Copper nutrition during infancy and childhood

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ABSTRACT  Full-term human infants are believed to possess adequate copper stores to last through weaning regardless of the copper content of the diet they are fed. This may not be generally true, however; a combination of low copper intake and low bioavailability from the diet may lead to copper deficiency. More information is needed on the bioavailability of copper from different infant diets, but it appears that copper is well absorbed from breast milk compared with infant formula. Several dietary factors that may affect copper absorption in infants, such as protein sources, amino acids, phytate, ascorbic acid, and other essential cations, need to be evaluated further. Studies in human infants evaluating these factors through use of stable isotope methods, as well as better indicators of copper status, are needed before the copper requirements of infants can be established. This is particularly important for premature infants who, born with inadequate copper stores, are prone to develop copper deficiency unless given higher provisions of copper. The possibility of copper excess also needs to be considered because there are limited opportunities to diagnose copper toxicity. Finally, the role of homeostatic regulation of copper metabolism in infants needs to be evaluated.  Am J Clin Nutr 1998(suppl):67:1046S–53S.

KEY WORDS  Copper, copper nutrition, copper status, copper bioavailability, premature infants, human milk, infant formula

INTRODUCTION  Copper nutrition in infants and children is not usually considered an area of concern unless the infant is born prematurely (1,2). Most diets are expected to provide adequate copper stores unless given higher provisions of copper. The possibility of copper excess also needs to be considered because there are limited opportunities to diagnose copper toxicity. Finally, the role of homeostatic regulation of copper metabolism in infants needs to be evaluated.

COPPER INTAKES OF INFANTS AND CHILDREN  The concentration of copper in breast milk is usually 0.2–0.3 mg/L (≈3–5 μmol/L) (3,4), with a slight decline during the lactation period (Figure 1). Maternal diet does not appear to affect milk copper concentrations (5), although this has not been examined in detail. Data from other species, however, suggest that copper intake has little or no effect on milk copper concentrations (6). Copper intake of a breast-fed infant will therefore be 0.14–0.27 mg/d, or 20–60 μg·kg⁻¹·d⁻¹. Most regular infant formulas have a copper concentration of 0.4–0.6 mg/L (≈6–9 μmol/L), which will result in a copper intake of 0.32–0.60 mg/d, or 50–150 μg·kg⁻¹·d⁻¹. There are, however, formulas in some countries that are not fortified with copper, and because cow milk is low in copper, they contain only 0.04–0.08 mg Cu/L (≈0.6–1.2 μmol/L) (7). In some areas, diluted condensed milk, which is also low in copper, is used for infants. In contrast, some formulas for premature infants are more generously fortified with copper and may contain 1–2 mg Cu/L (≈15–30 μmol/L). Although these formulas are intended for premature infants during their rapid catch-up growth phase, they may be used for longer periods of time and therefore must be evaluated with regard to exposure of the infant to copper. Other types of formulas may also have high concentrations of copper (7). Thus, in some instances copper intakes may range from 5 (unfortified formula) to 200 (preterm formula) μg·kg⁻¹·d⁻¹. These pronounced differences in copper intake are illustrated in Figure 2. It is obvious that the consequences of feeding such varying amounts of copper should be evaluated in some detail. If powdered formula is used and is reconstituted with water containing a high concentration of copper, these intakes will be even higher. The maximum acceptable amount of copper in tap water is currently 2 mg/L (≈30 μmol/L) (8); thus, water could enhance the copper intake of formula-fed infants with as much as 500 μg·kg⁻¹·d⁻¹. Although such high copper concentrations in water may be rare, it emphasizes that water can make a sizable contribution to daily copper intake. Weaning foods usually contain more copper than the milk-based diets of early life (9). Thus, copper intakes range from 0.8 to 1.9 mg Cu/d; most of the highest intakes are from vegetarian...
diets (10). These intakes are somewhat lower than the estimated safe and adequate daily dietary intake recommended by the Food and Nutrition Board of the National Research Council (11), which is 2.0–3.0 mg/d. Few studies have examined copper status during childhood, and there is little support for copper nutrition being of concern. Again, however, there should be some concern with regard to the sensitivity of the indexes used to evaluate copper status (see below).

BIOAVAILABILITY OF COPPER FROM INFANT DIETS

Studies assessing the bioavailability of copper from diets consumed by infants and children are scant. The radioisotopes of copper have very short half-lives and the stable isotopes have a high natural abundance, making both unsuitable for experiments in infants and children (12). To date, only one study of copper in infants has been performed using a stable isotope of copper, and it was in very-low-birth-weight infants (13). The investigators found that copper absorption was higher from breast milk than from infant formula, but it is difficult to evaluate the results because the copper concentration was quite different in the two diets. Hence, the absorption of copper from breast milk has been performed using a stable isotope of copper, and it was in very-low-birth-weight infants (13). The investigators found that copper absorption was higher from breast milk than from infant formula, but it is difficult to evaluate the results because the copper concentration was quite different in the two diets, which in itself may have affected copper absorption.

Dörner et al (14) performed balance studies in infants and found that copper retention in full-term, breast-fed infants was 88 μg·kg⁻¹·d⁻¹ in early life. With a copper intake of 114 μg·kg⁻¹·d⁻¹, this represents an absorption value of 77%. There was a decrease in copper retention with age; at age 2 wk, 130 μg·kg⁻¹·d⁻¹ was retained, whereas at age 16 wk, 64 μg·kg⁻¹·d⁻¹ was retained. Urinary copper was low at 6.4% of intake. When infants were fed copper-fortified formulas, mean copper retention was 55 μg·kg⁻¹·d⁻¹; 5 μg·kg⁻¹·d⁻¹ was retained from unfortified formula. Thus, just in full-term infants, copper retention varies 25-fold between infants fed different diets. Mean relative retention was 23% from the unfortified formula, 52% from copper-fortified formula, and 75% from breast milk. A linear relation between copper intake and copper retention was found, supporting the suggestion from studies in rats (15) that copper absorption is nonsaturable during infancy. Thus, within a normal range of copper intakes, copper retention increases with increases in dietary copper. We recently studied copper absorption in infant rhesus monkeys by using ⁶⁷Cu and whole body counting (16). Copper absorption ranged from 50% to 70%, similar to the values calculated from balance studies in full-term infants (14).

Because fetal copper accumulation occurs primarily during the third trimester, preterm infants are born with very low copper stores (17). Copper status of preterm infants is therefore an area of concern, and these infants are frequently fed copper-fortified formula. The capacity of preterm infants to utilize copper from the diet, however, may be limited. Studies by Cavell and Widdowson (18) and Dauncey et al (19) showed that copper balance can be negative for several months after birth. Most of the ingested copper was found in the stool, suggesting that either the absorption mechanisms of preterm infants are ineffective or the capacity of preterm infants to retain copper is poor, and copper is reexcreted in the bile. Negative copper balance was also found in a study on preterm infants by Tyrall (20); not even a formula with a copper concentration of 2.1 mg/L (≈32 μmol/L) resulted in consistently positive copper balance. At age 34 wk postconception, copper absorption from formula was estimated to be 11–13%. Another balance study on preterm infants by Dörner et al (14) showed a slightly negative balance (2–5 μg·kg⁻¹·d⁻¹) when the infants were fed unfortified formula [0.12 mg/L (≈1.8 μmol/L)], whereas they were in slightly positive balance (5 μg·kg⁻¹·d⁻¹) when given a copper-fortified formula [0.62 mg/L (≈10 μmol/L)].

We used a suckling rat pup model to study copper absorption from infant diets. Diets were extrinsically labeled with ⁶⁴Cu and the isotope was shown to exchange with native copper in the diets, thereby validating this approach (21). Copper bioavailability as assessed by liver uptake of copper 6 h postdosing was highest from human milk (25%), whereas it was slightly lower from cow milk formula (23%) and even lower from cow milk (18%), cereals (17%), and soy formula (10%) (Figure 3). We subsequently used this model to assess copper absorption from various types of infant formula (22). Generally, copper absorption and retention were high from milk formulas but not as high from soy formulas. One formula for premature infants resulted in lower copper absorption than the other products. The lower copper bioavailability from cow milk compared with its low copper concentration most likely explain the reports on copper deficiency in premature infants fed cow milk for extended periods.
(1, 2). Infants fed soy formula had low plasma zinc concentrations, but plasma copper concentrations in these infants were similar to those of infants fed milk-based formula (23). It is possible, however, that plasma copper may not adequately reflect copper status (see below).

There are few data on copper absorption in toddlers and children. Studies in suckling rats show that the mucosa retains a considerable fraction of absorbed copper, but this fraction decreases considerably with increasing age (21). With increasing postnatal age, copper is transported to the liver and less is retained in the small intestine. By the time of weaning, neither the intestine nor the liver retains much copper; the major part of the dose given is found in the cecum-colon and represents unabsorbed copper. By using perfused intestines from rats, Varada et al (15) found that copper absorption was saturable only in adolescent rats and that it was linear and unsaturable in infant and weaning rats. This may explain why we earlier found a similar percentage of copper absorption from human milk and human milk fortified with copper by addition of a copper salt to 10 times its original concentration (21). Varada et al (15) found copper retention to be concentration dependent and that suckling rats had considerably higher tissue copper concentrations than weaning or adolescent rats. Whether these pronounced age-related changes occur in human infants and children is not yet known. It does not appear that metallothionein is the protein binding copper in the small intestine during early life because induction of metallothionein is much higher in adolescent rats than in younger rats (15).

COPPER IN INFANT DIETS

It is well recognized that dietary ligands can affect the absorption of trace elements. In human milk, most of the copper (~75%) is in soluble form (in whey), part is associated with lipids (15–20%), and the remainder (~5%) is in insoluble form and is most likely bound to casein (24, 25). In whey, copper is loosely attached to serum albumin (26), whereas in lipid, copper is bound to the outer fat globule membrane (27). Part of the copper in whey is associated with low-molecular-weight ligands, such as citrate (26, 28).

In cow milk, however, most copper is bound to casein (75–80%), with smaller amounts bound to whey proteins (15%) and fat (5%). About 50–60% of the copper in milk and soy formulas is in insoluble form; 20–40% is associated with lipids and ~5–20% is in the soluble fraction (21). The effects of various ligands on copper absorption in infants and children have not yet been explored. We assessed the effect of adding human or cow milk to baby cereals on copper absorption in weanling rats (29). Copper absorption was lower from cereals than from milk and the addition of milk, human or bovine, to several types of cereals increased copper absorption significantly. It is unlikely that the protein ligands that bind copper in human and cow milk—serum albumin and casein, respectively—affected copper absorption from the cereals; rather, it is more likely that the high concentration of citrate in both milks was responsible for the enhanced copper absorption. Citrate has been shown to have a positive effect on copper absorption in animal models (30). It is also possible that free amino acids in milk contributed to the enhancing effect of milk on copper absorption. Further studies are needed to explore these issues.

COPPER STATUS OF INFANTS AND CHILDREN

Despite the fact that copper concentrations in human and cow milk are low [0.1–0.3 mg/L (~1.5–5 μmol/L)], copper deficiency appears to be rare in full-term infants (1). Further, feeding full-term infants formulas not fortified with copper has also resulted in satisfactory copper status (31, 32). However, copper deficiency in premature infants fed cow milk or unfortified formula has been observed in many studies (33–35). Copper stores, particularly in liver, accumulate dramatically during the third trimester (17), and any shortening of the fetal accumulation of copper results in lower neonatal copper stores than normal. It is believed that these copper stores are utilized during early infancy when copper intake is low. The rapid increase in serum copper and ceruloplasmin concentrations after birth makes this a likely scenario. When copper stores are lower than normal, diets low in copper (eg, cow milk) cannot provide adequate copper for incorporation into tissues and ceruloplasmin and the infant becomes copper deficient. Although breast milk is also low in copper, copper deficiency appears to be rare in premature infants fed breast milk, which may be a result of the higher bioavailability of copper from human than from cow milk (see above). Even in full-term infants, there must be a limit to how long neonatal copper stores can sustain adequate copper status. Levy et al (36) showed in a case report that full-term, healthy infants fed cow milk more or less exclusively for 6 mo became copper deficient, as manifested by low serum copper and ceruloplasmin, microcytic anemia, neutropenia, and skeletal and bone abnormalities. When the infants were given weaning foods, their copper status improved and the anemia resolved.

It should be recognized that assessment of copper status in infants is complicated. Traditionally, serum (or plasma) copper has been used as an index of copper status and it is evident that serum copper decreases during pronounced copper deficiency (2). However, serum copper concentrations are low in newborn infants and increase rapidly during the first 6 mo of life; thus, there is a need for age-related cutoff values for copper deficiency. To date, no such reference data are available. Furthermore, it has been shown in adults that serum copper concentrations are insensitive to marginal copper deficiency, a condition more likely to occur in infants than in overt clinical deficiency. Ceruloplasmin, the major copper-binding protein in serum, has also been used as an indicator of copper status (37). However, ceruloplasmin concentrations of infants fed different diets did
not correlate well with copper intake (32). A possible explanation is that the copper requirements of infants were met even at the lowest copper intake in the study. Similar to serum copper concentrations, ceruloplasmin concentrations increase during the first 6 mo of life, and it appears that the entire increase in serum copper is due to the increased ceruloplasmin in serum. It has been shown in adults that the ceruloplasmin concentration, like that of serum copper, is not a sensitive indicator of marginal copper status (38). The activity of the copper-dependent enzyme Cu/Zn superoxide dismutase (SOD) in erythrocytes has also been suggested as an index of copper status (39). Data from studies in children support this idea, but studies in human adults failed to show a pronounced effect of copper intake on Cu/Zn SOD activity in red blood cells (38). It is not certain, however, that the low copper intake of the subjects in this study truly represented a suboptimal intake. Our studies in human infants (40) and rhesus monkey infants (16, 41) show that red blood cell Cu/Zn SOD is responsive to copper intake and may be a useful indicator of copper status during early life.

PREMATURE INFANTS

Preterm infants are born with low serum copper concentrations (42), ranging from 0.2 to 0.3 μg/mL (≈3–5 μmol/L), that are somewhat lower than in full-term infants. However, whereas serum copper concentrations in full-term infants quickly reach adult levels, preterm infants have low serum copper up to 4–6 mo after birth (43). The increase in serum copper during infancy is dependent on growth; rapidly growing preterm infants had lower serum copper concentrations than did those with slow growth (44). Thus, healthy preterm infants with rapid catch-up growth are likely to have higher copper requirements than full-term infants who are growing normally. Infant formula manufacturers responded to these results by raising the copper content of for-

ard the increased copper in serum. It has been suggested that copper accumulation is not due to a simple bile duct obstruction, but that the metabolic pathway for copper excretion from the liver is different from that for bilirubin and bile acids. There was no correlation between bile copper and bile lipid or bile pigment excretion (50).

DIETARY FACTORS AFFECTING COPPER ABSORPTION IN INFANTS

Protein

Results from studies in premature infants and suckling rat pups suggest that copper is better absorbed from human milk than from cow milk or milk formula. It is likely, but not yet proven, that at least part of this difference is due to the differing protein compositions of these two milks. In cow milk, most of the copper is bound to casein, whereas there is little copper bound to human casein. It has been shown that cow casein can bind iron and zinc to phosphorylated casein subunits, and that casein may not be completely digested and absorbed, thus having a negative effect on iron and zinc absorption (51, 52). It is possible that cow casein may have a similar effect on copper absorption. In human milk, casein concentrations are much lower and human casein is much more readily digested; as a result, little copper remains bound to human casein. Gregor and Mulvany (53) studied the effects of bovine whey protein (lactalbumin) and soy protein on copper absorption in rats. Copper retention was lower with the whey protein diet, suggesting that zinc was better absorbed from this protein source than from soy, and that increased zinc absorption had a negative effect on copper absorption. In a recent study on infant rhesus monkeys, we found lower plasma copper concentrations in infants that had markedly elevated zinc absorption due to marginal zinc deficiency (54), giving some support to this hypothesis. It is also possible that the whey protein had a negative effect on copper absorption. Different milk protein sources have been shown to have differing effects on copper status in rats (55). Several studies have evaluated the effects of soy protein on copper absorption. It should be noted, though, that soy protein isolate contains phytate (discussed below) and there is no evidence thus far of the protein itself affecting copper absorption.

Amino acids

Some amino acids can form complexes with cations such as copper. For example, histidine can chelate copper with an affinity about three orders of magnitude higher than that for zinc (56). Using an intestinal perfusion technique, it was found that copper accumulation by the mucosa was higher when an excess of histidine to copper and zinc was used (57). It should be noted, however, that the time of study used was too short for induction of metallothionein, which may regulate copper absorption and transport across the mucosal cell. It is possible that a copper-his-

tidine complex may be an effective way to provide copper in an
absorbable form. Such a complex has been used successfully to administer copper subcutaneously to infants with low concentrations of circulating copper (58).

Novel copper–amino acid complexes have been developed, such as copper-methionine and copper-lysine. These complexes appear to have no significant effects on copper absorption directly (59, 60), although provision of copper in these forms may have a positive effect on copper absorption in the presence of inhibitors, such as cysteine (61) or ascorbate (see below). It is possible that copper presented this way is absorbed via an amino acid pathway rather than through the conventional zinc-copper transport mechanism (61), although it remains to be shown whether the copper-amino acid complexes remain in the small intestine after digestion. Most of the studies on amino acid–copper complexes have been performed in chicks and further evaluation in other species is needed.

Phytic acid

Legumes (eg, soy) and cereals contain phytic acid as a natural constituent. This storage form of phosphate in plants can form strong complexes with mineral ions and, as humans are not able to digest phytate, thereby inhibit mineral absorption. A negative effect of phytate on iron and zinc absorption has been clearly documented (62, 63). Some studies in experimental animals have also shown a negative effect of phytate on copper absorption (64, 65), whereas other studies fail to show such an effect (66). The results are difficult to evaluate, however, as the amount of phytate in the diet varied considerably between studies.

A study in human subjects in which stable isotope tracers were used found no inhibitory effect of phytate on copper absorption (67), even though zinc absorption was markedly reduced. The authors suggested that the fact that zinc-phytate complexes precipitate at the pH of the duodenum, whereas those of copper do not (68, 69), may explain the lack of an effect on copper absorption. Because phytate in the soluble copper-phytate complex can be replaced by other chelators, such as amino acids (generated from protein digestion), there may be little or no inhibitory effect of phytate on copper absorption. A study on cereal products supports this notion (70); zinc that had been solubilized from cereals by addition of acid completely precipitated out of solution when the pH was raised to 7, whereas copper stayed in solution. In a recent study on rhesus monkeys fed regular soy formula and the same formula with its phytate content markedly reduced, we showed that both copper absorption and copper status were reduced when the low phytate soy formula was fed (16). Because zinc absorption was increased by the removal of phytate, it is possible, as discussed above for protein, that the enhanced transport of zinc across the mucosa interfered with copper absorption and transport. When a low-phytate formula in which the protein had been partially hydrolyzed was fed, no negative effect on copper absorption or status was found, suggesting that a higher proportion of smaller peptides and amino acids may overcome the negative effect of phytate removal on copper absorption.

Ascorbic acid

Early studies on the effect of high concentrations of ascorbic acid on copper absorption in experimental animals indicated that copper absorption was reduced (71, 72). It was suggested that this effect was achieved by a reduction of cupric (II) ions to cuprous (I) ions and that the latter form is less well absorbed. This interpretation, however, may be too simplistic; it is evident that the interaction between copper and ascorbic acid is complex and occurs at several levels. Ascorbic acid may have an effect on copper at the absorptive stage as suggested by the earlier studies and also some recent work in rats (73), but it may also affect intracellular copper metabolism and transport of copper to the liver, as well as copper excretion. In many studies it is difficult to evaluate at which stage of copper metabolism ascorbic acid interferes. The possibility of species differences in copper metabolism should also be investigated as there appear to be differences between results from studies in rats and human data.

Support for a so-called postabsorptive effect of ascorbic acid on copper metabolism was provided in a study by DiSilvestro and Harris (74). When copper-deficient chicks were injected with ascorbic acid intraperitoneally, either in conjunction with copper or 75 min before the copper dose, copper utilization was markedly impaired. However, when ascorbic acid was injected 75 min after the copper dose, the activity of the copper-dependent enzymes increased. The authors proposed that ascorbic acid may be one of the reducing agents needed for the reduction of ceruloplasmin-bound copper to make it available intracellularly. It is also possible that ascorbate is needed for the transport of copper from the mucosal cell to other tissues. Van den Berg and Beynen (73) found that the major effect of high dietary intake of ascorbic acid in rats was decreased copper absorption, but that liver uptake and biliary excretion of copper also were increased. The effect of ascorbic acid on copper metabolism was more pronounced in copper-deficient than in copper-adequate rats. They suggested that the high biliary excretion of copper was due to increased liver copper uptake.

It is possible that the effect of ascorbic acid on copper metabolism is less pronounced in human subjects than in animal models. Finley and Cerklewski (75) found lower ceruloplasmin oxidase activity and a tendency toward lower serum copper concentrations after giving young, healthy volunteers 1500 mg ascorbic acid/d for 64 d. It is possible, however, that this was not due to decreased copper absorption, because Jacob et al (76) found no effect on copper absorption when ascorbic acid was given at different concentrations. These investigators suggested that ascorbic acid can cause release of copper from ceruloplasmin and thereby lower its oxidase activity. This is a distinct possibility because immuno logic determination of ceruloplasmin showed no change in ceruloplasmin protein concentrations. Feeding low-birth-weight infants ascorbic acid–fortified formula (50 mg/d) did not result in any negative effect on copper balance compared with feeding formula with the normal amount of ascorbic acid (77).

We recently found a weak positive effect of ascorbic acid on copper uptake by Caco-2 cells, a human cell line that in culture differentiates into cells with enterocyte-like characteristics (78). The effects were observed with concentrations of copper and ascorbic acid that were considered to be within a physiologic range, whereas no or negative effects were found with considerably higher concentrations of ascorbic acid. Thus, it is possible that ascorbic acid may have a positive effect on copper uptake at modest concentrations, but that unphysiologic concentrations may have no or negative effects.

ZINC-COPPER INTERACTIONS

It has been recognized for long time that zinc and copper can interact, in that high concentrations of one element can inhibit the absorption of the other (12, 79). The cause of this interaction
is that both of these elements have similar electron configurations and form similar coordination complexes in water solutions, thereby competing for absorptive pathways (80). That the interaction occurs at the level of absorption was shown by using an isotope of copper administered in the intestinal lumen and administering zinc intraluminally or intravenously (81). Only when zinc was given by the intestinal route was copper absorption reduced. Whereas it was earlier believed that the interaction was mediated in part by the induction of the zinc- and copper-binding protein metallothionein in the intestinal mucosa, creating a so-called mucosal block, this is now believed to occur only with very high concentrations of zinc or copper (82, 83).

Several studies in human adults failed to detect a significant effect of increased zinc intake on copper absorption when intakes were within a normal physiologic range. By using a stable isotope of copper, August et al (84) studied the effects of altering the ratio of dietary zinc to copper from 2:1 to 5:1 or 15:1, but found limited effects on copper absorption. Feeding a low copper diet, however, increased copper absorption compared with when a normal amount of dietary copper was given. When pharmacologic doses of zinc are given, there is no doubt that copper absorption is reduced. In fact, such doses are often used to treat Wilson disease (85). Similarly, we found that a teenager with acerodermitis enteropathea who received daily doses of zinc was copper deficient (86). Thus, it is obvious that some caution should be exercised with regard to the dosage used when infants and children with acerodermitis enteropathea are receiving zinc treatment. A recent report on an otherwise healthy infant who received daily doses of zinc (16-24 mg) and developed copper deficiency (87) emphasizes this concern. It should also be recognized that infants may be more vulnerable to changes in the ratio of zinc to copper in their diet. Salim et al (88) found that infants receiving copper-supplemented formula had lower plasma zinc concentrations, although they were still within the normal range. We found that feeding infant rhesus monkeys a formula with a lower ratio of zinc to copper resulted in a higher plasma copper concentration than when a formula with the regular ratio was fed (54). Again, the concentrations found were within the normal range, but the possibility of an effect of long-term feeding should not be ignored.

**IRON-COPPER INTERACTIONS**

The interaction between iron and copper may be of more concern in pediatric nutrition than that between zinc and copper. Because iron fortification and supplementation is common for infants and children, whereas copper intake often is low and copper is rarely added in significant quantities to infant foods, the ratio of iron to copper could be increased considerably. For example, whereas the ratio of iron to copper in human milk is ≈1:1, many infant formulas have a ratio of 20:1 (7). That this ratio may be nutritionally significant was suggested by a study by Haschke et al (89), who found that copper absorption in formula-fed infants was significantly lower when the formula was fortified with iron to a concentration of 10.8 mg/L (≈0.2 μmol/L) than when the concentration was 1.8 mg/L (≈0.03 μmol/L).

It was also shown that premature infants given iron supplements have lower erythrocyte Cu/Zn SOD concentrations than do unsupplemented infants (90). Older infants given iron drops, however, did not appear to have compromised copper status as assessed by serum copper (91). It is possible, though, that the interaction between iron and copper does not occur when the iron is given apart from meals. Morais et al (92) found decreased serum copper and ceruloplasmin concentrations in iron-deficient children given 5 mg iron/kg body weight for 2 wk, but it was not specified whether the iron was given with a meal or separately (or if it was standardized).

Animal studies suggest that high dietary iron affects copper absorption only when copper status is low or marginal (93–95), which may explain some of the discrepancies noted between studies on human subjects. It is also possible that high intakes of iron and ascorbic acid have a synergistic negative effect on copper. Johnson and Murphy (95) reported that high concentrations of dietary iron and ascorbic acid caused severe anemia in copper-deficient rats and reduced plasma ceruloplasmin concentrations by 44% in copper-adequate rats. Because infant formulas and other diets frequently are fortified with generous amounts of iron and ascorbic acid, the possibility of a negative effect on copper metabolism should be considered.

**COPPER IN WATER**

Most infant formulas worldwide are marketed in powdered form. Because household water has differing concentrations of copper, and concentrations in some areas may be quite high, the contribution of this source of copper to the copper intake of infants should be considered. Copper pipes are used in many countries and, because the water may be acidic, leaching from pipes is a possible source of copper contamination. In a study in formula-fed infants in Sweden, where copper pipes are used, we instructed mothers to dilute the powdered formula with tap water that had been allowed to stand in the pipes overnight, so as to maximize copper leaching (40). We found a modest increase in the copper concentration from 0.04 to 0.07 mg/L (compared with 0.4–0.6 mg/L in US formulas). This small difference had no effect on copper status.

In some countries, copper may get into the water as a result of the mining of copper. In Chile, concentrations of copper in water may be as high as 1–5 mg/L. In a recent study, infants were fed formula diluted with water with low (< 0.1 mg/L) or high (2 mg/L) copper concentrations daily for 9 mo (96). No significant difference was found between the groups for any of the indexes used to evaluate copper status (eg, serum copper, ceruloplasmin, red blood cell SOD, and metallothionein). It is possible that infants are able to homeostatically regulate copper absorption, such that the body burden of copper is not increased when dietary copper increases. Thus, moderately high concentrations of copper in water may have no adverse effects.

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