

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Statement on potassium-based replacements for sodium chloride and sodium-based additives.

Background

1. In 2013, the Department of Health (DH) asked the Scientific Advisory Committee on Nutrition (SACN) to review current recommendations on the use of potassium-based replacements for sodium chloride and sodium-based additives.
2. DH policy has been to lower sodium intakes in the population by gradually reducing levels of salt in food products in a way that will progressively accustom the palates of consumers to less salt. The DH has not recommended the use of potassium-based replacements for sodium chloride and sodium-based additives as a means of achieving salt reduction, as their use would continue to maintain a higher salt flavour in food. Furthermore, there has been concern that some population groups such as infants, the elderly and people with kidney disease, might be vulnerable to increased levels of potassium in food because of immature or impaired renal function. Some patients with diagnosed kidney disease are advised to restrict their intake of potassium, but other people with undiagnosed renal impairment might also be adversely affected if their consumption of potassium increased.
3. Companies that produce food have asked the DH to reconsider its recommendations, as some would like to use (and may already be using) potassium-based replacements to achieve lower levels of sodium in food. The products concerned are those for which further reductions in sodium are difficult to achieve by reformulation, and include items such as bakery goods (e.g. scones, scotch pancakes, crumpets) and meat products (e.g. sausages and bacon) in which the sodium compound has a culinary function – for example, as a raising agent or preservative – as well as flavouring properties. Potassium cannot totally replace sodium as it has a metallic aftertaste, and does not exactly replicate the flavour of sodium. However, it has been suggested that up to 25-30% of added sodium could be replaced by potassium (personal communication, Department of Health); the level of sodium replacement in bread is lower, being up to 15% (personal communication, Federation of Bakers).
4. Potassium chloride (E508) is a generally permitted food additive, approved for use in most processed foods, and can be employed as an ingredient without being subject to further regulation other than general food law. At present, products containing potassium rather than sodium chloride may be labelled with a warning that they contain potassium substitutes.

5. The COT was asked by the SACN to advise on possible adverse effects of increased potassium intakes as a consequence of salt replacement. The Committee agreed that various population groups should be considered: healthy adults; healthy infants; healthy children at older ages; and people with chronic kidney disease (CKD), other relevant morbidity, or taking medicines that could make them more vulnerable to higher potassium intakes.

Previous assessments of potassium by expert bodies

EVM

6. In 2003, the Expert Group on Vitamins and Minerals (EVM, 2003) concluded that there were insufficient data to set a Safe Upper Level (SUL) for potassium, but noted for guidance that supplements of up to 3.7 g/day (equivalent to 94.9 mmol/day) potassium appeared not to cause illness, although they might be associated with asymptomatic disease. It was also noted that “*patients with pre-existing hyperkalaemia, renal disease, acidosis, insulin deficiency or digitalis intoxication*” should not take potassium supplements without medical advice. A number of case reports of potassium poisoning from salt substitutes were noted.

EFSA

7. In 2005, the EFSA panel on Dietetic Products Nutrition and Allergies (NDA) (EFSA, 2005) concluded that there were insufficient data to establish a Tolerable Upper Level (TUL) of intake for potassium. However, it was noted that in subjects with reduced kidney function and reduced potassium excretion, daily doses of as little as 1 g potassium in addition to food were associated with elevated plasma¹ concentrations of potassium and adverse effects on the heart². They further noted that supplemental potassium doses of 5-7 g (128.2 – 179.5 mmol) per day could cause adverse effects on cardiac function in apparently healthy subjects (based on a study by Keith *et al.* (1941)).

8. The EFSA panel stated that certain population groups were sensitive to adverse effects of increased potassium intake on cardiac function, related to increases in plasma concentrations of potassium. These included people engaging in strenuous activities leading to dehydration, with diabetes mellitus, with impaired kidney function, on treatment with some drugs for cardiovascular disease, and with other metabolic disorders affecting potassium balance. Elderly people might be more vulnerable to adverse effects of potassium owing to reduced kidney function or use of drugs affecting potassium balance. The EFSA panel commented that the available case reports “emphasize the potential risk of excessive use of salt substitutes and

¹ Extracellular potassium concentration has been reported throughout as either plasma or serum potassium concentration depending on which term has been used in the original reference, these terms are not interchangeable. The Association of Clinical Biochemistry note that measurements of potassium in the plasma are usually 0.1 to 0.7 mmol/L lower than those in serum; this is believed to be due to the release of potassium from platelets during clotting (ACB, 2013).

² It is unclear to which reference this refers, but it may be to a study by Perez *et al.* (1984).

supplements, especially when used by those who are pre-disposed to retain potassium”.

9. An effect of potassium supplements (particularly certain formulations) on the gastrointestinal tract was also noted.

US IOM

10. When the US Institute of Medicine (IOM) considered potassium in 2005, they did not make any recommendations regarding a Tolerable Upper Level of intake, since they considered that intakes across the population were too low (IOM, 2005). It was noted that among individuals in whom urinary excretion of potassium was impaired, a potassium intake below the Acceptable Intake (AI) of 4.7 g/day (120.5 mmol) (set on the basis of beneficial effects on blood pressure) was indicated because adverse cardiac effects (arrhythmias) might result from hyperkalaemia at higher intakes, but that such individuals were typically under medical supervision. Medical conditions that were mentioned as being associated with impaired urinary excretion of potassium included diabetes, chronic renal insufficiency, end-stage renal disease, severe heart failure and adrenal insufficiency. Elderly people were considered to be at higher risk as they often had one or more of these conditions, or were treated with medicines that impair potassium excretion. After taking into account studies by Textor *et al.* (1982) and Reardon *et al.* (1998), the IOM stated that the AI would apply to healthy people treated with angiotensin converting enzyme (ACE) inhibitors (see paragraphs 79-84 for more information about medicines affecting potassium balance). The health effects of potassium in infants were judged to be uncertain, so an AI was established based on a calculated mean potassium intake of infants fed human milk or human milk and complementary foods. For older children, AIs were derived by extrapolating from the adult AI on the basis of the average of median energy intake levels.

11. The American Heart Association also recommended a potassium intake of 4.7 g/day (Appel *at al.*, 2006), taking into account both the scientific literature and the IOM opinion. They too agreed that a level lower than this would be appropriate for individuals with impaired potassium excretion, who could be at risk of adverse cardiac effects (dysrhythmias) from hyperkalaemia. They noted that the available evidence was insufficient to establish a level of renal function below which individuals with chronic kidney disease were at risk of hyperkalaemia, but noted that an expert panel (the Kidney Disease Outcomes Quality Initiative) had recommended that people with stage 3 or 4 chronic kidney disease (glomerular filtration rate (GFR) < 60 ml/min) should restrict their potassium intakes.

WHO 2012

12. In 2012, the World Health Organization (WHO) (2012a) concluded that public health interventions to increase potassium intake from food could be a cost-effective way of reducing the burden of mortality from certain non-communicable diseases (e.g. hypertension and stroke). However, they noted that the evidence for a beneficial effect on blood pressure and cardiovascular disease was not entirely consistent (available meta-analyses giving divergent results), and that possible adverse effects had not been considered. Therefore, to inform the development of a guideline on potassium consumption, the WHO commissioned a review on the

effects of potassium intake, to collate results from studies in apparently healthy adults and children.

13. The review in adults (also published as Arbuto *et al.*, 2013) considered randomised controlled trials (RCTs) only, most of these studies assessing interventions with potassium supplements. Overall 23 trials were analysed, involving a total of 1,606 participants. The primary outcome measures were blood pressure and renal function. Any other effects reported in the trials were noted as secondary outcome measures. The adverse effects considered included changes in total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL) or triglyceride concentrations in the blood, and in plasma adrenaline or noradrenaline concentrations. Changes in plasma potassium concentrations were not reported. The trials involved interventions of at least 4 weeks duration and the review excluded trials in which there was another concomitant intervention (unless it was also applied to the controls). Trials were considered if they were conducted in otherwise healthy populations who might have been at risk of, or have had, hypertension, or were known to have normal blood pressure. Trials were excluded if they targeted patients who were acutely ill, infected with human immunodeficiency virus or hospitalised.

14. Three trials assessed renal function by measuring serum creatinine (Bulpitt *et al.*, 1985; Patki *et al.*, 1990; Smith *et al.*, 1985 – see paragraphs 49-51). These found a non-significant reduction in serum creatinine of 4.86 $\mu\text{mol/L}$ was associated with higher potassium intake. The evidence that higher potassium intake did not adversely affect renal function was considered to be of high quality.

15. In Arbuto *et al.* (2013), it was noted that increased intakes of potassium had been shown to be safe in people with normal renal function, but that in individuals with impaired urinary excretion of potassium, there could be a risk of hyperkalaemia. However, the risk was confined to such patients, who would be largely under medical supervision and who were excluded from the review. It was noted that potassium intakes of 15.6 g (400 mmol) per day from food for several days or 4.49 g (115 mmol) per day for up to one year were not associated with adverse effects (Rabelink *et al.*, 1990 and Siani *et al.*, 1991). None of the trials in the review found evidence of side effects, minor or major, in the groups receiving potassium as compared with their controls.

16. A review was also conducted in children, using similar inclusion criteria, with blood pressure as an outcome measure (WHO, 2012b). Four studies were included in a meta-analysis, 2 RCTs, one non-randomised trial and one cohort study. None of the studies reported blood levels of lipids or catecholamines, or monitored adverse effects.

17. The WHO recommended that potassium intakes from food should be increased to reduce blood pressure and risk of cardiovascular disease and stroke in adults (this was considered to be a strong recommendation for which the desirable effects of adherence outweighed the risks) (WHO, 2012c). The WHO further

recommended a potassium intake of at least 3.51 g (90 mmol) per day for adults. This was stated to be a conditional recommendation³.

18. For children, the WHO made a conditional recommendation that potassium intakes should be based on those proposed for adults, with adjustment downwards based on energy requirements, and that individual countries should determine the requirements for the various age categories. It was noted that the recommendation did not apply to infants during exclusive breastfeeding (0-6 months) or to the period of complementary feeding and continued breast feeding.

19. It should be emphasised that some of the assessments discussed above, focussed on consumption of supplemental rather than dietary potassium. A wide range of potassium supplements are available on the market, either individually or as a part of multivitamin/mineral formulations, with daily doses ranging from 40 - 200 mg of potassium. In years 1 and 2 of the National Diet and Nutrition Survey (NDNS) rolling programme, the total number of people consuming dietary supplements containing potassium was small, with supplement use reported in less than 5% of most age groups. The exception was adults aged 65 – 74 years, among whom 10% of respondents reported using supplements containing potassium; in this group, potassium intakes from supplements alone ranged from 2 – 175 mg/day, which is low in comparison to dietary intakes (Bates *et al.*, 2011).

Physiology

20. Potassium is an essential nutrient and the most abundant intracellular cation, with a concentration in cells of 100-150 mmol/L (reported as mEq/L⁴) (Zhou and Satlin, 2004).

21. It has functions that relate closely to those of sodium: together they are essential for the maintenance of normal osmotic pressure in body fluids, and the physiological activities of certain cells. A steep potassium concentration gradient is maintained across cell membranes by sodium-potassium-adenosine triphosphatase (Na-K-ATPase), a ubiquitous enzyme that is present on the cell surface (Zhou and Satlin, 2004).

22. Levels of potassium intake can affect sodium balance. Low potassium intakes (10-30 mmol/day) may induce sodium retention and an increase in blood pressure, both in normotensive and hypertensive subjects (EFSA, 2005 citing Gallen *et al.*, 1998; Morris *et al.*, 1999; Coruzzi *et al.*, 2001).

23. Conversely, a number of studies in both normotensive and hypertensive subjects have indicated that an increased intake of potassium can lower blood pressure and increase urinary excretion of sodium (EFSA, 2005 citing Whelton *et al.*, 1997; Geleijnse *et al.*, 2003; Sacks *et al.*, 1998; Gu *et al.*, 2001; Naismith and

³ A conditional recommendation is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, but the group is not confident about the trade-off.

⁴ For potassium, 1mEq = 1mmol (Schaefer and Wolford, 2005)

Braschi, 2003). Not all studies have shown a clear dose-response effect, possibly because of differences in their duration, initial levels of blood pressure, sodium intakes, other aspects of diet, race, or age. However, 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 (EFSA, 2005 citing Appell *et al.*, 1997; Sacks *et al.*, 2001; Jula *et al.*, 1990; Geleijnse *et al.*, 1997; He and MacGregor, 2001).

24. The extracellular concentration of potassium is the critical determinant of nerve and muscle cell excitability. Potassium also helps to maintain acid-base and electrolyte balance, acts as a cofactor for numerous enzymes, and is involved in regulating cell growth and division. In addition, it is required for the secretion of insulin by the pancreas, for the phosphorylation of creatine, for carbohydrate metabolism, and for DNA and protein synthesis (EVM, 2003; Zhou and Satlin, 2004; EFSA, 2005).

Absorption and distribution

25. The absorption of potassium is “*highly effective with 85-90% of dietary potassium normally being absorbed from the gut*” (EFSA, 2005).

26. Approximately 98% of the total body potassium content is intracellular, primarily in muscle, the remaining 2% being in the extracellular fluid (EFSA, 2005). In the healthy adult, daily dietary intake of potassium generally approaches or exceeds the total amount of potassium that is present within the extracellular fluid (Gurkan *et al.*, 2007). The extracellular concentration of potassium is normally 3.5-5 mmol/L (Zhou and Satlin, 2004), and a serum potassium concentration greater than 5.5mmol/L is classed as hyperkalaemia (Schaefer and Wolford, 2005).

Excretion

27. The total body content of potassium depends on a homeostatic balance between intake and output. Excretion in the healthy adult generally matches dietary intake, 90% of the daily intake (~90 mmol/day) being eliminated by the kidneys with the other 10% lost in the faeces (~10 mmol/day) (Gurkan *et al.*, 2007; Sorenson *et al.*, 2010).

28. In contrast to adults, foetuses of more than 30 weeks gestational age and infants require a positive potassium balance (i.e. that more is absorbed than excreted) to meet the needs for incorporation into newly formed cells (Zhou and Satlin, 2004). Total body potassium increases from approximately 8 mmol/cm body height at birth to >14 mmol/cm body height at 18 years of age. The rate of potassium accumulation per kg body weight is more rapid in infants than in older children, correlating with the increase in cell number with age (Gurkan *et al.*, 2007). In infants and children, maintenance of the positive potassium balance is largely accomplished by the kidney (Zhou and Satlin, 2004).

Renal excretion

29. Although the maintenance of potassium balance in healthy adults depends on timely renal elimination of dietary intake, renal excretion is relatively slow and may take 6-12 hours (Gurkan *et al.*, 2007). During this time, protection against life-

threatening hyperkalaemia (LTHK) is achieved through rapid translocation of extracellular potassium into cells.

30. The processes involved in the renal handling of potassium are filtration by the glomerulus, followed by reabsorption into the blood from the proximal tubule and loop of Henle, then secretion from the blood back into the urinary space of the distal tubule, connecting tubule and collecting duct, and finally excretion. Distal nephron segments can secrete or reabsorb potassium, depending on the body's needs. In healthy adults, secretion of potassium predominates over its reabsorption (Gurkan *et al.*, 2007).

31. In the adult, urinary excretion of potassium can be up to 20% of the filtered load. Although neonates can excrete potassium at a rate that exceeds its filtration, reflecting a capacity for net tubular secretion, they are unable to excrete potassium loads as efficiently as adults (Gurkan *et al.*, 2007). The low capacity of the neonatal cortical collecting duct reflects a relative paucity of conducting potassium ion channels in the cellular membranes of the urinary tract. A relative excess of potassium reabsorption in this nephron segment may further reduce net urinary secretion. Under conditions prevailing *in vivo*, the balance between these factors contributes to the relatively high retention of potassium by the neonatal kidney, and helps to maintain the positive potassium balance that is required by older fetuses and infants (Zhou and Satlin, 2004).

32. The balance between excretion and reabsorption of potassium is regulated by both luminal and peritubular mechanisms (Gurkan *et al.*, 2007). These include the delivery and absorption of sodium within the distal nephron, the extent of which determines the electrochemical driving force for secretion of potassium into the luminal fluid. Processes that promote distal delivery of sodium and increase tubular fluid flow rate, such as expansion of extracellular volume and administration of diuretics, cause a simultaneous increase in urinary excretion of both sodium and potassium. The potassium-sparing diuretics block sodium reabsorption through inhibition of the epithelial sodium channel (see also paragraph 82 for further details). Secretion of potassium is also affected by changes in acid-base homeostasis (Gurkan *et al.*, 2007).

33. Secretion of potassium in the kidney is promoted by aldosterone. This is partly through stimulation of the epithelial sodium channel (ENaC) and Na-K-ATPase activity, which enhances the electrochemical gradient, favouring secretion of potassium. Premature infants and new-born babies have higher plasma concentrations of aldosterone than adults, but clearance studies suggest that the immature kidney is relatively insensitive to the hormone. The limited capacity of the neonatal distal nephron to secrete potassium has been postulated to contribute to the non-oliguric hyperkalaemia (serum potassium >6.5 mmol/l) that is observed in up to 30-50% of very-low birth weight infants (Zhou and Satlin, 2004).

34. In summary, the balance between urinary secretion and reabsorption of potassium is determined by both luminal and peritubular factors. Perturbation in any of these factors can lead to potassium imbalance (Gurkan *et al.*, 2007).

Colonic excretion

35. With a normal diet, the faecal content of potassium is approximately 100 mmol/L, leading to an average excretion of 0.38 g (9.8 mmol) per day (range 0.08 to 0.78 g (2 to 20 mmol)) per day depending on potassium intake) in a stool volume of around 100 ml. The faecal content of potassium is a consequence of its active secretion in the colon, coupled with colonic absorption of water, which favours an “*up-concentration of intra-luminal potassium*” (Sorenson *et al.*, 2010).

36. With severe restriction of dietary potassium intake, faecal excretion of potassium can fall to 0.12 g (3.5 mmol) per day. This is achieved through active absorption of potassium in the distal colon. Low dietary intakes of sodium can induce an increase in the net secretion of potassium in the colon, leading to faecal potassium wasting (Sorenson *et al.*, 2010).

37. When GFR falls below 30 ml/min (from the normal 130 ml/min), colonic loss of potassium may increase to as much as 0.39-0.78 g (10-20 mmol) per day (EFSA, 2005).

Regulation of extracellular potassium concentration

38. The concentration of potassium in extracellular fluid (which includes serum and plasma) is normally tightly regulated in the range from 3.5 to 5 mmol/L through mechanisms that govern the distribution of the mineral between the intra- and extracellular compartments, as well as those that maintain the balance between the body's intake and output (Zhou and Satlin, 2004).

39. The body is able to accommodate a high intake of potassium without any substantial change in plasma concentration, by synchronised alterations in both renal and extra-renal handling. Therefore the plasma concentration (which is usually slightly lower than the serum concentration) of potassium does not give a clear indication of the total body content of the mineral (EFSA, 2005).

40. The mechanisms which enable the body to cope with a wide range of potassium intakes involve changes in the kidney, muscle and colon over the short- and long-term. These mechanisms are complex and linked to the cellular handling of other minerals and to water homeostasis (EFSA, 2005).

41. In response to a large short-term increase in potassium intake, insulin-mediated uptake of potassium into skeletal muscle (and probably liver) is increased (Wang, 2004). This transfer of potassium from the extracellular to the intracellular space minimises any rise in plasma potassium in the short-term. The potassium, which has been buffered by uptake into muscle cells, is then later released into the extra-cellular fluid during the post-prandial period and excreted through the kidney (EFSA, 2005). Secretion of potassium in the collecting duct is stimulated within hours of a potassium-rich meal (EFSA, 2005).

42. The main mechanism through which the body content of potassium is regulated over the longer term is renal excretion. Healthy kidneys will respond to a sustained increase in potassium intake with a reduction in the reabsorption of potassium in the proximal tubules and adaptive changes in the collecting duct leading to prolonged enhancement of excretion (EFSA, 2005).

43. The combination of insulin-mediated buffering in muscle and enhanced renal secretion in the short-term, with more marked renal adaptive changes in the longer term, ensures that plasma concentrations are maintained within narrow limits, even when there is a sustained increase in potassium intake (EFSA, 2005).

44. The uptake of potassium into muscle appears to be reduced in insulin-resistant states such as obesity, and consumption of high fat diets. The EFSA NDA Panel (2005) commented that the capacity for muscle to hold potassium is presumed to be finite and therefore, if there is a sustained high intake of potassium, the body's ability to cope will be determined by the maximal rate of renal excretion, plus any increase in loss through the distal colon (EFSA, 2005).

Effects of supplementation on extracellular potassium concentration

45. Most studies investigating potassium supplementation have not documented changes in serum/plasma potassium concentrations or in renal function parameters. In the supplementation studies from which this information is available, there was generally little perturbation in serum/plasma concentrations of potassium, but a notable increase in urinary excretion of potassium when the supplementation was maintained over a number of weeks or months. This supports the view that the body can normally cope with increased potassium intakes over a prolonged period. Further information from supplementation studies is provided below. Mean values for serum/plasma potassium and parameters of renal function are noted, along with the ranges where they were reported.

46. In a randomised placebo-controlled study designed to establish whether supplemental potassium chloride reduced the need for anti-hypertensive medication, 142 men aged 45-68 y were given 3.75 g/day (96 mmol/day⁵) potassium chloride, while 147 were given a placebo (Grimm *et al.*, 1990). The participants, who were hypertensive and on a restricted sodium diet, were followed for an average of 2.2 y after withdrawal of their anti-hypertensive medication. At entry, the average serum potassium was 4.2 mmol/L and the average urinary excretion of potassium was 0.74 g (19 mmol) per 8 hours. Participants who were given supplemental potassium went on to have significantly higher serum potassium concentrations and urinary potassium excretion (4.5 mmol/L and 1.66 g (42.5 mmol) per 8 hours) than those given the placebo (4.2 mmol/L and 0.78 g (20 mmol) per 8 hours) ($P < 0.001$). However, the serum concentration remained within the normal range (3.5 – 5.0 mmol/L). Potassium intakes were not documented, but from data on potassium excretion at baseline, the 97.5th percentile for total potassium intake was estimated (by EFSA, 2005) to be 7-8 g/day.

47. In a randomised crossover study reported by Overlack *et al.*, (1991), 12 patients with essential hypertension were given 4.68 g (120 mmol) per day potassium (as citrate or bicarbonate) or placebo for 8 weeks. At baseline, the mean serum potassium concentration was 4.37 mmol/L. At the end of the treatment periods, the mean serum potassium concentrations were 4.33 (SE 0.1) mmol/L with potassium supplementation and 4.06 (SE 0.1) mmol/L with the placebo – values within the normal range.

⁵ One gram of potassium is equivalent to 25.64 mmol (Dickinson *et al.*, 2006).

48. Siani *et al.* (1987) conducted a 15-week randomised controlled trial, in which 37 patients who had mildly elevated blood pressure and normal dietary sodium intake received potassium supplements (1.87 g (48 mmol) per day) or placebo. No significant change was observed in plasma potassium concentrations, although the mean urinary excretion of potassium increased in the group that received the supplements (3.39 g (87 mmol) per 24 hours vs. 2.22 g (57 mmol) per 24 hours at baseline). Dietary potassium was not assessed, but participants were asked not to change their usual diet.

49. In a study by Bulpitt *et al.* (1985) 33 patients with hypertension who were receiving drug treatment that included a diuretic (not potassium-sparing⁶), were given 2.5 g (64mmol) per day of potassium chloride (n=14) or placebo (n=19) for 3 months. Mean plasma potassium concentration increased from 3.7 (SE 0.12) mmol/L at baseline to 3.8 (SE 0.09) mmol/L in the treated group, and decreased from 3.7 (SE 0.08) mmol/L to 3.5 (SE 0.09) mmol/L in the placebo group. The difference between the two groups at the end of the study was statistically significant, but the plasma concentrations were within the normal range. Mean urinary potassium excretion increased from 2.81 (SE 0.21) g (72 (SE 5.4) mmol) per 24 hours at baseline to 3.71 (SE 0.35) g (95 (SE 9.0) mmol) per 24 hours in the treated group, and decreased from 2.38 (SE 0.16) g (61 (SE 4.0) mmol) per 24 hours to 2.15 (SE 0.23) g (55 (SE 6.0) mmol) per 24 hours in the placebo group. Plasma creatinine concentration⁷ fell by 11% in the treatment group compared to a 6% rise in the control group (P<0.05). After 3 months, creatinine clearance was higher in the supplemented group, but the difference was not significant. It was suggested that the fall in plasma creatinine may have been partly through an increase in extracellular volume, since weight increased by a mean of 1.4 kg in the treated group. However it was also suggested that the supplements might have restored depleted potassium levels and thereby improved the GFR.

50. A double blind, randomised, placebo-controlled, crossover study was conducted by Patki *et al* (1990). Patients (n=37) with mild hypertension received placebo or 2.34 g (60 mmol) per day potassium alone or 2.34 g (60 mmol) per day potassium with 0.49 g (20 mmol) per day magnesium for 8 week periods with two-week washout intervals between each treatment. Mean serum potassium concentration was 3.6 (SD 0.42) mmol/L at baseline, with values of 3.6, 3.7 and 3.8⁸ at the end of the placebo, potassium, and potassium plus magnesium periods respectively. Urinary potassium excretion was 62 (SD 4) mmol per 24 hours at baseline. At day 56, urinary potassium excretion was significantly increased (P<0.05) with the two treatments compared to the control, the levels being 60 (SD 4), 82 (SD 6) and 80 (SD 5) mmol per 24 hours following the placebo, potassium and potassium plus magnesium periods respectively. These levels were within the normal range. There were no significant changes in serum creatinine concentration (76.02 (SD

⁶ Most diuretics promote potassium secretion and thus increased loss in the urine. In contrast, potassium-sparing diuretics promote retention of potassium, and thus increase the risk of hyperkalaemia.

⁷ High serum creatinine levels can indicate kidney damage.

⁸ The reported standard deviations corresponding to these means were implausibly high.

11.44) $\mu\text{mol/L}$ at baseline and 75.14 (SD 14.15), 73.38 (SD 6.96) and 70.72 (SD 10.06) $\mu\text{mol/L}$ following the placebo, potassium and potassium plus magnesium periods respectively).

51. Twenty patients with mild or moderate essential hypertension, who were not receiving other drug treatment and who were moderately restricting their sodium intake, were included in a double blind, randomised, placebo-controlled crossover study to compare one month's treatment with potassium supplements (2.5 g (64 mmol) daily) to placebo (Smith *et al.*, 1985). Mean urinary potassium excretion following potassium supplementation was significantly higher than after placebo (117 (SE 4.6) mmol per 24 hours vs. 67 (SE 6.9) mmol per 24 hours) ($p < 0.0001$). However, plasma potassium concentration was not significantly different, the means being 4.1 (SE 0.1) and 3.9 (SE 0.1) mmol/L with potassium supplementation and placebo respectively. Plasma creatinine was also unaffected, with means of 89 (SE 3.8) and 91 (SE 3.2) $\mu\text{mol/L}$ following the potassium supplementation and placebo periods.

52. A Cochrane systematic review (Dickinson *et al.*, 2006) evaluated the effects of potassium supplements on health outcomes and blood pressure in people with hypertension. The five studies included involved 425 participants with 8-16 weeks of follow-up and doses of potassium ranging between 1.87 and 4.68 g/day (48-120 mmol/day). It was noted that among the studies included in the analysis, only two (Overlack *et al.*, 1991; Siani *et al.*, 1987) reported serum/plasma potassium concentrations, and when these were included in a meta-analysis, levels were higher at the end of the study in the treated group than in the controls (mean difference 0.20 mmol/L), although still within the normal range. Renal effects were not considered. It was not explicitly stated, but from the descriptions of the studies it appears that they were conducted in otherwise healthy populations (i.e. without the complications of hypertension or co-morbidities). The authors commented that little information was reported about the normal diets of the study participants. It has been noted (nutrition evidence.com, 2006) that the inclusion criteria for this review were very restrictive.

53. Earlier, other authors (Geleijnse *et al.*, 2003; Whelton *et al.*, 1997) also conducted meta-analyses of the relationship between potassium supplementation and blood pressure. These included more studies than the Cochrane review, but did not consider possible adverse effects of high potassium intakes on either serum/plasma potassium or renal parameters.

Toxicity

54. Few adverse effects have been reported from excessive potassium intakes in the general population. Where adverse outcomes have been observed, they were rarely a simple consequence of high dietary potassium and more often related to interactions with medications, co-morbidities such as renal disease, or use of high-dose potassium supplements. In studies of potassium supplements, damage to the oesophagus has been reported as a consequence of physical injury by the treatment preparation. In some cases this has only been detectable by endoscopy (Grimm *et al.*, 1990). The severity of the effects observed may depend on the formulation of the supplement; slow release, wax-coated potassium chloride tablets appear to induce more lesions than microencapsulated tablets (EVM, 2003).

55. Cases of acute toxicity have generally been from deliberate or accidental overdose of potassium supplement tablets, but some have related to misuse of salt-replacer products. The main adverse effects detailed in reports of acute toxicity have been gastrointestinal damage and bleeding, and hyperkalaemia with cardiac dysrhythmia or arrest.

Hyperkalaemia

56. As already described, extracellular potassium is maintained within a narrow concentration range of 3.5-5 mmol/L, while the intracellular potassium concentration is much higher at 150 mmol/L. The resultant intracellular to extracellular ratio (150:4) induces a voltage gradient across the cell membrane and contributes to the resting cell membrane potential, which is particularly important in the function of nerve and muscle cells, including in the heart. Small absolute changes in the high intracellular concentration will have little effect on this ratio, whereas changes of similar magnitude in the extracellular concentration could affect the ratio profoundly, modifying the trans-membrane potential gradient and thereby impairing cellular function (Schaefer and Wolford, 2005).

57. The electrocardiographic (ECG) changes associated with hyperkalaemia are well established. Typically, the earliest manifestations occur at concentrations >6.5 mmol/L and take the form of peaked or tented T-waves, which are most prominent in pre-cordial leads. With further rise in serum concentrations, there is a diminished cardiac excitability, manifested by flattening of the P-wave, lengthening of the PR interval, and eventual disappearance of the P-wave. The QRS duration becomes prolonged, progressing to a sinusoidal appearance, and finally ending in either ventricular asystole or fibrillation when potassium concentrations reach 8-10 mmol/L (Schaefer and Wolford, 2005).

58. Hyperkalaemia and accompanying physiological changes can thus be classified as minimal (5.5-6.5 mmol/L - minor electrocardiographic changes), moderate (6.6-8 mmol/L - ECG changes limited to peaking of T-waves) and severe (>8 mmol/L - or any level with a widened QRS complex, atrioventricular block or ventricular dysrhythmia). However, it should be noted that ECG changes do not correlate exactly with serum potassium concentration, and depend also on the rate of rise in the potassium concentration, and the underlying cause of the hyperkalaemia (Schaefer and Wolford, 2005). Sudden increases in serum potassium levels may be more hazardous than chronic high potassium levels (Paice *et al.*, 1983; Indermitte *et al.*, 2007)

59. As well as the heart, hyperkalaemia affects the neuromuscular and gastrointestinal systems. Patients may present with vague feelings of malaise, gastrointestinal symptoms or generalised weakness. However, the most serious concern is impaired cardiac conduction with risk of sudden death from asystole or ventricular fibrillation. Neuromuscular symptoms and signs include muscle cramps, weakness, paralysis, numbness, tingling, and reduced deep tendon reflexes (Schaefer and Wolford, 2005).

60. In people with normal renal function, hyperkalaemia from excessive intake of potassium is very uncommon. Possible causes include overdose of potassium supplements, massive blood transfusion with hypoperfusion, and accidental

ingestion of potassium chloride crystals used in water softeners. Short-term intakes of up to 15 g/day potassium have been reported not to result in plasma potassium concentrations outside the normal range, provided that intake is spread over the day and fluid intake is sufficient. In a metabolic balance study, 6 healthy volunteers aged 22-26 y were given 15.6 g per day (400 mmol) potassium in 4 equal meals, every 6 hours to investigate the effects of short-term (72 hrs) and long-term (20 days) potassium-loading (Rabelink *et al.*, 1990). Throughout the study, each meal was followed by an acute transient increase in plasma potassium and aldosterone concentrations, and in urinary excretion of potassium. Potassium balance was achieved in the second 24-hour period of loading. This was associated with elevated plasma potassium, slightly negative sodium balance and stimulated plasma renin activity. After 20 days of loading, losses of sodium had been compensated. Discontinuation of loading was followed by negative potassium balance lasting only 24 hours, and by sodium retention for 72 hours. Mean plasma potassium concentration was 3.75 mmol/L on days 1 and 2 of the pre-treatment control period, increasing to 4.25, 4.77, 4.17 and 4.22 mmol/L after 24h, 48h, 72h and 20 days respectively. In the de-adaptation period, concentrations declined to 3.98 and 3.67 mmol/L at 24 and 96 hours. These values were all within the normal range. However, in a study by Keith (1941) severe hyperkalaemia, accompanied by paraesthesiae (tingling) of the hands and feet and T-wave changes on ECG, was observed within 2-3 hours in two of seven apparently normal subjects given doses of 12.5 or 17.5 g potassium chloride or potassium bicarbonate (6.5-6.8 g potassium).

61. The large majority of cases of hyperkalaemia (>80%) occur when potassium excretion is impaired by a medical condition or by the use of certain medications in a patient with some degree of underlying renal dysfunction. Dietary salt substitutes, potassium supplements, potassium penicillin therapy and drinking potassium-softened water may all induce hyperkalaemia in pre-disposed individuals (Schaefer and Wolford, 2005).

62. Similar factors affect the rate at which hyperkalaemia can develop. A randomised sample of 551 hospitalised patients was analysed in a study by Indermitte *et al.* (2007). Compared to the drug treatment at entry, significantly more patients were treated with drugs associated with hyperkalaemia such as heparins, ACE inhibitors or angiotensin receptor blockers (ARBs), potassium supplements, potassium sparing diuretics and/or NSAIDs selective cyclo-oxygenase 2 inhibitors during hospitalisation. Risk factors associated with the rapid development of hyperkalaemia were the use of potassium supplements, severe renal impairment, use of ACE inhibitors or ARBs, use of potassium sparing diuretics and diabetes mellitus. The rate at which hyperkalaemia developed was significantly increased in patients with two or more risk factors. Dose effects were reported for the use of potassium supplements and potassium sparing diuretics only. In patients treated with high dose potassium supplements (> 3 g/day) the median rate of change in the daily increase in serum potassium was higher than in those treated with low dose supplements (0.48 vs 0.40 mmol/L) $p = 0.006$.

Vulnerability to high potassium intakes

Healthy adults

63. Healthy adults would not be expected to suffer harm from increased dietary potassium. As stated previously, the body is able to cope with both short- and long-term increases in potassium intakes without substantial alterations to plasma potassium concentration. Through synchronised changes in renal and extra-renal handling, excess potassium will be excreted in due course to maintain a zero potassium balance (EFSA, 2005 and Gurkan *et al.*, 2007). The COT noted that there is no reason to expect that healthy pregnant women would be unusually vulnerable to higher potassium intakes. Women require a positive potassium balance during pregnancy (Palmer, 2015).

Healthy infants

64. It has been suggested that infants could be vulnerable to the effects of increased dietary potassium intakes owing to their immature kidney structure and function, and limited capacity for excretion (EFSA, 2005 quoting EVM, 2003). Several aspects of renal function in the first year of life differ markedly from that in adults.

Development of the kidney

65. The development of the human kidney begins in the first month after conception, and it is functional by the second month (Čukuranović and Vljaković, 2005). The antenatal period is characterised by significant nephrogenesis which begins at 9 weeks of gestation and is complete by 36 weeks (Kearns *et al.*, 2003). During the third trimester, the fetal kidney starts to undergo intensive maturation processes (Čukuranović and Vljaković, 2005).

66. After birth, the kidneys undergo further structural and functional maturation. With a permanent number of nephrons, renal mass increases at the expense of certain nephron structures and interstitium. A number of anatomical changes occur between one and six months of age, so that as early as the seventh month, the renal parenchyma shares the characteristics of that in the adult (Čukuranović and Vljaković, 2005).

67. Neonatal kidneys are functionally immature but rapid maturation enables the new-born infant to maintain homeostasis. Renal excretion is dependent on the GFR, tubular secretion, and tubular reabsorption. In turn, these processes depend on renal blood flow, which increases with age as a result of an increase in cardiac output and a reduction in peripheral vascular resistance. Limited data on renal blood flow indicate neonatal rates of only 10-20% of adult values (adjusted for body size) that rapidly increase to 50% by 6 months and then approach adult levels by 1-2 years of age (Fernandez *et al.*, 2011).

68. Active tubular secretion increases over the first months of life to reach the adult level (adjusted for body size) at approximately 7 months. Development and maturation of tubular reabsorption is a gradual and continuous process that lasts from birth to adolescence (Fernandez *et al.*, 2011).

69. The kidney achieves the adult's capacity to concentrate urine at around 18 months of age. The lower GFR is one of the reasons for the limited capacity to concentrate urine at earlier ages, as is lower sensitivity to antidiuretic hormone (ADH) in the distal tubule. The young infant's kidney is also characterised by a much

lower level of potassium excretion and resorption of amino acids than is achieved by the adult kidney. The activity of plasma renin and angiotensin II in infants is higher than that in adults (Čukuranović and Vlajković, 2005).

70. During childhood, adolescence and young adulthood, the structure and function of the kidney continue to mature. The cortex: medulla ratio increases from 1.64:1 in the new-born to 2.59:1 in adults. Kidney length and volume increase with age. Kidney functions (excretion of metabolic products and surplus water, maintenance of fluid homeostasis, maintenance of acid-base balance and endocrine activity) also continue to mature from infancy to young adulthood. The kidney reaches full anatomical and functional maturity by the end of the third decade of life (Čukuranović and Vlajković, 2005).

Occurrence of hyperkalaemia in healthy infants and young children

71. There are no documented cases of hyperkalaemia in healthy infants or young children from dietary exposures alone. Most reported cases have occurred following blood transfusions. In addition, there are a few reports of hyperkalaemia occurring in infants and young children as a consequence of accidental ingestion of salt substitutes or water softeners, or administration of large doses of potassium-based dietary supplements.

Older children

72. In view of their more mature renal function, healthy children at older ages would not be expected to exhibit unusual vulnerability to high intakes of potassium. As with healthy adults, they should tolerate modest increases in dietary exposure without any harm.

Older adults

73. Elderly people may be more liable to potassium toxicity because of reduced physiological reserve in renal function and the effects of co-morbidities (Beck, 1998). Ageing is associated with a progressive loss of kidney volume and GFR falls with each decade. This decline, as well as changes in, for example, renin release, leads to reduced capacity for potassium secretion and thus limits the ability to handle large potassium loads. The elderly are therefore more vulnerable to increased intake of potassium from the diet and/or supplements. In addition, they are more likely to be taking medication that can affect potassium balance (see paragraphs 79-84).

People with renal disease

74. Chronic Kidney Disease (CKD) is classified to stages, according to the level of kidney damage, as described in Table 1 below.

Table 1. Classification of Chronic Kidney Disease (CKD) by stage (National Institute for Health and Care Excellence (NICE) Clinical Guideline 182, 2014)

CKD stage	GFR ⁹ (ml/min/1.73 m ²)	Description
1	≥ 90	Normal or increased GFR, but with other evidence of kidney damage (e.g. findings in urine, structural abnormalities or a genetic trait).
2	60-89	Mild decrease in GFR (as compared with normal range for young adults), with other evidence of kidney damage (as for stage 1).
3A	45-59	Moderate decrease in GFR, with or without other evidence of kidney damage.
3B	30-44	
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage.
5	<15	Established or end-stage renal failure.

75. Whilst the vast majority of individuals would not be adversely affected by increased potassium intakes, there are some populations who are vulnerable to developing hyperkalaemia. These are people with medical conditions such as CKD or diabetes or who are taking certain medications. Whilst the majority would be under medical supervision, there are a significant number of individuals with CKD who have not been diagnosed. It has been estimated that in England, 2.6 million individuals aged >16 years have CKD stage 3-5; this is equivalent to 6.1% of the population of this age group (PHE, 2014). Of the individuals who have CKD stage 3-5, it has been estimated that 29% of them (750,000 individuals) are undiagnosed¹⁰. If these values are extrapolated to the UK population of 52.5 million who are aged > 16 (ONS, 2016) then 3.2 million individuals in the UK would be expected to have CKD stage 3-5, of whom, 929,000 would be undiagnosed. There are no accurate time series data nationally, but it seems likely that the prevalence will be rising, due to the ageing of the population and the increasing prevalence of obesity, type 2 diabetes and hypertension, all of which predispose to kidney disease. PHE (2014) estimated that by 2036 there would be 4.2 million people with stage 3-5 CKD in England, a prevalence of 8.3% of the population. Such an increase would be consistent with the findings of National Health and Nutrition Examination Surveys (NHANES) in the US.

76. Not all people with renal disease require a low potassium diet. It has been noted that patients are unlikely to need to restrict their potassium intake until renal function is less than 40% of normal (WHO, 2009), which would be those individuals in categories 4-5 (plus some in 3B). Nevertheless, this is still likely to represent many thousands of individuals nationally, not all of whom will have been diagnosed as having CKD. In England, the proportion of the population with stage 4-5 CKD is estimated to be approximately 1% of the population or 525,000 individuals (NICE, 2013). If 29% of this population were undiagnosed (see paragraph 75 above), this would be approximately 152,250 individuals. If these values are extrapolated to the

⁹ GFR over 90 (generally 90-110) mL/min is considered to be normal unless there is other evidence of kidney disease.

¹⁰ Based on the estimate that as only 71% of those with CKD stage 3-5 were on CKD registers, thus 29% of 2.6 million would be 750,000).

UK population of 52.5 million who are aged > 16 (ONS, 2016) then 0.53 million individuals in the UK would be expected to have CKD stage 4-5, of whom, 153,700 would be undiagnosed. The American Heart Association (Appel *et al.*, 2006) have recommended that people with a GFR of 60 ml/min or lower (CKD stages 3-5) should be advised to restrict their potassium intake, which would represent an even larger number.

77. Gennari and Segal, (2002) reported that in a sample of 18 patients from their clinic with serum creatinine levels of 132.6 – 530.4 µmol/L, who did not have diabetes and were not taking diuretics or ACE inhibitors, the prevalence of hyperkalaemia (> 5 mmol/L) was 55%.

78. To assess the frequency of hyperkalaemia, Einhorn *et al.* (2009) conducted a retrospective analysis of 2,103,422 records from 245,808 US veterans with at least one hospitalisation and one recorded inpatient or outpatient measurement of serum potassium during 2005. A total of 66,259 hyperkalaemic cases were identified, which corresponded to 3.2% of the records analysed. The veterans were 95.6% male, 79.6% white and 19.4% African-American. The mean age was 61 y in those without CKD and 73 y in those who had CKD. When classified by level of potassium, 212,171 veterans had serum potassium ≤ 5.5 mmol/L, among whom 75.2% did not have CKD and 21.6, 2.3 and 1% had stages 3, 4 and 5 CKD respectively. Of the individuals with serum potassium ≥ 5.5 mmol/L, 46.0% had no CKD but 35.6%, 10.5% and 8 % had stages 3, 4 and 5 CKD respectively. The risk of hyperkalaemia was elevated in patients treated with renin-angiotensin-aldosterone blockers. Patients with cancer, diabetes or CKD were also more likely to have elevated serum potassium. Odds ratios (ORs) with 95% confidence intervals (CIs) for these associations are shown in Table 2 below.

Table 2. Odds ratios for elevated serum potassium in patients with various diseases (relative to those without the disease) (Einhorn *et al.*, 2009)

Condition	Odds ratio (95%CI)
Cancer	1.16 (1.13 – 1.19)
Diabetes	1.51 (1.47 – 1.55)
Stage 3 CKD	2.24 (2.17 – 2.30)
Stage 4 CKD	5.91 (5.63 – 6.20)
Stage 5 CKD	11.0 (10.34 – 11.69)

Medicines that can affect potassium balance

79. As noted in previous sections, there are a number of medicines that can disrupt potassium balance and predispose to hyperkalaemia. People with underlying renal disease are particularly susceptible to the effects of some of these drugs. The most notable and common are discussed below.

80. Hypoaldosteronism is a condition characterised by a relatively well-preserved GFR but reduced levels of aldosterone, and can be sub-classified according to serum concentration of renin. In people with hyporeninaemic hypoaldosteronism,

non-steroidal anti-inflammatory drugs (NSAIDs) can induce hyperkalaemia by reducing GFR, increasing sodium retention, and further suppressing the secretion of renin through inhibition of the production of prostaglandin. Patients at increased risk of NSAID-associated hyperkalaemia include the elderly, those with serum creatinine concentrations greater than 105 $\mu\text{mol/L}$ (roughly equivalent to 1.2mg/dL), those with congestive heart failure, and those taking potassium-sparing diuretics. People with hyperreninaemic hypoaldosteronism may develop hyperkalaemia when treated with drugs that disrupt the renin-angiotensin-aldosterone system, such as ACE inhibitors (e.g. captopril, enalapril and lisinopril), angiotensin receptor blockers (ARBs) (e.g. irbesartan, losartan and valsartan), and heparin. It is difficult to identify in advance the patients who are particularly at risk of hyperkalaemia from these treatments, as it can occur in people with only moderate renal insufficiency, and may not be predicted by pre-treatment serum creatinine concentration (Schaefer and Wolford, 2005).

81. Spironolactone (a potassium-sparing diuretic) competitively binds to the aldosterone receptor and may therefore induce hyperkalaemia by causing end-organ resistance to aldosterone in the kidneys (Schaefer and Wolford, 2005).

82. The potassium-sparing diuretics amiloride and triamterene work by inhibiting the sodium channels in the kidney, leading to excretion of sodium and retention of potassium. The antibiotics, trimethoprim and pentamidine also cause sodium channel blockade, inhibiting sodium reabsorption and thus inducing potassium retention (Schaefer and Wolford, 2005).

83. Potassium penicillin therapy increases potassium load and may therefore induce hyperkalaemia in susceptible individuals (Schaefer and Wolford, 2005).

84. Hyperkalaemia may also be caused by redistribution of potassium from the intracellular to the extracellular space, known as transcellular shifting. Non-selective beta-blockers such as propranolol can interfere with the Na-K-ATPase pump and inhibit potassium uptake into cells. Generally, this effect is minimal and seems less likely to occur with selective beta-1 blockers such as atenolol. Digoxin also inhibits the Na-K-ATPase pump; this occurs in a dose-dependent manner, and at toxic doses, impairs potassium transport into cells and can thus cause hyperkalaemia. Succinylcholine may cause membrane leakage resulting in a rapid, transient hyperkalaemia; this occurs most often in patients with major burns, neuromuscular injury, or prolonged immobilisation (Schaefer and Wolford, 2005).

Incidence of hyperkalaemia among adults in the UK

85. To obtain information about the frequency of life-threatening hyperkalaemia (LTHK) among adults in the UK, an audit was conducted at a district general hospital covering a catchment population of approximately 600,000 people in south London. This audit was conducted specifically at the request of the COT. Over a four month period from January to April 2014, 1.3% of the admissions to the Emergency Department or Acute Medical Units involved patients with elevated serum potassium concentrations. Of these patients, 59 had levels >6.0 mmol/L, the mean concentration in this group being 6.9 (SD 0.7) mmol/L. They included two patients who presented with cardiac arrest and a third who died within 12 hours of presentation.

86. Among the subset of 37 patients with serum potassium >6.0 mmol/L who were treated at one of the hospital's two sites, 7 (19%) were on renal replacement therapy, a further 12 (32%) were under regular out-patient follow-up in the renal department because of known kidney disease, and an additional 4 (11%) were taking prescribed medicines that increase the risk of hyperkalaemia. The remaining 14 (38%) had diverse morbidity, but would not necessarily have been identified as requiring advice to avoid high intakes of potassium.

87. A crude scaling of these figures suggests that at a national level (population 64 million) over a year, some $59 \times 12/4 \times 64,000,000/600,000 = 18,888$ cases might present to hospital with life-threatening hyperkalaemia per year, of which $3/59 \times 18,888 = 960$ were fatal, and $14/37 \times 18,888 = 7,146$ would occur in people who could not reasonably be warned in advance to avoid high consumption of potassium.

88. There are major uncertainties associated with this analysis. In particular, the catchment population studied may not have been nationally representative, and the estimates, especially for mortality, are liable to random sampling error. The age range in the study may not be representative of the population as a whole since older adults are more likely to be vulnerable to hyperkalaemia. Nevertheless, they give a rough indication of the frequency of serious problems from hyperkalaemia.

Incidence of hyperkalaemia in other hospital and community populations

89. A number of observational studies have been conducted to estimate the prevalence of hyperkalaemia in different populations. Fleet *et al* (2012) reported that 2.6% of individuals present at a US Emergency Department had median potassium levels of 6.0 mmol/L, while 3.5% of the patients admitted had median potassium levels of 6.3 mmol/L. Hawkins (2003) reported that 1.5% of potassium analyses performed at a Singapore hospital had potassium levels greater than 6.0 mmol/L. Potassium levels > 5.8 mmol/L were reported in 0.84% of tests conducted in a US medical centre, in an ambulatory setting (Moore *et al.*, 2006). In a community study, mild hyperkalaemia was reported in up to 0.7% of 5179 individuals from the Rotterdam cohort, but severe hyperkalaemia (> 6.0 mmol/L) was not measured (Liamis *et al.*, 2013). Paice *et al.*, 1983 reported that 1.4% of 29,063 patients admitted to a UK teaching hospital, had significant hyperkalaemia (> 6.0 mmol/L on a single occasion) and mortality was higher in this group compared to controls. Of the 406 patients, 244, 93 and 69 patients had serum potassium levels of 6-6.4, 6.5-6.9 and ≥ 7.0 mmol/L respectively. Whilst these are not inconsistent with the hospital audit, described above, none of the studies were intended to assess the extent of undiagnosed hyperkalaemia.

Conclusions on vulnerability

90. The evidence reviewed indicates that a moderate increase in dietary potassium should not present problems for healthy adults, children or weaned infants. The people most vulnerable to higher dietary intakes of potassium are those with major impairment of renal function, and those taking certain prescribed

medicines that promote an increase in serum potassium, most of whom will be elderly.

Implications of sodium replacement for dietary intakes of potassium

Dietary intakes of potassium

91. In the UK, the Reference Nutrient Intake (RNI) for potassium in adults is 3.5 g (89.7mmol) per day, a level which was set to ensure optimal sodium metabolism (DH, 1991). For children, the RNIs are 0.8, 1.2, 2.0, 3.1 and 3.5 g per day (equivalent to 20.5, 30.8, 51.3, 79.5 and 89.7mmol per day) for ages 1-3, 4-6, 7-10, 11-14 and 15-18 years respectively. The EU Recommended Daily Amount (RDA) for potassium in adults is 3.1-3.5 g per day (79.5 – 89.7 mmol per day).

92. Important dietary sources of potassium include potatoes, fruit, berries, vegetables, milk products (excluding cheese) and nuts. Potassium occurs in foods mainly as salts of weak organic acids. It is also found in mineral, spring and table waters, although concentrations are generally low, reported levels ranging from <1 to 10.9mg/L (EFSA, 2005; Morton *et al.*, 1979; Powell *et al.*, 1986; Buckinghamshire County Council, 2005).

93. It has been suggested that, as a guide, patients with more severe CKD should not exceed a daily intake of 39 mg (1 mmol) potassium per kg body weight (personal communication, Department of Health¹¹). For a 70 kg adult, this would be equivalent to 2.73 g or 70 mmol per day.

94. Individuals on a low potassium diet avoid or restrict their consumption of foods high in potassium (including many fruits and vegetables) and use cooking techniques such as boiling and then discarding the cooking water to remove potassium from foods such as vegetables.

95. Data from the NDNS rolling programme published in 2014 (Bates *et al.*, 2014) show that mean potassium intakes in the UK were generally less than the recommended amounts (see Table 3 for current mean potassium intakes in adults aged 19 - 64 and 65+ years) but greater than the 2.73 g (70 mmol) maximum that has been advised for 70 kg adults who are on a restricted potassium diet.

Exposure assessment for adults

96. The calculations that follow focus on exposures in adults (aged 19-64 and 65+ years) as the large majority of people who would be most vulnerable to an increase in potassium intakes fall in this age range.

97. Information about the exact extent to which potassium might be used to replace sodium in food products is not available. However, as an approximation to

¹¹ The original reference may be Wiggins, K. L., ed. *Guidelines for Nutrition Care of Renal Patients*. Chicago, IL: American Dietetic Association, 2002.

an extreme case, it is assumed that replacement would occur at a level of 25% w/w in all of the food categories in which sodium could be replaced by potassium except for bread where the replacement has been assumed to be 15% (see Annex 1 for a list of the food categories that were included). Calculations based on this assumption and on data from the NDNS (Bates *et al.*, 2014), indicate that for adults aged 19 - 64 years there would be a mean increase of 680 and 500 mg for men and women respectively in daily intakes of potassium. For adults aged 65+ years, among whom the prevalence of impaired kidney function is likely to be higher, the corresponding mean increase would be 610 and 440 mg potassium respectively. When considered as one group, there would be a mean increase of 580 mg in daily intakes of potassium in adults aged 19+ years. Table 3 below shows the current mean potassium intakes, the potential increases following 15/25% w/w replacement, and the total mean potassium intakes after maximal replacement, for adults aged 19 – 64, 65+ and 19+ years. The table also provides comparisons with the UK RNI of 3.5g/day; showing potential increases following 15/25% w/w replacement of sodium with potassium. For adult men, the mean potassium intake increases to above 100% RNI in each age group. For adult women, the mean potassium intake increases from 73% to 87% and from 74% to 89% of RNI in 19-64 year olds and 65+ year olds respectively.

98. The largest contributions to the increase in potassium intakes would be from the cereal and cereal products group and the meat and meat products group. This reflects the replacement of sodium in raising agents and preservatives respectively.

99. These calculations are likely to over-estimate the maximal increases in potassium intakes, as they base the potassium replacement on the total sodium content of relevant foods, including naturally occurring sodium, rather than the added sodium content (i.e. that which could be replaced). However, the limited recipe data that are available from food manufacturers suggest that the assumption of 15/25% replacement is reasonable.

100. With regard to the potential for adverse effects from replacement of sodium with potassium, a more important consideration is the increase that would occur in the proportion of the population with daily intakes of potassium above specified thresholds. With the same assumptions about the extent of replacement, and again, using data from the NDNS, Table 4 gives estimates of the changes in the proportions of people in different age groups whose daily intakes of potassium would exceed a) 3.5 g and b) 2.73 g, following the introduction of salt replacement.

Table 3. Current mean potassium intakes, potential mean increases in potassium intakes following 15/25% w/w replacement of sodium in relevant food products, and total mean potassium intakes after replacement (g/day) for adults aged 19 - 64 and 65+ years compared to the UK RNI of 3.5g/day (Bates *et al.*, 2014)

Age (years)	Current mean intake (g/day)	% of RNI	Mean increase in intake (g/day)	Total mean intake after replacement (g/day)	% of RNI
Men 19 – 64 n = 710	3.1 (80 mmol)	89	0.68 (17 mmol)	3.8 (97 mmol)	110
Women 19 – 64 n = 945	2.5 (65 mmol)	73	0.50 (13 mmol)	3.1 (78 mmol)	87
Men & women 19 - 64 n = 1655	2.8 (73 mmol)	81	0.59 (15 mmol)	3.4 (88 mmol)	97
Men 65+ n = 191	3.2 (81 mmol)	91	0.61 (17 mmol)	3.8 (96 mmol)	110
Women 65+ n = 237	2.6 (68 mmol)	74	0.44 (11 mmol)	3.1 (79 mmol)	89
Men & women 65+ n = 428	2.9 (73 mmol)	83%	0.52 (13 mmol)	3. (87 mmol)	97
Men 19+ n = 901	3.1 (80 mmol)	89	0.67 (17 mmol)	3.8 (97 mmol)	110
Women 19+ n = 237	2.6 (66 mmol)	74	0.49 (13 mmol)	3.1 (78 mmol)	89
Men & women 19+ n = 2083	2.8 (73 mmol)	80	0.58 (15 mmol)	3.4 (88 mmol)	97

Data reported to 2 significant figures

101. Table 4 shows that some 19% of adults currently have daily potassium intakes that exceed the UK RNI of 3.5 g. Assuming 15/25% w/w replacement of sodium with potassium in all relevant foods, the proportion of the population exceeding the RNI would increase to approximately 43% (a 2.2-fold increase). The proportion of adults with daily intakes currently exceeding 2.73 g (the recommended maximum for a person weighing 70 kg who needs to restrict their consumption of potassium) is 52%; this would increase to an estimated 75% (a 1.4-fold increase) with widespread and maximal substitution of sodium by potassium in food products.

Table 4. Estimated proportions of adults with daily intakes of potassium exceeding specified thresholds, currently and following 15/25% w/w replacement of sodium in relevant food products (see Annex 1 for relevant food categories)

Age (years)	Estimated proportion of population with daily intakes exceeding 3.5 g			Estimated proportion of population with daily intakes exceeding 2.73 g		
	Currently	After replacement	Ratio	Currently	After replacement	Ratio
19 - 64	20%	46%	2.3	51%	74%	1.5
65+	18%	40%	2.2	53%	77%	1.5
19+	20%	43%	2.2	51%	75%	1.5

Data reported to 2 significant figures

Exposure assessment for infants

Current weaning recommendations

102. Currently DH advises that infants should be exclusively breast- or formula-fed until around 6 months of age. Recommended weaning foods include soft mashed fruit and vegetables, followed by soft cooked meat or fish, pasta, noodles, toast or pieces of chapatti, lentils or chopped/mashed hard boiled eggs and full fat dairy products such as fromage frais, yoghurt or custard (NHS, 2013). It is further recommended that gravy and stock cubes should be avoided as they contain high levels of salt, and that salt should not be added to weaning foods or used in family foods given to children. From around age 12 months, solid food should increase in variety and frequency until by the age of 5 years, a child is eating the same food as the rest of the family.

Additives permitted for use in foods for infants

103. Only a limited number of additives are permitted for use in weaning foods and other foods intended/marketed for infants. The permitted additives include both sodium and potassium salts (for example, potassium and sodium phosphates, citrates, ascorbates, acetates, lactates and alginates) at specified levels for specific purposes (EU, 2011).

104. Although very young infants would not be expected to be exposed to added potassium or sodium, from the age of 6 months there is the potential for some exposure to such additives in family foods, particularly in bread and bakery products, pasta and noodles, and to a lesser extent, dairy products. This is in addition to those present in weaning foods. As the infant gets older, exposure to potassium and sodium salts is likely to increase as more family foods, and especially processed foods, are introduced.

105. Overall, infants are less likely than adults to consume regularly the foods in which potassium-based replacements for sodium chloride and sodium based-

additives might be used. This dietary difference would help to offset any vulnerability because of immaturity of their kidney structure and function.

Implications for health

Healthy adults

106. Given the reserves in the body's capacity to maintain potassium balance, healthy adults would not be expected to suffer any harm from increases in dietary potassium of the magnitude that might result from replacement of sodium chloride and sodium-based additives.

Healthy infants

107. Adverse effects would not be expected in healthy infants since significant exposure to potassium-based replacements is unlikely to occur until they start to consume family food, by which time the function of the kidney will have undergone substantial maturation. Moreover, hyperkalaemia has not been reported in healthy infants from dietary exposures alone.

Healthy children at older ages

108. In view of their more mature renal function, healthy children at older ages would be expected to tolerate the increases in dietary potassium that would result from salt replacement without any harm.

People with kidney disease or other relevant morbidity, and those taking medicines that predispose to hyperkalaemia

109. The population groups in which adverse effects are most likely to occur if potassium is used to replace sodium in food products are people with CKD or other relevant morbidity, and those taking medicines that predispose to hyperkalaemia.

110. In paragraph 87, it was estimated that nationally there may be some 7,100 cases per year of life-threatening hyperkalaemia in adults presenting to hospital who could not reasonably be warned in advance to avoid high consumption of potassium. The daily intakes of potassium which vulnerable people of this sort can tolerate are not known, and it is likely that there will be a range. At one extreme some may require intakes lower than 2.73 g to protect them. On the other hand, there may be others who will develop life-threatening hyperkalaemia only when their intake exceeds some higher threshold.

111. The calculations summarised in paragraph 101 indicate that with 25% w/w replacement of all sodium by potassium in all relevant foods, the proportions of the population with intakes exceeding 2.73 g and 3.5 g would increase approximately 1.4-fold and 2.2-fold respectively. For higher thresholds, the proportionate increase would be even greater.

112. In the absence of empirical data on the distribution of tolerable intakes among people with unrecognised vulnerability to higher dietary potassium, as an illustrative calculation, it might be assumed that the increase in the proportion exceeding their individual tolerance would average to somewhere in the region of that for a threshold

of 3.5 g – i.e. 2.4-fold. This would imply that maximal replacement could add to the number of cases of life-threatening hyperkalaemia presenting to hospital by approximately $7,100 \times (2.2 - 1) = 8520$ cases per year.

113. To the extent that not all sodium in relevant foods would be replaced by potassium at a rate of 15/25% w/w, the true impacts would be lower than this estimate.

114. In addition to effects in people with unrecognised vulnerability to potassium, there could be an increase in the incidence of life-threatening hyperkalaemia among patients with known vulnerability (e.g. because of diagnosed renal impairment). In the audit described at paragraphs 85-88, such patients accounted for 62% of the cases of life-threatening hyperkalaemia. While in theory they can be advised to restrict their intakes of potassium, in practice this may not always be achieved, and the use of potassium replacement for sodium would increase the scope for errors in adherence.

Summary and discussion

115. Potassium-based replacements for sodium chloride and sodium-based additives (such as preservatives and raising agents) have not previously been recommended as a means of reducing salt intakes because there were concerns that their use could increase the incidence of hyperkalaemia and cardiac dysrhythmias in people with impaired or immature renal function. Vulnerable groups might include very young children, the elderly, people with kidney disease (not all of whom will have been medically diagnosed), and patients taking medicines which reduce renal excretion of potassium.

Physiology and vulnerability to potassium toxicity

116. Potassium is readily absorbed from food, and that which exceeds the body's requirements is excreted mainly in the urine. Most of the potassium in the body is contained within cells, but it is changes in the extracellular concentration (including that in the blood) which can give rise to disease. The extracellular concentration of potassium is tightly regulated within a narrow range, not only through excretion of excess intake, but also through rapid transfer of potassium between the extracellular and intracellular compartments.

117. The difference between intracellular and extracellular concentrations of potassium results in an electrochemical gradient across cell membranes, helping to establish the resting cell membrane potential, which is particularly important for the function of nerves and muscle (including in the heart). Abnormally high serum/plasma concentrations of potassium, especially if they result from a rapid increase, can lead to cardiac dysrhythmias, and in extreme cases, cardiac arrest and death.

118. Healthy adults can tolerate much higher intakes of potassium than normally occur through the diet. In the minority of trials of potassium supplementation that have assessed serum/plasma potassium concentrations or renal endpoints such as serum creatinine (most of which would have been conducted in healthy adults or people with uncomplicated hypertension), no adverse effects have been reported.

119. At birth, the neonatal kidney is immature in both structure and function. Rapid maturation then occurs over the first few months of life. However, whilst some aspects of renal function such as GFR are mature after the first year, the kidney is not fully developed until early adulthood. As in adults, long-term potassium balance in infants and young children is largely controlled by the kidney. However, whereas adults have a neutral potassium balance, the balance in infants is positive, meaning that they absorb more than they excrete. This provides the potassium that is required for cellular growth. Nevertheless, in the short-term, the infant kidney can if necessary excrete more potassium than is absorbed. There are no documented cases of hyperkalaemia in healthy infants or young children from dietary exposures alone.

120. Elderly people may be more prone to potassium toxicity as a consequence of age-related decline in renal function, co-morbidities, and more frequent use of medicines that reduce renal excretion of potassium.

121. Most chronic kidney disease occurs in adults, and it has been estimated that nationally there are many thousands of people with consequent impairment of renal function that is sufficient to warrant restriction of potassium intake. They include a substantial proportion whose disease is undiagnosed, and who are therefore unaware of their vulnerability.

122. Medicines that reduce renal excretion of potassium include ACE inhibitors, potassium-sparing diuretics and trimethoprim.

123. From an audit carried out in south London, it is estimated that there might be some 18,888 incident cases of life-threatening hyperkalaemia presenting to hospital per year in the UK, of which 960 are fatal, and close to 40% (i.e. about 7,100) occur in people who could not reasonably be warned in advance to avoid high consumption of potassium.

Exposures to potassium and changes that might occur if substitution for sodium were implemented

124. At present, average daily intakes of potassium among adults in the UK are in the region of 2.8 g, this being lower than the RNI of 3.5 g. Assuming widespread and maximal adoption, it is estimated that substitution of sodium by potassium in food products could increase mean daily intakes in adults by up to approximately 0.58 g, bringing them closer to the recommended level.

125. Currently, some 19% of adults have daily intakes in excess of 3.5 g. With widespread and maximal substitution of sodium by potassium in food products, it is estimated that this proportion might increase to some 43%, becoming approximately 2.2 -fold higher.

126. It is not expected that infants would be exposed to potassium-based additives before age 6 months. Only a limited number of additives are permitted in foods produced specifically for infants and young children, and recommended first foods (with the exception of bread and bakery products) tend to be low in sodium. Therefore it seems unlikely that infants would be exposed to salt-replacers until they were consuming family food.

Implications for health

127. Given the reserves in the body's capacity to maintain potassium balance, healthy adults and children older than one year would not be expected to suffer any harm from increases in dietary potassium of the magnitude that might result from sodium-replacement.

128. Adverse effects would not be expected in healthy infants since significant exposure to potassium-based replacements is unlikely to occur until they start to consume family food, by which time the function of the kidney will have undergone substantial maturation. Moreover, hyperkalaemia does not appear to be a problem currently in healthy infants from dietary exposures alone.

129. Potassium-based replacement could, however, threaten the health of people with major impairment of renal function because of CKD or other morbidity, and those taking medications such as ACE inhibitors and potassium-sparing diuretics that reduce renal excretion of potassium. Most, but by no means all of these vulnerable individuals will be elderly.

130. In theory, patients with diagnosed CKD and those taking medicines that predispose to hyperkalaemia could be advised by their doctors to avoid foods in which sodium has been replaced by potassium. However, this will only be practical if the food products concerned are clearly labelled, and suitable alternatives are readily available that do not contain potassium-based replacements. The finding that many of the patients who currently present to hospital with life-threatening hyperkalaemia, are already under care for known renal failure (and will therefore have been advised about the need to restrict their potassium intake) illustrates the challenges in adhering to potassium restriction.

131. Even more problematic are the people who are vulnerable because of kidney disease or other morbidity that has not been diagnosed, and who therefore will not be aware of any reason to be cautious about foods containing high levels of potassium. It is estimated that in the UK, such people might account for some 7,100 cases of life-threatening hyperkalaemia presenting to hospital per year. In the absence of empirical data on the distribution of potassium intakes that could be tolerated by this vulnerable sub-population, it is estimated that maximal salt replacement might cause a 2.2 -fold increase in the proportion of people with intakes exceeding their individual tolerance (see paragraph 109), leading to some 8,520 additional cases per year of life-threatening hyperkalaemia.

132. In deciding whether to permit or encourage potassium-based replacement of sodium chloride and sodium-based additives, policy-makers will need to balance the expected benefits against these potential adverse effects. If replacement were at a lower level than has been assumed in the above calculations, then adverse effects would be less frequent. In particular, it may be worth considering whether potassium-based replacement should be limited to foods that are easier for patients with known vulnerability to avoid. For example, it may be simpler to eliminate a single item such as crumpets from the diet than to avoid bread that might contain potassium-based additives. If required, other scenarios involving lower levels of salt-replacement could be modelled.

Uncertainties

133. It should be emphasised that there are substantial uncertainties in the calculations that have been presented. The most important sources of uncertainty include:

- Estimates of the frequency of life-threatening hyperkalaemia may be inaccurate because:
 - the population that was studied in south London was unrepresentative of the country more widely;
 - the audit failed to pick up some cases of hyperkalaemia in the study population (e.g. because they died without being admitted to hospital);
 - the study sample was small and may have been unrepresentative simply by chance (this is a greater concern in relation to the less frequent outcomes such as death)
- It is unclear to what extent potassium-based replacement would be implemented in practice – both the range and number of food products in which it would be used, and the level of substitution within those foods.
- No information is available about the distribution of tolerance to potassium among people with unrecognised vulnerability to high dietary intakes, and the assumption that their incidence of life-threatening hyperkalaemia will increase in proportion to the prevalence of daily intakes of potassium >3.5 g is a major simplification

134. For these reasons, the estimated number of additional cases of life-threatening hyperkalaemia nationally could be out by as much as a factor of 10.

135. The uncertainties could be reduced by further surveys of the incidence and characteristics of life-threatening hyperkalaemia in other parts of the country, and better information about the extent to which replacement would occur in different foods. In addition, if potassium-based replacement were to be implemented, it would be advisable to monitor its application, along with temporal trends in the incidence of life-threatening hyperkalaemia, both in patients with known vulnerability, and in those not previously recognised as being at risk. Ideally, such monitoring should include collection of baseline data before the salt-replacement began.

Conclusions and recommendations

136. Potassium-based replacement for sodium chloride and sodium-based additives would not be expected to cause any adverse effects in healthy adults, children or infants.

137. Potassium-based replacement could, however, threaten the health of people with major impairment of renal function because of CKD, and those taking medications such as ACE inhibitors and potassium-sparing diuretics that reduce renal excretion of potassium. Most, but by no means all of these vulnerable individuals will be elderly.

138. In theory, patients with diagnosed CKD and those taking medicines that predispose to hyperkalaemia could be advised to avoid foods in which sodium has been replaced by potassium. However, this will only be practical if the food products concerned are clearly labelled, and suitable alternatives are readily available that do not contain potassium-based replacements.

139. Among people who are vulnerable because of undiagnosed kidney disease, it is estimated that salt-replacement in the UK might lead to as many as 9,800 additional cases of life-threatening hyperkalaemia presenting to hospital per year. However, this figure is subject to substantial uncertainty and could be out by as much as a factor of 10.

140. Uncertainties in the estimated impact could be reduced by further surveys of the incidence and characteristics of life-threatening hyperkalaemia in different parts of the country, and better information about the extent to which replacement would occur in different foods.

141. In deciding whether to permit or encourage potassium-based replacement of sodium chloride and sodium-based additives, policy-makers will need to balance the expected benefits against these potential adverse effects. If replacement were at a lower level than has been assumed, then adverse effects would be less frequent.

142. It may be worth considering whether replacement should be limited to foods that are easier for patients with known vulnerability to avoid. If required, scenarios involving lower levels of potassium-based replacement could be modelled.

143. If potassium-based replacement of sodium chloride and sodium-based additives were to be implemented, it would be advisable to monitor its application, and any temporal trends in the incidence of life-threatening hyperkalaemia, both in patients with known vulnerability, and in those not previously recognised as being at risk. Ideally, such monitoring should include collection of baseline data before the replacement began.

COT Statement 2017/3
November 2017

Glossary

ACE – Angiotensin Converting Enzyme
ADH – Anti-diuretic Hormone
AI – Adequate Intake
ARB – Angiotensin Receptor Blocker
BW – body weight
CI – Confidence interval
CKD – Chronic kidney disease
DH – Department of Health
ECG – Electrocardiogram
EFSA – European Food Safety Authority
ENaC – Epithelial sodium channel
EVM – Expert Group on Vitamins and Minerals
g – grams
GFR – Glomerular Filtration Rate
GI – Gastrointestinal
HDL – High density lipoprotein
IOM – Institute of Medicine
K – potassium
KCl – potassium chloride
kg - kilogram
L – litre
LDL – Low density lipoprotein
LTHK – Life-threatening hyperkalaemia
mEq/L – milliequivalent/L
mmol – millimoles
mmol/L – millimoles/Litre
Na – Sodium
Na-K-ATPase – Sodium-potassium-adenosine triphosphatase
NDA – EFSA Panel on Dietetic Products, Nutrition and Allergies
NDNS – National Diet and Nutrition Survey
NHANES – National Health and Nutrition Examination Survey
NHS – National Health Service
NICE – National Institute for Health and Care Excellence
nmol/L – nanomoles/Litre
NSAID – Non Steroidal Anti-Inflammatory Drugs
OR – Odds ratio
QICKD – Quality Initiatives in Chronic kidney disease
QOF – Quality and Outcomes Framework
RCT – Randomised Controlled Trial
RDA – Recommended Daily Amount
RNI – Reference Nutrient Intake
SACN – Scientific Advisory Committee on Nutrition
SD – Standard Deviation
SEM – Standard error of the mean
SUL – Safe Upper Level
TUL – Tolerable Upper Level
 $\mu\text{mol/L}$ – micromoles/Litre
US – United States

WHO – World Health Organization
w/w – weight/weight
y – years

References

- Arbuto, N.J.; Hanson, S.; Gutierrez, H.; Hooper, L.; Elliott, P. & Cappuccio, F.P. (2013) 'Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses.' *British Medical Journal*; 346:f1378.
- Appel, L.J.; Moore, T.J.; Obarzanek, E.; Vollmer, W.M.; Svetkey, L.P.; Sacks, F.M.; Bray, G.A.; Vogt, T.M.; Cutler, J.A.; Windhauser, M.M.; Lin, P.H.; Karanja, N. (1997) 'A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group.' *New England Journal of Medicine* 336: 1117-1124.
- Appel, L.J.; Brands, M.W.; Daniels, S.R.; Karanja, N.; Elmer, P.J.; Sacks, F.M. (2006) 'American Heart Association Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association.' *Hypertension* 47(2):296-308.
- Arant, B.S. (1987) 'Postnatal development of renal function during the first year of life.' *Pediatric Nephrology* 1:308-13.
- Association of Clinical Biochemistry (2013) 'Potassium (serum, plasma, blood)' <http://www.acb.org.uk/Nat%20Lab%20Med%20Hbk/Potassium.pdf>
- Bates, B.; Lennox, A.; Bates, C.; Swan, G. (2011) 'National Diet and Nutrition Survey. Headline results from Years 1 and 2 (combined) of the rolling programme (2008/2009 – 2009/10).' Department of Health https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216484/dh_128550.pdf
- Bates, B.; Lennox, A.; Prentice, A.; Bates, C.; Swan, G. (2012) 'National Diet and Nutrition Survey. Headline results from Years 1, 2 and 3 (combined) of the rolling programme (2008/2009 – 2010/11).' Department of Health <http://transparency.dh.gov.uk/2012/07/25/ndns-3-years-report/>
- Beck, L.H. (1998) 'Changes in renal function with aging.' *Clinics in Geriatric Medicine* 14: 199-209.
- Buckinghamshire County Council (2005) 'Bottled Water Survey' Available at http://www.buckscc.gov.uk/media/137448/food_water_survey.pdf
- Bulpitt, C.J.; Ferrier, G.; Lewis, P.J.; Daymond, M.; Bulpitt, P.F.; Dollery, C.T.; (1985) 'Potassium supplementation fails to lower blood pressure in hypertensive patients receiving a potassium losing diuretic.' *Annals Clinical Research* 17:126-30.
- Coruzzi, P.; Brambilla, L.; Brambilla, V.; Gualerzi, M.; Rossi, M.; Parati, G.; Di Rienzo, M.; Tadonio, J.; Novarini, A. (2001) 'Potassium depletion and salt sensitivity in essential hypertension.' *Journal of Clinical Endocrinology and Metabolism* 86: 2857-2862.
- Čukuranović, R.; Vlajković, S. (2005) 'Age related anatomical and functional characteristics of human kidney.' *Facta Universatis, Medicine and Biology*, 12, 61-19.

Department of Health (1991) 'Dietary reference values for food energy and nutrients in the UK. Report on health and social subjects 41.' London: HMSO.

DeWoskin, RS.; Thompson, CM. (2008) 'Renal clearance parameters for PBPK model analysis of early lifestage differences in the disposition of environmental toxicants.' *Regulatory Toxicology and Pharmacology* Jun;51(1):66-86.

Dickinson, HO.; Nicolson, D.; Campbell, F.; Beyer, FR.; Mason, J. (2006) 'Potassium supplementation for the management of primary hypertension in adults (review).' *Cochrane Database of Systematic Reviews*, Issue 3. Art. No: CD004641. DOI:10.1002/14651858.CD004641.pub2.

EFSA (2005) '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)' *EFSA Journal* 193, 1-19

Einhorn, LM.; Zhan, M.; Hsu, VD.; Walker, LD.; Moen, MF.; Seliger, SL.; Weir, MR.; Fink, JC. (2009) 'The frequency of hyperkalemia and its significance in chronic kidney disease.' *Archives of Internal Medicine* Jun 22;169(12):1156-62.

EU (2011) EU list of food additives. Annex II of Regulation 1333/2008 – <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:295:0001:0177:En:PDF>

Expert Group on Vitamins and Minerals (2003) 'Safe Upper Levels for Vitamins and Minerals.' *Food Standards Agency*, <http://tna.europarchive.org/20110911090542/http://cot.food.gov.uk/pdfs/vitmin2003.pdf>

Fernandez, E.; Perez, R.; Hernandez, A.; Tejada, P.; Arteta, M.; Ramos, JT. (2011) 'Factors and mechanisms for pharmacokinetic differences between pediatric population and adults' *Pharmaceutics* 3 pp.53-72

Fleet, JL., Shariff, SZ., Gandhi, S., Weir, M., Jain, AK., Garg, AX. (2012). Validity of the International Classification of Disease 10th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. *BMJ Open*, 2012;2:e002011

Gallen, IW.; Rosa, RM.; Esparaz, DY.; Young, JB.; Robertson, GL.; Battle, D.; Epstein, FH.; Landsberg, L. (1998) 'On the mechanism of the effects of potassium restriction on blood pressure and renal sodium retention.' *American Journal of Kidney Diseases* 31: 19-27.

Geleijnse, JM.; Witteman, JC.; Hofman, A.; Grobbee, DE. (1997) 'Electrolytes are associated with blood pressure in old age: the Rotterdam Study.' *Journal of Human Hypertension* 11: 421-423.

Geleijnse, JM.; Kok, FJ.; Grobbee, DE. (2003) 'Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials.' *Journal of Human Hypertension* 17:471-480.

Gennari, FJ.; Segal, A. (2002) 'Hyperkalemia: An adaptive response in chronic renal insufficiency.' *Kidney International* 62:1–9

Graves, JW. (1998) 'Hyperkalaemia due to a potassium based water softener.' *New England Journal of Medicine* 339: 1790.

Grimm, RH Jr.; Neaton, JD.; Elmer, PJ.; Svendsen, KH.; Levin, J.; Segal, M.; Holland, L.; Witte, LJ.; Clearman, DR.; Kofron, P. (1990) 'The influence of oral potassium chloride on blood pressure in hypertensive men on a low-sodium diet.' *New England Journal of Medicine* 322: 569-574.

Gu, D.; He, J.; Wu, X.; Duan, X.; Whelton, PK. (2001) 'Effect of potassium supplementation on blood pressure in Chinese: a randomized, placebo-controlled trial.' *Journal Hypertension* 19: 1325-1331.

Gurkan, S.; Estilo, GK.; Wei, Y.; Satlin, LM. (2007) 'Potassium transport in the maturing kidney.' *Pediatric Nephrology* 22, 915-25.

Hawkins, RC. (2003) Gender and age as risk factors for hypokalaemia and hyperkalaemia in a multi ethnic Asian population. *Clinica Chemica Acta*, 331: 171-172.

He, FJ. and MacGregor, GA. (2001) 'Beneficial effects of potassium.' *British Medical Journal* 323: 497-501.

Indermitte, J., Burkolter, S., Drewe, J., Krähenbühl, S., Hersberger, KE. (2007). Risk factors associated with a high velocity of the development of hyperkalaemia in hospitalised patients *Drug safety* 30: 71-80.

IOM FNB (Food and Nutrition Board) (2004) 'Dietary Reference Intakes: water, potassium, sodium, chloride, and sulphate.' Institute of Medicine, National Academy Press, Washington DC. USA.

Jula, A.; Rönnemaa, T.; Rastas, M.; Karvetti, RL.; Mäki, J. (1990) 'Long-term non-pharmacological treatment for mild to moderate hypertension.' *Journal of Internal Medicine* 227: 413-421.

Kearns, GL.; Abdel-Rahman, SM.; Alander, SW.; Blowey, DL.; Leeder, JS.; Kauffman, RE. (2003) 'Developmental pharmacology--drug disposition, action, and therapy in infants and children.' *New England Journal of Medicine* 349, 1157-67.

Keith, NM.; Osterberg, AE.; Burchell, HB. (1941) 'Some effects of potassium salts in man.' *Annals of Internal Medicine* 16: 879-892.

Liamis, G., Rodenburg, EM., Hofman, A., Zietse, R., Stricker, BH., Hoorn, EJ. (2013) Electrolyte disorders in community subjects: prevalence and risk factor. *The American Journal of Medicine*, 126: 256-263.

Loggie, JM.; Kleinman, LI.; Van Maanen, EF. (1975) 'Renal function and diuretic therapy in infants and children. Part I.' *Journal of Pediatrics* 4, 485-96.

Mannan, MA.; Shahidulla, M.; Salam, F.; Alam, MS.; Hossain, MA.; Hossain, M. (2012) 'Postnatal development of renal function in preterm and term neonates.' *Mymensingh Medical Journal* 21, 103-8.

Moore, CR., Lin, JJ., Halm, EA. (2006). Follow up of markedly elevated serum potassium results in the ambulatory setting: implications for patient safety. *Am J Med Qual*, 21:115-124

Morris, RC Jr.; Sebastian, A.; Forman, A.; Tanaka, M.; Schmidlin, O. (1999) 'Normotensive salt sensitivity: effects of race and dietary potassium.' *Hypertension* 33: 18-23.

Morton, MS.; Elwood, PC.; Abernethy, M. (1976) 'Trace elements in water and congenital malformations of the central nervous system in South Wales.' *British Journal of Preventive and Social Medicine* 30:36-39.

Naismith, DJ. and Braschi, A. (2003) 'The effect of low-dose potassium supplementation on blood pressure in apparently healthy volunteers.' *British Journal of Nutrition* 90: 53-60.

NHS Kidney Care (2012) 'Chronic Kidney Disease in England: the human and financial cost' Available at:
http://www.kidneycare.nhs.uk/resources_old/online_library/

NHS Choices (2013) 'Pregnancy and baby: Your baby's first solid foods' Available at:
<http://www.nhs.uk/Conditions/pregnancy-and-baby/Pages/solid-foods-weaning.aspx#close>

NICE, 2013 clinical guideline 157
<https://www.nice.org.uk/guidance/cg157/chapter/introduction>

NICE Clinical Guideline 182 (2014) 'Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care' Available at: <https://www.nice.org.uk/guidance/cg182/resources/cg182-chronic-kidney-disease-update-classification-table>

Overlack, A.; Conrad, H.; Stumpe, KO. (1991) 'The influence of oral potassium citrate/bicarbonate on blood pressure in essential hypertension during unrestricted salt intake.' *Klinische Wochenschrift* 69: 79-83.

Paice, B., Gray, JMB., McBride, D., Donnelly, T., Lawson, DH. (1983). Hyperkalaemi in patients in hospital. *British Medical Journal*, 286: 1189-1191.

Palmer, BF. (2015) 'Regulation of potassium homeostasis' *Clinical Journal of the American Society of Nephrology*

Patki, PS.; Singh, J.; Gokhale, SV.; Bulakh, PM.; Shrotri, DS.; Patwardhan, B. (1990) 'Efficacy of potassium and magnesium in essential hypertension: a double-blind, placebo controlled, crossover study.' *British Medical Journal* 15;301(6751):521-3.

PHE (2014) Public Health England. Chronic kidney disease prevalence model.
<http://www.yhpho.org.uk/resource/view.aspx?RID=204689>

Powell, P.; Bailey, R.J.; Jolly, P.K. (1987) 'Trace elements in British tap-water supplies.' Swindon, WRc (Report PRD 706-M/1). Available at
<http://dwi.defra.gov.uk/research/completed-research/reports/dwi0007.pdf>

Rabelink, T.J.; Koomans, H.A.; Hene, R.J.; Dorhout Mees, E.J. (1990) 'Early and late adjustment to potassium loading in humans.' *Kidney International* 38: 942-947.

Reardon, L.C.; Macpherson, D.S. (1998) 'Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry?' *Archives of Internal Medicine* Jan 12;158(1):26-32.

Sacks, F.M.; Willett, W.C.; Smith, A.; Brown, L.E.; Rosner, B.; Moore, T.J. (1998) 'Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake.' *Hypertension* 31: 131-138.

Sacks, F.M.; Svetkey, L.P.; Vollmer, W.M.; Appel, L.J.; Bray, G.A.; Harsha, D.; Obarzanek, E.; Conlin, P.R.; Miller, E.R.; Simons-Morton, D.G.; Karanja, N.; Lin, P.H.; Aickin, M.; Most-Windhauser, M.M.; Moore, T.J.; Proschan, M.A.; Cutler, J.A. (2001) 'Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet.' *New England Journal of Medicine* 344: 3-10.

Siani, A.; Strazzullo, P.; Guglielmi, S.; Pacioni, D.; Giacco, A.; Iacone, R.; Mancini, M. (1988) 'Controlled trial of low calcium versus high calcium intake in mild hypertension.' *Journal of Hypertension* Mar;6(3):253-6

Schaefer, T.J.; Wolford, R.W. (2005) 'Disorders of Potassium' *Emergency Medicine Clinics of North America* 23:723-747

Smith, S.J.; Markandu, N.D.; Sagnella, G.A.; MacGregor, G.A. (1985) 'Moderate potassium chloride supplementation in essential hypertension: is it additive to moderate sodium restriction?' *British Medical Journal (Clinical Research Edition)* Jan 12;290(6462):110-3

Sorenson, M.V.; Matos, J.E.; Praetorius, H.A.; Leipziger, J. (2010) 'Colonic potassium handling' *Pflugers Archive – European Journal of Physiology* 459 pp.645-656

Textor, S.C.; Bravo, E.L.; Fouad, F.M.; Tarazi, R.C. (1982) 'Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril.' *American Journal of Medicine* Nov;73(5):719-25

Wang, W.H. (2004) 'Regulation of renal K transport by dietary K intake.' *Annual Review of Physiology* 66: 547-569.

Whelton, P.K. and He, J. (1997) 'Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials.' *Journal of the American Medical Association* 277: 1624-1632.

WHO (2009) 'Potassium in drinking-water. Background document for development of WHO Guideline for Drinking-water Quality' WHO/HSE/WSH/09.01/7

WHO (2012a) 'Effects of increased potassium intake on blood pressure, renal function, blood lipids, and other potential adverse effects.' WHO, Geneva. Obtainable from:

http://apps.who.int/iris/bitstream/10665/79331/1/9789241504881_eng.pdf

WHO (2012b) 'Effects of increased potassium intake on blood pressure and potential adverse effects in children.' WHO, Geneva. Obtainable from:

http://apps.who.int/iris/bitstream/10665/79338/1/9789241504850_eng.pdf

WHO (2012c) 'Guideline: Potassium intake for adults and children.' WHO, Geneva. Obtainable from:

http://www.who.int/nutrition/publications/guidelines/potassium_intake_printversion.pdf

Zhou, H.; Satlin, LM. (2004) 'Renal potassium handling in healthy and sick newborns.' *Seminars in Perinatology* 28,103-11.

Food categories used when calculating the potential increase in potassium intakes if sodium chloride and sodium-based additives were replaced with potassium-based alternatives at a level of 25% w/w in relevant foods

- Cereal and cereal products
 - Of which all baked goods (comprising all types of bread, biscuits, buns, cakes, pastries, fruit pies and puddings)
 - Of which all breakfast cereals
 - Of which pasta, rice and other cereals
- Milk and milk products
 - Of which semi-skimmed milk
- Eggs and egg dishes
- Fat spreads
- Meat and meat products
 - Of which chicken and turkey dishes
- Fish and fish dishes
- Vegetables, potatoes and savoury snacks
 - Of which potatoes and potato products
- Fruit and nuts
- Sugar, confectionary and preserves
- Beverages
- Miscellaneous (including table salt, artificial sweeteners, soups, sauces, etc.)