

Risk assessment of essential elements¹

by Walter Mertz, MD²

A workshop sponsored by the United States Environmental Protection Agency, the Agency for Toxic Substances and Disease Registry and the International Life Sciences Institute's Risk Science Institute addressed the risk assessment of essential elements on 10–12 March 1992 in Herndon, Virginia. The detailed proceedings, conclusions, and recommendations of the meeting are being published separately; therefore the reports on the risk assessment of essential elements in this volume are presented in condensed form as extended abstracts. Toxicologists and nutritionists discussed their common problem, the overlap of nutritional and toxicologic recommendations for some essential elements. Three days of intensive discussions produced agreement on the important principle that there is a "zone of safe and adequate exposure" for all essential elements, a zone compatible with good health. That zone represents a range of exposures via food, water, and air that is limited on one side by exposures producing the first indications of deficiency, and on the other by those resulting in the first signs of toxicity in the most susceptible populations. Although exposure levels that produce severe toxicity or severe deficiency are known for most essential elements, marginal states of toxicity and deficiency and their associated exposure levels are poorly defined. As evidence is emerging that vital cognitive and immune functions are affected, these subtle deviations from normal can be of great importance for public health. In view of the unsatisfactory state of present knowledge, there was agreement on the need for new data, especially for marginal states of exposure, and again the common interests of toxicologists and nutritionists were emphasized.

Another major result of the meeting was an examination of the criteria used in the interpretation of data in efforts to set exposure recommendations and limits, such as recommended dietary allowances (RDA) and reference doses (RfD). In the discussion,

attention was drawn to the discrepancies arising when different criteria were applied to RDA and RfD. It was suggested that, wherever possible, the following six principles should be taken into account and applied: (i) data on toxicity and deficiency should receive equally critical evaluation (data must have been confirmed independently or at least be compatible with accepted knowledge); (ii) the concept of biological availability should be applied (biologically effective doses can vary by whole orders of magnitude, depending on diet composition); (iii) the chemical species of the elements studied should be described (oxidation state, counter-ions, and binding can have profound effects on both toxicity and nutritional effectiveness in animal studies and in humans); (iv) different routes and modes of application can produce different effects (elements are generally less effective when given with diet than in water; the effects of air exposure are often completely different; results cannot be reliably extrapolated from one to another); (v) marginal states, although very difficult to determine, affect recommended exposure levels or limits the most strongly (when taken into consideration, they tend to increase dietary and decrease toxicologic recommendations and effectively narrow the range of safe and adequate intakes and even result in overlap; this tendency emphasizes their importance as a research priority); and (vi) safety margins and uncertainty factors are included on both sides of the range of safe and adequate intakes [they are typically much larger against overexposure (orders of magnitude) than against deficiency (30–50 %) and tend to decrease with increasing reliability of the data].

A third important topic, the "new essential" trace elements, was discussed, arsenic being taken as an example. This group consists of elements, previously known only as toxic, for which essentiality has been claimed by more than one investigator and in more than one animal species because of functional impairment, mainly related to reproduction, in experimental deficiency. An essential role in humans has so far been demonstrated only for boron; thus, no direct impact from the postulated essentiality of these elements on RfD values was expected in the present state of knowledge. Future studies may call for a reevaluation. The meeting ended with a strong commitment by the participants to improve collaboration and with recommendations for implementation.

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