

REVIEW
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THE TOXICITY/ESSENTIALITY OF DIETARY MINERALS

A Review on Some
Micronutrients Prepared in
Honor of the Award for Life
Achievement to Doctor Krista
Kostial

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Continued progress in the theory and practice of trace element analytical chemistry has made possible significant advances in investigating the role and fate of trace elements in biological systems.

Public health commissions and environmental protection agencies have subsequently established requirements for intakes of and exposures to trace elements both from the nutritional (copper-zinc) and from the toxicological (cadmium-mercury) perspectives. Some trace elements demonstrate the properties of both categories, and consequently give rise to questions about the toxicity of essential dietary minerals. Selenium and chromium are typical examples of this toxicity-essentiality paradox. The systemic intoxication by and/or nutritional importance of these elements are reviewed as are the criteria for assessing their toxicity and essentiality.

Key terms:
chromium, copper, essential trace elements, nutritional trace elements, selenium, trace element toxicity, zinc

Concerns for human health focus both on the entry of environmental pollutants such as cadmium, mercury, and lead into the food chain and on adequate dietary intakes of essential micronutrients such as copper, iron, and zinc.

Among those scientists whose research has provided important insights into the role and fate of trace elements in biological systems is Krista Kostial. She has made significant contributions to better understandings of mineral metabolism for meeting nutritional requirements and for avoiding toxic excesses. Her work on age and gender relationships with trace element metabolism is of special importance (1, 2).

Cadmium

The chronic toxicity of cadmium became known in 1955 as the painful consequences of bone decalcification in post-menopausal victims of *itai itai byo*. In the 15 years that followed, 200 cases of this disease, half of which resulted in death, were recorded in the Jintsu River Valley by Japanese public health officials. The disease was caused by the ingestion of food and water contaminated with cadmium. This *itai itai byo* or "ouch ouch" disease was characterized by a loss of bone material resulting in rheumatic symptoms with intense pain in the joints, and the bones becoming as flexible as soft tissue. Cadmium ingestion also resulted in renal tubular dysfunction. Some epidemiological evidence appears to relate cadmium intoxication with hypertension. The mechanisms of cadmium toxicity are ill-defined. They may involve inactivations of sulfhydryl-containing enzymes, competitions with zinc metabolism, and inhibitions of copper absorption (3). *Kostial*(4) has published a comprehensive review of cadmium metabolism and toxicity.

Mercury

Beginning in 1953, increasing numbers of adults and children residing near Minamata Bay showed loss of coordination, numbness of the limbs, partial blindness, and loss of hearing. Convulsions, coma, and death followed in 46 of 125 cases. By 1956, "congenital Minamata disease" was observed in the offspring of symptom-free parents. Japanese public health officials subsequently diagnosed Minamata disease as methyl mercury poisoning caused by consumption of fish that had concentrated mercury from industrial wastes discharged into Minamata Bay. The toxicity of mercury involves both tissue destruction and enzyme inactivation. Nephritis and hepatitis are frequent consequences of mercury poisoning. Mercury poisoning also causes irreversible neurologic damage. Circulatory or central nervous system collapse is often the cause of death from acute mercury poisoning (5, 6). According to some recent work by *Kostial and co-workers* (7-9), dimer-captosuccinic acid derivatives are effective in reducing body burdens of mercury in rats. It remains to be demonstrated whether or not these agents are effective in the treatment of mercury poisoning in the human.

Iron and copper

Clearly, ingestions of cadmium and mercury have adverse effects on human health. Failures to ingest copper and iron also have adverse effects on human health. Dietary deficiencies of copper and iron result in anemias. Copper is required for the synthesis of hemoglobin, and iron is necessary for hemoglobin structure and function. As early as 1681, Thomas Sydenham, an English physician, prescribed iron filings steeped in wine for the treatment of chlorosis, an iron-deficiency anemia (10). Two hundred years later in 1886, Doctor MacMunn (11) described the biochemical and physiological role of iron in hemoglobin composition, and in oxygen transport and utilization. The essentiality of iron was established over

a century ago, and its recommended dietary allowance, RDA, is currently from 10 to 20 mg/day depending on age and gender (12). This RDA corresponds to a daily dose of approximately 250 mg/kg for the average 70 kg human. The LD₅₀ (acute oral toxicity in the rat) for iron(II) sulfate is 1.5 g/kg. There appears to be a tolerance zone of from 0.5 mg/kg to 0.5 g/kg for iron. Whether a trace element is essential or toxic depends on dosage and, also on its chemical form (as will be shown later).

The influences of dosages on health are illustrated in the Figure. At zero dose there is no effect on health. For an essential trace element, a zero dose corresponds to an adverse health effect. As the dose increases, the beneficial effect of the trace element increases, and health is improved. An optimal dose corresponding to optimal health is followed by a tolerance zone beyond which toxic signs are observed. At high doses, all substances become toxic. For example, the LD₅₀ (mouse) for table salt, NaCl, is 4 g/kg.

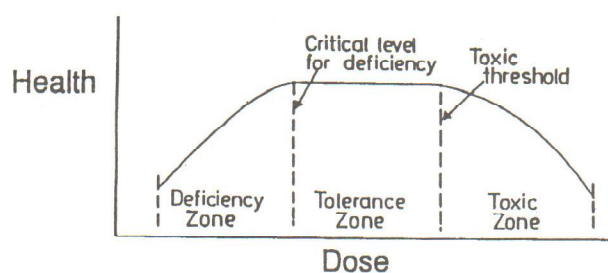


Figure Schematic representation of the dose response for an essential trace element

Toxic trace elements have no adverse effect on health at zero dose. As the dose of a toxic trace element increases, perhaps beyond a small tolerance zone, health decreases. At low to moderate doses, the neutral trace elements demonstrate neither beneficial nor harmful effects on health.

With these descriptions, trace elements can be classified as essential, neutral, and toxic. Some of the trace elements listed in Table 1 appear in more than one category as a result of dosage and chemical form considerations.

Table 1 Essential, toxic and neutral trace elements

Category	Trace elements
essential	copper, chromium, cobalt, fluorine, iodine, iron, manganese, molybdenum, nickel, selenium, vanadium, and zinc
toxic	arsenic, cadmium, chromium, lead, mercury, nickel, and selenium
neutral	aluminium, scandium, and titanium

Zinc

While heavy metal toxicity is thought to involve enzyme inhibition, the essentiality of metals such as zinc and copper has been attributed to enzyme activation. Zinc has been identified as a cofactor in over a hundred human and animal enzyme systems (13, 14). Among these systems are: acid phosphatase, alkaline phosphatase, glucokinase, enolase, carboxypeptidase A, carboxypeptidase B, alcohol dehydrogenase, glutamate dehydrogenase, lactate dehydrogenase, malate dehydrogenase, and carbonic anhydrase (15).

One of the major clinical abnormalities associated with zinc deficiency is acrodermatitis enteropathica. Acrodermatitis enteropathica is an inherited autosomal recessive trait. Infants are the most frequent victims of this disease some characteristics of which include chronic diarrhea and seborrheic skin lesions usually located at body orifices. *Van Wouwe and co-workers* (16) reported a decline in the zinc status of Dutch children with acute diarrhea. Zinc supplementation has been reported to clear the skin lesions and normalize the bowel function (17, 18). It is possible that the genetic defect effects the synthesis of picolinic acid, a facilitator of zinc absorption, and that the deficiency is a result of malabsorption rather than dietary deficiency. The clinical and laboratory diagnosis of acrodermatitis enteropathica has been reviewed by *Van Wouwe* (19).

Prasad (20) has reported that dietary zinc deficiency was responsible for retarded growth and delayed sexual maturation in Iranian and Egyptian males. As a result of 100 mg ZnSO₄ supplements to their daily diets, nine of nine affected subjects developed normal sexual function and grew in stature by an average of 10.5 cm during a 59-day confinement period. Eight similarly affected subjects fed the same diet without the zinc supplement required 224 days to sexually mature, and grew in stature by an average of only 4.2 cm during the 59-day confinement period.

Relationships between zinc status and recurrent infections of the respiratory tract in children (21), recovery of adult (human) burn victims (22), and bottle versus breast feeding of infants (23) have been investigated.

Hypogeusia is another consequence of zinc deficiency. This disorder is responsive to zinc supplementation.

The RDA for zinc is 15 mg/day, and the LD₅₀ (rabbit) for zinc sulfate is 2 g/kg. *Hambidge and co-workers* (24) have included nutritional requirements of several age and gender groups in their extensive review on zinc (24). Dietary zinc is absorbed from the duodenum and from the jejunum as complexes with mucosal protein. Many protein and amino acid complexes are involved in the transport of zinc. The blood reference range for zinc is from 12 to 17 μmol/L. Seminal concentrations of zinc are two orders of magnitude greater (25). Zinc may be an important factor in male fertility (26).

Copper

While zinc may be an important factor in male fertility, copper plays a role in female contraception (27-29). Intrauterine devices (IUD's) containing 200 mm² of metallic copper release approximately 45 mg/day of copper into the uterus.

At this level, copper demonstrates a potent antifertility action which may involve spermicidal effects. Hence, copper could be classified as a toxic element, but copper has been reported to be necessary for the proper functioning of over 50 different enzyme systems among which are those of the cytochrome oxidase system as well as those associated with hemoglobin synthesis (15). With respect to the latter, one consequence of dietary copper deficiency is anemia. *Van Den Berg and co-workers* (30) have described an *in vitro* approach to evaluating copper metabolism using liver parenchymal cells isolated from rats maintained on diets deficient in this micronutrient. *Steinebach* (31) has utilized this approach to investigate copper (and zinc) in the metabolic fate of metallothionein. While the US National Research Council (NRC) (12) has not yet established a RDA for copper, its estimated safe and adequate daily dietary intake is from 1.5 to 3 mg. The LD₅₀ for many soluble copper(II) compounds is in the range of 50 mg/kg.

Selenium

Selenium is classified both as an essential trace element and as a toxic trace element because its tolerance zone is quite short. For grazing animals, selenium is required in the diet at a minimum concentration of 0.04 ppm. Selenium remains beneficial to the animals at concentrations up to 0.1 ppm, but it becomes toxic at concentrations greater than 4 ppm. Cowboys of the American West from 100 years ago observed that cattle grazing on milk-vetch (legumes of the *Astragalus* family) grown in the selenium-rich soils of Wyoming and South Dakota became disoriented and suffered weakness, lassitude, visual impairment, loss of appetite, and paralysis with respiratory failure. In 1934, it was recognized that this vegetation concentrated large amounts of selenium from the alkaline soil and that the animals consuming this "loco weed" developed the "blind staggers", or "alkali disease" (32). In the human, the signs and symptoms of chronic, sub-lethal selenium intoxication include: discolored and decayed teeth, pallor or yellow skin color, skin eruptions, chronic arthritis, atrophic brittle nails, edema and gastrointestinal disorders, and in some cases, lassitude and partial or total loss of hair and nails (33). The deterioration of keratinized tissues may be a consequence of altered protein structure resulting from the replacement of sulfur by selenium in methionine, cystine, and other sulfur-containing amino acids.

At the other extreme, the calves, lambs, and foals of animals grazing in pastures with low soil selenium become afflicted with "white muscle disease", a degeneration of the striated muscles. Selenium deficiency in livestock has been reported in the United States, Canada, New Zealand, Australia, Scotland, Finland, Sweden, Denmark, France, Germany, Greece, and Russia. In Keshan County of the northern Chinese Heilungjiang Province, an endemic cardiomyopathy among children and young women has been attributed to a dietary selenium deficiency resulting from the consumption of vegetables grown in soil of low selenium content. This Keshan disease was reported (34) to have affected over 8,000 people in each of the three peak years, 1959, 1964, and 1970. Victims of Keshan disease show depressed selenium levels in body fluids and tissues (35). Keshan disease

is selenium responsive. *Iyengar and Gopal-Ayengar* (36) have reported that supplementing the diets with sodium selenite, Na_2SeO_3 , has become an established prophylactic procedure for residents of the narrow zone running between the Heilungjiang and the Yunnan Provinces where the disease is most prevalent.

Among the other consequences of selenium deficiency described by *Levander* (37) are: muscular dystrophy in young cattle, exudative diathesis in fowl, pancreatic atrophy in fowl, hepatitis dietetica in swine, unthriftiness in sheep and cattle, reproductive disorders in fowl, and anemia in swine.

Glutathione peroxidase is a selenium dependent enzyme that catalyzes the removal of hydrogen peroxide in the cellular environment. Without selenium, the apoenzyme of glutathione peroxidase is ineffective in preventing the formation of peroxides and free radicals which may be involved in some carcinogenesis. The RDA of selenium is 55 mg/day for females and 70 mg/day for males (12). The maximum contaminant level, MCL, established by the US EPA (38) for selenium in potable water is 10 mg/L, and the daily consumption of 2 L is equivalent to a daily dose of 20 mg. It appears that the upper limit for toxicity has been set below the lower limit for nutrition. The LD_{50} (rat) for selenium is 3 mg/kg. Ingested selenium is absorbed from the distal ileum as amino acid complexes, and it is transported as a seleno-methionine complex. The adult blood reference range for selenium is from 0.5 to 1.5 $\mu\text{mol/L}$.

Chromium

The essentiality-toxicity aspects of chromium are equally confounding. The ESADDI (12) for an average 70 kg adult human is from 50 to 200 mg, which corresponds to an approximate daily dose of 2 mg/kg. The chromium potable water MCL established by the US EPA (38) is 100 mg/L, and the consumption of 2 L/day is equivalent to a daily dose of 200 mg. On the basis of the MCL and the ESADDI, it would appear that the 200 mg/day dose corresponds to both the upper limit and to the lower limit for chromium intake.

In 1957, *Schwarz and Mertz* (39) demonstrated that a dietary-induced impairment of glucose tolerance in rats could be reversed by the administration of chromium (III) compounds. A decade later, *Davidson and Blackwell* (40) induced this impaired glucose tolerance in the squirrel monkey with a low-chromium diet, and then reversed the effect by supplementing the diet with a trivalent chromium compound. *Jeejeebhoy and co-workers* (41) reported glucose intolerance and peripheral neuropathy resulting from severe chromium deficiency in a patient on prolonged total parenteral nutrition (TPN). These symptoms were alleviated by supplementing the TPN solution with chromium at a rate of 250 mg/day. *Mertz* (42) has reviewed the role of chromium in human nutrition with respect to glucose and lipid metabolism. In this review, he has documented: (1) chromium deficiency results in insulin resistance, (2) insulin resistance caused by chromium deficiency

can be ameliorated by chromium supplementation, and (3) chromium deficiency is a current nutritional problem.

The LD₅₀ (rat) for K₂Cr₂O₇ is 57 mg/kg. For CrCl₃6H₂O, the LD₅₀ (rat) is 1870 mg/kg. On this basis, it would appear that hexavalent chromium compounds are at least twenty times more toxic to the rat when administered by the oral route. The initial toxic signs of hexavalent chromium ingestion in the human are abdominal pain, vomiting, diarrhea, and intestinal bleeding (43). These are followed by renal failure resulting from tubular necrosis (44). Hepatic failure secondary to primary hepatocellular damage, encephalopathy, methemoglobinemia, and hemolysis are frequent complications. Aggressive dialysis appears to be the best therapy for chromate ingestion (45), and the prompt administration of ascorbic acid has been recommended to reduce the highly toxic hexavalent chromium to the less toxic trivalent form (46, 47). It is paradoxical that chromium is both an essential micronutrient and a chemical carcinogen. The resolution of this paradox lies in the chemical speciation of the chromium (48). It is for this reason that chromium is listed both among the essential trace elements and among the toxic trace elements.

Acute Toxicity, LD₅₀

The LD₅₀ is a statistically derived expression for a single dose of a material that can be expected to kill half of the animals receiving it. The mouse and the rat are often selected for the determination of LD₅₀ because these animals are readily available, economical, and easy to handle. LD₅₀ values determined with mice and rats should not be linearly extrapolated to the human because of interspecies differences in biotransformation kinetics and mechanisms. Categories of relative toxicity have been established on the basis of LD₅₀. These are presented in Table 2.

Table 2 *Some relative toxicities*

Category	LD ₅₀
practically nontoxic	> 15 g/kg
slightly toxic	5 - 15 g/kg
moderately toxic	0.5 - 5 g/kg
highly toxic	50 - 500 mg/kg
extremely toxic	5 - 50 mg/kg
super toxic	< 5 mg/kg

The LD₅₀ values for typical poisons are presented in Table 3.

Table 3 Some typical poisons

Compound	Species	LD ₅₀
ethanol	mouse	10 g/kg
sodium chloride	mouse	4 g/kg
iron (II) sulfate	rat	1.5 g/kg
morphine sulfate	rat	0.9 g/kg
sodium phenobarbital	rat	150 mg/kg
DDT	rat	100 mg/kg
strychnine sulfate	rat	5 mg/kg
d-tubocurarine	rat	0.5 mg/kg
dioxin (TCDD)	guinea pig	0.001 mg/kg

It is customary to list the LD₅₀ for the most susceptible of the species in which the determination was made. The tetrachlorodibenzo-p-dioxin (TCDD) LD₅₀ values determined for several species are listed in Table 4. The LD₅₀ values for TCDD differ by nearly four orders of magnitude in species as closely related as the guinea pig and the hamster. This diverse array of LD₅₀ values reflects both interspecies and experimental variables. The purity of the TCDD, and the route by which it was administered must also be considered. The LD₅₀ values for trace elements must receive similar considerations.

Table 4 Some LD₅₀ values for dioxin (TCDD)

Species	LD ₅₀ (µg/kg)
guinea pig	0.5 - 2.5
mink	4
rat	22 - 320
monkey	< 70
rabbit	115 - 225
mouse	114 - 280
dog	> 100 - < 3000
hamster	1150 - 5000

Recommended Dietary Allowance, RDA

The RDA's are the levels of intake for essential nutrients that are judged by the Food and Nutrition Board of the NRC(10) on the basis of the best available scientific information to be adequate for meeting the known nutrient needs of practically all healthy persons. There are separate RDA's for seven of the mineral nutrients (mg/day: Ca, 800; Mg, 300 females, 350 males; P, 800; Fe, 10-20; Se, 0.055 females, 0.070, males; Zn, 15; and I, 0.15). Separate RDA's for each of these mineral nutrients are set according to 15 different age and gender categories and three additional categories for pregnancy and lactation. The work of *Kostial*

and her co-workers (1, 2) has been instrumental in the identification of age- and gender-related differences in the metabolism of metals.

Estimated Safe and Adequate Daily Dietary Intake, ESADDI

In addition to the RDA's, the Food and Nutrition Board of the NRC has set ESADDI's for five trace elements (Co, as 3 µg of vitamin B₁₂; Cu, 1.5-3 mg; Cr, 50-200 µg; Mn, 2-5 µg; and Mo, 75-250 µg). The ESADDI's are recommended in the form of ranges because the data are not sufficient for the establishment of RDA's.

Reference Dose, RfD

The US EPA (49) has approached the essentiality-toxicity paradox for elements such as chromium and selenium with the estimation of reference doses, RfD's. The RfD is defined as an estimate with an uncertainty spanning perhaps an order of magnitude of a daily exposure to the human population, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effects during a lifetime. The RfD's for selenium and for chromium are, respectively, 5 µg/kg/day and 1 mg/kg/day. The latter RfD applies to trivalent chromium. The RfD for the more toxic hexavalent species is 5 µg/kg/day.

Some of the nutritional and toxicological properties of these and other trace elements are summarized in Table 5.

Table 5 *Biological properties of some trace elements*

Trace element	Dietary deficiency	Systemic intoxication
arsenic		hepatitis and liver necrosis, nephritis, myelitis and encephalitis, neuritis
cadmium		hepatitis, nephritis, <i>itai itai byo</i> (ouch ouch disease)
chromium	glucose intolerance ESADDI = 50 - 200 µg	kidney damage, allergic dermatitis, lung cancers
cobalt	pernicious anemia from B ₁₂ deficiency ESADDI = 3 µg of B ₁₂	Quebec »beer drinkers«, myocardiopathy
copper	anemia ESADDI = 1 ^{1/2} - 3 mg	hepatic necrosis in Wilson's disease, and hemolytic anemia
fluorine	tooth decay ESADDI = 1 ^{1/2} - 4 mg	calcification of soft tissue
iodine	exophthalmic goiter RDA 150 µg/d	

Trace element	Dietary deficiency	Systemic intoxication
iron	anemia RDA = 10 - 20 mg/d	
lead		damage to CNS, hemopoiesis, reproductive system and kidney
manganese	sterility and bone deformation in animals ESADDI = 2 - 5 mg	renal and CNS damage
mercury		CNS, kidney, and liver damage
molybdenum	unknown ESADDI = 75 - 250 µg	
nickel	retarded growth in animals	sinusoidal and bronchial carcinoma from Ni(CO) ₄ , allergic dermatitis
selenium	Keshan disease RDA = 55 - 70 µg/d	blind staggers
vanadium	retarded growth in animals	
zinc	retarded growth and sexual maturation RDA = 15 mg/d	

Concluding Comment

The role and fate of trace elements in biological systems is complex. Considerations of chemical form and dosage are important. This is not a conclusion, this is encouragement for continued research efforts in this area.

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Summary

OTROVNOST/ESENCIJALNOST PREHRAMBENIH MINERALA
Prikaz o otrovnim djelovanjima i/ili esencijalnosti mikronutrienata u povodu
Nagrade za životno djelo akademice Kriste Kostial

Posljednjih desetljeća sve veća briga posvećuje se, s jedne strane, izloženosti kroz prehrambeni lanac onečišćivačima iz okoliša kao što su kadmij, olovo i živa te, s druge strane, odgovarajućem unošenju esencijalnih mikroelemenata npr. bakra, željeza i cinka. Među znanstvenicima čiji je znanstvenoistraživački rad pridonio značajnim iznašaćima o ulozi i sudbini elemenata u tragovima u biološkim sustavima je Krista Kostial. Ova međunarodno priznata znanstvenica značajno je pridonijela boljem razumijevanju mineralnog metabolizma, kako u spoznavanju prehrambenih potreba mikronutrienata, tako u izbjegavanju njihova otrovnog djelovanja zbog prekomjernog unošenja. Posebice je značajan rad K. Kostial o utjecaju dobi i spola u metabolizmu elemenata u tragovima. Stoga je ovaj prikaz o otrovnosti i/ili esencijalnosti prehrambenih minerala posvećen Kristi Kostial.

Trajni napredak u teoriji i praksi analitičke kemije elemenata u tragovima omogućili su značajne pomake u istraživanju uloge i sudbine elemenata u biološkim sustavima. Povjerenstva za javno zdravstvo i agencije za zaštitu okoliša posljedično tomu ustanovili su potrebne dnevne količine unešenih elemenata i najviše dopustive koncentracije za izloženost elementima u tragovima s gledišta prehrambenih potreba (bakar, željezo, cink), odnosno s gledišta njihove otrovnosti (kadmij, olovo, živa). Neki elementi u tragovima pokazuju svojstva iz obje kategorije, tj. i esencijalnost i otrovnost, i tako otvaraju pitanja o *otrovnosti prehrambenih minerala*. Selen i krom tipični su primjerci ovog paradoksa esencijalnosti i/ili otrovnosti. Prikazane su značajke otrovanja i/ili prehrambene potrebitosti ovih elemenata kao i kriteriji za procjenjivanje njihove toksičnosti i esencijalnosti.

Autor ističe složenost uloge i sudbine elemenata u tragovima u organizmu i važnost njihova kemijskog oblika i doziranja. Umjesto svakog drugog zaključka, izražava svoju želju za poticanjem daljnjih istraživačkih napora u tom području.

Ključne riječi:

bakar, cink, elementi u tragovima – esencijalni, elementi u tragovima – toksični, krom, mikronutrienti, selen

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