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Assessment of safe upper limits for vanadium, nickel, silicon, tin, potassium and phosphorus

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Assessed by

The report has been evaluated and approved by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of VKM.

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BACKGROUND

The European Commission is planning the setting of maximum limits of vitamins, minerals and trace elements in food supplements and in foods with added vitamins and minerals. For several vitamins, minerals and trace elements there is not sufficient data to determine a tolerable upper intake level.

TERMS OF REFERENCE

The Norwegian Food Safety Authority has asked The Panel on Nutrition, Dietetic Products, Novel Food and Allergy the following questions regarding vanadium, nickel, silicon, tin, potassium and phosphorus:

1. For those vitamins and minerals where there are not sufficient data to determine a tolerable upper intake level (UL): What should be set as an upper safe limit, based on which health risks? Opinions given by other expert groups should be taken into consideration.
2. Are there special conditions in Norway that should be taken into account when determining safe limits for vitamins and minerals without UL.

ASSESSMENT

Criteria for essentiality of vitamins and minerals

Most elements in the periodic table are found in the human body irrespective of having a known function or not. In addition to the elements that form the core of most molecules (“the

elements of life"), i.e. H, O, C, P, N and S, we know that some elements are essential for electrolyte balance, i.e. Na, K, Cl, Mg, and P. Furthermore, a number of elements are given the honorary title of essential minerals or trace elements, some of them having a dual function as electrolytes and minerals.

Unfortunately, there is no general consensus in the scientific world as to which trace elements should be classified as essential.

The first among the classical criteria for defining a compound as essential for humans, is that

a) a biological function for the nutrient should be known

Furthermore, in an otherwise adequate diet:

b) deficiency symptoms appear or biochemical activity is reduced when the nutrient in question is insufficient in the diet or the endogenous production is inadequate

c) the signs and symptoms disappear when the nutrient is reintroduced

Following these criteria very strictly, only iron, iodine, zinc, selenium, copper and (possibly) chromium are essential trace elements for humans.

However, the criteria for essentiality of trace elements have been modified, and in 1996 an Expert Consultation of the World Health Organization (WHO)/Food and Agricultural Organization (FAO)/International Atomic Energy Agency (IAEA) suggested a new definition (1): "An element is considered essential to an organism when reduction of its exposure below a certain limit results consistently in a reduction in a physiologically important function, or when the element is an integral part of an organic structure performing vital functions in the body".

According to these criteria, manganese, fluoride, cobalt and molybdenum are also essential to humans. They are integral parts of organic structures performing vital functions in the body, although deficiency symptoms have never been diagnosed in humans.

Several elements are on an imaginary "waiting list" for obtaining full status as essential trace elements for humans. Functions and deficiency symptoms have been identified in several animal species, but not in a number sufficient to substantiate essentiality for humans.

"Proof of essentiality of an element in one species does not prove essentiality in another, but the probability of an essential function in any species (including humans) increases with the number of other species in which essentiality has been proved" (1).

The process of becoming classified as an essential element for humans can be illustrated by selenium. It took 22 years from the discovery of selenium being essential to rats (1958) till it was accepted as essential to humans (in 1980), and a similar history applies to zinc and chromium. Diets deficient in arsenic, boron, bromine, lithium, molybdenum, silicon, tin or vanadium can induce deficiency signs in certain animals, and to some extent, their function has been revealed (2). Nevertheless, as long as no reduced biochemical activity or clear deficiency signs have been observed in humans, they are not universally accepted as essential to us (3).

The lack of consensus about which trace elements are essential and resulting differences in regulatory laws has given room for uncertainty among health professionals and consumers and has provided ample space for conditional input from food supplement promoters.

Nickel, tin, vanadium and silicon are not included in EU's positive-list for food supplements and not in the fortification regulations. Furthermore, the SCF/EFSA has claimed all four not to be essential for humans (4).

Vanadium (V)

Vanadium dependent enzymes have been found in lower organisms such as bacteria and algae, but in higher animals and humans no specific biochemical function has yet been identified. There are speculations that vanadium may play a role in the regulation of some enzymes connected to hormone, glucose and lipid metabolism, but conclusive evidence is lacking. In isolated cell systems, vanadium compounds have been shown to mimic the action of insulin. Their use in the therapy of diabetes mellitus has therefore been discussed (5).

The toxicity of vanadium depends on its physico-chemical state; particularly on its valence state and solubility. Data from animal studies suggest that vanadium has adverse effects on both male and female reproduction and on the development on the subsequent offspring. There are insufficient data to establish whether or not this effect could occur in humans (4). Vanadium is not classified as a carcinogen.

Dietary intake is estimated to be in the range of 10 – 20 µg/day, with highest concentrations found in whole grains, seafood, meats and dairy products. Vanadium is included in several mineral supplements on the European marked (at levels up to 25 µg/tablet), and is especially popular in supplements consumed by weight training athletes, where doses are at mg levels (5). The intake from such supplements can be similar to the doses causing adverse effects in rats and humans, in spite of vanadium compounds being poorly absorbed through the gastrointestinal system.

Based on animal studies and clinical experience with humans, there is not sufficient data to establish a tolerable upper intake level.

As vanadium has not been shown to be essential for humans and has no nutritional value, and since vanadium may act as a pro-oxidant in relatively low doses, excessive intake from fortified foods and food supplements should be avoided until a tolerable upper intake level can be established. Vanadium should not be permitted in supplements or fortified foods.

Nickel (Ni)

Nickel is essential for the catalytic activity of some plant and bacterial enzymes. However, biochemical functions in humans or higher animals have not been found. Nickel deficiency symptoms have been observed in rats, but not in humans (6).

Nickel at high doses and in certain forms is toxic to both man and animals. Chronic nickel poisoning can affect several organs including the cardiovascular and respiratory systems. Furthermore, the element is teratogenic and has carcinogenic potential. High dietary levels in animal experiments (pigs and hens) resulted in decrease of the Mg, Mn and Zn levels in different tissues (6).

Sensitized individuals may show an allergy to nickel affecting their skin, also known as dermatitis. Nickel is an important cause of contact allergy, partly due to its use in jewelry intended for pierced ears. The amount of nickel which is allowed in products which come into contact with human skin is regulated by the EU.

The intake of nickel from the average diet is estimated to be about 150 µg/day, cocoa, legumes, nuts and oatmeal having the highest content. If these food items are consumed in large amounts, the intake may be considerably higher. Release from kitchen utensils can increase the nickel content of foods.

As nickel has not been shown to be essential for humans and has no nutritional value, it seems meaningless to permit this element in foods or supplements.

Based on animal studies and clinical experience with humans, there is not sufficient data to establish a tolerable upper intake level (4).

As nickel has not been shown to be essential for humans and has no nutritional value, and since nickel may inhibit the absorption of divalent essential metals, excessive intake from fortified foods and food supplements should be avoided until a tolerable upper intake level can be established. Nickel should not be permitted in supplements or fortified foods.

Silicon (Si)

Silicon is found in connective tissues, including aorta, trachea, tendon, bone and skin. If having a function in the human body, this is probably connected to silicon functioning as a biological cross-linking agent contributing to the architecture of the connective tissue.

Short-term ingestion of silicate salts produces adverse renal effects in dogs and guinea pigs, but not in rats. Long-term oral administration of silica at high dose levels inhibits growth in rats and mice, probably due to the nutritional imbalance it causes. 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 data available are inadequate to derive a tolerable upper intake level (4).

The diet provides silicon in amounts between 20 – 50 mg/day, most of it coming from water, coffee and beer. Dietary supplements on the European market may contain 1-75 mg silicon/daily dose.

Based on animal studies and clinical experience with humans, there is not sufficient data to establish a tolerable upper intake level.

As silicon has not been shown to be essential for humans and has no nutritional value, this element should not be permitted in foods or supplements on the European market.

Tin (Sn)

Tin has no known biochemical function, although one study has shown that it might have a function in the tertiary structure of proteins. Rats fed a tin-rich diet exhibited poor growth, decreased efficiency of food utilizations, and changes in mineral concentrations in various organs. The latter is probably due to the extensive inhibition of zinc, copper and iron absorption. In man and animals, gastrointestinal effects (abdominal distension and pain, vomiting, diarrhoea) are the main acute manifestations of toxicity associated with the ingestion of tin (4).

Based on Dutch studies, the diet may provide between 0.65 and 1.7 mg tin/day, but if the consumption of tinned products is high, the intake may exceed 6 mg. The highest concentrations of tin in foods are found in tinned fruit and vegetables. Tin is present in some multi-vitamin and mineral food supplements on the EU market at levels up to 10 µg/tablet. The EU has set a maximum level for inorganic tin in canned foods (200 mg/kg) and canned beverages (100 mg/kg) (EC, 2004).

Based on animal studies and clinical experience with humans, there is not sufficient data to establish a tolerable upper intake level.

As tin has not been shown to be essential for humans and has no nutritional value, this element should not be permitted in foods or supplements.

Potassium

Potassium is an essential mineral in human nutrition; it is the major cation inside animal cells, and it is thus important in maintaining fluid, acid and electrolyte balance in the body.

Adequate intake can generally be ensured by eating varied, and deficiency is rare in healthy individuals eating a balanced diet. Fruits, vegetables, milk and nuts are our richest sources of potassium. A number of food additives also contain potassium, but their contribution to the total daily intake is small. Food supplements can contain substantial amounts. The average daily intake of potassium in European food surveys is in the range of 3000 – 4000 mg/day. Potassium intake has to our knowledge not been estimated in Norwegian country-representative dietary surveys.

About 90 % of ingested potassium is absorbed, irrespective of amount consumed.

The US Food and Nutrition Board set an intake of 4.4 g potassium per day from food as an adequate intake (7). Recommended daily intakes in Europe are in the order of 3.1 – 3.5 g/day (8). A similar recommendation was derived for the Nordic countries (9).

Daily intake of potassium from the diet does not exceed 5 – 6 g/day and has not been associated with any negative effects in healthy individuals. Elderly people may be more vulnerable to potassium toxicity due to reduced renal function.

Intake of potassium chloride (KCl) from tablets has been associated with acute poisoning in humans, with symptoms such as heart failure, cyanosis and cardiac arrest. Gastrointestinal effects include mucosal damage, ranging from mucosal lesions to ulceration. On the positive side, a number of studies have investigated the preventive effect of potassium supplementation on hypertension and heart disease. The majority of these studies show a beneficial effect of potassium supplementation.

In spite of many studies on human beings, the EU SCF has concluded that data are insufficient to establish a safe upper intake level for potassium (4). Intakes up to 5-6 g/day are considered safe if derived from food sources, while long-term intakes of 3 g potassium/day as KCl supplements, in addition to potassium from foods, have been shown to cause no adverse effects in healthy adults. However, some case reports exist showing that gastrointestinal symptoms may appear in healthy subjects taking potassium supplements with doses ranging from 1 to 5 grams potassium/day. In addition, elderly people and some sensitive patient groups, particularly those with impaired kidney function, may be vulnerable to quite low doses of potassium from supplements.

The UK Food Standards Agency has concluded that supplemental doses of up to 3700 mg potassium/day appear to be without effects and can be used as a guidance dose (10). However, their conclusion requires that older people do not take potassium supplements without medical advice. Even if being healthy, elderly people have a gradual decline in kidney function.

In view of elderly people being a large population subgroup, care should be taken to secure that the exposure level of potassium will not increase the risk of kidney malfunction among them, even if they are considered healthy. The Norwegian Panel has not had capacity to go in depth in the matter, but supports a careful approach to setting an upper safe limit.

Thus a safe upper limit from supplements and fortification should not exceed 1 g/day.

Phosphorus

Phosphorus is an essential mineral in human nutrition having multiple functions in the body.

In addition to a structural role in bone (as part of hydroxyapatite), phosphorus is essential in a wide range of biological processes, including membrane fluidity (as phospholipids), energy production and storage, chemical synthesis, cell-signalling, protein function, and nucleic acid synthesis.

Phosphorus is widely found in many food groups, largely as phosphate(s). Dietary sources rich in the element include red meats, dairy products, fish and cereals. A number of phosphate salts are used in foods and soft drinks as additives, and furthermore, phosphorus is used in food supplements and many medicines.

Estimates of habitual dietary intakes in European countries are on average around 1000 – 1500 mg/day, ranging up to about 2600 mg/day. Phosphorus intake has to our knowledge not been estimated in Norwegian country-representative dietary surveys.

Recommended daily intakes have traditionally been linked to calcium requirements. On a molar basis, the ratio Ca:Ph should be 1:1. With this in mind, the SCF established a Population Reference intake of 550 mg/day in adults, while it was set at 950 mg/day for lactating women (8). The US Food and Nutrition Board have made recommendations based upon maintenance of the serum inorganic phosphate level within the normal range, ending up with 700 mg/day for adults. The Nordic countries recommends 600 mg/day for adults (9).

Acute phosphate excess, although rare, can result in renal failure, hypo-calcemia, and hypotension. The condition will almost always be a result of kidney failure. In supplementation trials with humans, the predominant adverse reaction to orally administered phosphorus is osmotic diarrhoea, which has been reported at intakes of 750 mg/day and above. Other mild gastrointestinal effects, including nausea and vomiting, have been noted in some studies. Furthermore, changes in serum parathyroid hormone levels have been reported in supplementation trials in postmenopausal women with reduced mineral density and a history of fracture in healthy men (10). Physiological changes in calcium and parathyroid hormone levels have been associated with intakes of 1500 mg/day and above of supplemental phosphorus. Persons with hypo-vitaminosis D are vulnerable to hyperparathyroidism.

Both the UK Food Standards Agency and EU's SCF consider the data on phosphorus to be insufficient to establish a Safe Upper Level for inorganic phosphates.

The UK has suggested 250 mg/day from supplements to be a level not associated with adverse effects, including mild gastrointestinal upsets. The Norwegian Panel supports this suggestion.

CONCLUSIONS: ANSWER TO THE QUESTIONS POSED BY THE NORWEGIAN FOOD SAFETY AUTHORITIES:

Question: For those vitamins and minerals where there are not sufficient data to determine an UL: What should be set as an upper safe limit, based on which health risks? Opinions given by other expert groups should be taken into consideration.

Answer: It is not possible to set an upper safe limit for nickel, silicon, tin and vanadium, and based on available literature adverse effects from excessive intake can not be ruled out. Thus none of them should be permitted in dietary supplements or in fortified foods.

The UK has suggested 250 mg phosphorus/day from supplements to be a level not associated with adverse effects, including mild gastrointestinal upsets. The Panel on Nutrition, Dietetic Products, Novel Food and Allergy supports this suggestion.

Intake of potassium from supplements and fortified food should not exceed 1 g/day.

Question: Are there special conditions in Norway that should be taken into account when determining upper safe limits for vitamins and minerals without UL.

Answer: The Panel is not aware f special conditions pertaining to Norway that is relevant for the vitamins and minerals without UL.

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