

## **EXPERT GROUP ON VITAMINS AND MINERALS**

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### **REVISED REVIEW OF ZINC**

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The attached review of zinc is an amended version of the paper presented to the Expert Group at the meetings in July 1999 and in October 2001.

The following annexes are included with the paper:

- Annex 1. Intakes of zinc from food and supplements in the UK
- Annex 2. COT Review of zinc (hard copy only)

Expert Group on Vitamins and Minerals Secretariat  
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## Zinc

### Chemistry and Geochemistry

1. In nature, zinc occurs as the sulphide (ZnS) in blende and sphalerite, as the silicate (ZnSiO<sub>4</sub>) in calamine, willemite, and zinc spar, and as the oxide (ZnO) in zincite.
2. Zinc is classified as a group IIB post-transition metal and has an atomic weight of 65. Exposed zinc metal forms a covering layer of basic zinc carbonate that resists further corrosion. It is this property that accounts for many of the industrial uses of zinc. Zinc characteristically forms divalent cationic salts of varying solubility and also forms relatively stable co-ordinate bonds with electronegative ligands, such as oxygen, sulphur and nitrogen. However, unlike other transition metals, zinc is relatively stable in the divalent state and does not undergo redox changes.

### Natural Occurrence

3. Zinc is the 17<sup>th</sup> most abundant element, present in the earth's crust at a concentration of approximately 65 ppm and in seawater at a concentration of 9-21 ppb. Essential for life, zinc is found in all plant and animal tissues (Venugopal and Luckey, 1978).
4. The human body contains approximately 2 g of zinc, with about 65% found in muscle and 20% associated with bone. Zinc is present in all cells of all tissue types, particularly inside the nuclei. However, some tissues are particularly zinc rich. High concentrations are found in the adrenal gland, skin, certain areas of the brain, pancreas, choroid of the eye, prostate gland and semen.

### *Occurrence in food, food supplements and licensed medicines*

#### *Food*

5. Data on zinc intakes from foods and supplements are provided in Annex 1.

*Licensed Medicines products for oral use*

6. Products containing zinc (as the sulphate, oxide or gluconate) may be sold in supermarkets and other retail outlets without the supervision of a pharmacist. The maximum permitted daily dose is 5 mg elemental zinc.
7. Five licensed medicinal products contain zinc as the sole active constituent. Of these, one is licensed to be sold in supermarkets and other retail outlets. The other four may only be sold under the supervision of a pharmacist. The licensed indications relate mainly to the treatment and prevention of zinc deficiency.
8. Zinc is also included as an active ingredient in 18 multi-nutrient products. Of these, four may be sold in supermarkets and other retail outlets, whilst fourteen may only be sold under the supervision of a pharmacist. Their licensed uses include the prevention and treatment of nutrient deficiencies, debility, supplementation of special diets and malabsorption.
9. The maximum daily doses specified in the licences for the GSL products are up to 5 mg. For products sold under the supervision of a pharmacist, daily doses up to 150 mg are specified.

*Dietary supplements*

10. Zinc salts are also widely available in mineral supplements and health foods.

**Intake/Exposure**

*Food*

11. Intakes of zinc from food and supplements in the UK diet have been provided but since they contain unpublished data they have been attached at annex 1.
12. Results of the Second National Health and Nutrition Examination Survey (Mares Perlman *et al.*, 1995), suggest that zinc intakes are declining in the US. This is probably due to reduced meat consumption, modern food processing, and lower soil concentrations. Populations likely to have low intakes include infants, pre-school children, adolescents, women (particularly pregnant women), older adults, lower socio-economic groups, and vegetarians.

*Drinking water*

13. Under normal conditions, the intake of zinc from drinking water is very low ( $\mu\text{g}$  quantities per litre). According to the US National Academy of Sciences/National Research Council (NAS/NRC), the highest observed concentrations of zinc in

drinking water in the US were 1.3 – 1.5 mg/L (NAS/NRC, 1980). Consequently, a person drinking 2 litres per day would consume a maximum of 3 mg/day from this source.

14. Concentrations of zinc in tap water may be elevated as a result of dissolution from pipes. Contaminated wells may also lead to high exposure. The current regulatory limit in both the UK and US is 5 mg/l. However, this is based on taste and appearance rather than any safety criteria.
15. The WHO Guidelines for Drinking Water Quality (WHO, 1993) recommend a guideline value of 3 mg/l also on the basis of taste and appearance and adds that "derivation of a health-based guideline value is not required at this time".
16. The US Environmental Protection Agency has proposed a "health advisory" of 2 mg/l in water (see TOX/95/36, Annex K) which is attached as Annex 2.

#### *Galvanized food containers and cooking utensils*

17. Many reports of acute toxicity have been related to food poisoning incidents, several cases resulting from the storage of food or drink in galvanized containers. New, galvanised cooking utensils may also be a source of potentially high zinc exposure.

#### *Environmental/workplace exposure*

18. Zinc is used extensively in industry and exposure may be particularly high in industrial waste sites. Zinc itself is not considered an industrial health hazard. However, inhalation of dusts containing zinc or zinc compounds, in the presence of metals such as arsenic, cadmium, manganese and lead, can result in metal fume fever.

### **Recommended amounts**

19. Although average recommended intakes are often quoted, precise requirements for zinc vary with age and during pregnancy and lactation. Various recommendations from different advisory bodies are given in Table 1.

Table 1: Recommended daily zinc requirements

		RDA or RNI (mg/day)	Lower Reference Nutrient Intake (mg/day)	Estimated Average Requirement (mg/day)	Reference Nutrient Intake (mg/day)
UK <sup>1</sup>	Adult male	9.5	5.5	7.3	9.5
	Adult female*	7	4.0	5.5	7.0
US <sup>2</sup>	Adult male	15			
	Adult female	12			
Norway <sup>3</sup>	Adult male**	9			
	Adult female**	7			

\*plus 6 mg/day in the first four months of lactation, and 2.5mg/day for subsequent lactation.

\*\* upper limit set at 45 mg/day.

<sup>1</sup> COMA (1991).

<sup>2</sup> The US NAS/NRC (1989)

<sup>3</sup> The Standing Nordic Committee on Foods (1996)

20. Provisional estimates of average zinc requirements proposed by WHO are given in Tables 2 a and b (WHO, 1996). The basal requirement is the intake required to prevent pathologically relevant and clinically detectable signs of impaired function attributable to inadequacy of the nutrient. The normative requirement is the level of intake that serves to maintain a level of tissue storage or other reserve that is judged to be desirable. These estimates take into account age differences and different availabilities of zinc in different diets.

Tables 2 a and b (from WHO, 1996).

*Due to copyright restriction Tables 2 a and 2 b cannot be reproduced in this paper. Tables 2 a and 2 b come from the following publication:*

*WHO (1996). Trace elements in human nutrition and health. World Health Organisation. Geneva.*

## **Analysis of tissue zinc concentrations and zinc status**

### *Zinc Status*

21. Sensitive, pathologically relevant indices of tissue zinc concentrations related to dietary intake are at present lacking or are insufficiently validated (WHO, 1996). Zinc concentrations in plasma, blood and hair and urinary zinc excretion all decrease where there is zinc deficiency but these parameters can be affected by other conditions unrelated to zinc deficiency. The metallothionein gene is transcriptionally regulated by zinc and monocyte metallothionein mRNA or erythrocyte metallothionein protein may have potential as indices of dietary zinc status in humans (Sullivan *et al.*, 1998).
22. In a study by Davis *et al.* (2000) conducted on a metabolic ward, 25 healthy post menopausal women were fed diets containing low (1 mg/day) or high (10 mg/day) copper for 180 days. For one 90 day period, the women were given a supplement of 50 mg/day zinc, for the other 90 days a placebo. The basal diet contained 3 mg/day zinc. Zinc supplementation significantly increased extracellular but not erythrocyte superoxide dismutase activity. The effect was more apparent when the subjects received the low copper diet. Zinc supplementation of the low copper diet also resulted in an increase in amyloid precursor protein in platelets. Zinc supplementation also resulted in an increase in plasma zinc, free thyroxine and mononuclear 5' nucleotidase activity.

## Bioavailability

### *Bioavailability of zinc in food*

23. The zinc content and physiological and environmental factors affecting zinc uptake and utilisation determine a diet's adequacy for zinc (Sandstead, 1994; Walsh *et al.*, 1994; Sandstrom, 1997 and references therein).
24. The solubility of zinc at the site of absorption has a major impact on availability. Zinc in food is relatively extractable at gastric pH but binds to organic components at higher pH. This is reflected in the much lower fractional absorption of zinc in a meal compared with the same dose in solution. Low molecular weight ligands, e.g. amino acids or other organic acids have the potential to increase solubility and facilitate absorption, while other organic substances form poorly soluble complexes with zinc and reduce absorption.
25. Zinc bioavailability may be low in vegetarian diets due to the presence of phytates. In a study by Hunt *et al.*, 1998, 21 women were given a lactoovo vegetarian diet for 8 weeks and then a non-vegetarian diet for 8 weeks in a cross-over design. Diets were provided and labelled zinc was used to measure Zn absorption. Zn in the veg diet came from wholegrains and legumes and it contained 3 times more phytate than the meat diet. Both diets contained about 11.8 mg Zn / 9.6 MJ. Absorption in the vegetarian diet was less efficient: 2.4 mg/d (26%) compared to 3.7 mg/d (33%) in the meat diet,  $p < 0.01$ . Although this small difference is statistically significant, the authors question its physiological significance. Elemental Zn balance didn't differ significantly and plasma Zn was slightly lower on the vegetarian diet. The meat diet in this study met the WHO criteria for a 'high bioavailability' and the vegetarian diet for 'moderate bioavailability'. However, WHO assume that absorption is 50-55% for 'high' and 30-35% for 'moderate'. This study found much lower absorbencies, <35% even for a 'high bioavailability' diet. The results suggest greater risk of Zn deficiency in vegetarians but also suggest that Zn requirements can be met and balance maintained with a vegetarian diet containing wholegrains and legumes.
26. Table 3 (below) summarises negative and positive influences on the absorption of zinc.

Table 3

Compounds facilitating zinc absorption:

Histidine (and other amino acids)	Prostaglandins	Citric acid
d-penicillamine	Metallothionein	Picolinic acid
Essential fatty acids	Glucose	

Factors associated with decreased zinc absorption:

Dietary	Absence of appropriate absorption ligands	Gastrointestinal dysfunction
Calcium Copper Iron Phytate (inositol hexaphosphate) Alcohol Fibre Lignin EDTA Polyunsaturated fatty acids Products of maillard browning	Acrodermatitis enteropathica Hypothyroidism Cystic fibrosis Pancreatic dysfunction Phenylketonuria	Intestinal mucosal disease Malabsorption syndrome Gastrointestinal surgery

27. With the exception of zinc in maternal milk, which is estimated to be 80% bioavailable, zinc in the diet is approximately 20-40% absorbable (Solomons and Ruz, 1997; WHO, 1996). Cooking and processing may affect zinc content in some food products. Flesh foods provide the best sources of bioavailable zinc, in particular red meat, offal and oysters. The high phytate content of cereals and legumes results in impaired zinc absorption. However, legumes provide better sources of zinc than whole-grain cereals, although the latter can be improved by the separation of the bran. Animal proteins counteract the inhibiting effect of phytate. Dairy products are low in zinc.

28. Table 4 categorises diets according to their low, medium or high potential zinc bioavailability and the predicted fraction of zinc absorbed (WHO, 1996). The fractional zinc absorption is inversely dependent upon the zinc content of the meal or solution. At low concentrations, and in the absence of potential inhibitory agents, fractional absorption can be >50%. High intakes of zinc result in lower fractional absorption but this is not directly proportional to the increase in content so that a higher amount is always absorbed with a higher intake. The extent to which zinc uptake is modulated by interaction with *all* the other components within a meal is difficult to assess but it is clear that daily intake based on food table calculations may not proportionately be a good reflection of uptake.

Table 4. WHO provisional criteria for categorising diets according to their potential availability of zinc (adapted from WHO, 1996)

High availability	Refined diets low in cereal fibre, low in phytic acid content and with phytate/zinc (molar) ratio < 5; adequate protein content principally from non-vegetable sources, such as meats, fish. Includes semisynthetic
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	formula diets based on animal protein.
Moderate availability	Mixed diets containing animal or fish protein. Lacto-ovo, ovo-vegetarian or vegan diets not based primarily on unrefined cereal grains or high-extraction-rate flours. Phytate/zinc molar ratio of total diet within the diet is fortified with inorganic calcium salts ( $> 1 \text{ g Ca}^{2+}/\text{day}$ ). Availability of zinc in moderate availability foods improves when the diet includes animal or protein sources or milks.
Low availability	Diets high in unrefined, unfermented and ungerminated cereal grain, especially when fortified with inorganic calcium salts and when intake of animal protein is negligible. Phytate/zinc molar ratio of total diet exceeding $15^b$ . High-phytate soya-protein products constitute the primary protein source. Diets in which, singly or collectively, approximately 50% of the energy intake is accounted for by the following high-phytate foods: high-extraction rate (90%+) wheat, rice, maize grains and flours, oat-meal, millet; chapati flours and “tanok”; sorghum; cowpeas; pigeon peas; grams; kidney beans; blackeye beans; groundnut flours. High intakes of inorganic calcium salts ( $>1 \text{ g Ca}^{2+}/\text{day}$ ), either as supplements or as adventitious contaminants (e.g. from calcareous geophagia), potentiate the inhibitory effects of category C diets; low intakes of animal protein exacerbate these effects.

### *Bioavailability of zinc salts and supplements*

27. When taken with a meal, the bioavailability of zinc from salts in aqueous solutions or from proprietary supplements is affected by the same factors that affect zinc uptake from food. However, greater absorption is obtained if salts and supplements are taken in the fasting state.
28. The relative solubilities of the different salts vary considerably. Zinc sulphate and zinc chloride are both very soluble and zinc acetate is freely soluble. Zinc carbonate and zinc oxide are poorly soluble and both are poorly absorbed. Intragastric pH, which varies from pH 1-7, affects the solubility and therefore the bioavailability of zinc salts. Henderson *et al.* (1995) demonstrated that zinc acetate was the most highly bioavailable form at low pH, and zinc oxide was the least bioavailable at high pH.
29. A zinc-histidine complex has been proposed as a particularly well-absorbed and well-tolerated form of oral zinc; administration of 15 mg zinc as a zinc histidine complex (1:2) gave an identical serum-zinc response as 45 mg zinc taken as sulphate. Absorption was estimated to have been higher than 50% (Scholmerich *et al.*, 1987).

Neve *et al.* (1993) showed that 45 mg of zinc contained in gelatin capsules in the form of gluconate had greater bioavailability than capsules containing the equivalent dose as zinc sulphate. There was no difference between the bioavailability of zinc sulphate administered as a solution or within gelatine capsules. Bioavailability of zinc in either sulphate or gluconate form was improved when given as a divided dose (3 x 15 mg).

## Interactions

### *Zinc-copper interaction*

30. A mutual antagonism exists between copper and zinc in terms of uptake. This can be explained by similarities in electronic configuration in that both are  $d^{10}$  ions. As a consequence, imbalances may occur because of either deficient or excessive copper intake, or excessive intake of zinc relative to copper. Here, the negative effect of excessive zinc upon copper absorption will be considered.
31. Hall *et al.* (1979) found that high levels of dietary zinc in the rat induced the synthesis of intestinal metallothionein. Fischer *et al.* (1983) went on to show that a decrease in copper absorption correlated with the appearance of intestinal metallothionein. Since metallothionein has a greater affinity for copper than zinc, it was suggested that copper could displace zinc and that the metallothionein acted as a trap to sequester copper within the epithelial cell. The entry of copper to the body is therefore controlled, at least in part, by metallothionein. When the mucosal cells are rich in metallothionein, little copper traverses the cells in to the body but is returned to the intestinal lumen with the turnover of mucosa cells.
32. Studies in both humans and animals (Sandstead, 1982; Greger *et al.* 1978; Burke *et al.* 1981; Hall *et al.*, 1979) have demonstrated that elevated levels of dietary zinc can have a negative effect upon copper balance. Furthermore, the amount of copper required to maintain balance is directly related to the amount of dietary zinc (see Figure 1 below).

Figure 1. Effect of the zinc-copper antagonism on copper required for equilibrium. Based on a study in which diet intervals were 26-30 days, dietary protein was 100 g and balance was measured during the last 12 days of each diet interval. Adapted from Sandstead (1995)

33. In a study by Milne *et al.* (2001) 21 healthy post-menopausal women, housed in a metabolic unit, were fed diets containing 2 mg copper and 9 mg zinc for 10 days. They were then divided into two groups, and fed diets containing either 1 or 3 mg copper. After equilibration, the groups were fed a diet containing 3 mg zinc for 90 days. This was followed by another equilibration period, following which the dietary zinc content was raised to 53 mg/day. The women were in positive copper status only

when the diet contained 53 mg zinc and 3 mg copper. Immunoreactive ceruloplasmin concentrations and platelet cytochrome c oxidase activity on a platelet number basis were significantly lower and the ratio between enzymatic and immunoreactive ceruloplasmin significantly higher when the subjects received low rather than high dietary zinc. The authors concluded that low rather than high dietary zinc was more effective in inducing the changes associated with decreased copper status in post-menopausal women. Whole blood glutathione concentration and erythrocyte glutathione peroxidase activity were lower during the high than during the low zinc intake.

34. The effect of zinc on copper is exploited therapeutically to “de-copper” Wilson’s disease patients

#### *Zinc-iron interaction*

35. An interaction also arises between zinc and iron due to the similarity of their ionic electronic configuration resulting in mutual competition for common absorption sites.
36. When given in solution, high levels of iron negatively affect zinc absorption. However, zinc absorption from food is not affected by haem iron (Solomons 1986). Solomons postulated that it is the total amount of ionic species that affects the absorption of zinc and that  $> 25$  mg Fe may produce a measurable effect upon zinc absorption. Consequently, to avoid adverse effects on zinc uptake, the author recommended that iron supplements be taken between meals.
37. The reverse interaction has also been demonstrated. Sufficiently high zinc:iron ratios have been shown to inhibit iron uptake in animals (Solomons and Ruz, 1997 and references therein). Data from human studies are more scant.
38. Iron and zinc sulphate given in solution in molar ratios of 1:1 and 1:2.5 resulted in significantly reduced plasma iron AUC (area under the curve) in healthy males whereas a ratio of 2.41:1 had no such effect (Crofton *et al.*, 1989). Although increased plasma clearance of iron could not be discounted, the authors also suggested that it was physiologically reasonable to suppose that zinc could interfere with the intestinal uptake of iron. A five-fold ratio of zinc to iron (15 mg: 3 mg) given in solution resulted in a 56% reduction in iron absorption. However, the same 5:1 excess of zinc given in a hamburger meal had no effect (Rossander-Hulten *et al.*, 1991).
39. Studies in rats have shown that a high level of zinc supplementation can affect iron storage and encourage depletion, interfere with iron uptake in the liver, shorten red blood cell life-span and cause anaemia due to faster iron turnover. (Walsh *et al.*, 1994 and references therein). Since transferrin transports both iron and zinc in plasma, interaction between zinc and iron may be at the transport level. However, these effects may also be secondary to zinc-induced copper deficiency (Linder and Hazegh-Azam, 1996 and references there in).

*Zinc-magnesium and zinc-calcium interactions*

40. Daily supplements of 142 mg zinc, as sulphate, given to adult males, were shown to have a negative effect on the intestinal absorption of both dietary magnesium and dietary calcium. However, the adverse effect on calcium uptake occurred only when calcium intake was low and below the US Recommended Dietary Allowance (Spencer *et al.*, 1987, 1992 & 1994). Conversely, high levels of calcium in the diet can have a negative effect on absorption of zinc.

*Zinc-drug interactions*

41. Dosages prescribed for fluoroquinolone antibiotics often allow only a narrow margin between acceptable decreases in bioavailability and decreased effectiveness. Zinc (along with iron and calcium) reduces the bioavailability of these drugs (Lomaestro and Bailie, 1995).

**Absorption and distribution**

42. Uptake of ingested zinc is by both passive diffusion and an (unknown) membrane-associated carrier-mediated process. Carrier-mediated uptake is an active, energy requiring process and occurs throughout the small intestine, particularly the jejunum. During the digestion process, zinc is released from its dietary ligands and forms complexes with low molecular weight intestinal ligands, both endogenous and dietary derived. These ligands serve either to impede or to enhance the availability of zinc to the intestinal microvilli, depending on their relative affinity for zinc with respect to the membrane carrier. Following internalisation in the intestinal cell, zinc associates with an intracellular binding protein, metallothionein.
43. The processes involved in the transport of zinc across the intestinal wall, its export into plasma and its uptake into other tissues are uncertain. Once in plasma, zinc is carried by a number of proteins that include albumin, transferrin,  $\alpha$ -2-macroglobulin, and ceruloplasmin. Circulating zinc represents only a small fraction of total body zinc and plasma turnover is high. A large proportion of blood-borne zinc is carried by erythrocytes, bound to carbonic anhydrase, superoxide dismutase and haemoglobin. About 99% of total body zinc is intracellular. Very little is known about uptake and utilisation of zinc in the peripheral tissues although some tissues are particularly zinc rich, for example the choroid of the eye and the prostate gland. Prostatic secretions and semen also contain relatively high levels of zinc. The liver is central for the metabolism, distribution and transfer of zinc. Uptake from plasma into the liver seems to be an early step in the acute response to various physiological stimuli; corticosteroids, oestrogen and ACTH all reduce plasma zinc.
44. Uptake is increased when zinc is depleted. Conversely, excess intake increases zinc excretion. Urinary excretion is particularly sensitive to zinc status. There is no "store" of zinc in the conventional sense although zinc may be released during tissue catabolism and bone resorption. Consequently the homeostasis of zinc, essential to

maintenance of a broad biochemical spectrum of zinc-dependent functions, depends upon a balance between absorption and excretion (see reviews by Vallee and Falchuk, 1993; Walsh *et al.*, 1994; Reyes, 1996; Sandstrom, 1997)

### Metabolism and excretion

45. Plasma provides a metabolically active transport compartment for zinc (USDHHS, 1994). It is most often complexed to organic ligands in a loosely or tightly bound fraction rather than as metallic ions in free solution. In the blood, zinc is found in diffusible and non-diffusible forms. In the diffusible form, two thirds of the zinc is bound to albumin and is freely exchangeable. The diffusible form also includes zinc bound to amino acids. The zinc-amino acid complex can be passively transported across tissue membranes to bind to proteins. In the non-diffusible form, a small amount of zinc is bound to  $\alpha_2$ -macroglobulin in the plasma. Zinc is added to and dissociated from  $\alpha_2$ -macroglobulin only in the liver.
46. Excretion of zinc is primarily via the faeces. This includes zinc not absorbed from the gut and that derived from biliary and pancreatic secretions. Under normal circumstances, less than 10% of dietary zinc finds its way into the urine. Small fractions of zinc are excreted via sweat and ejaculate.
47. Zinc plays a key role in the synthesis and action of insulin. Hyperzincuria (increased zinc excretion due to hypozincaemia) may arise from the effect diabetes has on zinc homeostasis (Chausmer, 1998)

### Function

48. Zinc has many diverse functions in the human body, being essential for growth and development, maintaining appetite, testicular maturation, skin integrity, neurological function, wound healing and immunocompetence. More than 200 zinc-dependent enzymes exist, participating in carbohydrate, lipid, and amino acid metabolism, nucleic acid and protein biosynthesis and all other major biochemical processes. Zinc is a cofactor of the superoxide dismutase enzymes, which play an important antioxidant role in the detoxication of reactive oxygen species (ROS). Zinc is also an important component of DNA, acting to stabilise phosphate groups and co-ordinate with bases. About 1% of the human genome codes for zinc finger proteins that play an important regulatory function in gene expression. Zinc is also essential for the activities of the thymic, growth and sex hormones and for glucagon and insulin. Zinc is an absolute requirement for normal brain development and for the reproductive process. In addition, zinc is recognised for its anti-infective and anti-cancer properties (Walsh *et al.*, 1994; Vallee and Fulchuk, 1993 and references therein).

### Deficiency

49. The main clinical manifestations of severe zinc deficiency in humans are growth retardation, delay in sexual maturity, delay in skeletal maturation, development of orificial and acral dermatitis, diarrhoea, alopecia, failure of appetite, the appearance of behavioural changes and increased susceptibility to infections due to development of a defective immune system. Severe signs of deficiency are seen in patients with a acrodermatitis enteropathica which results from an acquired or hereditary (autosomal recessive) inability to absorb zinc, patients receiving total parenteral nutrition without zinc, and patients taking the chelating agent penicillamine.
50. Symptoms of marginal or mild zinc deficiency are less obvious and often missed. They include reduced growth rate, impaired resistance to infection, delayed wound healing, and neuro-sensory defects such as taste abnormalities (Walsh *et al.*, 1994; WHO, 1996; Prasad, 1985 and references there in).
51. Studies in animals indicate that zinc deficiency impairs reproductive performance, decreases voluntary food consumption and possibly restricts storage and utilisation of vitamin A (WHO, 1996 and references therein).

#### The use of zinc supplements to obtain other beneficial effects

52. The therapeutic uses of zinc supplements reported in the literature are summarised in Table 5.

Table 5: Zinc supplements used to obtain other beneficial effects

Dose (mg/day)	Treatment	Reference
~150	Wilson disease	Sandstead, 1995 and references therein
45-150	Zinc deficiency in sickle-cell anaemia and chronic renal disease patients, and the elderly	Prasad, 1993
~150	To enhance healing of wounds, leg and mouth ulcers	
~150	Skin problems, boils, bedsores, general dermatitis, acne	
Up to 100	To slow age-related macular degeneration	Newsome <i>et al.</i> , 1988
10	Stunted growth in children in developing countries	Rivera <i>et al.</i> , 1998
10	Prevention of diarrhoea in children in developing countries	Sazawal S <i>et al.</i> , 1997
5 mg/kg	Reduced gut permeability in Bangladeshi children with acute or chronic diarrhoea	Roy <i>et al.</i> , 1992

#### *Treatment for the common cold.*

53. It has been claimed that zinc exerts an effect by preventing the formation of viral capsid proteins and by stabilising and protecting cell membranes when adequate concentrations are achieved in saliva. It has been proposed that zinc may also induce

the production of interferon gamma. Typically, dissolvable zinc lozenges, containing up to 50 mg zinc, are sucked every 2 hours during the waking day, for up to 10 days or the duration of the cold. Efficacy trials have yielded mixed results but there have been reports of decreased symptoms and hastened recovery (Garland and Hagemeyer, 1998).

#### *Other therapeutic uses*

54. There are claims that zinc therapy has been effective in the treatment of prostate problems, taste and smell disorders, anorexia and mild mental complaints and Alzheimer's disease and can improve glucose tolerance in diabetics, relieve symptoms of inflammatory bowel disease, slow macular degeneration, boost the immune system in the elderly and enhance wound healing following herpes infection. For example, in AIDS patients receiving AZT supplemented with zinc for 30 days, their body weight stabilised and the frequency of opportunistic infections was reduced in the following two years (Mocchegiani *et al.*, 1995). When pregnant women at risk of delivering a small baby were supplemented with 22.5mg zinc daily the incidence of growth retardation was significantly reduced and health indices were better compared with controls (Simmer *et al.*, 1991).
55. Reports, anecdotal and otherwise, exist regarding the efficacy of zinc supplementation for the treatment of brittle nails, white spot on finger nails, acne, athlete's foot, Crohn's disease, hypoglycaemia, night blindness, and osteoporosis (references cited in review by Anon, 1998). Zinc may also have a role to play in thyroid hormone metabolism in patients with low T3 levels and may play a part in the conversion of T4 to T3 (Nishiyama *et al.*, 1994). In men with low sperm counts supplemental zinc for four months resulted in increased sperm counts (Tikkiwal *et al.* 1987).

### **Oral Toxicity**

#### *Human and Animal Toxicity*

56. For a summary of the relevant human and animal toxicity data available on zinc, pre-1995, the reader is referred to Table 2-2 and Figure 2-2 included in the 1995 COT review of zinc (TOX/95/36, Annex K) which is attached as annex 2 to this paper. The following draws upon this information and where appropriate adds to it.

### **Human Toxicity**

57. Zinc has generally been considered to be relatively non-toxic. Homeostatic mechanisms regulate the zinc body burden and it does not appear to accumulate in the body except within bone. Overt symptoms of zinc toxicity are associated with the

ingestion of relatively large amounts of zinc, usually through accidental ingestion or self-abuse.

*Toxicity following massive ingestion*

58. Acute toxicity following massive ingestion of zinc, as described in cases of accidental poisoning or self-administration, is generally characterised by gastric distress, abdominal cramps, dizziness, nausea, vomiting and diarrhoea (Chobanian, 1981; Burkhart *et al.*, 1990). A dose corresponding to 225-450 mg elemental zinc is usually adequate to produce an emetic response. However, one case reported a different set of symptoms that included drowsiness and lethargy but no gastrointestinal distress (Murphy, 1970). Other manifestations of zinc toxicity have included increased serum lipases and amylases (~1.5 x upper reference values) and decreased serum cortisol levels. Generally in these cases, chelation or irrigation therapy has resulted in complete recovery. Nonetheless, one zinc-associated fatality has been reported where a 55 year old male schizophrenic died from multi-organ failure following massive ingestion of coins containing a high zinc content (Bennett *et al.*, 1997).
59. Several cases of chronic massive zinc supplement abuse have been associated with the development of sideroblastic anaemia (Table 6, Fiske *et al.*, 1994). One case (Simon *et al.*, 1988) reported copper deficiency and sideroblastic anaemia following an ingestion of an alleged 26.6-40 mg zinc per day for 2 years (see paragraph 95). Another case reported by Botash *et al.* (1992) concerned a 13 month old girl (body weight 8.6 kg) who had been prescribed zinc (26 mg/day for 7 months) prophylactically from the age of 6 months.

*Acute effects associated with pharmacological intakes (~100-300 mg/day)*

60. Exposures of ~100-300 mg zinc, for therapeutic reasons, through excessive self-administration or as part of an experimental protocol have, in some cases, resulted in similar but less severe gastrointestinal effects to those described above. Samman and Roberts (1987) reported the occurrence of nausea, stomach cramps, diarrhoea and headache in ~50% of healthy volunteers who ingested 150 mg zinc sulphate daily in 3 divided doses for 6 weeks.

Table 6 (adapted from Fiske *et al.*, 1994)

Zinc intake (mg/day)	Duration (months)	Haemoglobin (g/dl)	Leukocytes (per mm <sup>3</sup> )	Absolute neutrophil count (per mm <sup>3</sup> )	Ringed sideroblasts?	Bone marrow vasculisation?	Time to normal blood counts
152	14	5.2	2200	88	No	No	4 weeks
152	24	6.5	8000	5000	No	No	8 weeks
2300	4	6.2	3900	702	Not reported	Not reported	4 weeks
450	24	5.1	900	153	Yes	Yes	9 weeks
405	12	4.0	1600	240	Yes	Yes	6 weeks
29-43	24	9.0	2000	120	Yes	Yes	4 weeks
110-170	10	10.2	2000	760	No	No	16 weeks
Coins	144	6.6	2100	Not reported	Yes	Yes	2 weeks
Not reported	24	8.7	1600	Not reported	Yes	Yes	2 weeks
1000-2000	3	3.7	2200	Not reported	Yes	Yes	10 weeks
152	22	5.5	1900	Not reported	Yes	Yes	20 weeks
26	7	7.2	4300	300	Yes	Yes	8 weeks
810	18	7.6	4900	2058	Not reported	Not reported	8 weeks
300-600	18	3.5	1500	60	Yes	Yes	6 weeks

61. The form of zinc ingested may be a factor in causation of gastrointestinal disturbance, some forms being less well tolerated than others. Zinc gluconate and zinc acetate have been reported to be relatively less irritating to the gastrointestinal tract. Nonetheless, nausea was one of the most frequently reported adverse effects during trials studying the efficacy of zinc in the treatment of the common cold. In these trials zinc gluconate or zinc acetate lozenges, containing 10-24 mg elemental zinc, were taken every 2 hours throughout the waking day for up to 10 days (Garland and Hagemeyer, 1998). Nausea and cramping were reported to occur following a single 50 mg dose of zinc in the form of sulphate (Henderson *et al.*, 1996 and 1995; Freeland-Graves *et al.*, 1980). In contrast, zinc acetate (25-50 mg 3x/day, given to Wilson disease patients to prevent copper accumulation) was reported to cause less dyspepsia than equivalent doses of zinc sulphate (Henderson *et al.*, 1995).

#### *Chronic and sub-chronic effects due to zinc-induced copper deficiency*

62. The non-acute effects of zinc are more a consequence of zinc-induced copper deficiency, due to the antagonistic effects of zinc on copper uptake (see paragraphs 30-33). Attendant effects of zinc-induced copper deficiency have included hypocupraemia, sideroblastic anaemia, leukopenia, neutropenia, decreased erythrocyte superoxide dismutase (ESOD), decreased ceruloplasmin, decreased cytochrome c oxidase, increased plasma cholesterol, increased LDL:HDL cholesterol, decreased glucose clearance, decreased methionine and leucine enkephalins,

abnormal cardiac function and impairment of pancreatic enzymes, amylase and lipase (Walsh *et al.*, 1994; Sandstead 1995 and references there in).

*Decreased erythrocyte superoxide dismutase (ESOD)*

63. The physiological significance of decreased ESOD activity is not established. The enzyme is responsible for the conversion of superoxide to hydrogen peroxide and oxygen and therefore modulates the toxicity of superoxide generated from both xenobiotic transformation and normal oxidative processes that occur within the cell. If decreases in ESOD activity, secondary to zinc-induced copper deficiency, reflect changes in SOD activity in other tissues, then protection against macromolecular damage incurred by ROS within those tissues will be reduced. As noted previously, Davis *et al.* (2000) reported that extracellular rather than erythrocyte SOD was sensitive to increased zinc levels.

*Altered LDL:HDL cholesterol*

64. Elevated serum cholesterol and increased LDL:HDL cholesterol are widely associated with an increased risk of coronary heart disease and it has been suggested that zinc may be atherogenic in man (Klevay, *et al.*, 1994; Hooper 1980; Klevay, 1975).
65. The associated mechanism is uncertain but thought to be related to induced copper deficiency. Studies in males have shown that ingestion of low (inadequate) copper containing diets (Zn:Cu >16) for up to 15 weeks can cause altered lipid profiles, namely decreased HDL cholesterol and increased LDL cholesterol (Bhathena *et al.*, 1986; Holbrook *et al.*, 1989; Reiser *et al.*, 1985 & 1987) or increased total and LDL cholesterol (Klevay, 1984). Other accompanying signs of copper deficiency in these studies included decreased ESOD and/or decreased plasma copper.
66. It is interesting to note that the above studies were prematurely terminated after some copper deficient individuals experienced cardiac abnormalities, including myocardial infarction, tachycardia, second degree heart block or arrhythmia. Low copper status is strongly but not conclusively implicated as the cause of these cardiac abnormalities. Prior copper status in these subjects was unknown and baseline cardiac function was normal. Cardiac arrhythmias were also observed in 3 of 12 postmenopausal women maintained on a low copper diet (Zn:Cu ~17.6). However, in this study there was no change in plasma lipid, although ESOD was decreased (Milne and Nielsen, 1994 – Meetings abstract). To put the above studies into an everyday context, the quantities of zinc and copper consumed by many Americans are 8-12 and 0.8-1.5 mg per day, respectively, i.e. Zn:Cu ratio 5-14 (Sandstead, 1995 and references there in).
67. There is an increasing body of evidence to suggest that LDL does not become atherogenic unless it has undergone oxidative modification (Steinberg *et al.*, 1989). It has been hypothesised that zinc possesses antioxidant properties, through both enzymatic (including Cu/Zn SOD) and non-enzymatic processes (Bray, 1990). A recent report of the DH Cardiovascular Review Group (DH 1994) also mentioned

zinc, in passing, as an essential trace element with an “antioxidant” effect in the containment of free radical damage. Indeed, over-expression of Cu/Zn SOD in epithelial cells *in vitro* has been associated with decreased oxidation of LDL (Fang, *et al.*, 1998). However, the findings of Gatto and Samman (1995) do not support the idea that supplementary zinc protects against the LDL oxidation in humans. Although there are no data available to support this, it seems more plausible to suggest that a decrease in Cu/Zn SOD activity, as a consequence of zinc-induced copper deficiency, could lead to an increased rate of lipid oxidation.

*Decreased ceruloplasmin activity, decreased iron mobilisation and anaemia*

68. Copper is a component of the ceruloplasmin (alternatively called ferroxidase), a key enzyme involved in the mobilisation of iron and its incorporation into transferrin. Zinc-induced copper deficiency can lead to a reduction in ceruloplasmin activity, which may result in the trapping of iron within the reticuloendothelial system. Consequently, iron is made unavailable for erythropoiesis and anaemia can ensue.

*LOAELs for zinc-induced copper deficiency*

69. The studies outlined below demonstrate that relatively modest levels of zinc supplementation can cause adverse effects, primarily due to decreased copper status:

70. Twelve healthy men (23-25 years) given 160 mg zinc daily (as sulphate, taken with meals) showed a 25% reduction ( $p < 0.001$ ) in HDL-cholesterol levels after 5 weeks, but there was no effect on total cholesterol, LDL-cholesterol, or triglyceride. Near baseline values were restored 11 weeks after the cessation of treatment. Plasma copper was not decreased throughout (Hooper *et al.*, 1980). The amounts of zinc and copper provided by food and beverages were not stated.

71. Male subjects (19-29 years) supplemented with 50 or 75 mg zinc daily (as gluconate, consumed after breakfast with water) for 12 weeks, showed decreases in HDL cholesterol ( $\sim 14\%$ ,  $p = 0.04$ ,  $n = 9-13$ ) at both 6 and 12 weeks in the higher dose group and at week 12 in the lower dose group. However, at week 8, levels of HDL cholesterol in both treated groups were actually higher than those in the placebo control group. Serum copper levels were not altered. The amount of zinc provided by food and beverages ranged between  $\sim 9-13$  mg/day. The amount of copper and zinc provided by food and beverages was 2.1, 1.8 and 1.7 mg/day and 12.6, 14.1 and 9.8 for placebo, 50 mg and 75 mg zinc supplement groups, respectively (Black 1988).

72. Twenty six healthy males, provided with a daily zinc supplement of 50 mg, taken as two doses (as gluconate, morning and night), for 6 weeks, exhibited elevated plasma zinc levels ( $p < 0.05$ ) and decreased ESOD activity (maximally  $\sim 20\%$ ,  $p < 0.05$ ). Plasma copper and ceruloplasmin activity were not affected (Fischer 1984). The amount of zinc and copper provided by food and beverages was not stated.

73. Females (25-40 years) given supplements of zinc gluconate capsules (25 mg zinc twice daily for 10 weeks) developed significant reductions (~50%, 5% and 30%, respectively, compared with pretreatment levels,  $p < 0.05$ ,  $n = 18$ ) in ESOD activity, haematocrit, and serum ferritin. Effects on ferritin and haematocrit but not ESOD were ameliorated with equal (mg for mg) iron supplementation (Yadrick 1989). The amount of zinc and copper provided by food and beverages was not stated.
74. Zinc capsules (50 mg daily, in the form of sulphate, type available OTC, taken with breakfast) caused a significant 20 % decrease ( $p < 0.02$ ) in ESOD in 6 healthy female volunteers (age range 18-36 years), after 12 days. Dietary zinc was estimated as 9-12 mg/day (Abdallah and Samman, 1993). Copper intake was not stated.
75. Cunningham (1994) reported 45% and 20% increases ( $p < 0.001$ ) in HbA<sub>1c</sub> in insulin dependent diabetes mellitus (IDDM) patients ( $n = 14$ , 18-37 years) and non-IDDM individuals ( $n = 15$ , 23-38 years), respectively, following supplementation with 50 mg/day zinc (as the gluconate) for 28 days, suggesting glycosylation becomes altered in a milieu of zinc excess. In this study, plasma and erythrocyte copper did not differ significantly from baseline levels.
76. Adult women of child bearing age were fed dietary regimes containing 2mg/day copper and 8, 16, or 24 mg/day zinc (as the sulphate) ( $n = 6$  or 7) for 18 day. Plasma levels of zinc and copper were increased and decreased, respectively. However, zinc had no effect on copper retention at any dose and the negative copper balance observed in each treatment group was unrelated to zinc dose (Taper *et al.*, 1980). There was no functional assessment of copper status in this study.
77. Festa (1985) reported that a total zinc intake of 18.5 mg/day for 2 weeks following on from a week at a lower intake resulted in reduced apparent retention and an increased excretion of copper. In this study, nine healthy males in their 20s consumed a basal egg-white diet that provided recommended levels of all essential nutrients, with the exceptions of zinc and protein where the diet provided 1.8mg zinc and 16.4g nitrogen daily. Copper intake was 2.63 mg/day, of which 2.5mg was in the form of copper sulphate. Zinc carbonate was added to give a total zinc intake of 20.7 mg/day (week 1), 18.5 mg/day (weeks 3,5,6,8,9), 1.8 mg/day (week 2) 1.8 or 8.0 mg/day (week 4) and 4, 6 or 8 mg/day (week 7). Mean plasma copper concentrations remained within the normal range throughout the study, but mean faecal copper excretion was elevated over copper intake in week 6. The biological significance of this result is uncertain. Negative copper balance was not repeated in week 9 and there was no measurement of any functional index of copper status.
78. However, other studies using similar doses have failed to demonstrate similar effects:
79. Women (18-40 years) given 0, 15, 50 or 100 mg zinc supplements as acetate in capsules with water at the evening meal, each day for 8 weeks, showed no change in HDL cholesterol except for transient decrease at 4 weeks in the top dose group. The amounts of zinc and copper provided by food and beverages were 8.5 mg/day and 2.7

mg/day respectively (Freeland-Graves *et al.*, 1982). No functional index of copper status was measured in this study.

80. 23 young men given 50 mg zinc per day (as gluconate) for 6 weeks, developed a statistically nonsignificant increase (~16%) in HDL cholesterol and decrease in total cholesterol with a significant decrease in diastolic blood pressure ( $p < 0.01$ ). Zn:Cu intake ratio was estimated to be 60:1. Haematocrit, haemoglobin and plasma copper levels were not significantly altered from baseline (Pachotikarn *et al.*, 1985).
81. As part of a double blind crossover study, healthy females (n=26, mean 27 years) and males (n=21, mean age 28 years) were given 150 mg zinc (as sulphate) per day for 6 weeks. There were no changes in total plasma cholesterol in either males or females. However, in females, LDL cholesterol was decreased by 9% while ESOD and ceruloplasmin activities were reduced. Plasma copper and haematocrit remained unchanged. Differences between the sexes were attributed to females receiving a higher dose on a mg/kg basis (Samman and Roberts 1988). Copper intake was not stated.
82. Reasons for the discrepancy are uncertain but may be attributed to differences in experimental design, age and sex of subjects and duration of study. Differences between the studies regarding zinc and copper intakes from food and beverages may have also been influential. Absence of other functional copper index measurements e.g. ESOD, in some studies preclude comparison of copper status.

*Adverse effects of zinc supplementation on functional indices of iron status.*

82. The effect of zinc supplementation on iron status is discussed in the following studies:
83. The growth of iron-deficient Iranian school-boys was found to be greater when supplementation was with 20 mg of iron alone rather a combination of 20 mg iron and 20 mg zinc (Mahloudji *et al.*, 1975).
84. Ferritin levels (an index of iron storage) in Jakarta school children responded positively to daily 30 mg iron supplements but not to similar supplements combined with 15 mg of zinc. However, haemoglobin and zinc protoporphyrin levels were increased in both groups (meeting abstract referred to by Solomons and Ruz, 1997).
85. Yadrick *et al.* (1989) reported significant reductions in haematocrit and serum ferritin in females (n=18) given daily supplements of 50 mg zinc as gluconate for 10 weeks. Levels of ESOD were also decreased.
86. Although the dietary requirements for iron and zinc in adult males are similar (~10 and 15 mg /day respectively), diet and dietary supplements generally provide greater amounts of iron (Solomons, 1986). Consequently, issues arising from the interference of iron on zinc uptake are more likely than an affect of zinc on iron.

*Adverse effects of zinc on immune function*

87. The effect of zinc on immune function has also been investigated.
88. A controlled double blind study of marasmic (nutritionally deficient) children in Chile undergoing nutritional rehabilitation showed that monocyte phagocytic and fungicidal activity *in vitro* decreased between the time of admission and following 60-150 days feeding with zinc-fortified formula ( $p < 0.04$ ,  $n = 19$ ). Children receiving the same formula, but unfortified with zinc, showed no depression in phagocytic activity between admission and 60 days ( $n = 20$ ). The number of impetigo episodes was significantly greater in the fortified group. Zinc intake in the fortified group was 1.9 mg/kg versus 0.35 mg/kg in the unfortified group. Nutritional, zinc, iron and copper status did not differ between the groups at any time (Schlesinger *et al.*, 1993).
89. Chandra (1984) reported depressed lymphocyte function in 11 adult males given 300 mg of zinc (as sulphate) per day for 6 weeks. However, Walsh *et al.* (1994) have criticised this study on a number of counts including failure to monitor copper status, the *in vitro* methodology used to measure immunocompetence and the lack of placebo controls.
90. Brewer *et al.* (1997) reported that lymphocyte function and NK activity were not adversely affected in Wilson disease patients maintained on 150 mg/day zinc (as acetate) for up to 27 years.

**Chronic toxicity**

91. Most experience of chronic zinc administration is from Wilson disease patients or sickle cell anaemia patients on long-term zinc therapy. Individual cases of chronic zinc supplement abuse or the habitual ingestion of zinc-containing coins have also been reported.
92. Chronic ingestion of zinc by Wilson disease patients (150 mg) as sulphate dissolved in water, for 3 years, has not been reported to cause gastrointestinal discomfort or other side effects. Some Wilson patients have received zinc therapy for 25 years without apparent adverse effects (Flodin, 1990 and references therein). Zinc treatment in Wilson disease patients has not been reported to increase LDL cholesterol or lower HDL cholesterol, presumably because high liver copper levels in these patients afford some protection against zinc-induced copper deficiency. However, a dose-related increased serum lipase and amylase was reported in Wilson disease patients treated chronically with 25-50 mg 3x/day or 200 mg 4x/day for 10 days (Yuzbasiya-Gurkan, 1989)
93. Zinc-deficient patients (elderly and sickle cell anaemia patients) supplemented with 30-45 mg elemental zinc per day for several months developed neither copper deficiency nor any other observed toxic effects. However, some sickle-cell anaemia

patients administered 150 mg/day in divided doses showed signs of copper deficiency (Prasad, 1993 and references therein).

94. 50 men and women (age 27-72 years) received 100 mg zinc per day (as sulphate) as treatment for taste and smell dysfunction, for up to 440 days apparently without any adverse effects. The amounts of zinc and copper provided by food and beverages were 13 mg/day and 2 mg/day respectively (Amond et al., 1982). This study was concerned with distribution, retention and excretion of zinc and not its toxic effects. No functional index of copper status was measured in this study.
95. Simon *et al.* (1988) reported the case of a 44 year old male who developed copper deficiency and sideroblastic anaemia after ingesting 26.6-40 mg zinc (as gluconate) as a non-prescribed single daily dose, usually after a light breakfast of coffee and juice, for at least two years. This subject was also taking non-prescribed large amounts of other nutrient supplements including vitamins E, A, B<sub>1</sub>, B<sub>2</sub>, and B<sub>12</sub>, niacinamide, d-biotin, choline, bitartrate, inositol, para-aminobenzoic acid, folic acid and pyridoxine. He was also taking prescribed L-lysine (2 g/day). Details of zinc and copper intakes from food and beverages alone were not reported. The patient had no genetic disorder that might predispose him to copper deficiency.
96. Zinc deficient (on the basis of leukocyte zinc concentrations) adult sickle cell patients were supplemented with 50 –75 mg/day zinc (as zinc acetate) for up to 3 years. Following chronic supplementation, there was a significant increase in leukocyte zinc concentrations, a significant increase in IL-2 production and a significant decrease in the number of bacterial infections, hospital admissions and painful crisis (Prasad *et al.*, 1999). Plasma copper levels were unaffected by zinc supplementation. The authors speculate that the observed clinically beneficial effects of zinc supplementation may have been due to a pharmacological action of zinc rather than simply correcting intracellular zinc deficiency as IL-2 production was increased over non zinc deficient SCD controls.

### **Epidemiological studies**

97. The association between zinc levels or intakes and a variety of physiological parameters has also been investigated.
98. Hiller *et al.* (1995) examined the relationship between fasting serum zinc and serum lipid levels in 778 adults (22-80 years) and reported higher serum zinc levels were associated with higher levels of total serum cholesterol, LDL cholesterol and triglycerides.
99. Hale *et al.* (1988) made a study of an elderly population (38 women and 31 men, “average” age 78) who were taking zinc supplements (range 20-150 mg/day, with 15% of the population taking >50 mg, range 60-150 mg/day), for an “average” duration of 8 years ( $\leq 2$  years 30%;  $>2 \leq 10$  years 55%;  $>10$  years 15%). The control

population consisted of 1,195 females and 637 males (age range not stated) who were not taking zinc or multi-mineral and vitamin supplements. Decreases in serum creatinine, total protein and uric acid and an increase in mean cell haemoglobin were observed in both male and female subjects ( $p < 0.05$ ) and RBC count was significantly reduced in females only ( $p < 0.01$ ). There were no differences in cholesterol and triglyceride levels or electrocardiogram. HDL measurements were not performed. Details of zinc and copper intake from food and beverages were not given.

#### *Adverse drug reactions reported under the Yellow Card Scheme*

100. Suspected adverse reactions to medicinal products are reported to the Committee on Safety of Medicines/Medicines Control Agency. Many factors influence the number of reports received, and in most situations there is considerable "under-reporting" of reactions. Most of the adverse reactions reported for oral products containing zinc relate to multiconstituent products, and may not, therefore, be directly attributable to the mineral. Single constituent products are associated with a low number of suspected adverse reactions. There was no trend or pattern to indicate any particular problem.

#### **Potentially Vulnerable groups or Genetic Variations**

##### *Genetic variations*

101. There are no known genetic disorders associated with zinc accumulation analogous to Wilson disease and copper accumulation. However, Smith *et al.* (1976) reported hyperzincaemia, in five out of seven members of one family and two out of three second generation individuals, suggesting that the condition was heritable. The excess zinc appeared to be bound to serum protein with enhanced binding to albumin (Failla *et al.*, 1982). There were no apparent symptoms.

102. More recently, there was a puzzling report concerning hyperzincaemia in an 11 year old boy. However, his symptoms were consistent with deficiency. Unusually, zinc in the boy's plasma was not associated with serum albumin but was found bound to an unidentified high molecular weight protein not present in the plasma of normal individuals. Stable isotope studies, using  $^{67}\text{Zn}$  and  $^{70}\text{Zn}$  and interpretation of data using a two-compartment model, showed certain abnormalities in the boy's zinc kinetics, namely increases in both plasma and exchangeable zinc, with a more rapid flux from the plasma pool to the exchangeable pool and slower removal from the system. Liver and muscle zinc (and copper) concentrations were raised but liver histology was not altered (Sampson *et al.*, 1997). The authors suggested that the boy was suffering from a previously unrecognised inborn error of zinc metabolism causing symptomatic zinc deficiency.

##### *Haemochromatosis sufferers*

103. Individuals homozygotic for haemochromatosis have increased gastrointestinal absorption of iron, cobalt and lead and there is some evidence that zinc absorption may also be increased (Adams *et al.*, 1991; Spencer *et al.* 1988). Barton and Bertoli (1997) have suggested that these people, who are largely undiagnosed, may be particularly vulnerable to zinc-induced copper deficiency if they were to take zinc supplements, for example as a cold treatment.

*Individuals suffering from magnesium or calcium deficiency or increased calcium requirement*

104. Zinc supplementation has been shown to have an adverse effect on the intestinal absorption of magnesium and calcium. The effect on calcium is thought to occur only when dietary calcium is low (see paragraph 39). Vulnerable groups may therefore include those individuals suffering from calcium or magnesium deficiency, or those groups with increased requirements e.g. pregnancy and lactation (increased calcium requirement); diabetes mellitus (magnesium deficiency). Dietary deficiency in calcium is rare in the UK and bodily calcium deficiency is usually a result of deficiency in vitamin D.

**Toxicity in animals (post-1994 update)**

*Acute toxicity*

105. No additional information available since the TOX/95/36 review.

*Sub-chronic toxicity*

106. The following additional studies are available:

107. Zinc-induced copper deficiency in the progeny of swine fed diet containing 5000 mg/kg zinc throughout pregnancy and lactation and weaned on similar diet, was associated with altered lipid metabolism, namely decreases in apolipoprotein A-1 and HDL cholesterol, and pathological changes seen in myocardium. The diet also contained 11 mg/kg copper (Klevay *et al.*, 1994).

108. Pigs fed a basal diet supplemented with 2500 ppm Zn (as ZnO) for 28 days following weaning demonstrated no changes in faecal E coli and enterococci numbers or the phagocytic capability of circulating neutrophils. At autopsy hepatic zinc concentrations were 4x controls (concentrations in renal tissue were 2x, concentrations in skeletal muscle were similar to controls); histological examination revealed mild-moderate fatty changes in the liver of supplemented animals. Zinc supplementation increased growth rate. None of the study animals exhibited any clinical signs of illness. The purpose of this study was to investigate potential mechanisms behind the routine use of ZnO in preventing postweaning diarrhoea (Waern *et al.*, 1998).

109. Administration of diet containing 200 mg/kg zinc, for 6 weeks, to genetically obese (ob/ob) or high-fat (HF) diet-induced obese (ICR) mice was associated with a significant increase in body fat (49.4% and 18.9%, respectively,  $p < 0.05$ ) relative to obese controls on a basal diet containing 4-6 mg/kg zinc. Body weights were not significantly different from respective controls. Both ob/ob and HF mice, maintained on basal diet, had significantly lower serum and carcass zinc and higher body fat relative to their respective lean controls ( $p < 0.01$ ) (Chen *et al.*, 1996).
110. Pancreatic lesions developed in 10 month old castrated sheep dosed with 240 mg/kg zinc (as zinc oxide), 3 x per week for 4 weeks (Smith and Embling, 1993).

### ***Chronic toxicity***

111. No additional information available since the TOX/95/36 review. The limited data available give no evidence to suggest that zinc is carcinogenic to laboratory animals.

### ***Reproductive toxicity***

112. In a series of experiments on the developmental toxicity of 2-ethylhexanoic acid (EHXA) in pregnant rats Bui *et al.* (1998) demonstrated that low maternal zinc intakes potentiated developmental toxicity while high intakes attenuated such developmental effects. Pharmacokinetic studies indicated that EHXA reduced embryonic zinc uptake, increasing zinc accumulation in the maternal liver due to increased liver metallothionein synthesis following induction of an acute phase response due to EHXA exposure. The authors conclude that the developmental toxicity of EHXA may be mediated in part by changes in maternal-foetal zinc metabolism.

### ***Mutagenicity and genotoxicity***

113. Tests for genotoxicity reported since the COT review (TOX/95/36) have continued to provide mixed results.

### ***In Vitro***

114. Zinc oxide was found to be negative in bacterial Ames tests using *Salmonella typhimurium* TA98 and TA100 (Stea *et al.*, 1994) and TA102 (Sawai *et al.*, 1998). Mutatox and SOS (UA-4537 and UA-4567) assays detected zinc as genotoxic (Codina *et al.*, 1995) but Ames (TA98 and TA100) and *E. coli* WP2 (uvrApKM101) assays were negative. Pagano and Zieger (1992) claimed zinc chloride to be reproducibly mutagenic in *Salmonella typhimurium* TA97 assays provided preincubations were carried out in sterile distilled deionized water or in Hepes buffer in sodium/potassium chloride. These workers suggested that standard media may contain components, which chelate zinc and thereby inhibit its mutagenicity potential. However, the significance of this result is questionable. Although the response was

dose-dependent to some extent, the number of zinc chloride-induced revertants was always less than 2x background.

*In Vivo*

115. Zinc chloride induced small spots with one or two mutant hairs in the *Drosophila melanogaster* wing spot test (Ogawa *et al.*, 1994).

***Carcinogenicity***

116. No additional information available since the TOX/95/36 review.

**Regulatory considerations**

117. There are no specific regulations on the maximum levels of zinc permitted in food. However, there are maximum levels of zinc in compositional standards for infant formula and weaning foods. In the UK, the general guideline limit for zinc is 50mg/kg in food and 5mg/kg in beverages sold ready to drink. These guidelines were recommended in 1953 by the Food Standards Committee (MAFF, 1981).

**Recommendations on maximum intake levels**

118. Recommendations on limits for the tolerable intake of zinc are somewhat confusing and can conflict with recommendations on the RDA.
119. In 1982, JECFA (WHO 1982) proposed a PMTDI in the range 0.3-1.0 mg/kg, corresponding to 18-60 mg/day for a 60 kg adult.
120. The US Environmental Protection Agency has defined a reference dose<sup>1</sup> of 0.3 mg Zn/kg/day, corresponding to 18 mg daily for a 60 kg adult. However, extrapolation of the RfD to younger age groups presents a conflict. For example, the RfD for a 2 year old child weighing 12 kg would be 3.6 mg/day. This is substantially less than an RDA for this age group of 10 mg/day. As Sandstead pointed out, this conflict would be further magnified in diets of low bioavailability (Sandstead, 1993).
121. The US Agency for Toxic Substances and Disease Registry (US DHHS, 1994) proposed a Minimal Risk Level (MRL) of 0.3 mg/kg daily. The MRL was derived from a LOAEL of 50 mg/day, based on haematological effects, namely decreased haematocrit, serum ferritin, and erythrocyte superoxide dismutase activity, observed in females given daily supplements of 50mg zinc for 10 weeks (Yadrick *et al.*, 1989),

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<sup>1</sup> The Reference Dose (RfD) is an estimate of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime.

plus 9.72mg zinc/day, the estimate of dietary zinc for females (20-30 years old) from the FDA Total Diet study for 1982-1986 (Pennington *et al.*, 1989).

122. The intermediate oral MRL<sup>2</sup> of 0.3 mg zinc/kg/day has been adopted as the chronic oral MRL. The chronic oral MRL is expected to be without adverse effects when consumed on a daily basis over a long period of time, neither inducing nutritional deficiency in healthy, non-pregnant, adult humans ingesting the average American diet nor causing undesirable inhibition of normal lipid transport. The MRL was not based on a chronic-duration oral study due to a lack of adequate long-term studies in humans and animals. The intermediate and chronic oral MRLs for zinc do not represent levels of concern in infants, children, or lactating women. Also, the MRLs are based on soluble zinc salts, and it is less likely that non-soluble zinc compounds would have adverse effects at this level.
123. WHO (1996) proposed upper limits to the safe range of population mean intake of zinc (Table 7) which were defined as those at which the increase in tissue zinc ultimately disturbs the metabolism of other nutrients. These limits were based on available human data that showed: clinically detectable changes or functional impairments when the average daily intake of zinc is 150 mg or more; interactions with other nutrients influencing their absorption and when the total daily intake of zinc (given in supplement form in addition to a diet assumed to provide 10 mg zinc/day) was 60 mg. To ensure that few individuals in a population have an intake of zinc >60 mg/day, the Expert Consultation recommended that the adult population mean should not exceed 45 mg/day if a 20% variation in intake is assumed. This figure was extrapolated to other age and sex groups on the basis of differences in basal metabolic rate.

Table 7: WHO upper limits of the safe ranges of population mean intakes of zinc (adapted from WHO, 1996)

Age (years)	Sex	Weight (kg)	Upper limit (mg/day)
0.5-1	M & F	9	13
1-6	M & F	16	23
6-10	M & F	25	28
10-12	F	37	32
12-15	F	48	36
15-18	F	55	38
18-60+	F	55	35
10-12	M	35	34
12-15	M	48	40
15-18	M	64	48
18-60+	M	35	45
Pregnancy & lactation			35

<sup>2</sup> In general, the MRL is an estimate of the daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (non-carcinogenic) over a specified duration of exposure.

**Recommendations on maximum supplementation levels**

124. In 1991 the DH/MAFF Working Group on Dietary Supplements and Health Foods (MAFF, 1991) advised that zinc would have undesirable effects at chronic doses (total intake) above 20 mg/day, and suggested that no daily supplemental dose should contain more than one tenth of the undesirable dose.
125. Sandstead (1995) has tentatively suggested a reference dose of 9 mg/day for zinc OTC medications. This was based upon a LOAEL for zinc of 50 mg (assuming 50% availability), a dietary contribution of 10 mg (assuming 25% availability), an uncertainty factor of 3 (due to uncertainties concerning copper intake) and a modifying factor of 60 kg. He added that if this reference dose were appropriate, almost all OTC zinc supplements would be considered unsafe.
126. The UK Trade Association, The Council for Responsible Nutrition recommend a maximum safe level of 15 mg/day zinc for long term supplementation and 50 mg/day for short term supplementation, noting that the latter should be combined with 5mg/day copper.

**Summary**

127. Zinc is an essential constituent of several hundred metalloenzymes, involved in all the major metabolic pathways. It plays a key role in the synthesis and stabilisation of genetic material. It is necessary for cell division and the synthesis and degradation of carbohydrates, lipids and proteins. It is essential for growth, development and repair. Zinc is therefore classified as an essential trace element in the diet.
128. Human exposure to zinc is largely through food. In the UK, the population average intake from food is 10-12 mg/day, excluding dietary supplements.
129. Zinc deficiency results in effects such as poor prenatal development, growth retardation, mental retardation, impaired nerve conduction and nerve damage, reproductive failure, skin problems, hair loss, diarrhoea, loss of appetite, loss of taste and smell, anaemia, susceptibility to infections, delayed wound healing, macular degeneration. The UK Reference Nutrient Intake (RNI) ranges are 5.5-9.5 mg/day for males and 4.0-7.0 mg/day for females (DH, 1991).
130. In humans, the acute toxic effects of zinc include abdominal pain, nausea and vomiting. Other reported effects include lethargy, anaemia and dizziness.
131. Prolonged use of high doses of zinc can result in secondary deficiency of copper. Symptoms of copper deficiency include hypocupraemia, impaired iron mobilisation, anaemia, leukopenia, neutropenia, decreased superoxide dismutase (particularly

ESOD), decreased ceruloplasmin, decreased cytochrome c oxidase, increased plasma cholesterol, increased LDL:HDL cholesterol, decreased glucose clearance, decreased methionine and leucine enkephalins, abnormal cardiac function and impairment of pancreatic enzymes, amylase and lipase.

132. Erythrocyte superoxide dismutase (ESOD) activity, one of the most sensitive indices of copper status, has been shown to decrease following supplementation with zinc for 12 days. Longer-term supplementation has resulted in reductions in haematocrit and serum ferritin. Higher doses of zinc have resulted in altered ratios of HDL:LDL cholesterol. One study reported a negative copper balance when a diet deficient in zinc and protein was supplemented with zinc salts, although this effect was not reproduced later on within the same study. Copper deficiency and sideroblastic anaemia, associated with chronic zinc ingestion, was reported in one individual who had taken non-prescribed zinc supplements for at least 2 years.
133. Animal studies have shown that very high doses of zinc can cause minor neural degeneration, acinar cell necrosis and metaplasia in the pancreas, decreased haematocrit and decreased WBC count. Lower doses have resulted in reduced ceruloplasmin activity and decreased haemoglobin.
134. Although zinc has been found to give positive results in some genotoxicity tests, there is no evidence to suggest that zinc is carcinogenic in humans.
135. Very high doses of zinc have been shown to cause reproductive toxicity in rats.

## Glossary

ACTH	adrenocorticotrophic hormone
AUC	area under the curve
Cu	copper
DH	UK Department of Health
DHSS	US Department of Health and Human Services
ESOD	erythrocyte superoxide dismutase
Fe	iron
FDA	US Food and Drug Administration
HDL	high-density lipoprotein
IDDM	insulin dependent diabetes mellitus
JECFA	The Joint WHO/FAO Expert Committee on Food Additives
LDL	low-density lipoprotein
LOAEL	lowest observed adverse effect level
MAFF	UK Ministry of Agriculture, Fisheries and Food
MCH	mean cell haemoglobin
MRL	minimum risk level
NAS	US National Academy of Sciences
NRC	US National Research Council

OTC	over the counter
PMTDI	provisional maximum tolerated daily intake
RBC	red blood cell
RDA	recommended daily allowance
RfD	reference dose
RNI	reference nutrient intake
ROS	reactive oxygen species
SOD	superoxide dismutase
WBC	white blood cell
WHO	World Health Organisation
Zn	zinc

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**ANNEX 1 to EVM/99/18/P****INTAKES OF ZINC FROM FOOD AND SUPPLEMENTS**

The data presented on zinc intakes are obtained from dietary surveys of specific population age groups in Britain carried out over the last 15 years<sup>34567</sup> (data from the National Diet and Nutrition Survey of young people aged 4-18 years have been deleted from this annex because they are unpublished data). In each survey food consumption data were collected by means of a dietary record (usually weighed) kept for 4 or 7 consecutive days. Nutrient intakes were calculated using a set of nutrient composition data contemporaneous with the time of the survey. Therefore some apparent differences in intakes between population age groups may be due to changes in the nutrient composition data and reflect changes in the nutrient composition of foods over time.

**Total intakes of zinc**

Table 1 provides information on the median intake, and upper and lower end of the intake distribution (defined as upper and lower 2.5 percentiles, respectively), of zinc by the British population, classified by age and sex.

Zinc intakes increased with age for pre-school children and young adults. Intakes in older people (aged 65 and over) decreased with age. Intakes were higher in males than females for most age groups. Median intakes of zinc were below the RNI for all age groups except adults aged 16-64 years. About 5-15% of each age group had intakes below the LRNI. Intakes adjusted for body weight showed an age related decrease.

**Sources of zinc in the diet**

Table 2 indicated the contribution that different types of food make, on average to intakes of zinc by young people aged 15-18 years. As this data has not yet been published the table has been deleted from the annex.

**Zinc intake from supplements**

Table 3 shows the number of consumers of dietary supplements containing zinc for each population age group, together with the median and range of intake for each group. Only a few participants in each survey took supplements containing zinc. The contribution of zinc supplements to population average intakes of zinc was very small, one percent for older people free-living in the community and negligible for all other age groups. For those few individuals who used zinc supplements they provided median intakes of around 2-3 mg/day for children, adults and older people living in the community. The range of

<sup>3</sup> Food and nutrient intakes of British infants. 1986

<sup>4</sup> National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3

<sup>5</sup> National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8 (unpublished)

<sup>6</sup> Dietary and nutritional survey of British adults. 1986/7

<sup>7</sup> National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

intakes from supplements was wide with maximum intakes from this source of over 10mg/day. The maximum intake of 43.6mg/day for men aged 16-64 years was due to one subject recorded as taking four tablets daily of a supplement containing zinc and other minerals.

**Table 1: Total intakes of zinc**

Age/sex	Absolute zinc intake (mg/day)			Bodyweight adjusted zinc intake (mg/kg bwt/day) <sup>8</sup>		
	<i>intakes from food and supplements</i>					
	2.5%ile	Median	97.5%ile	2.5%ile	Median	97.5%ile
<b>Infants (1986)<sup>9</sup></b>						
6-12mths/M&F	2.7	4.4	7.4	0.24	0.43	0.73
<b>Pre-school children (1992/3)</b>						
1½-2½ yrs/M&F	2.0	4.1	7.7	0.18	0.33	0.63
2½-3½ yrs/M&F	2.2	4.2	7.6	0.15	0.29	0.52
3½-4½ yrs/M	2.2	4.6	8.1	0.12	0.27	0.48
3½-4½ yrs/F	2.2	4.2	8.4	0.13	0.26	0.50
<b>Adults (1986/7)</b>						
16-24 yrs/M	5.2	10.4	18.4	0.07	0.14	0.27
16-24 yrs/F	3.3	7.5	12.5	0.05	0.13	0.21
25-34 yrs/M	6.1	11.0	19.0	0.08	0.15	0.25
25-34 yrs/F	3.4	7.8	14.4	0.05	0.13	0.25
35-49 yrs/M	5.6	11.1	19.0	0.08	0.15	0.24
35-49 yrs/F	4.0	8.5	14.0	0.06	0.13	0.23
50-64 yrs/M	6.0	11.1	20.2	0.08	0.14	0.25
50-64 yrs/F	4.5	8.3	13.7	0.06	0.13	0.23
<b>Older people free-living in the community (1994/5)</b>						
65-74 yrs/M	4.7	8.8	14.8	0.06	0.11	0.20
65-74 yrs/F	3.8	6.8	11.1	0.05	0.10	0.20
75-84 yrs/M	3.8	8.1	14.2	0.05	0.11	0.20
75-84 yrs/F	3.2	6.3	12.4	0.05	0.10	0.21
85 and over/M	3.4	7.9	12.3	0.05	0.12	0.19
85 and over/F	2.3	6.1	12.4	0.04	0.10	0.22
<b>Older people living in institutions (1994/5)</b>						
65-84 yrs/M	3.9	8.4	13.3	0.07	0.12	0.22
65-84 yrs/F	4.4	7.3	11.2	0.07	0.12	0.22
85 and over/M	3.5	7.8	14.1	0.05	0.13	0.22
85 and over/F	3.8	6.9	11.6	0.06	0.11	0.20

**Table 2: Sources of zinc in the diet**

<sup>8</sup> Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.

<sup>9</sup> Intakes for infants from food only

This table was based on data from the recent National Diet and Nutrition Survey of young children aged 4-18 years. As a report of the findings of this survey has not yet been published this table had been deleted.

**Table 3: Zinc intake from supplements**

Age/sex	Consumers of zinc supplements		Zinc intake from supplements (consumers only) (mg/day)	
	Number	%	Median	Range
<b>Infants (1986)</b> 6-12 mths/M&F	0	0	0	
<b>Pre-school children (1992/3)</b> 1½-4½ yrs/M&F	6	<1	2.6	0.1 - 3.6
<b>Adults (1986/7)</b> 16-64 yrs/M	15	1	3.1	0.1 - 43.6
16-64 yrs/F	24	2	3.4	<0.1 - 10
<b>Older people free-living in the community (1994/5)</b>				
65 and over/M	14	2	2.4	<0.1 - 15.0
65 and over/F	17	3	2.3	<0.1 - 15.0
<b>Older people living in institutions (1994/5)</b>				
65 and over/M	2	1	0.3	0.3 - 3.6
65 and over/F	6	3	1.0	

**ANNEX 2 to EVM/99/18/P**

**COT Review of Zinc**

TOX/95/36 Annex K was considered by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) and provided the basis of the summary of the toxicity of zinc by the COT which was published in Food Surveillance Paper No. 53, Cadmium, Mercury and other Metals in Food, London: The Stationery Office (1998). Therefore it has been approved for release with EVM/99/18 by the COT Secretariat.

