# Submission for Potassium

**Part A**
**1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.**

Potassium.

**2. Proprietary name(s).**

Not applicable.

**3. Name of the company / organisation / individual requesting a reclassification.**

Not applicable. This request is made on behalf of the natural health products industry.

**4. Dose form(s) and strength(s) for which a change is sought.**

Not applicable. This request is made on behalf of the natural health products industry.

**5. Pack size and other qualifications.**

Not applicable. This request is made on behalf of the natural health products industry.

**6. Indications for which change is sought.**

Not applicable. This request is made on behalf of the natural health products industry.

**7. Present classification of the medicine.**

At the present time, potassium is:

- Unscheduled when in products for external use.
- Unscheduled when in products for oral use, containing 100 mg or less.
- Unscheduled in medicines for oral rehydration therapy parenteral nutrition replacement or dialysis.
- Unscheduled in glucosamine sulphate complexed products containing 600 mg or less of potassium chloride per recommended dose.
- Pharmacy-only medicine when in slow-release or enteric coated forms for internal use.
- Pharmacy-only medicine when in medicines containing more than 100 mg per recommended dose (except in the situations described above when potassium is unscheduled)

Other potassium compounds that are specifically named in the Medicines schedule that are potentially affected are:

Potassium bromide Prescription medicine

| | |
|---|---|
| Potassium chlorate | Unscheduled when in medicines containing 10% or less, and Pharmacy-only medicine when in medicines containing more than 10% |
| Potassium perchlorate | Prescription medicine |

The request to increase the allowed dose of potassium does not involve the scheduling of these other specifically-named potassium substances.

**8. Classification sought.**

It is proposed that potassium is scheduled as:

- Pharmacy-only medicine when the Recommended Daily Dose (RDD) exceeds 3000 mg.
- Pharmacy-only medicine when in slow-release or enteric coated forms for internal use.

**9. Classification status in other countries (especially Australia, UK, USA, Canada).**

***Australia***
Potassium is unscheduled when used as Potassium chloride below 550 mg, or when it is used as Potassium sorbate or Potassium bicarbonate. (550 mg Potassium chloride contains approximately 286 mg potassium).

Potassium is a Schedule 4 substance (Prescription Medicine) only as a salt with other anions such as bromide, chloride, chlorate.

Potassium cation on its own is not mentioned in the schedule.

***Canada***
Potassium salts are Schedule II when in preparations containing more than 5 mmol per single dose (except potassium bromide, potassium gluconate when sold or recommended for administration to cats, potassium para-aminobenzoate, potassium citrate when recommended for the treatment of renal tubular acidosis and kidney stones).

Schedule II is equivalent to Pharmacist-only classification.
5 mmol is approximately 195 mg.

For natural health products, Health Canada mandates that the dose must contain at least 100 mg of potassium per day, if the product is proposed for:

- Source of/An electrolyte for the maintenance of good health.
- Helps to prevent potassium deficiency due to low dietary intake.

and only general uses or purposes are permitted at daily doses below 100 mg of potassium.

These general claims are:

- Source of vitamin(s)/mineral(s)/vitamin(s) and mineral(s), a factor/factors in the maintenance of good health.
- Source of vitamin(s)/mineral(s)/vitamin(s) and mineral(s), a factor/factors in normal growth and development.
- Source of vitamin(s)/mineral(s)/vitamin(s) and mineral(s) to support biological functions which play a key role in the maintenance of good health.

Health Canada requires the following advisory statement when the natural health product contains more than 100 mg/dose:

> Do not use with other potassium-containing supplements or with potassium-containing salt-substitutes (Sweetman 2015).

***UK***

The classification of potassium varies, depending on the nature of the salt. Most potassium salts are unscheduled. Some are scheduled as pharmacy medicines (eg, potassium benzoate) and others are prescription medicines (eg, potassium bromide).

**10. Extent of usage in New Zealand and elsewhere (eg sales volumes) and dates of original consent to distribute.**

No information.

**11. Labelling or draft labelling for the proposed new presentation(s).**

The draft indicative list of substances proposed to be permitted for use in natural health products proposes the following label advisory statement:

> *When intended for mineral supplementation: State the equivalent quantity of potassium.*

This is the same requirement for potassium in Listed Medicines in Australia.

**12. Proposed warning statements if applicable.**

> *When intended for mineral supplementation: State the equivalent quantity of potassium.*

If considered appropriate to allow the increase in maximum daily dose to 3000 mg, it is proposed that any risk could be managed by requiring a warning statement similar to:

> *Do not use with other potassium-containing supplements or with potassium-containing salt-substitutes*.

**13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.**

Manufacturers of current dietary supplement-type products will likely increase the quantity of potassium in their products. It should be noted that all dietary supplement products will be regulated under the NHP Bill. When the NHP Bill is passed, natural health products will have to meet a Code of Manufacturing Practice.

**Part B Reasons for requesting classification change including benefit-risk analysis. This section should be supported by the following:**

This change has been requested as a result of the consultation to inform the Regulations to the NHP Bill. The Ministry has received requests from three applicants that they would like the limit for potassium to be increased to allow for natural health products containing higher daily doses.

**1. A statement of the benefits to both the consumer and to the public expected from the proposed change.**

Specific reasons were not provided by applicants for the requests to increase the allowed daily maximum dose of potassium. One request stated that the current maximum daily dose of 100 mg for use in natural health products is less than 1% of the adequate intake.

Multi-ingredient supplements such as trace elements and essential nutrient formulations are usually taken to complement dietary intake of essential vitamins and minerals. Such products are generally regarded as dietary supplements.

At the present time, under the current Dietary Supplements Regulations regime, therapeutic claims are not permitted for dietary supplements. This creates a peculiar situation where, for example, iron supplements are recognised to aid in the treatment of iron deficiency and iron deficiency anaemia, and are taken for these purposes, yet such products cannot provide advice on their labels on how they should be used. The NHP Bill is intended to address this situation.

When the NHP Act comes into effect, certain health benefits will be able to be claimed for allowed health conditions, provided the manufacturer of the natural health product holds evidence to support the claim(s) being made. For example, iron deficiency anaemia is one of the allowed conditions permitted by the NHP Bill. Similarly, a claim for potassium to help with insulin resistance or high blood pressure could be allowed if there was sufficient evidence.

The clear benefit of allowing the requested change is that it will enable easier implementation of the NHP system by allowing the essential vitamin or mineral to be present in effective quantities or in effective doses in natural health products.

The Ministry of Health's 2006 publication Nutrient Reference Values for Australia and New Zealand's recommended intakes for potassium are:

| Age group and gender | | Potassium mg / day | |
|---|---|---|---|
| | | AI | UL |
| Children | 1-3 years | 2,000 | NP |
| | 4-8 years | 2,300 | NP |
| Boys | 9-13 years | 3,000 | NP |
| | 14-18 years | 3,600 | NP |
| Girls | 9-13 years | 2,500 | NP |
| | 14-18 years | 2,600 | NP |
| Men | 19-30 years | 3,800 | NP |
| | 31-50 years | 3,800 | NP |
| | 51-70 years | 3,800 | NP |
| | > 70 years | 3,800 | NP |
| Women | 19-30 years | 2,800 | NP |

| | | | |
|---|---|---|---|
| | 31-50 years | 2,800 | NP |
| | 51-70 years | 2,800 | NP |
| | > 70 years | 2,800 | NP |
| Pregnancy | 14-18 years | 2,800 | NP |
| | 19-30 years | 2,800 | NP |
| | 31-50 years | 2,800 | NP |
| Lactation | 14-18 years | 3,200 | NP |
| | 19-30 years | 3,200 | NP |
| | 31-50 years | 3,200 | NP |

AI adequate intake
UL upper level of intake
NP = not possible to set because of inadequate data or no clear level for adverse effects.

The Institute of Medicine's (IOM) recommendations regarding potassium are:

| Age group and gender | | Potassium mg / day |
|---|---|---|
| Infants | 0-6 months | 400 |
| | 7-12 months | 700 |
| Children and Adolescents | 1-3 years | 3,000 |
| | 4-8 years | 3,800 |
| | 9-13 years | 4,500 |
| | 14-18 years | 4,700 |
| Adults | 19 years and older | 4,700 |
| Lactation | | 5,100 |

The IOM concluded that there was no evidence of chronic excess intakes of potassium in apparently healthy individuals and thus no UL was established. (https://www.nlm.nih.gov/medlineplus/ency/article/002413.htm)

The WHO guideline for potassium intake in adults and children states that "there was a significant benefit of increased potassium intake when populations consumed 2-4 g/day of sodium; hence, with most populations around the world consuming more than 2-4 g/day of sodium, increased potassium intake should benefit most countries" (World Health Organisation, 2012).

WHO attempted to discern differences in the effect of increased potassium on outcomes according to type of intervention (i.e. supplements, fortification or food), type of potassium supplement (ie, potassium citrate, potassium chloride or other) and gender (World Health Organisation, 2012). In the systematic review and meta-analysis of RCTs in adults reporting blood pressure as an outcome (44), the subgroup analysis of 19 studies using potassium supplements showed a decrease in systolic blood pressure of 3.31 mmHg (95%CI: 1.55, 5.07) (quality of evidence high), and the subgroup analysis of three studies using dietary changes showed a decrease in systolic blood pressure of 4.19 mmHg (95%CI: 1.92, 6.46) (quality of evidence high). The results suggest that an increase in potassium intake from either supplement or food has a beneficial effect on blood pressure.

The IOM recommended daily allowance (RDA) is 4.7g of potassium for adults (Institute of Medicine, 2004). To get that amount of potassium from food, one would have to eat about 4

cups of raisins, 6 cups of spinach or 11 bananas. Nutrition surveys found that women get less than half of the IOM's RDA. The percentage of men and women who consumed equal to or greater than the AI was less than 10 and 1 percent, respectively, in the United States.

Diuretics (prescribed for high blood pressure) reduce potassium levels by flushing it out of the body along with other minerals (Institute of Medicine, 2004). Given potassium's proven blood pressure lowering effect and the low intake of potassium in the general population, it makes sense to supplement with adequate amounts of potassium for both heart and general health.

**2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.**

From the International Alliance of Dietary / Food Supplement Associations (IADSA) publication Vitamin and Mineral Safety (3rd Edition):

Normal serum potassium levels are between 3.5 and 5.0 mEq per L. The risk of exceeding this level through normal dietary or supplemental intake of potassium is small in healthy adults. Cases of hyperkalaemia (toxic levels of potassium in the blood, exceeding 6.5 mEq per L) are usually the result of renal failure or disorders such as Addison disease.

Hyperkalaemia can result in serious cardiac toxicity, but the amounts of potassium associated with such hyperkalaemic states depend heavily on water consumption and kidney function. Because of the impact of these factors as well as that of other electrolytes (principally sodium and chloride), the evidence for potassium safety or toxicity at any particular intake level must be judged cautiously.

Several trials have evaluated the effects of potassium supplementation. Siani et al. (1991) found no adverse effects of potassium chloride at daily doses of 1,900 mg. Fotherby and Potter (1992) found no adverse effects at 2,340 mg per day. However, the evaluations for possible adverse effects (Expert Group on Vitamins and Minerals [EVM] 2003) were not specified endpoints in these clinical trials.

Potassium doses of 1,250 mg administered 3 times per day (for a daily total of 3,750 mg) produced only minor and infrequent adverse effects as revealed by endoscopy (McMahon et al. 1982).

In a follow-up study, the wax-matrix formulation was administered in dosages ranging from 900 to 3,700 mg per day (McMahon et al. 1984). Endoscopically evident erosions of the upper GI tract were evident in a few subjects supplemented with 1,560 to 3,120 mg potassium per day for 21 months. Gastrointestinal symptoms were mild and did not correlate with lesions shown by endoscopic evaluation.

**Possible origin of the 100 mg limit for potassium**

The FDA in 1975 issued a statement that "there have been several reports, published and unpublished, concerning nonspecific small-bowel lesions" related to use of oral drug products containing 100 mg or more potassium. It subsequently required precautionary labeling of such products. The FDA did not provide any dose-response evaluation that would justify such a finding, but concluded that any capsule or coated tablet of a potassium salt intended for oral ingestion without prior dilution with an adequate volume of liquid to preclude gastrointestinal injury should carry the FDA prescribed warning statement.

This may be where the current limit of 100 mg per recommended dose for medicines scheduling originated.

**Expert Group on Vitamins and Minerals (EVM 2003) review**
The UK's EVM 2003 review concluded that the evidence was not sufficient to set an SUL for potassium but could support a guidance level. From the clinical trial evidence judged to be most relevant (McMahon et al. 1982; McMahon et al. 1984; Grimm et al. 1988, 1990), the EVM concluded that "supplemental doses of up to 3,700 mg potassium per day appear to be without overt adverse effects, but may be associated with gastrointestinal lesions diagnosed by endoscopy." Based on this conclusion (with no correction for uncertainty), the EVM set 3,700 mg per day as the guidance level. It was not specified whether this guidance level applied to supplemental potassium or total intake forms all sources. The EVM recognized that the recommended nutrient intake (RNI) in the UK for potassium was 3,500 mg for adults over 18 years of age, but did not identify any estimate of average potassium intake by the population as a whole.

A meta-analysis of clinical trials on potassium (mostly potassium chloride) for possible lowering of blood pressure indicated that this mineral "appeared to be well tolerated in all studies included" (Whelton et al. 1997). The potassium dosages in those clinical trials ranged from 1,876 to 7,820 mg per day. The dietary potassium levels were not identified, but are usually in the 2 to 5 g range.

**European Food Safety Authority (EFSA 2005) review**
EFSA concluded that the available data were insufficient to establish a UL for potassium, but noted that potassium intakes from foods in healthy individuals (average 3 to 4 g per day in adults, generally not exceeding 5 to 6 g per day), as well as supplemental potassium as potassium chloride of about 3 g per day, have not been associated with adverse effects. EFSA noted that certain groups are sensitive to increases in potassium intakes, in particular those with impaired renal excretion of potassium.

**European Food Safety Authority (EFSA 2010) review**
EFSA also published reviews of potassium and sodium sulfate safety in 2010. The EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS) was asked by the European Commission to deliver a scientific opinion on the safety of potassium sulfate and of sodium sulfate when added for nutritional purposes in food supplements as sources of, respectively, potassium and sodium. The review was limited to a review, per the petitioners' request, to review potassium sulfate used in food supplements to provide a maximum of 100 mg potassium per day for adults. EFSA concluded that the proposed use and use levels of potassium sulfate as a sources of potassium were not a safety concern.

**3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.**

Not applicable.

**4. Relevant comparative data for like compounds.**

Not applicable.

**5. Local data or special considerations relating to New Zealand.**

No information.

**6. Interactions with other medicines.**

ACE inhibitors, angiotensin receptor blockers and potassium sparing diuretics may interact with potassium and increase the risk of hyperkalaemia.

On the other hand, the use of medicines such as amnioglycosides, amphotericin B, beta-2-agonists, cisplatin, diurectics, fluconazole, glucocorticoids and mineralocorticoids, methylxanthines, penicillins, sodium phosphates and stimulant laxatives lead to moderate depletion of potassium levels, and potassium supplementation is recommended for some patients (NMD 2012).

**7. Contraindications and precautions.**

No information.

**8. Possible resistance.**

Not applicable.

**9. Adverse events - nature, frequency, etc.**

In double blind randomised placebo controlled clinical trials involving a multi-ingredient essential nutrient formulation also containing zinc, the following adverse events were reported (Rucklidge et al, 2014; Gordon et al 2015):

Headache, dry mouth, sleep disruption, gastrointestinal disturbances, nausea, constipation, agitation, sedation, anxiety, rash (diagnosed by the consulting psychiatrist as being unrelated), abdominal pain, weight gain, blurred vision.

There was no reported to be no significant difference in adverse events between the trial groups and placebo groups. One absence seizure was reported in one of the trials, but further investigations were unable to determine whether there was a seizure, or whether the observer had misinterpreted the event. As the products are a multi-ingredient product, any causal link to any particular ingredient is problematic.

**10. Potential for abuse or misuse.**
Potassium is not habit-forming or a drug of abuse. No potential for abuse or misuse is anticipated.

**References**

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