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Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium

(expressed on 4 April 2003)

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FOREWORD

This opinion is one in the series of opinions of the Scientific Committee on Food (SCF) on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Calcium (Ca) belongs to group II of the third period of the Periodic Table of Elements. It has an atomic weight of 40.08; its atomic number is 20, its valency is 2. It is the fifth most abundant element in the human body. The calcium content of the human body is 25 to 30 g at birth (0.8% of the body weight) and between 900 and 1300 g in adult men (up to 1.7% of body weight) (Weaver *et al.*, 1996). Over 99% of the total calcium of the body is located in the bones, where it accounts for 39% of the total body bone mineral content (Weaver, 2001), and in the teeth, mostly as hydroxyapatite. Bone mineral provides structure and strength to the body and, very important, a reservoir of calcium that helps to maintain a constant concentration of blood calcium. Less than 1% of total body calcium is found in soft tissues (~7 g) and body fluids (~1 g). Calcium in the extracellular fluid and the blood are kept constant at 2.5 mmol/L (10 mg/dL) (between 2.25 and 2.75 mmol/L) via cell surface calcium-sensing receptors in parathyroid, kidney, intestine, lung, brain, skin, bone marrow, osteoblasts and other organs. Calcium is present in blood in three different forms: as free Ca^{2+} ions, bound to protein (about 45%), and complexed to citrate, phosphate, sulphate and carbonate (about 10%). Ionised calcium is kept within narrow limits (Worth *et al.*, 1981) by the action of three hormones, parathyroid hormone, 1,25-dihydroxycholecalciferol, and calcitonin. Extracellular calcium serves as a source for the skeleton and participates in blood clotting and intercellular adhesion. Intracellular calcium varies widely between tissues and is predominantly bound to intracellular membrane structures of the nucleus, mitochondria, endoplasmatic reticulum or contained in special storage vesicles. Free Ca^{2+} is only 0.1 µmol/L in the cytosol, which is 10,000 times lower than in the extracellular fluid (1 mmol/L). Intracellular calcium rises in response to stimuli interacting with the cell surface receptor. The increase of intracellular calcium comes from influx of extracellular calcium or from release of intracellular calcium stores. This activates specific responses like hormone or neurotransmitter release, muscle contraction, cellular differentiation and many others.

2. NUTRITIONAL BACKGROUND

2.1 Food sources

Calcium must be ingested with the diet in sufficient amounts to allow for calcium deposition during bone growth and modeling and to compensate for obligatory intestinal, faecal and dermal losses during the life-time.

Foods vary widely in calcium content. The best sources are milk (120 mg/100 g) and milk products (up to 1100 mg/100 g), from which about 32% is absorbable (Weaver, 2001). In European diets about 45 to 70% of the dietary calcium intake is provided by dairy products (Guéguen and Pointillart, 2000; IUNA, 2001). Some plants are good sources of well-absorbable calcium, e.g. brassica, almonds, dried apricots. However, some vegetables contain considerable amounts of calcium, which is poorly absorbed because of a high content in oxalate (rhubarb, spinach) and which forms sparingly soluble calcium oxalate. Drinking water and mineral waters (>150 mg calcium/L) can also be good sources of absorbable calcium.

In the European Union the following calcium compounds are permitted as source of calcium in foods for particular nutritional uses and in food supplements: carbonate, chloride, citrates, gluconate, glycerophosphate, lactate, orthophosphates, hydroxide and oxide.

Within populations and population groups dietary calcium intakes show a great variability related to varying dietary habits. It appears from nutrition surveys that calcium intake is below actual recommended intakes in high percentages of the population.

2.2 Dietary intake

Dietary calcium intakes from various European countries are given in Table 1.

Table 1. Mean and 97.5 percentile calcium intakes (mg/day) from food and supplements

Country	Type of survey	n	Method	Supplements*	Mean	97.5%
Austria[a]	Individual	4972	7-day weighed 3-day weighed 24h-recall	Not defined	834	1678
Germany[b]	Individual (M) Individual (F)	2006	7-day record	-	753 683	1731 1421
Ireland[c]	Individual (M) Individual (F)	1339	7-day record	+	949 742	1657 1340
Netherlands[d]	Individual (M, F)	5958	2-day record	-	944	1970
UK[e]	Individual (M) Individual (F)	1087 1110	7-day weighed	+	940 730	1607 1317

* + data included supplements; - data excluded supplements.

[a] Koenig and Elmadfa, 2000.

[b] Heseker *et al.*, 1994.

[c] IUNA, 2001.

[d] Hulshoff and Kruizinga, 1999.

[e] Gregory *et al.*, 1990.

Men consume in absolute amounts about 10% more calcium than women. In Germany the highest calcium intake was observed in young men between 15 to 24 years: 2100 mg/day without supplements (Heseker *et al.*, 1994). A longitudinal observational study (*DONALD study*), which started in 1985 and follows children from the age of 3 months to 18 years (sample size 400 to 500 subjects) showed that the mean calcium intake values in these healthy children were below the recommended intake values beyond the age of 3 years. Less than 10% of adolescents (13 to 18 years) consumed more than the recommended calcium intake (Alexy and Kersting, 1999). In this group calcium from fortified food amounted to maximal 5% of the total daily intake between 2 and 14 years of age (Sichert-Hellert *et al.*, 2001).

Total calcium intake of men and women who consumed calcium supplements more than once per week was significantly higher (men: 1275-1394; women: 1146-1221 mg/day) than in those never taking calcium supplements (men: 1190-1242; women: 1081-1117 mg/day) (Mensink and Ströbel, 1999).

2.3 Absorption and regulation of absorption

Calcium must be in a soluble form or bound to soluble organic molecules to be absorbable. However, undissociated low-molecular-weight salts of calcium can also be absorbed independent of vitamin D by paracellular routes or pinocytosis. Depending on solubility, chemical form and on other factors of the food between 10 to 40% of dietary calcium is absorbed. The bulk of unabsorbed calcium is complexed to bile acids, free fatty acids, oxalic acid and excreted with the faeces (Heaney, 2002a). Lactose in the food, vitamin D, inulin, fructooligosaccharides and some casein phosphopeptides increase absorption, the latter by preventing precipitation of calcium by phosphates. Most calcium salts used in fortified foods or dietary supplements are absorbed to a similar extent as calcium from dairy foods. The absorbability of calcium citrate malate is higher (Weaver, 2001). Phytates, and especially oxalate inhibit calcium absorption. Fibre consumed without phytates does not have a negative influence. A combined high intake of predominantly insoluble fibre and phytate in the form of wheat bran over four weeks had no adverse effects on bone turnover markers in 19 healthy young women. The observed decrease in urinary calcium excretion sufficiently compensated for the reduced net absorption of dietary calcium without changing calcium retention (Zitterman *et al.*, 1999). Both the protein and the sodium content of diets have a negative effect on calcium retention by increasing urinary calcium losses. The effect of higher protein intakes on increased urinary calcium losses appears only to result in negative effects on bone status if the calcium intake is inadequate (Heaney, 2002a).

There are two kinds of calcium transport in the intestine:

a) Active transport in the duodenum and upper jejunum is saturable and regulated by dietary intake and the needs of the body. Active transport involves three stages, namely entry across the brush border of the enterocyte via calcium channels and membrane-binding transport proteins, diffusion across the cytoplasm attached to calcium binding protein calbindin-D9K, and secretion across the basolateral membrane into the extracellular fluid against an electrochemical gradient either in exchange for sodium or via a calcium pump, a Ca-ATPase activated by calbindin, calcium and calmodulin. Active transport is negatively correlated with dietary calcium intake. This control is mediated via parathyroid hormone and $1,25(OH)_2D$. The renal production of $1,25(OH)_2D$ is stimulated by increased parathyroid hormone secretion in response to a decrease in Ca^{2+} in blood and it stimulates the expression of the gene encoding calbindin, thereby enhancing calcium absorption in the intestine. Both

parathyroid hormone and 1,25$(OH)_2$D also increase renal reabsorption of calcium and bone resorption.

b) Passive diffusion down an electrochemical gradient together with water, sodium and glucose via intercellular junctions or spaces occurs in all parts of the gut and is predominantly dependent on the calcium concentration in the gut lumen. This process is independent of vitamin D and age (Bronner, 1992). Passive diffusion requires that calcium is kept in solution, which can be enhanced by casein phosphopeptides (Mykkänen *et al.*, 1980), by chelating with some amino acids (lysine and arginine) (Bronner, 1987), and by high doses of lactose (50 g/day) (Pansu *et al.*, 1979). Increases in the osmolarity of the luminal contents of the intestine stimulate passive diffusion. Except in premature infants passive calcium absorption accounts for not more than 8 to 23% of the total calcium absorbed (McCormick, 2002).

Fractional calcium absorption, is highest (about 60%) in breastfed infants (Abrams *et al.*, 1996). Net calcium absorption, defined as intake minus faecal excretion in percent of intake, is lower in infants fed cows' milk formula, decreases in young childhood, shows a rise in puberty, decreases to 15 to 20% in young adults (Matkovic, 1991; Miller *et al.*, 1988; Peacock, 1991) and declines gradually thereafter (Heaney *et al.*, 1989). Calcium absorption is increased in pregnant and lactating women compared to non-pregnant women (Moser-Veillon *et al.*, 2001).

Calcium absorption is under genetic control. The FF genotype for the Fok 1 polymorphism, a C $\rightarrow$ T transition in the vitamin D receptor translation initiation site, was related to increased calcium absorption in 72 children 7 to 12 years of age and it was associated with greater bone mineral density (Ames *et al.*, 1999a), but these findings were not confirmed in another study with 99 girls 16.9 ± 1.2 years old (Lorentzon *et al.*, 2001).

2.4 Calcium losses

The majority of absorbed calcium is stored in the skeleton. Excess absorbed calcium is excreted in urine, faeces, and sweat. Calcium balance is positive in healthy children, adolescents and young adults before bone growth and modeling cease, provided that they have an adequate calcium intake.

Renal calcium excretion is the result of glomerular filtration (about 8 to 10 g calcium per day in adults) and tubular reabsorption (normal over 98% of the filtered load), which is primarily passive in the proximal tubules and for 20% active in the distal part of the convoluted tubules and connecting tubules. Active transport is under the control of parathyroid hormone, calcitonin and 1,25$(OH)_2$D (Hoenderop *et al.*, 2002). Average 24-hour excretion of calcium is 40 mg in young children, 80 mg in prepubertal children and reaches about 150-200 mg in adults. It is not strongly related to dietary calcium intake (Charles *et al.*, 1991; Matkovic, 1991) in healthy persons. Calcium excretion is increased in hyperparathyroidism and decreased in untreated osteomalacia.

Urinary calcium excretion is increased by dietary sodium intake (30 to 40 mg of calcium excreted per each two grams of dietary sodium) (Matkovic *et al.*, 1995), by caffeine (Massey and Whiting, 1993) and in chronic metabolic acidosis (Bushinsky, 2001). Calcium excretion rises with excess dietary protein intake (by 0.5 mg for each gram of dietary protein, when intake was above 47 g/day) (Walker and Linkswiler, 1972; Whiting *et al.*, 1998). This effect can be offset by simultaneous phosphorus intake (Guéguen and Pointillart, 2000).

Increased calcium excretion is also observed in idiopathic (hypocalcaemic) hypercalciuria, a genetic disorder of heterogenous pathogenesis (absorptive, renal or dietary) observed in 2.2 to 6.4% of children and adults (Kruse *et al.*, 1984; Moore *et al.*, 1978) and which is the most frequent risk factor for nephrolithiasis. Idiopathic hypercalciuria could be the result of a defective renal epithelial Ca^{2+}-channel leading to decreased active renal reabsorption of calcium or to an increased intestinal activity of the epithelial Ca^{2+}-channel with augmented intestinal calcium absorption (Hoenderop *et al.*, 2002). Hypercalciuric stone formers are more sensitive to dietary sodium chloride than individuals without stones with respect to calcium excretion (Massey and Whiting, 1995) and than normocalciuric stone formers (Burtis *et al.*, 1994). Sodium restriction and/or protein restriction with a normal calcium intake reduces or normalises calcium excretion in hypercalciuric stone formers, whereas calcium restriction does not (Borghi *et al.*, 2002).

Calcium losses via the skin are between 4 and 96 mg/day in normal individuals, calculated from combined calcium balance and kinetic studies with ^{47}Ca in 11 subjects (Charles *et al.*, 1991). The authors consider the minimal obligatory loss to be 3 to 40 mg calcium per day. The amount rises with increasing serum calcium levels.

Calcium is also secreted throughout the gastrointestinal tract, where about 85% is available for reabsorption with the same absorption efficiency as dietary calcium. Faecal secretory calcium loss has been estimated to be 80 to 224 mg/day in normal individuals.

2.5 Calcium requirement and dietary reference values

Adequate dietary calcium intakes are determined by information from balance studies, from fractional estimates of required intakes to compensate for urinary, faecal and dermal calcium losses and more recently from the intakes necessary to achieve "maximal calcium retention" for bone mineral deposition, while taking into account calcium absorption, and also from studies on bone mineral density and bone mineral content development during life (Heaney, 2002b). From the analysis of pooled calcium balances performed in 519 individuals between birth and 30 years of age intakes of calcium were identified above which an increase in calcium intake did not further increase calcium retention (Matkovic and Heaney, 1992).

Different scientific bodies have applied different models to different data in order to derive dietary reference intake values. The population reference intakes defined by the Committee in 1992 are based on a factorial approach (compensation of obligatory calcium losses and accounting for absorption efficiency in adults and addition of desirable calcium retention corrected for absorption for children and adolescents) without considering measurements of bone mineral accretion under different calcium intakes (Kanis, 1991; SCF, 1993). The PRI (in mg calcium per day) is 400 for infants in the second half of the first year and for children up to age 3 years, 450 for children between 4 and 6 years, 550 for children between 7 and 10 years, 1000 and 800 for male and female adolescents between 11 and 17 years and 700 in adults and pregnant women. For lactating women it is 1200 mg per day. More recent reports include the attainment of peak bone mass during childhood, adolescence and young adulthood in their calculations (IOM, 1997; D-A-CH, 2000; AFSSA, 2001). The adequate intakes (AI) (IOM, 1997) and recommended daily intakes (RDA) (D-A-CH, 2000; AFSSA, 2001) thus derived are generally higher than the PRI. They are between 500 and 800 mg calcium per day for children up to the age of 7 years, 1200 to 1300 mg per day for older children and adolescents and 900 to 1200 mg calcium per day for adults. Pregnant and lactating women below the age of 18 years should receive between 1200 and 1300 mg calcium per day.

Some authors have suggested higher recommend intake values for calcium because of observed beneficial effects of calcium intakes of 1200 mg to 2000 mg per day on the risk of colon cancer, kidney stones, obesity and hypertension (Fujita and Palmieri, 2000; Heaney, 2002b). But there is no consensus on this.

2.6 Calcium deficiency

Calcium deficiency can result from low dietary intake, low absorption or excessive losses. A decrease in ionised calcium in the extracellular fluid stimulates the secretion of parathyroid hormone to mobilise calcium from bone and maintain the pre-set serum calcium level. Parathyroid hormone also increases the intracellular calcium concentration in many types of cells - cardiomyocytes, blood cells, adipocytes, hepatocytes and pancreatic endocrine cells as well as in osteoblasts and renal tubular cells. An increase in intracellular calcium sets off a large number of reactions involving the permeability of the plasma membrane, signaling pathways, including activation and deactivation of enzymes, cyclic-nucleotide formation and break-down, cytoskeletal rearrangement, and gene transcription (Saimi and Kung, 2002; Carafoli, 2002). The pathophysiologic changes and disorders resulting from this have been named *calcium paradox disease* (Fujita and Palmieri, 2000). They include hypertension and arteriosclerosis, Alzheimer's disease, muscular dystrophy, diabetes mellitus and malignancies. The role of parathyroid hormone secretion and its effects in the relevant target cells has been demonstrated in *in-vitro* models, animal experiments and/or epidemiological studies (Fujita and Palmieri, 2000).

3. HAZARD IDENTIFICATION

Calcium levels in the body are under control of genetic and hormonal factors. Therefore an excessive accumulation of calcium in blood or tissue solely through excessive calcium consumption should not occur in the absence of diseases such as bone cancer, hyperthyroidism, and hyperparathyroidism or in the absence of excessive vitamin D intake. Adverse effects which have been reported due to high calcium intakes include the so-called milk-alkali syndrome, the formation of kidney stones in persons with a propensity for nephrolithiasis, hypercalciuria and for hyperabsorption of calcium, and interference with the absorption of other minerals (Whiting and Wood, 1997).

3.1 Adverse effects in animals

3.1.1 Acute toxicity

The LD_{50} for calcium gluconate in rats is 10 g/kg body weight, corresponding to 930 mg calcium/kg (Sarabia *et al.*, 1999).

3.1.2 Short- and medium-term studies and reproductive studies

Greger *et al.* (1987) tested the bioavailability of different calcium sources (milk, dibasic calcium phosphate, oyster shell, calcium carbonate, calcium lactate, calcium amino acid chelate and dolomite) in rats fed diets with similar calcium contents (approximately 0.5%). Apparent calcium absorption was comparable with all calcium compounds. Dibasic calcium phosphate caused increased kidney size and more than 20-fold higher calcium content in kidneys.

Ten dogs (weight 14 to 25 kg) supplemented for two weeks with 100 mg calcium gluconate and 250 µg vitamin D/kg/day developed severe hypercalcaemia and hypomagnesaemia, polyuria, hyperexcretion of calcium, sodium and magnesium, hypotension, a decrease in the heart stroke volume and increased total peripheral arterial resistance (Zawada *et al.*, 1986).

Growing pigs fed *ad libitum* with diets which differed in the calcium-phosphorus ratio (1:1, 2:1, 3:1) and calcium content (0.3% up to 2.7%) but without extra vitamin K showed coagulation disorders. All pigs in the 2.7%-calcium group died between three and four weeks from internal haemorrhage (Hall *et al.*, 1985).

Pregnant rats fed diets differing in calcium content (0.01%; 0.6%; 1%) and calcium:phosphorus ratios (1.3; 0.02; 2.4) produced comparable litter numbers. However pregnant rats on the high-calcium diet decreased their food consumption excessively near term and lost weight and the weight of the foetuses were reduced. The calcium balance in the high-calcium rats was markedly negative in the days just before term. Their foetuses had a lower body calcium content than those of the calcium-free and normal-calcium diet groups (Lai *et al.*, 1984).

Rats fed diets with 1.5, 2 and 2.5 times higher than normal (0.5%) calcium contents (as calcium carbonate), starting after mating and continued during twenty days of gestation showed no dose related changes in maternal clinical findings, average numbers of implantation, foetal resorption and viable foetuses, neither were there adverse effects on foetal length and weight nor signs of foetotoxicity or teratogenicity. However, there were dose-related increases of the femoral calcium content as well as of the phosphorus, magnesium and zinc content of the liver in non-pregnant control rats on the same diets. There were dose-related decreases of the iron and copper contents in kidneys of non-pregnant animals and of iron in the liver of pregnant rats. Foetuses showed dose-related decreases in the whole body content of phosphorus, magnesium, iron and copper (Shackelford *et al.*, 1993 and 1994).

Richards and Greig (1952) tested the effect of four different calcium levels (0.3%, 0.5%, 0.7% and 1.1%) in four different diets on reproductive performance in mice and on survival and organ pathology in litters. All diets with a calcium (carbonate) content of 1.1% resulted in decreased number and total weight of litters and increased both the number and proportion of litter deaths. Young mice born to mothers on high-calcium diets showed pale speckled livers, enlarged hearts and small thymus when killed at age 21 days. Increased heart weights were negatively correlated with haemoglobin levels. Addition of iron to high-calcium diets diminished heart enlargement.

While studying the effects of diets with low (0.2%) and high (4%) calcium contents in rats over 31 weeks on lead toxicity (lead supplied in drinking water) it was observed that the high calcium diet resulted in higher blood pressure, in kidney and bladder stones, slower growth and death in half of the animals. In a similar experiment, feeding rats low (0.1%), normal (0.5%) and high (2.5%) calcium diets over one year, caused dose-related decreases of the iron content of the femur and testis, magnesium in plasma and femur, the zinc and calcium contents of the femur and the calcium content of the kidneys (Bogden *et al.*, 1992).

High intakes of dietary calcium (1.5% in 50 days pregnant ewes have caused disturbed bone formation from cartilage (osteochondrosis) and an increase in thyroid C cells (calcitonin producing) in the foetuses compared to the foetuses of ewes fed normal feeds (0.59% calcium) (Corbellini *et al.*, 1991).

3.2 Adverse effects in humans

3.2.1 Intervention studies

Intervention studies with supplemental calcium, predominantly in the form of calcium salts but also with milk products or with elemental calcium from chicken egg-shell powder, which have been performed in children, pregnant and lactating women and elderly men and women, have exposed subjects to total calcium intakes of up to 3000 mg/day for up to 4 years. Annex I lists some relevant studies.

Children between 6 and 14 years of age received up to 1900 mg calcium/day for one to 3 years to study the effect on bone status (Johnston *et al.*, 1992; Lloyd *et al.*, 1993; Chan *et al.*, 1995; Bonjour *et al.*, 1997 and 2001). The recommended dietary calcium intake for that age is 550 to 1200 mg/day.

Elderly men and women between 50 and 85 years of age have received calcium in amounts between 1300 and 3000 mg/day for 6 months to four years to study the effect of supplemental calcium on bone metabolism and bone loss (Kochersberger *et al.*, 1991; Reid *et al.*, 1993; Elders *et al.*, 1994; Riggs *et al.*, 1996; Heaney *et al.*, 1999; Peacock *et al.*, 2000; Dawson-Hughes and Harris, 2002; Schaafsma *et al.*, 2002). The recommended dietary calcium intake for that age range is 1200 mg/day.

Pregnant women have received calcium in amounts between 2000 and 3000 mg/day, starting between 13 and 23 weeks of gestation, to study the effects on hypertensive disorders of pregnancy, preeclampsia, preterm delivery, adverse perinatal outcomes, and foetal bone mineralisation (Villar and Repke, 1990; Belizán *et al.*, 1991; Bucher *et al.*, 1996; Levine *et al.*, 1997; Koo *et al.*, 1999). The recommended intake for pregnant women is between 700 and 1300 mg/day.

A calcium intake of 2000 mg/day was tested over 4 years in patients aged more than 60 years with colorectal adenomas to determine if there was an influence of calcium on the recurrence rate of adenomas (Baron *et al.*, 1999).

Calcium in amounts between 1300 and 2300 mg/day was given to healthy men and women and to lactating women with durations between 12 weeks and one year to study the effects on iron, zinc and magnesium status (Sokoll and Dawson-Hughes, 1992; Yan *et al.*, 1996; Minihane and Fairweather-Tait, 1998; Kalkwarf and Harrast, 1998). Recommended dietary calcium intakes for this population range between 800 and 1300 mg/day.

Adverse effects of calcium supplementation observed in these studies are given in the relevant sections below.

3.2.2 Hypercalcaemia and renal insufficiency (milk-alkali syndrome)

The milk-alkali syndrome is named after the adverse effects observed in consequence of the combined therapeutic application of calcium-rich milk and absorbable antacids (mostly sodium bicarbonate or calcium carbonate) for peptic ulcers. It results eventually in metabolic alkalosis and hypercalcemia, probably as a result of increased calcium retention by alkali, and leads to the usual consequences of hypercalcemia, i.e. loss of appetite, weight loss, nausea, constipation, polyuria, polydipsia, hyposthenuria, dehydration, renal failure, nephrocalcinosis and nephrolithiasis, apathy, confusion, lethargy and coma in variable combination and

severity. Onset can be insidious or acute within days or weeks after starting very high calcium and alkali intakes. It can be reversible or fatal (Orwoll, 1982; Abreo *et al.*, 1993).

The original therapeutic regimen (Sippy, 1915) included calcium intakes of 20 g/day from both milk and for example calcium carbonate. With changes in the therapy of peptic ulcers the frequency of the milk-alkali syndrome has declined. Whiting and Wood (1997) identified 29 reported cases of clinically adverse effects of high calcium intakes or combined high intakes of calcium and alkali in a review of the literature between 1980 and 1994. The youngest patient in their list was 29 years old with most cases over 50 years old. One third of the cases consumed both alkali and calcium (between 2.0 and 16.5 g/day of supplementary calcium) and symptomatology appeared to be precipitated by an increase of their calcium intake while consuming antacids, sometimes for many years. One third, however, developed symptoms of milk-alkali syndrome as a result of high calcium carbonate intakes alone (between 2 to 10.8 g additional calcium per day from several months to 30 years). About 40% of the listed cases were patients with associated promoting factors, such as the use of thiazide diuretics (which decrease renal calcium excretion), pre-existing renal failure, dehydration, or alkalosis. In these cases supplemental calcium intake was between 2 and 16 g/day. One study estimated that 12% of patients hospitalised in one hospital because of hypercalcemia were the result of excessive calcium carbonate consumption (Beall and Scofield, 1995). Annex II contains some details of the case reports evaluated by Whiting and Wood (1997) with additional cases added reported both before 1980 and after 1994. This compilation of 82 patients reported in the literature between 1965 and 2001, ranging in age from 24 to 95 years, shows that the milk-alkali syndrome occurs predominantly in patients with complaints of the stomach, oesophagus or duodenum (55 of 82), who ingested high amounts of milk (43 of 82) corresponding to more than 0.9 to 6.8 g calcium per day, and/or calcium supplements (76 of 82) containing between 1 and 23 g of calcium/day, or ingesting only calcium supplements (37 of 82). Thirty five high-milk consumers took calcium supplements. Eight of the high-milk consumers did not take calcium supplements, but consumed sodium bicarbonate regularly. Eleven calcium supplement-only users also took sodium bicarbonate. In 33 cases the use of “antacids” is reported, both absorbable or unabsorbable or unspecified. The reported range of total calcium intake was between 0.4 and 23 g/day. In many cases, however, calcium intake was inadequately documented.

All calcium supplements consisted of calcium carbonate The duration of a high calcium intake is reported to be between 3 days and 30 years. One case with a latency of 3 days only for the development of the milk-alkali syndrome was a 40 years old female patient who received 4.8 g calcium as carbonate for peptic ulcer prevention after a cardiac transplant, in addition to prednisone. She developed hypercalcaemia and transient renal failure (Kapsner *et al.*, 1986). The same authors report that 65 of 297 cardiac surgery patients on the same peptic ulcer prevention regime developed hypercalcaemia, accompanied by renal failure in 37 of these 65 patients within one week to 6 months. The therapeutic regimen in these cases consisted of calcium carbonate (1.3 to 4.6 g calcium/day) plus prednisone.

McMillan and Freeman (1965) randomised 40 patients with gastric or duodenal ulcers to receive either 11.2 g calcium as carbonate or a non-absorbable antacid in addition to milk every 2 hours, corresponding to 1.8 g per day calcium over 7 days. They observed a significant rise in serum calcium in the group on calcium carbonate only, from a mean of 2.45 mmol/L to a mean of 2.8 mmol/L on day 3, with 5 patients reaching values above 3 mmol/L. In the same group serum creatinine rose significantly, as did serum phosphorus and carbon dioxide content. No significant changes of these parameters were observed in the group treated with non-absorbable antacid.

A dose of 3.2 g of calcium per day given as the carbonate over 6 days under clinical conditions provoked hypercalcaemia (3 mmol/L) and hypercalciuria, a rise in serum phosphorus and 24 hours later in creatinine and a decrease in the glomerular filtration rate in a patient with recurrent severe hypercalcaemia due to 15 years of consumption of calcium carbonate in high amounts (Smit and Bijvoet, 1986).

Lin *et al.* (1996) describe the development of the milk-alkali syndrome in a 70 year old woman after 4 weeks of osteoporosis treatment with 3.75 g calcium (as carbonate) and 0.5 µg calcitriol per day. Of interest is also the report of Wu *et al.* (1996) on two men, who had chewed betel nut covered by a calcium carbonate containing paste (estimated amount of calcium 2.5 and 3.5 g) over 30 years and who demonstrated hypercalcaemia and persistent renal insufficiency.

The two cases in whom milk and calcium carbonate were ingested for some weeks for relief of pregnancy-associated gastric discomfort and emesis and one case of bulimia/anorexia with recent use of milk and calcium carbonate can be classified as cases of milk-alkali syndrome provoked by dehydration and alkalosis (Ullian and Linas, 1988; Kleinman *et al.*, 1991; Muldowney and Mazbar, 1996). The malformations of the stillborn foetus which was born after 37 weeks of pregnancy to a mother with milk-alkali syndrome in the 23rd week of gestation were not attributed to this disorder because the foetus revealed no signs of tissue calcification (Ullian and Linas, 1988). In many case reports, however, it is not clear if the symptoms described signify the manifestation of the milk-alkali-syndrome or are part of preexisting and predisposing disorders.

Milk-alkali syndrome was not observed in the course of intervention studies which involved between 11 and 2295 individuals (children, pregnant and pre- or perimenopausal women, elderly people) and lasted between 12 weeks to 4 years. The studies tested the effects of calcium supplements (500 to 2000 mg/day, given as milk or milk extracts, citrate, carbonate, citrate malate, gluconate or egg-shell powder) on bone metabolism, on hypertensive pregnancy complications, on recurrence of colorectal adenomas and on iron, zinc and magnesium status. However, in the *Calcium for Pre-eclampsia Trial*, in the course of which 2295 women pregnant for 13 to 21 weeks were supplemented daily with 2000 mg calcium as the carbonate, women with a known risk for nephrolithiasis and with elevated levels of serum calcium and creatinine were excluded (Levine *et al.*, 1997).

Elders *et al.* (1994) observed a mean increase of serum creatinine of 1.2 µmol/L in 64 perimenopausal women taking 2000 mg calcium (as lactogluconate and carbonate) as daily supplement in addition to a calcium intake of 1000 mg from the diet over 2 years. One case of hypercalcaemia was reported among 119 postmenopausal women supplemented during 4 years with 1600 mg calcium (citrate) per day (Riggs *et al.*, 1996). The constipation which has occasionally been reported in studies on calcium supplementation (750 to 1200 mg calcium/ day during 4 years and 6 months, respectively, can be a consequence of hypercalcaemia, however this was not looked for (Peacock *et al.*, 2000; Kochersberger *et al.*, 1991).

3.2.3 Kidney stones

Kidney stones affect between 8 to 15% of the population in Europe (Pak, 1998). About 80% of kidney stones are composed of calcium oxalate or a mixture of calcium phosphate and calcium oxalate. Stones form only in urine that is supersaturated. Hypercalciuria (more than 4 mg/kg body weight/day) is the most common abnormality in patients with calcium containing

stones. Thirty to 50% of patients with kidney stones and hypercalciuria have idiopathic hypercalciuria that is not secondary to causes like primary hyperparathyroidism, hyperthyroidism, malignancy, renal tubular acidosis, vitamin D intoxication, immobilisation and Paget's disease. The hypercalciuria may be either renal (increased calcium/creatinine quotient in the urine at all times) or hyperabsorptive (increased calcium/creatinine quotient after calcium load) (Pak *et al.*, 1975).

Dietary calcium is not the determining factor in kidney stone formation (Goldfarb, 1994) but higher intakes of oxalate, protein and vegetable fibre may play a role (Massey *et al.*, 1993). In a population-based study, which involved 1309 women aged 20 to 92 years, no relationship between renal stone formation (n=44) and high-oxalate food, vitamin C, protein, fibre, or alcohol consumption could be demonstrated. Neither was there a positive association between the amount of dietary calcium and the fluoride content of drinking water and kidney stones. Women with stones ingested on average 250 mg less calcium per day than women without stones (840 versus 1070 mg), but calcium supplements appeared to have no protective effect on kidney stone formation (Sowers *et al.*, 1998).

In two prospective observational studies with 45,619 men (aged between 40 and 75 years) followed over 5 years (*The Health Professionals Follow-up Study*) and 91,731 women (aged between 34 and 59 years) followed over 12 years (*Nurses' Health Study*), without kidney stones at the beginning of the observation period, it appeared that total calcium intakes above 1050 mg/day in men and above 1100 mg/day in women decreased the risk of kidney stone formation by approximately 35%. The mean calcium intake of stone formers was significantly lower than in those remaining free of stones, after adjustment for age, body mass index, intake of animal protein, alcohol, sodium, sucrose, fluid, and supplemental calcium (Curhan *et al.*, 1993 and 1997). The relative risk for stone formation was significantly lower in women in the highest quintile of dietary calcium intake (median 1303 mg) compared with women in the lowest quintile. Dietary vitamin D intake was 5.5 in the lowest and 9 µg/day in the highest quintile. Similar findings were reported for men. In the women's study the intake of calcium supplements in daily amounts between 1 and 100 mg increased the risk for stone formation by 20% compared to women who did not take supplemental calcium. There was no further increase in the relative risk for stone formation by higher intakes of supplemental calcium (Curhan *et al.*, 1997). In both studies a reduction of the risk of stone formation was observed with increasing intakes of dairy products (rich in phosphorus) and an increase of the risk with increasing sodium and sucrose intakes.

From the studies of Sowers *et al.* (1998) and Curhan *et al.* (1997) it can be concluded that a calcium intake in the range of the most recent dietary recommendations does not promote kidney stone formation on a population basis.

Dietary calcium reduces dietary oxalate absorption, whereas calcium restriction increases intestinal oxalate absorption and renal oxalate excretion. In a recent randomised trial over 5 years with 120 men with recurrent calcium oxalate stones and idiopathic hypercalciuria a diet normal in calcium (1200 mg/day) [30 mmol] and low in sodium [50 mmol] and normal in protein (15% of energy intake, 60% animal protein) reduced the risk of stone recurrence by 50% and decreased oxalate excretion more than a calcium restricted diet (400 mg [10 mmol]/day) (Borghi *et al.*, 2002).

Both calcium and sodium intake were positively associated with hypercalciuria in patients with kidney stones and a regression equation was developed to predict the effect of dietary calcium on urinary excretion of both. From this equation the calcium intake that would be

associated with hypercalciuria can be calculated to be 2243 mg/day for men and 1422 mg/day for women, assuming a sodium excretion of 100 mmol/day and defining hypercalciuria as >300 mg calcium/day for men and >250 mg/day for women (Burtis *et al.*, 1994)

One short report has been published on the occurrence of pure calcium carbonate gallstones in a two year old girl whose mother had taken calcium carbonate and vitamin D in unknown quantities during the last four months of pregnancy because of leg cramps (Powell, 1985).

Although intervention studies with supplemental calcium have not been performed to study the risk for kidney stone formation, no increased incidence can be deduced from those studies listed in Annex I with approximately 5000 subjects, who received between 500 and 2000 mg calcium as supplement in addition to 300 to 1800 mg of calcium from the diet (total intakes between 1300 and 3000 mg calcium/day during three months to four years. Women with an increased risk for nephrolithiasis were excluded from the big *Calcium for Pre-eclampsia trial* (Levine *et al.*, 1997). In a group of 124 women on calcium supplements (total daily intake 1400 mg/day) one patient with kidney stones was reported (Peacock *et al.*, 2000). Riggs *et al.* (1996) observed hypercalciuria (>350 mg/day) in 44 of 119 postmenopausal women taking calcium supplements (~1600 mg) for four years, and in seven of 117 women without supplements. One woman in the supplemented group developed mild hypercalcaemia. Three of 50 infants who received a calcium-rich formula from age 3 months onwards (1700 to 1560 mg calcium per day) developed hypercalciuria (Dalton *et al.*, 1997).

3.2.4 Interactions between calcium and dietary minerals

High calcium diets and supplements can affect the bioavailability of other essential minerals, iron, zinc, magnesium and phosphorus.

3.2.4.1 Iron

Calcium inhibits the absorption of both iron salts and heme-iron (Hallberg *et al.*, 1991) in a dose-dependent manner. A dose of 300 mg of calcium chloride added to a meal inhibited iron absorption maximally. An inhibitory effect was also seen with a variety of calcium sources both from supplements and food (Whiting and Wood, 1997). The absorption of non-heme iron (15 mg/day) was 16% with a low-calcium diet (<320 mg/day), but it decreased to <5% with the addition of 400 mg calcium (carbonate) to three daily meals (Minihane and Fairweather-Tait, 1998).

Long-term intervention studies on the effect of calcium supplementation on iron status failed to show reductions in indicators of iron status, unless the habitual calcium intake was very low. Calcium supplements had no effect on iron status in infants fed iron-fortified formula, in lactating women, adolescent girls and adult men and women (Lynch, 2000).

Three month old infants (n=103) who received either a calcium/phosphorus enriched formula (calcium intake from formula after 4 months 1700 mg, after 9 months 1560 mg/day) or a standard formula (calcium intake from formula 400 mg and 350 mg/day, respectively) showed no differences in serum ferritin, total iron-binding capacity, erythrocyte protoporphyrin or haematocrit during the remainder of the first year of life. Both formulae provided the same high amount of iron (12.8 mg/L) (Dalton *et al.*, 1997).

Eleven children between 3 and 5 years of age receiving for 5 weeks each a low-calcium (502 mg/day) and high-calcium (1180 mg/day) diet providing 9 and 9.7 mg iron per day were

tested for iron incorporation into red blood cells and calcium absorption and retention with ^{44}C and ^{58}Fe given orally with meals and ^{46}Ca given intravenously. There was no significant difference of iron incorporation into red blood cells 14 days after dosing with the low-calcium (6.9%) compared to the high calcium diet (7.9% of administered dose), while calcium absorption (36.2%, 181 mg/day versus 23.7%, 277 mg calcium/day on the low- versus the high-calcium diet) and net calcium retention (74 mg/day versus 124 mg/day) differed significantly (Ames *et al.*, 1999b).

Supplementation with 1000 mg calcium (carbonate) over five weeks did not affect serum ferritin levels in sixty women consuming diets low in calcium (280 mg/day) (Yan *et al.*, 1996). There were no differences in serum ferritin levels in 158 women who received either 500 mg calcium (carbonate) twice daily with meals or placebo during months 6 to 12 postpartum (Kalkwarf and Harrast, 1998). Intake of 500 mg calcium (citrate-malate) supplements twice daily by 354 girls aged 8-13 years during four years did not result in differences in serum ferritin values, haemoglobin concentration or erythrocyte indices compared to a placebo group. The basal dietary calcium intake in these girls was between 798 and 878 mg/day, the iron intake 12.1 to 14.3 mg/day (Ilich-Ernst *et al.*, 1998).

Seventy-five premenopausal women taking 500 mg calcium (carbonate) twice daily with meals during 12 weeks showed no effect on plasma ferritin, serum iron, total iron-binding capacity, transferrin saturation, haemoglobin level or haematocrit compared to a control group. Their dietary calcium intake was 600 mg/day (Sokoll and Dawson-Hughes, 1992).

Eleven iron-replete adults, aged 18 to 69 years, who received for six months daily calcium supplements of 1200 mg (as carbonate) in addition to dietary calcium of 1100 mg/day did not show changes in haemoglobin, haematocrit, zinc protoporphyrin and plasma ferritin (Minihane and Fairweather-Tait, 1998).

Seven of nine cross-sectional studies in various countries in adults, young adults and infants showed a small negative correlation between iron status and consumption of dairy products. It was calculated that for every 100 mg/day increase of calcium intake in girls, serum ferritin would be reduced by a factor of 1.6%, and by a factor of 3.3% in women (van de Vijver *et al.*, 1999). A threshold effect for dose could not be detected. However, these findings with dairy products were not reported with other calcium sources, suggesting that another milk constituent could be responsible. It appears that changes in the calcium content of Western diets are not likely to have significant influence on iron absorption (Lynch, 2000) and that supplementation with calcium at the levels found to enhance bone mineral density (1000 to 1200 mg/day) does not affect normal iron status in healthy menstruating females (Bendich, 2001).

3.2.4.2 Zinc

Whereas human studies have shown that added dietary calcium either as salts or milk did not interfere with the intestinal absorption of radiolabeled zinc, there are two studies that report a negative effect on dietary zinc absorption and balance. Stepwise increases in calcium intake from 230 mg to 860 mg to 2000 mg/day in older men decreased fractional net zinc absorption from 24% to 12% to minus 3% on a zinc intake of 14 mg/day. However, there was no effect on zinc excretion and zinc balance (Spencer *et al.*, 1984). When postmenopausal women were fed during two periods of 12 days a diet with approximately 1500 mg calcium, half of them were in negative zinc balance despite zinc intakes of 17 mg/day. However the directly

inhibitory effect of a calcium supplement (600 mg) on zinc absorption from a meal could be offset by additional zinc (Wood and Zheng, 1997).

Yan *et al.* (996) investigated the effect of calcium carbonate supplements (1000 mg/day on five days per week) given throughout one year to 30 lactating women aged 16 to 41 years on zinc status and found no difference compared to a placebo group. Both groups had a low habitual dietary calcium intake of less than 300 mg per day.

Ten healthy men who received calcium phosphate supplements of 600 and 1200 mg daily each for two weeks in addition to a dietary calcium intake of 1800 mg did not develop changes in renal and faecal zinc excretion. However, serum zinc concentrations decreased from 1.1 mg/dL to 0.9 mg/dL (Raschke and Jahreis, 2002)

3.2.4.3 Magnesium

High calcium intakes (2 g/day) can reduce intestinal magnesium absorption and decrease renal magnesium excretion. The combined effect would not result in magnesium depletion in the absence of other risks for magnesium depletion such as diabetes mellitus, malabsorption and alcoholism (Whiting and Wood, 1997). Abrams *et al.* (1997) determined magnesium balance (intake 6.4 mg/kg/day or 194 to 321 mg/day) in relation to dietary calcium intake (mean 1310 mg/day) in 25 children between 9 and 14 years of age and found no influence.

Calcium phosphate supplements of 600 and 1200 mg/day for 2 weeks, in addition to dietary calcium intakes of 1800 mg, did not influence magnesium metabolism in 10 healthy men (Raschke and Jahreis, 2002).

The magnesium status of lactating women with a low habitual calcium intake was not influenced by calcium carbonate supplements (1000 mg/day) during one year (Yan *et al.*, 1996).

3.2.4.4 Phosphorus

Calcium acetate and calcium carbonate bind phosphate in the intestinal lumen and are given in chronic renal failure (up to 2 g calcium/day) to reduce phosphorus absorption in the intestine. This inhibitory effect on phosphorus absorption can also be demonstrated in healthy humans; 1000 mg calcium doses reduced phosphorus absorption by 58%. In view of the usual high dietary phosphorus intake this effect is without significance (Whiting and Wood, 1997).

3.2.5 Cytogenetic effects

An increase in the number of micronucleated erythrocytes (damaged red blood cell precursors which are normally selectively removed from peripheral blood by the spleen) have been reported in those of splenectomised subjects who regularly used calcium supplements. However, no data on dietary or supplemental calcium intake were given (MacGregor, 1990; Smith *et al.*, 1990). These findings do not provide evidence that calcium supplements damage cells.

4. DOSE-RESPONSE ASSESSMENT

4.1 Kidney function

A trend for an increase in serum creatinine (by 1.2 µmol/l) with calcium supplements of 1000 and 2000 mg during 3 years in addition to dietary intakes of around 1000 mg/day (total intake 2000 and 3000 mg/day) was seen in a study involving 130 perimenopausal women (Elders *et al.*, 1994). No effects on serum creatinine were reported in 46 women aged between 50 and 70 years who ingested calcium supplements of 1000 mg daily over one year in addition to a dietary calcium intake of 1290 mg/day (Schaafsma *et al.*, 2002).

In conclusion, some perimenopausal women with total calcium intakes between 2 and 3 g/day may show a tendency for compromised glomerular function as indicated by increases in serum creatinine. No such effect was observed in another study with women receiving comparable calcium amounts. This finding should be investigated systematically before it is attributed to calcium.

4.2 Milk-alkali syndrome

Manifestation of the milk-alkali syndrome through the combined intake of calcium both from food and especially from supplements and of absorbable alkalinising substances is facilitated by renal insufficiency, alkalosis and dehydration due to vomiting and anorexia and/or the use of thiazide diuretics, which increase renal tubular calcium reabsorption. All reported cases of milk-alkali syndrome in association with the prolonged or acute ingestion of calcium supplements used calcium carbonate as the nutrient source. In these reports the supplemental calcium intakes were reported as between 1.0 and 23 g/day. These patients also differ in their medical history, use and duration of use of drugs and alkali consumption, and their diets. Their dietary calcium intakes are often not known.

The FNB of the IOM (1997) has taken the approximate median of 4.8 g of reported calcium supplements (the same value derives from our extended list) as the LOAEL for total calcium intake, applied an uncertainty factor of 2 and defined an upper level of 2.5 g calcium/day. From the number of reported cases with milk-alkali syndrome and calcium supplement intakes below or equal to 2.5 g/day (11 of 82) in the list in Annex II, this definition of the LOAEL is not appropriate. Seven of these low-supplement users are reported not to have an additional high dietary calcium intake (>0.9 g/day). Only five of these eleven are reported to have ingested additional sodium bicarbonate or other antacids. Moreover, it is questionable if it is justified to derive a LOAEL for the total dietary calcium intake from data on effects of alkalinising substances plus calcium.

The use of calcium carbonate supplements in doses up to 2000 mg/day, and thereby achieving total daily calcium intakes up to more than 3000 mg/day, for preventive purposes in presumably healthy subjects, has not provoked the development of the milk-alkali syndrome, whereas the administration of large amounts (11.2 g calcium/day) of calcium carbonate in addition to large amounts of milk (1.8 g calcium/day) over 7 days to 20 gastric/duodenal ulcer patients resulted in reversible hypercalcaemia (2.8 mmol/L) in nine patients and renal insufficiency in all. The control group of 20 patients with gastric/duodenal ulcers who received aluminium hydroxide and milk for the same duration did not develop these abnormalities (McMillan and Freeman, 1965).

A patient with a 15-year history of calcium carbonate use (3.3 g/day) had recurrent episodes of severe hypercalcaemia. He was known to have diabetes mellitus, hypothyroidism and renal insufficiency and it is not known if the renal insufficiency was the consequence of recurrent hypercalcaemic episodes or if it was the promoting factor (Smit and Bijvoet, 1986).

Hypercalcaemia occurred in 65 of 297 patients who had undergone major cardiac surgery and who received between 1.3 and 10 g of calcium/day as carbonate (total daily intake 7 to 11 g calcium) for peptic ulcer prevention. It was accompanied by renal failure in 50%, which developed within days of starting the regimen in a few patients, and was completely reversible after stopping calcium carbonate (Kapsner *et al.*, 1986).

Cases of milk-alkali syndrome have been reported with long-standing calcium intakes in the range of 2 to 2.5 g/day with chronic high intakes of antacids (Barragry and Counihan, 1975; Gibbs and Lee, 1992) and of low supplemental calcium intakes (1g/day) in addition to unknown dietary intakes plus sodium bicarbonate (Abreo *et al.*, 1993). These observations seem to indicate that the harmful calcium dose can be lower than 3 g/day if taken together with alkali.

In conclusion, on the basis of the available evidence, a calcium dose which by itself might cause milk-alkali syndrome cannot be identified.

4.3 Kidney stones

The quantitative relationship between calcium intake, both from the diet and from supplements, and hypercalciuria as a risk factor for nephrolithiasis is far from clear. Also, it is dependent on other dietary factors, especially sodium intake. From epidemiologic studies it appears that dietary calcium intakes in the range of recent recommendations have a favourable effect in the prevention of kidney stone formation and that lower intakes increase the risk (Curhan *et al.*, 1993 and 1997; Sowers *et al.*, 1998).

The influence of a controlled diet for 3 days (1000 mg calcium, 100 mmol sodium, 32.3 mmol potassium/day and 1 g protein/kg body weight/day) and of an oral calcium tolerance test (1000 mg) on urinary calcium excretion was investigated in 124 patients with hypercalciuria (more than 4 mg/kg/day or more than 300 mg/day in men and more than 250 mg/day in women of calcium excreted) identified from 282 patients with calcium oxalate stones. The strongest correlation was found between urinary calcium and sodium. Calcium excretion was less strongly correlated with calcium intake, sodium intake, phosphorus intake, carbohydrate and protein intake. From the regression equation derived from these investigations (Burtis *et al.*, 1994) hypercalciuria in men would be associated with a calcium intake of 2243 mg/day and in women with a calcium intake of 1422 mg/day assuming a moderate sodium excretion of 100 mmol/day. A higher sodium intake (e.g. 150 mmol/day) would result in even lower hypercalciuric calcium intakes, 1685 mg for men and 866 mg/day for women, which are lower than the recommended calcium intake in many countries. The validity of these calculated predictions has never been systematically investigated in hypercalciuric subjects.

From the available data no conclusion is possible on a detrimental calcium dose in individuals with idiopathic hypercalciuria (up to 6% of the population). From the study in patients with kidney stones and idiopathic hypercalciuria it can be deduced that a sodium restricted diet with a normal recommended calcium content of 1200 mg/day does not raise urinary calcium excretion but reduces it (Borghi *et al.*, 2002).

Hypercalciuria which is a risk factor for kidney stone formation has been observed in three of 50 infants receiving 1200 mg of supplemental calcium/day (Dalton *et al.*, 1997) and in postmenopausal women during 4 years of taking calcium supplements of 1600 mg six times as often as in unsupplemented women (Riggs *et al.*, 1996). Different doses have not been systematically tested.

In conclusion, both observational studies on the relationship between total calcium intake and kidney stone incidence and interventional studies with calcium supplements do not allow definition of a calcium intake on a population basis which promotes kidney stone formation. On dietary calcium intakes in the range of the recommended dietary intake the risk of nephrolithiasis is determined by other dietary components and by genetic factors.

In persons with idiopathic hypercalciuria, which is in itself a heterogeneous disorder, the risk of stone formation is not increased with calcium intakes in the range of recommended intakes, when sodium intake is restricted (Borghi *et al.*, 2002). Higher dosages have not been tested.

4.4 Interaction with minerals

The studies of acute effects of single calcium supplements at various doses and from various sources on iron and zinc absorption (Spencer *et al.*, 1984; Hallberg *et al.*, 1991) cannot be converted into general statements on a dose dependent negative effect of total daily dietary calcium intake, because the timing of the supplement and other interfering factors of the diet have to be taken into account.

Observational epidemiological studies on the influence of dietary calcium intake in different populations and age groups on parameters of iron status do not allow the identification of threshold values of calcium intake that lead to reductions in these parameters (Lynch, 2000). Intervention studies with calcium supplements up to 1200 mg/day in addition to dietary intakes between 280 and 1100 mg/day did not show adverse effects on iron status (Lynch, 2000). Negative interactions of calcium intakes in excess of 2000 mg/day that have been reported for iron, phosphorus, magnesium and zinc would be a problem only when these are ingested in inadequate amounts (Whiting and Wood, 1997).

In conclusion, single-dose experiments demonstrate interference of both dietary and supplemental calcium with the absorption of other minerals. This effect is not demonstrable in long-term observational and interventional studies at dietary calcium intakes in the range of recommended intakes and at supplemental calcium of up to 2000 mg/day in adults and up to 1200 mg/day in one study with infants (Dalton *et al.*, 1997).

The decrease of serum zinc levels in 10 healthy adults after two weeks of a total calcium intake of 3000 mg/day (Raschke and Jahreis, 2002) is of insufficient power to consider it as a systematic effect. The cross-sectional study in seven countries which shows a dose dependent effect of calcium intake from dairy products on serum ferritin levels in young women did not define a threshold dose of calcium intake (van de Vijver *et al.*, 1999).

4.5 Cytogenetic effects

The data are insufficient to allow conclusions to be drawn from the available studies.

5. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

5.1 Adults

The Committee decided to base the derivation of an UL for calcium on the evidence of different interventional studies of long duration in adults, some of which were placebo-controlled and in which total daily calcium intakes of 2500 mg from both diet and supplements were tolerated without adverse effects. Because of the abundance of data the application of an uncertainty factor was considered unnecessary. An UL of 2500 mg of calcium per day for calcium intake from all sources is proposed.

5.2 Pregnancy and lactation

Large placebo controlled intervention studies for preventive purposes with supplemental calcium carbonate of up to 2000 mg calcium in addition to the calcium intake from the diet (>400 mg/day) have been conducted in more than 3000 pregnant women and no adverse effects have been reported. There are no data to suggest an increased susceptibility for lactating women. Therefore, the UL of 2500 mg calcium per day applies also to pregnant and lactating women.

5.3 Children and adolescents

Six percent of 50 infants who received a calcium-enriched formula after the third month of life (1700 to 1560 mg calcium per day after 4 and 9 months, respectively), developed hypercalciuria (Dalton *et al.*, 1997). These data are insufficient to define an UL for infants.

No adverse effects of calcium citrate-malate supplements (500 to 1000 mg calcium over 1.5 to 3 years) and of extra dairy foods or foods fortified with milk extracts (700 to 820 mg calcium extra over one year) were reported in 217 children between 6 and 14 and 6.6 and 11 years, respectively in comparison to unsupplemented controls.

These data are considered insufficient to derive an UL for children and adolescents. The Committee decided that it was inappropriate to base the UL for calcium for this age group on the tolerable upper level for adults of 2500 mg calcium/day, with correction for differences in basal metabolic rate using scaling according to body surface area (body weight$^{0.75}$). For calcium deposition in bone during the growth period proportionality to lean body mass cannot be assumed. Therefore, the Committee cannot propose age-dependent ULs for children and adolescents.

6. CHARACTERISATION OF RISK

Data from European populations indicate that the intakes of calcium from all sources in adolescents and adults can be close to the UL in a small percentage of the population, especially in those taking supplements. In the United Kingdom the 97.5 percentile of calcium intake in men 16 to 49 year old is 1600 mg/day (EGVM, 2001). In the Netherlands with a traditionally high consumption of milk products the 95 percentile of calcium intake without supplements is 2100 mg per day in young men between 16 to 22 years old (Hulshof and Kruizinga, 1999). In Germany the mean calcium intake of male subjects between 15 and 24 years old is 2100 mg/day (Heseker *et al.*, 1994), but some 10% of adolescents consume more than 2100 mg per day (Alexy and Kersting, 1999).

In Dutch children the 95 percentile of calcium intake in boys and girls between one and 4 years of age is around 1300 mg/day, it is between 1400 and 1700 mg/day in boys and girls 4 to 13 years of age (Hulshof and Kruizinga, 1999). Somewhat lower 97.5 percentile intakes of 1200 to 1500 mg/day have been observed in British children between 1.5 and 14 years of age. The 90 percentile of calcium intake of 750 German children participating in a longitudinal observational study was 800 to 1000 mg/day between age one and 2 years, 700 to 900 mg/day between age 4 to 6 years and 1000 to 1600 mg/day between age 7 to 14 years (Alexy and Kersting, 1999).

These calcium intakes are quite similar to the calcium intakes of 1100 to 1900 mg/day supplied in intervention trials with children between 6 and 14 years of age which studied the effect on bone mineral mass and bone density (Johnston *et al.*, 1992; Lloyd *et al.*, 1993; Chan *et al.*, 1995; Bonjour *et al.*, 1997).

In British infants the 97.5th percentile of calcium intake was 1400 mg/day (EGVM, 2001). In German non-breast-fed infants the 90th percentile of calcium intake was 700 to 900 mg/day (Alexy and Kersting, 1999).

Although there are no data to set a numerical UL for children and adolescents no appreciable risk has been identified even with current extreme levels of calcium intake in this age group.

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Annex I. Intervention studies with calcium supplements

No	Authors	Study aim	Study design	Dietary calcium mg/d	Calcium supplement mg/d	Calcium compound	Effects	Adverse effects
1	Johnston *et al.*, 1992	Effects of calcium supplementation on BMD in identical twins n = 70 pairs	Randomised double-blind placebo-controlled				n = 20 prebubertal supplemental twins greater increases in BMD at 5 of 6 sites by 2.8 to 5.1% compared to control twin after 3 years There was no benefit in supplemented 23 twins who were in or post puberty	None reported
			control n = 70	908				
			supplement n = 70	894 (total 1612)	1000	citrate malate		
			age 6 to 14 y over 3 years One twin control for the other 45 pairs completed the study					
2	Lloyd *et al.*, 1993	Effect of calcium supplementation on bone acquisition n = 94	Randomised double-blind placebo-controlled				BMD increased by 1.3% more with supplement. Calcium excretion with supplement by 17 mg/24 h higher	None reported
			placebo control n = 48	935	-	citrate malate		
			supplement n = 46 age 11.3 years, 18 months	1020	350			
3	Chan *et al.*, 1995	Effect of extra dairy products on bone n = 46	randomised, controlled				BMD increased by 10% more with supplement	None reported
			control n = 24	700				
			supplement n = 22	1400		dairy products		
			age 11 years, 12 months					
4	Bonjour *et al.*, 1997	Effect of calcium supplementation on bone mass in prepubertal girls	double blind placebo-controlled age 6.9-9.4 y				None reported mean increment in bone mass greater at 6 sites; more so if spontaneous dietary Ca intake <860 mg/d; greater height 1 year after treatment ended effect persisted	None reported
			placebo n = 67	880		unfortified food		
			supplement n = 77	920	810	milk-extracted fortified foods		
			1 year					
			n = 100 placebo n = 54 supplement n = 55					
	Bonjour *et al.*, 2001		n = 16 placebo n = 54 supplement n = 62				3.5 years after treatment ended BMD still higher in supplemented, also BMC and bone area, height	
5	Kochersberger *et al.*, 1991	Effects of calcium supplementation on PTH and bone metabolism in elderly	Randomised double-blind placebo-controlled				Decrease in PTH with decrease 1,25-OHD_3 Increase in urinary calcium from 120 to 188 mg/d creatinine	Constipation in supplemented
			placebo n = 24	726	-			
			supplement n = 26	708	1200	carbonate		
			66-83 y 6 months					

No	Authors	Study aim	Study design	Dietary calcium mg/d	Calcium supplement mg/d	Calcium compound	Effects	Adverse effects
6	Reid *et al.*, 1993	Effect of calcium supplementation on BMD of postmenopausal women	Randomised placebo-controlled				BMD decline less in supplement group Serum PTH lower	None reported
			placebo n = 61	730	-	sucrose		
			supplement n = 61	760	1000	lactate gluconate carbonate		
			age 58 ± 5 2 years					
7	Elders *et al.*, 1994	Effect of two doses of calcium supplementation on bone loss in perimenopausal women	Randomised controlled				Rate of bone loss and bone turnover less in supplemented in 1rst year, similar to control in 2nd year. Bone loss after 3 y in early menopausal women 3.2% in control versus 1.6% in supplement groups (lumbar and metacarpal)	Gastrointestinal discomfort → change to calcium citrate n = 35 Mean increase of serum creatine (1.2 µm/L) in supplement II, trend in supplement I
			control n = 84	1065	-	-		
			supplement I n = 66	994	1000	lactogluconate + carbonate		
			supplement II n = 64	1052	2000	lactogluconate + carbonate		
			age 46-55 y 2 years + 1 years					
8	Riggs *et al.*, 1996	Effect of calcium supplementation on serum PTH, bone turnover and bone loss in the elderly	Randomised placebo-controlled				Decrease in serum PTH, bone resorption and bone loss (weak effects)	One case of hypercalcaemia in supplement group Hypercalciuria in 51 cases (44 supplemented. 7 unsupplemented)
			control n = 117		-			
			supplement n = 115		1600	citrate		
			menopausal women (66 ± 0.2 y) 4 years					
9	Heaney *et al.*, 1999	Effect of dietary calcium supplementation on calcium economy in older adults	controlled intervention				Extra calcium decreased serum PTH by 9% and N-telopeptide in urine by 13%. Urine calcium increased by 21 mg/d. Bone specific alkaline phosphatase fell by 9% in both groups Serum IGF-1 rose by 10% in the milk group	Extra weight gain of 0.7 kg in milk group
			control n = 103	649-779	5-36			
			intervention n = 101	690-801	714-755	milk		
			age 55-85; men and women; 12 weeks					
10	Peacock *et al.*, 2000	Effect of calcium supplement or 25-OH-D on bone loss, bone turnover	Randomised double-blind placebo-controlled				Control group lost BMD at total hip, the Suppl. II group did not lose BMD. The 25-OH-D group was intermediate. Lowest fracture rate in group II, highest in group I	Constipation in group II One proband with kidney stone in group II
			placebo n = 129	629	-			
			supplement I n = 124	739	25(OH)D			
			supplement II n = 124	670	750	citrate malate		
			60-74 years over 4 y ♂ and ♀					

No	Authors	Study aim	Study design	Dietary calcium mg/d	Calcium supplement mg/d	Calcium compound	Effects	Adverse effects
11	Dawson-Hughes and Harris, 2002	Influence of calcium plus vitamin D on protein intake effect on BMD in older adults	Randomised placebo-controlled				A higher protein intake had favourable effect on 3-y change in total body BMD in the supplemented group only	None reported
			placebo n = 184	755-940	-	-		
			supplement n = 158	809-855	500 17.5 µg Vit. D	citrate malate		
			Healthy ♂ and ♀, age >65 y 3 years					
12	Schaafsma *et al.*, 2002	Effect of two calcium supplements on femoral BMD, biochemical markers of bone and calcium metabolism in late postmenopausal women	Randomised double-blind placebo-controlled over 12 m age >50 <70 y				Increase of BMD femoral neck supplement II versus control, Supplement groups showed changes in serum markers of bone resorption and bone formation indicating decreased bone turnover	None reported No changes in serum calcium, phosphate, creatinine
			placebo n = 27		50	skimmed milk powder		
			supplement I n = 24	1294 ± 421	1000	egg-shell powder		
			supplement II n = 22		1000	carbonate		
			supplements provided Vit. D 10 µg Vit. K 80 µg Mg 350 mg					
13	Villar and Repke, 1990	Effect of calcium supplementation on risk of preterm delivery	Randomised double-blind placebo-controlled				Preterm delivery: (<37th week) placebo 21.1%, suppl. 7.4%. Low birth weight: placebo 21.1%, suppl. 9.6%. Duration of labour: placebo 9.9 h, suppl. 12 h suppl. increased gestation by 1.3 weeks birth weight by 189 g	None reported
			placebo n = 95	1200	-	-		
			supplement n = 94	1200	2000 (1500)	carbonate		
			age <17 y 23rd week of gestation					
14	Belizán *et al.*, 1991	Effect of calcium supplementation on hypertensive disorders of pregnancy	Randomised double-blind placebo-controlled				Hypertensive disorders Placebo 14.8%, Suppl. 9.8%. OR 0.63 (95% Cl 0.44-0.9) Preeclampsia Placebo 3.9%; Suppl. 2.6% OR 0.65 (95% Cl 0.35-1.25)	None reported
			placebo n = 588	642 ± 448	lactose			
			supplement n = 579	646 ± 396	4 x 500	carbonate		
			Nulliparous women 20 weeks pregnant					
15	Bucher *et al.*, 1996	Effect of calcium supplementation during pregnancy on blood pressure, preeclampsia and adverse outcome metaanalysis	Metaanalysis 1966-1994 14 randomised placebo-controlled studies n = 2459		357- 1500- 2000		Reduction in systolic blood pressure by 5.4 mm Hg and in diastolic blood pressure by 3.44 mm Hg. Preeclampsia OR 0.38 (95% Cl 0.22-0.65) for calcium supplements	

No	Authors	Study aim	Study design	Dietary calcium mg/d	Calcium supplement mg/d	Calcium compound	Effects	Adverse effects
16	Levine *et al.*, 1997	Effect of calcium supplementation during pregnancy on preeclampsia hypertension, adverse perinatal outcome	Randomised double-blind placebo-controlled				No significant differences for preeclampsia, hypertension nor in perinatal outcome	None. Women with increased risk for nephrolithiasis, with increased serum calcium and creatinine had been excluded
			placebo n = 2294	~1000	corn-starch	-		
			supplement n = 2295		2 x 1000 (total 2400)	carbonate		
			Nulliparous women 13-21 weeks pregnant age 21 ± 4 y					
17	Koo *et al.*, 1999	Effect of maternal calcium supplement during pregnancy on fetal bone mineralisation	Randomised double-blind placebo-controlled Pregnant <22 w				No significant difference in infants in BMC, BMD total body and lumbar spine of infants Increase in BMC in infants of supplemented mothers in lowest quintile of spontaneous dietary calcium intake and with increasing maternal calcium intake of all source	Non reported
			placebo n = 128	1035 (83-3613)	-	-		
			supplement n = 128	1010 (83-3613)	2 x 1000 (mean 1300)	carbohydrate		
18	Baron *et al.*, 1999	Effect of calcium supplementation on recurrence of colorectal adenomas	Randomised double-blind placebo-controlled				Recurrence risk ratio for supplement compared to placebo 0.85 (95% CI: 0.74-0.98) after one years; after 4 years 0.81 (95% CI: 0.67-0.99)	No difference between placebo and supplement
			placebo n = 466 completed n = 423	865	-	cellulose/sucrose		
			supplement n = 464 completed n = 409	889	1200	carbohydrate		
			age 61 y over 4 years					
19	Sokoll and Dawson-Hughes, 1992	Effect of calcium supplementation on iron stores in healthy premenopausal women	Randomised controlled				No differences between control and treatment groups in plasma ferritin, serum iron, total iron binding capacity, transferrin saturation, haemoglobin, haematocrit	None reported
			control n = 52	610	-	-		
			supplement n = 57	559	1000	carbonate		
			12 weeks					
20	Yan *et al.*, 1996	Effect of calcium supplementation on indices of iron, zinc, magnesium status in lactating women	Randomised double-blind placebo-controlled				No differences in status indices for zinc, iron, magnesium	None reported
			placebo n = 30	290	-	dextrose		
			supplement n = 30	280	1000 5 d/week	carbonate		
			One year 16-41 years					
21	Minihane and Fairweather-Tait, 1998	Effect of calcium supplementation on body iron in healthy adults	Controlled				No effect of calcium (400 mg per meal) supplementation on functional iron indices (Hb, haematocrit, zinc, protoprophyrin, plasma ferriti	None reported
			control n = 13	980	-	-		
			supplement n = 11	1090	1200	carbonate		
			age 18-69 y over 6 months					

No	Authors	Study aim	Study design	Dietary calcium mg/d	Calcium supplement mg/d	Calcium compound	Effects	Adverse effects
22	Kalkwarf and Harrast, 1998	Effect of calcium supplementation on iron status lactating women	Randomised double-blind placebo-controlled				No effect of calcium on iron status	None reported
			placebo n = 80	680-780		lactose		
			supplement n = 78	680-744	1000	carbonate		
23	Raschke and Jahreis, 2002	Effect of calcium and phosphorus on calcium and mineral metabolism	Intervention of 2 weeks each after 3 weeks control n = 10 healthy men				Increase of faecal calcium excretion and decrease of urinary calcium excretion with supplement II. No change on calcium balance No influence on magnesium metabolism No influence on iron status No influence on renal and faecal zinc excretion	Decrease in serum zinc control 1.1 mg/dl suppl. II 0.9 mg/dl
			basis	1800				
			supplement I	1800	600 (+800 mg P)	phosphate		
			supplement II	1800	1200 (+1600 mg P)			

Annex II. Milk-alkali syndrome (from 1965 to 2001)

No	Author	Patient No.	Male/ Female	Age (years)	Pre-existing disease	Calcium intake			Calcium salt	Alkalising drugs/antacids	Other drugs	Duration of Ca intake	Provoking factor	Symptoms			Outcome
						Total	Milk	supple-ments						Ca in Serum mmol/L	Renal failure	(Nephro)calcinosis	
1	Mc Millan + Freemann, 1965	A17	M	51	peptic ulcer 3 y	n.r.	high 2 g			Alka Seltzer, bicarbonate 2 y	reserpine	chronic 2 y					
							acute 1.8 g	11.2 g	carbonate	Al(OH)		4 d		4.5	+	-	hypertension
2-20				28-64	gastric/duodenal ulcer	n.r.	1.8 g	11.2 g	carbonate		-	7 day-test		8/19>2.8	creatine in serum in-creased creati-nine clearance decreased by 19%	-	normal
														4/19>3.0			
21	Cameron + Spence, 1967		F	40	"heartburn", thirst 8 y	n.r.	< 0.8	6.4	carbonate	+ (Rennie)		11 y	thirst	2.85	+	+	partial renal insufficiency
22	Riley, 1970		M	66	duodenal ulcer	n.r.		3.2	carbonate	Al(OH)	-	30 y	anorexia, thirst	3.75	+	keratopathy	persistent renal insufficiency
										Mg(OH)							
23	Assari + Vennes, 1971		M	52	gastric ulcer	n.r.	4.5-6.8	-	-	sodium bicarbonate	-	2.5 y	salt-losing nephropathy, polyuria	2.8	+	-	persistent renal insufficiency
24	Danells *et al.*, 1972	1	F	45	duodenal ulcer	n.r.	>2.4			bismuth	anticholinergica	3 y		4.0	+	+	persistent renal insufficiency
25		2	M	45	duodenal ulcer	n.r.	1.8-2.4	+	carbonate	magnesium trisiliconate	anticholinergica	14 d	vomiting	3.5	+	-	normal
26	Barragry + Counihan, 1975	1	M	35	duodenal ulcer	n.r.	1.8	-	-	60 g/d Soda	-	5 y	polyuria	3.0	+	-	normal
27		2	M	39	epigastric pain, hypertension	n.r.	3.4	+	carbonate	-	-	6 y + 7 y	-	2.3-3.7			chronic renal insufficiency
28	Junor + Catto, 1976	1	M	53	gastric ulcer 20 y	n.r.	large	-	-	sodium bicarbonate	-	20 y	vomiting	n.r.	+	+	normal
29		2	M	40	gastric ulcer 25 g	n.r.	4.5	-	-	sodium bicarbonate	-	25 y	-	n.r.	+	+	persistent renal insufficiency
30		3	M	47	duodenal ulcer >25 y	n.r.	large	-	-	sodium bicarbonate	-	> 25 y	vomiting	n.r.	+	+	persistent renal insufficiency
31	Rochman *et al.*, 1977		M	60	duodenal ulcer	n.r.	n.r.	11-23	carbonate	-	-	3 y	vomiting	3.0	+	+	renal acidosis
32	Frame et al, 1981		F	51	Münchhausen syndrome	n.r.	n.r.	5-15	carbonate	-	thiazide	months	-	5.0	(+)	-	normal
33	Hart *et al.*, 1982		M	65	duodenal ulcer	n.r.	2.3-4.5	+	carbonate	sodium bicarbonate	-	many years	constipation, dehydration	3.5	+	keratopathy	normal
34	Roberts + Tuthill, 1984		M	57	indigestion anxiety	n.r.	n.r.	7.2	carbonate	+	aspirin cimetidine	several months	vomiting	3.4	+	soft tissue calcification	normal
35	Schumann + Jones, 1985	1	M	32	gastric ulcer 10 y	n.r.	4.5	-	-	bismuth	cimetidine acetaminophene	6 w	vomiting	3.5	+	-	normal
		2	M	43	epigastric pain, renal failure 14 m	9.8	2.3	+	carbonate	-	-	20 y	-	3.3	+	soft tissue calcification	persistent renal insufficiency
36	Dorsch, 1986		F	52	epigastric pain 8 y , renal failure 6 m	n.r.	n.r.	2.1	carbonate	-	-	8 y	vomiting, weight loss	3.3	+	-	normal
37	Smit + Bijvoet, 1986		M	55	diabetes mellitus, hypothyroidism, renal insufficiency			3.3	carbonate	Rennie +	insulin thyroxine	15 y	dehydration	4.6 recurrent	+	band keratopathy	normal, no diabetes mellitus

No	Author	Patient No.	Male/ Female	Age (years)	Pre-existing disease	Calcium intake			Calcium salt	Alkalising drugs/antacids	Other drugs	Duration of Ca intake	Provoking factor	Symptoms			Outcome
						Total	Milk	supple-ments						Ca in Serum mmol/L	Renal failure	(Nephro)calcinosis	
38	French *et al.*, 1986	1	M	49	gastritis, indigestion, hypertension	8	0.8	6.7	carbonate	+	-	years	polyuria, polydipsia 2 w	3.7	+	-	normal
39		2	M	43	hypertension, renal failure	n.r.	n.r.	4.2	carbonate	+	indomethacin thiazide	many years	-	4.0	+	-	normal
		3	F	62	pyelonephritis, analgesic abuse	5	n.r.	4.2	carbonate	+	-	5 y	-	4.0	-	-	normal
		4	F	71	malaise, kidney stones, renal failure	n.r.	n.r.	n.r.	carbonate	+	-	many years	-	3.5	+	-	normal
40	Kapsner *et al.*, 1986	1	F	32	cardiac transplantation	>0.6	n.r.	10	carbonate	-	hydrochlorothiazide prednison	10 m	vomiting	5.5	+	-	normal
41		2	M	24	cardiac transplantation	>3.8	n.r.	3.2	carbonate	-	furosemide + prednison	10 m	-	6.7	+	-	normal
42		3	M	40	cardiac transplantation, kidney stones	n.r.	n.r.	4.8	carbonate	-	prednison	3 d	-	3.1	+	-	normal
		65/297 cardiac transplant patients	52 M 13 F	9-64	peptic ulcer prevention	n.r.	n.r.	1.3-4.8	carbonate	-	prednison	1 w - > 6 m	-	2.7->3.5	37/65	-	normal
43	Kallner + Karlsson, 1987		F	41	anorexia nervosa, bulimia	up to 16		-	-	-	chlorthalidone	12 y	vomiting	4.0 recurrent	+	-	normal
44	Bullimore + Miloszewski, 1987		F	35	achalasia	6	2.3	3	carbonate	Rennies +	-	20 y	nausea, vomiting	4.1	+	-	normal
45	Jenkins *et al.*, 1987		M	65	epigastric pain, oesophagitis	n.r.	n.r.	2.4-4.8	carbonate	+	triamterene hydrochlorothiazide	1 year, dose increase 2 w	dehydration	5.5	+	-	normal
46	Canning + Slater, 1987		F	61	duodenal ulcer 8 y, renal failure	n.r.	n.r.	1.1	carbonate	sodium bicarbonate	-	8 y	vomiting, dehydration	4.3 recurrent	+	+	persistent renal insufficiency
47	Schaefers, 1987		M	46	alcoholic gastritis	n.r.	n.r.	4.6	carbonate	sodium bicarbonate +	-	many years	vomiting	3.7	+	-	persistent renal insufficiency
48	Ullian + Linas, 1988		F	31	hyperemesis of pregnancy	n.r.	large amounts	+	carbonate	-	-	weeks	vomiting 3 d, diarrhea	3.6	+	-	stillborn fetus 37 w with malformation of limbs and ears
49	Gora et al, 1989		M	47	hypertension, kidney stones, hypothyroidism	n.r.	n.r.	3-4	carbonate	-	hydrochlorothiazide thyroxine	2 y	-	3.4	+	-	normal
50	Kleinman *et al.*, 1991		F	31	pregnancy 36 w, nausea	n.r.	1.2	6	carbonate	+	-	2 w	vomiting 3 d	5.6	+	-	normal (child normal 40 w)
51	Gibbs + Lee, 1992		M	51	peptic ulcer	n.r.	2.4	-	-	+ AlOH Mg carbonate sodium bicarbonate	-	years	vomiting, polyuria, polydipsia	3.5	+	keratopathy	normal
52	Nakanishi et al, 1992		M	74	cerebral infarction constipation	n.r.	0.4	n.r.	-	magnesium oxide	-	weeks	dehydration	3.6	+	-	n.r.
53	Abreo *et al.*, 1993	1	M	60	diabetes mellitus, hypertension	n.r.	n.r.	1	carbonate	sodium bicarbonate	insulin	15 y	vomiting 1 w	3.8	+	(+)	persistent renal insufficiency
54		2	M	60	dyspepsia	n.r.	2.3	7.2	carbonate	-	-	> 3 m	venous thrombosis	3.3	+	-	normal
55		3	F	54	breast cancer, peptic ulcer	n.r.	n.r.	+	carbonate	-	-	years	-	3.7	+	-	persistent renal insufficiency
56		4	M	53	diabetes mellitus, coronary artery disease	n.r.	> 2.7	6	carbonate	-	-	3 m	nausea 2 m	3.4	+	-	persistent renal insufficiency

No	Author	Patient No.	Male/ Female	Age (years)	Pre-existing disease	Calcium intake			Calcium salt	Alkalising drugs/antacids	Other drugs	Duration of Ca intake	Provoking factor	Symptoms			Outcome
						Total	Milk	supple-ments						Ca in Serum mmol/L	Renal failure	(Nephro)calcinosis	
57		5	M	65	hypertension	n.r.	> 0.8	3	carbonate	-	reserpine enalapril hydrochlorothiazide	several years	vomiting	3.3	+	-	persistent renal insufficiency
58	Newmark + Nugent, 1993		M	55	kidney stones, hypertension, chronic pulmonary disease	n.r.	n.r.	8.4	carbonate	+	-	30 y	vomiting 5 d	4.0	+	-	normal
59	Campbell *et al.*, 1994		M	53	epigastric pain		0.6	4.5	carbonate	-	-	months	3 w of thirst, polyuria, vomiting	3.6	+	-	normal
60	Brandwein + Sigman, 1994		M	47	peptic ulcer	5.4	n.r.	2-3	carbonate	-	-	several years	nausea, vomiting 1 w	3.9	+	-	normal
61	Beall + Scofield, 1995	1	F	45	dyspepsia	n.r.	n.r.	2.4	carbonate	+	prednison	1 year	increase of calcium dose 2 w	4.9	+	-	normal
62		2	F	42	peptic ulcer	n.r.	1.2	2.4-4	carbonate	-	-	2 w	vomiting	3.0	-	-	normal
63		3	F	34	fever	n.r.	n.r.	1.6-2.5	carbonate	prednison	prednison	1 m	increase calcium dose	3.0	-	-	normal
64		4	M	60	n.r	n.r	n.r.	1.6-4.6	carbonate	n.r	n.r.	n.r.	n.r.	3.5	n.r.	n.r.	n.r.
65		5	F	58					carbonate					3.5			
66		6	F	53					carbonate					4.9			
67		7	F	95					carbonate					2.8			
68	Duthie *et al.*, 1995		M	65	hypertension, diabetes mellitus	n.r.	n.r.	6-12	carbonate	sodium bicarbonate	-	1.5 y	dehydration	4.3	+	soft tissue calcified	persistent renal insufficiency
69	Muldowney + Mazbar, 1996		F	35	bulimia 15 y, chronic vomiting	n.r.	> 0.9	0.8	carbonate	-	-	recently	nausea, constipation	4.0	+	-	normal
70	Wu *et al.*, 1996	1	M	55	bladder stones, betelnut chewing	n.r.	n.r.	3.5	carbonate	-	piroxicam	30 y	-	3.4	+	+	persistent renal insufficiency
71		2	M	63	epigastric pain, betelnut chewing	n.r.	n.r.	2.5	carbonate	-	famotidine	> 30 y	-	3.8	+	nephrolithiasis	persistent renal insufficiency
72	Olschewski *et al.*, 1996		M	54	duodenal ulcer 10, kidney stone	n.r.	1.2-2.4	2.4	carbonate	+ bismuth	doxepin chlormezanon bezafibrate	4 y	nausea	3.9	+	+	persistent renal insufficiency
73	Lin et al, 1996		F	70	osteoporosis	n.r.	n.r.	3.75	carbonate	-	0.5 µg calcitriol	4 w	anorexia, dehydration	4.0	+	soft tissue calcification	normal
74	Fiorino, 1996		M	66	alcoholism	n.r.	n.r.	+	carbonate	+	laxatives	n.r.	anorexia, vomiting 3 w	4.4	+	-	death, multiorgan failure
75	Fitzgibbons + Snoey, 1999		M	39	peptic ulcer, alcoholism	n.r.	n.r.	+	carbonate	sodium bicarbonate	-	n.r.		3.1	+	-	persistent renal insufficiency
76	George + Clark, 2000		F	44	dyspepsia, kidney stones	n.r.	n.r.	2.7	carbonate	-	-	2-3 y	vomiting 2 d	4.0	+	-	normal
77	Vanpee *et al.*, 2000		M	64	carcinoma, renal insufficiency 2 y	n.r.	n.r.	2.7	carbonate	-	-	2 w dose increase	vomiting, dehydration 1 w	3.5	+	+	persistent renal insufficiency
78	Grundfast *et al.*, 2001		M	59	gastric/duodenal ulcers	n.r.	n.r.	6-10	carbonate	-	+	n.r.	vomiting 2 d, anorexia 2 w	4.1	+	-	n.r.
79	Carroll + Clark, 1983	1	M	50	duodenal ulcer	n.r.	2.3	1	carbonate	sodium bicarbonate	-	10 y	polyuria, polydipsia 6 m	3.2	+	+ soft tissue calcification keratopathy	normal

No	Author	Patient No.	Male/ Female	Age (years)	Pre-existing disease	Calcium intake			Calcium salt	Alkalising drugs/antacids	Other drugs	Duration of Ca intake	Provoking factor	Symptoms			Outcome
						Total	Milk	supple-ments						Ca in Serum mmol/L	Renal failure	(Nephro)calcinosis	
80		2	M	60	oesophagitis	n.r.	2.3	7	carbonate	-	-	years	n.r.	4.0	+	+ soft tissue calcification	persistent renal insufficiency
81		3	M	60	tongue, carcinoma, pain	n.r.	2.3	0.5	carbonate	-	Vit A 6 mg, Vit E 2 g	2 m	n.r.	3.2	+	+ soft tissue calcification	normal, died from carcinoma
82		4	M	77	dyspepsia	n.r.	n.r.	0.6-2	carbonate	-	-	5 y	anorexia 2 w	4.5	+	-	normal