Responses to Major Comments on Technical Support Document

Public Health Goal
For
Copper
In Drinking Water

Prepared by

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INTRODUCTION

The following are the combined responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for copper, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the draft posted on the OEHHA Web site. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from Joyce Donohue, Ph.D., Health and Ecological Criteria Division, Office of Water, U.S. Environmental Protection Agency (U.S. EPA)

Comment 1: "I am concerned that the EPA MCLG for copper and the Actions Level are, in my opinion, not characterized uniformly throughout this document. The MCLG is based on a case study (Wylie, 1957) which identified acute gastrointestinal effects as the critical effect. Although the data are old, none of the more recent controlled-exposure studies of acute copper exposures or the published US epidemiology studies have demonstrated a gastrointestinal effect from exposure to water at a concentration of 1.3 mg/L. Thus, the MCLG concentration is protective for the identified critical effect. The NAS (2000) assessment of the copper data concurred with that conclusion. The enforceable value for copper under the U.S. EPA lead and copper rule is the Action Level. A statement is made on page 31 that the maximum amount of copper allowed in tap water is 1.3 mg/L under the U.S. EPA lead and copper rule. That statement is not completely correct. The Lead Copper Rules requires that 90% of the at the first draw tap samples collected after a period of at least six hour stagnation be less than 1.3 mg/L. This monitoring arrangement insures that the flowing taps water samples in most homes will be well below 1.3 mg/L for most of each day and is not equivalent to a maximum contaminant level (MCL). I believe that it is important to clarify this point. In the discussion of the USEPA MCLG, it is my opinion that it is important to make it clear that the U.S.EPA acknowledges that the MCLG is not protective for individuals with Wilson's Disease. Both consumer confidence and public notification language recommend consultation with a personal physician for this population."

Response 1: We do not agree that the MCLG, which is based on the Wylie (1957) study, is protective for copper-induced GI effects. The Wylie (1957) study entailed a one-time exposure to copper-contaminated water in adults, and was based on a dose reconstruction. More recently, Stenhammar (1999) attributed prolonged diarrhea and weight loss in three infants to copper in drinking water. The copper drinking water concentrations were very low, and ranged from 0.22 to 1 mg Cu/L. Two of the infants' homes had recently been built, whereas the third was an old house that had just had its copper pipes replaced. The children had normal serum ceruloplasmin concentrations but moderately increased serum copper levels (23-36 µmol Cu/L); one child had a substantially elevated urinary copper concentration of 6.1 µmol/L (the reference range is: 0-1.6 µmol/L). The diarrhea promptly disappeared when the children were given drinking water of low copper concentration in the hospital, but reappeared when they were sent home and drank their home water. The U.S. EPA Action Level of 1,300 ppb does not take into account children as a sensitive subpopulation, and was not derived using data in (human) infants, which OEHHA has identified as a subpopulation of concern. At the MCLG of 1.3 mg Cu/L, assuming a water consumption rate of 1.2 L/day for infants and a bodyweight of 3.5 kg, a formula-fed infant consuming water and formula reconstituted with tap water (infant formulas sold in the U.S. typically contain 75 µg Cu per 100 kcal and the median

intake is 700 kcal) would receive as much as 596 µg/kg-day of dietary copper. This exceeds the 150 µg/kg-day set by the World Health Organization (WHO, 1996) as the upper limit of the safe range for mean copper intakes by almost 4-fold. More voracious infants can consume at rates 30 to 50 percent higher than average.

Comment 2: "In my opinion, the omission of information on the timing of the gastrointestinal response to copper in the controlled human studies is a deficiency of the data summaries of the recent studies of the acute gastrointestinal effects. In almost all instances, the nausea, abdominal pain and vomiting response is acute, occurring within 15-20 minutes of the exposure, making it more of a concentration-response than a dose-response. Nausea and/or abdominal pain were observed when human adults were exposed to 200 ml of water containing 4 mg/L dissolved copper as copper sulfate (0.8 mg) yet subjects exposed in other controlled studies were able to use water containing 1 mg/L (Pizarro *et al.* 1999) and 2 mg/L (Araya *et al*., 2004) throughout the day for their beverage and food preparation without suffering the acute gastrointestinal effects, a total intake that exceeded the dose in the single 200 mL exposure. These data support the hypothesis that gastric concentration of free copper ion is more important than dose, at least for the nausea, abdominal pain and vomiting responses. Animal studies which are not cited in the PHG and which provide important mode of action data on the link between gastric wall receptors and the nausea/vomiting response are the following. An important human study on the topic of concentration versus dose is the following: Araya et al. (2003) Confirmation of an acute no-observes-adverse-effect and low-observed-adverse-effect level for copper in bottled drinking water in a multi-site study Regulatory Toxicology and Pharmacology 38:289-299."

Response 2: All of the studies mentioned above have been reviewed and added to the PHG document. In the majority of the copper drinking water studies, the most prevalent symptom reported is nausea, with the highest incidence of reporting within the first 15 minutes of exposure. In the Araya *et al.* (2003a) study, subjects were given 100-200 mL of bottled drinking water with copper amounts ranging from 0.4-1.2 mg once each week, for 12 weeks. As volume increased, the effect of Cu-induced nausea decreased; as Cu dose increased, the incidence of nausea increased. While the overall prevalence of nausea did decrease between time points, the probability of an occurrence of nausea was elevated over controls at both time points (15 and 60 minutes). While most of those reporting nausea at 60 minutes also reported nausea at 15 minutes, there were some new responders at 60 minutes, which is still an "acute" effect. In addition, there was an increased probability of experiencing nausea in female subjects. The interaction of volume by dose was not statistically significant ($p = 0.97$); a NOAEL of 0.8 mg Cu, 4 mg/L, was reported.

Comment 3: "The references to the WHO drinking Water Guidelines for copper cite the 1993 guideline document. That version has been supplanted by two later versions with the most recent one being the 2004 version. The basis of the drinking water guideline is now totally different from what it was in 1993 because of the studies published in the past

decade. The new guideline document can be accessed at http://www.who.int/water_sanitation_health/dwq/chemicals/copper.pdf."

Response 3: The 1998 and 2004 WHO Drinking Water Guideline documents have been reviewed and the PHG document has been updated to reflect the changes. The initial basis for the 2 mg/L guideline value was based on a lack of adverse effects in animals, a NOAEL from a small-scale unpublished study conducted in dogs (Shanaman *et al*., 1972). A ten percent allocation of the tolerable daily intake (TDI) was made to water, and based on a standard body weight of 60 kg and a water consumption of 2 L/day, a figure of 1.5 mg/L was derived. This was rounded up to 2 mg/L to reflect uncertainty in the data and assumptions.

The current basis for the WHO guideline of 2 mg Cu/L is based on evidence from human studies by Araya *et al.* (2001, 2003a,b), Olivares *et al.* (1998, 2001), Pizarro *et al.* (1999, 2001) and Zeitz *et al.* (2003). According to WHO (2004), the 2 mg Cu/L value "provides an adequate margin of safety in populations with normal copper homeostasis", and "should permit consumption of 2 or 3 litres of water per day, use of a nutritional supplement and copper from foods without exceeding the tolerable upper intake level of 10 mg/day (IOM, 2001) or eliciting an adverse gastrointestinal response". The 2 mg/L guideline is not intended to be health protective for certain sensitive populations, "such as those with defects in the gene for Wilson disease and other metabolic disorders of copper homeostasis" (WHO, 2004).

Most of the studies referenced by WHO (2004) were acute drinking water studies conducted in healthy adults. Periods of exposure duration and volume of water consumed varied considerably between studies. In the case of the Olivares *et al.* (2001) study, adult volunteers drank a single 200 mL bolus of copper-enhanced water once per week for a total of 12 weeks. Thus, subjects ingested only one-tenth the standard daily default drinking water consumption rate of 2 L/day for adults, and were only exposed at this concentration once per week. The endpoints under evaluation were GI effects: nausea, abdominal pain, vomiting, and diarrhea. The NOAEL for this study was identified as 2 mg Cu/L for acute GI effects (nausea, vomiting). For other studies referenced by WHO (2004) (Olivares *et al.*, 1998; Araya *et al.*, 2003a,b) a NOAEL of 4 mg/L was reported. Although WHO stated in their 2004 drinking water guideline that the 2 mg Cu/L value "provides an adequate margin of safety in populations with normal copper homeostasis", no adjustments to the 2 mg/L NOAEL were made for the full default water consumption rate or for daily consumption, nor does the guideline reflect the use of any uncertainty factors. Nevertheless, based on the Olivares *et al.* (2001) study above, and other studies, WHO (2004) stated that the 2 mg Cu/L guideline "should permit consumption of 2 or 3 liters of water per day.…" Given that in the Araya *et al.* (2003a) study GI effects were reported by at least one subject at each dose level, the statement by WHO (2004) that the 2 mg/L value "provides an adequate margin of safety" is not well supported by the study findings. In the Olivares *et al.* (1998) study cited by WHO (2004), the study population was comprised of human infants. No differences in growth and morbidity or liver function were observed between supplemented and unsupplemented groups. However, both of the high copper exposure groups that received drinking water containing 2 mg Cu/L in this study had higher drop-out rates than the low copper (<0.1 mg Cu/L) groups. In the formula-fed, copper-supplemented group the

number of infants withdrawn from follow-up was three times the rate of unsupplemented formula-fed infants. The authors stated that the higher withdrawal rate of infants in the high copper content groups "could be the consequence of a higher prevalence of unreported symptoms of intolerance." For this reason and others, the conclusion that 2 mg Cu/L (the highest dose administered in the study) represents a true NOAEL is a tenuous one. (A number of drinking water studies in infants/children provide evidence that children represent a sensitive subpopulation for copper toxicity). In the study by Pizarro *et al.* (1999b), acute GI symptoms (diarrhea, nausea, abdominal pain, vomiting) appeared to occur in adults at copper intake levels below the WHO TDI limit of 0.5 mg/kg-day of copper.

Comment 4: "The draft PHG document treats all infant idiopathic copper toxicoses as if they are Indian Childhood Cirrhosis. This should be corrected. There are a family of these toxicoses that are referred to by a variety of different names. The underlying genetic factors for each may or may not be the same. The uniting factor is the fact that they impact the very young. The exact cause of these disorders, to my knowledge, has not been determined, although it does appear to have a genetic component. The following is a recent article on the link between copper and childhood cirrhoses.

Dieter HH, Schimmelpfennig W, Meyer E, Talbert M (1999). Early childhood cirrhoses (ECC) in Germany between 1982 and 1994 with special consideration of copper etiology. *European Journal of Medical Research,* 4:233-242."

Response 4: The wording of this discussion has been modified to avoid giving the impression that all such syndromes have the same etiology.

Comment 5: "In my opinion, the discussion of the data from the Olivares et al. study seems to incompletely characterize the data, possibly leading the reader to conclude that there is evidence of subclinical copper toxicity even though the highest dose is characterized as a no-observed-adverse-effect level (NOAEL). This is particularly true of the discussions on pages 19, 23 and 31. The reader is not informed that ceruloplasmin concentration and superoxide dismutase activity are measures for the nutritional adequacy of copper becoming low when copper intake is inadequate (IOM, 2001 pp 230-231) and, thus, the significant difference in ceruloplasmin activity between the infants that were given the copper supplement is one that indicates that they were better nourished relative to copper than those without the supplement (Table 1). In addition, the PHG does not state that elevated SGOT, GGT, SGPT and total bilirubin are indicators of adverse effects on the liver and, thus, the significant elevation of the total bilirubin and SGOT in the breast fed infants compared to the formula fed infants could be taken to mean that the breast fed group had minimal signs of impaired liver function, but that it was unrelated to copper since there was no significant difference between the supplemented and unsupplemented breast fed infants (Table 1)."

Response 5: Because of the high drop-out rate of infants in those groups who received water supplemented with copper at a concentration of 2 mg Cu/L, liver enzyme function between groups could not be satisfactorily compared with regard to copper's effect on

liver enzymes. (In the formula-fed, copper-supplemented group, the number of infants withdrawn from follow-up was three times the rate of unsupplemented formula-fed infants.) For the same reason, and additionally because of other study weaknesses outlined in the PHG document, the Olivares *et al*. (1998) study should not be relied upon to draw strong conclusions about safe copper drinking water exposure levels in young infants. The lack of consistency with regard to when breast-fed infants were started on formula, etc., further clouds the study findings.

While ceruloplasmin (and serum copper) concentrations are typically used to assess copper status; they are not currently used to evaluate copper overload, and may not be the best markers for excess copper. A number of studies in both laboratory animals and humans, and including human infants, have determined that indicators of copper status such as serum copper and ceruloplasmin concentrations do not change significantly when different amounts of copper are consumed, even with exposures 3-10 times the standard copper intake (up to 9 mg Cu/day) (Araya *et al.*, 2003b,c, 2005; Olivares *et al*., 1998; Pizarro *et al.*, 2001; Salmenpera *et al*., 1989; Zietz *et al.,* 2003). However, the effects of copper on small intestine and liver, tissues that play a principal role in copper homeostasis, show evidence of regulatory responses (Araya *et al.*, 2005). Studies in young rats have shown that copper supplementation resulted in significantly higher small intestine copper concentrations despite the lack of effect on plasma copper concentration (Bauerly *et al*., 2004). In addition, young copper-treated rats accumulated more hepatic copper, had more severe liver changes, and had higher serum liver enzyme activities than did adult rats (Fuentealba *et al.*, 2000). In the Olivares *et al.* (1998) study in human infants, significant differences in ceruloplasmin activity were found between infants who received drinking water with high vs. low copper content, 350 $\pm$ 85 mg/L versus 322 $\pm$ 75 mg/L, respectively. In addition, there were significant differences for this parameter in the breast-fed groups between infants who received drinking water with high and low copper content. Because tissue samples could not be taken, for obvious reasons, it is not possible to know what effect, if any, the copper supplementation may have had on liver copper concentration in these infants.

Comment 6: "The discussion of the critical study seems to indicate that gastrointestinal effects are considered to be the critical effect for copper in infants. The discussion states that infants cannot point to the source of their pain or distress and that diarrhea and colic are common in young children and (potentially have life threatening consequences). Based on my experience as a parent/grandparent, I would say that infants let you know when they [have] gastrointestinal discomfort even though they cannot speak. In addition, I am not sure that colic is life threatening."

Response 6: The acute adverse GI effects associated with copper toxicity include the following: abdominal pain, nausea, vomiting and diarrhea. GI effects such as vomiting and diarrhea, which contribute to fluid loss, can pose a significant threat to the health of a young infant.

Comment 7: "The infants in the Olivares study were studied from 3 months to 12 months. The quantification is based on a NOAEL. Accordingly, it is difficult to

understand why the body weight used for the calculation was based on one standard deviation less than the average birth weight. In my opinion, a better value would be the average weight for the infants over the 9 month period of the study. Those data are not provided in the study but age-related average body weights for infants are available from NHANES data."

Response 7: We agree. The revised PHG is calculated based on drinking water consumption, calculated on a body-weight basis, for infant weights more representative of the study population.

Comment 8: "OW recently updated the report on water ingestion from USDA Continuing Survey of Food Intakes by Individuals (CSFII) survey data (www.epa.gov/waterscience/criteria/drinking/percapita/2004.pdf) using data that includes a over sampling of children. The values for median (548 mL) and 90 percentile (968 ml) intakes for consumers only (direct and indirect intake) are below the (OEHHA, 2000) mean (1166 mL/day, page 28) for infants less than one year of age On the basis of CSFII survey data, the 1.2 L used in the quantification seems to be high for a mean value."

Response 8: The drinking water rate of 0.221 L/kg-day for infants less than six months of age is now used in the revised risk assessment. This is the upper 95th percentile value of community water supplies consumed by infants zero to six months of age in the U.S. EPA (2004) analysis of drinking water consumption rates. OEHHA considers the use of the upper 95th percentile value to be more appropriately protective of the entire population.

Comment 9: "In my opinion, there should be no adjustment for duration. Infants are judged to be the most sensitive population since people with Wilson's disease were excluded. Infants only remain infants for 12 months and this study covered 9 of the first 12 months. The Olivares et al. (2004) study provides some coverage for the first 3 months. Accordingly, I do not see any justification for a using a duration adjustment. In my opinion, the factor for differences in sensitivity should not be as high as a 10. Dividing the total daily intake (an average of 2.4 mg/day for the supplemented children) by 10 (0.24 mg/day) would bring one very close to the average AI value for infant across the period studied (0.21 mg/day), a value which by definition lacks precision. The AI for young infants is the **mean** value for the nutrient supplied by human milk (780 or 600 mL) to apparently healthy infants and may be different for formula fed infants for which the bioavailability of a nutrient may be different from that in human milk (IOM, 2001 pp 231-238). An uncertainty factor of 3 for sensitivity would be more appropriate if one were trying to protect neonates with a sensitivity to one of the infantile liver cirrhosis disorders. Concerns for sensitivity must be balanced with the needs of premature children for higher levels of copper to make up for inadequate copper stores (See page 9)."

Response 9: Copper concentrations in drinking water can vary widely, depending on a number of factors. As both you and we have stated, "Drinking water should not be viewed as a nutritional source of copper." The accepted method for ensuring that

premature infants receive adequate copper is to provide a special, highly copper-fortified formula, specific for premature infants. Food, not water, is the primary source of copper intake. Copper in drinking water is not intended to nor appropriate to serve as a source for inadequate copper stores in premature infants. A term infant fed a standard copper-fortified formula prepared with stagnant water, particularly if pipes are new, is at risk for copper excess. Given all these caveats, we nevertheless agree with the point that an uncertainty factor of three should be adequate, and have made this change in the PHG document.

Comment 10: "I agree that drinking water should not be viewed as a nutritional source of copper. However, it is difficult for me to put faith in the proposed PHG when I look at Table 3 of the PHG document and see that the copper intake for even the lowest 5% of 2-6 month old infants exceeds the AI value by the PHG of 0.1 mg/day, and the 50 percentile copper intake for 2-6 month old infants exceeds it by 0.6 mg/day. Because AI values by definition lack precision, the public health goal should not impinge too tightly on the range of uncertainty that surrounds this nutritional guideline during a period in life when good nutrition is essential and when cows milk, which is low in copper and has been reported to lead to copper deficiency in infants, may be used after weaning by some segments of the population (IOM, 2001; page 238)."

Response 10: U.S. formulas contain (on average) 75 µg Cu per 100 kcal, and the median intake is 700 kcal, representing 525 µg of copper. This is adequate to meet copper nutrition requirements as set forth by the Food and Nutrition Board in young infants. Infants who are weaned (from a solely milk-based liquid diet) are presumably fed weaning foods (e.g., soups, solids). Weaning foods are typically higher in copper content than formulas (and copper in food is typically more bioavailable), so that even if weaned infants were fed cow's milk as a portion of their diet, they would be receiving adequate copper from other food sources. Therefore the setting of a low PHG for copper will not likely lead to any copper deficiencies. However, our change from the PHG of 100 ppb proposed in the first public draft (July 2005) to 300 ppb in the final version should somewhat ameliorate this concern.

Comment 11: "There are Total Diet Study data published for periods after 1986 (IOM, 2001)."

Response 11: These data have been added to the PHG document.

Comment 12: "I believe that FNB (2000) should be IOM (2001). We called and asked the NAS as the appropriate citation and they indicated that IOM was preferred. In addition, the actual publication date on the book is 2001."

Response 12: The citation has been changed to IOM (2001).

Comments from Carl Keen, Ph.D., UC Davis, for the Copper Development Association, Inc.

Comment 1. "The argument that there is a need for a new PHG for copper in drinking water to reduce the risk for copper toxicity in infants is flawed. The confirmed cases of copper deficiency in infants far exceed the number of putative cases of copper toxicity. In summary, while I found the OEHHA report to be well prepared and documented, I cannot support the conclusion that there is a need to change the current PHG for copper in drinking water."

Response 1: Health and Safety Code Section 116365 requires that PHGs be reviewed at least once every five years, and revised as necessary based on the availability of new data. The Olivares *et al*. (1998) study used as the basis for the revised copper PHG provides new information about copper drinking water exposure in human infants, a sensitive subpopulation of concern for this contaminant. Copper deficiency is an area of concern in pre-term infants, but rare in full-term infants. For this reason, formulas for premature infants are typically generously fortified with copper to meet the premature infant's nutritional needs. Food is the primary source of copper in the diet. Drinking water contaminated with copper is not a required source of copper in the diet. The risk of excess copper exposure in young infants fed formulas reconstituted with water containing high concentrations of copper is a concern in areas where drinking water may contain more than a few milligrams of copper per liter of water. Neonates show a reduced capacity for biliary excretion of copper (the primary route of copper excretion) and a number of studies in young animals, including primates, have shown newborns to be especially susceptible to copper toxicity compared to adults (Araya *et al.*, 2005; Bauerly *et al.*, 2005; Fuentealba *et al*., 2000). The final PHG has been raised to 300 ppb from the previous PHG value of 170 ppb and the initial proposed value of 100 ppb, which should relieve the concern expressed in this comment.

Comment 2. "With respect to the proposed PHG for copper, the value that is being advanced is actually lower than the concentration of copper that is present in a large number of commercially available infant formulas."

Response 2. The primary source of copper in the diet comes from food, and breast milk/infant formulas would be expected to provide the bulk of a young infant's dietary copper consumption. Copper in drinking water is not generally a significant nor an essential source of dietary copper; it can, however, contribute to copper overload/excess. The FNB recently established recommended daily allowances (RDAs) for copper in adults and children (IOM, 2001). The data were judged not sufficient to establish RDAs for infants. However, intakes for infants in the first year of life were estimated based on the copper concentration of human milk; copper intakes of 200 µg/day were deemed adequate for the first six months of life and 220 µg/day for the second six months. At the PHG value of 300 µg Cu/L and a drinking water consumption rate of 1.2 L/day, drinking water alone would exceed this value. Water would make up over half an infant's daily copper intake if the infant formula contained 0.4-0.8 mg Cu/L. According to WHO, only ten percent of daily dietary copper is assumed to come from drinking water.

Comments from Dick Wilson, Environmental Services Mgr., Anaheim Public Utilities Department

Comment 1: "Since almost all water systems have copper monitoring data over the current PHG and there have been no reports of adverse health effects, it's perplexing why the PHG for copper is considered a priority for revision."

Response 1: The Calderon-Sher Safe Drinking Water Act requires OEHHA to develop a PHG for each regulated drinking water contaminant and review and revise the assessments at least every five years, as necessary based upon the availability of new scientific data (HSC 116365(e)(l)). The copper PHG was first published by OEHHA in 1999 and a literature review revealed significant new studies on copper exposure in infants, which we sought to address in this PHG revision. In addition, copper concentrations vary widely in individual homes with copper plumbing, depending in part on the age of the home, and the pH and hardness of the tap water. Acute symptoms of copper poisoning, which include nausea, abdominal pain, vomiting, and diarrhea, can mimic many other illnesses, such as food poisoning, and may be underreported.

Comment 2: "The draft states (paragraph 1, page 1), "The proposed PHG is based on children as a sensitive group…" yet the proposed PHG is actually based on a newborn infant weighing 2.85 kg (6.27 lbs.). Though an infant is a "child, when one hears the word, "children", they are more likely to think of persons between 2 and 10 years old, not a newborn infant. For clarity and accuracy, we suggest you change the phrase to read, "The proposed PHG is based on newborn infants as a sensitive group.…"

Response 2: The infant represented in the formula now used to calculate the PHG is now zero to six months old, which is more representative of the weight of infants in the formula-fed, copper-supplemented group in the critical study. Where appropriate, we have changed the terminology from children to infants.

Comment 3: "Please provide an explanation why the PHG advocates a copper intake level below the Food and Nutrition Board's Adequate Intake value of 200 µg/day for infants (page 10 of the draft). The PHG draft proposes an Acceptable Daily Dose of 42.6 µg/kg/day. At that dose, a 2.85 kg infant would be allowed only 121.4 µg/day, below the 200 µg/day recommended by FNB."

Response 3: Food is the primary source of dietary copper intake. Most diets are expected to provide ample quantities. The PHG is developed for the drinking water component only, and drinking water is not generally considered a required source of copper. The FNB Adequate Intake value takes into account copper from all dietary sources (food, water, supplements, etc). For infants, both breast milk and commercial baby formulas are copper sources (also soup, fruit and other soft foods). Nevertheless, raising the PHG from the proposed value of 100 ppb to 300 ppb should help relieve this concern.

Comment 4: "We believe that an uncertainty factor of 10 is not justified because a) the Federal Action Level of 1,300 ppb is considered to be adequately protective for both acute and chronic effects with a reasonable margin of safety by the US EPA; and, b) the Lead and Copper Rule compliance monitoring methodology is ultra conservative and results in worst-case copper levels which in effect, provides an additional safety margin."

Response 4: The U.S. EPA Action Level of 1,300 ppb does not take into account children as a sensitive subpopulation, and was not derived using data in (human) infants, which OEHHA has identified as a subpopulation of concern. At the MCLG of 1.3 mg Cu/L, the average daily copper intake during the first six months of life from powdered infant formula plus the water used to reconstitute it would exceed the 150 µg/kg-day set by WHO (1996) as the upper limit of the safe range for mean copper intakes. Our revised PHG of 0.3 mg/L would provide 66 µg/kg-day (from water) for formula-fed infants. Drinking water at this level or lower would help avoid a potential concern.

Comments from Association of California Water Agencies (ACWA) - Krista Clark

Comment 1: "In calculating the PHG, OEHHA has used the birthweight of low-weight infants in Group I of the Olivares et al. (2001) study, as represented by the Group I mean birth weight for girls minus one standard deviation. The daily water consumption, however, was based on water consumption for infants less than one year. There is therefore a mismatch between the body weight (at birth) and assumed water consumption (from birth to one year of age)…ACWA believes it is inappropriate to use the weight of a newborn and the drinking water consumption for infants under one year of age."

Response 1: We agree; the calculation has been changed to utilize the drinking water consumption rate for infants <six months old from the community water consumption data in the National Health and Nutrition Examination Survey, as summarized in U.S. EPA, 2004. This group includes the mean birthweight for infant girls in the Olivares *et al*. (2001) study for high copper-exposed formula-fed infants (Group I).

Comments from Ray Arnold, Ph.D., on behalf of the Copper Development Association, Inc. and Ruth Danzeisen, Ph.D., on behalf of the International Copper Association Ltd.

Comment 1: "We believe that a 9-month period is enough to be considered "chronic" especially since this is a study regarding risk in neonates and the first months of life. The use of an uncertainty factor to extrapolate from subchronic to chronic is therefore incorrect."

Response 1: The final version of the PHG document does not include an uncertainty factor for less-than-chronic exposure.

Comment 2: "It has to be stressed that the uncertainty factor of 10 is clearly controversial…the homeostatic model is the risk assessment model proposed for Essential Trace Elements (ETEs). The homeostatic model takes into account copper excretion, down-regulation of copper absorption in conditions of high dietary copper intake, etc."

Response 2: The uncertainty factor has been decreased to 3.

Comment 3: "The WHO [copper drinking water limit] already includes a safety factor (an Uncertainty Factor of 10 was already used to derive the 2 mg/L WHO limit).

Response 3: The current WHO (2004) drinking water guideline for copper references a number of human studies as the basis for the guideline value. Several of these studies (Olivares *et al.*, 1998, 2001; Araya *et al.*, 2003a,b) identified NOAELs of 2 or 4 mg Cu/L for GI effects. Thus it appears to us that the 2 mg/L guideline does not include the use of any uncertainty or safety factors.

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