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

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

Introduction

1. The Committee on Toxicity (COT) has been asked by the Scientific Advisory Committee on Nutrition (SACN) to advise on the possible effects of increased potassium intakes in vulnerable groups as a consequence of widespread use of potassium-based replacements for sodium chloride and sodium-based additives. Discussion papers (TOX/2013/31, 44 and 45) were presented to Members in June and December 2013.

2. At the meeting in December 2013, Members asked for further refinements to be made to the current potassium intake modelling. Members also asked to be provided with additional information on the number of people presenting to medical care with hyperkalaemia, who were not previously known to be vulnerable (e.g. because of undiagnosed chronic kidney disease (CKD)).

3. Members will wish to note that the SACN has requested an update on the views of the COT. It is hoped that the conclusions of this statement can be agreed upon at this meeting, and an update provided to the SACN in the near future. Since this is a draft, there will be further opportunities to revise the statement if needed.

Questions on which the views of the Committee are sought

4. Members are invited to comment on the structure and content of the first draft statement.

Secretariat
November 2014

This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

TOX/2014/39

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

First Draft 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, and to provide advice that would inform the setting of new targets for salt reduction as part of the Responsibility Deal.

2. Current DH policy is to lower sodium intakes in the population by gradually reducing levels of salt in food products in a way that would progressively accustom the palates of consumers to less salt. The DH does not currently recommend 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, it was noted that increasing potassium levels in food could have potential adverse effects in some vulnerable groups, including very young children, the elderly and individuals with kidney disease. These groups could be at risk of hyperkalaemia due to immature or impaired kidney function. With regard to individuals with kidney disease or impaired kidney function, there are those with diagnosed problems, some of whom will have been advised to consume a low potassium diet, and those whose problems have not yet been diagnosed and who might be adversely affected by increased levels of potassium in the diet.

3. Industry has been asking the DH to reconsider their recommendations as some producers would like to use, and may already be using, potassium-based replacements to achieve sodium reduction in food. The products concerned are those where further sodium reduction would not be possible by reformulation and includes items such as bakery goods (e.g. scones, scotch pancakes, crumpets) and meat products (e.g. sausages and bacon) where the sodium compound has a function, such as a preservative or raising agent, as well as flavouring properties. Potassium cannot totally replace sodium as it is considered to have a metallic aftertaste and it does not have the flavouring properties of sodium. It has been suggested that a maximum 25-30% of added sodium could be replaced by potassium.

4. Potassium chloride (E508) is a generally permitted food additive approved for use in most processed foods, but it can also be used as an ingredient without being subject to further regulation other than general food law. At present, products

containing potassium rather sodium chloride are generally labelled with a warning that they contain potassium salt substitutes, but labelling such as this is currently voluntary.

5. The COT has been asked by the SACN to advise on the possible effects of increased potassium intakes in vulnerable groups as a consequence of salt replacement. The Committee agreed that four population groups should be considered: healthy adults; adults known to be vulnerable such as those with diagnosed chronic kidney disease (CKD); vulnerable adults who are not aware of their increased risk (e.g. with undiagnosed CKD); and infants and young children.

Previous assessments of potassium – Expert bodies

EVM

9. 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 that for guidance, supplements of up to 3.7 g/day potassium appeared to be without adverse effects but could be associated with gastro-intestinal lesions diagnosed by endoscopy. It was 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

10. The EFSA panel on Dietetic Products Nutrition and Allergies (NDA) (EFSA, 2005) concluded that there were insufficient data to establish a Tolerable Upper Level of intake for potassium. However, it was noted that in subjects with reduced kidney function and reduced potassium excretion, doses as low as 1 g potassium in addition to food were associated with elevated plasma potassium and adverse heart effects[1]. They further noted that supplemental potassium doses of 5-7 g/day could cause adverse effects on heart function in apparently healthy subjects (based on the study by Keith *et al*., (1941)).

11. The EFSA panel stated that certain groups, particularly those with impaired kidney function, were sensitive to adverse effects of increasing potassium intake on heart function associated with increases of plasma potassium. These included subjects engaging in strenuous activities leading to dehydration, with diabetes mellitus, with impaired kidney function, on cardiovascular disease drug treatment or other metabolic disorders affecting potassium balance. Elderly people might be more vulnerable to adverse effects of potassium due to reduced kidney function or due to 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 supplements, especially when used by those who are pre-disposed to retain potassium”.

[1] It is unclear which reference this is referring to but it may be the study by Perez et al., 1984.

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

US IOM

13. The US Institute of Medicine (IOM) did not make any recommendations on a Tolerable Upper Level of potassium intake, since they considered that intakes throughout the population were too low (IOM, 2005). However, it was noted that in individuals in whom urinary excretion of potassium was impaired, a potassium intake below the Acceptable Intake (AI) of 4.7 g/day (set on beneficial effects on blood pressure) was appropriate because of adverse cardiac effects (arrhythmias) from the resulting hyperkalaemia, but that such individuals were typically under medical supervision. Medical conditions that were associated with impaired urinary potassium excretion included diabetes, chronic renal insufficiency, end-stage renal disease, severe heart failure and adrenal insufficiency. Elderly individuals were at increased risk as they often had one or more of these conditions or were treated with medication that impaired potassium excretion. The health effects of potassium in infants were considered 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 set on the basis of energy requirements for children of different ages.

14. ACE inhibitors are used in the treatment of hypertension and heart failure, and may be used to slow the progression of CKD; they are one of a number of drug classes that are known to affect potassium balance. However, taking into account studies by Textor *et al*., (1982) and Reardon *et al*., (1998) which investigated serum potassium levels in individuals taking ACE inhibitors, the IOM concluded that the AI would also apply to healthy individuals on angiotensin converting enzyme (ACE) inhibitor therapy.

15. 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 also 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 (arrthymias) from hyperkalaemia. They noted that the available evidence was insufficient to identify the level of kidney function at 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 individuals with stage 3 or 4 chronic kidney disease (GFR < 60 ml/min) should restrict their potassium intake.

WHO 2012

16. The health effects of potassium in adults were reviewed in 2012 by WHO (2012a) who noted that lower potassium intake had been associated with elevated blood pressure, hypertension and stroke and higher levels of consumption could be protective against these conditions. They considered that public health interventions to increase the potassium intake from food could be a cost- effective measure for reducing the burden of mortality from non-communicable diseases. However, the WHO also noted that the evidence for a potential beneficial effect on blood pressure

and cardiovascular disease was not entirely consistent, with the available meta-analyses providing different results and without adverse effects being considered. Therefore, to inform the development of a guideline on potassium consumption, WHO commissioned a review on the effects of potassium intake, to compile results from studies in apparently healthy adults and children.

17. The review in adults (also published as Arbuto *et al*., 2013) considered randomised controlled trials (RCTs) only, 23 studies were included in the analysis, involving a total of 1606 participants and contributing 22 comparisons between potassium supplementation and a corresponding control group. The primary outcome measures were blood pressure (systolic, diastolic or both) and renal function. As secondary outcome measures, any other outcomes reported in the study were noted. The adverse effects considered included increased total cholesterol, LDL, HDL, triglycerides, increased adrenaline or noradrenaline, or other adverse effects as reported. Changes in serum potassium levels were not reported. The studies involved intervention of at least 4 weeks duration and excluded studies where there was a concomitant intervention unless this was also conducted in the controls. Studies were considered in apparently healthy populations who may have been at risk of, or have had, hypertension, were known to have hypertension or were known to have normal blood pressure. Studies were excluded where they targeted those who were acutely ill, infected with human immunodeficiency virus or hospitalised.

18. Three studies measured renal function by measuring serum creatinine (Bulpitt *et al*., 1985; Patki *et al*., 1990; Smith *et al*., 1985 – see paragraphs 66-68. These reported a non-significant decrease in serum creatinine of 4.86 µmol/L with increased potassium intake. The evidence that increased potassium intake did not affect renal function was considered to be of high quality.

19. The adverse effects were discussed in Arbuto *et al*., 2013. It was noted that increased potassium intake had been shown to be safe in people without renal impairment, but that in individuals with impaired urinary potassium excretion there could be a risk of hyperkalaemia. However, the risk was confined to those patients, who were largely under medical supervision and who were excluded from the review. It was noted that potassium intakes of 400 mmol (15.6 g)/day from food for several days or 115 mmol (4.49 g)/day for up to year were not associated with adverse effects (the studies concerned were Rabelink *et al*., 1990 and Siani *et al*., 1991). The authors further noted that none of the studies in the review reported increased side effects, minor complaints or major adverse effects in the increased potassium groups compared with the controls.

20. A review was also conducted in children, using the same inclusion criteria and an outcome measure of blood pressure (WHO, 2012b). Again, adverse effects were considered as an outcome; these included increased total cholesterol, low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides, increased adrenaline or noradrenaline, or other adverse effects as reported. Four studies were included in the meta-analysis, 2 RCTs, one non-randomised trial and one cohort study. However no studies meeting the inclusion criteria reported blood lipid or catecholamine levels, or, monitored adverse effects.

21. WHO recommended that potassium intake from food should be increased to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults (this was considered to be a strong recommendation where the desirable effects of adherence outweigh the risks) (WHO, 2012c). The WHO further recommended a potassium intake of at least 90 mmol/day (3.51 g/day) for adults. This was stated to be a conditional recommendation where the desirable effects of adherence probably outweigh the risks but that the group were not confident of the trade-off. For children, WHO made a conditional recommendation that the recommended potassium intake should be adjusted downwards based on the relative energy requirements of children 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 a period of exclusive breastfeeding (0-6 months) or to the period of complementary feeding and continued breast feeding.

22. It should be noted that some of the assessments discussed above have focussed on consumption of supplemental potassium and not dietary potassium. Data from the National Diet and Nutrition Survey (NDNS) – rolling programme published in July 2012 (Bates *et al*., 2012) indicated that the contribution of dietary supplements to total daily potassium intake was very small and average intakes including supplements were similar to the average intakes from food only.

Potassium intakes

23. In the UK, the Reference Nutrient Intake (RNI) for potassium is 3.5 g/day for adults based on ensuring optimal sodium metabolism (DH, 1991). For children, the RNIs are 0.8, 1.2, 2.0, 3.1 and 3.5 g/day for ages 1-3, 4-6, 7-10, 11-14 and 15-18 years of age respectively. The EU Recommended Daily Amount for potassium in adults is 3.1-3.5 g/day.

24. Important sources of potassium include potatoes, fruit, berries, vegetables, milk products (excluding cheese) and nuts. Potassium occurs in foods mainly associated with weak organic acids. Potassium is also found in mineral, spring and table waters, although the concentrations are very variable (EFSA, 2005). Potassium is readily absorbed from foods.

25. It has been suggested that, as a guide, CKD patients who need to restrict potassium intake should not exceed an intake 1 mmol (39 mg) K per kg body weight (personal communication, Department of Health). For a 70 kg adult, this would be equivalent to 2.73 g/day. An intake of 50-75 mmol K is recommended for patients with clinically significant renal failure (Graves, 1998). This is equivalent to 1.95-2.93 g potassium.

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

27. Data from the National Diet and Nutrition Survey (NDNS) rolling programme published in July 2012 (Bates *et al*., 2012) show that mean potassium intakes in the UK were generally less than the recommended amounts, being 78 and 64% of the RNI in boys and girls aged 11-18 years (2.58 and 2.12g) respectively, whereas in adults aged 19-64, intakes were 91 and 74% of the RNI in males and females respectively (3.18 and 2.56 g). In adults aged 65+ intakes were 90 and 74% of the RNI in males and females (3.14 and 2.59 g). The mean intakes in males would be higher than 2.73 g maximum estimated for a 70 kg individual on a restricted potassium diet.

Potassium in the body

Introduction

28. Potassium is an essential nutrient and the most abundant intracellular cation at 100-150mmol/L (reported as mEq/L)[2] (Zhou and Satlin, 2004). Approximately 98% of the total body potassium content is contained intracellularly, primarily within muscle cells, with the remaining 2% being present in the extracellular fluid (EFSA, 2005).

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

30. Potassium has functions that are closely related to those of sodium and together they are essential for the maintenance of normal osmotic pressure within cells (EVM, 2003). Steep potassium and sodium concentration gradients are maintained across cell membranes by Na-K-adenosine triphosphatase (Na-K-ATPase), a ubiquitous enzyme that is present on the cell surface. Na-K-ATPase transports 2 potassium ions into the cell for every 3 sodium ions it transports out. This process happens at the expense of hydrolysis of ATP but ensures a high intracellular potassium concentration is maintained (Zhou and Satlin, 2004).

31. Potassium also helps to maintain acid-base and electrolyte balances, acts as a cofactor for numerous enzymes, and is involved in regulating cell growth and division. In addition, potassium 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).

32. Extracellular potassium is the critical determinant of nerve and muscle cell excitability (EVM, 2003). The extracellular potassium concentration is in the range of 3.5-5mmol/l (reported as mEq/L); this is tightly regulated by mechanisms that govern distribution between intra- and extracellular compartments, and balance between intakes and outputs (Zhou and Satlin, 2004). A serum potassium level greater than 5.5 mmol/L is defined as hyperkalaemia (Schaefer and Wolford, 2005).

Serum/plasma potassium levels and their regulation

[2] For potassium, 1mEq = 1mmol (Schaefer and Wolford, 2005)

33. As previously stated, the concentration of potassium in the extracellular fluid or plasma is tightly regulated within a narrow concentration range of about 3.5-5 mmol/L (Zhou and Satlin, 2004). 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 of potassium does not give a clear indication of the total body content of potassium (EFSA, 2005).

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

35. In response to a short term, large 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 extra-cellular 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 released into the extra-cellular fluid during the post-prandial period and excreted through the kidney. There is a short term renal response to increased potassium in the diet, with stimulation of potassium secretion in the collecting duct within hours of a potassium rich meal (EFSA, 2005).

36. The main process through which the body content of potassium is regulated over extended periods of time is renal excretion. Healthy kidneys will respond to a sustained increase in potassium intake through a decrease in the absorption of potassium in the proximal tubules and adaptive changes in the collecting duct leading to prolonged enhancement of excretion. The combination of insulin-mediated buffering in muscle and enhanced renal secretion in the short term, and more marked renal adaptive changes in the long term, ensure that plasma levels are maintained within narrow limits when there is a sustained increase in potassium intake (EFSA, 2005).

37. 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 presumably the capacity for muscle to hold potassium is finite and therefore, if there is a sustained high intake of potassium, the ability to cope with the dietary intake will be determined by the maximal rate of renal excretion, plus any increase in loss through the distal colon. Colonic losses of potassium may achieve 10-20 mmol/day when glomerular filtration rates fall below 30 ml/min (from the normal 130 ml/min). Therefore the adverse effects of prolonged higher intakes of potassium are determined by a) local effects on the gastrointestinal tract, and b) metabolic effects determined by the maximum capacity for renal excretion, and to a lesser extent colonic excretion (EFSA, 2005).

Renal handling of potassium

38. Since renal handling is an important determinant of potassium homeostasis, this has been considered in more detail below.

39. The processes involved in renal K^+ handling are filtration, reabsorption and secretion.

40. K^+ is freely filtered at the glomerulus, with the concentration of K^+ entering the proximal convoluted tubule being similar to that of plasma. 50 to 60% of the filtered load is reabsorbed along the first two thirds of the tubule, closely following that of water and sodium. Most reabsorption is passive. Further reabsorption occurs in the loop of Henle, where reabsorption is mediated, at least in part, by the apical bumetanidine-sensitive Na-K- 2-chloride co-transporter; the activity of this transporter is ultimately driven by low intracellular sodium (Gurkan *et al*., 2007).

41. K^+ secretion then occurs as follows: Na^+ passively diffuses into the connecting tubule/principal cell from the urinary fluid through the luminal amiloride-sensitive epithelial Na^+ channel and is then transported out of the cell in exchange for K^+ via the basolateral Na-K-ATPase. The resulting high intracellular K^+ concentration and lumen-negative voltage creates a favourable electrochemical gradient for intracellular K^+ to diffuse into the urinary space through apical K^+ selective channels. Basolateral K^+ channels in these same cells provide a route for intracellular K^+ to recycle back into the interstitium, thereby maintaining the efficiency of the Na-K pump. Any factor that increases the electrochemical gradient across the apical membrane or increases the apical K^+ permeability will promote K+ secretion (Gurkan *et al*., 2007).

42. The late distal convoluting tubule, connecting tubule and cortical collecting duct are the primary sites of K^+ secretion in the fully differentiated kidney contributing largely to urinary K^+ excretion, which can be up to 20% of the filtered load in the adult. Although neonates (as with adults) can excrete K^+ at a rate that exceeds its filtration, reflecting the capacity for net tubular secretion, they are unable to excrete a K^+ load as efficiently as adults (Gurkan *et al*., 2007).

43. The balance between excretion and absorption is regulated by both luminal and peritubular factors (Gurkan *et al*., 2007). These include Na^+ delivery and absorption within the distal nephron, where the magnitude of these processes determines the electrochemical driving force for K^+ secretion into the luminal fluid. Processes that promote distal Na^+ delivery and increase tubular fluid flow rate, such as extracellular volume expansion or administration of diuretics, cause a simultaneous increase in urinary excretion of Na^+ and K^+. The K^+ sparing diuretics block Na^+ absorption via inhibition of the epithelial Na^+ channel. Renal K^+ secretion responds to changes in K^+ intake with increasing intake resulting in an increase in secretion. In rats, an increase in dietary K^+ results in an increase in SK/ROMK channels within 6 hours, possibly by activation of a previously “silent” pool of channels or closely associated proteins. Chronic K^+ loading also leads to an increase in maxi-K channel message, apical immune-detectable protein and function in the distal nephron. Secretion of K^+ is affected by changes in acid-base homeostasis (Gurkan *et al*., 2007).

44. K^+ secretion is stimulated by aldosterone. This is partly due to the mineralocorticoid-induced stimulation of the epithelial Na^+ channel (ENaC) and Na-K-ATPase activity which enhances the electrochemical gradient favouring K^+ secretion. Premature infants and newborns have higher plasma aldosterone

concentrations compared to adults, but clearance studies suggest that the immature kidney is relatively insensitive to aldosterone. The limited K^+ secretory capacity of the neonatal distal nephron has been proposed to contribute to the nonoliguric hyperkalaemia observed in up to 50% of very-low birth weight infants.

45. In summary, both luminal and peritubular factors regulate the balance between K^+ secretion and absorption. Perturbation in any of these factors can lead to K^+ imbalance (Gurkan *et al*., 2007).

46. It has been argued (Gennari and Segal, 2002; Einhorn *et al*., 2009) that the elevated plasma potassium levels measured in individuals with impaired kidney function could be an adaptive response to promote potassium excretion.

Potassium balance

Adults

47. As previously stated, total body K^+ content depends on the balance between K^+ intake and output. The homeostatic goal of the adult is to remain in zero K^+ balance. Therefore, in the healthy adult, excretion matches dietary intake with 90% of the daily intake (usually 1 mmol/kg (reported as mEq/kg)) eliminated by the kidneys and the residual 10% being lost in the faeces. (Gurkan *et al*., 2007).

48. In the adult, the daily dietary intake of K^+ generally approaches or exceeds the total K^+ normally present within the extracellular fluid space. Although K^+ balance depends on timely renal elimination of dietary intake, renal excretion is relatively sluggish and may take 6-12 h to occur. Life threatening hyperkalaemia (LTHK) is not generally observed during this time due to the rapid translocation of extracellular K^+ into cells.

49. The distal nephron and colon are the primary sites for regulation of K^+ homeostasis responsible for maintaining a zero balance in adults (Gurkan *et al*., 2007). Distal nephron segments can secrete or reabsorb potassium, depending on the needs of the individual. In the healthy adult, K^+ secretion predominates over K^+ absorption.

Infants and young children

50. In contrast to adults, infants of greater than 30 weeks gestational age maintain a state of positive K^+ balance (i.e. more is absorbed than excreted) to ensure the adequate availability of substrate for incorporation into newly formed cells. The tendency to retain K^+ in early post-natal life is reflected in the observation that infants tend to have higher plasma K^+ concentrations than children. In addition, data from studies in experimental animals suggest that in foetal life, K^+ is transferred across the placenta from mother to foetus and foetal K^+ concentrations are maintained at levels ≥ 5 mM even when there is maternal deficiency (calculated as intracellular K^+ from levels in muscle). Hyperkalaemia is briefly observed in 30-50% of very low birth weight infants (Zhou and Satlin, 2004).

51. Total body K^+ increases from approximately 8 mmol/cm body height at birth to >14 mmol/cm body height at 18 years of age. The rate of K^+ 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).

52. As noted, growing infants need to maintain a state of positive potassium balance, which is largely accomplished by the kidney. The low capacity of the neonatal cortical collecting duct reflects a relative paucity of conducting K^+ channels in the urinary membrane. A relative excess of K^+ absorption in this nephron segment may further reduce net urinary secretion. Under conditions prevailing *in vivo*, the balance of fluxes in the cortical collecting duct, contributes to the relative K^+ retention characteristic of the neonatal kidney (Zhou and Satlin, 2004).

53. As stated previously, infants, like adults, can excrete K^+ at a rate that exceeds its filtration in response to exogenous K^+ loading (Gurkan *et al*., 2007).

Adverse effects of high potassium intakes

Non hyperkalaemia adverse effects and acute toxicity

54. Few adverse effects have been associated with excess potassium in the general population. However, in studies using potassium supplements, damage to the oesophagus has been reported as a result of the supplement causing physical damage as it moves through the gastrointestinal tract. 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.

55. Acute cases of toxicity are generally from deliberate or accidental overdose of potassium supplement tablets, but some relate to misuse of salt replacer products. The main adverse effects detailed in reports of acute toxicity are gastrointestinal damage and bleeding, and hyperkalaemia with cardiac arrhythmia or arrest.

Hyperkalaemia

56. Serum potassium is maintained over a narrow concentration range of 3.5-5 mmol/L. In comparison, the intracellular potassium concentration is 150 mmol/L. The intracellular to extracellular ratio (150:4 mmol/L) results in a voltage gradient across the cell membrane and plays a major role in establishing the resting cell membrane potential, particularly in cardiac and neuromuscular cells. Whilst changes in the large intracellular concentration would have little effect on this ratio, even small changes in the extracellular concentration would have significant effects on this ratio, the trans-membrane potential gradient and thereby the function of neuromuscular and cardiac tissues (Schaefer and Wolford, 2005).

57. Hyperkalaemia is defined as serum blood potassium greater than 5.5 mmol/L. Hyperkalaemia and accompanying physiological changes can be further divided into 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 the serious complications do not strictly correlate with a given potassium level and are related more to the rate of rise

in the potassium level, the effect on cardiac conduction and the underlying cause of the hyperkalaemia (Schaefer and Wolford, 2005).

58. The organ systems affected by hyperkalaemia are cardiac, neuromuscular and gastrointestinal. Patients may complain of only vague feelings of not feeling well, gastrointestinal symptoms or generalised weakness. The most serious concern is impaired cardiac conduction with risk of sudden death from asystole or ventricular fibrillation. Neuromuscular signs and symptoms include muscle cramps, weakness, paralysis, paresthesia (tingling or numbness in the skin) and decreased deep tendon reflex (Schaefer and Wolford, 2005).

59. Usually, severe symptoms do not occur until serum potassium levels reach >7 mmol/L and a rapidly rising level is more dangerous than a slowly rising level. The classic ECG changes associated with hyperkalaemia are well established. The earliest changes occur at concentrations of >6.5 mmol/L and are peaked or tented T waves which are most prominent in pre-cordial leads. With further rise in serum levels there is a diminished cardiac excitability manifested by flattening of the P-wave, PR interval lengthening and the eventual disappearance of the P wave. The QRS duration becomes prolonged, progressing to a sine wave appearance and finally ending in ventricular asystole and fibrillation with potassium levels of 8-10 mmol/L. Hyperkalaemia results from an imbalance of normal potassium handling, this can result from increased potassium loads, transcellular shifting of potassium, or decreased potassium elimination (Schaefer and Wolford, 2005).

60. In individuals with normal renal function, hyperkalaemia from excess potassium load is very uncommon. Possible causes include potassium supplement overdose, massive blood transfusion with hypoperfusion or accidental ingestion of potassium chloride crystals used in water softeners. Short term intakes of roughly 15 g/day potassium do not result in serum potassium levels being outside the normal range provided that fluid intake is sufficient and intake is spread over the day (Rabelink *et al*., 1990). In this balance study, 6 healthy volunteers aged 22-26 y were given 400 mmol (15.6 g) potassium in 4 equal meals, every 6 hours to investigate short term (72 hrs) and long term (20 day) potassium loading. Throughout the study, each meal was followed by an acute transient increase in plasma potassium and aldosterone and potassium excretion in the urine. 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. At 20 days loading sodium loss had been compensated. Discontinuation of loading was followed by negative potassium balance lasting only 24 hours and by sodium retention lasting 72 hours. Mean plasma potassium was 3.75 mmol/L at days 1 and 2 of the 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, levels had declined to 3.98 and 3.67 at 24 and 46 hours. These values were all in the normal range. However, in a study by Keith (1941) symptoms of increased T-wave ECG and paraesthesia of the hands and feet in parallel with marked or severe hyperkalaemia were observed within 2-3 hours in 2/7 apparently normal subjects given doses of 12.5 or 17.5g 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, penicillin potassium therapy and drinking potassium softened water may also cause hyperkalaemia in the pre-disposed individual (Schaefer and Wolford, 2005).

Supplementation studies

62. As noted elsewhere, the majority of studies investigating potassium supplementation have not recorded changes in serum potassium levels or on renal function parameters. Studies where this has been done have been considered below.

63. 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 96 mmol (0.27 g/day) potassium chloride while 147 were given a placebo (Grimm *et al*., 1990). The men were hypertensive and were on a restricted sodium diet and were followed for an average of 2.2 y after the withdrawal of their anti-hypertensive medication. Participants who were given supplemental potassium had significantly higher serum potassium levels and urinary potassium excretion (4.5 mmol/L and 42.5 mmol/8 hours) than those given the placebo (4.2 mmol/L and 20 mmol/8 hours) (P<0.001). However, this was within the normal range for serum potassium. Potassium intakes were not calculated in this study, but the 97.5th percentile total potassium intake was estimated (by EFSA, 2005) to be 7-8 g/day calculated from baseline data on potassium excretion.

64. In a randomised, crossover study reported by Overlack *et al*, (1991)[3], 12 patients with essential hypertension were given 4.68 g K as potassium citrate or bicarbonate or placebo for 8 weeks. At the end of the trial, mean (SE) serum potassium was 4.33 (0.1) mmol/L in the treated group and 4.06 (0.1) mmol/L in the controls. These values are within the normal range.

65. Siani *et al*., 1987 conducted a 15 week RCT, in which 37 patients who had mildly increased blood pressure and normal dietary sodium intake received potassium supplements (1.87 g/day) or placebo. No significant change was found in plasma potassium, though urinary potassium was increased in the group that received the supplements. Dietary potassium was not assessed but participants were asked not to change their usual diet.

66. In a study by Bulpitt *et al* (1985) 33 patients with hypertension receiving drug treatment that included a normal diuretic[4] were given a 2.5 g supplement of potassium chloride (n=14) or placebo (n=19) for 3 months. Plasma creatinine[5] fell by 11% in the treatment group compared to a 6% rise in the control group (P<0.05).

[3] The details are taken from the abstract and from Dickinson et al., 2006 as the full paper has not been obtained.

[4] Most diuretics encourage potassium secretion and thus increased loss in the urine. Potassium sparing diuretics do not have this effects, hence the risk of hyperkalaemia associated with these.

[5] Increasing serum creatinine levels can indicate kidney damage.

Mean creatinine levels changed from 94 ± 6 to 84 ± 5 µmol/L and 104 ± 8 to 110 ±9 µmol/L in the supplement and placebo groups respectively. When analysed within patient, the fall in plasma creatinine remained significant; at 3 months creatinine clearance was lower in the supplemented group but this was not significant. Plasma potassium increased from 3.7 mmol/L at baseline to 3.8 mmol/L in the treated group and decreased to 3.5 mmol/L in the placebo group. The difference between the two groups at the end of the study was significant but the plasma concentrations were within the normal range. It was suggested that the fall in serum creatinine could be partly due to water retention since weight increased by a mean of 1.4 kg in the treated group. However it was also suggested that the supplements could be restoring depleted potassium levels and improving the glomerular filtration rate (GFR).

67. 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 potassium alone or 2.34 g potassium with 20 mmol (0.49 g) magnesium for 3 x 8 weeks with a two week washout period between each treatment. At baseline, mean (SD) serum creatinine was 76.02 (11.44) µmol/L. At day 56 the levels were 75.14 (14.15), 73.38 (6.96) and 70.72 (10.06) µmol/L in the placebo, potassium and potassium plus magnesium groups respectively. The changes were not significantly different. Serum potassium was 3.6 (0.42) mmol/L at baseline changing to 3.6 (8.4), 3.7 (8.5) and 3.8 (8.6) in the placebo, potassium, and potassium plus magnesium groups respectively at day 56. Urinary potassium was significantly increased in the two treatment groups compared to the controls but was within the normal range.

68. 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 to placebo (Smith *et al*., 1985). Mean urinary potassium excretion increased with treatment but plasma potassium did not significantly change with mean (SEM) being 4.0 (0.1), 4.1 (0.1) and 3.9 (0.1) mmol/L with sodium restriction only, potassium supplementation or placebo respectively. Plasma creatinine was also unaffected with mean (SEM) being 91 (4.0), 89 (3.8) and 91 (3.2) µmol/L with sodium restriction only, potassium supplementation or placebo respectively.

Published reviews or meta-analyses

Cochrane reviews

69. A Cochrane review (Dickinson *et al*., 2006) evaluated the effects of potassium supplements and health outcomes and blood pressure in people with high blood pressure. The 5 included studies involved 425 participants with 8-16 weeks of follow up. It was noted that of the studies included in the analysis, only 2 (Overlack *et al*., 1991; Siani *et al*., 1987) reported blood potassium levels and when these were included in a meta-analysis, serum potassium was higher at the end of the study in the treated group compared to the controls (mean difference 0.20 mmol/L) but still within the normal range. Renal effects were not considered. It is not stated, but from the descriptions of the studies it appears that they were conducted in apparently

healthy populations. It has been noted (nutrition evidence.com, 2006) that the inclusion criteria for this study were very restrictive.

Other meta-analyses

70. Earlier authors (Geleijnse *et al*., 2003; Whelton *et al*., 1997) had conducted meta-analyses investigating the relationship between potassium supplementation and blood pressure. These have included more studies than the Cochrane review, but have not considered adverse effects of high potassium intakes on either serum potassium or renal parameters.

Vulnerable population groups

Infants and young children

71. It has been suggested that infants may be vulnerable to excessive potassium due to limited excretion and immature kidney structure and function (EFSA, 2005 quoting EVM, 2003). Several aspects of kidney function vary considerably in the first year of life and differ markedly from the equivalent values in the adult.

Development of the kidney

Fetal development

72. The development of the human kidney begins in the first month of embryonic development and it is functional within the second month of antenatal life (Čukuranović and Vlajković, 2005). In the last trimester, the fetal kidney already shows involutive changes (the ingrowth and curling inward of a group of cells). From then on until adult maturity, the kidney undergoes intensive processes of maturation and involutive changes.

73. The antenatal period is characterised by significant nephrogenesis in three phases of renal development: pronephros, mesonephros and metanephros, the first two phases being a temporary system, whilst the third phase represents the permanent system of excretion (Čukuranović and Vlajković, 2005). Nephrogenesis begins at 9 weeks of gestation and is complete by 36 weeks of gestation (Kearns *et al*., 2003).

74. The GFR increases little prior to the time an infant reaches the conceptional age of 34 weeks, the point in renal development at which the absolute GFR increases gradually to mature values when linear growth is completed during adolescence (Arant, 1987) .

Neonatal development

75. After birth, there is a further process of structural and functional maturation of the kidneys. With a permanent number of nephrons, renal mass increases at the expense of certain nephron structures and interstitium. The kidney reaches its full

anatomical and functional maturity by the end of the third decade of life (Čukuranović and Vlajković, 2005).

76. Under normal circumstances, the cortex is mature at birth and all layers of glomeruli are fully formed, though the kidney glomeruli occupy a much larger volume of the cortex compared to the adult kidney. A number of anatomical changes occur between the first and 6th month of life, so that as early as the seventh month, the renal parenchyma shares the characteristic of the adult one. During the first year of life, the nephrons grow while tubular structures extend (Čukuranović and Vlajković, 2005).

77. The neonatal kidneys are also functionally immature. The newborn begins to maintain homeostasis on its own due to a rapid structural and functional maturation of the kidney. The increase in GFR is very rapid in the first three months of life, the rate of increase then slowing down until the adult rate is reached at the end of the second year of life. DeWoskin and Thompson (2008) noted that in full-term neonates (<1 month) GFR is about 30% of the adult value, subsequently approaching adult levels between 6 months and 1 year of age. GFR corrected for body size is not comparable with adult normal values until after 12 months of age. Kearns *et al*. (2003) quote a GFR of 2-4 ml/minute in the term neonate, which increases rapidly in the first two weeks of life, rising steadily until adult values are reached at 8-12 months of age. Blood flow is relatively low in the fetal and neonatal kidney due to the small volume of the heart. Adult values for renal blood flow are reached by the end of the first year of life. The low GFR might also be due to a low filtration coefficient, the small pore radii in the glomerular membrane (restricting water flow) and a reduced surface area available for filtration in the immature glomerulus (Loggie *et al*., 1975).

78. The neonatal kidney has a reduced capacity to concentrate urine, which increases the risk of dehydration, when fluids are restricted. The kidney reaches the concentration capacity of the adult at around 18 months of age. Tubular secretion is around 25% of adult rates at birth and increases more slowly and variably than GFR, not approaching adult rates until 1-5 years of age. Similarly, tubular secretion is immature at birth and reaches adult capacity during the first year of life (Kearns *et al*., 2003). The lower GFR is one of the reasons for the reduced concentration capacity as is decreased sensitivity to Anti Diuretic Hormone (ADH) in the distal tubule (Čukuranović and Vlajković, 2005). There is also reduced capacity for the excretion of excess fluid, leading to a tendency towards the development of hyponatraemia. The young infant's kidney is also characterised by a much lower level of potassium excretion and resorption of amino acids compared to the adult kidney. The activity of plasma renin and angiotensin II is higher than in adults.

79. The renal immaturity and impaired concentrating ability of the neonatal kidney is probably of no clinical significance in all but the most extreme circumstances (certain illnesses, inadequate fluid or pharmacological stress) and is not a major factor in an infant becoming dehydrated, developing hypernatremia or being at greater risk of acute renal injury (Arant, 1987). The neonatal kidney may be more prone to pyelonephritis and calculosis than an adult kidney.

80. Limited data on renal plasma flow indicate neonatal rates of only 10-20% of adult values that rapidly increase to 50% by 6 months and then approach adult levels by 1-2 years of age.

81. The maturation of renal function occurs earlier in term babies compared with pre-term babies (Mannan *et al*., 2013). [Abstract only available]

Development beyond infancy

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

Potassium exposure

Current weaning recommendations

83. Current DH advice recommends that infants are 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 12 months, solid food should increase in variety and frequency until by the age of 5 years, a child would be eating the same food as the rest of the family.

Permitted additives

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

85. 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 from family foods, most likely in bread/bakery products (especially raising agents in scones and crumpets), pasta and noodles and, to a lesser extent, dairy products 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 are introduced, especially processed ones.

86. Overall, infants and young children may be less likely to regularly consume the foods in which potassium-based replacements for sodium salt chloride and sodium based additives might be used.

Older adults

87. Elderly people may be more vulnerable to potassium toxicity due to reduced physiological reserve in renal function (Beck, 1998). Ageing is associated with a progressive loss of kidney volume and GFR fall with each decade. This decline as well as changes in, for example, renin release, leads to decreased capacity for potassium secretion and thus limits the ability to handle large potassium loads. The elderly are therefore more vulnerable to increased intake from the diet and/or supplements or due to drugs that affect potassium balance. These drugs include potassium sparing diuretics, β-adrenergic blockers, ACE inhibitors, digitalis and non-steroidal anti-inflammatory drugs (NSAIDs).

Individuals with renal disease

88. Chronic Kidney Disease (CKD) is divided into a number of stages, according to the level of kidney damage and the ability of the kidney to filter blood, as below:

CKD stage	GFR[6] (ml/min/1.73 m^2)	Description
1	≥ 90	Normal or increased GFR, but with other evidence of kidney damage.
2	60-89	Slight decrease in GFR, with other evidence of kidney damage.
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 renal failure.

89. In a recent NHS Kidney Care report, it was noted that the quality and outcomes framework (QOF) register indicated that in 2009-10, 1,817,871 adults in England had stages 3-5 CKD, a diagnosed prevalence rate of 4.3% of the population over the age of 18 (NHS Kidney care, 2012). It is likely that the total prevalence is higher as there are thought to be a substantial number of undiagnosed cases of CKD

[6] GFR over 90 (generally 90-110) ml/min is considered to be normal unless there is other evidence of kidney disease.

in the population. Comparing data from health surveys with the number of individuals on the QOF register indicates that between 900,000 – 1.8 million individuals may have undiagnosed stage 3-5 CKD (2.1-4.3%). There are no accurate time series data from England but it seems likely that the prevalence could be rising due to the ageing population and the increasing incidence of conditions such as obesity, type 2 diabetes and hypertension which are associated with kidney disease. This increase would be consistent with the findings of NHANES studies in the US. These data apply to England but it seems likely that the findings would be comparable elsewhere in the UK. Data from the Quality Improvement in CKD (QICKD) study quoted in the report estimated a prevalence rate of 5.41% of the population and thus a total of 2.81 million people with stage 3-5 CKD, 97% (2.73 million) of those affected were at stage 3. Data from the renal transplant register quoted in the NHS Kidney care report indicate that in 2009, 40,962 individuals in England were receiving renal replacement therapy (either receiving haemodialysis or having received a transplant).

90. Not all individuals with renal disease need to have a low potassium diet. It has been noted that patients are unlikely to need to restrict potassium intake until renal function is less than 40% of normal (WHO, 2009) which would be those individuals in categories 4-5, (some in 3B); however, this is still likely to be many thousands of individuals, not all of whom will have been diagnosed as having CKD (3% of 2.8 million (the individuals not at stage 3 or below-see above), being 84,000). However, the American Heart Association (Appel *et al*., 2006) state that individuals with a GFR of 60 ml/min or below (CKD stages 3-5) would be advised to restrict their potassium intake, suggesting that the numbers involved could be a lot higher. Gennari and Segal, (2002) noted that the incidence of hyperkalaemia in CKD was difficult to assess because of the almost universal use of drugs which affect plasma potassium. In a random sample of 300 patients with serum creatinine levels of 1.5 – 6 mg/dl taken from their clinic, excluding individuals with diabetes or those taking diuretics or ACE inhibitors, an incidence of hyperkalaemia (> 5 mmol/L) of 55% was found in the remaining sample (n =18). Based on these limited data, hyperkalaemia was as likely to occur in individuals with glomerular disease as those with tubulointerstitial disease. The authors argue that hyperkalaemia is potentially an adaptive response to promote urinary potassium excretion and needs further investigation.

91. 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 1 hospitalisation and 1 inpatient or outpatient serum potassium record during 2005. A total of 66, 259 hyperkalaemic events occurred which represented 3.2% of the records analysed. The veterans were 95.6% male and 79.6% white, 19.4% African-American. The mean age of the veterans was 61y in those individuals without CKD and 73y in those that had CKD. When analysed by potassium level, 212,171 had serum potassium ≤ 5.5 mmol/L, with 75.2, 21.6, 2.3 and 1 % of them having no CKD, stage 3, 4 or 5 CKD respectively. Of the individuals with serum potassium ≥ 5.5 mmol/L, 46.0, 35.6, 10.5 and 8 % had no CKD, stage 3, 4 or 5 CKD respectively. The risk of hyperkalaemia was elevated in individuals treated with renin-angiotensin-aldosterone blockers. Individuals with cancer and diabetes were also more likely to have elevated serum potassium compared to individuals without the condition; ORs 1.16 (1.13-1.19) and 1.51 (1.47-1.55) respectively were calculated for these conditions. Compared to individuals without CKD the OR (95% CI) for elevated

potassium were 2.24 (2.17-2.30) 5.91 (5.63-6.20) and 11.00 (10.34-11.69) in those with stage 3, 4 or 5 CKD respectively. The occurrence of hyperkalaemia also increased the odds of mortality within 1 day of the hyperkalaemic event but the odds ratios were higher in those without CKD. For moderate hyperkalaemia (≥5.5 -<6 mmol/L) the ORs of death were 10.32, 5.35, 5.73 and 2.31 for no CKD, stage 3, 4 and 5 respectively. Whereas for severe hyperkalaemia (>6 mmol/L) the ORs of death were 31.64, 19.52, 11.56 and 8.02 for no CKD, stage 3, 4 and 5 respectively.

92. Data from Epsom St Helier study to be included.

Exposure assessment

93. Detailed data on the possible increase in potassium intakes if there was wide-spread use of potassium equivalents are not available. However, as an approximate estimate it has been assumed that all the food categories in which sodium could be replaced by potassium, have been replaced a maximum level of 25 % w/w. This quantity has then been added to potassium intakes calculated from NDNS, this suggests that for children aged 1.5-3 there could be an increase in potassium intakes of up to 328 mg and for adults (19-64) there could be a potential increase of up to 593 mg potassium. For adults aged 65-74 and over 75, who would be more likely to have impaired kidney function, there could increases of up to 557 and 485 mg potassium respectively. For the purposes of comparison, the UK RNI is 3500 mg/day. The largest contributors to the increased potassium intakes would be from the cereal and cereal products group and the meat and meat products group due to the replacement of sodium in raising agents and preservatives respectively.

94. These calculations are likely to substantially over-estimate the potential increase in potassium as it has been assumed that all the sodium in the foods (not just the added sodium) has been partially replaced with potassium at the maximum likely level of use and that mean levels of all of the relevant foods are being consumed. However, the limited recipe data available from industry suggest that the 25% replacement is not unreasonable.

95. There are no maximum intake levels of potassium to compare these values against; however, in adults the intakes do not reach or significantly exceed the RNI and in toddlers the % of the RNI increases from 226% to 267% of the RNI. However, as noted earlier, current estimated intakes of potassium in adults (as well as the RNI itself) would exceed an intake of 1 mmol/kg bodyweight, assuming a 70 kg adult, and the replacement of sodium with potassium would increase this exceedance.

96. Revise following COT meeting.

Summary and discussion

97. Potassium-based replacement for sodium chloride and sodium-based additives (such as preservatives and raising agents) have not previously been recommended as a means of reducing salt levels because there were concerns that the increased intake could increase the risk of hyperkalaemia and subsequent

cardiac problems in individuals with reduced or impaired renal function, particularly as many individuals with kidney disease may not have been diagnosed. It was thought that other vulnerable groups could include the elderly, as renal capacity diminishes with age, young children and individuals taking drugs which reduce potassium excretion such as ACE inhibitors and potassium sparing diuretics.

98. Potassium is readily absorbed from food and the excess readily excreted in the urine in healthy adults. Serum potassium levels are tightly regulated within a narrow concentration range and the difference in concentration between intracellular and extracellular potassium results in a voltage gradient across cell membranes, helping to establish the resting cell membrane potential, particularly in cardiac and neuromuscular tissue.

99. When serum potassium levels increase through impaired excretion, hyperkalaemia and subsequent adverse physiological changes can occur, potentially leading to cardiac arrest. There are numerous case reports of potassium toxicity from supplements and salt substitutes in individuals with renal impairment.

100. The beneficial effects of potassium on blood pressure have been assessed in a number of trials but these have not generally assessed relevant endpoints such as serum/plasma potassium levels or renal endpoints such as serum creatinine levels. Where these have been measured, no adverse effects have been reported. The majority of such studies have also been conducted in healthy populations (or those with some degree of hypertension). It is therefore unclear whether any adverse effects would have been detected since the most at risk populations would not have been included.

Infants and young children

101. At birth, the neonatal kidney is immature in both structure and function. Rapid maturation occurs over the first few months of life. However, whilst aspects of renal function such as GFR are mature after the first year, the kidney is not completely mature until early adulthood.

102. Potassium balance is largely maintained by the kidney. Adults have a neutral potassium balance, whereas infants have a positive one, meaning that they absorb more than they excrete since potassium is required as a substrate for growing cells. However, although immature, the infant kidney is able to excrete more potassium than is absorbed if required.

103. Infants would not be expected to be exposed to potassium based additives, or sodium based ones that could be replaced by potassium for the first 4-6 months of life. A limited number of additives are permitted for foods 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 or children would be exposed to salt replacers until they were consuming family food, by which time the kidney would be more mature and more able to deal with any potassium excess.

Adults with diagnosed chronic kidney disease

104. It has been estimated that 4.3% of the UK population (1.8 million adults) have stage 3-5 CKD, the majority as stage 3; a number which may be increasing due to aging population as well as the increasing incidence of obesity, type 2 diabetes and hypertension. Of these individuals only a small percentage may need to restrict potassium intake, but this will still represent tens of thousands of adults.

105. Individuals with CKD needing to restrict their potassium intakes may find this more difficult if the use of potassium equivalents to sodium became widespread in dietary staples. However, it is not possible to specify the additional intake of potassium that would be a problem for these adults as low potassium diets are specifically tailored so the additional intake would vary between individuals.

Adults with undiagnosed chronic kidney disease

106. It has been estimated that the number of individuals with undiagnosed CKD is comparable to the number of individuals with diagnosed CKD. However, it is unclear whether these individuals would be at a less advanced stage and thus, less likely to need to restrict their potassium intakes. [To be revised following the 9/12/14 COT meeting, taking into account new data].

Exposure assessment

107. At present, intakes of potassium in the UK are lower than the current recommendations.

108. As an approximate estimate of the potential increase in potassium intake, it has been assumed that 25% of added sodium chloride or other sodium based additives would be replaced with potassium and the increase has been added to the current potassium intake. This suggests that potassium intakes could increase by a maximum of 557 mg potassium in adults compared to the RNI of 3500 mg.

Conclusions

109. The use of potassium-based replacement for sodium chloride and sodium-based additives would not be of concern for healthy adults as they can readily excrete excess potassium.

110. Infants and young children would not be more sensitive to excess potassium than adults and their exposure from sodium replacers is likely to be low since few sodium or potassium-based additives are permitted in food for infants and, with the exception of bakery products, potassium-based sodium salt and additive replacers were unlikely to be present in family foods consumed by very young children.

111. The potential increase in potassium would not be of concern for adults with diagnosed CKD if adequate risk management measures are used.

112. Adults with undiagnosed CKD [- to be agreed following the 9/12/14 COT meeting, taking into account new data].

Secretariat
December 2014

Glossary

ACE – Angiotensin Converting Enzyme

AI – Adequate Intake

BW – body weight

CKD – Chronic kidney disease

DH – Department of Health

ECG – Electrocardiogram

EFSA – European Food Safety Authority

EVM – Expert Group on Vitamins and Minerals

g – grams

GI – Gastrointestinal

HDL – High density lipoprotein

IOM – Institute of Medicine

K – potassium

KCl – potassium chloride

L – litre

mmol – millimoles

mmol/L – millimoles/Litre

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

nmol/L – nanomoles/Litre

NSAID – Non Steroidal Anti-Inflammatory Drugs

QICKD – Quality Initiatives in Chronic kidney disease

QOF – Quality and Outcomes Framework

RCT – Randomised Controlled Trial

RNI – Reference Nutrient Intake

RDA – Recommended Daily Amount

SACN – Scientific Advisory Committee on Nutrition

SD – Standard Deviation

SEM – Standard error of the mean

TUL – Tolerable Upper Level

UL – Upper Level

US – United Sates

WHO – World Health Organisation

y – years

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