Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Silicon

(Request No. EFSA-Q-2003-018)

(adopted on 28 April 2004)

SUMMARY

The European Food Safety Authority is asked to derive an upper level for the intake of silicon from food that is unlikely to pose a risk of adverse health effects.

Silicon has not been shown to be essential for humans. Silicon occurs naturally in foods as silicon dioxide (silica) and silicates, and may also be added as an anti-caking and anti-foaming agent in the form of silica, silicates and dimethylpolysiloxane. Silicate-containing antacids have been widely used for a number of decades.

Short-term oral ingestion of sodium or magnesium silicate produces adverse renal effects in dogs and guinea pigs, but not in rats; similar doses of silicon dioxide and aluminum silicate did not produce adverse renal effects in dogs or rats. Long-term oral administration of silica at high dose levels inhibits growth in rats and mice. This effect was not regarded as a toxic effect, but was rather due to nutritional imbalance because of the high dose of silica added to the diet. In humans, apart from occasional reports of renal stones, mainly associated with long-term use of silicate-containing antacids, there is little evidence of adverse effects of orally ingested silicon. The available data are inadequate to derive a tolerable upper intake level.

The estimated typical dietary intake (20-50 mg silicon/day) corresponds to 0.3-0.8 mg/kg body weight/day in a 60 kg person. These intakes are unlikely to cause adverse effects.

KEY WORDS

Silicon, tolerable upper intake level, metabolism, function, food safety.

BACKGROUND


In addition, and as announced in its White Paper on Food Safety, the Commission aims to put forward a proposal for harmonising legislation concerning the addition of vitamins and minerals to foods.

With a view to providing scientific support to the European Commission’s legislative work in this field, the Scientific Committee on Food (SCF) issued, from October 2000 to April 2003, a series of opinions on tolerable upper intake levels of individual vitamins and minerals and safety factors in relation to their use in fortified foods and food supplements (available on the Internet at: http://europa.eu.int/comm/food/fs/sc/scf/out80_en.html).

The SCF opinions covered 22 out of the 29 nutrients, which were considered to be within their mandate for this task. The SCF did not have sufficient time to adopt opinions for the following vitamins and minerals: vitamin C, chloride, fluoride, iron, phosphorus, potassium and sodium. In addition, during the decision making process for the adoption of Directive 2000/46/EC on food supplements the Parliament requested that boron, nickel, silicon, vanadium and tin should be allowed to be used in food supplements. Therefore, the European Food Safety Authority is asked to provide scientific opinions on the remaining 12 vitamins and minerals in accordance with the present terms of reference.

TERMS OF REFERENCE

With respect to the outstanding 12 vitamins and minerals, the European Food Safety Authority is asked 1) to review the upper levels of daily intakes that are unlikely to pose a risk of adverse health effects; 2) to provide the basis for the establishment of safety factors, where necessary, which would ensure the safety of fortified foods and food supplements containing the aforementioned nutrients.

ASSESSMENT

1. INTRODUCTION

Silicon is a non-metallic element with atomic weight of 28. It occurs in the earth’s crust at an average concentration of about 28%, but does not exist in nature in forms other than as silicon dioxide (silica) or as silicates (Friedberg and Schiller, 1988). Silica consists of free silicon dioxide, which is amorphous (e.g. diatomaceous earth) or crystalline (e.g. quartz, tridymite and cristobalite), or in combination with various cations as silicates (e.g. Fuller’s earth, asbestos, talc and mica). Silicon in water is present as ortho-silicic acid Si(OH)₄. Silicic acid exists as monosilicic acid. A saturated solution contains 0.1% silicic acid. Silicic acid can also exist as oligomers and as polysilicic acid, which is colloidal. The chemistry of silicon has many similarities to that of carbon. It forms bonds with silicon, hydrogen, oxygen, nitrogen and carbon. The substitution of carbon for silicon in organic compounds results in molecules with different properties due to a larger size and electronegativity of silicon.

2. NUTRITIONAL BACKGROUND, FUNCTION, METABOLISM AND INTAKE

The essentiality of silicon for man has not been established and a functional role for silicon in humans has not yet been identified. In animals silicon is found in bound form that has never been fully characterised. Probably, it is present as silicic acid or silanolate, which may play a role in the structural organisation of some mucopolysaccharides (Nielsen, 1994). In chicken and rats, silicon appears to be involved in bone formation and metabolism (Nielsen, 1994).
Silicon is found in connective tissues, including aorta, trachea, tendon, bone and skin. In blood silicon is not bound to protein and exists as silicic acid (Carlisle, 1984). Both the distribution of silicon in animals and the effect of silicon deficiency on the form and composition of connective tissue support the view that silicon functions as a biological cross-linking agent contributing to the architecture of connective tissue (Carlisle, 1984 and 1988). In 1972, Carlisle and Schwartz and Milne reported that silicon deprivation in chicks and rats led to abnormally shaped bones and cartilagenous tissue, which both were restored upon supplementation with soluble silicon. Subsequent studies confirmed these findings and also extended them to calves (Carlisle 1980a and b; Calomme and Vanden Berghe, 1997). Silicon was detected in small areas of ossifying bone during mineralisation, but less silicon was found in bone at a later stage in bone development. Rats deprived in silicon show decreased bone hydroxyproline and alkaline- and acid phosphatase activity (Seaborn and Nielsen, 1993 and 1994). Furthermore, silicon deprivation in rats decreases collagen formation in wounds and bone and liver ornithine transaminase activity a key enzyme in proline synthesis (Seaborn and Nielsen, 2002). Silicon appears to increase prolyl-4-hydroxylase, galactosyl-hydroxyl-lysyl glucosyl-transferase and lysoxidase activities, enzymes that modify collagen (Nielsen, 1994). Silicon is apparently also involved in bone calcification, but the mechanisms are unclear (Nielsen, 1994). While a role for silicon has not been defined in humans, recent in vitro studies show that orthosilicic acid at physiological concentrations stimulated collagen type 1 synthesis, probably by modulating prolyl hydroxylase activity, in human osteoblast-like cells and to a lower degree in skin fibroblasts, and promoted osteoblastic differentiation (Reffitt et al., 2003).

A significant portion of dietary silicon (20-50 mg/day) is excreted in the urine (8.7 to 33.1 mg/24 hours) suggesting that silicon in the diet is fairly well absorbed (literature reviewed in Reffitt et al. 1999). Silicon from beverages is apparently well absorbed as Bellia et al. (1994) found that 42-75% of silicon in beer was excreted in the urine. However, there are only a few reports where the uptake and excretion of silicon ingested as orthosilicic acid in water are described. Popplewell et al. (1998) used 32Si and determined silicon in urine by accelerator mass spectrometry in one healthy male. Within 48 hours 36% of the dose was excreted into the urine and the elimination appeared to be near to complete. Two first-order phases of elimination with half-lives of 2.7 and 11.3 hours were found. Reffitt et al. (1999) studied silicon kinetics following intake of orthosilicic acid in water (27-55 mg/L) in healthy individuals, six men and two women. Based on urinary excretion, the uptake was about 50% (range: 21-74%). Silicon peaked in blood after about 1 hour. Renal clearance was 82-90 mL/min suggesting high renal filtration and a significant correlation was found between creatinine clearance and silicon levels in urine or serum. In a second study they compared the bioavailability of monomeric and oligomeric silicic acid (Jugdaohsingh et al., 1999). Following administration of monomeric silicic acid 53% was excreted in urine, whereas ingestion of oligomeric silicic acid only caused a marginal increase of silicon in urine. Recently the bioavailability of silicon from solid foods, excluding silicon from fluids, was studied, and Jugdaohsingh et al. (2002) found that a mean of 41% was excreted in urine. This is contrary to the common belief that bioavailability of silicon from phytolithic silica in plant-based food is low.

Fasting concentrations of silicon in plasma are 2-10 µM, increasing to 20-30 µM after meals. Urinary excretion is approximately 700 µmol/day, equivalent to 19.6 mg silicon/day (Jugdaohsingh et al., 2000; Reffitt et al., 1999). The significance of renal elimination of silicon is demonstrated by higher serum concentrations of silicon in patients with chronic renal failure compared to healthy controls (Dobbie and Smith, 1986).
Mean silicon intakes in US population groups were estimated on the basis of the original Framingham and Framingham Offspring cohorts by Jugdaohsingh et al. (2002), who found intakes to be 30 and 33 mg/day in men and 24 and 25 mg/day in women in the two cohorts, respectively. Silicon intake decreased with age.

The daily intake from the British diet has been estimated to 20-50 mg (Bellia et al., 1994; Pennington, 1991). The relative contributions were 55% from water, coffee and beer, 14% from grain products and 8% from vegetables.

Silicon in the form of silica is found in supplements and, according to the recommended doses by the producers, provides 1-75 mg silicon/day, corresponding to 0.017-1.5 mg silicon/kg body weight/day (e.g., products on the Norwegian market, according to the Norwegian Institute of Public Health).

Silicon in the form of amorphous silica, silicates and dimethylpolysiloxane is added to food as anti-caking and anti-foaming agents. Dimethylpolysiloxane is used for the treatment of infant colic. JECFA established ADIs as non-specified for silica and a number of silicates and the SCF established a group ADI as non-specified for silica and a number of silicates (SCF, 1991; WHO, 1969, 1974a and b).

A Recommended Intake for silicon has not been established due to insufficient data and lack of functional criteria (FNB, 2001; SCF, 1993).

3. HAZARD IDENTIFICATION

3.1 Genotoxicity

Silica is considered not to be genotoxic in vitro or in vivo (IARC, 1987).

3.2 Animal toxicity data

Virtually no studies on the toxic effects of soluble silica have been identified. A few quite old studies in rabbits showed that intravenous injection of polysilicic acid (“colloidal silica”) 100 mg/kg body weight caused immediate death due to blood clotting. Daily intravenous injection of ≥5 mg “silica sol” in rabbits caused liver fibrosis, enlargement of the spleen and interstitial nephritis. Focal areas of necrosis were seen in midzones of the liver lobules and an increase in transaminases in serum (Friedberg and Schiller, 1988).

Ruminants consuming plants with a high content of silicon may develop silicate renal calculi (Bailey, 1981).

Amorphous silicon dioxide, aluminium, calcium, magnesium and sodium aluminium silicates were evaluated by JECFA in 1969 and 1974 (WHO, 1969, 1974a and b). In these reports several studies on oral amorphous silica fed to rats were reported. Generally no adverse effects were seen except for a reduction in body weight gain in rats fed 2.5% micronised silica gel in the diet or in rats fed a hydrophobic preparation of amorphous polymeric silica, in which silanol groups on the surface had been reacted with dimethyl-dichlorosilane, when the dose had been raised to 8000 mg/kg body weight. No adverse effects were observed in rats fed 100 mg amorphous silica/kg body weight/day for 2 years.
Kawate (1969) studied groups of rats fed 0.375 to 3 g of silica per day and rat for seven days. No fatalities, clinical signs or changes in gross pathology were reported.

Dobbie and Smith (1982) investigated nephrotoxicity of magnesium trisilicate, crushed and ball-milled quartz and granite in guinea pigs. The three substances were suspended in their drinking water (250 mg/L) and given five days per week for four months. The concentrations of silicon in the supernatants of the suspensions in drinking water were 10, 267 and 29 µmol/L for tap water, magnesium trisilicate and granite, respectively. Renal lesions involving distal tubule and collecting ducts including interstitial inflammation between affected tubuli were found in all animals given magnesium trisilicate (estimated dose: 50-100 mg magnesium trisilicate/kg body weight/day) and two of six animals given crushed quartz.

Newberne and Wilson (1970) showed that oral administration of sodium silicate and magnesium trisilicate (1.8 g/kg body weight/day) for four weeks produced renal tubular damage and chronic interstitial inflammation in dogs, but no nephrotoxicity in rats. No renal lesions were found in dogs following equivalent doses of silicon dioxide and aluminium silicate.

Takizawa et al. (1988) fed groups of 40 B6C3F1 mice 0, 12500, 25000 or 50000 ppm (mg/kg) of food grade micronised silica (SYLOID) (an anti-caking agent) in the diet for up to 21 months. Mean cumulated intakes by week 93 were 38.5, 79.8 and 160.2 g/male mouse and 37, 72.5 and 157.6 g/female mouse. The growth in the groups on the top dose (corresponding to 7500 mg silica/kg body weight/day or 3500 mg silicon/kg body weight/day) was reduced. No other observations or adverse effects were reported following gross and microscopic pathology. Lymphomas and leukaemia occurred in controls and treated groups, but tests for positive dose-related trends were not significant, and these malignancies were therefore not considered to be treatment-related.

Takizawa et al. (1988) fed groups of 40 Fischer rats 0, 12500, 25000 or 50000 ppm (mg/kg) of food grade micronised silica (SYLOID) (an anti-caking agent) in the diet for up to 21 months. Mean cumulated intakes by week 103 were 143.5, 179.6 and 581.2 g/male rat and 107.3, 205 and 435.3 g/female rat. Liver weights were reduced in the mid- and high dose only in females at 12 and 24 months, but not dose-related. However, the body weights were also reduced and no specific changes were reported on liver histopathology. The high dose corresponds to 2500 mg silica/kg body weight/day or 1170 mg silicon/kg body weight/day).

### 3.3 Reproductive and developmental toxicity

A two-generation reproduction study was performed in rats with oral administration of 100 mg amorphous silica/kg body weight/day. No adverse effects were observed (WHO, 1974).

### 3.4 Human data

There are no reports on human toxicity following intake of silicon occurring naturally in food. Humans have for decades consumed low levels of amorphous silicates as food additives used for anti-foaming and anti-caking purposes without any reported deleterious effects (Nielsen, 1994).

Humans have used silicon in the form of magnesium trisilicate extensively as an antacid for several decades. The only adverse effect that has been reported is the formation of renal
silicate stones (Farrer and Rajfer, 1984; Lee et al., 1993). Silica urolithiasis is generally rare and up to mid 1980 was reported only in patients exposed to magnesium trisilicate (Haddad and Kouyoumdjian, 1986). In only one case urinary silicon was determined and it was 1 mmol/L (Haddad and Kouyoumdjian, 1986). More recently a few cases with silica stones were reported in subjects not ingesting trisilicate antacid (Ichiyanagi et al., 1998). In these cases the source of silicon was unknown. Very recently, renal silica calculi were reported in an infant in whom the aetiology was ascribed to consumption of milk diluted with silicon-rich spring water (172 mg silicon/L) (Nishizono et al., 2004). The silicon concentration in the water was approximately 7- to 34-fold higher than the average concentrations in tap water in Japanese prefectures and far above concentrations of silicon in drinking water in the UK, which were all below 6 mg silicon/L (Dobbie and Smith, 1986). It was estimated that the intake of silicon in this infant was approximately 172-206 mg/day. Urinary concentration of silicon was not measured.

Inhaled silica, particularly crystalline forms, is well known to cause the lung disease silicosis. Chronic inhalation may apparently also result in renal toxicity characterised by glomerular and tubular changes and a number of cases and some epidemiological studies have been reported (Stratta et al., 2001). Nephropathy occurs in silica-exposed individuals both with and without silicosis. Affected patients may also show elevated levels of silicon in the kidneys (Saldanha et al., 1975). Ceramic workers exposed to silica dust were found to have an increased risk of end stage renal disease (Rapiti et al., 1999). Increased prevalence of renal disease was also seen in fluorspar miners exposed to silica (Fenwick and Main, 2000). The mechanism of silicon induced nephropathy is not known.

Patients with renal failure generally have a higher concentration of silicon in plasma than healthy subjects. In two dialysis patients with high silicon levels, 137 and 84 µmol/L, painful skin eruptions, folliculitis, and disturbed hair growth were observed. The authors suggested that these symptoms could be caused by silicon (Saldanha et al., 1997). Abnormal hair growth following exposure to organic silicon compounds has been reported previously. Penetrating folliculitis has been reported in dialysis patients previously, but was not specifically related to high silicon concentrations in plasma (Saldanha et al., 1997). Such lesions were, however, not reported in another report on haemodialysis patients who had silicon plasma concentrations in the same range (Parry et al., 1998). Thus, a causal relationship between these symptoms and silicon exposure cannot be established.

### 3.5 Interactions with aluminium

Silicon is thought to act as an antidote to aluminium toxicity by reducing the bioavailability of aluminium. Even modest levels of silicon in water can protect against aluminium toxicity in fish (Parry et al., 1998). Silicon reduces aluminium accumulation in the brain of aluminium-exposed rats (Belles et al., 1998), but does not apparently protect against aluminium-induced developmental effects in rats (Belles et al. 1999). Silicon addition to drinking water containing aluminium reduces the plasma peak of aluminium in humans (Edwardson et al., 1993). Oligomeric, but not monomeric silicic acid prevents aluminium absorption in humans (Jugdaohsingh et al., 2000). Silicon in beer has been shown to promote the excretion of aluminium from body stores (Bellia et al. 1996), but this was not confirmed in a recent study on monosilicic acid (Jugdaohsingh et al. 2000). It has been proposed that silicon in drinking water might protect against the neurotoxicity of aluminium; however, there are no clear conclusions (Rondeau, 2002).
In patients undergoing renal transplantation, serum silicon, unlike aluminium, progressively decreased with improving renal function (Bellia et al., 1994). In a study on haemodialysis patients, Parry et al. (1998) found that patients with high serum silicon had a lower serum concentration of aluminium. The authors suggested that patients with high serum aluminium levels might be protected from aluminium-related toxicity provided they had a serum concentration of silicon in the range of 100-150 µmol/L.

Red cell superoxide dismutase (SOD) is reduced in haemodialysis patients (Shankin-Kestenbau et al., 1990a). It is well known that aluminium can inhibit SOD; however, recently it was also found that silicon concentrations similar to those found in serum of uraemic patients inhibit SOD in vitro (Shankin-Kestenbau et al., 1990b).

4. DOSE-RESPONSE ASSESSMENT

There are no data demonstrating a dose-response relationship for adverse effects, such as silicate renal stones or other renal effects, in humans.

Short-term oral exposure with daily intakes of 1.8 g/kg body weight of sodium or magnesium silicate produces adverse renal effects in dogs, but not in rats (Newberne and Wilson, 1970). Similar doses of silicon dioxide and aluminium silicate did not produce adverse renal effects in either species. Renal effects have been reported in guinea pigs exposed orally to high doses of magnesium trisilicate (50-100 mg/kg body weight/day) (Dobbie and Smith, 1982).

Long-term toxicity studies in rats and mice (Takizawa et al., 1988), show apparent effects on growth at 2500 and 7500 mg silica/kg body weight/day, corresponding to 1170 and 3500 mg silicon/kg body weight/day, respectively. This effect was not regarded as a toxic effect, but was rather due to nutritional imbalance because of the high dose of silica added to the diet. These studies do not provide any information on the bioavailability of water-soluble forms of silicon from silica, which presumably is low, and hence the systemic load of silicon is not known. The extrapolation of these data to other forms of silicon (such as silicates) is inappropriate.

CONCLUSIONS

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

There are no suitable data for dose-response for establishment of an upper level.

2. RISK CHARACTERISATION

Silicon has not been shown to be essential for humans.

In addition to naturally occurring silicon in the diet, food also contains silicon in form of additives. The systemic availability of silicon from these additives varies, but is generally low. The estimated typical dietary intake (20-50 mg silicon/day) corresponds to 0.3-0.8 mg/kg body weight/day in a 60 kg person. These intakes are unlikely to cause adverse effects.
REFERENCES


PANEL MEMBERS


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