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 POTASSIUM

(REQUEST N° EFSA-Q-2003-018)
(ADOPTED ON 22 FEBRUARY 2005)

SUMMARY

Potassium is an essential nutrient involved in fluid, acid and electrolyte balance and is required for normal cellular function. Dietary deficiency of potassium is very uncommon due to the widespread occurrence of potassium in foods. Available evidence suggests that potassium can modulate blood pressure and increasing dietary potassium intake is associated with lower blood pressure.

Gastrointestinal symptoms (discomfort, mucosal lesions and sometimes ulceration) have been seen in healthy subjects taking some forms of potassium supplements (e.g. slow-release, wax matrix formulations) with doses ranging from about 1 to 5 g potassium per day, or more, but incidence and severity seem to be more dependent on the formulation than on dose. In healthy adults administration of single doses of 5-7 g potassium or more (as chloride or bicarbonate solutions) have been reported to cause elevated plasma potassium, adverse changes in heart function and peripheral nerve symptoms in a limited number of case reports.

In subjects with impaired kidney function and reduced urinary potassium excretion, elevated plasma potassium with adverse effects on heart function have been reported with intakes of potassium in the form of supplements or sodium-reduced salts equivalent to 1 g potassium per day or more in addition to food.

The available data are insufficient to establish a safe upper intake level for potassium.

Based on estimates of current potassium intakes in European countries, the risk of adverse effects from potassium intake from food sources (up to 5-6 g/day in adults) is considered to be low for the generally healthy population. Long-term intakes of about 3 g potassium per day as potassium chloride supplements, in addition to intake from foods, have been shown not to cause adverse effects (elevated plasma potassium or gastrointestinal symptoms) in healthy adults. However, a few case studies have reported that supplemental potassium in doses of 5-7 g/day can cause adverse effects on heart function in apparently healthy adults. In addition, gastrointestinal symptoms have been seen in healthy subjects taking some forms of potassium supplements with doses ranging from about 1 to 5 g potassium per day.

Certain groups, particularly those with impaired kidney excretion of potassium, are sensitive to adverse effects of increasing potassium intake on heart function associated with increases in plasma potassium. These include subjects engaging in strenuous activities leading to dehydration, with diabetes mellitus, with impaired kidney function, on cardiovascular disease drug treatment or other metabolic disorders affecting potassium balance. Elderly people may be more vulnerable to adverse effects of potassium due to reduced kidney function or due to use of drugs affecting potassium balance.

KEY WORDS

Potassium, tolerable upper intake level, gastrointestinal effects, hyperkalaemia, food safety.

BACKGROUND

In 2002, the European Parliament and the Council adopted Directive 2002/46/EC[1] related to food supplements containing vitamins and minerals.

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.

1 - Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements. OJ L 183. 12.7.2002, p. 51.

With a view to provide 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

Potassium is widely distributed in the earth's crust, seawater as a mono-valent cation. It occurs naturally in the form of several mineral salts but does not occur as metallic potassium. Potassium in foods is associated with salts of weak organic acids. Various potassium salts, e.g. KCl, are used in many applications, amongst others as ingredients in foods (e.g. additives), food supplements and drugs, household chemicals etc. In this opinion, the term potassium refers to ionic potassium, except where specific potassium compounds are stated. One mmol potassium is equivalent to 39.1 mg.

2. NUTRITIONAL BACKGROUND, FUNCTION, METABOLISM AND INTAKE

2.1. Food levels and dietary intake

Important potassium sources include potatoes, fruit and berries, vegetables, milk products (excl. cheese) and nuts. Potassium occurs in foods mainly associated with weak organic acids. Potassium is also found in mineral, spring, and table waters, but the content varies considerably. Some mineral waters available on the market can, when consumed in large quantities, contribute significantly to the daily intake. The average dietary intake of potassium according to European food consumption studies is in the range of 3000 to 4000 mg/day. (Table 1). The 95th to 97th percentile intake is in the range of 4000-5500 mg/day.

A number of food additives also contain potassium as the cation. The level of potassium added to foods as additives generally contribute only to a minor degree to the daily intake. Salt substitutes, in which part of the sodium chloride has been substituted with potassium salts (usually KCl), can contribute to the potassium intake.

Food supplements can contribute significant amounts of potassium (usually as KCl), but according to recent food consumption surveys average reported contributions were only up to 5 % of the total potassium intake (see Table 1).

Table 1. The daily intakes of potassium in some EU countries (mg/day)

	Population	N	Method	Supplements	Mean	97.5%
Denmark[a]	males 1-80 y females 1-80 y	1516 1582	7-day record	- -	3500 2900	5200 4300
Finland[b]	men women	912 1095	48-h recall	- -	4000 3200	- -
Germany[c]	men women men women	1268 1540 240 347	Computer-assisted dietary interview	- - + +	3930 3240 4140 3360	- - - -
Netherlands[d]	household	6250	2-day record	-	3448	5339
Sweden[e]	men women	589 626	7-day record	- -	3540 3060	5300 4400
UK[f]	men women men women	833 891 833 891	7-day record	- - + +	3367 2653 3371 2655	5504 4183 5504 4183

[a] Andersen *et al* (1995) - values are means and 95th percentiles.
[b] Männistö *et al* (2003).
[c] Mensink and Ströbel (1999).
[d] Hulshof *et al* (1998) - values are mean and 95th percentiles.
[e] Becker and Pearson (2002) - values are means and 95th percentiles.
[f] Henderson *et al* (2003).

2.2. Nutritional requirements and recommendations

Recommended daily intakes in Europe are in the order of 3.1-3.5 g/day (SCF, 1993). The US Food and Nutrition Board have set an intake of 4.7 g potassium per day from food as an adequate intake, mainly based on the beneficial effects on blood pressure (FNB, 2004).
The losses of potassium via the gastrointestinal tract, urinary excretion and sweat, comprises about 800 mg/day (20 mmol), but 1.6 g/day (40 mmol) is needed to avoid low plasma levels and loss of total body potassium in adults (SCF, 1993).

Potassium deficiency can develop as a consequence of increasing losses from the gastrointestinal tract and kidneys, e.g. during prolonged diarrhoea or vomiting, and in connection with use of laxatives or diuretics. Potassium deficiency due to low dietary intake only is very uncommon, due to the widespread occurrence of potassium in foods. Treatment with diuretics without potassium compensation can, however, lead to deficiency. Symptoms of potassium deficiency are associated with disturbed cell membrane function and include muscle weakness, disturbances in heart function, which can lead to arrhythmia and heart seizure. Mental disturbances, e.g. depression and confusion, can also develop.

The potassium intake may affect sodium balance and low potassium intakes (10-30 mmol/day) may induce sodium retention and an increase in blood pressure, both in normotensive and hypertensive subjects (Gallen *et al*, 1998; Morris *et al*, 1999; Coruzzi *et al*, 2001).

A number of studies of both normotensive and hypertensive subjects indicate that an increased potassium intake, mainly given as a supplement, can lower blood pressure and increase urinary sodium excretion (Whelton *et al*, 1997; Geleijnse *et al*, 2003; Sacks *et al*, 1998; Gu *et al*, 2001; Naismith and Braschi, 2003). However, not all studies showed a clear dose-response effect which could be due to factors such as differences in duration of studies, initial blood pressure, sodium intake, habitual diet, race and age. Other clinical trials and population surveys also indicate that a diet rich in potassium alone, or in combination with calcium and magnesium, may have a favourable effect on blood pressure (Appell *et al*, 1997; Sacks *et al*, 2001; Jula *et al*, 1990; Geleijnse *et al*, 1997; He and MacGregor, 2001).

2.3. Function, uptake and distribution

The total body potassium is estimated to be approximately 135 g in a 70 kg adult man. Extra-cellular potassium, which constitutes around 2% of the body pool, is important for regulating the membrane potential of the cells, and thereby for nerve and muscle function, blood pressure regulation etc.

Potassium also participates in the acid-base balance. The major part of the potassium in the body (98%) is found in the cells where it is the main intracellular cation. Thus intracellular concentrations are substantially greater than extracellular concentrations. A large proportion of the body pool of potassium is found in muscle and the skeleton, and it is also present in high concentrations in the blood, central nervous system, intestine, liver, lung and skin.

The absorption of potassium is effective and about 85-90% of the dietary potassium is normally absorbed from the gut (EGVM, 2003; FNB, 2004). The potassium balance is primarily regulated by renal excretion in urine. A small proportion can be lost in sweat. The major excretory route of potassium is via the kidneys. It is secreted by the renal tubules, in exchange for sodium of the glomerular filtrate (ion exchange mechanism). Excretion in sweat and faeces is negligible, the latter changing only slightly as dietary potassium intake varies over a wide range.

The concentration of potassium in plasma is tightly regulated within a narrow range of about 3.5 to 5 mmol/L. The body is able to accommodate a high intake of potassium, without any substantial change in plasma concentration by synchronized alterations in both renal and extra-renal handling, with potassium either being excreted in the urine or taken up into cells. Thus the plasma or extracellular concentration of potassium does not give a clear indication of the body content of potassium.

Both the renal and extra-renal mechanisms through which potassium homeostasis are achieved are complex in nature, and intimately linked to the cellular handling of other minerals, such as sodium, magnesium and calcium, as well as to water homeostasis. The main process through which the body content of potassium is regulated over extended periods of time is renal excretion. Most of the potassium which is filtered in the glomerulus is re-absorbed in the proximal tubule and loop of Henle. Regulated excretion is determined by the rate at which potassium is secreted in the distal tubule and collecting ducts (Wang, 2004). For the normal unadapted kidney, the maximum excretion rate following an oral dose of 8 g potassium chloride (4.2 g potassium) was up to 130 μmol potassium/minute (5 mg potassium/minute) (Berliner *et al* 1950). If sustained this would be equivalent to excreting 7.3 g K+/day (188 mmol/day). The usual diet provides 0.75 to 1.25 mmol potassium/kg body weight/day, or 29-49 mg/kg body weight/day. On a normal diet a glomerular filtration rate (GFR) below 10 mL/min is rate limiting for potassium secretion if the urine output is less than 600 mL/day. However, balance can be maintained with intakes up to 5 to 10 mmol potassium/kg body weight/day (195-390 mg/kg body weight /day), as renal excretion through a healthy kidney which is adapted to high intakes of potassium can effectively excrete potassium at 10 to 20 times the rate of a kidney which has not been adapted to a high intake.

There are effective mechanisms which enable the body to cope with a wide range of habitual intakes of potassium. These involve complex changes in the kidney, colon and muscle over the shorter and longer term. In response to a large increase in dietary potassium intake, insulin-mediated uptake into skeletal muscle (and probably liver) is increased (Wang, 2004). This transfer of potassium from the extra-cellular to the intracellular space minimizes any rise in plasma potassium concentration in the short term. The potassium which has been buffered by uptake into muscle is eventually released into the extra-cellular fluid during the post-prandial period, and excreted through the kidney. There is a short term renal response to increased potassium in the diet, with stimulation of potassium secretion in the collecting duct within hours of a potassium rich meal. The kidney responds to a sustained increase in potassium intake through a decrease in absorption of potassium in the proximal tubules and adaptive changes in the collecting duct leading to prolonged enhancement of excretion. The combination of insulin mediated buffering in muscle and enhanced renal secretion in the short term, and more marked renal adaptive changes in the long term combine to ensure that plasma levels are maintained within narrow limits when potassium intake is increased. The uptake of potassium into muscle appears reduced in insulin resistant states, such as obesity, and consumption of high fat diets. Presumably this capacity for muscle to hold potassium is finite and therefore on a sustained high intake of potassium, the ability to cope with the dietary intake will be determined by the maximal rate of renal excretion, plus any increase in loss through the distal colon. Colonic losses of potassium may achieve 10 to 20 mmol/day, when glomerular filtration rates fall below 30 mL/minute (from the normal 130 mL/minute).

Therefore, the adverse effects of prolonged higher intakes of potassium are determined by a) local effects on the gastrointestinal tract, and b) metabolic effects determined by the maximum capacity for renal excretion, and to a lesser extent colonic excretion.

3. HAZARD IDENTIFICATION

The available animal data are of limited relevance to human risk assessment and this section is limited to selected considerations of oral toxicity.

3.1. Animal data

3.1.1. Acute toxicity

Acute oral administration of potassium to animals causes changes in acid-base balance, hyperkalaemia, changes in respiratory rate and hypernatraemia. Acute oral administration of potassium chloride in animals has been reported to cause death by respiratory failure, with gastroenteritis and renal tubular necrosis (EGVM, 2003). In rats the oral LD_{50} of KCl is reported to be 2.4-3.0 g/kg body weight (Von Oettingen, 1956; Boyd and Shanas, 1961). The acute toxicity of potassium bromate and potassium iodate has been studied in rats and dogs (Kurata *et al*, 1992; Webster *et al*, 1966). Four of five rats given single intragastric doses of 600 mg potassium bromate died within 24 hours of dosing, while the minimal lethal dose in dogs given orally administered potassium iodate was estimated to 200-250 mg/kg body weight. The higher toxicity of these potassium salts compared to KCl can be attributed to the anions.

3.1.2. Subacute/subchronic toxicity

Effects produced with potassium nitrate (hypertrophy of the adrenal zona glomerulosa) and potassium iodate (haemosiderin deposition in the renal tubules) were attributed to the anions (i.e. the nitrate and iodate moieties) (EGVM, 2003).

3.1.3. Carcinogenicity

There are limited data on the carcinogenicity of potassium chloride (Lina and Kuijpers, 2004). Potassium bromate, potassium iodide and potassium hydrogen carbonate produced cancers in experimental studies, but the effects were attributed to the anions (i.e. the bromate, iodide and hydrogen carbonate moieties) and are thus not relevant to this risk assessment (EGVM, 2003).

3.1.4. Genotoxicity

There are no data on genotoxicity of potassium chloride.

3.1.5. Reproductive toxicity

There are no data on reproductive toxicity of potassium chloride.

3.2. Human data

Daily intakes of potassium from the habitual diet generally do 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 physiological reserve in renal function. Ageing is associated with a progressive loss of kidney volume and GFR fall with each decade (Beck, 1998). This and changes in for example renin release leads to decreased capacity for potassium secretion and thus limits the ability to handle large potassium loads. Elderly are therefore more vulnerable to potassium overload due to increased intake from diet and/or supplements or due to drugs affecting potassium balance. Individuals with pre-existing renal disease, hyperkalaemia, adrenal insufficiency, acidosis or insulin deficiency are also vulnerable, as are those using certain drugs, such as potassium-sparing diuretics, β-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, digitalis, non-steroidal anti-inflammatory drugs. Infants may also be vulnerable to excessive potassium due to limited excretion capacity and immature function (EGVM, 2003).
In some situations for therapeutic purposes relatively large amounts of oral potassium chloride might be given as a matter of course with substantial benefit and no adverse consequence. Low body potassium is ubiquitous in people who are severely malnourished, and in treatment a high priority is given to the provision of potassium. The World Health Organization recommends that up to 4 mmol (156 mg) potassium/kg body weight/day is given as an oral supplement of potassium chloride once an adequate flow of urine has been established, in the acute treatment of infants and young children (WHO, 1999). One report suggests that over 7 mmol (274 mg)/kg body weight/day of potassium might be tolerated without adverse effects in some situations (Manary and Brewster, 1997).

Intake of potassium chloride has been associated with acute poisoning in humans. Case reports have described heart failure, cyanosis and cardiac arrest after ingestion of high doses of potassium chloride tablets (see section 3.2.1).

Gastrointestinal toxicity has also been described after chronic ingestion of potassium chloride in case studies and supplementation studies. This is characterised by abdominal pain, nausea and vomiting, diarrhoea, and ulceration of the oesophagus, stomach and duodenum and ileum.

3.2.1. Hyperkalaemia and cardiac effects

Short-term studies (2-3 weeks) on healthy adults have shown that serum potassium levels were within normal ranges at intakes up to around 15 g potassium per day, provided that fluid intake is sufficient and that intake is evenly distributed over the day (FNB, 2004; Rabelink *et al*, 1990). In a metabolic ward study by Rabelink *et al* (1990) six healthy young subjects (3 males and 3 females) were given a KCl solution to the meals (in total 3.9 g K per meal), which were provided every sixth hour during a 20-day period, i.e. one meal was given during the night, as well 200 mL water was given hourly. The total intake of potassium was 15.6 g/day. Plasma potassium levels rose initially and the mean level after 48 hours was 4.77 mmol/L. About 95% of the ingested potassium was excreted in the urine. The plasma levels then decreased and remained stable throughout the study period. A similar, but more pronounced pattern was seen for aldosterone and plasma renin activity. There was an indication of some initial volume loss, e.g. fall in body weight, which normalised during the study period. This study indicates that intakes up to about 15 g/day, distributed over the day and with adequate fluid intake, may be tolerated in healthy subjects without exceeding the normal range of serum potassium, at least under metabolic ward conditions.

In a long-term study supplementation of the sodium-restricted diet with 3.7 g potassium per day given as KCl tablets 3 times a day was not reported to lead to hyperkalaemia in hypertensive males, although serum potassium levels increased during the first six months compared to the placebo group (Grimm *et al*, 1990). In this study the dietary potassium intake was not given, but can be roughly calculated from baseline data on urinary excretion, which was given per 8 hours (overnight). The mean intake from diet is estimated to about 2.5-3 g/day and the 97.5 percentile to about 4.5-5 g/day (allowing for absorption and incomplete urinary data). The KCl tablets provided 3.7 g/day, but the mean intake was about 3.1 g/day, taking compliance into account. Thus, the estimated total high intake would be about 7-8 g/day.

Acute high doses of potassium might, however, exceed the capacity of the kidney to eliminate potassium and thereby lead to elevated serum potassium levels and disturbed clearance of for example urea. In a study by Keith *et al* (1941) seven normal subjects received single doses of 9.5-17.5 g potassium chloride or bicarbonate (4.9-6.8 g K) in solutions after having a standardized breakfast. In two of the subjects, who received a single dose of 12.5 or 17.5 g potassium chloride or bicarbonate, respectively (6.5-6.8 g K), symptoms as increased T-wave ECG and paresthesia of hands and feet in parallel with marked/or severe hyperkalaemia (8 mmol/L) were observed within 2-3 hours. However, symptoms did not appear in other subjects receiving the same amount of potassium. The data indicate that acute intakes of 80-100 mg/kg body weight (equivalent to 4.8-6 g for a 60 kg person) could cause acute adverse effects in some apparently normal subjects. In subjects with impaired kidney function the capacity to eliminate potassium is limited and a number of drugs also influence potassium elimination. In such cases lower doses of potassium may affect potassium homeostasis negatively.

Case reports of adverse effects associated with high doses of potassium containing supplements (KCl) and salt substitutes have described chest tightness, nausea and vomiting, diarrhoea, hyperkalaemia, shortness of breath and heart failure. The reported doses causing acute effects were 1-94 g/day in adults and 1.5-7 g/day in infants (see Annex 1). Fatal cases of acute or chronic potassium intake have been reported. For example, a fatality resulted from hyperkalaemia and resultant asystole after ingestion of 21 g of salt substitute representing an oral bolus of 11 g potassium (Restuccio, 1992). A 2 month-old boy died after being given three doses of 1.5 g potassium chloride in two days (2.3 g potassium in total), with breast milk over one and a half days (Wetli and Davis, 1978).

Severe cardiac complications (fatal and non-fatal) and hyperkalaemia have also been reported following sub-chronic and chronic ingestion of salt substitutes or supplements.

A 75 year-old women with previous myocardial infarction developed heart failure after 6 weeks of consuming salt substitutes and a low-sodium diet (Snyder *et al* 1975).

Schim van der Loeff *et al* (1988) report of a 29-year-old woman who suffered a cardiac arrest, due to profound hyperkalaemia, which was attributed to the use of a potassium-containing salt substitute. The patient was resuscitated, but post-hypoxic brain damage occurred.

A 31 year-old body builder developed ventricular tachycardia and collapse due to myocardial infarction, while consuming potassium supplements (5 g/day, duration unknown) in addition to anabolic steroids, amphetamines and potassium sparing diuretics (Appleby *et al,* 1994).

Parisi *et al* (2002) report a case of a 14-year old football player suffering from premature ventricular beats. He used to take regularly a hydrosaline supplementation, which gave him a daily intake of potassium of about 5 g. Hyperkalaemia was found. After refraining from potassium supplementation and sport for 3 months clinical examination showed no ventricular arrhythmias and plasma concentration was normal.

In subjects with impaired kidney function high potassium intakes from diet and potassium containing salt substitutes may lead to hyperkalaemia. A typical case is reported by Doorenbos *et al* (2003), in which a 74-year old woman with end stage renal disease developed severe hyperkalaemia after use of a potassium-containing salt substitute, of which at least two-thirds was potassium chloride. After ceasing to use the salt substitute, no further episodes of severe hyperkalaemia occurred.

These case reports emphasize the potential risk of excessive use of salt substitutes and supplements, especially when used by subjects who are predisposed to retain potassium.

3.2.2. Gastrointestinal effects

Administration of potassium as KCl supplements has been associated with negative effects on the gastrointestinal mucosa. The majority of studies refer to patients treated with potassium supplements. Reported side effects include mild mucosal lesions to ulceration, sometimes leading to death. The occurrence and severity of the effects depend on a number of factors of which formulation of the preparation, dose and gut transit time seem to be the most important.

Other symptoms such as nausea, stomach pain, vomiting and diarrhoea have been reported in supplementation studies but they were often seen in the control groups as well (Svetkey *et al*, 1987; Grimm *et al*, 1990; Gonzalez *et al*, 1998)

McMahon *et al* (1982) studied the effects of two types of potassium chloride supplements (microencapsulated or wax-coated) on gastrointestinal lesions. Forty-eight healthy volunteers were given a supplement of 96 mmol/day (3.7 g) or 24 mmol (0.9 g) potassium for a week. Twelve subjects were given glycopyrrolate and either of the KCl preparations. The remaining 24 subjects were randomised on either preparation without glycopyrrolate. Subjects were gastroscoped, the endoscopist being blind to the type of preparation taken. Wax-matrix formulations were associated with a higher incidence of upper gastrointestinal lesions (score 26-41) than microencapsulated (score 0-3). Lesion scores were of the same magnitude on 96 mmol/day and 24 mmol/day - score 30 and 26, respectively. The lesions were not accompanied by epigastric symptoms. Glycopyrrolate, given to delay gastric emptying, was associated with higher lesion score for gastric and duodenal side effects. Gastrointestinal erosions occurred with only mild symptoms being apparent. The total potassium intake was not stated.

In another study by the same group (McMahon *et al*, 1984), eight controlled 1- or 2-week experiments involving 225 healthy male subjects and one study of 18 patients with hypertension, nine of whom were long-term users of a wax-matrix potassium chloride preparation, were conducted to evaluate the upper gastrointestinal safety of oral KCl supplements. Subjects were given either wax-matrix KCl tablets, KCl liquid, microencapsulated KCl, a potassium-sparer, or placebo and were examined after treatment. Some subjects received an anticholinergic drug with treatment to induce delayed gastric motility. Results indicated that upper mucosal injury, particularly erosions (43%) and ulcerations (11%), were more frequent after wax-matrix tablets. These changes occurred less frequently after liquid KCl (0%), microencapsulated KCl (10.5% erosions, 1.2% ulcers), and the potassium-sparing drug (0%). More serious and more frequent lesions were associated with slowed motility. No occult bleeding was noted. Symptomatic complaints did not correlate with endoscopic findings. In the long-term study with patients with hypertension, endoscopic examination after 19 to 23 months on KCl showed that six of nine of the patients given a wax-matrix KCl supplement had significant lesions. One had developed ulceration after 7 days. However, the nature of the placebo given was not stated and the incidence of mucosal damage was higher in the placebo group than for subjects given some of the potassium preparations.

McLoughlin (1985) compared 7-day administration of three different forms of KCl preparations (wax matrix, microencapsulated and controlled release systems) administered three times daily in 45 healthy subjects. Oesophagus, stomach and duodenum were examined with endoscopy. The preparations were given in a random order and endoscopist was unaware of the order. Seven of the 15 subjects taking wax matrix KCl

showed erosions and two showed hyperaemia only. Of the 15 subjects taking microencapsulated KCl, one showed erosions and two showed hyperaemia only, while none of those taking the controlled release preparation showed erosions and four had hyperaemia. The dosage was not stated.

Small bowel ulceration at an incidence of 3 per 100,000 patient year of medication in 13 surgical clinics in Stockholm County treated with slow-release (wax matrix) KCl tablets during 1970-83 (Leijonmarck and Räf, 1985). The figure is higher than figures given by the authors for the USA, 1 per 100, 000.

A large number of studies have investigated the preventive effect of potassium supplementation on hypertension and heart disease (Whelton *et al*, 1997). The study groups included both normal, healthy subjects and subjects with hypertension and heart disease. The majority of these studies have shown beneficial effects of potassium supplementation (usually as KCl). Although adverse effects have not generally been reported, except gastrointestinal effects, it is often unclear whether adverse effects were investigated. In the study by Grimm *et al* (1990) supplementation with 96 mmol microcrystalline KCl (3.7 g K, with an effective dose of 3.1 g) or placebo for 2 years the reported incidence of side effects was comparable in the placebo and treatment groups. In a double-blind, placebo-controlled study by Svetkey *et al* (1987) 101 subjects with mild hypertension were allocated either 120 mmol microencapsulated KCl (4.7 g K in 5 capsules 3 times daily) or placebo for 8 weeks. Side effects of mostly mild character were reported in both groups and confined to a few subjects. Subjects in the treatment group reported somewhat more frequently abdominal pain (18% vs 9%) and belching or flatulence (20% *vs.* 10%). One subject in the treatment group and two in the placebo group discontinued the study due to side effects. The authors state that clinically evident irritation of the gastric mucosa did not occur, nor was occult gastrointestinal bleeding detected. Obel (1989) reported no notable untoward effects in 48 subjects with mild hypertension given 64 mmol/day of potassium (2.5 g K) supplements for 16 weeks.

A few studies have investigated gastrointestinal effects of other potassium salts than KCl. In a randomised, controlled trial Gonzalez *et al* (1998) compared effects on the gastric mucosa of potassium-magnesium citrate with potassium citrate and placebo in 36 healthy adults. Five tablets providing 70 mmol potassium (2.7 g K) or placebo per day were given for 7 days. In addition all subjects took 2 mg/day of glycopyrrolate to delay gastric emptying. On day 8, stools were examined for occult blood and an oesophago-gastroduodenoscopy was performed. Mucosal lesions were scored at five anatomic sites. No significant differences were observed in the endoscopic scores at any site, or in the total lesion scores among the three groups. Erosion or ulcers were found in about 20% of the subjects with no differences between the groups. However, subjects receiving both potassium supplements more frequently reported symptoms like epigastric pain, cramps and loose stools.

In a randomised, crossover study Overlack *et al* (1995) investigated the effect of potassium citrate or chloride supplementation on blood pressure in 25 patients with essential hypertension. Tablets providing 120 mmol/day (4.7 g K) or placebo were given for 8 weeks. Unwanted, unspecific gastrointestinal side effects were observed in 12 patients on KCl, 10 patients on potassium citrate and two patients on placebo. In two patients these were stated to be mild. More severe symptoms were reported in one patient receiving potassium citrate (headache, dizziness and fatigue) and in one patient receiving potassium chloride (*ulcus duodeni*), which needed treatment. Four patients ceased to take the potassium supplements for personal reasons. In another study (Overlack *et al* 1991) the authors compared the effect of a potassium citrate/bicarbonate supplement with placebo on blood pressure in 12 patients with essential hypertension. However, no information on side effects was given.

In summary, potassium supplementation in the form of tablets may cause gastrointestinal symptoms, from mild symptoms and damage of mucosa to ulcers. The effects seem to be more dependent on the formulation than on dose. Slow release, wax coated KCl tablets appear to induce more lesions than microencapsulated tablets (McMahon *et al*, 1982 and 1984). It is unclear if effects depend on type of potassium salt, since few studies have included other salts than potassium chloride.

4. DOSE-RESPONSE ASSESSMENT

4.1. Hyperkalaemia and cardiac effects

There are no reports of adverse effects associated with potassium naturally-occurring in food in healthy subjects. In adults high-level intakes (95 or 97.5 percentile) from diet are reported to 5-6 g/day. A few experimental studies indicate that healthy adults can tolerate potassium intakes up to about 15 g per day provided that the intake is evenly distributed over the day and that fluid intake is sufficient and the renal function is normal (Rabelink *et al*, 1990).

Long-term intake (more than 2 years) of KCl supplements providing an effective dose of 3.1 g potassium per day in 3 separate doses did not cause hyperkalaemia in middle-aged, hypertensive men (Grimm *et al*, 1990) on a sodium-restricted diet. The 97.5 percentile total potassium intake in this study is estimated to be about 7-8 g/day. However, single doses of 6.5-6.8 g potassium given as KCl solution to apparently healthy adults (80-100 mg/kg body weight) have been associated with acute hyperkalaemia, ECG characteristic of hyperkalaemia and paresthesia of hands and feet in a few subjects (Keith *et al*, 1941).

Case studies of adverse effects associated with high to very high doses (Annex 1) of potassium from salt substitutes or supplements (KCl) have described chest tightness, nausea and vomiting, diarrhoea, hyperkalaemia, shortness of breath and heart failure. The reported acute and chronic effects have usually been seen in subjects with impaired renal function, heart disease, on medication for various diseases including heart disease, e.g. diuretics and antihypertensive drugs, or in subjects taking anabolic steroids. A case of hyperkalaemia and compromised heart function in an apparently healthy young subject, which was associated with high intakes of a potassium salt containing beverage has been reported in the literature (Parisi *et al*, 2002). The reported dose was estimated to about 5 g potassium per day, in addition to the dietary intake, which was not stated. It is well known that plasma potassium levels increase during exercise (Lindinger, 1995). Therefore excessive potassium supplementation in connection with exercise may pose an increased risk for conductive heart effects, even in apparently healthy subjects.

4.2. Gastrointestinal effects

Controlled studies show that gastrointestinal symptoms (ranging in severity from discomfort to mucosal erosion and ulceration) can occur in healthy subjects taking some forms of potassium supplements, e.g. slow release, wax-matrix formulations, with doses ranging from 24 to 120 mmol/day (0.9 to 4.7 g K) or more, but incidence and severity seem to be more dependent on the formulation than on dose (McMahon *et al*, 1982 and 1984; McLaughlin, 1985; Overlack *et al*, 1995).

CONCLUSIONS AND RECOMMENDATIONS

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

The available data are insufficient to establish an upper level for potassium.

2. RISK CHARACTERIZATION

Potassium intakes from foods have not been associated with adverse effects in normal, healthy children and adults. The average intake in adults from the diet is 3-4 g and the intake generally does not exceed 5-6 g per day.

A long-term intake of potassium supplements as potassium chloride of about 3 g per day in addition to intakes from foods has been showed not to have adverse effects. Supplemental potassium in doses of 5-7 g/day in addition to dietary intake has in a few cases, however, been reported to cause conductive effects and compromised heart function in apparently healthy adults.

Gastrointestinal symptoms have been seen in healthy subjects taking some forms of potassium supplements, e.g. slow release, wax-matrix formulations, with doses ranging from 0.9 to 4.7 g/day or more, but incidence and severity seem to be more dependent on the formulation than on dose.

Elderly people may be more vulnerable to adverse effects of potassium due to reduced physiological reserve in renal function or due to drugs affecting potassium balance. Certain other groups are also sensitive to increases in potassium intakes. These include subjects engaging in strenuous activities leading to dehydration, with impaired renal function, on cardiovascular disease drug treatment or other metabolic disorders affecting potassium homeostasis. Case reports of various adverse effects such as hyperkalaemia, conductive effects and compromised heart function have been reported in such subjects after moderate to high acute or sub-chronic intakes of potassium in the form of supplements or potassium-containing salt substitutes.

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