Zinc Toxicity in Humans
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Introduction

In dealing with zinc’s essentiality/toxicity (Dr. Jekyll and Mr. Hyde) duality, biological systems have developed the homeostatic ability to tightly regulate the zinc levels through a complicated framework for import and export, transport and distribution and sensing of zinc status to ensure that zinc does not participate in toxic reactions. In spite of the thousands of papers that have been published on biological effects of zinc, the challenge of quantifying the range of exposure doses that constitute zinc deficiency versus excess remains unresolved. Recent studies with better design and more sensitive methods point to a considerable overlap between what has generally been considered to be the essential dose and toxic dose, suggesting that the dose-response curve for zinc may not be a “U” but a “V”.

Although zinc is not involved in cellular redox cycle and has traditionally been regarded as relatively nontoxic, recent studies increasingly show that free ionic zinc (Zn$^{2+}$) is a potent killer of neurons, glia and other cell types. Zinc concentrations in the brain are maintained within a narrow range of 600-800 ng/L with deviations substantially above and below this range being proconvulsive and cytolethal respectively. Free zinc ion may be much more toxic biologically than is generally realized. The physiologically optimal Zn$^{2+}$ concentration in eukaryotic cells is around 10 ng/L and when the zinc level falls below 0.06 ng/L apoptosis can be triggered but when the level rises above 60 ng/L toxicity can ensure. The evolution of biomolecules to scavenge the zinc ions was crucially important in ameliorating the cellular toxicity and facilitating the myriad cellular uses for zinc.

Functions of Zinc in Humans

Zinc is extraordinarily useful in biological systems. It is involved in many biochemical processes that support life and required for a host of physiological functions including normal immune function, sexual function, neurosensory function such as cognition and vision. Numerous proteins, enzymes and transcription factors depend on zinc for their function. Zinc is an essential component of hundreds of proteins and metalloenzymes including alkaline phosphatase, lactate dehydrogenase, carbonic anhydrase, carboxypeptides, and DNA and RNA polymerases found in most body tissues. Zinc plays specific and important catalytic, co-catalytic and structural roles in enzyme molecules and in many other proteins and biomembranes. A well-known example of the structural role of zinc in cellular and subcellular metabolism is the zinc finger motif, ubiquitous in transcription proteins. The configuration of zinc fingers, critical to DNA binding, is determined by the single zinc atom at their base. The linking of zinc fingers to corresponding sites on the DNA initiates the transcription process and gene expression. Motifs similar to zinc fingers have been identified in nuclear hormonal receptors including those for vitamin D, estrogen and testosterone.

Zinc plays an important role as ionic signaling in large number of cells and tissues. Many individual zinc-secreting cell types are known throughout the body, including the CNS neurons, submandibular salivary glands (modified to venom glands in snakes), prostate epithelial cells, pancreatic exocrine cells, pancreatic β-cells, mast cells, granulocytes, Paneth cells in the intestine, and pituitary cells. The biological and physiological roles of these somatic zinc signals are still poorly understood.

Zinc-binding proteins account for nearly half of the transcription regulatory proteins in the human genome, and during the past two decades, well over 2000 zinc-dependent transcription factors involved in gene expressions of various proteins have been reported. In addition to being critical enzymatic cofactors involved in regulation the DNA transcription, other important functions of zinc in humans include (a) cell proliferation, differentiation and apoptosis; (b) immune response onset and regulation; (c) protein synthesis; (d) DNA metabolism and repair; (e) energy metabolism; (f) vitamin A metabolism; (g) insulin storage and release; (h) spermatogenesis and steroidogenesis; (i) neurogenesis, synaptogenesis and neuronal growth; (j) sequestration of free radicals and...
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It is not clear whether these functions are hierarchical in terms of zinc utilization, in other words, whether all zinc-dependent functions are affected to the same extent or some pathways are partially compromised for the sake of homeostasis as zinc becomes increasingly limiting. One thing is clear, however. Zinc insufficiency or excess can moderate a cascade of metabolic processes that adversely affect the health of human beings and other organisms.

Epidemiology

In general, well-conducted epidemiological studies risks of exposure to zinc in the environment with adequate characterization of the exposure matrices are lacking, and the available data are not adequate data to establish an association between environmental exposure to zinc and health outcomes. Inhalation exposure to zinc chloride fume occur primarily during military or civilian fire-drill exercises. An accidental ignition of several smoke generators at a storage site led to the poisoning of 70 people, ten of whom died.

Numerous cases of accidental and intentional (self-harm) ingestion of zinc salts have been reported. A few of these accidental exposures have resulted in death but debilitating sequelae is often the recorded consequence, such as vomiting, diarrhea, red urine, icterus (yellow mucous membrane), liver and kidney derangement and anemia.

At present, 10 pesticides containing zinc salts (including the oxide, sulfate, chloride and phosphide) are commercially available in the United States. These zinc salts are used as herbicides to control the growth of moss on patios, walkways, lawns and structures. Zinc oxide is used as a bacteriostat and as industrial preservatives, incorporated into carpet fibers to inhibit bacterial and fungal growth and as pressure treatment to preserve cut lumber. The pesticidal (environmentally dissipative) use exposes a large number of people to zinc but there is no indication that the levels of exposure constitute a significant health hazard to the people or the environment.

Millions of people are currently being exposed to various levels of zinc as food supplements and additives, as medicines, disinfectants, antiseptic and deodorant preparations and in dental cement. The risks associated with zinc exposure from these routes have become a matter of intense debate in the annals of toxicology and human nutrition (see Zinc Deficiency in Human Health).

There are inherent difficulties in estimating zinc requirements for humans, with a number of physiological, dietary and environmental factors affecting various populations. Strategies that have been used to estimate human requirements include the metabolic balance studies, in which zinc intake was compared with zinc excretion in the urine and faeces and factorial calculations that account for the zinc required for growth, losses (including zinc lost in sweat, shed hair and skin, semen and milk) and bioavailability. The factorial estimates for zinc requirements are outlined in Table 1. Growing infants, children, growing adolescents, and pregnant and lactating mothers require more zinc per kilogram of body weight than do mature adults. The data in the table may be compared with reported averages for dietary intake of zinc vary from 5 to 20 mg/d. While average intakes may be adequate for a segment of any given population, every community has groups that are at risk of zinc deficiency.

Values for the recommended dietary allowance should be compared with the reference dose (RfD) for zinc, which is an estimate of the daily exposure to which human population may be continuously exposed over lifetime without an appreciable risk of adverse health effect and is aimed at protecting sensitive subpopulations. The US Environmental Protection Agency (US EPA) has set an RfD of 0.3 mg/kg-day for zinc, based on reported lowest observed adverse effect level (LOAEL) from a clinical study of the effects of oral zinc supplementation on copper and iron status. This RfD corresponds to 21 mg zinc for a 70-kg male and 18 mg for a 60-kg female and is higher than the recommended acceptable daily intakes recommended by the WHO in some instances. On the other hand, the US Food and Nutrition Board has set the tolerable upper intake level (UL) at 40 mg/d for adults older than 19 years. The UL is another form of toxicity risk assessment value designed to protect 97–98% of the population.

The apparent conflicts in RDA, RfD and UL values above primarily reflect the huge uncertainties in our ability to associate zinc status with normal states of human health and in detecting mild to moderate zinc deficiency and toxicity endpoints. A comparison of the RDA with RfD nevertheless points to the fact that there is little margin between the safe and unsafe doses for zinc. The narrow margin of safety raises a number of concerns about the current framework for managing the risks of zinc deficiency in human populations. The growing tendency to add zinc to increasing number of food items raises the issue of cumulative exposure of zinc additives in relation to the RDA. New food preparation, processing and preservation technologies can affect the zinc bioavailability and significantly change the amount of food one needs to consume to meet one’s daily zinc requirement.
And then there is the issue of zinc supplements. While there is no doubt that supplementation to correct for zinc deficiency is beneficial, the amounts being recommended may have no practical relevance to public health in many instances. Increasingly, people are taking zinc supplementation either as a single micronutrient or as a component of multimicronutrient mix for prophylactic purposes (such as to ward off colds and flu). The beneficial effects of such practice are open for debate.

Near some major mining and smelting areas and major hazardous waste site, the integrated exposure from dietary, supplementary, medicinal and cosmetic sources may exceed the safe threshold for zinc.

### Acute Health Effects

The acute effects of zinc are usually the result of short-term, high dose exposure and depend strongly on the point of contact. Chronic somatic effects tend to be associated with low-dose exposure over an extended period of time. A number of reports have outlined the effect of acute exposure to zinc in humans. Most of these reports are generally old and poorly documented, with inadequate characterization of the actual exposure doses in spite of the fact that some estimates of exposure have been made. Few well designed studies have been conducted to assess the toxicity of zinc at environmental and pharmacological levels of exposure. The signs and symptoms discussed in this article should be viewed in a circumspect manner. In case studies, the most common effects associated with long-term, excessive zinc intakes (ranging from 150 mg/day to 1–2 g/day) have included sideroblastic anaemia, hypochromic microcytic anaemia, leukopenia, lymphadenopathy, neutropenia, hypocupraemia and hypoferraemia. Patients often recover to normal blood patterns after cessation of zinc intake with or without copper supplementation.

### Inhalation

The first type of well studied toxic reactions to zinc in human beings was the “metal fume fever” induced by intense inhalations of industrial fumes containing zinc oxide. The most prominent respiratory effects of metal fume fever include fever, chills, gastroenteritis, substernal chest pain, and cough. The impairment of pulmonary function may be accompanied by reduced lung volume and decreased diffusion capacity for carbon monoxide and there may be an increase in bronchiolar leucocytes. The impairment in pulmonary function is temporary (disappears in exposed individuals in 1–4 days) and rarely progresses to chronic lung disease.

“Zinc chloride fume” refers to smoke from a bomb made by exploding a mixture of zinc oxide and hexachloroethane. The smoke is used for fire-fighting exercises, crowd dispersal and military screens. It consists of a mixture of chemicals including zinc chloride,
zinc oxychloride, phosgene, carbon tetrachloride, tetra-
chloroethane, carbon monoxide, carbon dioxide and
hexachloroethane, and is fairly toxic. The signs and
symptoms of acute exposure to zinc chloride fume
include irritation of the nose and throat, conjunctivitis,
cough, hoarseness, dyspnea, wheezing, rales, rhonchi,
chaste tightness or pain, nausea, vomiting, epigastic pain,
light-headedness, listlessness, metallic taste in the mouth
and even death. These effects may be accompanied by
comorbid neurological and cardiovascular features.
Detailed discussion of metal fume and zinc chloride
fevers can be found in the annals of industrial hygiene
and occupational health and the hazards of these smokes
are not addressed in this article.

Dermal

Skin contact with zinc powders or concentrated solutions
can result in severe corrosive effects including ulceration,
blistering and permanent scarring. Contact dermatitis has
been reported in rare instances, for instance, following use
of shampoos containing zinc pyrithione but the specific
etiological role for zinc was not clear. Zinc salts are also
dermal irritants.

Zinc can be absorbed into the body when applied to
sores and wounds. A male child presented with anemia
and neutropenia and showed signs of developmental
delay following treatment for atopic dermatitis with
45 mg/day of zinc. Evidence that harmful effects may
result from dermal exposure is not plentiful in the scien-
tific literature, however.

Ocular

Zinc salts are strong eye irritants, causing pain and
erythema which may be complicated by corneal ulcerations,
edema and burns, iritis, hyperemia, hemorrhaging,
bullous keratopathy, glaucoma and cataract formation.
Discrete grey spots on the lens, lacrimation and signifi-
cant reduction in visual acuity with conjunctival
hemorrhage and inflammation have also been reported.
In some cases, the effects are permanent.

Dilute solutions of zinc chloride (<1%) are non-irri-
titating and have been used as eye drops. In the past, a 20%
solution of zinc sulfate was used to treat a number eye
problems. The treatment resulted in the formation of
white flecks on the lens of the eye and this particular
has been discontinued.

Ingestion

Zinc is relatively non-toxic if taken orally and instances of
acute poisoning due to zinc exposure from environmental
sources are extremely rare. Intake of zinc in drinking
water needs to exceed 15 mg/L (highly unusual potable
water) to produce nausea, vomiting and diarrhea.

Zinc salts tend to be corrosive and ingestion can result in
severe injury to the mouth, throat and stomach. Initial
symptoms include burning of the mouth and pharynx
with vomiting and may be accompanied by erosive
pharyngitis, esophagitis, and gastritis. Complications
may include gastrointestinal hemorrhage and acute
pancreatitis.

A woman who swallowed 28 g of zinc sulfate (~7 g of
zinc) suffered hypoglycemia and tachycardia and event-
ually died as a result of pancreatic hemorrhage and renal
damage. Poisoning by an emetic dose of zinc sulfate
(containing 1-2 g zinc) presented symptoms that included
vomiting, nausea, abdominal cramps, epigastic pain and
bloody diarrhea. The symptoms in a 26-year old woman
who was poisoned by swallowing 10 mL of a correction
fluid (containing 26% zinc chloride and 0.5% methanol)
included oropharyngeal and gastric burns, epigastric tend-
erness, dysphagia, diarrhea, gross oral mucosal and
pharyngeal edema; the patient subsequently experienced
hematemesis and melaena which required multiple blood
transfusions. Gastrointestinal distress and diarrhea have
also been reported in several cases following the con-
sumption of food and beverages stored in galvanized
zinc containers.

Cardiovascular Toxicity

Reported symptoms in people exposed to high levels of
zinc include premature atrial beats, hypertension second-
arly to intravascular volume, hypovolemic shock (pulse
over 120 beats per minute) and hypertension.

Hemotoxicity

Gastrointestinal ulcerations and burns following ingestion
of toxic quantities of zinc salt can precipitate an acute fall
in hemoglobin and hematocrit levels and intravascular
hemolysis may follow. Acute exposure to zinc sulfate for
one week at a dose of ~3 mg/kg/day resulted in anemia
which could have been secondary to gastrointestinal
hemorrhaging. Changes in serum lipid profile, serum
ferritin and erythrocyte superoxide dismutase activity
have been reported in a number of patients who have
ingested high doses of zinc. Microcytic anemia and decreased blood platelets have been reported as a result of sustained hands to zinc chloride solution.

**Pulmonary Toxicity**
Ingestion of correction fluid by an asthmatic patient brought about an acute episode of bronchospasms and severe oropharyngeal and laryngeal inflammation which led to stridor and dysphonia. Swallowing of one tablespoon of soldering flux (containing 22.5% zinc chloride) by a child triggered severe coughing and wheezing in addition to the features of gastrointestinal toxicity.

**Hepatic Toxicity**
Excess copper and zinc levels in a small number of Cree and Ojibwa-Cree children have been associated with severe chronic cholestatic liver disease progressing to end-stage biliary cirrhosis in these children. Since there was no data to indicate that any exposure to excess zinc had occurred in these children, it could be that the effects might have been due to an inborn error of metal metabolism, secondary dietary or environmental factors, or genetic factors.

**Nephrotoxicity**
Microscopic hematuria unaccompanied by renal failure and mild albuminuria have been associated with ingestion of high doses of zinc.

**Neurotoxicity**
Ingestion of high levels of zinc have resulted in lethargy, lightheadedness, staggering, difficulty in writing clearly, anxiety, depression, somnolence and comatose.

**Hepatotoxicity**
Transiently increased liver enzyme activities have been linked to severe gastrointestinal corrosive effects of high-dose ingestion of zinc.

**Cancer**
Zinc has not been shown to be a human mutagen or carcinogen. Zinc deficiency impairs the molecular mechanisms designed to protect against DNA damage, influences genetic stability and function, enhances the susceptibility to DNA-damaging agents and furthermore affects cellular differentiation, proliferation and apoptosis. This has led some people to speculate that zinc deficiency is a potential risk factor for cancer. The link between zinc deficiency and human cancer remains tenuous, however.

**Chronic and Subchronic Toxicity**
Ingestion of zinc and zinc-containing compounds can result in a variety of chronic effects in the gastrointestinal, hematological and respiratory systems along with alterations in the cardiovascular and neurological systems of humans.

The intake of zinc in the range of approximately 100–300 mg/d (doses likely to induced chronic toxicity) is common among people using zinc-containing supplements and oral zinc medicines (self-medication, prescribed by a physician or traditional remedies). Prolonged zinc exposure via these routes has been shown to result in copper deficiency characterized by hypocupremia, anemia, leucopenia and neutropenia; some subjects additionally report headache, abdominal cramps and nausea. The antioxidant enzyme Cu-Zn-superoxide dismutase (SOD) is said to be very sensitive to changes in plasma Zn/Cu ratio and alterations in SOD activity with zinc supplementation may result in excess free radicals that are damaging to the cell membrane. Studies have also noted some competitive interaction between zinc and iron that can result in decreased serum ferritin and hematocrit concentrations especially in women. A number of studies have been conducted to examine the effects of zinc intake on blood lipid levels. The lowest dose of zinc that affects lipid metabolism is ill-defined, but it was approximately twice the US recommended daily allowance. Doses of zinc of 50–300 mg in excess of dietary amounts generally have potentially harmful effects on lipid metabolism. The majority of these studies show that zinc supplements and therapeutics has recently been shown to adversely affect the serum cholesterol balance, with generally an increase in low-density lipoprotein (LDL) cholesterol and a decline in high-density lipoprotein (HDL) cholesterol.

Under normal circumstances, the major route of zinc excretion is via the pancreas. Prolonged consumption of supplements may lead to an accumulation of zinc and impairment of the pancreatic function, resulting in increased release of amylase, lipase and alkaline phosphatase into the blood stream.

An interesting body of scientific literature suggests that zinc is a neurotoxin. Zinc is selectively stored and released from presynaptic vessels of neurons found primarily in the mammalian cerebral cortex. Because the zinc-releasing neurons also release glutamate, they are sometimes referred to as “gluzinergic” neurons. The zinc- and glutamate-secreting terminals are conspicuously accumulated in the vast network of neocortex and limbic structures (amygdala and septum). Zinc can modulate the overall excitability of the brain possibly through its effects on glutamate, γ-aminobuthric acid (GABA) receptors of this network. The gluzinergic neurons may play a role in the synaptic plasticity that underlies learning and memory – the plasticity of young mammalian brain is frequently accompanied by changes in innervation by zinc-containing neurons. The zinc produced synaptically or from other dynamic sources (such nitric oxide-mediated release from metallothioneins) promotes...
neuronal death by inhibiting cellular energy production by interfering with a number of processes such as mitochondrial electron transport chain, the tricarboxylic acid cycle and enzymes of glycolysis. There is evidence to suggest that synaptically released zinc contributes to excitotoxic brain injury after seizures, stroke and brain trauma.

Studies with molecular biomarkers suggest that maternal zinc supplementation (in the presence of methyl-containing substances such as folic acid, vitamin B₁₂ and choline) can have a significant influence on mechanisms of epigenetic regulation, imprinting and specific gene expressions. The reprogramming of some fetal genes allows the effects of zinc deficiency or copper deficiency secondary to excessive zinc supplementation to become cross-generational. The review above suggests that sustained exposure to doses of zinc found in supplements and medicines carry a health risk attributable to interference with the metabolic cycles of copper and other essential elements, impairment of the immune and pancreatic functions, and dysregulation of epigenome.

The role of zinc in the pathogenesis of Alzheimer’s disease (AD) is gaining interest since it was reported that zinc can precipitate amyloid beta-peptide (Aβ) and induce β-amloid aggregation in senile plaque. The zinc theory of AD is based on the fact that Aβ deposits are limited to the neocortex where the highest zinc concentration occurs, even though Aβ is ubiquitously produced in the brain. Early-phase clinical trials show that zinc chelation inhibits Aβ-plaque deposition. Furthermore, therapeutic strategies designed to remove zinc bound to proteins, in particular to Aβ, with the use of metal-protein-attenuating compounds (MPACs), such as clioquinol, have resulted in significant reduction in the cognitive decline in patients with moderately AD. This drug, however, led to the appearance of subacute myelo-optic neuropathy, which is a condition strictly related to zinc deficiency and had to be withdrawn. Neocortical tissue affected by Alzheimer’s disease tends to accumulate zinc to high levels, suggesting that besides the direct effect of zinc on amyloid aggregation, zinc may also contribute to the pathology of the disease through other pathways.

The abnormal form of the prion protein (PrP) is believed to be responsible for the Creutzfeldt-Jakob disease, bovine spongiform encephalopathy and other transmissible spongiform encephalopathies. One of the peptides containing the human PrP106-126 residues share a number of biophysical properties with the amyloid β (Aβ) peptide of Alzheimer’s disease. For instance, the Aβ residues 25-35 of Alzheimer’s disease are similar to the PrP106-126 core sequence and both play an important role in stabilizing the Aβ aggregates that induce neurotoxicity. There is a growing body of evidence to suggest zinc modulates the Aβ aggregation and the neurotoxic properties of PrP106-126.

Interactions with a number of trace elements can affect the absorption, distribution, metabolism and excretion of zinc and hence the zinc’s toxicity. Exposure to higher than normal levels of zinc can induce copper deficiency and anemia and may influence the activity of superoxide in humans, as noted previously. Zinc interaction with cadmium tends to be protective in that zinc reduces the organ levels of cadmium under normal circumstances. Exposure to high levels cadmium (high Cd/Zn ratio) may cause changes in inter-organ distribution of zinc with an accumulation of zinc in the kidney and a deficiency in other organs. Under severe limitation, the cells increasingly rely on cadmium to meet their zinc requirements, thereby converting cadmium into an “essential” trace element; this process increases the risk of cadmium toxicosis. Zinc is required for the activity of δ-aminolevulinic acid dehydratase (ALAD) activity which plays a protective role in heme biosynthesis. Both tin and zinc are said to attach to the same sites in the ALAD but the effects of changes in tin/zinc ratio on the activity of this enzyme is unknown. Prolonged exposure to high doses of zinc can lower the serum levels of manganese thereby increasing the susceptibility to autoimmune reactions. The effects of dietary zinc insufficiency or excess on blood levels of children remain equivocal.

Potential for Zinc Accumulation

An average 70-kg adult contains 2-3 g of zinc, making it nearly as abundant as iron. The zinc is widely distributed in the skeletal muscle, bone, brain, GI tract, liver, kidney, lung, heart, retina, pancreas, sperm and uterus. The highest concentration (~100 mg/kg wet weight) is found in the prostate. Concentration of zinc in whole blood is about 5 mg/L and about 5-fold less in plasma and serum. Unlike iron, there is no particular body store for zinc and metabolic zinc requirement must be met by intake of food and supplements coupled to poorly understood homeostatic processes. The biological half-life of zinc is about 280 days, consistent with the fact that only a small fraction (2-3 mg) of the total body burden of zinc is renewed (required) daily. The body controls the amount of zinc stored in the body by reducing the absorption and increasing excretion when intakes is increased above the metabolically set threshold.

The distribution of zinc in some tissues may be regulated by age to some degree. Zinc concentrations increase in the pancreas, liver, and prostate but decrease in the aorta and uterus with age. Levels of zinc in the kidney and heart tend to peak at about 40–50 years of age and then decline.

See also: 00002
Further Reading


Web-based Resources