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Benefit and risk assessment of increasing potassium intake by replacement of sodium chloride with potassium chloride in industrial food products in Norway

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A R T I C L E I N F O

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A B S T R A C T

High sodium chloride (NaCl) intake is associated with health risks. NaCl may be replaced by potassium chloride (KCl) to decrease sodium intake. However, increased potassium may also have negative health effects. We conducted a benefit and risk assessment of increasing potassium by ratios of 30:70, 50:50, 70:30 (weight % K^+: weight % Na^+) in children, adolescents and adults in Norway, using intake data from national food consumption surveys and available literature on potassium health effects. An intake of at least 3.5 g/day of potassium decreases risk of stroke and hypertension, and this level was used in the benefit assessment of the healthy population. Three g/day of potassium added to mean food intake is assumed safe, and these levels were used in the risk assessment. Not all persons reached the protective level of potassium, and increasing numbers exceeded the safe levels, in these scenarios. In addition, elderly above 85 years and infants below one year of age, as well as several patient groups and medication users, are particularly vulnerable to hyperkalemia. In conclusion, the number of Norwegians facing increased risk is far greater than the number likely to benefit from this replacement of sodium with potassium in industrially produced food.

1. Introduction

The World Health Organization (WHO) and the European Union (EU) have developed strategies to reduce sodium chloride (NaCl, "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 reducing the sodium chloride intake in the Norwegian population (Norwegian National Nutrition Council, 2011). High sodium chloride intake is associated with development of high blood pressure and is a risk factor for cardiovascular disease (CVD), stroke and kidney disease. In 2012, WHO strongly recommended a reduction in sodium intake to lower blood pressure and thereby the risk of blood pressure-related disorders in both adults and children (WHO, 2012a). A reduction to less than 5 gram sodium chloride per day was recommended for adults, and for children this value should be adjusted based on their energy requirements (WHO, 2012a). There is still no definite explanation for why sodium chloride increases blood pressure (Garfinkle, 2017; Titze and Luft, 2017).

Sodium chloride has several functions in processed foods. It adds flavour, preserves, increases the binding of water to proteins in meat and fish and has additional technological functions in the production of bread and cheese. In the diet, approximately 3/4 of the sodium chloride comes from industrially produced foods (Norwegian National Nutrition

Abbreviations: ACE, angiotensin-converting enzyme; AI, adequate intake; CI, confidence interval; CVD, cardiovascular disease; FFQ, food frequency questionnaire; HR, hazard ratio; KCl, potassium chloride; NaCl, sodium chloride; NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomised controlled trial; RR, relative risk

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Council, 2011). Reducing the use of sodium chloride in industrial food production may thus result in a reduction of the sodium chloride intake by the population.

Sodium chloride may be replaced by potassium chloride (KCl) in industrially produced food in order to decrease sodium intake. However, the increased potassium may have negative health effects. Potassium chloride (E508) is regulated in Europe by the Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December (EU, 2008), which states that potassium chloride may be added "*quantum satis*" to food, i.e. the amount necessary for its function, but not higher. This was implemented in Norwegian regulation in 2011 (HOD, 2011).

The National Institute for Health and Care Excellence in United Kingdom 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 get used to less salty foods and to avoid additives which may have other potentially adverse effects on health.

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 the remaining percentage (Traeger and Wen, 2008). The concentration of potassium in plasma is tightly regulated within the narrow range of approximately 3.5–5 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, as well as for other functions (Taber and Thomas, 1997).

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 (ACE) inhibitors, angiotensin receptor blockers, β-blockers and non-steroidal anti-inflammatory (NSAID) drugs. However, there is no evidence of adverse effects from increased dietary potassium in individuals with unimpaired potassium excretion (NNR, 2012; WHO, 2012b).

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, in connection with use of laxatives or diuretics or after high intake of licorice. Potassium deficiency due to low dietary intake is uncommon due to the presence of potassium in most foods (Traeger and Wen, 2008; EFSA, 2005; NNR, 2012).

Sodium chloride (NaCl) may be replaced by potassium chloride (KCl) in industrially produced food in order to decrease sodium intake. However, in spite of potassium's essential functions in the body and beneficial effects, the increased potassium may also have negative health effects. We therefore conducted a benefit and risk assessment of increasing potassium by ratios of 30:70, 50:50, 70:30 (weight % K^+: weight % Na^+) in children, adolescents and adults in Norway on request from the Norwegian Food Safety Authority, using intake data from national food consumption surveys and available literature on health effects of potassium.

2. Materials and methods

The levels of potassium having beneficial or adverse effects were obtained from previous risk assessments and publications retrieved by literature searches in this benefit and risk assessment on the Norwegian population.

2.1. Literature searches and previous reports on beneficial and adverse health effects of potassium

Literature searches were conducted to retrieve scientific documentation for beneficial effects of potassium in the general population, and for adverse effects in the general population and in groups that are particularly vulnerable to potassium. Test searches were conducted to find relevant terms, search words and controlled vocabulary (MeSH and EMTREE). For beneficial effects, the following search strings were used: Potassium in title AND Meta-Analysis (as MeSH-term) OR meta-analysis* (as text word), and a search was conducted in Medline. Publications in English, Norwegian, Danish and Swedish without limitations in publication year were included. The search was conducted in June 2013 and resulted in 47 hits. Another 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 person. Non-systematic reviews, papers reporting not clinically relevant health effects and papers including other substances together with potassium were excluded. Eight systematic reviews and meta-analyses were included in the results. In February 2017, four new relevant papers published since 2014 and an opinion from the European Food Safety Authority (EFSA) on dietary reference values for potassium were also included in this assessment, based on the same criteria as before.

For adverse effects, literature searches were conducted in Medline, Embase and ISI web of Science. 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 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 English, Norwegian, Danish, Swedish and German. Since it was assumed that relevant literature published prior to 2004 was covered by EFSA's "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. Searching the reference lists of these reports also resulted in some relevant publications.

2.2. Intake calculations of sodium and potassium from the national food consumption surveys

Intakes of sodium and potassium were computed from participants in Norwegian dietary surveys (Norkost 3, Småbarnskost and Ungkost, 2000) 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 (FCT, 2016; Rimestad et al., 2000). For calculation of the three different scenarios (K^+:Na^+ in ratios of 30:70, 50:50, 70:30), first the naturally occurring sodium in food, 12% of calculated intake, was subtracted (EFSA, 2005). Then the percentages in the three scenarios were calculated from the remaining sodium intake where sodium was replaced by potassium weight % by weight %

(in mg). The scenarios were calculated for each participant and the results were given as mean and percentiles for each gender/age group in Tables 2–7.

Norkost 3 (for adults) 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 1,787 adults aged 18–70 years participated. The participation rate was 37%.

Småbarnskost (two-year-old children) is based on a semi-quantitative food frequency questionnaire (FFQ). In addition to predefined household units, food amounts were also estimated from photographs. A total of 1,674 2-year-old children participated. The participation rate was 56% (Kristiansen et al., 2009).

Ungkost 2000 (4-, 9- and 13-year-olds) is based on four consecutive days of 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-year-old children and 13-year-old adolescents was conducted in 2000, and had 810 and 1005 participants, respectively (Øverby and Andersen, 2002).

It is not known whether the 12% naturally occurring sodium in food and drinks of the total sodium intake (EFSA, 2005) 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.

It was not feasible to separate sodium in home-cooking recipes from industrialised foods. The remaining sodium intake is therefore from added sodium chloride, i.e. both added in home-cooking recipes and in industrialised food production. Table salt and sodium chloride used in home-cooking were not registered in any of the dietary surveys, and are therefore not included in the calculations or scenarios. The types of salt used in home-cooking were not registered. In some households, a sodium-reduced type of salt replaces the more ordinary sodium chloride.

3. Results and discussion

3.1. Previous reports on positive health effects of potassium

The United Kingdom Expert Group on Vitamins and Minerals (EVM) published two reports including discussion of beneficial effects and toxicity of potassium (EVM, 2002; EVM, 2003), and gave a reference nutrient intake for adults of 3.5 g of potassium.

In 2005, the Institute of Medicine (IOM) of the National Academy of Sciences, USA, suggested an adequate intake in adults of potassium at 4.7 g/day (120 mmol/day) (IOM, 2005).

The recommended intake of potassium by the Nordic Nutrition Recommendations (NNR) issued in 2012 was based on the data from NNR (2004) on the effect of potassium on blood pressure, and were set at 3.5 g/day (90 mmol/day) for men and 3.1 g/day (80 mmol/day) for women, including pregnant and lactating women (NNR, 2012). The reference values for children and adolescents were extrapolated from adult values on needs for growth and adjusted to body weight.

WHO issued a guideline on potassium intake from food, strongly recommending that adults should elevate their potassium intake in order to decrease blood pressure and the risk of CVD, stroke and coronary heart disease (WHO, 2012b). WHO also suggested a potassium intake of at least 3.5 g/day (90 mmol/day) for adults as a conditional recommendation, based on the findings by Aburto et al. (2013). For children, a conditional recommendation to increase potassium intake to control blood pressure was given (WHO, 2012b), using the value that was recommended for adults adjusted downward based on the energy requirements relative to those of adults.

In 2013, the United Kingdom Department of Health's Scientific Advisory Committee on Nutrition (SACN) concluded that potassium intake was not significantly related to risk of cardiovascular or coronary artery disease, but the potassium intake appeared significantly related to decreased risk of stroke (both conclusions were based on D'Elia et al., 2011; Aburto et al., 2013).

In 2016, the Panel on Dietetic Products, Nutrition and Allergies (NDA) of the European Food Safety Authority (EFSA) stated that there was evidence that for the adult European population an intake of 3.5 g (90 mmol) per day has beneficial effects on blood pressure and that potassium intakes below 3.5 g per day were associated with a higher risk of stroke (EFSA, 2016). They derived an adequate intake (AI) of 3.5 g per day of potassium for adult women and men. An AI of 750 mg (19 mmol) per day was set for infants 7–11 months of age and AIs from 800 mg (20 mmol) per day for 1-3-year-olds to 3.5 g per day for 15-17-year-olds were set by extrapolation from AI for adults by isometric scaling and including a growth factor.

3.2. Results from the literature researches on positive health effects of potassium

3.2.1. Stroke

D'Elia et al. (2011) performed a meta-analysis of prospective studies on habitual potassium intake and CVD. The study included 247,510 individuals, pooled from 11 published studies with follow-up 5–19 years. 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. The data were reported as relative risk (RR) with corresponding 95% confidence intervals (CI). 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).

Larsson et al. (2011) performed a dose-response meta-analysis of prospective cohort studies on dietary potassium intake and risk of stroke. After exclusion of 97 papers, they analysed ten papers (268,276 adult participants, follow-up 4–19 years). Their main conclusion (after adjustment for 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).

Aburto et al. (2013) performed a systematic review of the literature and meta-analysis of the available data on association between increased potassium intake and cardiovascular risk factors and disease. They reported data from 11 cohort studies in adults (127,038 participants) and one randomised controlled trial and one cohort study in children, with follow-up > 1 year, after screening 5,310 papers. 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.

Adebamowo et al. (2015) examined associations between intakes of potassium (as well as magnesium and calcium) and risk of incident stroke in 86,149 women in the Nurses' Health Study (NHS) I and 94,715 women in the NHS II study. In these prospective cohort studies, they calculated hazard ratios (HRs) of stroke by quintiles of intake for each mineral by multivariate Cox proportional hazard models. In addition, they updated meta-analyses of dietary intakes of these minerals and risk of stroke. During follow-up, 30 years in NHS I and 22 years in NHS II, a total of 3,780 incident stroke cases were documented. Pooled multivariate RRs of total stroke for women in the highest compared with the lowest quintiles were 0.89 (95% CI: 0.80, 0.99) for total potassium. In the updated meta-analyses of all prospective studies to date, the combined RR of total stroke was 0.91 (95% CI: 0.88, 0.94) for a 1 g/day increase in potassium intake.

Vinceti et al. (2016) published a systematic review and dose-response meta-analysis of all studies included in Larsson et al. (2011) and those that were published later. They carried out a meta-analysis of 16 cohort studies (involving 19,522 stroke events in 639,440 participants) based on the RR of stroke comparing the highest versus lowest intake categories, and plotted a pooled dose-response curve of RR of stroke according to potassium intake. Relative to the lowest category of potassium intake, the highest category of potassium intake was associated with a 13% reduced risk of stroke (RR 0.87, 95% CI 0.80, 0.94) in the blood pressure-adjusted analysis. Summary RRs tended to decrease when original estimates were unadjusted for blood pressure. Analysis for stroke subtypes yielded comparable results. In the spline regression analysis, the pooled RR was lowest at 90 mmol of potassium daily intake (RR 0.78, 95% CI 0.70, 0.86) in blood pressure-adjusted analysis and 0.67 (95% CI 0.57, 0.78) in unadjusted analysis. The authors concluded that this study confirmed the inverse association between potassium intake and stroke risk with potassium intake of approximately 3.5 g/day (90 mmol/day) being most effective.

In this assessment, it was concluded that a total intake of at least 3.5 g potassium per day reduced the incidence of stroke in adults of both gender, based on mostly the same studies as in WHO (2012b) and EFSA (2016). Currently, there is insufficient evidence to give separate conclusions for men and women or to give a clear recommendation of potassium intake in children. This level of potassium intake is closely in line with the Nordic Nutrition Recommendations of 3.5 g/day for men and 3.1 g/day for women.

In Norway, approximately 9,600 individuals suffer from acute stroke each year (data from 2014), and about 50% are under 76 years of age (NIPH, 2015a).

3.2.2. Blood pressure

A review of 19 clinical trials examining the effects of oral potassium supplementation on blood pressure involved a total of 586 participants (mean age 39.6 years, 412 had essential hypertension) (Cappuccio and MacGregor, 1991). Average amount of potassium given was 3.4 g/day (86 mmol/day) and average duration of the supplement administration was 39 days (range 5–112 days). The meta-analysis indicated that an oral potassium supplementation of 3.4 g/day (86 mmol/day) gave a significant reduction in systolic blood pressure of (mean, 95% CI) −5.9 mm Hg (−6.6 to −5.2 mm Hg) and in diastolic blood pressure of −3.4 mm Hg (−4.0 to −2.8 mm Hg) in the participants overall, and a greater and significant reduction in systolic blood pressure of −8.2 mm Hg (−9.1 to −7.3 mm Hg) and for diastolic blood pressure −4.5 mm Hg (−5.2 to −3.8 mm Hg) in patients with a high blood pressure.

A meta-analysis of 33 randomised, controlled clinical trials assessed the effects of supplementation with oral potassium supplements on blood pressure (Whelton et al., 1997). The total number of study participants was 2,609 with ages ranging from 18 to 79 years. The trials varied from 4 days to 3 years, with a median of 5 weeks. 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.

Burgess et al. (1999) updated evidence-based recommendations for dietary intake of potassium, magnesium and calcium for the prevention of hypertension in healthy adults (except pregnant women). The weight of the evidence from the randomised controlled trials indicated that increasing intake of or supplementing the diet with either potassium, magnesium or calcium was neither associated with prevention of hypertension nor was it effective in reducing high blood pressure. Potassium supplementation was 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).

Dickinson et al. (2006) evaluated the effects of potassium supplementation on health outcomes and blood pressure in adult persons with elevated blood pressure in a meta-analysis, which included five randomised controlled trials of parallel or cross-over design with an intervention period of at least eight weeks. The meta-analysis enrolled 425 participants (range in each trial 12–212). The medium duration of follow-up was 12 weeks (range 8–16 weeks). Overall, 75% of the participants were male and mean age was 50 years (range 36–52 years). The data indicated that potassium supplementation compared to control resulted in large but statistically non-significant reductions in systolic blood pressure (mean difference: −11.2 mmHg, 95% CI: −25.2 to 2.7) and diastolic blood pressure (mean difference: 5.0 mmHg, 95% CI: −12.5 to 2.4).

A summary paper by Houston (2011) on the importance of potassium in managing hypertension concluded that dietary potassium intake had 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. The main conclusion of Houston (2011) was that increasing potassium intake to 4.7 g/day (120 mmol/day) would shift the population distribution of systolic blood pressure down by 1.7–3.2 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 8–15% and the reduction in coronary heart disease risk would be 6–11%.

Houston (2011) also referred to different guidelines which had 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 potassium/day (Appel et al., 2006). In 2010, the American Society of Hypertension (ASH) recommended about 4.7 g/day of potassium (Appel et al., 2010). In addition, the 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement recommended a diet high in fruits and vegetables, reduced dietary sodium intake and increased dietary potassium intake to reduce the incidence of hypertension (Whitworth, 2003).

The meta-analyses by Aburto et al. (2013) showed that increased potassium intake significantly reduced systolic and diastolic blood pressure in hypertensive persons (based on 16 studies on hypertensive persons and two studies of mixed groups with or without hypertension) but not in normotensive persons (3 studies). Subgroup analyses 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.

Binia et al. (2015) performed a meta-analysis of 15 randomised controlled trials (5 with parallel design and 10 with cross-over design) of potassium supplementation in 917 patients who were not on antihypertensive medication. Most of the studies used a potassium intervention of 2.3–2.5 g/day (60–65 mmol/day), three had an intervention of 1.6 g/day (40 mmol/day) or less, and only one study had an intervention of at least 4.7 g/day (120 mmol/day). The potassium supplementation resulted in a reduction of systolic blood pressure of −4.7 mmHg (95% CI -7.0 to −2.4) and of diastolic blood pressure of −3.5 mmHg (95% CI -5.7 to −1.3) based on all patients. In hypertensive patients, the effects were greater, with a reduction of systolic blood pressure of −6.8 mmHg (95% CI -9.3 to −4.3) and of diastolic blood pressure of −4.7 mmHg (95% CI -7.5 to −1.8).

A randomised, placebo-controlled cross-over study examined blood pressure in 36 subjects on a controlled diet low in sodium and given potassium supplementation of 2.8 g/day or placebo, four weeks on each treatment (Gijsbers et al., 2015). During potassium supplementation, 24-hour ambulatory blood pressure was significantly reduced compared with placebo; the mean difference was −3.9 mmHg (95% CI -6.9 to −0.9, $P = 0.013$) in systolic blood pressure and −1.6 mmHg (95% CI -3.2 to −0.1, $P = 0.039$) in diastolic blood pressure. Office systolic blood pressure (−3.0 mmHg, 95% CI -6.7 to 0.6, $P = 0.10$) and diastolic blood pressure (−0.3 mmHg, 95% CI -2.1 to 1.6, $P = 0.77$) were reduced, but not statistically significant.

In this assessment, it was concluded that an intake of at least 3.5 g potassium per day promotes blood pressure reduction in hypertensive subjects. This conclusion is based on the same studies as in WHO (2012b) and EFSA (2016) and is also closely in line with the Nordic Nutrition Recommendations (NNR, 2012). Despite inconsistent data, a total intake of 3.5 g/day from foods and supplements should also be considered for normotensive subjects to prevent hypertension in the general population. The blood pressure-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 (Whelton et al., 1997; Aburto et al., 2013).

It is not known exactly how many persons suffer from hypertension in Norway today, but data from 2000 to 2003 indicated that among 40-year olds approximately 2.3% of men and 1.1% of women had hypertension (NIPH, 2015b).

3.3. Previous reports on negative health effects of potassium

The United Kingdom Expert Group on Vitamins and Minerals (EVM) published two reports, which included discussion of toxicity of potassium (EVM, 2002; EVM, 2003). Cases of acute poisoning of humans were all related to high intake of potassium chloride from supplements or sodium chloride substitutes. The 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 also resulted in chest tightness, shortness of breath and heart failure. From case reports, EVM considered that large doses could result in hyperkalemia and hypernatremia and lead to changes in acid-base balance and the heart rate (EVM, 2002; EVM, 2003). However, supplementation studies reported 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 (see 3.4.1). EVM concluded that there was 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.

According to the Institute of Medicine (IOM) of the National Academy of Sciences, USA, a potassium intake below 4.7 g/day was considered appropriate for individuals with impaired urinary potassium excretion, i.e. patients with diabetes, chronic renal insufficiency, end-stage renal disease, severe heart failure and adrenal insufficiency (IOM, 2005). Drugs reported to impair potassium excretion were angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and potassium-sparing diuretics.

The EFSA NDA Panel's opinion related to the tolerable upper intake level of potassium (EFSA, 2005) reviewed the available hazard information from animal and human studies. They concluded that no adverse effects in healthy children or adults due to potassium intake from foods were found. They reviewed various short-term studies (2–3 weeks) in healthy adults with intake up to 15 g potassium per day, which showed normal serum potassium levels provided that fluid intake was sufficient and that the intake was evenly distributed over the day. However, some adverse effects such as gastrointestinal effects and unexpected acute effects, even fatal ones, in a few persons were reported after intake of potassium supplements at these dose levels. As opposed to intake of potassium from food, gastrointestinal erosion and ulcers had occasionally been reported in healthy persons after oral potassium chloride supplementation with doses from 1 to 5 g/day, especially with wax-matrix formulations. Based on absence of adverse effects after long-term intake of potassium chloride supplements, the panel concluded that in healthy persons an increase of 3.0 g/day in potassium in addition to the intake from foods had not been reported to cause adverse effects (EFSA, 2005).

It was, however, reported that occasionally single supplementation doses of 5–7 g could lead to adverse changes in heart function and peripheral nerve system in apparently healthy adults EFSA (2005). Twenty different case reports of intoxications caused by potassium supplements were included. 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 94 g/day in adults and from 1.5 to 7 g/day in infants. Also some fatal cases were reported both after acute and chronic potassium intake.

The guideline from WHO (2012b) stated that increasing potassium consumption from food was 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 the needs. They did not provide recommendations for individuals with impaired urinary potassium excretion from medical conditions or drug therapy. It was stated that there was no report of toxicity from consumption of food. Acute toxicity from extremely high potassium intake as supplements in healthy adults was evaluated (WHO, 2012b).

3.4. Results from the literature researches on negative health effects of potassium

3.4.1. Healthy population

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 was 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 evaluated by endoscopy, such as mucosal erosions and gastric ulcers, 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 such effects were observed. The same research group performed a follow-up study of 9 hypertensive patients and 9 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 6 out of the 9 patients given wax-matrix formulated potassium and in none of the controls.

Effects of potassium given as supplements were also investigated in a long-term double-blind study (Grimm et al., 1988; 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. Adverse effects, such as abdominal pains, nausea, vomiting, diarrhea and bright red blood in the stools, were reported, but these events were not significantly different between the treatment and the placebo groups.

3.4.2. Vulnerable groups

Persons with severe renal failure are often undergoing intermittent hemodialysis with a frequency depending on the severity of the renal failure. Since these patients have quite a reduced capacity to regulate the potassium level they will also be particularly vulnerable to even modestly increased dietary intake of potassium. In a clinical study following 224 hemodialysis patients for 5 years, the dietary potassium intake was determined by a FFQ (Noori et al., 2010). Analysed by quartiles, the potassium intake was determined to be 879, 1,342, 1,852 and 3,440 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 hemodialysis patients should ingest less than 1.5 g/day of potassium (Noori et al., 2010).

The ultimate treatment for hemodialysis patients is kidney transplantation. By the end of 2014, 4,713 Norwegian patients had received kidney replacement, whereas 285 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, 2014). 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 (Traeger and Wen, 2008; Desai, 2009; Noori et al., 2010). In Norway, it is estimated that 10–11% of the general population (in the order of 500,000–600,000 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 hematuria and proteinuria.

Patients with heart failure may be treated with ACE inhibitors, β-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. Disturbances in potassium balance can lead to 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 of patients using the respective drugs in Norway (Table 1).

Persons with diabetes mellitus may have elevated glucose in the extracellular fluid, which 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% (90,000–120,000 persons) (Stene et al., 2004). The estimated number of undiagnosed diabetes may be almost as high as the number of diagnosed diabetes (Stene et al., 2004). Employing data on dispensed drugs in the Norwegian Prescription Database as a proxy for diabetes, it was shown that in 2005, 117,541 individuals (2.5% of the population) used blood-glucose-lowering drugs, whereas in 2011, this number was 156,540 individuals (3.2% of the population) (Strøm et al., 2014).

Persons using drugs that affect the potassium balance are vulnerable to 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 (Moore and Linas, 2012). The estimated use of various drugs affecting the potassium balance among Norwegians is shown in Table 1.

Table 1
The main drugs affecting potassium balance including the number of daily defined doses of use in the period 2008–2012 based on Sakshaug et al. (2013).

Drug group	Indication/Effect	Doses (DDD/ 1,000)[a]
NSAIDs[b]	Anti-inflammatory	47.5
Angiotensin-converting enzyme (ACE) inhibitors	Renin/angiotensin system	45
β-blockers	Decrease cellular potassium uptake	38
Digitalis	Cardiac failure	2.21
Trimethoprim	Antibiotic	0.87
Tacrolimus	Immune suppression	0.36
Cyclosporine	Immune suppression	0.41

[a] DDD/1,000 is the number of daily defined doses (DDD) per 1,000 inhabitants, including both short-term and long-term use.
[b] NSAIDs: non-steroidal anti-inflammatory drugs.

Infants below one year of age have immature renal function and are therefore more vulnerable to increased potassium intake (EVM, 2002). In Norway, this age group accounted 119,487 infants in 2016 (SSB, 2017).

Most persons at the age of 85 years and older have a moderate or serious reduction in the glomerular filtration rate, which will interfere with their renal function (Norsk legemiddelhåndbok, 2015). In Norway, the age group 85 years and above accounted 115,761 persons in 2016 (SSB, 2017).

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).

For other vulnerable groups than hemodialysis patients, a safe level of potassium has not been identified.

To summarize, there were no reports of toxicity to healthy humans as a result of potassium consumption from food (EFSA, 2005; WHO, 2012b). According to EVM (2003) and EFSA (2005), 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) in most healthy adults. We endorsed the EFSA value of 3.0 g/day. In the present assessment, the term 'assumed safe intake' is used when 3 g potassium/day is added to the mean intake from food.

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).

3.5. Calculation of potassium intake by replacement of sodium in the Norwegian population

The calculated mean potassium intake in adults was 3,800 mg/day. Since the intake of potassium differs between the genders, the intakes for both genders were presented separately. The mean potassium intake was 3,380 mg/day for women (Table 2) and 4,250 mg/day for men (Table 3). For 2-, 4- and 9-year-old children and 13-year-old adolescents, the mean potassium intakes were 2,270, 2,130, 2,630 and 2,730 mg/day, respectively (Tables 4–7).

Estimated sodium and potassium intakes in scenarios where 30%, 50% and 70% of sodium in added salt was replaced by potassium for women, men, 2-, 4-, 9-, and 13-year-olds were also presented in Tables 2–7. For each of the scenarios, the mean, the median, the 5th, 25th and the 95th percentiles of the estimated intakes were presented. Please note that the intake of sodium and potassium (in mg), not sodium chloride and potassium chloride, was given in the tables. The scenarios were calculated for each participant and the results were given as mean and percentiles for each gender/age group. Thereby, the differences between sodium and potassium reflect person-specific values for each percentile in each scenario.

3.6. Benefit characterization

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) was conducted.

It was concluded that a potassium intake necessary to reduce the risk of stroke is at least 3.5 g/day in adults (see 3.2.1). Most likely an intake of 3.5 g/day will also reduce high blood pressure (see 3.2.2). The intakes of potassium in adults, children and adolescents in Norway are

Table 2
Sodium and potassium intake in women (n = 925), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride is replaced by potassium.

	5th percentile (mg/day)	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium and potassium intake in women as reported in Norkost 3					
Sodium	1,242	1,860	2,540	2,370	4,280
Potassium	1,900	2,700	3,380	3,290	5,120
Scenario 30:70. Estimated sodium and potassium intake in women when 30% of added sodium is replaced by potassium					
Sodium	910	1,370	1,870	1,750	3,150
Potassium	2,360	3,290	4,050	3,940	6,040
Scenario 50:50. Estimated sodium and potassium intake in women when 50% of added sodium is replaced by potassium					
Sodium	700	1,040	1,430	1,330	2,400
Potassium	2,660	3,660	4,500	4,390	6,700
Scenario 70:30. Estimated sodium and potassium intake in women when 70% of added sodium is replaced by potassium					
Sodium	480	720	980	910	1,640
Potassium	2,910	4,000	4,940	4,840	7,300

Table 3
Sodium and potassium intake in men (n = 862), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride is replaced by potassium.

	5th percentile (mg/day)	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium and potassium intake in men as reported in Norkost 3					
Sodium	1,660	2,600	3,570	3,360	6,110
Potassium	2,410	3,310	4,250	4,120	6,560
Scenario 30:70. Estimated sodium and potassium intake in men when 30% of added sodium is replaced by potassium					
Sodium	1,230	1,910	2,630	2,470	4,490
Potassium	2,970	4,120	5,190	5,040	7,710
Scenario 50:50. Estimated sodium and potassium intake in men when 50% of added sodium is replaced by potassium					
Sodium	930	1,450	2,000	1,880	3,420
Potassium	3,400	4,660	5,820	5,670	8,670
Scenario 70:30. Estimated sodium and potassium intake in men when 70% of added sodium is replaced by potassium					
Sodium	640	1,000	1,370	1,290	2,350
Potassium	3,750	5,200	6,450	6,270	9,780

Table 4
Sodium and potassium intake in 2-year-old children (n = 1,674), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride is replaced by potassium.

	5th percentile (mg/day)	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium and potassium intake in 2-year-old children as reported in Småbarnskost 2007					
Sodium	830	1,230	1,560	1,500	2,460
Potassium	1,240	1,770	2,270	2,180	3,560
Scenario 30:70. Estimated sodium and potassium intake in 2-year-old children when 30% of added sodium is replaced by potassium					
Sodium	610	900	1,150	1,100	1,810
Potassium	1,530	2,110	2,680	2,600	4,130
Scenario 50:50. Estimated sodium and potassium intake in 2-year-old children when 50% of added sodium is replaced by potassium					
Sodium	460	690	880	840	1,380
Potassium	1,700	2,350	2,950	2,870	4,520
Scenario 70:30. Estimated sodium and potassium intake in 2-year-old children when 70% of added sodium is replaced by potassium					
Sodium	320	470	600	570	940
Potassium	1,880	2,570	3,230	3,140	4,870

Table 5
Sodium and potassium intake in 4-year-old children (n = 391), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride is replaced by potassium.

	5th percentile (mg/day)	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium and potassium intake in 4-year-old children as reported in Ungkost 2000					
Sodium	1,010	1,360	1,680	1,630	2,560
Potassium	1,250	1,780	2,130	2,060	3,110
Scenario 30:70. Estimated sodium and potassium intake in 4-year-old children when 30% of added sodium is replaced by potassium					
Sodium	740	1,000	1,240	1,200	1,890
Potassium	1,610	2,200	2,580	2,490	3,700
Scenario 50:50. Estimated sodium and potassium intake in 4-year-old children when 50% of added sodium is replaced by potassium					
Sodium	560	760	940	910	1,440
Potassium	1,800	2,450	2,870	2,770	4,120
Scenario 70:30. Estimated sodium and potassium intake in 4-year-old children when 70% of added sodium is replaced by potassium					
Sodium	390	520	650	630	980
Potassium	2,040	2,700	3,170	3,070	4,570

presented in 3.5. Approximately 60% of the women and 30% of the men in Norway have an intake below 3.5 g/day.

However, there was a high variability between the results in different studies of benefits of potassium. This could to some extent be explained by heterogeneous study populations, with several ethnicities included (Afro-Americans are often more prone to increased blood pressure than Caucasians (Appel et al., 2010)), the variability in the design of the studies, the duration of the studies or of follow-up, the form of the potassium (either from dietary sources or from supplementation), different ways of assessing potassium intake (e.g. 24-hours urine samples or FFQs), and also that the composition of the total diets showed 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 were not focusing on solely one mineral.

The recommendation from WHO on at least 3.5 g potassium per day in adults was conditional. As the suggestion was mainly based on one

Table 6
Sodium and potassium intake in 9-year-old children ($n = 810$), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride is replaced by potassium.

	5th percentile (mg/day)	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium and potassium intake in 9-year-old children as reported in Ungkost 2000					
Sodium	1,210	1,760	2,260	2,150	3,560
Potassium	1,460	2,120	2,630	2,570	4,020
Scenario 30:70. Estimated sodium and potassium intake in 9-year-old children when 30% of added sodium is replaced by potassium					
Sodium	890	1,290	1,660	1,580	2,620
Potassium	1,880	2,620	3,230	3,170	4,830
Scenario 50:50. Estimated sodium and potassium intake in 9-year-old children when 50% of added sodium is replaced by potassium					
Sodium	680	980	1,260	1,210	1,990
Potassium	2,140	2,970	3,620	3,590	5,300
Scenario 70:30. Estimated sodium and potassium intake in 9-year-old children when 70% of added sodium is replaced by potassium					
Sodium	470	670	870	830	1,370
Potassium	2,390	3,290	4,020	3,950	5,870

Table 7
Sodium and potassium intake 13-year-old adolescents ($n = 1{,}005$), including scenarios where 30%, 50% or 70% of sodium in added sodium chloride is replaced by potassium.

	5th percentile (mg/day)	25th percentile (mg/day)	Mean (mg/day)	Median (mg/day)	95th percentile (mg/day)
Sodium and potassium intake in 13-year-old adolescents as reported in Ungkost 2000					
Sodium	1,090	1,670	2,360	2,240	4,060
Potassium	1,290	1,980	2,730	2,560	4,740
Scenario 30:70. Estimated sodium and potassium intake in 13-year-old adolescents when 30% of added sodium is replaced by potassium					
Sodium	800	1,230	1,740	1,650	2,990
Potassium	1,590	2,510	3,350	3,170	5,690
Scenario 50:50. Estimated sodium and potassium intake in 13-year-old adolescents when 50% of added sodium is replaced by potassium					
Sodium	610	940	1,320	1,250	2,270
Potassium	1,810	2,830	3,770	3,560	6,300
Scenario 70:30. Estimated sodium and potassium intake in 13-year-old adolescents when 70% of added sodium is replaced by potassium					
Sodium	420	640	910	860	1,560
Potassium	2,020	3,110	4,180	3,960	7,040

meta-analysis (Aburto et al., 2013) and several of the studies included in this meta-analysis showed no dose response, this was considered the major uncertainty factor in this benefit assessment.

Since the intake calculations showed that persons in the Norwegian population had intake levels of potassium from food below the level of 3.5 g/day, in the following further calculations were given to examine how many men and women, in percentage, will benefit from an increase in dietary potassium. The benefit characterization was therefore focused on the women (Table 2) and men (Table 3) with a present intake of potassium below 3.5 g/day.

For women, in the 30:70 scenario 33% had a potassium intake below 3.5 g/day, in the 50:50 scenario the percentage was 21, and in the 70:30 scenario 13% of the women still had an intake below 3.5 g/day. For men, in the 30:70 scenario 10% had a potassium intake below 3.5 g/day, in the 50:50 scenario the percentage was 6, and in the 70:30 scenario 4% of the men had an intake below 3.5 g/day.

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 in all individuals. 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 might best be obtained by increasing the intake of foods high in potassium (Dickinson et al., 2006; D'Elia et al., 2011; Aburto et al., 2013).

3.7. Risk characterization

There were few studies available on tolerable doses of potassium, conducted either with healthy subjects or patients, and those existing had limitations in design, size, investigated parameters, gender selection and quality. The assumed safe level of potassium intake (3.0 g/day) in addition to food sources is approximate. The scientific basis for setting this intake level is limited and the estimated level should not be taken as a safe upper level.

3.7.1. Healthy population

An important statement put forward in all previous assessments of potassium intake is that the potassium intake from foods with natural potassium content has not been associated with adverse effects in healthy adults or children (EVM, 2003; EFSA, 2005; IOM, 2005; WHO, 2012b). All reported incidences of potassium intoxication have been observed in healthy persons taking potassium supplements or in vulnerable groups (see 3.4).

In healthy persons, intake of potassium from food does not result in hyperkalemia. Based on the scientific data detailed in this paper, the majority of healthy adult 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, referred to as the assumed safe level of potassium.

For the risk assessment of replacement of sodium in sodium chloride with potassium, the mean value and the 95th percentile were used. For adult Norwegian women, the mean potassium intake was 3,380 mg/day. Since an additional potassium intake of 3.0 g/day most probably is without negative health effects, a total intake of 6,380 mg potassium/day was assumed to be safe (Supplementary Table 1). All intake values in the scenarios were compared with the assumed safe value of 6,380 mg potassium/day, showing that the 95th percentile intake in the 50:50 and 70:30 scenarios was above the assumed safe level (Supplementary Table 1). In Norkost 3, 1% of the women had a potassium intake above the assumed safe level. Women with a potassium intake above the assumed safe level was 3% for the 30:70 scenario, 7% for the 50:50 scenario, and 15% for the 70:30 scenarios.

With similar calculations for adult Norwegian men, the 95th percentile intake in all scenarios was above the assumed safe level (Supplementary Table 1). In Norkost 3, 2% of the men had a potassium intake above the assumed safe level, which increased to 9% for the 30:70 scenario, 19% for the 50:50 scenario, and 30% for the 70:30 scenario (Supplementary Table 1).

For the risk characterization for 2-, 4- and 9-year-old children and 13-year-old adolescents, the 3.0 g potassium that may be ingested per day by adults in addition to normal intake from food without negative health effects was adjusted for the daily energy intake (WHO, 2012b).

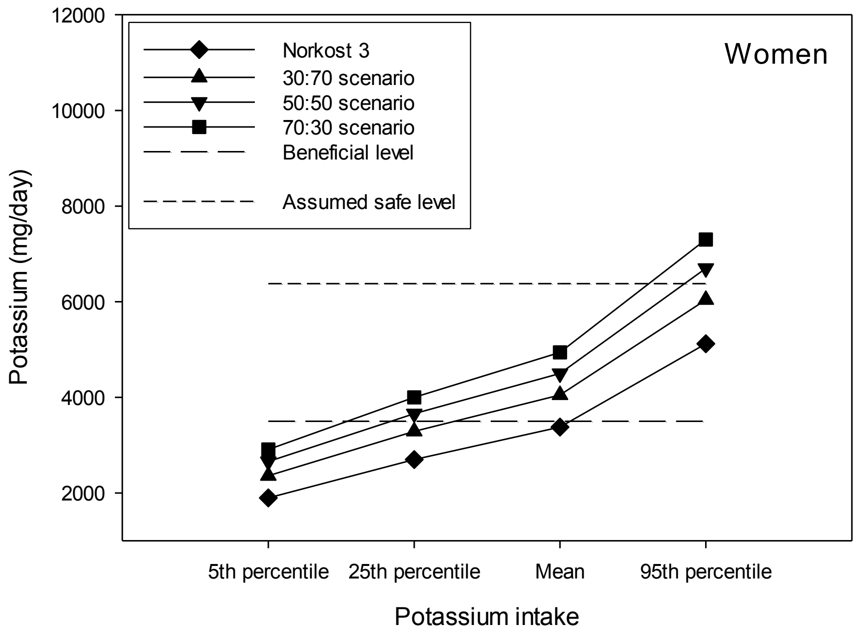

Fig. 1. Potassium intake in women (n = 925) in the 30:70, 50:50 and 70:30 scenarios.

For 2-year-old children and 13-year-old adolescents, the 95th percentile intake in all three scenarios was above the assumed safe level (Supplementary Table 1). For 4-year-old children and 9-year-old children, the 95th percentile intake in the 50:50 and 70:30 scenarios was above the assumed safe level. As opposed to the 95th percentile intake, the mean intake values were below the assumed safe level in adult women and men, 2-, 4-, 9-year-old children and 13-year-old adolescents (Supplementary Table 1).

3.7.2. Vulnerable groups

Groups in the population that are particular 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. Increasing the potassium content in several industrially produced foods, which are not originally rich dietary sources of potassium, may complicate medical dietary guidance to the persons in these vulnerable groups. The number of persons affected in Norway is summarised in 3.8.2.

Patients with serious renal failure, whether undergoing hemodialysis 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 in 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.

There are considerable overlaps between the various vulnerable groups. An example is elderly persons also having diseases or taking drugs making them more vulnerable to hyperkalemia than just the age-dependent impairment of renal function. Many patient groups are also 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.

There are many uncertainties regarding the vulnerable 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 have not yet been identified.

3.8. Benefit and risk characterization

The benefit and risk characterization is done in two different ways: by looking at in which scenarios the levels of intake of potassium in Norway exceed the levels determined for beneficial and adverse effects (3.8.1), and by looking at the percentages of persons with an intake of potassium in Norway that will exceed the levels determined for beneficial and adverse effects in the scenarios (3.8.2).

3.8.1. A comparison of potassium intakes in healthy adults with both the suggested levels of benefit and risk

Because available data from studies in children and adolescents are scarce, only adults could be compared for both the benefit and risk of increased potassium in the given scenarios. This was illustrated 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 with the assumed safe level of 3.0 g/day in addition to mean potassium intake from food used in the risk assessment, in the same figures (Figs. 1 and 2).

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 (Fig. 1). Women with median (50 percentile) potassium intakes will achieve an intake 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 assumed safe level and potentially be at risk for hyperkalemia. Only the women having a mean potassium intake from food or lower will be below the assumed safe level for any of the replacement scenarios (Fig. 1).

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 above 3.5 g/day (Fig. 2). Men with mean potassium

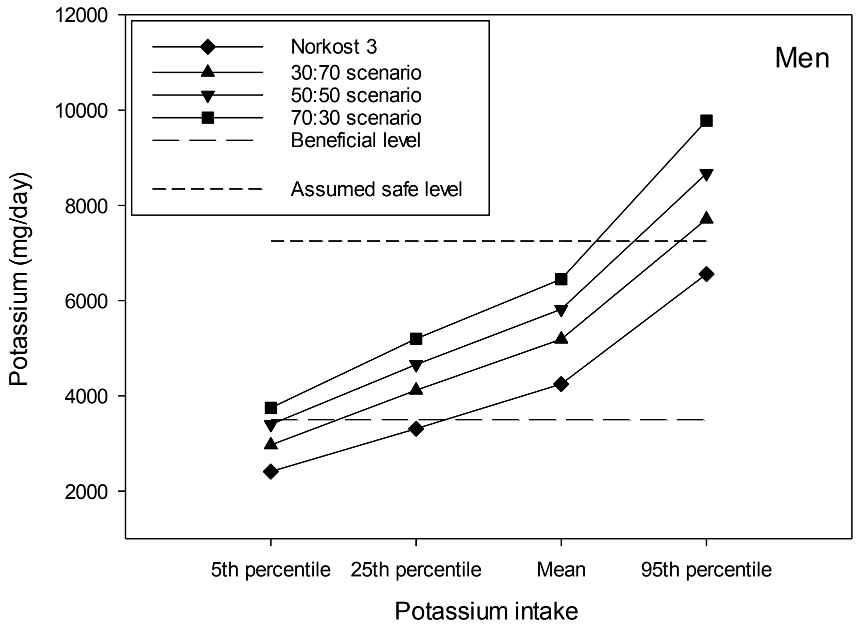

Fig. 2. Potassium intake in men (n = 862) in the 30:70, 50:50 and 70:30 scenarios.

intakes will achieve an intake above 3.5 g/day in all the three scenarios. The men having 25th percentile intake will also reach an intake above 3.5 g/day in all the three scenarios. For all three scenarios, the mean intakes does not exceed the assumed safe level (Fig. 2). For all three scenarios, men with 95th percentile intake will exceed the assumed safe level and be at potential risk for hyperkalemia.

3.8.2. Comparison of percentages of persons getting either benefit or risk of increased potassium

Fifty-nine percent of the healthy 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 (see 3.5).

Thirty percent of the healthy 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 (see 3.5).

One percent of the healthy women have a daily intake of potassium above the assumed safe level based on Norkost 3. In the 30:70 scenario, 3% of the women have a potassium intake above the assumed 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 assumed safe level.

Two percent of the healthy men have a daily intake of potassium above the assumed safe level based on Norkost 3. In the 30:70 scenario, 9% of the men have a potassium intake above the assumed 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 assumed safe level.

In Norway, approximately 9,600 individuals suffer from acute stroke each year (data from 2014), and about 50% are under 76 years of age (NIPH, 2015a) (see 3.2.1). In addition, the approximately 1–2% of the Norwegian population who suffer from high blood pressure will probably benefit from the increased potassium (NIPH, 2015b) (see 3.2.2).

In Norway, 285 persons were waiting for a kidney graft (Leivestad, 2014), about 500,000–600,000 persons had diagnosed or undiagnosed chronic kidney disease (Hartmann et al., 2006), both the prevalence of diagnosed diabetes (type I and II) and estimated number of undiagnosed diabetes were 90,000–120,000 persons (Stene et al., 2004), 156,540 individuals (3.2% of the population) had diabetes in 2011 based on data on dispensed drugs in the Norwegian Prescription Database as a proxy for diabetes (Strøm et al., 2014), the estimated number of users of various drugs affecting the potassium balance was at least 1,500,000 (Sakshaug et al., 2013), the number of infants (one year or below) was 119,487 in 2016, and the number of persons aged 85 years and older was 115,761 in 2016 (SSB, 2017) (see 3.4.2).

A previous study modelled the impact in the general healthy Dutch population aged 18–65 years of replacing 20%, 50% or 100% of sodium chloride with potassium chloride in foods (van Buren et al., 2016). They concluded that a better compliance with the recommended potassium intake of 3.5 g/day would be achieved, however, as we found in Norwegians, a substantial percentage (40%, 33% and 30%) of the Dutch population would still not reach the recommended level in the three scenarios, respectively. They also concluded that the suggested replacements of sodium chloride with potassium chloride would be safe for this age groups of the general population. However, in the paper by van Buren et al. (2016) the intakes of potassium in children and adolescents were not calculated, and neither these age groups nor the numbers of persons in the various vulnerable groups for hyperkalemia were quantified and taken into consideration.

There are many sources of uncertainties in the data used for this evaluation; therefore, it is not possible to say clearly how the uncertainties would affect either the benefit or risk of potassium. The 24-hour recall method used among adults in Norkost 3 has not been validated. However, in 2007–2008 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 were performed to evaluate the reporting accuracy of dietary sodium and potassium intakes using the EPIC-soft 24-hour dietary recall method and compared with 24-hour urinary excretions. Mean sodium reporting accuracy (95% confidence interval (CI)) was 0.73 (0.68, 0.81) for Norway, indicating an underestimation of dietary sodium intake (De Keyzer, 2014). For potassium, the underestimation of intake was 1.6% for men and 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 was used as the food database. If misreporting of sodium and potassium is of the same magnitude as for total energy (Subar et al., 2003; Poslusna et al., 2009), the estimates for sodium and potassium are more likely to be underreported than overreported. However, if potassium containing foods are overreported and sodium containing foods are underreported, the uncertainty will be increased.

Validation studies among 2-year-olds were performed on a previously established FFQ and the results showed a significantly higher energy intake with the FFQ than with the reference method, which was weighed record (Andersen et al., 2004; 2009).

The uncertainty related to the fact that it was not feasible to separate sodium in home-cooking recipes from industrialised foods contributes to an overestimation of intake of sodium from industrial food production and consequently an overestimation of potassium in the scenarios.

Since all salt used in the recipes in the database is sodium chloride, this might lead to an overestimation of sodium intake for those using sodium-reduced types of salt, and also for those who do not add any kind of salt to home-cooked food.

However, 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.

A full quantitative benefit and risk assessment (i.e. by using DALY or QALY) and including an evaluation of severity of risk versus benefit could not be conducted, because of lack of data. 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 industrially produced foods was not possible since it could not be predicted how an increase in potassium would affect stroke incidence or reduction in high blood pressure and we did not have data on the safe level of potassium for most of the vulnerable groups.

4. Conclusions

This benefit and risk assessment describes how many Norwegians, healthy adults, adolescents and children in the general population and persons in specific vulnerable groups, who will be affected if the three scenarios replacing sodium with potassium in industrially produced food were made a reality in Norway. As an overall conclusion, the number of persons likely to face an increased risk was far greater than the number of persons likely to benefit from this measure. This benefit and risk assessment was used as basis for recommendations by the Norwegian Food Safety Authority regarding how to reduce sodium intake in Norway.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.11.044.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.11.044.

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