Paragraph 3

Massive DNA damage was observed in hepatocytes from patients with Indian childhood cirrhosis, and was postulated to result from excessive accumulation of copper in the nucleus leading to the production of free radicals that cause DNA strand breakage (Prasad et al., 1996). Similarly, distinct bulky DNA adducts but no increases in 8-hydroxydeoxyguanosine were seen in the livers of six out of eight patients with Wilson's disease. The adduct levels of one patient were elevated 100-fold over background adduct levels in control patients (Carmichael et al., 1995). In LEC rats, which abnormally metabolize copper, the formation of etheno-DNA adducts was positively correlated with age-dependent elevated levels of hepatic copper (Nair et al., 1996).

Paragraph 4

At high concentrations, copper may be genotoxic or enhance the genotoxicity of other agents, possibly through the generation of reactive oxygen species/free radicals or through effects on DNA-related enzyme processes. However, it should be noted that results from *in vitro* tests may not be directly applicable to *in vivo* circumstances because *in vivo* copper is generally bound to protein or amino acid ligands.

### 6.6 Carcinogenicity

Paragraph 1

A number of older studies have examined the carcinogenicity of various copper compounds in laboratory animals, but all are inadequate by current methodology standards (NRC, 2000). Nonetheless, it is evident that the limited available data provide no suggestion that copper or its salts are carcinogenic in animals having normal copper homeostasis. The U.S. EPA classifies copper as Group D, not classifiable as to human carcinogenicity (U.S. EPA, 1991).

## 7. GUIDELINE VALUE

Paragraph 1

The IPCS Environmental Health Criteria monograph for copper (WHO, 1998a) concluded that the upper limit of the acceptable range of oral intake (AROI) in adults is uncertain but it is most likely in the range of several but not many mg per day in adults (several meaning more than 2 or 3 mg/day). This evaluation was based solely on studies of gastrointestinal effects of copper-contaminated drinking-water. However, the data on the gastrointestinal effects of copper must be used with caution since the effects observed are influenced by temporal aspects of exposure and the concentration of ingested copper to a greater extent than the total mass or dose ingested in a 24-hour period. A single glass of tap-water with a concentration greater than 3 mg/L copper is more likely to elicit nausea than a liter of water containing the same amount (mass) of copper, but ingested episodically throughout a day. The available data on toxicity in animals were not considered helpful in establishing the upper limit of the AROI, due to uncertainty about an appropriate model for humans but do help to establish a mode of action for the response.

Paragraph 2

In 1998, WHO established a provisional copper level of 2 mg/L in drinking-water to be protective against adverse effects of copper and provide an adequate margin of safety in populations with normal copper homeostasis (WHO, 1998b). This limit remains appropriate. For adults with normal copper homeostasis, this limit should permit consumption of two or three liters of water per day, use of a nutritional supplement, and copper from foods without exceeding the recommended dietary upper limit of 10 mg/day or eliciting an adverse gastrointestinal response.

Paragraph 3

Recent studies have delineated the threshold for the effects of copper in drinking water on the gastrointestinal track but there is still uncertainty regarding the long-term effects of copper on sensitive populations such those with defects in the gene for Wilson's disease and other metabolic disorders of copper homeostasis. Owing to limitations of the available data for these populations, it is not possible to establish a clear effect level with any precision. Thus, it is recommended that this guideline value for copper of 2 mg/L remain provisional.

Copper tubing is used widely as a plumbing material in a variety of circumstances. In most of these, concentrations of copper will be below the guideline value. However, there are some conditions , such as highly acidic or aggressive waters that will give rise to much higher copper concentrations and copper tubing would not be appropriate in such circumstances.

Paragraph 4

Staining of laundry and sanitary ware occurs at copper concentrations above 1 mg/L. At levels above 2.5 mg/L copper imparts an undesirable bitter taste to water; at higher levels the color of water is also impacted.

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