Submission for Zinc

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

Zinc.

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, zinc is:

- Unscheduled when in products for external use, except zinc chloride in medicines containing more than 5%.
- Unscheduled when in products for internal use, containing 25 mg or less per recommended daily dose.
- Unscheduled in medicines for internal use containing 50 mg or less per recommended daily dose and more than 25 mg per recommended daily dose and in packs which have received the consent of the Minister or the Director-General to their distribution as general sale medicines and that are sold in the manufacturer's original pack and when labelled with a statement that the product may be dangerous if taken in large amounts or for long periods.
- Pharmacy-only medicine when the substance is zinc chloride for dermal use in medicines containing more than 5%.
- Prescription medicine except in the above circumstances.

8. Classification sought.

It is proposed that zinc is scheduled as:

- Unscheduled when in products for external use, except zinc chloride in medicines containing more than 5%.
- Unscheduled when the recommended daily dose does not exceed 50 mg.
- Pharmacy-only medicine when in slow-release or enteric coated forms for internal use.
- Prescription medicine except in the above circumstances.

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

Australia

Zinc is:

- Unscheduled when for internal use, with a recommended daily dose of less than 25 mg.
- Unscheduled when for internal use, where the recommended dose is between 25 mg and 50 mg, when compliant with the requirements of the Required Advisory Statements for Medicine Labels (labels require a statement to the effect that the product may be dangerous if taken in large amounts or for long periods).
- Zinc chloride is scheduled as a Pharmacy medicine when for human dermal use except in preparations containing 5% or less of zinc chloride.
- Zinc compounds are scheduled as Prescription medicines when for internal use, except
  a) in preparations with a recommended daily dose of 25 mg or less of zinc; or
  b) in preparations with a recommended daily dose of more than 25 mg but not more than 50 mg of zinc when compliant with the requirements of the Required Advisory Statements for Medicine Labels.

Canada

Zinc compounds are unscheduled except for zinc chloride and zinc sulfate in injectable form for parenteral nutrition. A number of zinc salts are allowed to be used in natural health products at no more than 50 mg/day.

Health Canada requires that where a product provides more than 40 mg zinc per day, a specific use or purpose statement must be included on the label. These are:

Helps in connective tissue formation.

Helps to maintain healthy skin.

Helps to maintain immune function.

Helps in energy metabolism and tissue formation.

Helps to maintain normal DNA synthesis.

Helps to maintain normal acid-base metabolism.

Helps to maintain healthy bones, hair, nail and/or skin.

Helps to prevent zinc deficiency.

If the following statement is used, it must be verbatim:

Helps to maintain the body's ability to metabolize nutrients.

No warning statements are required by Health Canada for natural health products containing zinc.

UK
Zinc compounds are unscheduled when the daily dose of elemental zinc is below 5 mg a day.

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

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

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

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

12. Proposed warning statements if applicable.

If considered necessary to allow the increase in maximum daily dose to 50 mg (the current cut-off for requiring product to be in a pack approved by the Minister or Director-General of Health), it is proposed that any risk can be managed by requiring the following warning statement:

Prolonged or excessive use can be harmful.

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 zinc 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.

Elevit with Iodine Film coated tablet containing 7.5 mg zinc. This product is currently scheduled as a Pharmacy medicine due to the quantities of other active ingredients. However, should the requested change be approved, it is possible that the manufacturer of this product may increase the quantity of zinc present.

Menevit liquid filled capsule containing 25 mg zinc. This product is currently unscheduled. If the requested change is approved, the manufacturer may increase the quantity of zinc in the product so that the recommended dose is 50 mg.

All other approved medicines containing zinc are either products for external use (including a mouthwash and a toothpaste) or are injections, which are not allowed to be natural health products by the NHP Bill. These will not be affected by the change.

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

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

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 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 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. A claim to treat the common cold with zinc tablets could be allowed.

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.

Medline Plus (US National Library of Medicine) lists a range of conditions where the recommended dose of zinc is 9 to 220 mg daily:

- For treating the common cold: one zinc gluconate or acetate lozenge, providing 9-24 mg elemental zinc, dissolved in the mouth every two hours while awake when cold symptoms are present.
- For diarrhoea in malnourished or zinc-deficient children: 10-40 mg elemental zinc daily.
- For preventing and treating pneumonia in undernourished children in developing countries: 10-70 mg/day.
- For hypogeusia (sense of taste is abnormal): 25-100 mg zinc.
- For the eating disorder anorexia nervosa: 100 mg of zinc gluconate daily.
- For treating stomach ulcers: zinc sulfate 200 mg three times daily.
- For muscle cramps in zinc deficient people with liver disease: zinc sulfate 220 mg twice daily.
- For osteoporosis: 15 mg zinc combined with 5 mg manganese, 1000 mg calcium, and 2.5 mg copper has been used.
- For sickle cell disease: zinc sulfate 220 mg three times daily.
- To increase growth and weight gain in children with sickle cell disease who have not reached puberty: 10 mg elemental zinc per day.
- For treating attention deficit-hyperactivity disorder (ADHD) in children: doses of zinc sulfate 55 mg (15 mg elemental zinc) to 150 mg (40 mg elemental zinc) daily.
- For treating acne: 30-135 mg elemental zinc daily.

- For treating age-related macular degeneration (AMD): elemental zinc 80 mg plus vitamin C 500 mg, vitamin E 400 IU, and beta-carotene 15 mg daily.

See: https://www.nlm.nih.gov/medlineplus/druginfo/natural/982.html

While most of these conditions would not be allowed conditions permitted by the NHP Bill, some are (eg common cold, diarrhoea, acne), and would benefit by having a dose of 50 mg allowed.

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

The Ministry of Health's 2006 publication Nutrient Reference Values for Australia and New Zealand's recommended intakes for zinc and the US National Academies of Sciences, Engineering and Medicine's Institute of Medicine (IOM) recommended zinc intakes presented in the following table:

Age group and gender		Zinc mg / day					
		EAR		RDI		UL	
		NZ	IOM	NZ	IOM	NZ	IOM
Children	1-3 years	2.5	2.5	3	3	7	7
	4-8 years	3.0	4.0	4	5	12	12
Boys	9-13 years	5.0	7.0	6	8	25	23
	14-18 years	11.0	8.5	13	11	35	34
Girls	9-13 years	5.0	7.0	6	8	25	23
	14-18 years	6.0	7.3	7	9	35	34
Men	19-30 years	12.0	9.4	14	11	40	40
	31-50 years	12.0	9.4	14	11	40	40
	51-70 years	12.0	9.4	14	11	40	40
	> 70 years	12.0	9.4	14	11	40	40
Women	19-30 years	6.5	6.8	8	8	40	40
	31-50 years	6.5	6.8	8	8	40	40
	51-70 years	6.5	6.8	8	8	40	40
	> 70 years	6.5	6.8	8	8	40	40
Pregnancy	14-18 years	8.5	10.5	10	12	35	34
	19-30 years	9.0	9.5	11	11	40	40
	31-50 years	9.0	9.5	11	11	40	40

Lactation	14-18 years	9.0	10.9	11	13	35	34
	19-30 years	10.0	10.4	12	12	40	40
	31-50 years	10.0	10.4	12	12	40	40

EAR estimated average requirement
RDI recommended dietary intake
UL upper level of intake

The main concern over zinc from zinc supplementation is zinc toxicity.

The IADSA Vitamin and Mineral Safety Handbook (2014) states that zinc toxicity can occur either acutely or chronically. Acute zinc toxicity includes nausea, vomiting, loss of appetite, abdominal cramps, diarrhoea, and headache (IOM 2001).

The acute effects of excess zinc typically result from ingesting gram quantities of zinc, which could occur by consuming 40 to 60 servings of a typical multivitamin that provides RDA levels of essential nutrients.

Chronic adverse effects of zinc excess are more subtle. The Institute of Medicine (IOM) set its UL value based on a clinical trial in which 60 mg of zinc produced an inhibition of copper-dependent superoxide dismutase. However, the researchers did not determine how much reserve functional capacity is available for this enzyme and whether a small decrease in activity would have any relevant clinical impact. The IOM applied an uncertainty factor of 1.5 to calculate an adult UL of 40 mg zinc per day.

Supplemental zinc has been shown to influence several biomarkers that may have clinical relevance in certain populations. Zinc supplements of 150 mg per day for 6 weeks have been shown to suppress lymphocyte stimulation response, thereby compromising immune function in healthy subjects (Chandra 1984; Greger 1994).

Zinc supplements of 50 mg or more per day have been shown to decrease serum HDL cholesterol levels (Hooper et al. 1980; Freeland-Graves et al. 1982; Black et al. 1988).

Total intakes of 60 mg of zinc decreased levels of copper (Fischer et al. 1984) and iron (Yadrick et al. 1989).

IOM Review (2001)
The IOM found the adverse effects of excess zinc to include a suppressed immune response, decreased HDL cholesterol levels, and a reduced copper status. The IOM did not find adverse effects on human reproduction from excess zinc in their study.
Of the various effects, the IOM selected the reduced copper status as the critical effect for deriving a UL for zinc. Specifically, the IOM used the data showing suppression of copper-dependent superoxide dismutase at 50 mg of zinc supplementation (Yadrick et al. 1989) to identify a Lowest-observed-adverse-effect level (LOAEL).

Although no zinc intake from food was identified by Yadrick and coworkers, the IOM used population data to estimate a dietary zinc intake of 10 mg for the study. Thus, the IOM identified a LOAEL of 60 mg per day for total intake from all sources. A UF of 1.5 was selected to correct for uncertainty in extrapolation from a LOAEL to a NOAEL; the UF of 1.5

was judged to be adequate because reduced copper status is rare. Thus, the IOM UL for zinc is 40 mg per day for total intake from all sources.

European Commission, Scientific Committee on Food (EC SCF 2003)
The EC SCF identified a No-observed-adverse-effect level (NOAEL) for zinc of approximately 50 mg per day. This NOAEL represents an overall conclusion based upon several studies. Although zinc intakes as low as 18.2 mg may decrease copper retention (Festa et al. 1985), this effect is readily corrected by adequate copper intake. Studies looking at the interplay between zinc and copper (Davis et al. 2000; Milne et al. 2001) indicate that copper balance and other indicators of copper status can be maintained when zinc intake is as high as 53 mg.

No adverse effects were observed with 30 mg of supplemental zinc when dietary zinc was near 10 mg (Bonham et al. 2003a, 2003b).

From these data collectively, the EC SCF identified its NOAEL of 50 mg of zinc and proposed an uncertainty factor of 2 to derive a UL of 25 mg for total intake from all sources.

Expert Group on Vitamins and Minerals (EVM 2003)
The UK's EVM selected a LOAEL of 50 mg for supplemental zinc based on several studies (Black et al. 1988; Yadrick et al. 1989; Cunningham et al. 1994; Davis et al. 2000).
To extrapolate from a LOAEL to a NOAEL, the EVM selected a UF of 2, resulting in a derived SUL of 25 mg per day for supplemental zinc. The total daily intake of 42 mg per day would not be expected to result in any adverse effects

Comment
The main concerns other than zinc toxicity (which is unlikely except in gram doses) are the effects on copper absorption (decreased copper may cause anaemia), and a possibility that long term use at high doses may increase the risk of prostate cancer (Leitzmann et al 2003). In the Leitzmann study, the median value of the highest category of zinc intake was 143 mg, but the authors also reported that those who used zinc supplementation were also more likely to supplement with other substances. Ho and Song (2009) summarised more recent findings on the role of zinc in prostate cancer and suggested that the experimental data strongly suggest a protective role of zinc in the prostate, instead of being a cause.

The proposed dose of 50 mg is within the range generally used to treat minor health conditions (for example, the recommended therapeutic dosage of supplemental zinc for athletes is 30-60 mg a day. For the common cold, doses have ranged from 4.5-24 milligrams of zinc (gluconate or acetate) in the form of lozenges taken by mouth every 1-3 hours for 3-14 days or until symptoms resolved) (Mayo Clinic, 2016). Assuming the highest dose every hour, the total zinc intake per day would be 576 mg.

It is considered that the risks posed by increasing the daily dose to 50 mg are low. If there are risks of concern, it is proposed that these and can be managed with an appropriate label advisory statement:

Prolonged or excessive use can be harmful.

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.

Not applicable.

6. Interactions with other medicines.

From the IADSA Vitamin and Mineral Safety Handbook (2014):

There are several medications that can interact with zinc, including antibiotics such as quinolone compounds and penicillamine, as well as several diuretics, such as hydrochlorothiazide. Zinc supplementation can interfere with the activity of medications, or in some cases medication can result in zinc depletion. A full discussion of drug-nutrient interactions is beyond the scope of this report, and individuals taking prescription medication should be advised to consult with their health care provider about potential drug-nutrient interactions.

Certain zinc–folic acid interactions are well documented (Butterworth and Tamura 1989).

But the crucial issue is whether higher intakes of either zinc or folic acid may disrupt the bioavailability or function of the other and, if so, what the intakes associated with such effects are. Some reports of zinc–folic acid interactions suggest the possibility that supplemental folic acid could adversely affect zinc nutriture (Milne et al. 1984; Mukherjee et al. 1984; Simmer et al. 1987), but more recent reports have not uncovered any such interaction (Tamura et al. 1992; Kauwell et al. 1995).

There are no Medline reports of high zinc intakes causing adverse effects through an antagonism of folic acid. Reports of anaemia related to zinc intakes above 110 mg per day all describe the microcytic, hypochromic anaemia associated with copper deficiency, a condition that could also interfere with iron utilisation (Frambach and Bendel 1991; Gyorffy and Chan 1992; Summerfield et al. 1992; Greger 1994).

Certain chemical similarities cause zinc and copper to interact extensively (King and Keen 1999).

Large quantities of zinc can interfere with copper uptake and modify copper binding, and this effect has been used in treating Wilson disease, a defect that leads to excessive copper storage. Iron can interfere with zinc absorption when zinc is administered as a solution, but such interference has not manifested itself when zinc is consumed as part of a meal. Although high levels of calcium can also interfere with zinc absorption, the effect has no demonstrated practical importance. There are indications that large doses of zinc (as high as 80 mg daily) in combination with copper 2 mg can be used safely for approximately 6 years without significant adverse effects (AREDS 2001; AREDS 2002)

7. Contraindications and precautions.

No information. However, as zinc can interfere with copper uptake, it might possibly be contraindicated in people with copper deficiency.

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.

Zinc is not habit-forming or a drug of abuse. No abuse or misuse is foreseen.

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