



Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Benefit and risk assessment of increasing potassium by replacement of sodium chloride with potassium chloride in industrial food production

Part I: Benefit and risk assessment for human health of increasing potassium by replacement of sodium chloride with potassium chloride in industrial food products

Part II: Microbiological risk assessment of replacement of sodium chloride by potassium chloride in industrial food production

Opinion of the Scientific Steering Committee

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Background

Sodium chloride

The World Health Organization (WHO) and the European Union (EU) have developed strategies to reduce sodium chloride ("salt") intake in the population (WHO, 2006, The Council of the European Union, 2010). Since 2008 Norway has joined this strategy, and in 2011, the former Norwegian National Nutrition Council prepared a strategy aiming at the reduction of the sodium chloride intake in the Norwegian population (Nasjonalt råd for ernæring, 2011).

High sodium chloride intake is associated with development of high blood pressure, and is a risk factor for heart disease, stroke, and kidney disease. In 2012, WHO strongly recommended a reduction in sodium intake to reduce blood pressure and risk of cardiovascular diseases, stroke and coronary heart diseases in adults and to control blood pressure in children (WHO, 2012b). A reduction to less than 5 gram sodium chloride per day was recommended for adults, and for children this value should be adjusted downward based on the energy requirements relative to those of adults (WHO, 2012b). There is still no definite explanation for why sodium chloride increases blood pressure.

Sodium chloride has several functions in processed foods. It adds flavor, preserves, increases the binding of water to proteins in meat and fish, and has in addition other technological functions in the production of bread and cheese. In the diet, about approximately 3/4 of the sodium chloride stems from industrially produced foods (Nasjonalt råd for ernæring, 2011). Reducing the use of sodium chloride in industrial food production may result in a reduction of the sodium chloride intake in the population.

Sodium chloride substitution

Potassium chloride (E508) is regulated in the Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December, which states that potassium chloride may be added "*quantum satis*" to food, i.e. the amount necessary for its function, but not higher¹. Replacing sodium chloride with potassium chloride will contribute to increased intake of potassium. The average dietary intake of potassium according to European food consumption studies is in the range of 3 to 4 g/day while food supplements contributed to up to 5% of the total intake (EFSA, 2005)

The British Health Authorities discouraged the use of potassium and other substitutes to replace sodium chloride (NICE, 2010). The aim of avoiding potassium substitution was twofold: to help consumers' readjust their perception of "saltiness" and to avoid additives which may have other effects on health. However, in a report from the UK's food industry (British Retail Consortium and the Food and Drink Federation) an evaluation of sodium chloride substitutions in some food groups is requested (FDF and BRC, 2012). In this report, potassium chloride is referred to as the most popular sodium chloride substitute having a similar antimicrobial effect on pathogenic bacteria as sodium chloride. However, the amounts of potassium chloride used are anticipated to be limited by its bitter and metallic taste.

The Norwegian Food Safety Authority and The Norwegian Directorate of Health requested VKM to perform a benefit and risk assessment for human health of potassium chloride in

¹Implemented in Norwegian regulation: Forskrift om tilsetningsstoffer til næringsmidler, 6. juni 2011 nr. 668.

relation to increased substitution of sodium chloride with potassium chloride in industrially produced food.

VKMs Panel on Nutrition, Dietetic products, Novel Food and Allergy was responsible for performing the benefit part of this assessment (Part I), and VKMs Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics was responsible for the risk assessment in Part I. Two working groups consisting of members of each Panel were established. VKMs Panel on Biological Hazards was responsible for performing the microbiological risk assessment (Part II). A working group consisting of members from the panel and an external expert was established.

In the present assessment the following is not included:

- The effect of reduced intake of sodium chloride as a result of substituting sodium chloride with potassium chloride.
- If reduced sodium chloride impairs the technological function in food production.
- The effect on health of increasing the potassium intake for hypokalemic persons.

Terms of reference

The Norwegian Food Safety Authority requested the Norwegian Scientific Committee for Food Safety (VKM) to perform a benefit and risk assessment of potassium chloride in relation to substitution of sodium chloride with potassium chloride in industrial food production. The task has been divided between three of VKMs scientific panels.

The Panel on Nutrition, Dietetic products, Novel Food and Allergy has answered the following questions:

- What is the estimated dietary intake of potassium in the population? (This question is answered in Part I, Chapter 4).
 - What is the dietary intake of potassium if the following scenarios for replacement of sodium chloride (NaCl) with potassium chloride (KCl), 30:70, 50:50, 70:30, are set up? (This question is answered in Part I, Chapter 4).
- What positive health outcomes may be the result of an increased use of potassium chloride in industrial food production? (This question is answered in Part I, Chapter 2).
 - How high must the potassium intake be to achieve positive health effects? (This question is answered in Part I, Chapters 2 and 7).
- Has there been established a safe upper limit (UL) for potassium by EFSA or an equivalent body? (This question is answered in Part I, Chapter 3).

The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics has answered the following questions:

- Will the increased use of potassium chloride in foods as a substitute for sodium chloride according to the above scenarios provide a total intake of potassium that may have adverse health consequences? (This question is answered in Part I, Chapter 8).
- Are there specific population groups vulnerable to an increased intake of potassium?
 - It is desirable with a description of the vulnerable groups. (This question is answered in Part I, Chapters 3 and 8).

It is preferable to have a combined conclusion of the benefit and risk assessment for human health of replacement of sodium chloride by potassium chloride in industrial food production. This is answered in Part I, Chapter 9.

The Panel on Biological Hazards has answered the following question:

- Will the microbiological risks in foods increase using KCl instead of NaCl? (This question is answered in Part II).

To limit the extent of the assessment, the following scenarios for replacement of sodium chloride (NaCl) with potassium chloride (KCl), 30:70, 50:50, 70:30, should be considered.

Food products should be divided into food groups matching the food groups in the KBS database.

Calculations, if necessary, should be done in grams and with molar concentrations in parentheses.

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PART I Benefit and risk assessment for human health of increasing potassium by replacement of sodium chloride with potassium chloride in industrial food products

Summary part I

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM), has at the request of the Norwegian Food Safety Authority (Mattilsynet), conducted a benefit and risk assessment for human health of increasing potassium by replacement of sodium chloride with potassium chloride in industrial food products. The assessment includes intake calculation for three different scenarios for replacement of sodium in sodium chloride with potassium; 30:70, 50:50 and 70:30. The calculations were based on the national food consumption surveys Norkost 3 (18-70 years), Småbarnskost (2-year old), and Ungkost (4-, 9- and 13-year old).

Benefit

An intake of at least 3.5 g/day of potassium in adults will most likely lead to a decrease in risk of stroke. An intake of at least 3.5 g/day of potassium will most likely also have a beneficial effect on blood pressure in individuals with hypertension. In Norway, approximately 13 000 individuals suffers from acute stroke each year.

The intake calculations showed that 59% of the women and 30% of the men based on Norkost 3 had an intake of potassium below 3.5 g/day. In the 30:70, 50:50 and 70:30 scenarios (where 30, 50 or 70% of sodium in sodium chloride is replaced by potassium), the percentage of women with potassium intakes below 3.5 g/day will decrease from 59% to 33, 21 and 13%, respectively. For men, the decreases will be from 30% to 10, 6 and 4%, respectively.

Risk – healthy population

An intake of 3.0 g potassium/day (energy adjusted for children) in addition to the mean intake of potassium from food is anticipated to be safe for the healthy population.

In the 30:70, 50:50 and 70:30 scenarios, adult women with mean potassium intakes have no risk of adverse effects when compared with the anticipated safe level, whereas adult women with 95th percentile intakes will exceed this level in the 50:50 and 70:30 scenarios. Adult men with mean potassium intakes have no risk of adverse effects when compared with the anticipated safe level in any of the scenarios, whereas adult men with 95th percentile intake will exceed this level in all the scenarios.

In the 30:70, 50:50 and 70:30 scenarios, healthy children aged 2, 4, 9 or 13 years with a mean intake of potassium, will have no risk of adverse effects when compared with the anticipated safe level. However, 4- and 9-year-old children with 95th percentile intake will exceed this level in the 50:50 and 70:30 scenarios. Two- and 13-year-old children with 95th percentile intake will exceed this level in all the scenarios.

In the 30:70, 50:50 and 70:30 scenarios, the percentage of women with potassium intakes above the anticipated safe level will increase from 1% to 3, 7 and 15%, respectively. For men, the percentage will be increased from 2% to 9, 19 and 30%, respectively.

Risk – vulnerable groups

Groups vulnerable to an increased intake of potassium, in decreasing order of severity, is haemodialysis or kidney replacement patients, other patients with more moderate renal failure, coronary heart disease or diabetes, patients using one of the numerous drugs increasing the risk for hyperkalemia, and in general infants below one year of age, elderly persons and persons undergoing strenuous physical activity. For persons with impaired kidney function, hyperkalemia may occur even with a modest increase in potassium intake and they are advised to keep their potassium intake below 1.5 g/day.

To reduce the prevalence of hyperkalemia in the vulnerable groups, there is a need for individual assessment of every patient and the dose of medication, advice related to diet, interaction with other medications and careful control of the plasma potassium level.

In Norway, 202 persons are waiting for a kidney graft, about 500 000 persons have diagnosed or undiagnosed chronic kidney disease, the prevalence of diagnosed diabetes (type I and II) is estimated to be 90-120 000 persons and it is estimated that the number of undiagnosed diabetes are about the same numbers, the number of infants (below one year) was 60 530 in 2013, and the number of persons aged 85 years and older was 113 700 in 2013.

Benefit – risk characterization

A full benefit and risk assessment including an evaluation of severity of risks versus benefits was not conducted. Furthermore, an exact comparison of the percentage of persons in the Norwegian population who will either benefit or be at risk as a result of an increase of potassium in industrial produced foods was not possible since we did not have data on the acceptable level of potassium for most of the vulnerable groups, and it could not be predicted how an increase in potassium will affect stroke incidence or reduction in high blood pressure.

However, VKM concludes that it is reasonable to anticipate that the percentage of persons likely to face an increased risk is far greater than the percentage of persons likely to benefit from this measure.

Sammendrag del I

Vitenskapskomiteen for mattrygghet (VKM) har på oppdrag fra Mattilsynet vurdert om det å øke mengden kaliumklorid i mat vil ha en betydning for befolkningens helse. For å besvare oppdraget har VKM gjort en nytte- og risikovurdering av økt inntak av kalium, ved erstatning av natrium i natriumklorid (vanlig bordsalt) med kalium, i industrielt produsert mat.

Vurderingen omfatter inntaksberegning for tre ulike scenarier hvor natrium i natriumklorid erstattes med kalium i forholdet 30:70, 50:50 og 70:30. Beregningene ble gjort for 2-, 4-, 9- og 13-åringer og voksne kvinner og menn. Beregningene er basert på de nasjonale kostholdsundersøkelsene Småbarnskost (2-åringer), Ungkost (4 -, 9 - og 13-åringer) og Norkost 3 (18-70 år).

Nytte

Et inntak på minst 3,5 g kalium per dag for voksne vil mest sannsynlig føre til redusert risiko for hjerneslag. I Norge er det om lag 13 000 personer som får hjerneslag hvert år. Et inntak på minst 3,5 g kalium per dag for voksne vil mest sannsynlig også har en gunstig virkning på blodtrykket hos personer med høyt blodtrykk.

Inntaksberegningene viste at 59 % av kvinnene og 30 % av mennene hadde et inntak av kalium som lå under 3,5 g per dag. I 30:70, 50:50 og 70:30 scenariene, vil andelen kvinner med inntak av kalium under 3,5 g per dag reduseres fra 59 % til henholdsvis 33, 21 og 13 %.

For menn vil andelen med inntak av kalium under 3,5 g per dag reduseres fra henholdsvis 30 % til 10, 6 og 4 %.

Risiko – frisk befolkning

Det er ikke fastsatt noen øvre grense for hvor mye kalium man kan innta uten at det fører til negative helseeffekter. Ut i fra det som er tilgjengelig av studier og rapporter, har VKM konkludert med at et ekstra inntak av kalium på 3,0 g per dag i tillegg til gjennomsnittlig inntak fra mat ikke vil utgjøre noen helserisiko for den friske delen av befolkningen. Dette omtales som forventet trygt inntak. I 30:70, 50:50 og 70:30 scenariene, der 30, 50 eller 70 % av natrium i natriumklorid er erstattet med kalium, vil andelen kvinner med inntak av kalium over forventet trygt nivå øke fra 1 % til henholdsvis 3, 7 og 15 %. For menn vil andelen øke fra 2 % til henholdsvis 9, 19 og 30 %.

En sammenligning av det beregnede inntaket med forventet trygt inntak viste at

- verken voksne kvinner eller menn med et gjennomsnittlig inntak av kalium vil få i seg så mye kalium at det gir negative helseeffekter i noen av scenariene
- voksne kvinner med et høyt inntak av kalium (95-persentilen) vil få i seg for mye kalium i 50: 50 og 70:30 scenariene
- voksne menn med et høyt inntak av kalium (95-persentilen) vil få i seg for mye kalium i alle scenariene
- barn i alderen 2, 4, 9, og 13 år, med et gjennomsnittlig inntak av kalium, ikke vil få i seg for mye kalium i noen av scenariene
- barn i alderen fire - og 9 år, med et høyt inntak av kalium (95-persentilen), vil få i seg for mye kalium i 50:50 og 70:30 scenariene
- barn i alderen to - og 13 år, med et høyt inntak av kalium (95-persentilen), vil få i seg for mye kalium i alle scenariene

Risiko - sårbare grupper

Pasienter med alvorlig nyresykdom, for eksempel hemodialyse pasienter og nyretransplanterte, er spesielt sårbare for høyt inntak av kalium. Andre sårbare grupper omfatter pasienter med mild eller moderat nyresvikt, pasienter med hjertesykdom eller diabetes, pasienter som bruker et av de mange legemidlene som øker risikoen for å få for høyt nivå av kalium i plasma (hyperkalemi), spedbarn under ett år, eldre fra 85 år, og personer som driver anstrengende fysisk aktivitet. For personer med nedsatt nyrefunksjon kan selv små økninger i inntaket av kalium føre til hyperkalemi, og de rådes til å holde inntaket av kalium under 1,5 g per dag. I Norge er det om lag 200 personer som venter på nyretransplantasjon, det er rundt 500 000 personer med diagnostisert eller udiagnostisert kronisk nyresykdom, forekomsten av diagnostiserte diabetikere (type I og II) er anslått til 90-120 000 personer og det samme antallet er anslått for udiagnostisert diabetikere, antall spedbarn (under ett år) var 60 530 i 2013, og antall personer i alderen 85 år og eldre var 113 700 i 2013.

Nytte- og risikovurdering

En fullstendig nytte- og risikovurdering, inkludert en vurdering av alvorlighetsgraden av risiko versus fordeler, ble ikke gjennomført. Videre var det ikke mulig å sammenligne prosentandelen av personer i den norske befolkningen som enten vil ha nytte eller risiko som følge av en økning av kalium i industriproduserte matvarer, fordi vi ikke har kunnet fastsette hvor mye kalium som kan inntas uten at det fører til negative helseeffekter for personer i de fleste av de sårbare gruppene. Det kunne ikke forutsies hvordan en økning av kalium vil påvirke forekomsten av akutte hjerneslag eller høyt blodtrykk.

VKM konkluderer at det derfor er rimelig å anta at andelen personer som vil få økt risiko for negative helseeffekter ved en økning av kalium i industrielt produsert mat er langt større enn andelen av personer som kan ha nytte av det.

1 Potassium – multiple roles in the organism

The absorption of potassium is effective and about 90% of the dietary potassium is normally absorbed from the gut. The total body potassium is approximately 135 g in a 70 kg adult. Of the total body stores, about 98% is located in the intracellular fluid, whereas the extracellular compartment contains only 2% (Traeger and Wen, 2009). The plasma or extracellular concentration of potassium does not give a clear indication of the body content of potassium (Traeger and Wen, 2009). The extracellular/intracellular concentration gradient is maintained by active transport of sodium out of and potassium into the cell (Sweadner and Goldin, 1980). The concentration of potassium in plasma is tightly regulated within the narrow range of approximately 3.5 to 5 mmol/L (135-195 mg/L). The body is able to handle high intakes of potassium, without any substantial change in plasma concentration by synchronised alterations in renal excretion and cellular uptake or release. Tight regulation of the potassium level is essential for the membrane potential of cells, and thereby for nerve and muscle function, blood pressure regulation and cardiac function. Potassium also participates in the regulation of osmotic pressure, the acid/base balance, is a cofactor for many enzymes and is required for the pancreatic secretion of insulin (Taber and Thomas, 1997).

The atomic weight for potassium is 39 g/mol, and the atomic weight for sodium is 23 g/mol.

There is an important physiological balance between sodium and potassium, implying that excess intake of sodium can deplete potassium. Similarly, there is also a balance between potassium and magnesium and other minerals (EVM, 2003). These balances are important in absorption, excretion and active transmembrane transport. As these processes are interlinked, it can be difficult to foresee the consequences of shifting the intake level of one or more of these minerals.

The present Norwegian recommendation for intake of potassium is 3.1 g/day for women and 3.5 g/day for men (Directorate of Health and Social Affairs, 2005). In general, recommended intakes for nutrients refer to the amount of nutrient that can meet the known requirement (amount to prevent physiological signs of insufficient nutrition) and to maintain good nutritional status among practically all healthy individuals.

Hyperkalemia, defined as plasma potassium concentration higher than 5.0 mmol/L, may result from release of potassium from tissues, and/or inadequate renal potassium excretion. Impaired renal excretion of potassium may be caused by disease states such as renal malfunctioning,

hypoaldosteronism and Addison disease, and/or treatment with potassium-retaining drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers and nonsteroidal anti-inflammatory drugs. However, there is no evidence of adverse effects from increased dietary potassium in individuals with unimpaired potassium excretion (NNR, 2012, WHO, 2012a). Symptoms of hyperkalemia are associated with neuromuscular function, cardiac effects and metabolic effects (Traeger and Wen, 2009).

Hypokalemia, defined as plasma potassium concentration below 3.5 mmol/L, may develop as a consequence of increased losses from the gastrointestinal tract and kidneys, for example during prolonged diarrhea or vomiting, and in connection with use of laxatives or diuretics. Potassium deficiency due to low dietary intake is uncommon, due to presence of potassium in most foods (Traeger and Wen, 2009, EFSA, 2005, NNR, 2012). Symptoms of potassium deficiency are associated with neuromuscular conductivity and include muscle weakness, cardiac complications, metabolic disturbances, and also central nervous system disorders such as depression and confusion (Traeger and Wen, 2009).

2 Positive health effects

2.1 LITERATURE SEARCH OF POSITIVE HEALTH EFFECTS

This section describes the literature search conducted for retrieving the scientific documentation available for the benefit assessment in this opinion.

Test searches were conducted to find relevant terms and search words. A simple search strategy was then developed and literature search conducted in MEDLINE. The following search strings have been used: Potassium in title (including only papers with the word potassium in the title) AND Meta-Analysis (as MeSH-term) OR meta-analysis* (as text word). Publications of all ages in English, Swedish, Danish and Norwegian were included. The search was conducted in June 2013, and resulted in 47 hits. A final search was conducted in January 2014, but no relevant new systematic reviews or meta-analyses were found

Initially the titles and abstracts of all papers identified in the search were independently assessed for relevance by two reviewers. Sixteen meta-analyses and systematic reviews including papers investigating clinically relevant health outcomes were selected. In the next step, full text articles were assessed by one reviewer. Not-systematic reviews and papers reporting not clinically relevant health effects were excluded as were papers also including other substances e.g. calcium and magnesium. Finally eight systematic reviews and meta-analyses were included in the results. It should be noted that not all of the studies included in these systematic reviews and meta-analyses have controlled their results for sodium. In some of the papers, the content of sodium is not given.

2.2 POSITIVE HEALTH EFFECTS FROM POTASSIUM – RESULTS

Several of the included systematic reviews and meta-analyses report more than one health outcome. The reported positive health outcomes in the included systematic reviews and meta-analyses are mostly related to reduction in stroke in healthy individuals. Moreover, dietary potassium intake has been demonstrated to significantly lower blood pressure in hypertensive subjects in observational studies, clinical trials, and several meta-analyses. The blood pressure-lowering effect in normotensives is less well documented. Dietary therapies known to lower blood pressure include reduced sodium intake and increased potassium intake.

Beneficial effects on other cardiovascular diseases (CVD) of increasing the potassium intake were not identified, and hence are not discussed further in this report.

2.2.1 STROKE

Three systematic reviews and meta-analyses reporting health outcomes related to stroke are included from the literature search. They are described below:

Aburto et al., 2013. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses.

The aim of this study was to conduct a systematic review of the literature and meta-analyses of the available data on association between increased potassium intake and cardiovascular risk factors and disease (Aburto *et al.*, 2013). This systematic review and meta-analysis is based on three WHO reports (“Effect of increased potassium intake on blood pressure and potential adverse effects in children”; “Effect of increased potassium intake on blood pressure, renal function, blood lipids and other potential adverse effects” and “Effect of increased potassium intake on cardiovascular disease, coronary heart disease and stroke”) from 2012 prepared by the same authors as in this systematic review including both intervention studies and cohorts. They report data from eleven cohort studies (127 038 participants, both adults and children, follow-up ≥ 1 year) after screening 5310 papers. Their data are reported as relative risk (RR) with corresponding 95% confidence intervals (CI).

Among adults they found that intake of potassium in the range 3.5-4.7 g/day (90-120 mmol/day) decreased stroke by 24% (RR 0.76, 95% CI 0.66-0.89). No conclusion could be made for potassium intake and risk of stroke among children.

Larsson et al., 2011. Dietary potassium intake and risk of stroke: a dose-response meta-analysis of prospective studies.

Although not directly stated, this paper is considered to be a systematic review (Larsson *et al.*, 2011). After exclusion of 110 papers they analysed ten papers (268 276 adult participants; prospective cohorts, follow-up four to 19 years). Due to different intakes of potassium in these studies they report the effect of 1 g increase in potassium on stroke risk. The total actual potassium intakes were not detailed.

Their main conclusion (after adjustment of relevant confounders e.g. diabetes, hypertension, body mass index, smoking, alcohol, age) was that for every 1 g (25 mmol) increase in potassium intake, the risk of stroke decreased with 11% (RR 0.89, 95% CI 0.83-0.97).

D'Elia et al., 2011. Potassium intake, stroke, and cardiovascular disease a meta-analysis: prospective studies.

The objective of this meta-analysis was to assess the relation between the level of habitual potassium intake and the incidence of CVD (D'Elia *et al.*, 2010). The study included 250 000 individuals, pooled from eleven published studies. Average potassium intakes ranged between 1.8 and 3.3 g per day (45 and 85 mmol/day) in all but one population in which an average daily intake of 4.9 g (125 mmol) was reported.

In the pooled analysis, a 1.64 g (42 mmol) per day higher potassium intake was associated with a 21% lower risk of stroke (RR 0.79, 95% CI 0.68-0.90).

2.2.2 BLOOD PRESSURE

Six systematic reviews and meta-analyses reporting blood pressure are included from the literature search. They are described below:

Aburto et al., 2013. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses (also described in section 2.2.1).

The meta-analyses showed that increased potassium intake significantly reduced systolic and diastolic blood pressure in hypertensive (16 studies) but not in normotensive patients (three studies) (Aburto *et al.*, 2013). The studies in subjects without hypertension were of short duration and did not consider protective effects of long-term increased potassium intake. Subgroup analysis showed comparable reduction in blood pressure following increased potassium intake from supplements and from dietary changes implying that increased intake does not need to be through supplements but rather from increased consumption of potassium rich food. Subgroup analyses also showed that an increased potassium intake of 3.5-4.7 g/day (90-120 mmol/day) was associated with reduced blood pressure while intake above 4.7 g/day (120 mmol/day) had no additional effect.

Houston, 2011. The importance of potassium in managing hypertension.

This summary paper concludes that dietary potassium intake has been demonstrated to significantly lower blood pressure in a dose responsive manner in both hypertensive and normotensive patients in observational studies, clinical trials, and meta-analyses (Houston, 2011). Although the results from observational trials are relatively consistent, data from individual clinical trials have been less consistent. The authors suggest that limited or different experimental designs such as short duration and various types and doses of potassium used have caused the inconsistent results.

Although variable results, the data demonstrate dose–response relationship between potassium intake and reduced blood pressure. Doses of potassium in the range of 1.9 to 4.7 g/day resulted in decrease in blood pressure of approximately 2 to 6 mm Hg for systolic blood pressure, and 2 to 4 mm Hg for diastolic blood pressure.

The authors refer to different guidelines which have incorporated recommendations for increased dietary intake of potassium for the prevention and treatment of hypertension. Daily intake of at least 3.5 g was recommended by the National High Blood Pressure Education Program Coordinating Committee in 2003. In 2006, the American Heart Association (AHA) recommended daily intake of 4.7 g. In 2010, the ASH recommended about 4.7 g/day of potassium. In addition, the 2003 World Health Organization (WHO)/ISH statement recommends a diet high in fruits and vegetables, reduction of dietary sodium intake, and increased dietary potassium intake to reduce the incidence of hypertension.

The main conclusion of the paper was that increasing potassium intake to 4.7 g/day (120 mmol/day) would shift the population distributions of systolic blood pressure down by 1.7 to 3.2 mm Hg, similar to the predicted result of reducing sodium intake from 9 to 5 g/day. The estimated reduction in CVD mortality would be 8% to 15%, and the reduction in coronary heart disease (CHD) risk would be 6% to 11%.

Dickinson et al., 2006. Potassium supplementation for the management of primary hypertension in adults.

The objective of this meta-analysis was to evaluate the effects of potassium supplementation on health outcomes and blood pressure in people with elevated blood pressure (Dickinson *et al.*, 2006).

The meta-analysis included five randomised controlled trials of parallel or crossover design with an intervention period of at least eight weeks. The meta-analysis enrolled 425 participants and the number of participants in each trial ranged from 12 to 212. The median duration of follow-up was 12 weeks (range from 8 - 16 weeks). Overall, 75% of the participants were male and mean age was 50 years (range 36-52 years).

Data indicated that potassium supplementation compared to control resulted in a large but statistically non-significant reduction in systolic blood pressure (mean difference: -11.2, 95% CI: -25.2 to 2.7) and diastolic blood pressure (mean difference: 5.0, 95% CI: -12.5 to 2.4). Out of five studies included in these meta-analyses only two were blinded. The authors suggest that the inconsistent results across the trials could be due to unreported differences in the study populations of such as dietary potassium or sodium intake.

Burgess et al., 1999. Recommendations of potassium, magnesium and calcium.

The objective of this peer-reviewed article was to provide updated evidence based recommendations for dietary intake of potassium, magnesium and calcium for the prevention of hypertension in healthy adults (exception pregnant women) (Burgess *et al.*, 1999).

The weight of the evidence from the randomised controlled trials indicates that increasing intake of or supplementing the diet either with potassium, magnesium or calcium is neither associated with prevention of hypertension nor is it effective in reducing high blood pressure.

Potassium supplementation is not recommended for normotensive people to prevent an increase in blood pressure or for treatment of high blood pressure when given in addition to an average dietary intake of 2.4 g/day (60 mmol).

Whelton et al., 1997. Effect of oral potassium on blood pressure.

This is a meta-analysis of 33 randomised, controlled clinical trials to assess the effects of supplementation with oral potassium supplements on blood pressure (Whelton *et al.*, 1997). Potassium supplement was the only difference between the intervention groups and control groups. Information on participant numbers, duration, study design, potassium dose, participant characteristics and treatment results were independently obtained by the authors using a standard protocol.

The total number of study participants was 2609 with ages ranging from 18 to 79 years. The dose of potassium prescribed for participants in the active treatment was 2.5–4.7 g/day (median 3.2 g/day).

Using a random-effects model, potassium supplementation was associated with significant reduction in mean (95% CI) systolic and diastolic blood pressure of -3.11 mm Hg (1.91 to 4.31 mm Hg) and 1.97 mm Hg (0.52 to 3.42 mm Hg) respectively. These blood pressure-lowering effects were especially pronounced in subjects with a high sodium intake.

In addition to the blood pressure lowering effect, the authors suggested that potassium may have an independent vascular protective effect as an added incentive to include potassium treatment for lowering blood pressure.

Cappuccio and MacGregor, 1991. Does potassium supplementation lower blood pressure?

This is a review of 19 clinical trials examining the same endpoint and involving a total of 586 participants (412 had essential hypertension) (Cappuccio and Macgregor, 1991).

The participants were given oral potassium. Mean age was 39.6 years. Average amount of potassium given was 3.4 g/day (86 mmol/day), and average duration of the supplement was 39 days (range 5-112 days).

The meta-analysis indicated that an oral potassium supplement of 3.4 g/day (86 mmol/day) gave a significant reduction in systolic blood pressure of 5.9 mmHg (6.6-5.2 mmHg) and the diastolic blood pressure 3.4 mmHg (4.0-2.8 mmHg) in the participants overall, and a greater and significant reduction in systolic blood pressure of 8.2mmHg (9.1-7.3 mmHg) and for diastolic blood pressure 4.5 mmHg (5.2-3.8mmHg) in patients with a high blood pressure.

Based on these results the authors recommended an increase in potassium intake to the control of blood pressure in uncomplicated hypertension.

2.3 PREVIOUS REPORTS

The papers included in the previous reports described below are mainly the same papers as included in the systematic reviews and meta-analyses included in the benefit part of this assessment.

2.3.1 POTASSIUM BASED SALT REPLACEMENTS, SACN 12/06, 2013

The report prepared by the Scientific Advisory Committee on Nutrition (SACN) in the UK is a brief review of potassium related to blood pressure, cardiovascular disease, coronary heart disease and stroke (SACN, 2013). The main conclusions are that potassium intake is not significantly related to risk of cardiovascular- or coronary artery disease (based on D'Elia *et al.*, 2011 and Aburto *et al.*, 2013), but the potassium intake appears significantly related to decreased risk of stroke (also based on D'Elia *et al.*, 2011 and Aburto *et al.*, 2013).

2.3.2 WORLD HEALTH ORGANIZATION (WHO), 2012

WHO (WHO, 2012a) issued in 2012 a guideline on potassium intake from food, strongly recommending² that adults should elevate their potassium intake in order to decrease blood pressure and the risk of cardiovascular diseases, stroke and coronary heart disease. WHO suggests a potassium intake of at least 3.5 g/day (90 mmol/day) for adults (conditional recommendation³).

²A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects.

³A 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.

The scientific evidence for this recommendation stems from the findings reported in Aburto *et al.* (2013) quoted above. For children, a conditional recommendation to increase potassium intake to control blood pressure was given (WHO, 2012a), and the recommended potassium intake for children should be based on the value that is recommended for adults and adjusted downward based on the energy requirements relative to those of adults. This guideline did not provide recommendations for individuals with impaired urinary potassium excretion from a medical condition or drug therapy.

2.3.3 NORDIC NUTRITION RECOMMENDATION (NNR), 2012

In general, recommended intakes for nutrients refer to the amount of nutrient that can meet the known requirement (amount to prevent physiological signs of insufficient nutrition) and to maintain good nutritional status among practically all healthy individuals.

The recommended intake of potassium in the Nordic Nutrition Recommendation (NNR) issues in 2012 was based on the data from the NNR 2004 on the effect of potassium on blood pressure (NNR, 2012). Several clinical trials and population surveys published thereafter support the finding that a diet rich in potassium alone or in combination with calcium and magnesium, may have favorable effect on blood pressure. The reference values are kept unchanged compared to NNR 2004, since there are no new scientific data to justify any major changes. The recommended intakes are set at 3.5 g/day (90 mmol/day) for men and 3.1 g/day (80 mmol/day) for women. For women the figure also includes pregnant and lactating women. It is pointed out that potassium intakes somewhat over and above these values might have further beneficial effects. The reference values for children and adolescents are extrapolated from adult values on needs for growth and adjusted to body weight.

2.3.4 INSTITUTE OF MEDICINE (IOM), 2005

In 2005, IOM suggested an adequate intake of potassium at 4.7 g/day (120 mmol/day) for adults to maintain lower blood pressure levels, reduce the effects of sodium chloride intake on blood pressure, reduce the risk of kidney stones and possibly decrease bone loss. Due to lack of data, recommended dietary allowances could not be established (IOM, 2005).

2.4 METHODOLOGICAL ISSUES

Possible limitations of the quoted studies include several factors such as heterogeneous study populations, different ways of assessing potassium intake (e.g. 24-hours urine samples or food frequency questionnaires), variable follow-up durations, several ethnicities included (Afro-American are often more prone to increased blood pressure than Caucasians), different modes of potassium intake (food or supplements) and medication.

There is a high variability between the results in different studies. This could to some extent be explained by the variability in the design of the studies, the duration of the studies, the form of the potassium (either from dietary sources or from supplementation) and also that the composition of the total diets shows a high variability. Blood pressure is also influenced by many dietary factors such as intake of magnesium, calcium and other ions. Some of the studies are not focusing on solely one mineral.

2.5 DISCUSSION OF POSITIVE HEALTH EFFECTS

2.5.1 POTASSIUM INTAKE AND STROKE

In Norway, approximately 13 000 individuals suffers from acute stroke each year. Half of these are under 76 years of age (Folkehelseinstituttet, 2012) Stroke is a debilitating disease drawing heavily on health resources in terms of hospitalisation and need for rehabilitation, in addition to the dramatic consequences for the patients and their relatives.

Among the cardiovascular diseases, the evidence pointing to the beneficial effect of lowering sodium is strongest for stroke. This may argue for the possibility of replacing sodium chloride with potassium chloride. Intriguingly, the evidence linking potassium intake to a reduction of cardiovascular disease is also strongest for stroke. Notwithstanding the potential weaknesses of the published studies, as described in section 2.4, VKM finds that a conclusion can be made for stroke regarding the potential benefit of potassium on human health. VKM concludes that a total intake of at least 3.5 g potassium per day reduces incidence of stroke in adults of both gender. This conclusion is based on the same studies as in the WHO guideline, and is also closely in line with the Nordic Nutrition Recommendations at 3.5 g/day for men and 3.1 g/day for women. Presently there is insufficient evidence to give a clear recommendation for potassium intake in children or to give separate conclusions for men and women.

2.5.2 POTASSIUM INTAKE AND BLOOD PRESSURE

Pathologically elevated blood pressure (hypertension) is both a risk factor for other diseases (e.g. stroke, coronary artery disease and kidney disease) and a disease entity itself. Among the dietary factors most often linked to the development of hypertension is intake of sodium. Most national and international authorities thus recommend an upper intake limit of 4-6 g of sodium chloride per day. This is based on recent meta-analyses and long-term follow-up studies of intervention trials, as outlined elsewhere (Nasjonalt råd for ernæring, 2011). Replacement of sodium chloride with potassium chloride may therefore be a reasonable way of reducing sodium intake.

The prevalence of hypertension varies to a great extent within and between populations and increases with increasing age. Dietary factors like sodium chloride and saturated fat are reported as significant risk factors for hypertension (Nasjonalt råd for ernæring, 2011). Modification of all these factors is important for obtaining blood pressure control. Many questions have however been raised as the mechanism of potassium on hypertension is not known. The evidence on the potential beneficial effect of increased potassium on blood pressure is not consistent. Three systematic reviews with meta-analyses, all published 10 or more years ago, suggest that increased potassium intake lowers blood pressure in adults with and without hypertension while one meta-analysis of studies that included only people with hypertension (five studies) reported no significant effect of increased potassium. However, in the recent WHO initiated review and meta-analyses (22 studies) it was concluded that robust evidence exists which demonstrate significant association between increased potassium intake and reduced blood pressure in people with hypertension (Aburto *et al.*, 2013).

Despite inconsistent data, dietary potassium intake are reported to reduce blood pressure in both hypertensive and non-hypertensive individuals. Furthermore, the potassium-lowering effect is suggested to be higher in Afro-Americans compared to Caucasians and more pronounced in individuals with a diet high in sodium chloride. Increasing potassium intake to 4.7 g/day (120 mmol/day) would shift the population distributions of systolic blood pressure

down by 1.7 to 3.2 mm Hg, similar to the predicted result of reducing sodium intake from 9 to 5 g/day.

The meta-analysis by Aburto *et al.* (2013) showed that that dietary potassium intake of 3.5-4.7 g/day (90-120 mmol/day) was associated with reduced blood pressure while intake above 4.7 g/day (120 mmol/day) had no additional effect. Furthermore, in a summary paper by Houston (2011) it was concluded that an increased potassium intake to 4.7 g/day (120 mmol/day) would shift the population distributions of systolic blood pressure down by 1.7 to 3.2 mm Hg, similar to the predicted result of reducing sodium intake from 9 to 5 g/day.

WHO guidelines on potassium intake from food, recommends adults to increase the potassium intake to at least 3.5g/day. For children, WHO recommends that the potassium intake should be based on the adult value and adjusted according the energy requirements relative to those of adults (WHO, 2012a). Nordic Nutrition Recommendation (NNR) recommends intakes at 3.5 g/day for men and 3.1 g/day for women (NNR, 2012).

VKM concludes that an intake of at least 3.5 g potassium per day promote blood pressure reduction in hypertensive subjects. This conclusion is based on the same studies as in the WHO guideline, and is also closely in line with the Nordic Nutrition Recommendations at 3.5 g/day for men and 3.1 g/day for women (WHO, 2012a, NNR, 2012). Despite inconsistent data, a total intake of 3.5 g/day⁴ should also be considered for normotensive subjects to prevent hypertension in the general population.

The available literature on association between potassium and other cardiovascular disease outcomes are limited and inconclusive.

2.6 SUMMARY OF POSITIVE HEALTH EFFECTS

Based on the scientific evidence detailed in this report, a total daily intake of at least 3.5 g potassium among adults will most probably lead to a decrease in the risk of stroke. Such a daily potassium intake will most likely also have a beneficial effect on blood pressure, at least in individuals with hypertension. A total intake of at least 3.5 g/day of potassium is based on the same studies as the guideline from WHO for adults, and is also closely in line with the Nordic Nutrition Recommendations at 3.5 g/day for men and 3.1 g/day for women.

3 Negative health effects

3.1 LITERATURE SEARCH

The literature search was performed in order to retrieve publications on adverse effects caused by potassium in food in the general population and in groups that are particularly vulnerable for increased dietary potassium. Test searches were conducted to find relevant terms and search words, and controlled vocabulary (MeSH and Emtree) in some relevant publications were examined. The literature search was conducted in Ovid Medline, Embase and ISI web of Science. These databases were used to ensure comprehensive study retrieval. The search was conducted in August 2013 using a combination of both controlled vocabulary and text word searching. The search terms included potassium in title, and the following words in the title, abstract, subject heading, name of substance, or registry word fields: food* OR dietary intake

⁴From foods and supplements.

OR diet* AND adverse effect* OR adverse reaction* OR risk factor* OR health risk* OR risk assessment*. The search was limited by requiring that potassium should be in the title, by excluding animal studies and by limiting the languages to Danish, English, German, Norwegian and Swedish languages. Since it was assumed that relevant literature published prior to 2004 were covered by the EFSA report “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” (EFSA, 2005), the search was limited to publications from 2004 onwards. The search resulted in 60 publications. Publications were excluded if adverse health effects related to dietary intake of potassium were not addressed. One reviewer assessed the titles and abstracts of all publications identified in the search process for relevance, and then the full text versions of potentially relevant articles. Additional articles were retrieved by other PubMed searches, and these searches were not limited by publication year. In addition to the publications retrieved by the literature searches, reports from other risk assessment institutions were used. This includes “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” (EFSA, 2005), “Guideline: Potassium intake for adults and children” (WHO, 2012a), “Dietary Reference Intakes for Water, Potassium, Sodium, Chloride and Sulfate” (IOM, 2005), “Revised Review of Potassium” (EVM, 2002), and “Safe Upper Levels for Vitamins and Minerals” (EVM, 2003). Searching the reference lists of the above-mentioned reports also resulted in some relevant publications.

3.2 PREVIOUS REPORTS

3.2.1 WORLD HEALTH ORGANIZATION (WHO), 2012

In a guideline from WHO, an increase in potassium intake from food was strongly recommended⁵ for healthy adults to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease. A conditional recommendation⁶ that the potassium intake should be at least 3.5 g/day for healthy adults was also given (WHO, 2012a). The guideline did not provide recommendations for individuals with impaired urinary potassium excretion from medical conditions or drug therapy. It was stated that increasing potassium consumption from food in the population is safe in individuals without renal impairment caused by medical conditions or drug therapy since the body is able to efficiently adapt and excrete excess potassium via the urine when consumption exceeds needs.

Acute toxicity from extremely high potassium as supplement in healthy adults was evaluated, and it was stated that there is no report of toxicity from consumption of food (WHO, 2012a).

3.2.2 EUROPEAN FOOD SAFETY AUTHORITY (EFSA), 2005, 2010 AND 2011

The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) has prepared an opinion related to the tolerable upper intake level of potassium (EFSA, 2005). The opinion included nutritional requirements, function, uptake and distribution of potassium. The average

⁵A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects.

⁶A conditional recommendation is one for which the guideline development group concludes that the desirable effects of the adherence probably outweigh the undesirable effects, but the group is not confident about the trade-off.

adult potassium intake in Denmark, Finland, Germany, Netherlands, Sweden and UK was in the range of 3 to 4 g/day. The 95th to 97th percentile intake was in the range of 4 to 5.5 g/day.

The available hazard information from animal and human studies was reviewed, and no reports of adverse effects in healthy children or adults due to potassium intake from foods were found. It was, however, reported that single supplementation doses of 5 to 7 g can lead to adverse changes in heart function and peripheral nerve system in apparently healthy adults.

The NDA panel has on three later occasions assessed various health claims on dietary potassium intake (EFSA, 2010, EFSA, 2011b, EFSA, 2011a). The panel concluded that a cause and effect relationship was established between dietary potassium and maintenance of normal blood pressure (EFSA, 2010), and a cause and effect relationship was also established between dietary potassium and normal muscular and neurological function (EFSA, 2010). A cause and effect relationship between dietary potassium intake and both maintenance of normal acid-base balance (EFSA, 2011a) and maintenance of normal bone (EFSA, 2011b) have not been established.

It was stated that the available data were insufficient to establish a safe upper intake level for potassium. The panel further concluded that in healthy persons an increase of 3.0 g/day in potassium in addition to the intake from foods has not been reported to cause adverse effects. This value was based on absence of adverse effects after long-term intake of potassium chloride supplements (EFSA, 2005).

Groups identified to be vulnerable to potassium included elderly persons, persons engaging in strenuous activities leading to dehydration, patients with impaired renal function, patients on drugs for treatment of cardiovascular diseases or patients suffering from metabolic disorders affecting potassium homeostasis.

3.2.3 INSTITUTE OF MEDICINE (IOM), 2005

The US Institute of Medicine advised that an adequate intake of potassium for all adults was 4.7 g/day (120 mmol/day) (IOM, 2005). However, a potassium intake below 4.7 g/day is appropriate for individuals with impaired urinary potassium excretion. Medical conditions associated with impaired urinary potassium excretion include diabetes, chronic renal insufficiency, end-stage renal disease, severe heart failure, and adrenal insufficiency. Drugs reported to impair potassium excretion were ACE-inhibitors, angiotensin receptor blockers and potassium-sparing diuretics.

3.2.4 THE EXPERT GROUP ON VITAMINS AND MINERALS (EVM), 2002 AND 2003

The UK Expert Group on Vitamins and Minerals (EVM) published two reports including discussion of beneficial effects and toxicity of potassium (EVM, 2002, EVM, 2003). Important nutritional sources were identified as milk, fruit, vegetables and meat. The reference nutrient intake for adults was 3.5 g (definition of reference nutrient intake: the intake level sufficient to meet the daily nutrient requirements of most individuals in a specific life-stage and gender group and is based on an estimated average nutrient requirement plus two standard deviations above the mean).

Cases of acute poisoning of humans were all related to high intake of potassium chloride from supplements or sodium chloride substitutes, and reported effects were heart failure, cyanosis and cardiac arrest.

Adverse effects after subchronic and chronic ingestion of potassium, reported from both case studies and supplementation trials, were gastrointestinal toxicity characterised by abdominal pain, nausea and vomiting, diarrhea, and ulceration of the oesophagus, stomach, duodenum and ileum. Potassium in sodium chloride substitutes have also resulted in chest tightness, shortness of breath and heart failure.

Infants, older people, and individuals with pre-existing renal disease, hyperkalemia, adrenal insufficiency, and acidosis or insulin deficiency were described as vulnerable to potassium. In addition, persons using the following drugs, potassium-sparing diuretics, β -adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, digitalis, non-steroidal anti-inflammatory drugs, arginine hydrochloride and succinylcholine, were also described as vulnerable to potassium.

EVM concluded that there were insufficient data to establish a safe upper level for potassium, however; an addition of 3.7 g potassium/day in addition to food appeared to be without overt adverse effects.

3.2.5 HAS THERE BEEN ESTABLISHED A SAFE UPPER LIMIT (UL) FOR POTASSIUM BY EFSA OR AN EQUIVALENT BODY?

The VKM panel is not aware of new published safety studies which could justify the establishment of a safe upper limit for potassium since the assessments performed by EVM (2003), IOM (2005) and EFSA (2005), and therefore VKM agrees with these bodies that there are still insufficient data to establish a safe upper limit for potassium in healthy persons.

3.3 NEGATIVE HEALTH EFFECTS CAUSED BY DIETARY POTASSIUM

3.3.1 HUMAN DATA - HEALTHY POPULATION

A healthy body is able to efficiently adapt and excrete excess potassium via urine when consumption of potassium exceeds the needs (Traeger and Wen, 2009). This capacity apparently includes potassium from food as there is no report of toxicity to healthy humans as a result of potassium consumption from food (WHO, 2012a). However, toxic effects of potassium supplementation to healthy humans are reported (EVM, 2002, EVM, 2003, EFSA, 2005).

A particular potential toxicity of potassium is represented by ^{40}K , a long-lived radioactive potassium isotope emitting mainly beta particles. This isotope is present (0.012%) in practically all naturally occurring potassium. ^{40}K is the largest source of radioactivity within the body, and it is the second (next to radon) most important origin of background radiation. According to US EPA, ^{40}K contributes to 11% of the background radiation (U.S. Environmental Protection Agency, 2012). If increasing the potassium intake results in higher body content of potassium, this will also increase the background radiation. However, due to limited data, this hazard was not assessed further.

Supplementation studies

McMahon *et al.* (1982) examined 48 healthy young men ingesting 3.7 g potassium/day for seven days in the form of wax-matrix formulations or microencapsulated formulations. The wax-matrix formulations resulted in considerable mucosal pathology, with erosions, gastric ulcers, inflammatory lesions and bleeding as evaluated by endoscopy, whereas the microencapsulated formulations resulted in significantly fewer effects. In a controlled follow-

up study including 225 males, up to 3.7 g potassium per day were given for one or two weeks as wax-matrix formulation, microencapsulated formulation, liquid potassium chloride or a potassium free placebo (McMahon *et al.*, 1984). Gastrointestinal effects as mucosal erosions and gastric ulcers, evaluated by endoscopy, were observed rather frequently. With the wax-matrix formulation, mucosal erosions were observed in 43% of the participants and gastric ulcers in 11%. With the microencapsulated formulation, mucosal erosions were observed in 10.5% of the participants and gastric ulcers in 1.2%. With liquid potassium chloride no effects were observed. The same research group performed a follow-up study of 9 hypertensive patients and nine matching controls, given either up to 3.1 g potassium per day for almost two years as wax-matrix formulation or a potassium free placebo. Mucosal erosion was reported in six out of the nine patients given wax-matrix formulated potassium. No mucosal erosion was observed in the control group. Gastric ulcers were not reported.

Effects of potassium given as supplements were also investigated in a long term double-blind study (Grimm *et al.*, 1988, Grimm *et al.*, 1990). Doses of 3.7 g potassium per day formulated as microcrystalline potassium chloride in capsules (n=148) or potassium free placebo (n=150) were given to hypertensive, but comparatively healthy males, for more than two years. The treatment did not result in hyperkalemia although the serum potassium levels increased during the first six months compared to the placebo group. Adverse effects as abdominal pains, nausea, vomiting, diarrhea and bright red blood in the stools were reported but these were not significantly different between the treatment and the placebo group.

From case reports, EVM considered that large doses can result in hyperkalemia and hypernatraemia and lead to e.g. changes in acid-base balance and the heart rate (EVM, 2002, EVM, 2003). However, supplementation studies report few side effects, except local irritation in the gastrointestinal tract, leading to erosion and ulceration, which was mainly observed when potassium chloride was administered as wax-matrix tablets (as described above).

The assessment conducted by EFSA (2005) reviewed various short term (2-3 weeks) studies in healthy adults with intakes up to 15 g potassium per day showing normal serum potassium levels provided that fluid intake was sufficient and that the intake was evenly distributed over the day. Tolerance data from long-term potassium supplementation to healthy subjects and patients mentioned above were also reviewed by EFSA.

Twenty different case reports of intoxications caused by potassium supplements were included in the EFSA-assessment. The adverse effects included chest tightness, nausea and vomiting, diarrhea, hyperkalemia, shortness of breath and heart failure. The reported doses causing adverse effects ranged from 1 to 9.4 g/day in adults and from 1.5 to 7 g/day in infants. Also fatal cases were reported both after acute and chronic potassium intake.

3.3.2 HUMAN DATA - VULNERABLE GROUPS

Within the population there are several groups that are sensitive to increased potassium intake and might experience adverse effects from increased dietary intake (Traeger and Wen, 2009, EVM, 2003, EFSA, 2005). These groups include persons with renal failure, persons with heart failure, persons with diabetes mellitus, persons using drugs that affect the potassium balance, infants, elderly, and persons undergoing highly strenuous activities.

Persons with severe renal failure are often undergoing intermittent haemodialysis with a frequency depending on the severity of the renal failure. Since these patients have a quite

reduced capacity to regulate potassium level, they will also be particularly vulnerable to increased dietary intake of potassium.

In a clinical study following 224 haemodialysis patients for 5 years, the dietary potassium intake was determined by a food frequency questionnaire (Noori *et al.*, 2010). Analysed by quartiles the potassium intake was determined to be 879, 1342, 1852 and 3440 mg/day. This was significantly ($p < 0.001$) related to the 5-years mortality of 21, 37, 36 and 50% in the respective quartiles. This association is in line with the advice that haemodialysis patients should ingest less than 1.5 g/day of potassium.

A typical case is reported by Doorenbos and Vermeij (2003) who describe a 74 year old woman with renal failure who underwent haemodialysis three times weekly and became critically ill with bradycardia at two different occasions with serum potassium of 9.2 mmol/L and 9.7 mmol/L. At both occasions she was successfully resuscitated. On questioning, it turned out that she had used a potassium-containing salt substitute. After refraining from this she had no further episodes.

The ultimate treatment for haemodialysis patients is kidney transplantation. By the end of 2012, 4448 Norwegian patients had received kidney replacement, whereas 202 were waiting for a kidney graft. This is a limited sized group under good medical surveillance, however, with regard to potassium exposure they are rather sensitive (Leivestad, 2012). To avoid graft rejection, persons with kidney replacement often use the drugs tacrolimus or cyclosporine, both known to reduce renal potassium clearance.

Persons with mild to moderate renal failure have reduced capacity to eliminate potassium. For this group, higher dietary potassium intake is associated with hyperkalemia and increased risk of complications (Noori *et al.*, 2010). In Norway, it is estimated that 10-11% of the general population (in the order of 500 000 persons) have diagnosed or undiagnosed chronic kidney disease (Hartmann *et al.*, 2006). The diagnosis mild or moderate kidney failure is based on glomerular filtration rate and kidney injury evaluated from haematuria and proteinuria.

Patients with heart failure may be treated with angiotensin converting enzymes inhibitors (ACE inhibitors), beta-blockers, angiotensin blockers and aldosterone antagonists, all known to potentially increase serum potassium and thereby increase the risk of hyperkalemia (EFSA, 2005, EVM, 2003). In the heart muscle cells, potassium has a particular function in maintenance of cardiac rhythm. This is mediated by channels gating potassium ions over the cell membrane and failure of the gating due to particular drug molecules or disturbances in potassium balance can be observed as disturbances in the ECG-diagram depicting the heart rhythm. Such disturbances can indicate life-threatening arrhythmias (Vandenberg *et al.*, 2012). Desai (2009) reviewed the mechanism, incidence, predictors and management of hyperkalemia in heart failure, emphasizing the importance of careful patient selection for medical treatment and regular surveillance of potassium and creatinine. With regard to the prevalence of heart failure, it is relevant to consider the number using the respective medicines (Table 3.1).

Persons with diabetes mellitus may have elevated glucose in the extracellular fluid, and this may result in release of intracellular potassium. The total prevalence of diagnosed diabetes in Norway (type I and II) is estimated to be 2.3% (90-120 000 persons). The estimated number

of undiagnosed diabetes may be almost as high as the number of diagnosed diabetes (Linas S. L., 2012) .

Persons using drugs that affect the potassium balance are vulnerable for increased potassium. Decreased renal potassium excretion can result from e.g. interfering with the renin-angiotensin-aldosterone axis by drugs such as ACE inhibitors, cyclosporine and NSAIDs. The use of β -blockers decrease cellular potassium uptake (Perazella, 2000). Digitalis is a drug that e.g. impair the sodium and potassium exchange (Perazella, 2000), and trimethoprim is an example of a drug that blocks sodium and potassium exchange in the distal nephron (Linas S. L., 2012). The estimated use of drugs affecting the potassium balance among Norwegians is shown in Table 3.1 (Sakshaug *et al.*, 2013).

Table 3.1: The main drugs affecting potassium balance including the number of daily defined doses and the estimated frequency of use in the period 2008-2012.

Drug group	Indication/effect	Doses (DDD/1000)*	Estimated frequency**
NSAIDs	Antiinflammatory	47.5/day	4.8%
ACE-inhibitors	Renin/angiotensin system	45/day	4.5%
β -blockers	Decrease cellular potassium uptake	38/day	3.8%
Digitalis	Cardiac failure	2.21/day	0.2%
Trimethoprim	Antibiotic	0.51/day	0.5%
Tacrolimus	Immune suppression	130/year	0.036%
Cyclosporine	Immune suppression	149/year	0.041%

*DDD/1000 is the number of daily defined doses per 1000 inhabitants, including both short-term and long-term use.

**Estimated frequency of use among total Norwegian population (5 096 000 persons 01.10.2013, number from www.ssb.no).

Infants (below one year) have immature renal function and are therefore more vulnerable to increased potassium intake (EVM, 2002). In Norway, this group accounted 60 530 in total in 2013 (the numbers are from www.ssb.no). Children above one year have well-developed kidneys and should not be at particular risk.

Most persons at the age of 85 years and older have a moderate or serious reduction in the glomerular filtration rate (this will interfere with the renal function) (Norsk

legemiddelhåndbok, 2013). In Norway, this group accounted 113 700 persons in 2011 (the numbers are from www.ssb.no.)

Persons undergoing highly strenuous activities will be at risk because muscle tissue can be impaired and leak potassium. In addition, dehydration can further increase the risk of hyperkalemia (EFSA, 2005).

3.4 DISCUSSION OF NEGATIVE HEALTH EFFECTS

An important finding with regard to potassium toxicity is that there is no report of toxicity to healthy humans as a result of potassium consumption from food (WHO, 2012a). This finding shows that a healthy body is fully capable of dealing with potassium from foods naturally rich in this element without any risk of adverse effects.

Several expert groups and national or international bodies have evaluated and summarised the optimal potassium intake. Their reports conclude that healthy persons are fully capable to handle increased potassium intake from food through increased renal excretion, whereas there are subgroups in the population which are particularly vulnerable to increased potassium intake (EVM, 2003, EFSA, 2005, IOM, 2005, WHO, 2012a). In addition to patients with mild, moderate or severe renal failure, there are several other vulnerable groups. These include patients with heart failure, diabetes mellitus and persons using medications that affect the potassium balance and cause hyperkalemia.

Infants and elderly people in general and persons undergoing very strenuous activities are also vulnerable for hyperkalemia.

There are insufficient data to set a safe upper level for potassium (EVM, 2003, IOM, 2005, EFSA, 2005). However, according to EVM and EFSA additional potassium intake of 3.7 g or 3.0 g per day, respectively, in addition to potassium in food appears not to cause adverse effects (elevated plasma potassium or gastrointestinal symptoms) for healthy adults. These numbers are based on the same studies (McMahon *et al.*, 1982, Grimm *et al.*, 1988, Grimm *et al.*, 1990). These studies alone are not considered sufficient for setting a safe upper limit, since they have limitations in size and design. They were primarily designed to follow effect parameters, and include almost exclusively men. With regard to an additional dose without apparent adverse effects, the EFSA panel was more conservative (3.0 g/day) than the EVM panel (3.7 g/day), and the VKM panel endorses the EFSA value of 3.0 g/day. In the present report, the term anticipated safe intake is used when 3 g potassium/day is added to the mean intake from food.

3.5 SUMMARY OF NEGATIVE HEALTH EFFECTS

Healthy persons

Intake of potassium from food does not cause hyperkalemia in healthy persons. Based on the scientific evidence detailed in this report, healthy persons can probably tolerate an increase of 3.0 g/day in potassium intake in addition to the intake from foods (EFSA, 2005). The assessment conducted by EFSA (2005) reviewed various short term (2-3 weeks) studies in healthy adults with intakes up to 15 g potassium per day showing normal serum potassium levels provided that fluid intake was sufficient and that the intake was evenly distributed over the day.

As opposed to intake of potassium from food, gastrointestinal erosion and ulcers have been reported in healthy persons after oral potassium chloride supplementation, especially with wax-matrix formulations.

Vulnerable groups

The vulnerable groups include patients with various severities of renal failure, heart failure, diabetes mellitus and persons on a long range of medications able to affect the potassium balance, infants below one year of age, people aged 85 and older, and persons undergoing very strenuous activities.

For persons with impaired kidney function, hyperkalemia may occur even with a modest increase in potassium intake (Traeger and Wen, 2009). Thus, excessive dietary potassium intake may be an important contributor to hyperkalemia in patients with impaired renal function (Desai, 2009). It is advised that haemodialysis patients should ingest less than 1500 mg/day of potassium (Noori *et al.*, 2010). For the other vulnerable groups, a safe level of potassium has not been identified.

To reduce the prevalence of hyperkalemia in the vulnerable groups, there is a need for individual assessment of every patient and their dose of medication, advice related to diet, interaction with other medications and careful control of the plasma potassium level (Bugge, 2010).

4 Intake of sodium and potassium

National food consumption surveys

The intakes of sodium and potassium in adults are calculated from the national food consumption survey Norkost 3. Norkost 3 is based on two 24-hour recalls by telephone at least one month apart. Food amounts were presented in household measures or estimated from photographs (Totland *et al.*, 2012). Norkost 3 was conducted in 2010/2011 and 1787 adults aged 18-70 years participated. The participation rate was 37%. Unfortunately, no national dietary information among the older population (>70 years) exists in Norway.

The intakes of sodium and potassium in 2-year old children are calculated from the national food consumption survey Småbarnskost, which is based on a semi-quantitative food frequency questionnaire. In addition to predefined household units, food amounts were also estimated from photographs. A total of 1674 2-year old children participated. The participation rate was 56% (Kristiansen *et al.*, 2009).

The intakes of sodium and potassium in 4-, 9- and 13-year old children are calculated from the national food consumption survey Ungkost 2000, which is based on a 4-day food intake registration with a precoded food diary. Food amounts were presented in predefined household units or as portions estimated from photographs. The study in 4-year old children was conducted in 2001, and 391 children participated (Pollestad *et al.*, 2002). The study in 9- and 13-year old children and adolescents was conducted in 2000, and 810 9-year old children and 1005 13-year old adolescents participated (Øverby and Andersen, 2000).

Intake calculations

In accordance with the terms of reference, three different scenarios for replacement of the sodium in sodium chloride with potassium were considered. Assuming that potassium replaced sodium, weight by weight, the scenarios were designated 30:70, 50:50 or 70:30.

According to the EFSA opinion, naturally occurring sodium in food and drinks constitutes approximately 12% of the total sodium intake. The naturally occurring sodium (12% of calculated intake) was subtracted from the sodium intakes, and the remaining sodium intake was used for the scenarios. This sodium intake includes both added salt (sodium chloride) in home cooking recipes (e.g. baked bread, meat balls etc.) and salt in industrialised food production. Table salt, and sodium chloride used in home cooking are not registered in the dietary surveys, and are therefore not included in the calculations or scenarios. The exception is sodium chloride included in recipes for homemade foods, such as e.g. meatballs or stew, which for practical reasons could not be subtracted. The three different scenarios for substitution of sodium with potassium, 30:70, 50:50, or 70:30, were calculated for each person participating in the dietary survey.

Intake of sodium and potassium were computed by the software system (KBS) developed at the Institute of Basic Medical Sciences, Department of Nutrition, at the University of Oslo. The food databases are mainly based on different versions of the official Norwegian food composition table (Rimestad *et al.*, 2000).

The mean potassium intake in adults was 3800 mg/day. By gender, the mean potassium intake was 3380 mg/day for women and 4250 mg/day for men. Since the intake of potassium differs between the genders, the intakes for both genders are presented.

Estimated potassium and sodium intakes in scenarios where 30%, 50% and 70% of sodium in added salt is replaced by potassium for women, men, 2-, 4-, 9-, and 13-year olds are presented in the Tables 4.1-4.6. For each of the scenarios, the mean, the median, the 5th, 25th and the 95th percentiles of the estimated intakes are presented.

Please note that the intake of sodium and potassium, not sodium chloride and potassium chloride, is given in the tables. The weight of sodium chloride is 2.55 the weight of sodium, the weight of potassium chloride is 1.91 the weight of potassium.

It is important to be aware that there are uncertainties in the intake calculations (see Chapter 5) although the figures are given in milligrams.

Through the entire report, calculations for Norkost 3 and the 3 scenarios is illustrated in various green colors.

Table 4.1: Sodium and potassium intake in women (n=925), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride (salt) is replaced by potassium.

Sodium and potassium intake in women as reported in Norkost 3					
	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	1242	1860	2540	2370	4280
Potassium	1900	2700	3380	3290	5120

Scenario 30:70					
Estimated sodium and potassium intake in women when 30% of added sodium is replaced by potassium.					
	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	910	1370	1870	1750	3150
Potassium	2360	3290	4050	3940	6040

Scenario 50:50

Estimated sodium and potassium intake in women when 50% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	700	1040	1430	1330	2400
Potassium	2660	3660	4500	4390	6700

Scenario 70:30

Estimated sodium and potassium intake in women when 70% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	480	720	980	910	1640
Potassium	2910	4000	4940	4840	7300

Table 4.2: Sodium and potassium intake in men (n=862), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride (salt) is replaced by potassium.

Sodium and potassium intake in men as reported in Norkost 3

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	1660	2600	3570	3360	6110
Potassium	2410	3310	4250	4120	6560

Scenario 30:70

Estimated sodium and potassium intake in men when 30% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	1230	1910	2630	2470	4490
Potassium	2970	4120	5190	5040	7710

Scenario 50:50

Estimated sodium and potassium intake in men when 50% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	930	1450	2000	1880	3420
Potassium	3400	4660	5820	5670	8670

Scenario 70:30

Estimated sodium and potassium intake in men when 70% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	640	1000	1370	1290	2350
Potassium	3750	5200	6450	6270	9780

Table 4.3: Sodium and potassium intake in 2-year old children (n=1674) including scenarios where 30%, 50% or 70% of sodium in added sodium chloride (salt) is replaced by potassium⁷.

Sodium and potassium intake in 2-year olds as reported in Småbarnskost 2007					
	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	830	1230	1560	1500	2460
Potassium	1240	1770	2270	2180	3560

Scenario 30:70					
Estimated sodium and potassium intake in 2-year olds when 30% of added sodium is replaced by potassium.					
	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	610	900	1150	1100	1810
Potassium	1530	2110	2680	2600	4130

Scenario 50:50					
Estimated sodium and potassium intake in 2-year olds when 50% of added sodium is replaced by potassium.					
	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	460	690	880	840	1380
Potassium	1700	2350	2950	2870	4520

Scenario 70:30					
Estimated sodium and potassium intake in 2-year olds when 70% of added sodium is replaced by potassium.					
	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	320	470	600	570	940
Potassium	1880	2570	3230	3140	4870

Table 4.4: Sodium and potassium intake in 4-year old children (n=391), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride (salt) is replaced by potassium⁸.

Sodium and potassium intake in 4-year olds as reported in Ungkost 2000					
	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	1010	1360	1680	1630	2560
Potassium	1250	1780	2130	2060	3110

⁷Calculations made in AE10 database, see further description in Chapter 5 Uncertainty.⁸Calculations made in AE10 database, see further description in Chapter 5 Uncertainty.

Scenario 30:70

Estimated sodium and potassium intake in 4-year olds when 30% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	740	1000	1240	1200	1890
Potassium	1610	2200	2580	2490	3700

Scenario 50:50

Estimated sodium and potassium intake in 4-year olds when 50% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	560	760	940	910	1440
Potassium	1800	2450	2870	2770	4120

Scenario 70:30

Estimated sodium and potassium intake in 4-year olds when 70% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	390	520	650	630	980
Potassium	2040	2700	3170	3070	4570

Table 4.5: Sodium and potassium intake in 9-year old children (n=810), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride (salt) is replaced by potassium⁹.

Sodium and potassium intake in 9-year olds as reported in Ungkost 2000

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	1210	1760	2260	2150	3560
Potassium	1460	2120	2630	2570	4020

Scenario 30:70

Estimated sodium and potassium intake in 9-year olds when 30% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	890	1290	1660	1580	2620
Potassium	1880	2620	3230	3170	4830

⁹Calculations made in AE10 database, see further description in Chapter 5 Uncertainty.

Scenario 50:50

Estimated sodium and potassium intake in 9-year olds when 50% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	680	980	1260	1210	1990
Potassium	2140	2970	3620	3590	5300

Scenario 70:30

Estimated sodium and potassium intake in 9-year olds when 70% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	470	670	870	830	1370
Potassium	2390	3290	4020	3950	5870

Table 4.6: Sodium and potassium intake in 13-year old adolescents (n=1005), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride (salt) is replaced by potassium¹⁰.

Sodium and potassium intake in 13-year olds as reported in Ungkost 2000

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	1090	1670	2360	2240	4060
Potassium	1290	1980	2730	2560	4740

Scenario 30:70

Estimated sodium and potassium intake in 13-year olds when 30% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	800	1230	1740	1650	2990
Potassium	1590	2510	3350	3170	5690

Scenario 50:50

Estimated sodium and potassium intake in 13-year olds when 50% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	610	940	1320	1250	2270
Potassium	1810	2830	3770	3560	6300

¹⁰Calculations made in AE10 database, see further description in Chapter 5 Uncertainty.

Scenario 70:30

Estimated sodium and potassium intake in 13-year olds when 70% of added sodium is replaced by potassium.

	5th percentile mg/day	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium	420	640	910	860	1560
Potassium	2020	3110	4180	3960	7040

For the benefit assessment of replacement of sodium in sodium chloride with potassium, an evaluation of women and men with an intake below 3.5 g (90 mmol/L) has been conducted in Chapter 7.

For the risk assessment of replacement of sodium in sodium chloride with potassium, the mean value and the 95th percentile are used in Chapter 8.

5 Uncertainty

5.1 SODIUM CONTENT IN FOODS

According to the terms of reference, the exposure characterisation in this benefit and risk assessment is focused on replacement of sodium chloride with potassium chloride in industrial food production. The uncertainty factors below are therefore limited to issues relevant for the intake of sodium chloride from industrialised food production.

Naturally occurring sodium was assumed to be 12% of total sodium intake for all population groups (EFSA, 2005). It is not known whether this is representative for Norwegian conditions, or if the naturally occurring sodium content in Norkost 3, Småbarnskost (2007) or Ungkost (2000) is actually higher or lower. The remaining 88% of sodium intake is from added salt (sodium chloride) i.e. both added salt in home cooking recipes (e.g. baked bread, meat balls etc.) and salt in industrialised food production. It was not feasible to divide sodium in home cooking recipes from industrialised foods, and both types of foods are therefore included in the calculations. This uncertainty factor contributes to an overestimation of intake of sodium from industrial food production and consequently an overestimation of potassium in the scenarios, and it is uncertain if this can lead to an over- or underestimation of sodium intake.

There are uncertainties related to the representativeness of the sodium values used in the food database based on the Norwegian food composition table (Matvaretabellen, 2006, Rimestad *et al.*, 2000). The amounts of sodium in commercial recipes are constantly changing, and the number of brands and foods offered for sale are increasing. Although the Norwegian food composition table is under constant revision, the food composition table only has one sodium value for each food. This single value represents the range of sodium content in similar foods. In addition, the variation in sodium chloride used in each recipe, both in home cooking and in commercial recipes, adds a level of uncertainty to the sodium concentration used as a background in the scenarios.

The types of salt used in home cooking are not registered. In some households a sodium reduced type of salt replaces the more ordinary sodium chloride. All salt used in recipes in the database are sodium chloride, and this might lead to an overestimation of sodium intake for those using other kinds of salt, and also for those who do not add any kind of salt to home

cooked food. None of the dietary assessment methods used in this risk assessment assess any use of table salt.

Norkost 3 is calculated in a database (N3, based on AE10) containing sodium and potassium values for all foods, and is the only dietary survey calculated in a database where both sodium and potassium are fully included. For older Norwegian food databases some foods were not assigned potassium or sodium values. Therefore, the 2010 database was used for the calculations using the dietary surveys Ungkost 2000 and Småbarnskost 2007. To examine the differences between the different food databases, Ungkost 2000 and Småbarnskost 2007, were calculated both with the original food database and with the database from 2010 (data not shown) to compare energy intake. The differences between the databases were for the mean energy intake in the range of 1-2% which indicates that most foods were present both in the original and the new database. Therefore, the sodium and potassium intake were calculated in the most updated database (AE10 or N3). Using a food database from a later period than the original database adds a level of uncertainty since the sodium and potassium values might have changed in the years between.

5.2 DIETARY ASSESSMENT

Every dietary assessment is associated with uncertainty. A description of the most important uncertainties and assumptions in the dietary exposure calculations is presented below.

Three concepts are fundamental to understand the limitations of dietary assessment: habitual consumption, validity and precision (Livingstone and Black, 2003).

The habitual consumption of an individual is the person's consumption averaged over a prolonged period of time, such as weeks and months rather than days. However, this is a largely hypothetical concept; the consumption period covered in a dietary assessment is a compromise between desired goal and feasibility. In the Norwegian dietary surveys, the time period covered is 14 days among the 2-year olds (Småbarnskost 2007), four consecutive days among the 4-, 9- and 13-year olds (UNGKOST 2000), and two non-consecutive days among the adults (Norkost 3) (Kristiansen et al., 2009, Totland et al., 2012).

Dietary patterns are constantly changing. The data collections of the different dietary surveys were performed from 2000 till 2011.

When evaluating high consumers, the uncertainty associated with the 95th percentile is higher than for the mean value, especially among the age groups with a low number of participants.

The validity of a dietary assessment method refers to the degree to which the method actually measures the aspect of diet that it was designed to measure (Nelson and Margetts, 1997). Lack of validity is strongly associated with systematic errors (Burema et al., 1988). With systematic errors all respondents in a dietary study or each subgroup in a population produce the same type of error, like systematic underestimation or overestimation of intake. The three different dietary assessment methods used in this risk assessment have limitations when it comes to validity. The validation studies among 2-year olds were performed on a previously established questionnaire, but the results showed a significantly higher energy intake with the FFQ than with the reference method: weighed record (Andersen et al., 2004, Andersen et al., 2009). The Norwegian 24-hour recall method used among adults in Norkost 3 has not been validated. However, in 2007-8 Norway participated in the EFCOVAL study with a number of 124 men and women aged 45-64 years of age (de Boer et al., 2011). Studies have been performed to evaluate the reporting accuracy of dietary sodium and potassium intakes using the EPIC-soft 24-hour dietary recall method and compare with 24-hour urinary excretions.

Mean sodium reporting accuracy (95% CI) was 0.73 (0.68,0.81) for Norway indicating a underestimation of dietary sodium intake (De Keyzer, 2014). For potassium the underestimation of potassium intake varied from 1.6% for men to 6.9% for women (Crispim et al., 2011). Although the study participants differed from the Norkost 3 participants, the 24-hour recall methods are comparable, and KBS were used as the food database.

Regarding energy intake other similar 24-hour recall methods have been validated and an underestimation in energy intake of around 15% have been shown (Subar et al., 2003, Poslusna et al., 2009). Although neither sodium nor potassium contributes to energy intake, the nutrients are related to the total energy intake and underestimation of energy intake indicates that not all foods eaten are reported. However, it is more difficult to assess which foods are underreported. It has been shown that foods perceived as unhealthy such as fats, sweets, desserts and snacks tend to be underreported to a larger degree than foods perceived as healthy (Olafsdottir et al., 2006). Salty foods with added sodium can be perceived as unhealthy, and fruit and vegetables containing potassium are by most perceived as healthy. If misreporting of sodium and potassium is of the same magnitude as for total energy, the estimates for sodium and potassium are more likely to be under-reported than over-reported. However, if potassium containing foods are over-reported and sodium containing foods are under-reported, the uncertainty will be increased.

The Norkost 3 study has a participation rate of 37 %. This is rather low for a cross sectional dietary survey where the aim is to get a representative selection of the population. When comparing the participants in Norkost 3 with the Norwegian population, the Norkost 3 participants were more educated. After weighting cases with low education more than those with high education, the results for nutrients did not shift considerable. However, the intake of vegetables, fruit/berries and juice were somewhat lower (Totland et al. 2012). It has been shown that health conscious people are more likely to participate in a dietary survey. This can indicate a somewhat different dietary pattern among the participants than among the whole population. The direction of the uncertainty is difficult to estimate, but without drawing strong conclusions, it seems that the Norkost 3 participants with high education eat a diet more rich in potassium than the low educated participants.

The precision of a technique is high when a repeated administration gives the same results (Livingstone and Black, 2003). Poor precision derives from large random errors in the techniques of dietary assessment. The effect of random errors can be reduced by increasing the number of observations, but cannot be entirely eliminated (Rothman, 2002).

5.3 BENEFIT ASSESSMENT

The suggestion from WHO on at least 3.5 g potassium per day in adults is conditional. A conditional recommendation is one for which the guideline development group in WHO concluded that the desirable effects of adherence probably outweigh the undesirable effects, but was not confident about the trade-off. As the suggestion is mainly based on one meta-analysis (Aburto *et al.*, 2013), and several of the studies included in this meta-analysis show no dose response, this is considered the major uncertainty factor in the benefit assessment.

5.4 RISK ASSESSMENT

Uncertainties to consider in the evaluation of the potential adverse effects resulting from replacing sodium with potassium in industrially produced foods include the following points.

- There are few studies available on tolerable doses of potassium, conducted both with healthy subjects and patients, and those existing have important limitations with design, size, investigated parameters, gender selection and quality. Such studies of high quality are needed in order to set a safe upper level.
- The anticipated safe level of potassium intake (3.0 g/day) in addition to food sources is very approximate, and must be used with caution. The scientific base for setting these intake levels is quite limited and the estimated levels should by no means be taken as a safe upper level.
- Several groups are identified as being particularly vulnerable to increased potassium intake. However, there are still many uncertainties regarding these groups, such as how many persons are there in the different groups, and at which doses are they vulnerable to potassium. In addition, there may be additional groups in the population which are vulnerable, but haven't yet been identified.

5.5 SUMMARY OF UNCERTAINTIES

Evaluations of the overall effect of identified uncertainties are presented in Table 5.1, highlighting the main sources introducing uncertainty, and indicating whether the respective source of uncertainty might have led to an over- or underestimation of the exposure and/or the resulting risk.

Table 5.1: Qualitative evaluation of influences of uncertainties in the assessment of sodium and potassium.

Source of uncertainty	Direction
<i>Content of sodium</i>	
Variation in salt content in recipes	+/-
Sodium chloride used in recipes for home cooking	+
Sodium chloride used in industrial food production	+/-
Naturally occurring sodium at 12%	+/-
<i>Dietary exposure assessment</i>	
Different dietary assessment methods	+/-
Bias due to mis-reporting/underreporting	(-)
<i>Småbarnskost 2007</i>	
Use of 95th percentile	+/-
FFQ time span is 14 days	+/-
Used newer database than original for sodium and	+/-

potassium calculations (AE10 instead of AE07/IE96)	
<i>Ungkost 2000</i>	
Study conducted in 2000-2001	+/-
<ul style="list-style-type: none"> • Possible changes in the food patterns can have occurred 	
Use of 95 percentile	+/-
<ul style="list-style-type: none"> • The number of participants among 4-year olds is only 391 	
Participation rate among 4-year olds	+/-
Four registration days	+/-
<i>Norkost 3</i>	
Participation rate	+/-
Two registration days	+/-
Use of 95th percentile	+/-
<i>Benefit assessment</i>	
Suggested at least 3.5 g potassium per day	+/-
<i>Risk assessment</i>	
No established UL for potassium	+/-
Insufficient data on tolerable levels of potassium for healthy persons	+/-
Insufficient data on tolerable levels of potassium for vulnerable persons	+/-
Identification of additional vulnerable groups	-
Overall	+/-

+: uncertainty likely to cause overestimation of exposure.

-: uncertainty likely to cause underestimation of exposure.

The intake of sodium and potassium is considered realistic for each age group, despite the limitations in assessing the sodium chloride consumption and the uncertainties related to estimating the exposures as outlined in Table 5.1. There are many sources of uncertainties in the data used for this evaluation; therefore, it is not possible to say clearly whether the uncertainties will lead to an overall overestimation or an underestimation.

6 Data gaps

Data for intake of sodium and potassium in various population groups are insufficient and associated with a high degree of uncertainty.

Good data for content of sodium and potassium in foods and drinks are lacking.

There are few studies on healthy subjects examining the tolerable levels of potassium, and especially not sufficient good quality studies to set tolerable upper level of potassium for all age groups.

The studies on health effects related to potassium in adults have high heterogeneity both in design and results.

There are especially few studies on health effects related to potassium in children and adolescents.

The studies are often short terms.

Also for most of the vulnerable groups, there are insufficient data on tolerable levels of potassium.

The specific form of potassium used is often not stated, and there are not clear if and when this does matter for evaluation of benefit and risk of potassium.

7 Benefit characterisation

It is concluded that a potassium intake to reduce the risk of stroke is at least 3.5 g/day in adults (see Chapter 2). Most likely an intake of 3.5 g/day will also reduce high blood pressure. The intakes of potassium in women, men and children in Norway are presented in Chapter 4. Approximately 60% of the women and 30% of the men in Norway have an intake below 3.5 g/day.

What is the estimated dietary intake of potassium in the population?

What is the estimated dietary intake of potassium if the following scenarios for replacement of sodium chloride (NaCl) with potassium chloride (KCl), 30:70, 50:50, 70:30, are set up?

This question stated in the terms of reference is answered in Chapter 4.

What positive health outcomes may be the result of an increased use of potassium chloride in industrial food production?

How high must the potassium intake be to achieve positive health effects?

This question stated in the terms of reference is answered in Chapter 2.

How many Norwegians will benefit from replacement of sodium in added sodium chloride with potassium in the three scenarios?

This is not stated as a separate question in the terms of reference. However, since the intake calculations showed that persons in the Norwegian population have intake levels of potassium from food which is below the level of 3.5 g/day, in the following further calculations are

given to see how many men and women, in percent, will benefit from an increase in dietary potassium. The benefit characterisation is therefore focused on the women and men with a present intake of potassium below 3.5 g/day.

Scatter plots for sodium-potassium correlation in women are shown in Figure 4.2, all women (upper panel) and women with potassium intake below 3.5 g per day (lower panel).

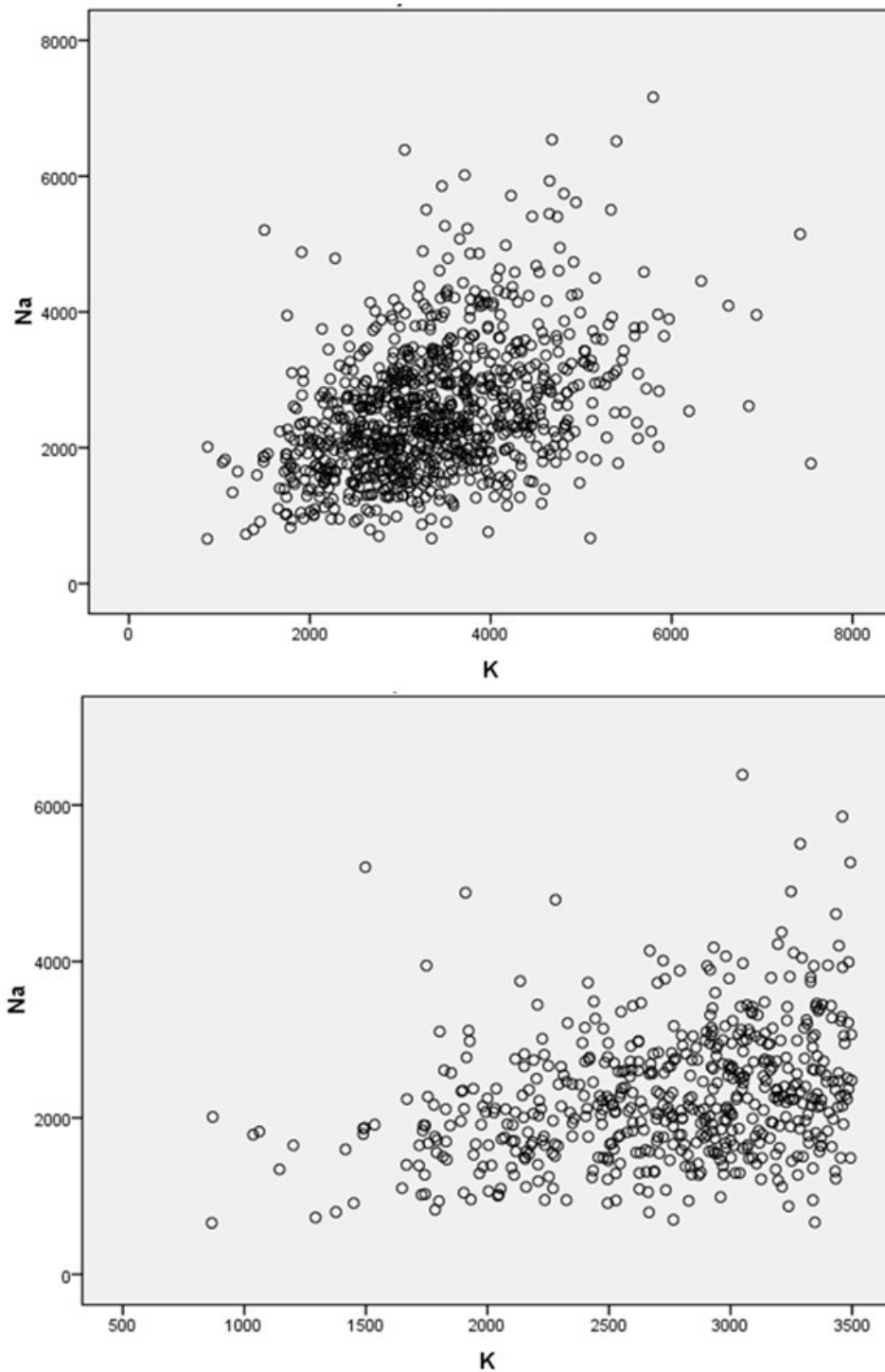


Figure 7.1: Scatter plot for sodium-potassium-correlation in all women (upper panel), and for the women with potassium intake ≤ 3.5 g/day (lower panel).

Pearson correlation coefficient for all the women in Norkost 3 is considered as a medium correlation ($r=0.40$) (Cohen, 1988). Out of 925 women, 543 have a daily intake of potassium below 3.5 g/day (59% of the women in Norkost 3). When only looking at women with an intake of potassium under 3.5 g/day, the Pearson correlation coefficient is 0.30.

In the 30:70 scenario, 33% of the women have a potassium intake below 3.5 g/day, in the 50:50 scenario, the percentage is 21, and in the 70:30 scenario 13% of the women still have an intake below 3.5 g/day.

Reduction in percentage of women with potassium intakes below 3.5 g/day in the 30:70, 50:50 and 70:30 scenarios is presented in Table 7.1.

Table 7.1: Percentage of women with intakes of potassium below 3500 mg/day in the 30:70, 50:50 and 70:30 scenarios.

	Norkost 3	30:70 scenario	50:50 scenario	70:30 scenario
Women with potassium intakes below 3.5 g/day	59%	33%	21%	13%

Scatter plots for sodium-potassium correlation in men are shown in Figure 7.2, all men (upper panel) and men with potassium intake below 3.5 g per day (lower panel).

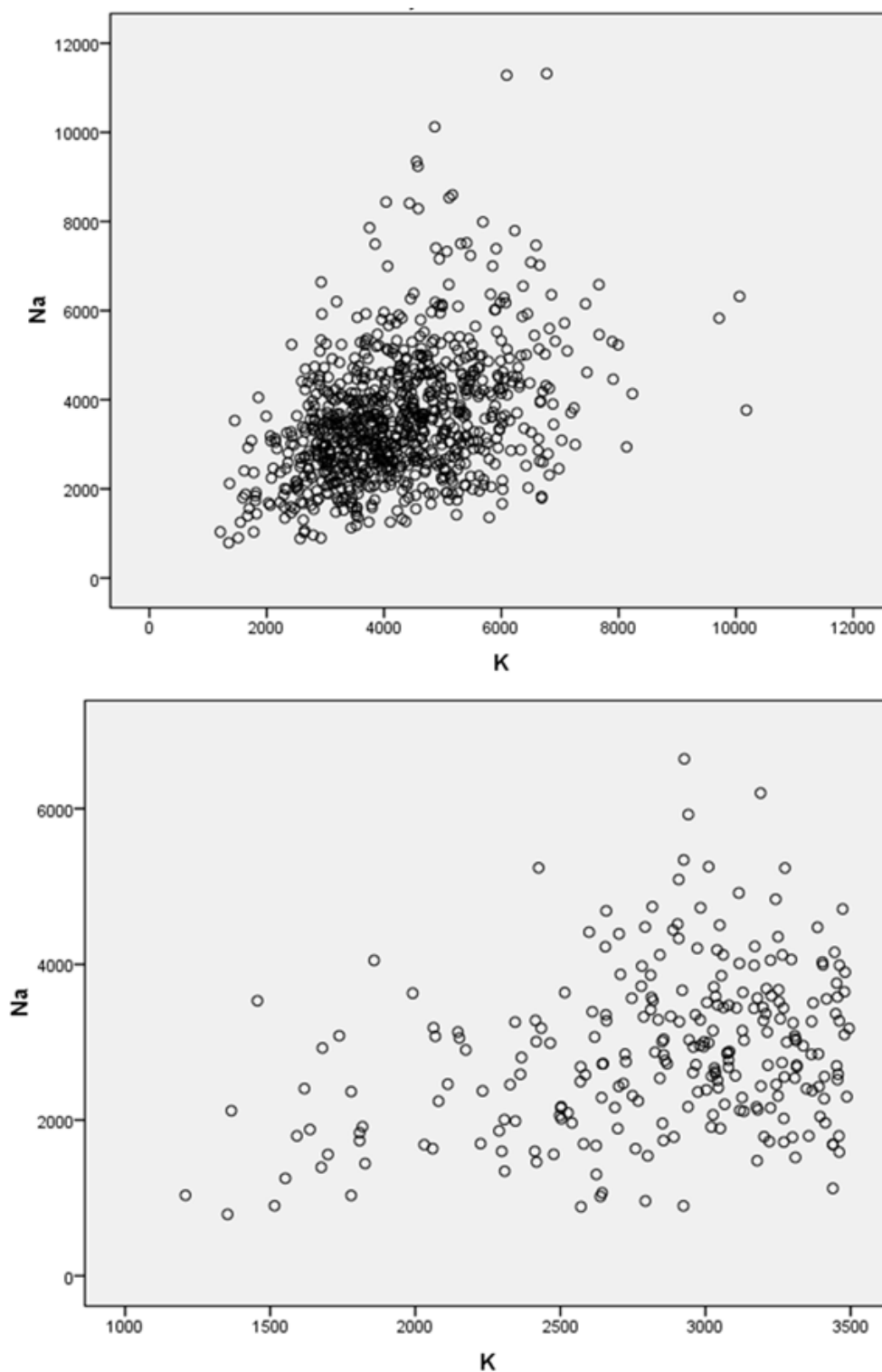


Figure 7.2: Scatter plot for sodium-potassium-correlation in all men (upper panel) and for men with potassium intake ≤ 3.5 g/day (lower panel).

Pearson correlation coefficient for all the men in Norkost 3 is considered as a medium correlation ($r=0.38$) (Cohen, 1988 p 79-81). Out of 862 men, 255 have a daily intake of potassium below 3.5 g/day (30% of the men in Norkost 3) Pearson correlation coefficient for

these men is also medium (0.30). The correlation between intake of potassium and sodium is lower in men with low potassium intakes.

In the 30:70 scenario, 10% of the men have a potassium intake below 3.5 g/day, in the 50:50 scenario, the percentage is 6, and in the 70:30 scenario 4% of the men have an intake below 3.5 g/day.

Reduction in percentage of men with potassium intakes below 3.5 g/day in the 30:70, 50:50 and 70:30 scenarios is presented in Table 7.2.

Table 7.2: Percentage of men with intakes of potassium below 3.5 g/day in the 30:70, 50:50 and 70:30 scenarios.

	Norkost 3	30:70 scenario	50:50 scenario	70:30 scenario
Men with potassium intakes below 3.5 g/day	30%	10%	6%	4%

It is important to notice, that especially for women, but even in some men, a replacement of sodium chloride with potassium chloride in industrial food production will not result in an intake of potassium at or above 3.5 g/day. The highest potassium increase, from this measure will be seen for individuals with present high sodium chloride intake.

It has been suggested by several authors in the included reviews, meta-analyses and reports that an increase in dietary potassium intake best might be obtained by increasing the intake of food high in potassium.

The intake of potassium is to a great extent a matter of dietary choices. The potassium content in foods varies widely. Foods rich in potassium include beans and lentils, dried fruits, nuts and seeds, green vegetables and root vegetables, banana, fish and meat (Matvaretabellen, 2006). Both in men and women, potatoes and vegetables are the food groups contributing with most potassium in Norkost 3 (21 and 20%, respectively). In men, milk/milk products and cheese contributes with 18% of the total potassium in the diet, bread and cereals with 15%, fruit/berries and juice with 13% and meat/meat products with 12%. In women, fruit/berries and juice contributes with 17% of the total potassium in the diet, milk/milk products and cheese with 15%, bread and cereals with 13% and meat/meat products with 10%. An increased intake of vegetables and fruits is in line with the Norwegian food consumption recommendations (Nasjonalt råd for ernæring, 2011).

7.1 SUMMARY OF BENEFIT CHARACTERISATION

A replacement of sodium in sodium chloride with potassium in industrial food production will not result in an intake of potassium at or above 3.5 g/day for all adults. The highest potassium increase from this measure will be seen for individuals with present high sodium chloride intakes.

It has been suggested by several authors in the included literature that an increase in dietary potassium intake best might be obtained by increasing the intake of food high in potassium.

According to Norkost 3, potatoes and vegetables, fruit/berries and juice and milk/ milk products and cheese are all good sources for potassium in the Norwegian diet. There are some

variation in men and women regarding which food groups contribute with the most potassium.

8 Risk characterisation

Questions in the terms of reference on risks related to substituting sodium with potassium are addressed below as follows.

Will the increased use of potassium chloride in foods as a substitute for sodium chloride according to the above scenarios provide a total intake of potassium that may have adverse health consequences?

This question stated in the terms of reference is answered for the healthy population in 8.1.

Are there specific population groups vulnerable to an increased intake of potassium? It is desirable with a description of the vulnerable groups.

This question stated in the terms of reference is answered in 8.2.

8.1 HEALTHY POPULATION

An important statement put forward in all previous safety assessments of potassium intake, is that the potassium intake from foods with natural potassium content has not been associated with adverse effects in healthy children or adults (EFSA, 2005, EVM, 2003, IOM, 2005, WHO, 2012a). All reported incidences of potassium intoxication have been observed in healthy persons taking potassium supplements, or in vulnerable groups (see 8.2).

Based on the scientific data detailed in this report, healthy persons can most probably tolerate an increase of 3.0 g/day in potassium intake in addition to the intake from foods without negative health effects.

8.1.1 ADULTS

For adult Norwegian women, the mean potassium intake is 3380 mg/day. Since an additional potassium intake of 3.0 g/day most probably is without negative health effects, a total intake of 6380 mg potassium/day is acceptable.

The average daily intake and the 95th percentile intake for adult Norwegian women, including the scenarios, are shown in Table 8.1. All values are compared with the considered acceptable value of 6380 mg potassium/day, showing that the 95th percentile intake in the 50:50 and 70:30 scenarios is above the anticipated safe level (marked with orange colour).

Table 8.1: Potassium intake (all values mg/day) among women compared with the anticipated safe intake in the 30:70, 50:50 and 70:30 scenarios.

Safe level is assumed to be 3380 (mean) + 3000 = 6380				
	Norkost3	30:70 scenario	50:50 scenario	70:30 scenario
Mean intake	3380	4050	4500	4940
95th percentile	5120	6040	6700	7300

In orange: Intake above the anticipated safe level (6380 mg potassium/day).

In Norkost 3, 1% of the women have a potassium intake above the anticipated safe level (6380 mg potassium/day) (Table 8.2). Women with a potassium intake above the anticipated level is 3% for the 30:70 scenario, 7% for the 50:50 scenario, and 15% for the 70:30 scenario (Table 8.2).

Table 8.2: Percentage of women (n=925) with intakes of potassium above the anticipated safe level (6380 mg/day) in the 30:70, 50:50 and 70:30 scenarios.

	Norkost 3	30:70 scenario	50:50 scenario	70:30 scenario
Women with potassium intakes above 6380 mg/day	1	3	7	15

For adult Norwegian men, the mean potassium intake is 4250 mg/day. Since an additional potassium intake of 3.0 g/day most probably is without negative health effects, a total intake of 7250 mg potassium/day is acceptable.

The average daily intake and the 95th percentile intake for adult Norwegian men, including the scenarios, are shown in Table 8.3. All values are compared with the considered acceptable value of 7250 mg potassium/day, showing that the 95th percentile intake in all scenarios is above the level considered acceptable (marked in orange colour).

Table 8.3: Potassium intake (all values mg/day) among men compared with the anticipated safe intake in the 30:70, 50:50 and 70:30 scenarios.

Safe level is assumed to be 4250 (mean) + 3000 = 7250				
	Norkost3	30:70 scenario	50:50 scenario	70:30 scenario
Mean intake	4250	5190	5820	6450
95 percentile	6560	7710	8670	9780

In orange: Intake above the anticipated safe level (7250 mg potassium/day).

In Norkost 3, 2% of the men have a potassium intake above the anticipated safe level (7250 mg potassium/day) (Table 8.4). Men with a potassium intake above the anticipated level is 9% for the 30:70 scenario, 19% for the 50:50 scenario, and 30% for the 70:30 scenario (Table 8.4).

Table 8.4: Percentage of men (n=862) with intakes of potassium above the anticipated safe level (7250 mg/day) in the 30:70, 50:50 and 70:30 scenarios.

	Norkost 3	30:70 scenario	50:50 scenario	70:30 scenario
Men with potassium intakes above 7250 mg/day	2	9	19	30

8.1.2 CHILDREN

For the risk characterisation for children (2, 4, 9 and 13 years), the 3.0 g potassium that may be ingested per day by adults in addition to normal intake from food without negative health effects is adjusted for the daily energy intake (Table 8.5) as suggested in the WHO guideline (WHO, 2012a).

Table 8.5: Additional potassium intake without negative health effects. All values as mg/day.

	Adults	13-year olds	9-year olds	4-year olds	2-year olds
Additional potassium	3000	2750	2570	1960	1790

For **2-year old children** the mean potassium intake is 2270 mg/day. Since an additional potassium intake of 1790 mg/day most probably is without negative health effects, a total intake of 4060 mg potassium/day is considered acceptable.

The average daily intake and the 95th percentile intake for 2-year old children, including the scenarios, are shown in Table 8.6. All values are compared with the considered acceptable value of 4060 mg potassium/day, showing that the 95th percentile intake in all scenarios is above the anticipated safe level (marked in orange colour).

Table 8.6: Potassium intake (all values mg/day) among 2-years old compared with the anticipated safe intake in the 30:70, 50:50 and 70:30 scenarios.

Safe level assumed is to be 2270 (mean) + 1790 = 4060				
	Småbarnskost 2007	30:70 scenario	50:50 scenario	70:30 scenario
Mean intake	2270	2680	2950	3230
95 percentile	3560	4130	4520	4870

In orange: Intake above the anticipated safe level (4060 mg potassium/day).

For **4-year old children** the mean potassium intake is 2130 mg/day. Since an additional potassium intake of 1960 mg/day most probably is without negative health effects, a total intake of 4090 mg potassium/day is acceptable.

The average daily intake and the 95th percentile intake for 4-year old children, including the scenarios, are shown in Table 8.7. All values are compared with the considered acceptable value of 4090 mg potassium/day, showing that the 95th percentile intake in the 50:50 and 70:30 scenarios is above the anticipated safe level (marked in orange colour).

Table 8.7: Potassium intake (all values mg/day) among 4-year olds compared with the anticipated safe intake in the 30:70, 50:50 and 70:30 scenarios.

Safe level is assumed to be 2130 (mean) + 1960 = 4090				
	Ungkost 2000	30:70 scenario	50:50 scenario	70:30 scenario
Mean intake	2130	2580	2870	3170
95 percentile	3110	3700	4120	4570

In orange: Intake above the anticipated safe level (4090 mg potassium/day).

For **9-year old children** the mean potassium intake is 2630 mg/day. Since an additional potassium intake of 2570 mg/day most probably is without negative health effects, a total intake of 5200 mg potassium/day is acceptable.

The average daily intake and the 95th percentile intake for 9-year old children, including the scenarios, are shown in Table 8.8. All values are compared with the considered acceptable value of 5200 mg potassium/day, showing that the 95th percentile intake in the 50:50 and 70:30 scenarios is above the anticipated safe level (marked in orange colour).

Table 8.8: Potassium intake (all values mg/day) among 9-year olds compared with the anticipated safe intake in the 30:70, 50:50 and 70:30 scenarios.

Safe level is assumed to be 2630 (mean) + 2570 = 5200				
	Ungkost 2000	30:70 scenario	50:50 scenario	70:30 scenario
Mean intake	2630	3230	3620	4020
95 percentile	4020	4830	5300	5870

In orange: Intake above the anticipated safe level (5200 mg potassium/day).

For **13-year old children** the mean potassium intake is 2730 mg/day. Since an additional potassium intake of 2750 mg/day most probably is without negative health effects, a total intake of 5480 mg potassium/day is acceptable.

The average daily intake and the 95th percentile intake for 13-year old children, including the scenarios, are shown in Table 8.9. All values are compared with the considered acceptable value of 5480 mg potassium/day, showing that the 95th percentile intake in the 50:50 and 70:30 scenarios is above the anticipated safe level (marked in yellow).

Table 8.9: Potassium intake (all values mg/day) among 13-year olds compared with the anticipated safe intake in the 30:70, 50:50 and 70:30 scenarios.

Safe level is assumed to be 2730 (mean) + 2750 = 5480				
	Ungkost 2000	30:70 scenario	50:50 scenario	70:30 scenario
Mean intake	2730	3350	3770	4180
95 percentile	4740	5690	6300	7040

In orange: Intake above the anticipated safe level (5480 mg potassium/day).

8.2 VULNERABLE GROUPS

Groups in the population that are particularly sensitive to increased potassium intake and might experience adverse effects include patients with renal failure, heart failures, diabetes mellitus, infants below one year of age, people aged 85 years and older, and persons using medications able to interfere with the potassium balance. The sensitivity to dietary potassium varies for each group. The number of persons affected is summarised in Chapter 3.3.2.

Patients with serious renal failure, whether undergoing haemodialysis or kidney replacement, are particularly sensitive to dietary potassium and are advised to reduce their potassium intake to <1.5 g/day (Noori *et al.*, 2010). The impact of increased dietary potassium for these patients can be severe side-effects including fatalities. However, this group is rather limited in size. For the other vulnerable groups, such as patients with mild or moderate renal impairment, diabetes type 1 and 2, or coronary heart disease, data on tolerable upper level of potassium were not available in the literature. However, because these dietary conditions affect potassium regulation, elevated dietary potassium intake may constitute an increased risk of negative health effects also for these groups.

For persons using medications that may provoke hyperkalemia, any increase of potassium levels may increase the risk of negative health effects. The fact that such medications are in frequent use is a matter of concern in the case of increased dietary intake of potassium. Additionally, population groups of infants below one year of age, the elderly and persons undergoing strenuous activities are at risk for negative health effects from increased dietary potassium.

There are considerable overlaps between the various vulnerable groups. Examples are elderly persons also having diseases or taking drugs making them more vulnerable to hyperkalemia than just the age-dependent impairment of renal function, and many patient groups taking more than one type of drug increasing hyperkalemia. However, due to lack of such data, quantitative estimates on this issue cannot be provided in this risk assessment.

8.3 SUMMARY OF RISK CHARACTERISATION

Potassium has a crucial role in the body regulating several vital functions, and if the blood concentration is changed outside the tightly regulated, narrow range, serious side-effects can appear. Normally, the body is able to handle rapid changes in potassium intake, but patients and even healthy persons have been reported to develop hyperkalemia from high potassium intake, for instance from supplement

For adult healthy persons, it has been assumed that a potassium intake of 3.0 g/day, in addition to what is ingested from food, is acceptable from a safety point of view. A corresponding safe level for children has been calculated by adjusting for energy intake. For adult women and men, as well as children aged 2, 4, 9 and 13 years, the total potassium intakes have been calculated for three scenarios of substituting sodium with potassium (30:70, 50:50, 70:30). For persons with a mean potassium intake, none of the three scenarios gave potassium intakes above the anticipated safe level. However, for persons with an intake at the 95th percentile, all groups had total potassium intake above the anticipated safe level in case of substitution scenarios 50:50 and 70:30. For adult men, 2-year olds and 13-year olds, all three substitution scenarios gave total potassium intakes above the anticipated safe level for the 95th percentile intake.

The data which are the basis for the estimated safe potassium intake in addition to that from food is weak. In addition, the finding that persons at the 95th percentile potassium intake

exceed this intake in all three or in two out of three substitution scenarios, calls for caution also for healthy persons in case of substituting sodium with potassium.

Several groups in the population have been identified as vulnerable to increased potassium intake. These groups include patients suffering particular diseases, patients taking certain medications and otherwise healthy infants and elderly, and persons undergoing strenuous physical activities.

Patients with serious renal failure, whether undergoing haemodialysis or kidney replacement, are advised to reduce their potassium intake to <1.5 g/day. For the other vulnerable groups, the level of potassium that may be harmful is not known.

9 Benefit and risk characterisation

Based on the scientific evidence detailed in this report, a daily total intake of at least 3.5 g potassium among adults will most probably lead to a decrease in the risk of stroke. Such a daily potassium intake will most likely also have a beneficial effect on blood pressure, at least in individuals with hypertension. In Norkost 3, the mean intake of potassium in women (3380 mg/day) is below, while the mean intake in men (4250 mg/day) is above 3.5 g/day.

The benefit assessment concludes that a replacement of sodium in sodium chloride with potassium in industrial food production will not result in an intake of potassium at or above 3.5 g/day for all adults. The best effect, or highest potassium increase from replacement of sodium in sodium chloride with potassium, will be seen for individuals with high sodium chloride intakes.

In healthy persons, intake of potassium from food does not result in hyperkalemia. Based on the scientific evidence detailed in this report, an increase of 3.0 g/day in potassium intake in addition to the intake from foods would probably not result in adverse health effects for healthy adults. The mean (95th percentile) intake of potassium from food among women in Norway was 3380 (5120) mg/day (see Chapter 4). For men, the intake of potassium from food was 4250 (6560) mg/day.

As opposed to intake of potassium from food, gastrointestinal erosion and ulcers have been reported in healthy persons after oral potassium chloride supplementation, especially with wax-matrix formulations.

The vulnerable groups include patients with renal failure (from mild to severe), heart failure, diabetes mellitus and persons on a long range of medications able to affect the potassium balance, infants below one year of age, people aged 85 years and older, and persons undergoing very strenuous activities.

For persons with impaired kidney function, hyperkalemia may occur even with a modest increase in potassium intake (Traeger and Wen, 2009). Thus, excessive dietary potassium intake may be an important contributor to hyperkalemia in patients with impaired renal function (Desai, 2009).

To reduce the prevalence of hyperkalemia in the vulnerable groups, there is a need for individual assessment of every patient and their dose of medication, advice related to diet, interaction with other medications and careful control of the plasma potassium level (Bugge, 2010). Increasing the potassium content in several industrial produced foods, not originally rich potassium sources in the diet, may complicate medical dietary guidance.

A comparison of potassium intakes in healthy adults with the suggested levels for benefit and risk

Because available data from studies in children and adolescence is scarce, only adults could be compared for both the benefit and risk of increased potassium according to the given scenarios. This is done by presenting intake values for potassium in Norwegian women and men, and the comparison of these values with the level of at least 3.5 g/day used in the benefit assessment, and the anticipated safe level of 3.0 g/day in addition to mean potassium intake from food used in the risk assessment, in the same Tables and Figures (9.1 and 9.2).

Table 9.1 Potassium intake in women (n=925) in the 30:70, 50:50 and 70:30 scenarios.

	5th percentile	25th percentile	Mean	95th percentile
Norkost3	1900	2700	3380	5120
30:70 scenario	2360	3290	4050	6040
50:50 scenario	2660	3660	4500	6700
70:30 scenario	2910	4000	4940	7300

In yellow: Intake below 3.5 g/day.

In orange: intake above 6380 mg/day.

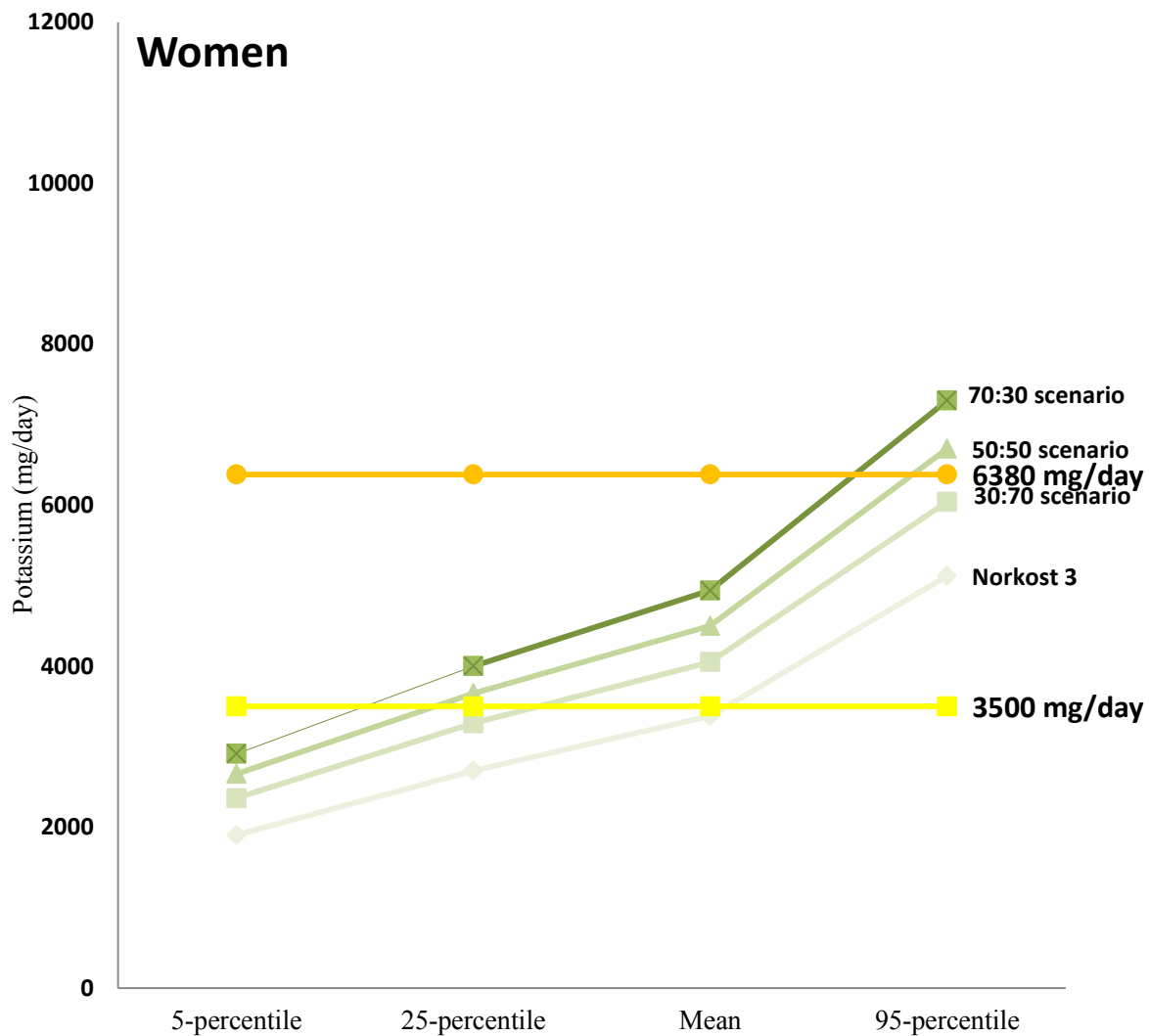


Figure 9.1 Potassium intake in women (n=925) in the 30:70, 50:50 and 70:30 scenarios.

For women with the present lowest potassium (5th percentiles) and sodium intakes, the scenarios (30:70, 50:50 or 70:30) will not result in an intake of potassium at or above 3.5 g/day (illustrated in Figure 9.1). Women with mean potassium intakes will achieve an intake at or above 3.5 g/day in all the three scenarios. The women having 25th percentile intake will reach an intake at 3.5 g/day and have a benefit from the 50:50 and 70:30 scenarios. On the other hand, already with the 50:50 scenario, women with 95th percentile intake will exceed the anticipated safe level and potentially be at risk for hyperkalemia. Only the women having a mean potassium intake from food will be below the anticipated safe level for any of the replacement scenarios (Table 9.1, Figure 9.1).

Table 9.2 Potassium intake in men (n=862) in the 30:70, 50:50 and 70:30 scenarios.

	5th percentile	25th percentile	Mean	95th percentile
Norkost3	2410	3310	4250	6560
30:70 scenario	2970	4120	5190	7710
50:50 scenario	3400	4660	5820	8670
70:30 scenario	3750	5200	6450	9780

In yellow: Intake below 3.5 g/day.

In orange: intake above 7250 mg/day.

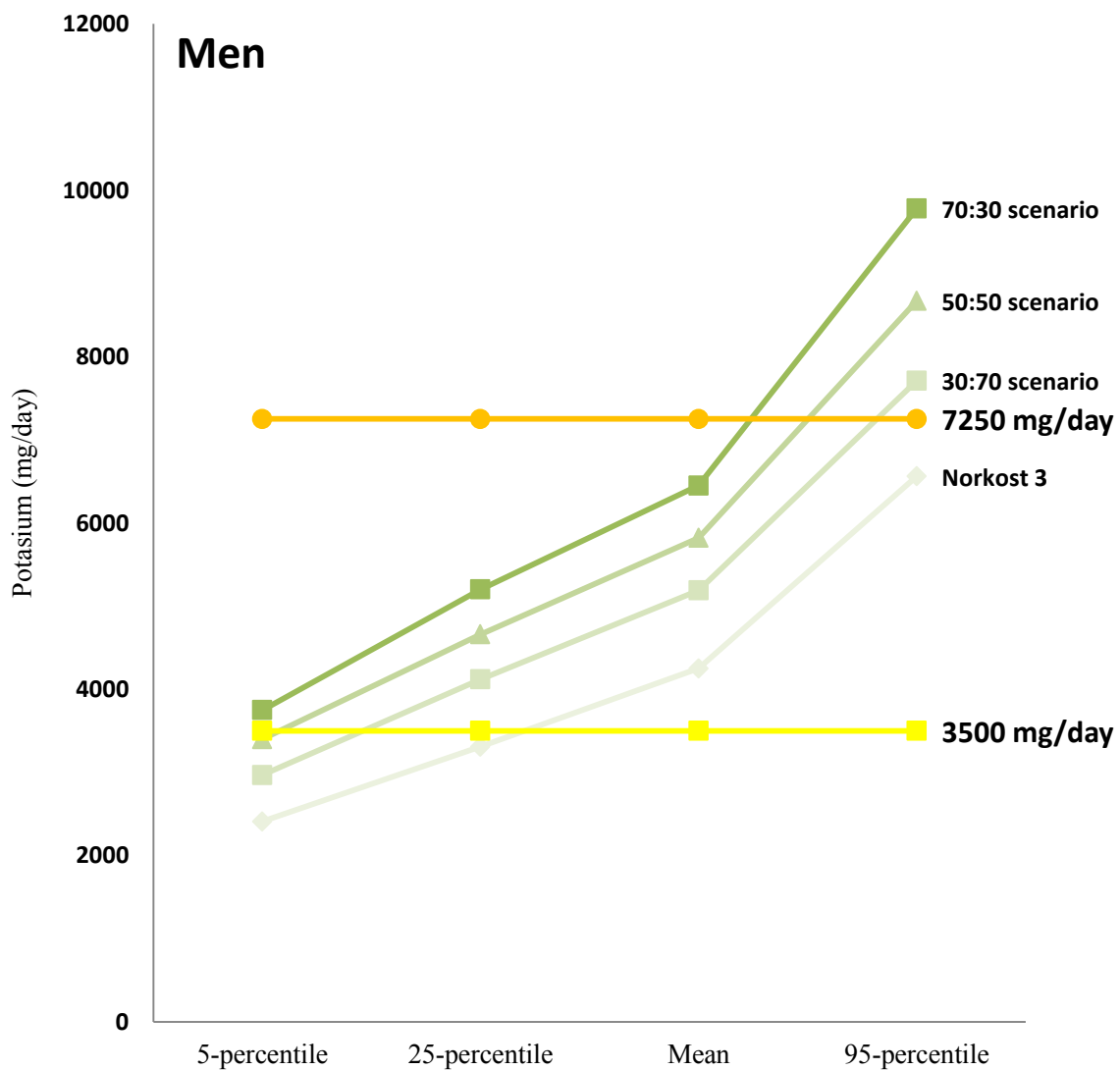


Figure 9.2 Potassium intake in men (n=862) in the 30:70, 50:50 and 70:30 scenarios.

For men with the present lowest potassium (5th percentiles) and sodium intakes, the scenarios (30:70 or 50:50) will not result in an intake of potassium at or above 3.5 g/day (illustrated in Figure 9.2). Men with mean potassium intakes will achieve an intake at or above 3.5 g/day in

all the three scenarios. The men having 25th percentile intake will also reach an intake at 3.5 g/day in all the three scenarios.

For the 30:70, 50:50 or 70:30 scenarios, the mean intakes does not exceed 7250 mg/day (Table 9.2, Figure 9.2). For all scenarios, men with 95th percentile intake will exceed the anticipated safe level and be at potential risk for hyperkalemia.

Comparison of percentage of persons getting either benefit or risk of increased potassium

Fifty-nine % of the women have a daily intake of potassium below 3.5 g/day based on Norkost 3. In the 30:70 scenario, 33% of the women have a potassium intake below 3.5 g/day, in the 50:50 scenario, the percentage is 21, and in the 70:30 scenario 13% of the women still have an intake below 3.5 g/day.

Thirty percent of the men have a daily intake of potassium below 3.5 g/day based on Norkost 3. In the 30:70 scenario, 10% of the men have a potassium intake below 3.5 g/day, in the 50:50 scenario, the percentage is 6, and in the 70:30 scenario 4% of the men have an intake below 3.5 g/day.

One % of the women have a daily intake of potassium above the anticipated safe level based on Norkost 3. In the 30:70 scenario, 3% of the women have a potassium intake above the anticipated safe level, in the 50:50 scenario, the percentage is 7, and in the 70:30 scenario 15% of the women have an intake above the anticipated safe level.

Two % of the men have a daily intake of potassium above the anticipated safe level based on Norkost 3. In the 30:70 scenario, 9% of the men have a potassium intake above the anticipated safe level, in the 50:50 scenario, the percentage is 19, and in the 70:30 scenario 30% of the men have an intake above the anticipated safe level.

In Norway, approximately 13 000 individuals suffers from acute stroke each year, about 50% is under 76 years of age (Folkehelseinstituttet, 2012) (see 2.5.1). In addition, an unknown number of persons suffering from high blood pressure will probably benefit from the increased potassium (see 2.5.2).

In Norway, 202 persons are waiting for a kidney graft (Leivestad, 2012), about 500 000 persons have diagnosed or undiagnosed chronic kidney disease (Hartmann *et al.*, 2006), the prevalence of diagnosed diabetes (type I and II) is estimated to be 90-120 000 persons and it is estimated that the number of undiagnosed diabetes are about the same numbers (Stene *et al.*, 2004), the estimated frequency of use of drugs affecting the potassium balance is presented in Table 3.1, the number of infants (below one year) were 60 530 in 2013, and the number of persons aged 85 years and older were 113 700 in 2013.

A full benefit and risk assessment including an evaluation of severity of benefits versus risks could not be conducted. Furthermore, an exact comparison of the percentage of persons in the Norwegian population who will either benefit or be at risk as a result of an increase of potassium in industrial produced foods was not possible since we did not have data on the acceptable level of potassium for most of the vulnerable groups, and it could not be predicted how an increase in potassium will affect stroke incidence or reduction in high blood pressure.

10 Answers to the terms of reference

Since the answers to the terms of reference are spread out in this document, an overview over where they can be found is included here:

The Panel on Nutrition, Dietetic products, Novel Food and Allergy has answered the following questions:

- What is the estimated dietary intake of potassium in the population? This question is answered in Chapter 4.
 - o What is the dietary intake of potassium if the following scenarios for replacement of sodium chloride (NaCl) with potassium chloride (KCl), 30:70, 50:50, 70:30, are set up? This question is answered in Chapter 4.
- What positive health outcomes may be the result of an increased use of potassium chloride in industrial food production? This question is answered in Chapter 2.
 - o How high must the potassium intake be to achieve positive health effects? This question is answered in Chapters 2 and 7.
- Has there been established a safe upper limit (UL) for potassium by EFSA or an equivalent body? This question is answered in Chapter 3.

The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics has answered the following questions:

- Will the increased use of potassium chloride in foods as a substitute for sodium chloride according to the above scenarios provide a total intake of potassium that may have adverse health consequences? This question is answered in Part I, Chapter 8.
- Are there specific population groups vulnerable to an increased intake of potassium?
 - o It is desirable with a description of the vulnerable groups. This question is answered in Chapters 3 and 8.
- It is preferable to have a combined conclusion of the benefit and risk assessment for human health of replacement of sodium chloride by potassium chloride in industrial food production. This is answered in Chapter 9.

11 Conclusions

- In VKM's opinion, there are no new studies since 2005 that justify establishment of an upper safe level of potassium intake.
- A dose-response relationship could not be established, but an intake of at least 3.5 g/day of potassium in adults will most likely lead to a decrease in the risk of stroke.
- An intake of at least 3.5 g/day of potassium will most likely also have a beneficial effect on blood pressure in individuals with hypertension.
- Fifty-nine percent of the women and 30 percent of the men in Norway have an intake of potassium below 3.5 g/day based on Norkost 3.

- In the 30:70, 50:50 and 70:30 scenarios (where 30, 50 or 70% of sodium in sodium chloride is replaced by potassium), the percentage of women with potassium intakes below 3.5 g/day will decrease from 59% to 33, 21 and 13%, respectively. For men, the decreases will be from 30% to 10, 6 and 4%, respectively.
- In the absence of a tolerable upper level, VKM regards an intake of 3.0 g/day of potassium (energy adjusted for children) in addition to the mean intake of potassium from food as an anticipated safe level for most of the healthy population. However, some adverse effects such as gastrointestinal effects and unexpected acute effects, even fatal ones, cannot be entirely ruled out at these intake levels.
- In the 30:70, 50:50 and 70:30 scenarios, adult women with mean potassium intakes have no risk of adverse effects when compared with the anticipated safe level, whereas adult women with 95th percentile intakes will exceed this level in the 50:50 and 70:30 scenarios. Adult men with mean potassium intakes have no risk of adverse effects when compared with the anticipated safe level in any of the scenarios, whereas adult men with 95th percentile intake will exceed this level in all the scenarios.
- In the 30:70, 50:50 and 70:30 scenarios, healthy children aged 2, 4, 9 or 13 years with a mean intake of potassium, will have no risk of adverse effects when compared with the anticipated safe level. However, 4- and 9- year old children with 95th percentile intake will exceed this level in the 50:50 and 70:30 scenarios. Two- and 13-year-old children with 95th percentile intake will exceed this level in all the scenarios.
- One percent of the women and 2 percent of the men in Norway have an intake of potassium above the anticipated safe level based on Norkost 3.
- In the 30:70, 50:50 and 70:30 scenarios, the percentage of women with potassium intakes above the anticipated safe level will increase from 1% to 3, 7 and 15%, respectively. For men, the percentages will increase from 2% to 9, 19 and 30%, respectively.
- There are many groups vulnerable to hyperkalemia, which in decreasing order of severity is haemodialysis or kidney replacement patients, other patients with more moderate renal failure, coronary heart disease or diabetes, patients using one of the numerous drugs increasing the risk for hyperkalemia, and in general infants below one year of age, elderly persons and persons undergoing strenuous physical activity.
- For persons with impaired kidney function, hyperkalemia may occur even with a modest increase in potassium intake and they are advised to keep their potassium intake below 1.5 g/day. Thus, excessive dietary potassium intake may be an important contributor to hyperkalemia in patients with impaired renal function.
- To reduce the prevalence of hyperkalemia in the vulnerable groups, there is a need for individual assessment of every patient and their dose of medication, advice related to diet, interaction with other medications and careful control of the plasma potassium level.
- A full benefit and risk assessment including an evaluation of severity of risks versus benefits could not be conducted. Furthermore, an exact comparison of the percentage of

persons in the Norwegian population who will either benefit or be at risk as a result of an increase of potassium in industrial produced foods was not possible since we did not have data on the acceptable level of potassium for most of the vulnerable groups, and it could not be predicted how an increase in potassium will affect stroke incidence or reduction in high blood pressure.

However, VKM concludes that it is reasonable to anticipate that the percentage of persons likely to face an increased risk is far greater than the percentage of persons likely to benefit from this measure.

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PART II Microbiological risk assessment of replacement of sodium chloride by potassium chloride in industrial food production

Summary part II

The Panel for Biological Hazards have assessed possible effects of replacement of NaCl with KCl on food safety as indicated by effects on food-borne pathogens.

The preserving effects of NaCl are due to a combination of several factors such as effects on water activity and direct toxic effects on cell metabolism. It may also modify thermal resistance of the pathogens depending on the species and stage of growth. However, knowledge regarding mechanisms of action is limited.

For efficient preservation a concentration of NaCl in the range 5 – 15% is needed. Most foods contain less than 1.5% NaCl. Hence, NaCl plays a preservation role only in a few food products.

A central aspect regarding NaCl's role for food safety is its effect on the water activity. This effect is practically the same for equal molar concentrations of NaCl and KCl.

The committee concludes: if NaCl is replaced, partially or fully, by KCl, at the same molarity, then the microbiological risk would remain the same irrespective of food group.

Sammendrag del II

Faggruppen for hygiene og smittestoffer har vurdert mulig effekt av erstatning av NaCl med KCl på mattrygghet, herunder effekt på matbårne patogener.

Konserveringseffekten av NaCl er resultat av en kombinasjon av flere faktorer, som for eksempel effekt på vannaktivitet og direkte toksiske effekter på celled metabolismen. Det kan også modifisere varmeresistens av patogener avhengig av species og fasen av veksten. Kunnskap om virkningsmekanismene er imidlertid begrenset.

For effektiv konservering er en konsentrasjon av NaCl i området 5 – 15 % nødvendig. De fleste matvarer inneholder mindre enn 1,5 % NaCl. Derfor har NaCl en konserveringseffekt i kun noen svært få matvarer.

Et sentralt aspekt for NaCl's rolle for matvaresikkerhet er effekten på vannaktivitet. Denne effekten er praktisk talt den samme for like molare konsentrasjoner av NaCl og KCl.

Faggruppen konkluderer: hvis NaCl erstattes, delvis eller helt, av KCl, ved samme molaritet, vil den mikrobiologiske risiko være den samme uansett matvaregruppe.

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Introduction

In the following assessment the Panel for Biological Hazards has evaluated possible effects on food microbiological safety by replacement of NaCl by KCl. This part of the assessment mainly concerns possible effects on survival, growth or toxin production of food-borne pathogens.

A list of abbreviation used in the text is presented as Appendix 1.

Literature search

Primary literature search

The primary literature search was undertaken using the Advanced Search Builder provided by PubMed (www.ncbi.nlm.nih.gov/pubmed). The following search terms were used:

- salt OR sodium OR NaCl
- chloride OR Cl OR Cl-I
- replace OR replacement
- reduce OR reduction
- inhibit OR inhibitory
- potassium
- food safety OR foods
- Listeria OR Staphylococcus OR Clostridium OR Toxoplasma OR Vibrio OR Salmonella OR E. coli OR Escherichia coli OR Shigella OR Yersinia OR Bacillus OR Anisakis OR Histamine

Spoilage bacteria were considered not relevant for the present assessment.

All terms were sought in the search field Title/Abstract.

Search strings were constructed by combining selected search terms using the Boolean variable AND. The search strings employed are shown below. There was no restriction on language or publication year. Some searches were limited to reviews as shown in search strings. The primary literature search resulted in 495 citations.

Relevance screening

Titles and abstracts of all identified citations were screened for relevance by the members of the project group, independently. Citations were excluded if they did not relate to the terms of reference. The reference lists in selected citations were scrutinized to identify additional articles or reports, overlooked by the PubMed searches. All (53) relevant articles were included in the reference list.

Search strings

Search: (salt[Title/Abstract] OR sodium[Title/Abstract] OR NaCl[Title/Abstract]) AND (replace[Title/Abstract] OR replacement[Title/Abstract]) AND potassium[Title/Abstract] AND ("food safety"[Title/Abstract])

Search: (salt[Title/Abstract] OR sodium[Title/Abstract] OR NaCl[Title/Abstract]) AND (replace[Title/Abstract] OR replacement[Title/Abstract]) AND (Listeria[Title/Abstract] OR Staphylococcus[Title/Abstract] OR

Clostridium[Title/Abstract] OR Toxoplasma[Title/Abstract] OR Vibrio[Title/Abstract] OR Salmonella[Title/Abstract] OR "E. coli"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR Yersinia[Title/Abstract] OR Bacillus[Title/Abstract] OR Anisakis[Title/Abstract] OR Histamine[Title/Abstract] OR Shigella[Title/Abstract])

Search: (salt[Title/Abstract] OR sodium[Title/Abstract] OR NaCl[Title/Abstract]) AND (reduce[Title/Abstract] OR reduction[Title/Abstract]) AND (Listeria[Title/Abstract] OR Staphylococcus[Title/Abstract] OR Clostridium[Title/Abstract] OR Toxoplasma[Title/Abstract] OR Vibrio[Title/Abstract] OR Salmonella[Title/Abstract] OR "E. coli"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR Yersinia[Title/Abstract] OR Bacillus[Title/Abstract] OR Anisakis[Title/Abstract] OR Histamine[Title/Abstract] OR Shigella[Title/Abstract]) Filters: Review

Search: (salt[Title/Abstract] OR sodium[Title/Abstract] OR NaCl[Title/Abstract]) AND (replace[Title/Abstract] OR replacement[Title/Abstract]) AND (Listeria[Title/Abstract] OR Staphylococcus[Title/Abstract] OR Clostridium[Title/Abstract] OR Toxoplasma[Title/Abstract] OR Vibrio[Title/Abstract] OR Salmonella[Title/Abstract] OR "E. coli"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR Yersinia[Title/Abstract] OR Bacillus[Title/Abstract] OR Anisakis[Title/Abstract] OR Histamine[Title/Abstract] OR Shigella[Title/Abstract]) Filters: Review

Search: (salt[Title/Abstract] OR sodium[Title/Abstract] OR NaCl[Title/Abstract]) AND (replace[Title/Abstract] OR replacement[Title/Abstract]) AND potassium[Title/Abstract] AND (Listeria[Title/Abstract] OR Staphylococcus[Title/Abstract] OR Clostridium[Title/Abstract] OR Toxoplasma[Title/Abstract] OR Vibrio[Title/Abstract] OR Salmonella[Title/Abstract] OR "E. coli"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR Yersinia[Title/Abstract] OR Bacillus[Title/Abstract] OR Anisakis[Title/Abstract] OR Histamine[Title/Abstract] OR Shigella[Title/Abstract])

Search: (salt[Title/Abstract] OR sodium[Title/Abstract] OR NaCl[Title/Abstract]) AND (reduce[Title/Abstract] OR reduction[Title/Abstract]) AND potassium[Title/Abstract] AND (Listeria[Title/Abstract] OR Staphylococcus[Title/Abstract] OR Clostridium[Title/Abstract] OR Toxoplasma[Title/Abstract] OR Vibrio[Title/Abstract] OR Salmonella[Title/Abstract] OR "E. coli"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR Yersinia[Title/Abstract] OR Bacillus[Title/Abstract] OR Anisakis[Title/Abstract] OR Histamine[Title/Abstract] OR Shigella[Title/Abstract])

Search: (chloride[Title/Abstract] OR Cl[Title/Abstract] OR Cl-I[Title/Abstract]) AND (inhibit[Title/Abstract] OR inhibitory[Title/Abstract]) AND (Listeria[Title/Abstract] OR Staphylococcus[Title/Abstract] OR Clostridium[Title/Abstract] OR Toxoplasma[Title/Abstract] OR Vibrio[Title/Abstract] OR Salmonella[Title/Abstract] OR "E. coli"[Title/Abstract] OR "Escherichia coli"[Title/Abstract] OR Yersinia[Title/Abstract] OR Bacillus[Title/Abstract] OR Anisakis[Title/Abstract] OR Histamine[Title/Abstract] OR Shigella[Title/Abstract])

Search: (chloride[Title/Abstract] OR Cl[Title/Abstract] OR Cl-I[Title/Abstract]) AND (inhibit[Title/Abstract] OR inhibitory[Title/Abstract]) AND (food[Title/Abstract] OR foods[Title/Abstract])

Abbreviations and definitions

Commercially sterile - "Commercial sterility" of thermally processed food means the condition achieved:

1. By the application of heat which renders the food free of:
 - a. Microorganisms capable of reproducing in the food under normal non-refrigerated conditions of storage and distribution; and
 - b. Viable microorganisms (including spores) of public health significance
2. By the control of water activity and the application of heat, which renders the food free of microorganisms capable of reproducing in the food under normal non-refrigerated conditions of storage and distribution.

Critical Control Point (CCP) — a point in the process of manufacturing a food (raw material, location, practice, procedure) at which one or more factors can be controlled to minimize or prevent hazard.

D-value is used to define heat-resistance. It indicates the length of time required at a given temperature to reduce the microbial population to 10% of its initial count (one log reduction), also called Thermal death time.

Intermediate moisture food (IMF) - semi-moist food with about 25% (15–50%) moisture but with some of the water bound (and so unavailable to micro-organisms) by the addition of glycerol, sorbitol, salt, or organic acids, so preventing the growth of micro-organisms.

Low Acid Food is food (other than alcoholic beverages) with a pH between 4.6 and 7.0. Does not refer to foods with a low pH, e.g. most vegetables, meat, milk, some tropical fruits, fish, eggs.

Oz – ounce, 28.4 g

Processed foods are foods that have been treated or prepared by a special method, including methods in order to preserve them.

Ready-to-eat (RTE) foods are foods intended to be consumed as they are. These foods do not require additional cooking and are usually stored in refrigeration or at room temperature.

Salt% is the weight percent of NaCl in a solute. It is defined as the weight of solute (NaCl) divided by the weight of solution (NaCl + solution) and multiplied by 100%.

Shelf-life is the length of time between packaging and use that a food product remains of acceptable quality to the user.

Shelf-Stable foods are considered non-perishable at room temperature for an extended period of time (generally weeks or months).

TR is the abbreviation used for thermal resistance

Water Activity (a_w) represents the ratio of the water vapor pressure of the food to the water vapor pressure of pure water under the same conditions and it is expressed as a fraction. If we multiply this ratio by 100, we obtain the equilibrium relative humidity (ERH) that the foodstuff would produce if enclosed with air in a sealed container at constant temperature.

Water Phase Salt (WPS) means the amount of salt compared with the amount of moisture (water) in the product and is calculated as follows:

$$\% \text{ Water Phase Salt} = (\% \text{ salt} / (\% \text{ Salt} + \% \text{ Moisture})) \times 100$$

(where % moisture = 100 - % total solids)

z-value is the temperature increase required to reduce the *D*-value by a factor of 10.

Functions of NaCl in control of microorganisms in foods

NaCl has been used for food safety benefits for several thousand years based on its

- ability to reduce a_w in solutes and thereby lower the water availability to microorganisms
- osmotic activity which can be used to dry meat and fish and thereby reduce a_w in such products
- ability to modify and inhibit bacterial growth through direct effects on their metabolism
- modifying effects of food processing, such as heat treatment and pressure, on food microbiota and virus

It can be stated that for foods in which NaCl does not play a part in preservation there will be no microbiological food hazard implications from NaCl reduction or substitution for most food groups. Foods added NaCl includes commercially-sterile, canned products, products with a pH under 3.8, frozen products intended for immediate consumption after thawing and products with a low a_w unrelated to the use of NaCl (Stringer&Pin 2005).

Relevant viruses and parasites do not grow in food (Koopmans&Duizer 2004) and replacement of NaCl would therefore not influence food safety in terms of their growth. The effect of NaCl on virus inactivation by high pressure processing has been investigated, due to the common practice of high pressure treatment of shellfish and the presence of virus in harvesting waters. NaCl (6%) reduced the effectivity of high pressure inactivation for both hepatitis A virus and feline calicivirus, a norovirus surrogate (Kingsley&Chen 2008, Kingsley&Chen 2009). When feline calicivirus was exposed to both NaCl and sucrose, an additively increased the barotolerance (Kingsley&Chen 2008).

Water activity, temperature and pH

Most bacteria require a_w above 0.91 for growth and development but some can grow at a_w down to 0.85 (Hennekinne et al. 2012). Fungi in general can tolerate lower a_w and many grow at activities down to about 0.7. Besides the effect of NaCl on a_w direct toxicity of the Cl^- ion, caused by removal of oxygen from the medium, increased sensitization of the bacteria towards CO_2 , as well as effects on bacterial proteins including enzymes (Rockwell&Ebertz 1924). The exact mechanism of Cl^- ion toxicity for bacteria is, however, not fully known (Taormina 2010).

Table 1 gives an overview of water activities of NaCl solutions as a function of molarity at 25 °C, whereas Table 2 and Table 3 shows tolerance limit for a_w of selected bacteria. Table 3 also contains examples of on foods with the corresponding a_w .

Table 1. Water activities of NaCl and KCl solutions as a function of molarity at 25 C. Adapted from Robinson (1945)

Molarity	NaCl	KCl	Dif. in a_w	Molarity	NaCl	KCl	Dif. in a_w
0.1	0.9966	0.9967	-0.00002	2.8	0.9011	0.9103	-0.0092
0.2	0.9934	0.9934	-0.0001	3.0	0.8932	0.9037	-0.0105
0.3	0.9901	0.9903	-0.0002	3.2	0.8851	0.8971	-0.0120
0.4	0.9868	0.9871	-0.0003	3.4	0.8769	0.8904	-0.0135
0.5	0.9836	0.9839	-0.0004	3.6	0.8686	0.8837	-0.0151
0.6	0.9803	0.9808	-0.0005	3.8	0.8600	0.8770	-0.0170
0.7	0.9769	0.9776	-0.0007	4.0	0.8515	0.8702	-0.0187
0.8	0.9736	0.9745	-0.0009	4.2	0.8428	0.8634	-0.0206
0.9	0.9702	0.9713	-0.0011	4.4	0.8339	0.8566	-0.0227
1.0	0.9669	0.9682	-0.0013	4.6	0.8250	0.8498	-0.0248
1.2	0.9601	0.9619	-0.0018	4.8	0.8160	0.8429	-0.0269
1.4	0.9532	0.9556	-0.0024	5.0	0.8068		
1.6	0.9461	0.9492	-0.0031	5.2	0.7976		
1.8	0.9389	0.9428	-0.0039	5.4	0.7883		
2.0	0.9316	0.9364	-0.0048	5.6	0.7788		
2.2	0.9242	0.9299	-0.0057	5.8	0.7693		
2.4	0.9166	0.9234	-0.0068	6.0	0.7598		
2.6	0.9089	0.9169	-0.0080				

[†]0.1 M corresponds to 0.58% NaCl and 0.75% KCl

Table 2. Limiting conditions for the growth of bacterial pathogens (modified from Table A1 in (FDA 2011))

Bacterial pathogens	Min. a_w	Max. % Water-phase NaCl	Min pH
<i>Bacillus cereus</i>	0.92	10	4.3
<i>Campylobacter jejuni</i>	0.987	1.7	4.9
<i>Clostridium botulinum</i> , type A, and proteolytic types B and F	0.935	10	4.6
<i>Clostridium botulinum</i> , type E, and nonproteolytic types B and F	0.97	5	5.0
<i>Clostridium perfringens</i>	0.93	7	5
<i>Escherichia coli</i>	0.95	6.5	4
<i>Listeria monocytogenes</i>	0.92	10	4.4
<i>Salmonella</i> spp.	0.94	8	3.7
<i>Shigella</i> spp.	0.96	5.2	4.8
<i>Staphylococcus aureus</i> growth	0.83	20	4
<i>Staphylococcus aureus</i> toxin formation	0.85	10	4
<i>Vibrio cholerae</i>	0.97	6	5
<i>Vibrio parahaemolyticus</i>	0.94	10	4.8
<i>Vibrio vulnificus</i>	0.96	5	5
<i>Yersinia enterocolitica</i>	0.945	7	4.2

Table 3. Microorganism growth according to water activity. Adapted from Beuchat (1974)¹

a_w	Microorganisms generally inhibited by a_w at this point	Examples of food within this range of water activity
0.95	<i>Pseudomonas</i> , <i>Escherichia</i> , <i>Proteus</i> , <i>Shigella</i> , <i>Klebsiella</i> , <i>Bacillus</i> , <i>Clostridium perfringens</i> , some yeasts	Highly perishable foods (fresh and canned fruits, vegetables, meat, fish), milk, cooked sausages, breads, foods with up to 4 oz (113.4g) (w/w) sucrose or 7% NaCl
0.91	<i>Salmonella</i> , <i>Vibrio parahaemolyticus</i> , <i>C. botulinum</i> , <i>Serratia</i> , <i>Lactobacillus</i> , <i>Pediococcus</i> , some moulds, <i>Rhodotorula</i> , <i>Pichia</i>	Some cheese (Cheddar, Swiss, Provolone), cured meat, fruit juice concentrates with 55% sucrose or 12% NaCl
0.87	Many yeasts (<i>Candida</i> , <i>Torulopsis</i> , <i>Hansenula</i>), <i>Micrococcus</i>	Fermented sausage, sponge cakes, dry cheese, margarine, foods with 65% sucrose (saturated) or 15% NaCl
0.80	Most moulds (mycotoxigenic penicillia), <i>Staphylococcus aureus</i> , most <i>Saccaromyces (baillii)</i> spp., <i>Debaryomyces</i>	Most fruit juice concentrates, condensed milk, syrup, flour, high-sugar cakes, some meat jerky products
0.75	Most halophilic (salt tolerant) bacteria, mycotoxigenic aspergilli	Jam, marmalade, glace fruits, marzipan, marshmallows, some meat jerky products
0.65	Xerophilic moulds (<i>Aspergillus chevalieri</i> , <i>A. candidus</i> , <i>Wallemia sebi</i>), <i>Saccharomyces bisporus</i>	Rolled oats with 10% moisture, jelly, molasses, nuts
0.60	Osmophilic yeasts (<i>Saccaromyces rouxii</i>), few molds (<i>Aspergillus echinulatus</i> , <i>Monascus bisporus</i>)	Dried fruits with 15-20% moisture, caramel, toffee, honey
0.50	No microbial growth	Noodles with 12% moisture, spices with 10% moisture
0.40		Whole egg powder with 5% moisture
0.30		Cookies, crackers, bread crusts with 3-5% moisture
0.03		Whole milk powder with 2-3% moisture, dehydrated soups

The a_w limits shown by microorganisms depend on temperature as well as on pH of the environment. Figure 1 illustrates this relationship for some important bacteria.

¹ <http://www.aqualab.com/education/microorganism-growth-according-to-water-activity/>

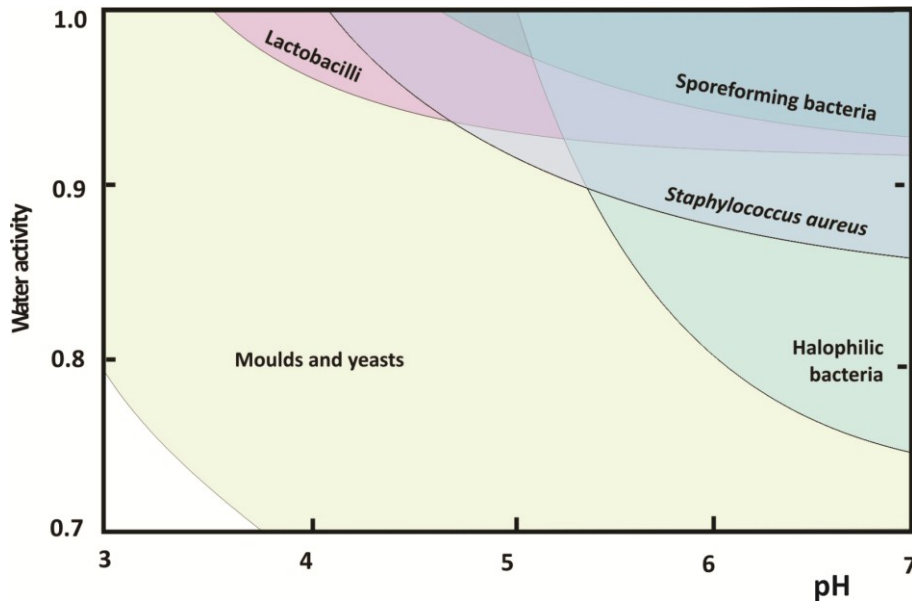


Figure 1. A schematic diagram showing the combined influence of water activity (a_w) and pH on growth of some bacteria (Pitt&Hocking 2009)

As clearly shown by the information presented above, and in line with statements in reports by FAO (2002) and OMAFRA (2013) very few foods have a NaCl concentration that will markedly prevent growth of bacteria. The exceptions are some salted and dried meat and fish products containing more than 8-10% NaCl in the water phase are available in many countries (Henney et al. 2010). Also some products stored in high salt solutions such as the Norwegian fermented trout (rakfisk) containing about 6% salt, are produced.

Impact of NaCl on thermal resistance (TR) of bacteria and spores

Research has shown that NaCl may affect TR of bacteria. The observed effects differ between studies and depend on microorganism involved and their phase of growth (Corry 1975). D-value may be affected.

Results from relevant studies found in the literature search are summarized below.

Details from the study of Juneja et al (1999) on nonproteolytic *C. botulinum* type B are shown in

Table 4. In this case increasing NaCl concentration reduced thermal resistance.

Table 4 Heat resistance (75 to 90 °C) expressed as D-values in minutes and Z-values in °C for nonproteolytic *C. botulinum* type B in turkey slurry (adapted from Juneja et al., 1999).

Menstruum	Temp (°C)				D-values
	75	80	85	90	
Turkey+1%NaCl	42.1	17.1	7.8	1.1	10.08
Turkey+2%NaCl	25.7	15.1	5.5	0.6	8.82
Turkey+3%NaCl	17.7	13.1	3.2	0.5	8.47

Exposing spores of *C. botulinum* to heat in the presence of NaCl showed results opposite of those of Juneja et al (1999), i.e. a strengthening effect on TR, at inclusion levels of 0.5 and 1% (Esty 1922). Between 2 and 8% little or no effect on TR was seen, whereas above 8% and up to 20% NaCl the effect was rather weakening observed as decreasing D-value.

Strengthening effects of NaCl on TR was observed for bacterial spores in pea liquor at concentrations of 1 to 2.5%, while 4% NaCl slightly weakened TR (Viljoen 1926). NaCl appeared to exert a strengthening of TR in micrococci. Alkaline conditions during heat treatment, however, markedly reduced TR of spores (Jensen 1944).

When two *B. cereus* strains (ATCC14579 and ATCC 10987) were exposed for 30 min at 50 °C to increasing concentrations of NaCl, both strains showed strengthened TR (den Besten 2006). The effect varied however, depending on the stage of development of the bacteria and was more pronounced for bacteria in the exponential growth phase than the stationary phase.

Information on TR of *S. Typhimurium* (ATCC 13311) heated and recovered in media with 0, 1, 2, 3, 4, or 5% NaCl is available (Manas et al. 2001). Sodium chloride in the heating medium had a strengthening effect on TR whereas the effect was the opposite for NaCl in the recovery medium. The results showed an interaction between NaCl concentrations in both media on $D_{58}^{\circ\text{C}}$ values. A lower concentration in the heating media led to a greater effect of the NaCl concentration in the recovery media. When the NaCl concentration was the same in both media, the strengthening effect on TR in the heating media dominated over its weakening effect in the recovery media.

From the results of a thorough study of the heat resistance of *Salmonella* serovars in ground beef, it was concluded that increasing NaCl levels (up to 4.5%) increased the TR for temperatures below 63.5°C, but for higher temperatures and highly lethal treatments, NaCl levels did not significantly affect TR (Juneja et al. 2003). Based on a study of effects of heat on *S. Typhimurium*, Csonka (1989) concludes that NaCl has a strengthening effect on TR. However, D-values of *S. flexneri*, another member of the *Enterobacteriaceae* family, were not greatly affected in a study by NaCl (Zaika 2002).

It is possible that the Cl^- ion is responsible for altering TR in bacteria. Whereas increasing the NaCl concentration increased TR in *L. monocytogenes*, high sodium pyrophosphate concentrations decreased TR (Juneja&Eblen 1999). Moreover, when spores of *Cl. sporogenes* were generated in media containing CaCO_2 at pH 5.0, the TR was not significantly higher than when sporulated in the presence of CaCl_2 (Mah et al. 2008). However, in the study of Juneja et al. (Juneja et al. 2003) increasing levels of both NaCl and sodium pyrophosphate significantly increased TR indicating that the Na^+ ion was the active component of NaCl.

The presence of NaCl can also impact inactivation of bacteria under high-pressure processing. Bacterial barotolerance appears to be related to intracellular accumulation of compatible solutes as a response to the osmotic stress (Molina-Hoppner et al. 2004). *L. lactis* treated with pressures ranging from 200 to 600MPa was protected if suspended in buffer containing 4 M NaCl and to a lesser extent 0.5 M sucrose (Molina-Hoppner et al. 2004). Another lactic acid bacterium, *L. sanfranciscensis*, exhibited barotolerance to 300MPa for 30min when preincubated in NaCl (Scheyhing et al. 2004).

Summary

The importance of NaCl in controlling growth of microbial pathogens seems minor at level of NaCl found in most foods.

Within the range of common foods NaCl may have a variable impact on bacteria's heat resistance. The mechanism underlying the effects of NaCl on TR of bacteria remains unclear and it may depend on species, phase of growth and environmental conditions.

Impact of replacing NaCl with KCl

The molar mass (g/mol) of NaCl is 58.5, whereas the molar mass of KCl is 74.5. Thus, a weight-to-weight substitution of NaCl by KCl would give a reduction in the concentration of ions and in water activity (a_w) with negative effects on preservation properties in some foods (See Table 1).

Table 5 gives an overview of available documentation where NaCl and KCl in equal molar concentrations are reported to give comparable preservation effects and thus food safety margins.

Experiments with *L. monocytogenes* (Boziaris et al. 2007) and *S. aureus* (Bidlas&Lambert 2008) demonstrated that KCl can directly replace NaCl at the same molar ratio with the same antimicrobial effects on these foodborne pathogens in laboratory media. These results are in line with those of Beuchat (1974) reporting that, at equivalent a_w , NaCl and KCl had equivalent effects against *V. parahaemolyticus*. Furthermore, it was observed that in fermented meat products, the replacement of NaCl with KCl did not affect the degree of inhibition and or inactivation, but did alter the taste of the foodstuffs.

Potassium, sodium, and calcium lactates have been found to be equally effective in controlling growth of bacteria in meat packaged in modified atmospheres (Devlieghere et al. 2001), indicating the equivalent effect of potassium, sodium, and calcium ions.

However, a report on the survival of bacteria at low a_w values revealed that bacterial responses may be solute dependent. The adjustments to secure the desired a_w levels were made with NaCl, KCl, or glucose. Solute identity had a bearing on the amount of growth for a given a_w , with KCl having a greater preserving effect than NaCl (Strong et al. 1970).

Table 5 Overview of available documentation where NaCl and KCl in equal molar concentrations are reported to give comparable preservation effects.

Organism	Reference
<i>Bacillus thermosphacta</i>	(Nielsen&Zeuthen 1986)
<i>Bacillus cereus</i>	(Nielsen&Zeuthen 1986)
<i>Clostridium botulinum</i> type E	(Pelroy et al. 1985)
<i>Staphylococcus aureus</i>	(Bidlas&Lambert 2008)
<i>Staphylococcus liquefaciens</i>	(Nielsen&Zeuthen 1986)
<i>Lactobacillus</i> spp.	(Terell et al. 1983, Nielsen&Zeuthen 1986)
<i>Listeria monocytogenes</i>	(Larson et al. 1993, Boziaris et al. 2007, Zarei et al. 2012)
<i>Micrococcus</i> spp.	(Terell et al. 1983)
<i>Moraxella</i> spp.	(Terell et al. 1983)
<i>Salmonella</i>	(Nielsen&Zeuthen 1986, Larson et al. 1993)
<i>Shigella flexneri</i>	(Bidlas&Lambert 2008)
<i>Aeromonas hydrophila</i>	(Bidlas&Lambert 2008)
<i>Enterobacter sakazakii</i>	(Bidlas&Lambert 2008)
<i>Yersinia enterocolitica</i>	(Nielsen&Zeuthen 1986, Raccach&Henningesen 1997, Bidlas&Lambert 2008)
<i>Vibrio parahaemolyticus</i>	(Beuchat 1974)

Summary

The two salts NaCl and KCl appear to function similarly in controlling growth of microorganisms in foods. However, present information is limited. As KCl, in the present context, may fully or partially replace NaCl at the same molarity, there should be no need to evaluate the consequences of different replacement scenarios further as the food safety most likely would not be altered.

The microbiological part of this risk assessment only concerns possible effects of partial or full replacement of NaCl with KCl on the survival, growth or toxin production by food-borne bacteria.

NaCl has an impact during processing of food. The preservative functionality of KCl has been shown to be equivalent to that of NaCl when calculated on molar basis (Bidlas&Lambert 2008) thus not increasing risk for survival, growth or toxin production by food-borne bacteria..

Irrespective of food group, NaCl can be fully or partially replaced by KCl at the same molarity, without altering microbiological food safety.

Data gaps

Data are missing on the kinetics of microbial inactivation using traditional heat treatments (D- and z values) when using equivalent molarities of KCl and NaCl.

Data are also missing on the kinetics of microbial inactivation using newer, alternative food processing technologies such as: microwave and radio frequency, ohmic and inductive heating, high pressure processing, pulsed electric field, high voltage arc discharge, pulsed light, oscillating magnetic fields, ultraviolet light, ultrasound, and X-rays.

Overall conclusion

The current risk assessment covers possible effects on microbiological food safety by full or partial replacement of NaCl by KCl.

Irrespective of food group, NaCl can be fully or partially replaced by KCl at the same molarity, without compromising microbiological food safety.

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