Brief profiles on systemic toxicological effects of common counter-ions in metal substances:

3. Potassium

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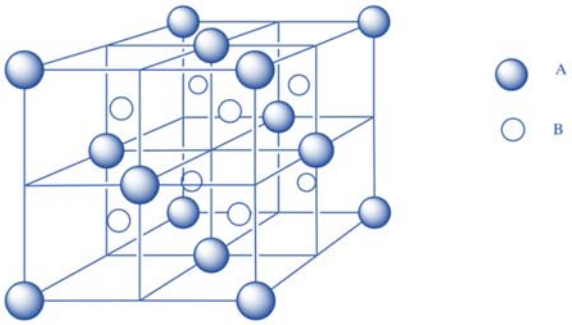

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Potassium: Brief profile on systemic toxicological effects

1. Identification

Name: potassium (cation)
Chemical formula: K^+
Molecular mass: 39.1 g/mol

2. Introductory remarks

Ions such as K^+ are not defined as a substance under REACH since they are always associated with a counterions to maintain electrical neutrality (formation of "salts"). Toxicology of such salts is always a combination of both ions, so that toxicological information is – in most cases - not available for the ion on its own. Potassium is a common cation in salts e.g. of halogens or (oxo)anionic metals.
The aim of this summary on the systemic toxicity of potassium is to assist the assessor of health hazards of such potassium containing substances, in determining whether the potassium moiety contributes to the overall toxicity of the substance. This document does not discuss primary literature or studies in detail. Instead, reference is made to most recently published authoritative reviews (e.g. European Food Safety Authority or WHO). If no other citation is given, statements in this document have been either copied or adopted from EFSA (2016).

3. Natural occurrence, physiological function and dietary intake

Potassium is an essential component in the human diet and is the predominant osmotically active element inside cells. In combination with sodium and chloride, which are characteristic of the extracellular fluid, potassium contributes to osmolarity and plays a major role in the distribution of fluids inside and outside cells. In addition, potassium is involved in the regulation of the acid–base balance. Differences in potassium and sodium concentrations across cell membranes are maintained by the specific permeability of membranes to each of these ions and by Na^+/K^+-ATPase activity, which pumps sodium out of and potassium into the cells (Bailey et al., 2014; Gumz et al., 2015). The enzyme Na^+/K^+-ATPase plays an important role in the strict homeostatic control of plasma potassium concentrations. As a result, the intracellular potassium concentration is about 30 times higher than that of plasma and interstitial fluid. This concentration gradient (largely responsible for driving the membrane potential) is important for the transmission of electrical activity in nerve fibres and muscle cells. Small changes in the ratio of extracellular to intracellular potassium concentration have large effects on neural transmission, muscle contraction and vascular tone (Bailey et al., 2014; Gumz et al., 2015). Potassium transport across the membranes of the endothelial and vascular smooth muscle cells has important effects on their contractile state, which can, in turn, influence endothelial function, blood flow and blood pressure (Haddy et al., 2006). The concentration of potassium in cells of the collecting duct system of the kidney is important for the excretion of sodium. Maintenance of the transmembrane gradient is the key element for electrolytes and fluid homeostasis, a critical factor in blood pressure regulation (Bailey et al., 2014; Gumz et al., 2015). Passive transport of potassium occurs via intracellular and paracellular pathways. The intracellular transport mechanism involves potassium channels.
Potassium has a role in cell metabolism, participating in energy transduction, hormone secretion and the regulation of protein and glycogen synthesis. Potassium is a cofactor for a number of enzymes including glycerol dehydrogenase, mitochondrial pyruvate carboxylase, pyruvate kinase, L-threonine dehydratase, ATPases and aminoacyl transferase (Page and Di Cera, 2006; Toraya et al., 2010).
Potassium is present in all natural foods, in particular starchy roots or tubers, vegetables, fruits, whole grains, dairy products and coffee. Based on the data from 13 dietary surveys in nine countries of the European Union, average potassium intakes ranged between 821 and 1,535 mg (21 and 39 mmol)/d in infants (< 1 year), between 1,516 and 2,005 mg (39 and 51 mmol)/d in children aged 1 to < 3 years, between 1,668 and 2,750

mg (43 and 70 mmol)/d in children aged 3 to < 10 years, between 2,093 and 3,712 mg (54 and 95 mmol)/d in children aged 10 to < 18 years, and between 2,463 and 3,991 mg (63 and 102 mmol)/d in adults (≥ 18 years) (paragraph quoted from EFSA, 2019).
No tolerable upper intake level (UL) has been set for potassium by EFSA due to insufficient data (EFSA, 2016).[1]

4. Toxicokinetics

About 90% of dietary potassium is absorbed, mainly in the small intestine. Body potassium content is regulated by the balance between dietary intake and renal excretion. Urine is the major route of potassium excretion, while the remaining part is eliminated in the faeces and, to a lesser extent, in the sweat.
Studies in humans reported average urinary excretion of potassium between 77% and 92% of total dietary intake (Mickelsen et al., 1977; Pietinen, 1982; Holbrook et al., 1984; Tasevska et al., 2006; Yoshida et al., 2012). Urinary excretion of potassium varies with dietary intake. According to results published by the Intersalt Cooperative Research Group in late 1980s (Intersalt Cooperative Research Group, 1988), a typical range observed with a mixed Western diet was 46–77 mmol/d. Urinary potassium excretion, based on 24-h urine collection, is regarded as a reliable biomarker of dietary intake in adults on a population basis (EFSA, 2016).
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 (EFSA, 2005).
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^+/d (188 mmol/d) (paragraph quoted from EFSA, 2005).
Most of body potassium is located in the muscle, with lower amounts present in the bone, liver, skin and red blood cells. Because of tight homeostatic mechanisms, blood potassium concentrations and total body potassium content are only minimally affected by variations in dietary potassium intake.
EFSA therefore considered that there is no suitable biomarker of potassium status which can be used for setting DRVs for potassium in the general population (paragraph quoted from EFSA, 2019).

5. Toxicological effects

Based on its omnipresence and physiological function in humans, potassium in ionic form can be considered as “non-toxic”. However, health consequences of both chronic and acute deficiencies and excesses of potassium can occur. Due to the close interrelationship between potassium, sodium and chloride physiology and intakes, it is practically not possible to address standard toxicological data requirements for potassium on its own. The information in the subchapters below is therefore often based on the substance potassium chloride and provided for orientating purposes only. Key information regarding to the setting of safe intake levels of potassium is discussed in the sub-chapter on “repeated dose toxicity” and in the concluding remarks.

Deficiency:
Potassium deficiency, presenting as hypokalaemia, is defined as a serum potassium concentration lower than 3.5 mmol/L (Pepin and Shields, 2012). Hypokalaemia is generally associated with increased morbidity and

[1] Adequate Intake (AI): a value based on observed or experimentally determined approximations of nutrient intake by a group (or groups) of healthy people—used when an RDA cannot be determined.
Tolerable Upper Intake Level (UL): the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases.

mortality, especially from cardiac arrhythmias or sudden cardiac death. When serum potassium concentration is < 3 mmol/L, the prevalence of malignant ventricular arrhythmia has been observed to increase twofold in patients on diuretic treatment (Byatt et al., 1990). The risk of atrial fibrillation is higher in hypokalaemic subjects compared to the general population (Krijthe et al., 2013). Other adverse consequences of hypokalaemia include polyuria, muscle weakness, decreased peristalsis possibly leading to intestinal ileus, mental depression and respiratory paralysis in severe cases (Rodenburg et al., 2014).

Excess:
Hyperkalaemia is commonly defined as a serum potassium concentration greater than approximately 5.5 mmol/L in adults (Pepin and Shields, 2012; Michel et al., 2015). Clinical manifestations of mild to moderate hyperkalaemia are usually non-specific and may include generalised weakness, paralysis, nausea, vomiting and diarrhoea (Pepin and Shields, 2012). Severe hyperkalaemia may lead to life-threatening cardiac arrhythmias (Paice et al., 1983; Lehnhardt and Kemper, 2011). 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 (EFSA, 2005).
The Panel considered that the risk of adverse effects from potassium intake from food sources (up to 5,000–6,000 mg (129–154 mmol)/d in adults) is low for the general healthy population. It also stated that long-term intakes of about 3,000 mg (77 mmol) potassium/d as potassium chloride supplements, in addition to intake from food, have been shown not to have adverse effects in healthy adults (EFSA 2016).

5.1. Acute toxicity

Acute oral administration of potassium to animals causes changes in acid-base balance, hyperkalaemia, changes in respiratory rate and hypernatremia. For potassium chloride, the reported LD_{50} value was 3,000 mg/kg bw in rats (EFSA 2005).

5.2. Sensitisation

Potassium is the predominant osmotically active element inside cells. Due to its omnipresence and physiological function in humans systemic effects such as allergic/sensitising effects are not to be expected and are not reported to date. Thus, no sensitising properties are attributed to the potassium ion.

5.3. Repeated dose toxicity

The literature on the relationship between potassium intake and selected health outcomes, i.e. blood pressure, cardiovascular disease-related endpoints and bone health, was systematically screened and is summarised in several review articles of WHO and EFSA. To minimise the risk of bias in the evidence used in the assessment, the reviews were restricted to randomised controlled trials (RCTs) and prospective studies, that excluded participants who were pregnant, acutely ill or infected with human immunodeficiency virus (HIV).

Estimating potassium intake:
Urinary potassium excretion is a common and valid form of estimating potassium intake. Data from 4680 men and women from 17 cities in four countries showed that average urinary potassium excretion was approximately 77% of intake (12). Therefore, a factor of 1.30 is used to convert urinary potassium excretion to potassium intake. Because original studies reported urinary potassium excretion, data were analysed based on that value. Using the factor of 1.30:

- 70 mmol urinary potassium/day equals approximately 91 mmol potassium intake/day;
- 90 mmol urinary potassium/day equals approximately 117 mmol potassium intake/day;
- 120 mmol urinary potassium/day equals approximately 156 mmol potassium intake/day.

Low potassium intake has been associated with a number of noncommunicable diseases (NCDs), including hypertension, cardiovascular disease, chronic kidney stone formation and low bone-mineral density. An increased potassium intake may reduce blood pressure, decrease risk of cardiovascular disease, have beneficial effects on bone-mineral density, and mitigate the negative consequences of high sodium consumption (WHO 2012).
Evidence in relation to diabetes mellitus type 2, kidney stones and bone health were also reviewed but the available data could not be used to derive DRVs for potassium (EFSA 2016).
Regarding associations between potassium (quantified as urinary sodium "UNa") and cardiovascular disease (CVD), blood pressure and bone mineral density (BMD), EFSA concluded as follows:

- The Panel noted the strengths and limitations of the evidence on the relationship between potassium intake and cardiovascular outcomes and considers that there is evidence that a potassium intake of 3,500 mg (90 mmol)/d has beneficial effects on blood pressure in adults. Furthermore, there is consistent evidence that potassium intakes below 3,500 mg (90 mmol)/d is associated with a higher risk of stroke. Results on the association between potassium intake and coronary heart disease are unclear and inconsistent.
- The Panel considered that there is evidence from RCTs lasting from 4 weeks to 3 years for a beneficial effect of potassium intake on blood pressure in subjects classified as hypertensive (with or without medication), but not in subjects classified as normotensive. Overall, the Panel considered that the evidence on the relationship between potassium intake and blood pressure and stroke can be used for setting DRVs for potassium for adults.
- The Panel noted the lack of evidence about an association between potassium intake and fracture risk and the limited and inconsistent evidence for an effect of potassium supplementation on bone mineral density (BMD). The Panel also noted that most studies used alkaline potassium salts and cannot conclude on an independent effect of potassium on bone health.

5.4. Mutagenicity/genotoxicity

In vitro genotoxic effects of hydrochloric acid and its salts (potassium, calcium and magnesium) were observed only at high concentrations that were associated with low pH or high osmolality of the experimental media, which cannot occur under the physiological conditions *in vivo*. The Panel concluded that the use of hydrochloric acid and its potassium, calcium and magnesium salts as food additives does not raise concern for genotoxicity (EFSA 2019).

5.5. Reproductive/developmental toxicity

No information (epidemiological or animal studies using standardized methods) on reproductive toxicity is available for potassium. Nevertheless, there are no indications that KCl influences fertility in humans. In a prenatal developmental toxicity study, groups of 25 virgin adult female albino CD-1 outbred mice no significant effects of potassium chloride exposure up to 235 mg potassium chloride/kg_{bw} per day (corresponding to 123 mg potassium/kg_{bw} per day) were observed on maternal survival, body weight, total number of corpora lutea, implantation sites, resorptions, live offspring, sex ratio, fetal weight, external abnormalities, soft tissue defects or skeletal defects (EFSA 2019). In a prenatal developmental toxicity study, groups of 21–28 virgin adult female albino Wistar rats no significant effects of potassium exposure up to 163 mg/kg_{bw} per day were observed on maternal survival, body weight, total number of corpora lutea, implantation sites, resorptions, live offspring, sex ratio, fetal weight, external abnormalities, soft tissue defects or skeletal defects (EFSA 2019).

5.6. Carcinogenicity

No treatment-related tumours were observed in male rats fed potassium chloride in the diet (up to approximately 2,000 mg potassium chloride/kg bw per day corresponding to 1049 mg potassium/kg_{bw} per day) for 2 years (Imai et al., 1986). After feeding 1,500 mg/kg_{bw} per day potassium chloride corresponding to 787 mg potassium/kg_{bw} per day) for 18 months, no tumours were reported (Lina and Kuijpers, 2004).

Discussion and conclusion

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 [sic] *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* (paragraph quoted from EFSA 2005).

EFSA (2016) provided a comprehensive overview of dietary reference values (adequate intakes) for potassium. For adults, a dietary reference value of approx. 3.5 g K/d was proposed.

High potassium intakes have been reported to be associated with several health outcomes, particularly cardiovascular endpoints. Overall, the Panel considered that randomised controlled trials and an observational cohort study carried out in a European adult population provide evidence that a potassium intake of 3,500 mg (90 mmol)/d has beneficial effects on blood pressure in adults. Furthermore, there is consistent evidence from observational cohort studies that potassium intakes below 3,500 mg (90 mmol)/d are associated with a higher risk of stroke. Evidence on the association between potassium intake and coronary heart disease is unclear and inconsistent. Evidence in relation to diabetes mellitus type 2, kidney stones and bone health were also reviewed but the available data could not be used to derive DRVs for potassium.

The Panel decided to set DRVs for potassium based on the relationship between potassium intake and blood pressure and stroke. Currently, available data cannot be used to determine the average requirement of potassium but can be used as a basis for deriving an adequate intake (AI). A potassium intake of 3,500 mg (90 mmol)/d can be considered adequate for the adult population and an AI of 3,500 mg (90 mmol)/d for adult men and women is proposed.

No data are available on which to base an average potassium requirement for infants and children. The Panel derived AIs extrapolated from the AI for adults, taking into account differences in reference body weight (isometric scaling) and including a growth factor to take into account requirements for growth. The AI set for infants aged 7–11 months is 750 mg (19 mmol)/d. For children, AIs range from 800 mg (20 mmol)/d (1–3 years old) to 3,500 mg (90 mmol)/d (15–17 years old).

The EFSA Panel considered that the requirement for the daily accretion rate of potassium in fetal and maternal tissues can be met by the adaptive changes which maintain potassium homeostasis during pregnancy. The AI for pregnant women was set at 3,500 mg (90 mmol)/d, the same as for nonpregnant women.

Considering evidence which indicates that total body potassium content decreases in lactating women, a conservative approach was taken, and the amount of potassium needed to compensate for the losses of potassium through breast milk is added to the AI for adult. Thus, an AI of 4,000 mg (102 mmol)/d was proposed for lactating women (paragraph quoted from EFSA 2016).

Potassium "in a nutshell":

Key / leading adverse systemic effect on human health:	See discussion and conclusion.
Relevant (CLP) Hazard Classification(s) for systemic effects:	none
Numerical toxicological descriptor:	An intake of 3.5 g K/d is considered as safe for adults (EFSA 2016), which corresponds to ca. 50 mg K/kg_{bw}/d for a 70-kg person.

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