living in institutions (1994/5)</b> 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

<sup>6</sup> Data in brackets = intakes from food and supplements, excluding prescribed supplements

**Table 2: Bodyweight adjusted Calcium intake**

Age/sex	Bodyweight adjusted Calcium intake (mg/kg bwt /day) <sup>7</sup>		
	<i>intakes from food and supplements</i> <sup>8</sup>		
	Mean	Median	97.5%ile
<b>Infants (1986)<sup>9</sup></b> 6-12mths/M&F	82.2	79.3	150.1
<b>Pre-school children (1992/3)</b> 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
<b>Young people (1997/8)</b> 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
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
<b>Adults (1986/7)</b> 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
<b>Older people free-living in the community (1994/5)</b> 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
<b>Older people living in institutions (1994/5)</b> 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

<sup>7</sup> Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.

<sup>8</sup> Data includes intakes from prescribed calcium supplements.

<sup>9</sup> Intakes for infants aged 6-12 months are from food only.

**Table 3<sup>10</sup>: 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	
<b>Total intake from food</b>	<b>768</b>	<b>100</b>	
<i>Intake from dietary supplements</i>	<i>0</i>	<i>0</i>	
<b>Total intake from food and supplements</b>	<b>768</b>	<b>100</b>	

<sup>10</sup> NDNS: young people aged 4-18 years. 1997/8. 15-18 year group

**Table 4: Calcium intake from supplements<sup>11</sup>**

<i>Age/sex</i>	<b>Consumers of Calcium Supplements</b>		<b>Calcium intake from supplements (consumers only) (mg/day)</b>		
	<i>Number</i>	<i>%</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
<b><i>Infants (1986)</i></b> 6-12 mths/M&F	*	*	*	*	*
<b><i>Pre-school children (1992/3)</i></b> 1½-4½ yrs/M&F	9	<1	85	70	5 - 324
<b><i>Young people (1997/8)</i></b> 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
<b><i>Adults (1986/7)</i></b> 16-64 yrs/M	21	1	133	60	3 - 822
16-64 yrs/F	36	3	99	66	1 - 500
<b><i>Older people free-living in the community (1994/5)</i></b> 65 and over/M	9	1	87	60	0 - 210
65 and over/F	36	6	311	246	0 - 1250
<b><i>Older people living in institutions (1994/5)</i></b> 65 and over/M	4	2	88	41	25 - 145
65 and over/F	6	3	214	92	56 - 500

\* Data unavailable

<sup>11</sup> Data includes intakes from prescribed calcium supplements

## ANNEX 2 TO EVM/01/12.REVISED JAN2002

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

<i>Subject</i>	<i>Symptoms and Duration</i>	<i>History</i>	<i>Serum Calcium</i>	<i>Treatment</i>	<i>Ingested</i>	<i>Outcome</i>	<i>Reference</i>
60-year old male 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 <i>et al.</i> , (1993)
60-year old male	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 <i>et al</i> (1993)
53-year old male	Weakness, sleep problems, nausea, vomiting, left-sided back pain and depression	Type 2 diabetes mellitus, diabetic neuropathy, coronary artery disease, previous myocardial infarction, hypothyroidism	13.7 mg/dl on admission	Intravenous saline and loop diuretics. Thyroid medications were readjusted.	Drank 3-4 gallons of whole milk each week and ingesting 15 calcium carbonate tablets (Roloids™) daily, each tablet containing 1000 mg.	On discharge, serum calcium and phosphorus levels were normal.	Abreo <i>et al</i> (1993)
45-year old female	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 calcium carbonate).	Patient became hypocalcaemic with an elevated PTH after treatment but survived	Beall and Scofield (1995)
42-year old female	2 weeks of epigastric pain, nausea, vomiting, and intermittent headaches	Peptic ulcer disease and bipolar disorder (lithium treated)	Fell to 10.2 mg/dl AFTER treatment	Intravenous saline and H <sub>2</sub> 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 female	Admitted for evaluation of fever of unknown origin of 2 years		12.0 mg/dl on admission	Discontinuation of calcium carbonate and increased fluids by	1-2 tablets of calcium carbonate (Tums™) as needed for indigestion and in the month before admission,	2 years follow-up: no recurrence of hypercalcaemia	Beall and Scofield (1995)

	duration. Glucocorticoids had been prescribed 6 months previously.			mouth	increased intake to an average of 8-10 tablets daily.		
47-year old male	Nausea, vomiting, diarrhoea, severe epigastric pain	Peptic ulcer disease	15.4 mg/dl	Diuresis for hypercalcemia	12-15 TUMS™ tablets daily (each contains 200 mg Ca, total ingestion of elemental calcium 2.4-3.0 g/day)	Asymptomatic after 1 year	Brandwein & Sigman (1994)
35-year old female	Chronic constipation, anorexia	Six week history of nausea and vomiting	16 mg/dl	Rehydration and low calcium diet	6.5 g calcium/day (in form of 4 pints milk 12 Rennie®, Complan plus large amount of absorbable alkali)	Serum calcium normal in 9 days	Bullimore & Miloszewski (1987)
54-year old male	Back pain, increased thirst, polyuria, nausea, vomiting and pruritis for three weeks	Impaired renal function	14.2 mg/dl	Rehydration and cessation of antacids	5 g/day of elemental calcium (4.5 g in form of proprietary antacid, plus milk)	Acute symptoms improved on cessation of antacids, serum calcium normal (9.6 mg/dl) after three months	Campbell et al (1994)
50-year old male	Fatigue, polyuria and polydipsia for six months prior to admission	Duodenal ulcer disease	11.8-12.8 mg/dl	Rehydration and low calcium diet	2 quarts of milk plus numerous TUMS™ tablets (200 g elemental calcium per tablet)	Serum calcium normal after 7 months (9.6 mg/dl), hypercalcemia recurred after 2 years with increase milk consumption	Carroll & Clark (1983)
60-year old male	Fatigue and weakness for six months prior to admission	Reflux oesophagitis	up to 16 mg/dl	Low calcium diet	2 quarts of milk plus 36 TUMS™ tablets (200 mg elemental calcium per tablet giving intake of approximately 7.2 g) per day	Serum calcium normal (9.0 mg/dl) after five months	Carroll & Clark (1983)
66-year old male	Nausea, anorexia and constipation for 3 weeks. Alkalosis and renal failure diagnosed.	History of ethanol abuse	17.8 mg/dl on admission	Rehydration and then calcium supplementation (for hypocalcaemia which developed after 1 <sup>st</sup> week of admission)	Large amounts of laxatives, Tums™ and Roloids™ 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 (not	Fiorino (1997)

						related to MAS)	
65-year old male	Increasing fatigability (sleeping 20h/day) muscle weakness, constipation, epigastric pain	Vagotomy and pyloroplasty for duodenal ulcer	14.1 mg/dl	Intravenous saline	30/40 calcium carbonate containing antacids daily (Ca content not stated) plus ½-1 gallon milk	Serum calcium normal (9.6 mg/dl) after one month	Hart <i>et al</i> (1982)
56-year old male	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	13.6 mg/dl on admission	Very low calcium diet and intake of antacids stopped	1 litre milk and up to 10 tablets of 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)
32-year old woman	Nausea, vomiting, headaches, constipation, myalgias and puritis	Cardiac transplant	19.9 mg/dl	Rehydration and forced diuresis	>10 g elemental calcium per day, in form of Titalac® and milk consumption	Symptoms resolved over five days, serum calcium normal 1 year later	Kapsner <i>et al</i> (1986)
24-year old male	Polyuria, nocturia, fatigue and dizziness	Cardiac transplant	14.7 mg/dl	Intravenous fluids and Frusemide	Approximately 6.8 g/day, in form of Titalac® 1.5l milk and 1.5l yoghurt daily	Serum calcium returned to normal	Kapsner <i>et al</i> (1986)
31-year old female (pregnant)	3-day history of disorientation, ataxia, nausea, vomiting	Gastritis. Presented at 36 weeks of gestation	22.5 mg/dl	Intravenous infusion of normal saline, haemodialysis and Frusemide	5 glasses of milk plus 30 antacid tablets (containing 500mg CaCO <sub>3</sub> ) daily for two weeks	2 days after admission serum calcium 10 mg/dl, discharged after 9 days	Kleinman <i>et al</i> (1991)
70-year old female	Anorexia, nausea, lethargy and altered level of consciousness	Severe osteoporosis	15.9 mg/dl	Rehydration with saline and 5% glucose plus withdrawal from calcium supplements	CaCO <sub>3</sub> supplements, 1250 mg three times per day	No follow up reported	Lin <i>et al</i> (1996)
35-year old female	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 Roloids and yoghurt consumption	Roloids preparation containing calcium carbonate and 4 Roloids 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 Roloids and yoghurt consumption	Muldowney and Mazbar (1996)

					TOTAL = 1,700 mg calcium/daily.		
31-year old female (pregnant)	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)
32-year old male	Epigastric pain, nausea, vomiting, weakness and headache.	Epigastric pain	14 mg/dl	Low calcium diet, intravenous saline and Frusemide	1 gallon milk/day	Renal function normal after 3 weeks, repeat episode 1 year later	Schuman and Jones (1985)
43-year old male	Epigastric pain and rising serum creatinine conc.	Epigastric pain	13 mg/dl	Low calcium diet plus Frusemide	2 quarts of milk plus 15 CaCO <sub>3</sub> tablets daily	Creatinine clearance had risen to normal value in six months, no change in clinical status at 3 year follow up	Schuman and Jones (1985)
64-year old male	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 <i>et al</i> (2000)

**Table 2. Chronic Human Toxicity, multi- and increasing doses (Case-Reports).**

<i>Subject</i>	<i>Symptoms and Duration</i>	<i>History</i>	<i>Serum Calcium</i>	<i>Treatment</i>	<i>Ingested</i>	<i>Outcome</i>	<i>Reference</i>
54-year old female	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 tablet contains 500 mg calcium carbonate and 1 roll contains 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 <i>et al.</i> (1993)
65-year old male	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 (Titalac™) 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 phosphorus.	Abreo <i>et al.</i> (1993)
40-year old female	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)
77-year old male	Anorexia, lethargy, weakness and confusion for two weeks prior to admission	Dyspepsia	18 mg/dl	Intravenous infusion of normal saline, frusemide, diuretics and low calcium diet	3-10 TUMS™ tablets daily for five years (200 mg elemental calcium per tablet giving an intake of up to 2 g/day)	Serum calcium normal (9.5 mg/dl) after four months	Carroll & Clark (1983)
52-year old female	Nausea, vomiting and weight loss over six months	Epigastric pain	12 mg/dl	CaCO <sub>3</sub> therapy stopped. Non-absorbable antacids prescribed	10 (or more) CaCO <sub>3</sub> tablets per day for eight years (200 mg elemental calcium per tablet giving an intake of 2 g Ca or more/day)	Serum calcium 10 mg/dl three months and two years later	Dorsch (1996)
49-year old male	Unconscious having had 2 grand mal seizures in previous 2 hours. Subsequently gave history	2 episodes of renal colic and had mild bilateral renal scarring	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 Titalac (calcium carbonate 168 mg	8 months later the patient remained normocalcaemic and milk gastritis was	French <i>et al.</i> (1986)

	of 2 weeks of polyuria, polydipsia and malaise.				Ca/tablet)	found the only cause for his indigestion	
43-year old male	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)	16 mg/dl	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 <i>et al.</i> (1986)
62-year old female	Admitted for excision of lipoma – over 9 days developed hypercalcaemia	Chronic pyelonephritis and analgesic abuse.	12 mg/dl on admission, rising to 16 mg/dl	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 <i>et al.</i> (1986)
71-year old female	3 weeks of vague abdominal pain, lethargy and malaise	Renal calculi and mild chronic renal failure	14 mg/dl	Advised to stop taking antacids. Primary hyperparathyroidism was diagnosed but exploration revealed no abnormalities.	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 <i>et al.</i> (1986)
44-year old female	2 days of generalised abdominal pain and vomiting	Renal calculi (removed some years previously)	16 mg/dl	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 asymptomatic with normal electrolytes and normocalcaemia	George and Clark (1999)
47-year old male	Dizziness and weakness, 'heartburn'	Hypertension, hypothyroidism, urinary tract infections and kidney stones	13.6 mg/dl	Intravenous saline plus Frusemide and orally administered phosphates	15-20 TUMS™ tablets daily for two years (200 mg elemental calcium per tablet giving an intake of up to 4 g/day)	Discharged after five days, serum calcium normal after 8 weeks	Gora <i>et al.</i> (1989)
67-year old female	One week of anorexia, irritability, lethargy, nausea and vomiting, plus dizziness and confusion for three days	Mild hypertension, mild epigastric pain	10 mg/dl	Intravenous saline plus Frusemide	5 TUMS™ tablets daily for many years, increasing to >10/day three weeks prior to admission and then >15/day 3 g elemental calcium) three days prior to admission	Serum calcium 8.9 mg/dl at discharge. All clinical parameters normal four months after discharge.	Hakim <i>et al.</i> (1979)
55-year old male	Nausea, malaise, weakness, dizziness, occasional vomiting and	Chronic obstructive pulmonary disease, hypertension, hiatus	15.8 mg/dl	Oral calcium intake stopped, vigorous hydration with intravenous saline solution	Large quantities of over-the-counter antacids for 30 years but recently increased his daily intake to 50	Renal function and calcium levels returned to normal 3	Newmark and Nugent (1993)

	nocturia for 5 days	hernia and renal calculi.		and diuresis with intravenous frusemide.	tablets (each tablet containing 420 mg calcium carbonate). Total calcium intake = 21g/day.	months after discharge.	
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**Table 3. Studies of calcium supplementation in patients with polyps.**

<b>Subjects</b>	<b>Design</b>	<b>Dose (as elemental calcium)</b>	<b>Duration of treatment</b>	<b>Findings</b>	<b>Comment</b>	<b>Reference</b>
Adults with previous bowel adenoma aged 50-75 y, 173 in treatment group, 160 in placebo group	Randomised, double blind	placebo or 1.2 g/day	6-9 months	No adverse effects noted.	Results published in different papers.	Baron <i>et al.</i> , 1995
100 adults with previous colonic polyps aged 50-75 y, in 4 treatment groups: low or high calcium +low or high fibre	Randomised, double blind	250 mg or 1.5 g/day	3 or 9 months	No adverse effects noted.	250 mg dose considered to be placebo. Results published in different papers.	Alberts <i>et al.</i> , 1996 Alberts <i>et al.</i> , 1997
Adults with previous polyps, 29-30/ treatment group	Randomised, single blind	Control or additional 1.2 g/day Ca in dairy products.	1 year	No adverse effects noted.		Holt <i>et al.</i> , 1998
193 adults with previous polyps aged 30-74 y, 63-66/treatment group	Randomised, double blind	Placebo, 1 or 2 g/day	4-6 months	No adverse effects noted. No effect on total or HDL cholesterol or blood pressure	Results published in different papers.	Bostick <i>et al.</i> , 1995 Bostick <i>et al.</i> , 1998
930 adults with previous polyps. 466-464/treatment group	Randomised, double blind	Placebo or 1.2 g/day	4 years	Questionnaires sent every 6 months. No treatment related adverse effects apparent.		Baron <i>et al.</i> , 1999

10 Adult asymptomatic members of families with increased colon cancer	Unblinded, no controls	1.25 g/day	2-3 months	No adverse effects noted.		Lipkin <i>et al.</i> , 1985
9 Adults with previous polyps, 26 first degree relatives	Unblinded, no controls	1.25-1.5 g/day	3 months	No adverse effects noted.		Rozen <i>et al.</i> , 1989
Adults with previous polyps (14), colorectal cancer (17) or controls (12).	Double-blind crossover	Placebo or 1.25 g/day	2 month for each treatment period	No adverse effects noted.		Barsoum <i>et al.</i> , 1992
19 Adults with previous polyps	Unblinded, no controls	1.4 g/day	12 weeks	No adverse effects noted.		Welberg <i>et al.</i> , 1993
6 Adults with history of polyps	Unblinded, no controls	1.5 g/day	13 weeks	Patients monitored for GI and other effects. No toxic/adverse effects observed		Wargovich <i>et al.</i> , 1992
17 Adults (39-69y) with previous polyps	Unblinded, no controls	1.5 g/day	12 weeks	Patients asked, no adverse effects reported.		Kleibeuker <i>et al.</i> , 1993
116 adults with previous polyps aged 50-75 y, 63-66/treatment group	Randomised, double blind	Placebo or 1.6 g/day + antioxidant vitamins	18 months	Patients asked : Preliminary report: 4 drop outs due to side effects (abdominal discomfort and unacceptable stool frequency) Final report: 5 patients	Results published in different papers.	Hofstad <i>et al.</i> , 1992 Hofstad <i>et al.</i> , 1998 Hofstad <i>et al.</i> , 1998

				with constipation (1 control). Other symptoms (bloating, diarrhoea) equally between groups.	
20 adults with history of polyps	Placebo controlled single blind crossover	Placebo or 2 g/day	4 weeks	Patients monitored for GI and other effects. No toxic/adverse effects observed	Wargovich <i>et al.</i> , 1996
6 Adults (39-69y) with previous polyps	Unblinded, no controls	2 g/day	30 days	Patients monitored for GI and other effects. No toxic/adverse effects observed	Wargovich <i>et al.</i> , 1992
48 adults with previous polyps aged 30-75 y. 15 /treatment group analysed	Randomised, double blind	Placebo or 2 g/day	9 months	No adverse effects noted	Weisberger <i>et al.</i> , 1996
665 adults with previous polyps aged 35-75 y g 176-198 /treatment group	Randomised, double blind	Placebo, fibre or 2 g Ca/day	3 years	Side effects assessed every 6 months by interview. Major side effects (severe abdominal pain or diarrhoea) higher in calcium group, 6 vs 3 and 3.	Bonithon-Kopp <i>et al.</i> , 2000

## ANNEX 3 TO EVM/01/12.REVISED JAN2002

**Calcium: Summary table of selected nutrition related information and existing guidance on intakes**

Unit of usage	mg calcium/d		mg /100 kcal	mg /100g
	male	female		
<i>UK DRV<sup>12</sup> for adults (19-50+)</i>				
LRNI	400	400		
EAR	525	525		
RNI	700	700		
Mean adult UK dietary intake <i>From food (all sources)</i>				
Adults (16-64 years) <sup>13</sup>	937 (940)	726 (730)		
Adults 65 years and over <sup>14</sup>				
Free living	836 (837)	690 (697)		
Institutionalised	(953) 954	861 (865)		
EU labelling RDA <sup>15</sup>	800 mg			
Supplemental doses				

<sup>12</sup> 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.

<sup>13</sup> Dietary and nutritional survey of British adults. 1986/7

<sup>14</sup> National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

<sup>15</sup> The Food Labelling Regulations 1996

<p><b>Regulations</b>          Infant formula<sup>16</sup></p> <p>Follow-on formula</p> <p>Cereal-based baby foods<sup>17</sup></p> <p>Weight reduction<sup>18</sup>          Whole daily diet replacement          Meal replacement</p> <p>Bread and flour regulations<sup>19</sup></p>		<p>50 – minimum</p> <p>400</p> <p>Not less than 20 mg/100 kcal</p> <p>700 210</p>	<p>Calcium carbonate          Not less than 235 mg,          not more than 390 mg</p>
<p><i>Maximum total safe daily intake</i>          COMA 1991<sup>1</sup></p> <p>The Food and Nutrition Board, USA<sup>20</sup></p> <p>EHPM 1997<sup>21</sup></p>	<p>Panel unconvinced that high intakes of 2g/d were of value in the prevention or treatment of osteoporosis.</p> <p>Upper tolerable intake level of 2000mg/day for most adults and 2500mg/d for other population groups</p> <p>Upper safe level 1500mg          Long term consumption          Upper limit &gt;2500 mg          Short term consumption</p>		

<sup>16</sup> The Infant Formula and Follow-on Formula Regulations 1995

<sup>17</sup> The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations 1997.

<sup>18</sup> The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997.

<sup>19</sup> The Bread and Flour Regulations 1998

<sup>20</sup> The Food and Nutrition Board of the USA National Institutes of Medicine. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. Washington: National Academy Press, 1997.

<sup>21</sup> Vitamins and Minerals A Scientific Evaluation of the Range of Safe Intakes. European Federation of Health Product Manufacturers 1997.