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# Zinc

| Zinc mg/d | Women | Men | Children 2-5y | 6-9y | 10-13y Girls/boys |
|---|---|---|---|---|---|
| Recommended intake | 7 | 9 | 6 | 7 | 8/11 |
| Average requirement | 5 | 6 | | | |
| Lower level of intake | 4 | 5 | | | |



## Introduction

The biochemical role of zinc ($Zn^{2+}$) is as an essential part of more than 300 enzymes involved in synthesis, metabolism and turnover of proteins, carbohydrates, lipids, nucleic acids and some of the vitamins, for example vitamin A. Well known zinc containing enzymes include superoxide dismutase, alkaline phosphatise and alcohol dehydrogenase. Zinc is essential for normal function of the immune system, normal DNA synthesis and cell division and protects proteins and lipids from oxidative damage. Dietary intake of zinc has also been related to maintenance of normal bone, cognitive function, fertility and reproduction, normal metabolism of fatty acids, acid-base metabolism, normal vitamin A metabolism and maintenance of normal vision (Brown et al 2004, EFSA 2009). However, well defined, clinical zinc deficiency has only been reported in a limited number of cases, related to incomplete total parenteral nutrition, malabsorption and use of drugs. Estimates based on evaluation of zinc intakes and diet composition in different parts of the world suggest that the populations of many countries in Asia and Africa have high risk for developing zinc deficiency, while the risk is low in European countries and North America (Brown et al 2004).

## Dietary sources and intake

Good sources of zinc are meat, milk and milk products and whole-grain cereals. Foods with a high content of fat and sugar have a low content of zinc. Intake of zinc in the Nordic countries is approximately (9.1-13.0 mg/day 1.2-1.4 mg/MJ (see Chapter XX Intake of Vitamins and minerals in Nordic countries).

## Physiology and metabolism

Absorption of zinc is dependent on dose and mainly takes place in the upper part of the small intestine. Absorbed zinc is transported in the blood, mostly bound to albumin. The main proportion of body zinc is located within the cells. The total body content of zinc in an adult is estimated to be between 2 and 4 grams, of which approximately 2/3 is located in muscle tissue and 30 % in bone tissue. Plasma zinc only represents 0.1 % of total body zinc.

High concentrations of zinc are found in parts of the eye and in prostate liquid. Zinc is excreted through the kidneys, skin and gastrointestinal tract. Strong homeostatic mechanisms keep the zinc content of tissues and fluids constant over a wide range of intakes through changes in excretion and absorption. The molecular mechanisms involved in this regulation are not fully understood.

The clinical manifestations of severe zinc deficiency are growth retardation, delayed sexual maturation, skin lesions adjacent to the body orifices, hair loss and behavioural disturbances (Prasad 2003). These clinical signs have almost exclusively been observed in subjects with an inborn error in zinc transport (Acrodermatitis enteropathica) and in adolescents subsisting on diets with a presumably very low availability of zinc. The consequences of moderate and mild zinc deficiency are still unclear. In a meta-analysis of randomized controlled trials by Brown et al. (2002), covering the years 1966- 2001, zinc supplementation was associated with increments in both height and weight. The responses were greater in children with low initial weight-for-age z scores. However, results from a more recent meta-analysis did not show any improvements in linear growth in intervention studies including zinc supplementation only (Ramakrishnan et al. 2009). Studies published after those included in the study by Brown et al. accounted for the difference, possibly reflecting secular improvements in zinc status in many parts of the world (Ramakrishnan et al. 2009). Further, zinc has successfully been used as a pharmacological agent to treat chronic diarrhoea in countries where zinc deficiency is prevalent (Lazzerini M, Ronfani L 2012). Zinc plays a role in the synthesis and action of insulin and seems to stimulate insulin action and insulin receptor tyrosine kinase activity, but the role of zinc supplementation in the prevention of type 2 diabetes mellitus remains unclear (Beletate et al. 2007). Further studies are also needed to assess potential benefits and risks of maternal zinc supplementation on pregnancy and lactation outcomes (Hess & King 2009).

## Requirement and recommended intake

*Adults*

The only biochemical indicator recommended by WHO/UNICEF/IAEA/IZiNCG (2007) to assess the zinc status of populations (not individuals) is measurement of serum or plasma zinc concentration. Serum zinc concentrations fall sharply when dietary zinc intakes are less than ~ 2 to 3 mg/d, but rise slightly but continuously when intakes are greater, reaching plateau when intakes reach ~ 25 to 30 mg/d (Gibson et al 2008), However, since plasma zinc concentration is influenced also by factors unrelated to zinc status, such as food intake, infection, tissue anabolism or catabolism, the measurement cannot be used for estimating zinc requirements. In addition, the activities of the zinc dependent enzymes explored so far have not proven sensitive enough to identify optimal or desired levels of zinc intake. In populations where signs of zinc deficiency have been observed, reliable food intake data are usually not available. Consequently, zinc requirements have to be estimated by the factorial method, i.e. estimates of the daily losses of zinc and the corresponding amount of zinc to be ingested to replace these losses. Additional zinc is needed during periods of tissue growth. The use of the factorial method to estimate zinc requirements is complicated by a strong homeostatic regulation of body zinc, primarily through changes in endogenous zinc excretion and by the pronounced impact of diet composition on zinc absorption and potentially also on excretion of zinc. At zinc intakes close to zero, total endogenous zinc losses through urine, faeces and skin are of the order of 0.5-0.6 mg/d (Baer and King 1984, Hess et al 1977), while on an intake of 10-15 mg of zinc, losses will amount to > 4 mg/d.

During the first days on low zinc intakes, before adaptive mechanisms have had full effect, zinc losses are approximately 1.0 and 1.4 mg/day for women and men, respectively (Baer and King 1984, Hess et al 1977).

To reach a *dietary recommendation* from a figure for *physiological* requirement, an estimate of the efficiency of absorption has to be applied. Fractional zinc absorption is dependent on zinc content; when intakes are increased, fractional absorption decreases. However, the relationship is not linear and the amount of zinc absorbed increases when zinc intake increases. Superimposed on the relationship between intake and fractional absorption is the effect of enhancing and inhibiting components in the diet (Sandström and Lönnerdal 1989). At low intakes of zinc in diets with no inhibitors the fractional absorption can be > 50 % (Sandström 1992), while at more common intakes 15-40 % is absorbed, depending on the composition of the diet. Phytic acid, which is present in cereals and leguminous plants, inhibits zinc absorption, while animal protein counteracts this inhibition (Rossander-Hultén et al 1992, Sandström et al 1980). From a cereal-based meal with a high content of phytic acid, 10-15 % of the zinc is absorbed, while from meals based on animal protein sources 20-40 % can be absorbed depending on zinc content. The negative effect of phytic acid is in some foods partly counteracted by a high zinc content.

A number of single meal studies using radioisotope techniques have been undertaken to identify the dietary factors affecting absorption and their relative impact. Relatively few studies have measured zinc uptake from total diets with realistic compositions and the techniques used in these studies are based on the use of stable zinc isotopes, which are typically added in amounts which account for 20 % or more of the total zinc content.

The Food and Nutrition Board in the USA (2001) recommends a daily intake of 11 mg/d for men and 8 mg/d for women. Although the absolute numbers are similar to those of the other reports and the approach used is the same factorial method, they have introduced a partly different concept in the calculations. The data used are almost exclusively derived from total diet studies using semi-synthetic basic diets or blended low zinc foods with added zinc and stable zinc isotopes for the absorption estimates. This committee uses a three-step approach to reach the average requirement of zinc. First, the losses of zinc via routes other than the intestine are estimated. These losses are regarded as constant over the range of intake that encompasses zinc requirements. For men the estimates for losses via kidneys and sweat, integumental losses and losses in semen are estimated to be 0.63, 0.54 and 0.1 mg/d, respectively. For women menstrual zinc losses are estimated to be 0.1 mg/d and losses via kidney and skin 0.44 mg/d and 0.46 mg/d, respectively. Thus, total losses via these routes are 1.27 mg/d and 1.0 mg/d for men and women, respectively. The second step and partly new concept is the use of the relationship between quantity of zinc absorbed and the excretion of endogenous zinc via the intestine. In the stable isotope/balance studies used for this calculation the data suggest a linear relationship between absorbed zinc and intestinal (endogenous) excreted zinc. The constant losses via other routes are added and the point where the absorbed zinc is equal to the sum of the endogenous intestinal excretion and the other losses is taken as the minimum requirements for absorbed zinc (i.e. the *physiological* requirement) (3.84 mg/d for men and 3.3 mg/d for women). The same studies are then used to calculate the amount of zinc that has to be ingested to give this amount of absorbed zinc. These calculations give an average dietary requirement of zinc of 9.4 mg/d and 6.8 mg/d, respectively. (It should be noted that these values correspond to fractional absorption of 0.41 and 0.48). A CV of 10 % is used as an estimate of the inter-individual variations and the RDA is set to 11 mg/d and 8 mg/day. Thus, the major differences in the American estimates compared to other reports are a much higher estimate of the physiological requirement, especially the estimates of the endogenous intestinal losses, a higher estimate of the fractional absorption and a smaller figure for the inter-individual variations.

In the Nordic Nutrition Recommendations 2004, the following estimates were made. For the estimate of the endogenous losses and routes other than the intestine the Food and Nutrition Board figures (2001) have been used, although it should be noted that the majority of the studies quoted in that report were performed at a time when e.g. reference urine samples were not available for quality control. Losses via kidneys, skin, semen or menses are thus set to 1.27 mg/d for men and 1.0 mg/d for women. Endogenous intestinal losses are estimated to 1.4 mg/d for both genders based on the observed losses at low intakes (1-5 mg/d). Thus, 2.67 mg/d and 2.4 mg/d for men and women, respectively, have to be absorbed in order to replace these losses. At these levels of intake, absorption from a mixed animal and vegetable protein diet more realistic for Nordic conditions is assumed to be 40 %. The average dietary requirement of zinc is consequently 6.4 mg and 5.7 mg, respectively. The inter-individual variation in requirement is set to 15 %, based on resulting in recommended intakes of 9 (8.3) mg/d for men and 7 (7.4) mg/d for women. This recommended intake probably has a high safety margin as the ability to adapt to lower intakes appears to be substantial. In NNR 2012 the RI from 2004 are kept unchanged.

*Lower limit of intake*

Balance studies with a combination of a semi-synthetic formula based on egg white and low zinc foods have shown that an intake of 4.4 or 4.6 mg/day for 35 days or 10 weeks do not give any indications of an impaired zinc status or the need for adaptation, based on plasma levels and zinc excretion in urine (Johnson et al 1993, Pinna et al 2001). The latter study also showed no changes in exchangeable zinc pool mass during the low intake. These data are used as the basis for the lower limit of zinc intake.

*Children*

Data on endogenous losses of zinc at different intakes are almost completely lacking for children. In relation to body weight, children appear to have larger losses of zinc than adults. The need of zinc for growth is approximately 175 μg/kg/day during the first month and then decreases to approximately 30 μg/kg/day at 9-12 months (Krebs and Hambidge 1986). For growing children the need for zinc is based on basal losses of 0.1 mg/kg and a zinc content in new tissue of 30 mg/kg. For adolescents, growth is assumed to result in an average zinc content in new tissue of 23 mg/kg, due to an increase in fat tissue with a lower zinc content than in children. The *physiological* needs for rapidly growing adolescents can consequently be increased by 0.3-0.4 mg/day. Applying the same principles as for adults, the recommended zinc intake varies from 2 mg in the youngest age group to 12 mg for adolescent boys.

*Pregnancy and lactation*

The total need for zinc during pregnancy for the foetus, placenta and other tissues is approximately 100 mg (King 2000). This additional need for zinc in pregnancy can be met by an increase in zinc intake or by adjustment in zinc homeostasis. There is no evidence that pregnant women increase their intake of zinc, therefore homeostatic adjustments in zinc utilization must be the primary mechanism for meeting the additional zinc demands for reproduction (King 2000). It is assumed that an increased efficiency of zinc absorption or other metabolic changes occur during pregnancy and these changes ensure that the requirement for zinc can be met at unchanged intake. However, studies in this area are inconclusive and there are some that show increased absorption during pregnancy (Swanson and King 1982), while other studies found no significant increase in fractional absorption (Fung et al 1997). The results from the latter study might reflect inadequate power of the study design. The U.S. recommendations from 2001 for zinc intake in pregnancy are based on this reference. In NNR 2012, the recommended intakes are based on an increase of the physiological requirement by 0.7 mg/day, with adjustment for absorption. With adjustment for absorption the additional dietary intake is set to 2 mg/day.

Ortega and co-workers (1997) showed lower zinc concentration in human milk of women consuming less than 7.5 mg/day during the third trimester. Zinc content in human milk is approximately 2.5 mg/L in the first month of lactation and thereafter falls to approximately 0.7 mg/L after 4 months (Krebs and Hambidge 1986). Theoretically this means that zinc requirement of lactating women is double that of non-lactating women. A fractional increase in zinc absorption of 75-80 % has been shown for lactating women compared with non-lactating-postpartum or never-pregnant women (Fung et al 1997, Moser-Veillon et al 1995). Release of zinc from bone tissue could also possibly be an explanation why zinc concentrations in human milk are relatively independent of the mother’s zinc intake and do not seem to result in zinc deficiency of the mother even after a long time of lactation. An elevated intake corresponding to the zinc content in human milk is recommended to women lactating for a long time, i.e. a physiological need of 1.7 mg/day. With adjustment for absorption additional dietary intake is set to 4 mg/d.

## Reasoning behind the recommendation

The recommended daily intake in NNR 2004 was based on estimated zinc requirements by the factorial method, i.e. estimates of the daily losses of zinc and the corresponding amount of zinc to be ingested to replace these losses. Additional zinc is needed during periods of tissue growth. The reference values are kept unchanged compared to NNR 2004, since there are no new scientific data to justify any major changes.

## Upper intake levels and toxicity

The risk of excessive intake of zinc from food alone is very low. Symptoms of acute toxicity from excessive intake occur at intakes of gram quantities of zinc and are related to consumption of dietary supplements. At considerably lower intakes, there is a risk for negative effects on the metabolism of other trace elements, especially copper. Reduced activity of copper-containing enzymes has been observed with intakes of 50 mg Zn/day and with a slightly higher intake ≥150 mg, more pronounced signs of impaired copper metabolism have been observed and also negative changes in immune defence and blood lipids (Fischer et al 1984, Yadrick et al 1989, Hooper et al 1980). More recent studies in which strictly controlled intakes of copper and zinc were given showed that at intakes of 50 mg zinc/day, no adverse effects on a wide range of relevant indicators of copper status could be observed (Davis et al 2000, Milne et al 2001, Bonham et al 2003a, Bonham et al 2003b). Based on these data, the EU Scientific Committee on Food set an uncertainty factor of 2 and arrived at an upper level of 25 mg zinc per day. As there are no data on adverse effects of zinc intakes on children and adolescents, they extrapolated upper levels for children on a surface area basis.

With this background it is recommended that the intake of zinc does not exceed 25 mg/day for adults and 12.5 mg/day for children.

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