

## Risk Assessment

## Potassium

### General information

#### Chemistry

Potassium is an alkaline, metallic element. It is not found in the elemental form in nature and is always found combined with other substances, most commonly as the chloride salt (KCl). Potassium is widely distributed in silicate rocks, and occurs in salt beds and seawater. Within this risk assessment, the word potassium refers to ionic potassium, except where specific potassium compounds are stated.

#### Occurrence in food, food supplements and medicines

Potassium is present in all animal and plant tissues. Major dietary sources include milk (1.4-1.5 mg/kg), fruit and vegetables (0.8-4.4 mg/kg), fish (1.9-3.5 mg/kg), shellfish (0.3 to 3.9 mg/kg), beef (2-3.5 mg/kg), chicken and turkey (3 mg/kg); liver is also a rich source of potassium (2.5 to 4.2 mg/kg). Potassium chloride is used in fertilisers and plant nutrients and thus may increase the potassium content of plants. Potassium chloride is the major ingredient used in salt substitutes to satisfy the taste for salt whilst reducing sodium intake.

A range of food additives are potassium salts. Potassium iodide can be added to foods and is used in other countries to supplement iodine intake in iodine deficient regions.

UK food supplements can contain up to 200 mg potassium per tablet as potassium chloride. Licensed medicines containing potassium chloride (300 mg/dose) are available by general sale, for replacement of potassium loss following acute diarrhoea.

#### Other sources of exposure

The potassium content of mineral, spring, table and spa water varies widely.

#### Recommended amounts

The RNI for potassium is 3500 mg/day for adults (over 18 years) of both sexes (COMA, 1991). There is no increased requirement during pregnancy or lactation.

#### Analysis of tissue levels and potassium status

Potassium levels can be measured by flame emission spectroscopy, electron microprobe X ray analysis or measuring the dilution of radioactive isotopes of potassium. Total body potassium is estimated to be approximately 135 g in a 70 kg adult man.

#### Brief overview of non-nutritional beneficial effects

Potassium exerts a beneficial effect on hypertension by lowering blood pressure.

### Function

Potassium, together with sodium, is essential for the maintenance of normal osmotic pressure within cells. About 98% of the total body potassium is located intracellularly where the concentration can be 30 times that of the extracellular concentration. The extracellular potassium concentration is a critical determinant of neuromuscular excitability. Potassium is also a cofactor for numerous enzymes and is required for secretion of insulin by the pancreas, for phosphorylation of creatine and for carbohydrate metabolism and protein synthesis.

### Deficiency

Hypokalaemia most commonly results from increased loss of the element, secondary to diarrhoea, diabetic acidosis, vomiting, intense and prolonged sweating, body burns or diuretic drugs. Rarely, 'crash' or very low calorie diets can result in reduced intake, sufficient to cause potassium deficiency. Hypokalaemia can cause rapid and irregular heart rhythm, muscle weakness and irritability, occasional paralysis, nausea and vomiting, diarrhoea and low muscle tone in the gut, and has been reported to predispose to hypertension.

### Interactions

The balance between sodium and potassium is very important. Excess sodium intake can deplete potassium. Magnesium deficiency results in failure to retain potassium and conversely, excessive levels of potassium may interfere with magnesium absorption. Thallium interacts with potassium in the body, because the active transport mechanisms for potassium do not differentiate between thallium and potassium. In animals, the rate of loss of thallium from the body increases as dietary potassium increases.

### Absorption and bioavailability

About 90% of ingested potassium is absorbed, irrespective of the amount consumed. The majority of potassium absorption occurs in the small intestine, mainly through passive mechanisms.

### Distribution and metabolism

Potassium is transported in the extracellular fluid, and its distribution between cells is tightly controlled, with only 1.5 – 2.5% of total body potassium found in the extracellular fluid.

A large proportion of the body burden 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.

### Excretion

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.

## Toxicity

### Human data

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. 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.

Case studies of toxicity resulting from high doses of salt substitutes have described chest tightness, nausea and vomiting, diarrhoea, hyperkalaemia, shortness of breath and heart failure. For example, a fatality resulted from hyperkalaemia and resultant asystole after ingestion of 21,000 mg of salt substitute representing an oral bolus of 11,065 mg potassium (Restuccio, 1992). A 2 month old boy died after being given three doses of 1500 mg potassium chloride with breast milk over one and a half days (Wetli and Davis, 1978).

### *Supplementation trials*

Numerous potassium supplementation studies have examined the association between increased potassium intake and decreased risk of hypertension and heart disease. The majority of these studies have shown beneficial effects of potassium supplementation. Although adverse effects have not generally been reported, outside the gastrointestinal effect, it is often unclear whether adverse effects were investigated. Although few details were given, it was stated that no adverse effects were apparent in 18 subjects aged 66-79 given 2340 mg potassium (as potassium chloride) for 4 weeks (Fotherby and Potter, 1992) or in subjects aged 21-61 given 1900 mg potassium (form not stated) for 15 weeks (Siani *et al.*, 1987).

In a number of supplementation studies, potassium treatment resulted in ulceration of the gastrointestinal tract, the severity of the effect related to the formulation of the treatment and to factors such as gut transit time. Hyperkalaemia also occurs as a result of potassium treatment.

### Animal data

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.

The subchronic or chronic toxicity of potassium has not been investigated with inert salts such as potassium chloride. 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).

### Carcinogenicity and genotoxicity

There are no data on the carcinogenicity of potassium chloride. 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.

Genotoxicity studies have found that potassium bromate is mutagenic in animal and human cells and can produce DNA oxidation.

### Mechanisms of toxicity

No relevant data have been identified.

### Dose response characterisation

No relevant data have been identified.

### Vulnerable groups

Older people may be vulnerable to potassium toxicity due to reduced physiological reserve in renal function. 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,  $\beta$ -adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, digitalis, non-steroidal anti-inflammatory drugs, arginine hydrochloride and succinylcholine. Infants may be vulnerable to excessive potassium due to limited renal reserve and immature function.

### Genetic variations

No genetic variations that increase susceptibility to toxic effects of potassium have been identified.

## Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD).

*McMahon et al., 1982*

The effect of differing formulations of potassium chloride supplementation on the gastrointestinal tracts of 48 healthy young men was investigated by endoscopy. Wax-matrix potassium chloride preparations (providing 1250 mg potassium) three times a day for seven days (total daily dose, 3700 mg potassium) resulted in considerable mucosal pathology, with erosions, gastric ulcers, inflammatory lesions and bleeding at endoscopy. A microencapsulated form of potassium chloride caused significantly fewer mucosal lesions.

*McMahon et al., 1984*

In a further study, 225 healthy male subjects received either potassium chloride as wax-matrix tablets, in liquid form or microencapsulated, a potassium-sparer or placebo for one or two weeks. The doses used ranged from 900 – 3700 mg potassium/day). Upper mucosal injury (erosions and ulcerations) was more frequent after wax-matrix potassium chloride treatment. It was noted that gastro-intestinal effects were mild and did not correlate with endoscopic evidence of lesions. When hypertensive subjects were treated with 1560-3120 mg potassium/day) slow-release wax-matrix potassium chloride for an average of 21 months, 6/9 subjects developed erosions compared with 1/9 matched controls. Following 7 days of in-patient treatment, one of the 6 subjects with erosions developed an ulcer and a further 2 placebo subjects developed erosions. The authors concluded that cyto-adaptation to potassium chloride treatment did not seem to occur.

*Grimm et al., 1988, 1990*

In a double blind study, groups of males aged 45-68 years were given 3700 mg potassium/day (as potassium chloride) or a placebo (n = 148 in potassium group and 150 in placebo group). Adverse effects reported in both groups after 12 weeks and two years included abdominal pains, nausea and vomiting, diarrhoea and bright red blood in the stools. The effects were not investigated by endoscopy. The incidence was stated to be similar in the two treatment groups.

## Exposure assessment

Total exposure/intake

Food	Mean: 2800 mg/day (from NDNS, 1986/7) 97.5 <sup>th</sup> percentile: 4700 mg/day
Water	Up to 24 mg/day (assuming 2 L/day at the maximum permitted level in the UK)
Supplements	Up to 200 mg/day (Annex 4)

Estimated maximum intake:  $4700 + 24 + 200 = 4900$  mg/day

No potential high intake groups have been identified.

## Risk assessment

A number of case reports of accidental and deliberate poisoning with potassium have shown that large doses of potassium result in hyperkalaemia and hypernatraemia and lead to in changes in acid-base balance and respiratory and heart rates. However, the dose associated with the onset of hyperkalaemia and adverse effects varies depending on potassium status and clearance time.

Supplementation studies have generally not reported side effects, although it is unclear whether side effects were specifically investigated in many of these studies. However, endoscopic investigation following periods of potassium supplementation has shown that potassium supplementation may cause local irritation in the gastrointestinal tract, leading to erosion and ulcerations.

The available animal data are not relevant to this risk assessment as the effects described are considered to be due to the anionic components, such as bromate and iodate.

Older people and infants may be more vulnerable to potassium toxicity due to lower renal function, as may patients with conditions such as pre-existing hyperkalaemia, renal disease, acidosis, insulin deficiency or digitalis intoxication.

#### **ESTABLISHMENT OF GUIDANCE LEVEL**

There are insufficient data to establish a Safe Upper Level for potassium. The amounts of potassium reported to cause adverse effects are variable and depend on factors which include formulation. In the study by Grimm *et al.* (1998, 1990), subjects received 3700 mg/day potassium for 2 years, with the incidence of side effects being comparable in placebo and treatment groups. However, in studies by McMahon *et al.* (1982, 1984), in which subjects were treated with 3700 mg/day potassium, endoscopic examination indicated that gastrointestinal erosions could occur with only mild symptoms being apparent.

Overall, for guidance purposes, it can be concluded that supplemental doses of up to 3700 mg potassium/day appear to be without overt adverse effects (this is equivalent to 60 mg/kg bw/day in a 60 kg adult), but may be associated with gastrointestinal lesions diagnosed by endoscopy. No uncertainty factor has been applied for inter-human variation as this is based on data from a number of human studies. The available animal data are not relevant to this risk assessment. Since the effect appears to relate to the ingestion of potassium supplements, rather than potassium in food, a guidance level for total potassium intake has not been calculated. Extrapolation of the guidance level to children on a bodyweight basis may be inappropriate.

Infants, older subjects and patients with conditions such as pre-existing hyperkalaemia, renal disease, acidosis, insulin deficiency or digitalis intoxication should not take potassium supplementation without medical advice.

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