Chapter 4

Research Needs

While compiling the present document, we identified several knowledge gaps. The research needed to bridge these gaps can be grouped according to the following issues: zinc and function; zinc requirements and toxicity; zinc absorption; assessment of zinc status; and zinc intervention programs. Each of these sets of research needs is described briefly below.

4.1 Zinc and function

Additional information on the functional consequences of zinc deficiency is needed, both to support advocacy for zinc intervention programs and to define the full range of conditions for which zinc interventions might be desirable. Moreover, some of these functional outcomes may provide useful indicators of zinc status and response to intervention programs. Specific functional domains that require additional research are zinc and infection, zinc and reproductive health, and zinc and neurobehavioral development.

In the area of zinc and infection, further information is needed on the mechanisms of the protective effects of zinc against infection. Also, the effects of zinc on specific etiologies of infection, including malaria and other parasitic diseases, tuberculosis, and HIV, should be studied. Finally, additional information is needed on the role of zinc in reducing the risk of mortality.

Further information is required to define the role of zinc in reproductive health and the consequences of zinc deficiency during pregnancy, including fetal development, delivery complications, postpartum maternal health, and infant health. Clinical trials that take into consideration the possible risk factors for poor zinc status during pregnancy (e.g., initial serum zinc concentration, pre-supplementation nutrition status, maternal health, and reproductive history) may help to better define those outcomes that are associated with zinc deficiency.

Little is known about the magnitude of effects of zinc deficiency on neurobehavioral development. Studies in a variety of populations and age groups are needed to define the range and magnitude of these effects.

4.2 Zinc requirements and toxicity

Many questions remain regarding zinc requirements in different subgroups, as defined by age, sex, and physiologic status. Information is needed on the presence and size of zinc stores at birth (in term, pre-term, and small-for-gestational-age babies) and whether these contribute to zinc homeostasis of the newborn and young infant. More information is also needed on quantitative losses of endogenous zinc from different sites, including integument, semen, and menstrual fluid, in individuals with adequate zinc status and different stages of depletion. Empirical data are needed on total endogenous zinc losses (and hence physiologic requirements) in infants (including low-birthweight infants) and children, so that these do not need to be derived by extrapolation from data on adults. Investigation is also needed on the possible impact of common conditions that affect the integrity of the intestinal tract, such as tropical enteropathy or intestinal parasitemia, on the control of endogenous losses of zinc via the intestine. Finally, information is needed on zinc requirements for optimal compensatory growth of patients recovering from severe malnutrition and/or infectious disease.

Relatively little empirical data are available regarding risk assessment of zinc toxicity. Information is needed to define intakes at which there are no observable adverse effects (NOAEL) and levels of intake at which these effects first occur (LOAEL) in different population groups. Adverse effects may include interference with maintenance of nutrition adequacy with regard to other nutrients.

4.3 Zinc absorption

Additional studies are needed on zinc absorption from a broad range of mixed diets with varying levels of factors known to modify zinc absorption (e.g., levels of zinc, phytate, protein from different sources, and calcium and other minerals). Information is needed with particular urgency for diets with high phytate: zinc ratios. Studies are also needed on the effects on

zinc absorption of commonly occurring diseases, such as tropical enteropathy, acute and persistent diarrhea, and intestinal helminthic infections. Studies that measure zinc absorption from a total day's diet and that estimate the true absorption of zinc for individuals by correcting for intestinal losses of endogenous zinc are recommended.

4.4 Assessment of zinc status

A critical area for future investigation is the development of better methods to assess the zinc status of individuals and populations. Identification of easily obtainable, low-cost biomarkers of individual zinc status and their relationship to functional outcomes of zinc deficiency and excess is an area of high priority. Pending the development of such biomarkers, the risk of population zinc deficiency can be inferred from ecologic evidence, such as the absorbable zinc content of the food supply, rates of stunting, dietary zinc intake, and possibly rates of anemia and other diseases. Research is needed to validate these indicators against other markers of zinc status and to develop more information on appropriate cutoffs that are associated with widely recognized public health problems.

With regard to dietary assessment, information is needed on the zinc and phytate contents of local foods with the goal of incorporating this information into food composition databases. Moreover, simplified dietary methods, such as food frequency questionnaires or other techniques, should be developed and evaluated with regard to their ability to predict the risk of zinc deficiency.

Additional information is needed on appropriate reference values and cutoffs of serum zinc concentration of healthy individuals, especially for children less than 3 years of age, elderly individuals, and pregnant and lactating women.

4.5 Zinc intervention programs

There is relatively little programmatic experience to date in the control of zinc deficiency. Thus, information is needed on the efficacy and effectiveness of different strategic approaches, as well as their cost-effectiveness and acceptability. Specific research needs are described, as follows, for each of the different programmatic approaches that have been proposed.

4.5.1 Supplementation

Research is needed on the optimal doses (amount, frequency, and duration) of zinc supplements for different groups, as defined by age and physiologic status. The extent to which these dosage recommendations should be modified according to the method of administration (e.g., with or after meals) and whether the supplements are provided as zinc alone or combined with other micronutrients should also be determined. The efficacy of weekly versus daily supplementation and of short-course treatment with supplemental zinc, also deserve study. Evaluation is needed of the effects of different chemical forms (i.e., the particular zinc salt or organic ligand) and physical forms (liquid, tablet, sprinkles, spreads, etc.) of supplements on zinc absorption and the cost, shelf-life, and acceptability of the supplement. Cultural and behavioral factors that influence adherence to the proposed dosage schedules should also be assessed, and studies are needed on the effectiveness and efficiency of different distribution systems.

4.5.2 Fortification

The absorption of zinc from a variety of chemical forms of zinc fortificant compounds in different food vehicles requires further study. Sensory trials are also needed in relation to the chemical form and amounts of zinc fortificants added to different food vehicles. The effects of zinc fortification on final product cost, shelf-life, and acceptability should also be determined. Studies of both the efficacy and the effectiveness of fortified food products, including fortified complementary foods, to improve zinc status are needed. Interactions of zinc with other nutrients should be assessed, in cases where these nutrients may be included in a mixture of multiple fortificants.

4.5.3 Dietary diversification/modification

Studies are needed to plan and evaluate different approaches for enhancing dietary zinc intake and absorption, including food production and processing and nutrition education. Agricultural methods to increase the zinc content of foods and/or improve zinc absorption from foods need to be evaluated, not only in terms of their efficacy but also in terms of their possible economic and environmental impact. Possible approaches include the use of zinc-containing fertilizers, plant-breeding strategies to select for high-zinc strains, and genetic modification to alter the content of inhibitors and enhancers of zinc absorption. Studies are also needed on household processing techniques that could be applied to improve zinc absorption. Finally, the feasibility and nutrition impact of incorporating non-traditional zinc-rich foods into the diet (e.g., animal-source foods, insects, and wild plants) should be evaluated.