

Concluding remarks on the toxicity of essential metals

by Robert A Goyer, MD¹

Interest in the toxicity of essential trace metals has evolved from the need for government regulatory agencies such as the United States Environmental Protection Agency (EPA) to set environmental standards for these metals, as well as classic toxic metals such as lead, mercury, and cadmium. It has also become apparent that the recommended dietary allowances (RDA) and reference doses (RfD) are very similar for several of the essential trace elements, the result being a narrow margin of safety between deficiency and toxicity. A workshop sponsored by the EPA, the Agency for Toxic Substances and Disease Registry and the International Life Sciences Institutes' Risk Science Institute held in March 1992 in Herndon, Virginia, reviewed the problem and identified several topics that had been inadequately considered to date.

Discussions at the present symposium gave further support for the following considerations: In the past there has been more concern about the health effects of "too little," rather than "too much." This emphasis is understandable in that one tends to regard an essential trace metal as having only beneficial effects. However, at higher levels of exposure, a number of problems can occur.

It was also noted that many of the essential trace metals are metabolically interactive and that the metabolism of some essential metals can alter the metabolism of other metals. For example, the gastrointestinal absorption of copper, iron, and zinc are interrelated so that an increase or decrease in one alters the absorption or metabolic requirement of the other. Variation in exposure levels of some essential metals can alter activity of enzymes requiring these metals as co-factors, but it is uncertain at what point such changes become evidence of toxicity (eg, erythrocyte copper-zinc superoxide dismutase). Supplementation with zinc can decrease serum ferritin. Criteria for determining when such changes are phys-

iological or adverse health effects have not been established. Other potentially adverse effects of zinc supplementation include effects on serum high-density lipoproteins and an alteration in the adhesiveness of lymphocytes. In addition, essential metals tend to be metabolically conserved, and therefore the risk of deficiency is reduced even with less than adequate intake.

Another major difference between many of the essential metals and nonessential toxic metals is variation in the requirements of different populations and during periods of different physiological need. An example is the increased need for iron during infancy and pregnancy and the potential toxicity of iron supplementation in susceptible populations, as in persons who have one of the various forms of hemochromatosis.

Recognizing some of these problems and specific gaps in available information, the workshop identified the following research questions and topics that require further study:

1. There is need to differentiate the biological end points that reflect toxicologic or adverse health effects from changes that reflect physiological adaptations.
2. There is need to identify markers of subclinical toxicity, that is, markers that can be recognized at a level of exposure below that which produces overt or clinical toxicity.
3. Markers of toxicity identified in experimental models must be validated in human subjects.
4. Knowledge of the biokinetics or toxicokinetics of essential trace metals must be expanded to levels of exposure beyond the range of deficient-to-adequate intakes.
5. The biokinetics of these elements must be determined in highly susceptible members of the general population, including the very young and elderly and those with particular biological requirements (pregnancy) and those with genetic abnormalities or pathological states that enhance susceptibility.

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