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Copper in Drinking Water

Guideline Technical Document for Public Consultation

Prepared by the Federal-Provincial-Territorial
Committee on Drinking Water

Consultation period ends
May 25, 2018

**Copper in Drinking Water
Document for Public Consultation
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Copper in Drinking Water

Purpose of consultation

The Federal-Provincial-Territorial Committee on Drinking Water (CDW) has assessed the available information on copper with the intent of updating the current drinking water guideline and guideline technical document on copper in drinking water. The purpose of this consultation is to solicit comments on the proposed guideline, on the approach used for its development and on the potential economic costs of implementing it, as well as to determine the availability of additional exposure data.

The existing guideline on copper, last updated in 1992, established an aesthetic objective of ≤ 1.0 mg/L, to ensure palatability and to minimize staining of laundry and plumbing fixtures. This new updated document proposes a health-based maximum acceptable concentration (MAC) of 2 mg/L for copper in drinking water. The proposed MAC is considered to be protective of both short-term effects (i.e., gastro-intestinal effects) as well as longer-term effects (including potential effects in the liver and kidneys). The document is based on currently available scientific studies and approaches, taking into consideration the mode of action. It provides exposure information as well as sampling considerations, analytical methods and treatment technologies for copper in drinking water. The document also proposes an aesthetic objective (AO) of 1 mg/L, based on taste and staining considerations.

The CDW has requested that the guideline technical document on copper in drinking water be made available to the public and open for comment. Comments are appreciated, with accompanying rationale, where required. Comments can be sent to the CDW Secretariat via email at water_eau@hc-sc.gc.ca. If this is not feasible, comments may be sent by mail to the CDW Secretariat, Water and Air Quality Bureau, Health Canada, 3rd Floor, 269 Laurier Avenue West, A.L. 4903D, Ottawa, Ontario K1A 0K9. All comments must be received before May 25, 2018.

Comments received as part of this consultation will be shared with the appropriate CDW member, along with the name and affiliation of their author. Authors who do not want their name and affiliation shared with their CDW member should provide a statement to this effect along with their comments.

It should be noted that this guideline technical document on copper in drinking water will be revised following evaluation of comments received, and a drinking water guideline will be established, if required. This document should be considered as a draft for comment only.

March 2018

Copper

Part I. Overview and Application

1.0 Proposed guideline

A maximum acceptable concentration (MAC) of 2 mg/L (2000 µg/L) is proposed for total copper in drinking water, based on a sample of water taken at the tap. An aesthetic objective (AO) of 1 mg/L (1000 µg/L) is also proposed for total copper in drinking water.

2.0 Executive summary

Copper is present in tap water principally as a result of leaching from copper-containing components of distribution and plumbing systems. Copper has been, and continues to be, broadly used in drinking water applications, including in household pipes and in fittings.

This guideline technical document reviews and assesses all identified health risks associated with copper in drinking water. It assesses new studies and approaches and takes into consideration the availability of appropriate treatment technology in order to propose a maximum acceptable concentration that is protective of human health, measurable and achievable by both municipal and residential scale treatment technologies. Based on this review, the proposed guidelines for copper in drinking water are a maximum acceptable concentration of 2 mg/L (2000 µg/L) and an aesthetic objective of 1 mg/L (1000 µg/L).

During its fall 2016 meeting, the Federal-Provincial-Territorial Committee on Drinking Water reviewed the guideline technical document on copper and gave approval for this document to undergo public consultation.

2.1 Health effects

Copper is an essential element in humans. Copper deficiency may cause several health effects, but is not expected to be a concern in Canada, based on copper intake from food. The U.S. National Academy of Medicine (formerly called the Institute of Medicine) has established recommended daily allowances of 900 µg/day for adults and 340–890 µg/day for children, as well as tolerable upper intake levels of 10,000 µg/day for adults, and between 1,000 and 8,000 µg/day for children.

International agencies have determined that the data available on copper are not sufficient to classify it with respect to carcinogenicity. Short-term exposure to copper may result in effects in the gastrointestinal tract (nausea, pain and vomiting, diarrhea). Long-term effects are less well documented; current evidence indicates that, in the general population, chronic exposure to very high levels of copper may lead to effects in the liver and kidney. The proposed MAC was developed based on bottle-fed infants (aged 0 to 6 months) and is considered to be protective of all health effects, both short-term and longer-term.

2.2 Aesthetic considerations

The presence of copper can affect the taste of the water and cause the staining of laundry and plumbing fixtures at levels below the proposed MAC. Although there are no adverse effects associated with such levels, they will affect the acceptability of the water by consumers.

Although the proposed AO for copper in drinking water is 1 mg/L (1000 µg/L), some individuals can readily perceive copper at levels below the AO. Nevertheless, corrosion control practices should target the MAC and not the elimination of aesthetic concerns as this could jeopardize other water quality priorities such as lead control. Utilities may choose to use the AO to trigger a site-specific or localised water quality/corrosion investigation.

2.3 Exposure

Copper occurs naturally in the Earth's crust, either in mineral deposits or, less frequently, as a metal. Copper can enter water sources from natural processes, such as soil weathering, and human activities such as agriculture, mining and manufacturing. The National Plumbing Code of Canada considers copper to be an acceptable material for service lines and plumbing systems. Consequently, copper in drinking water can also result from the corrosion of copper-containing pipes and fittings in distribution and plumbing systems, depending on the chemistry of the water.

Canadians can be exposed to copper through food, drinking water, air, soil and consumer products. Although the most significant source of copper intake is food for the general population, the bioavailability of copper in drinking water may be greater than that in food. Based on the physical and chemical properties of copper, inhalation and dermal absorption of copper are not expected from exposure to drinking water.

2.4 Analysis and treatment

The establishment of a drinking water guideline must take into consideration the ability to measure the contaminant. There are several methods available for the analysis of total copper in drinking water. Based on the capacity of commercial laboratories in Canada, analytical methods are available to reliably measure total copper in drinking water below the proposed MAC. These methods should include sample preparation to ensure that they are able to detect both dissolved and particulate copper.

Copper levels in source water are typically very low. Although there are treatment technologies that can remove copper efficiently at the treatment plant, municipal treatment is not generally an effective strategy. This is because copper is an acceptable material for service lines and plumbing systems. However, in certain water qualities, copper may be released into drinking water from pipes, service lines and brass fittings. The treatment approach for copper is generally focused on corrosion control through approaches such as water quality adjustments and the use of corrosion inhibitors.

As the primary source of copper in drinking water is the leaching from plumbing and distribution system components, drinking water treatment devices offer an effective option at the residential level, although their use should not be considered to be a permanent solution. There are a number of certified residential treatment devices available that can remove copper from drinking water to below the proposed MAC.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

The proposed MAC for copper is established to be protective of both short-term gastrointestinal effects and longer-term effects in bottle fed infants as well as in the general population. Considering that copper levels at the consumer's tap may be significantly higher than levels at the treatment plant or in the distribution system, strategies to reduce exposure to copper

will need to focus on controlling corrosion within the distribution and plumbing systems. The water quality factors that have the greatest effect on copper corrosion are pH and alkalinity. Dissolved oxygen and/or chlorine residual/oxidants are also important considerations for copper. Copper monitoring should focus on areas known or likely to have new copper piping and where water quality conditions are potentially corrosive (e.g., low pH, dead ends, low or high alkalinity waters) and in consecutive systems.

An exceedance of the proposed MAC should be investigated and followed by the appropriate corrective actions to reduce the copper levels below the MAC. These actions include, but are not limited to, resampling, public education and corrosion control measures. However, these actions should be based on an assessment of the cause of the exceedance using appropriate protocols, such as those found in *Guidance on Controlling Corrosion in Drinking Water Distribution Systems*.

3.1 Monitoring

Sampling protocols will differ, depending on the desired objective (i.e., identifying sources of copper, controlling corrosion, assessing compliance, estimating exposure to copper). As monitoring of copper at the tap can be done using different sampling protocols, it is important that the selected protocol be appropriate to meet the desired objective. It is important to note that although the analysis of metals can be undertaken from the same sample bottle, sample sites for copper and lead differ. As such, copper results from lead sampling sites are unlikely to properly identify areas with copper issues.

The objective of sampling protocols in this document is to monitor for typical community exposure to total copper to determine whether there are concerns about human health effects. Compliance monitoring should be conducted at the consumer's tap and focus on areas known or likely to have new copper pipe installations and should include areas or zones (geographical areas within which the quality of drinking water is considered approximately uniform) supplied by potentially corrosive water (e.g., low pH, low or high alkalinity). Specifically, priority should be given to sites known to have new copper plumbing or when the water supply has a pH < 7, with or without disinfection or oxidation processes and alkalinity < 25 mg CaCO₃/L, or pH > 7 and alkalinity > 200 mg CaCO₃/L with disinfection or oxidation processes, regardless of the age of copper.

The addition of corrosion inhibitors can prevent the formation of stable malachite scales or displace sorbed oxyanions (e.g., copper) from distribution system piping. A water system using orthophosphate treatment for corrosion control having a PO₄ residual less than 3.3 mg PO₄/L, should also monitor for copper. Daycare facilities should also be prioritized for monitoring to ensure that the most sensitive population (i.e., infants) is captured. Sampling should be conducted at least once per year, with the number of sites to be monitored determined based on the size of the drinking water system and the type of building. The frequency may be reduced if no failures have occurred in a defined period as determined by the regulator, or if water quality conditions are not corrosive to copper.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

4.1 Chemical and physical properties

Copper (Cu, CAS Registry No.7440-50-8) is a transition element that naturally occurs in four oxidation states: elemental copper metal (Cu(0) or Cu⁰), cuprous (monovalent)ion (Cu(I) or Cu⁺), cupric (divalent)ion (Cu(II) or Cu²⁺) and rarely trivalent copper ion (Cu(III) or Cu³⁺). Copper has two stable (⁶³Cu and ⁶⁵Cu) and 27 less stable-isotopes (Turnlund et al., 1998; Riedel, 2008; EFSA, 2015). Copper metal has a reddish-brown color, an atomic mass of 63.55 Da, a density of 8.92 g/cm³ and a vaporization point of 2350°C (Georgopoulos et al., 2001; Kiaune and Singhasemanon, 2011; Ellingsen et al., 2015). In the sections below, “total copper” will be used when referring to all of the major oxidation states. However, “copper” will be used when referring to both Cu(I) and Cu(II), which cycle from one to the other (see section 9.1), are soluble, bioavailable, and considered the most relevant from a toxicological standpoint (see sections 4.3, 8 and 9.3); otherwise, the specific form will be used.

4.2 Sources and uses

With an average concentration of 50 ppm in the Earth’s crust, copper occurs in several primary mineral deposits, mostly as sulphide ores (the most abundant being chalcopyrite, and chalcocite) and less frequently in its metallic form (CCME, 1999; Mauceri and Mishra, 2014). In general, weathering of these primary mineral deposits liberates secondary forms of copper including copper carbonate ores (e.g., malachite and azurite) and copper oxide ores (e.g., cuprite) (CCME, 1999; ATSDR, 2004; Ellingsen et al., 2007; Riedel, 2008; Mauceri and Mishra, 2014). In addition, anthropogenic activities like mining, municipal and industrial wastes management, agriculture (e.g., pesticides), and water treatment (e.g., copper sulphate pentahydrate in algaecides) can generate localized copper deposits and increase levels in the neighborhood (ATSDR, 2004; Mauceri and Mishra, 2014). Thus, copper can enter water sources from natural processes (e.g., soil weathering), human activities (e.g., agricultural runoffs), or from the corrosion of pipes/fittings in water distribution systems; the latter depends on water chemistry (e.g., low pH, high temperature, reduced hardness) (WHO, 1998; NRC, 2000; Ellingsen et al., 2007).

In Canada, the mining industry has produced 580,082; 652,595 and 695,513 tonnes of total copper in 2012, 2013 and 2014, respectively (British Geological Survey, 2016). Owing to its malleability, conductivity, alloying potential and resistance to corrosion and wear, copper metal is used in many products, such as pipes, paint pigments, antifouling agents, refinery oils, and in construction materials such as flashing electronic components, tubes, sheets, and rods for roofing (ATSDR, 2004; WHO, 2011; Stewart et al., 2012; Gaetke et al., 2014; Ellingsen et al., 2015). As a component of bronze and brass, it is used in marine equipment, cooking utensils, coins, to name a few. Copper nanoparticles are increasing in use for example in antimicrobial products such as biomedical and surgical devices (Ingle et al., 2014), or in copper nanowires (Yang et al., 2014). In addition, total copper is used by the health industry as a component of birth control pills, intrauterine devices (IUDs), dental amalgam, anti-microbial/bacterial agents, vitamin and mineral supplements, and by the food industry as a colouring agent (Barceloux, 1999; Grass et al., 2011; Park et al., 2012; Stewart et al., 2012; Shaligram and Campbell, 2013). Finally, copper is used as an active ingredient in pesticides (fungicides, algaecides, and antimicrobials). There are currently nine copper compounds (e.g., cuprous oxide, copper

sulphate, copper carbonate) registered as pesticides, for use in combination with other active ingredients, in Canada (Health Canada, 2009a).

Copper is present in tap water principally as a result of dissolution or leaching (i.e., corrosion) from components of distribution and plumbing systems that contain copper, particularly from the extensive use of copper pipes in household plumbing. In addition, fittings or service connections to homes and brass fittings may also represent a source of copper (Schock and Neff, 1988; Kimbrough, 2001, 2007, 2009). Copper leaching will vary with the types of alloys used and the manufacturing and fabrication processes (Lytle and Schock, 1996, 2000; Oliphant and Schock, 1996; Dudi et al., 2005). Several factors can influence copper corrosion, including the age of the piping and the water quality characteristics in the system. These factors are discussed in greater detail in section 7.2.

Copper release may result in blue water, which can stain bathroom fixtures and hair and may be caused by the presence of particulate copper. It is more difficult to determine the cause of particulate copper corrosion, but it is thought to primarily be the result of microbiological, chemical, or physical factors, or some combination of factors that also result in pitting corrosion and/or pipe failure (Edwards et al. 2000; Bremer et al. 2001; Arnold et al., 2012). The most significant home plumbing failures that occur as a result of internal corrosion are copper pitting and pinhole leaks. Pitting corrosion is not a well understood cause of copper release, but it can cause significant damage to copper plumbing, leading to leaks that can also cause substantial damage to homes and result in mould growth (Scardina et al., 2008). Pitting can occur relatively rapidly (a few months to years) after installation in cold water plumbing; whereas pitting generally takes many years (typically more than 8 years) to perforate pipe walls in hot water systems (Ferguson et al., 1996).

4.3 Environmental fate

In the environment, copper metal and Cu (I) are unstable. Conversely, Cu(II) is more stable and the most abundant and frequently encountered species in the environment, including water and biological systems (Georgopoulos et al., 2001; Ellingsen et al., 2007; Riedel, 2008; Shike, 2009; Kiaune and Singhasemanon, 2011; Omur-Ozbek and Dietrich, 2011; Gaetke et al., 2014; Ellingsen et al., 2015). Hence, in general, surface oxidation leads to copper(I) oxide or hydroxide; but, due to its instability, Cu(I) is frequently oxidized to Cu(II) (WHO, 2004). Cu(II) is subject to redox reactions and tends to be hydrated. The hydrated Cu(II) ion rarely occurs free, but usually adsorbs to particulate matter or a variety of dissolved (inorganic and organic) compounds such as hydrated metal oxides (including those of iron, aluminium and manganese), polyvalent organic anions and humic acids (WHO, 1996, 2004; IPCS, 1998).

In the air, copper is mainly removed from the atmosphere by wet deposition (rain and snow), followed by gravitational settling and dry deposition (Kieber et al., 2004; WHO, 2004). In soil, copper strongly adsorbs to particles and has low mobility, with greatest retention at neutral pH (Health Canada, 2009a). Applied copper usually persists in topsoil, accumulating in upper layers (≈ 15 cm) (CCME, 1999; Kiaune and Singhasemanon, 2011). Its fate and availability in soils depend on many soil features: soil types (high mobility in sand vs. clays), pH (acidity and high reductive capacity favor release from oxide complexes), cation exchange capacity, water content, organic/inorganic matter content, redox potential, and the presence of oxides (e.g., of iron, manganese, aluminum) and clay (IPCS, 1998; Kiaune and Singhasemanon, 2011). Also, copper does not bioaccumulate, hydrolyze or breakdown in soil (Health Canada, 2009a).

In water, copper speciation is complex and influenced by many factors such as water source (e.g., Cu(II) is less bioavailable in hard water than in soft water), water chemistry (i.e.,

alkalinity, ionic strength, dissolved oxygen, pH and redox potential), sediments-water clays interaction (pH-dependent), presence of complexing (inorganic and organic) ligands and suspended particulate matter and carbon (WHO, 2004; Cuppett et al., 2006; Kiaune and Singhasemanon, 2011). The formation of Cu(I) and Cu(II) complexes can impact the solubility, color, and taste of water. Thus, when dissolved, Cu(I) is colourless while most Cu(II)-compounds impart a light blue-green colour and a metallic, bitter taste to drinking water (Georgopoulos et al., 2001; Cuppett et al., 2006; Omur-Ozbek and Dietrich, 2011). In raw water, copper primarily occurs as complexed Cu(II) and to a lesser extent as precipitated Cu(II) particles (Cu(II)-particulate matter), assuming typical pH values and oxidation-reduction potentials (Lide, 1993). The primary copper-complexing ligands are dissolved molecules such as organic (e.g., dissolved organic carbon or matter) and inorganic species. On one hand, copper-organic complexes and copper-particulate matter compounds usually precipitate, rendering them non-bioavailable (Kiaune and Singhasemanon, 2011). On the other hand, inorganic ligands commonly form Cu(II) and Cu(I) complexes, alongside the ubiquitous copper hydroxo complexes; the latter, however, mostly precipitate (commonly at pH 6.5–12) as copper hydroxide (Cuppett et al., 2006). Thus the further dissolution of the remaining copper complexes and the relative stability of Cu(II) as compared to Cu(I) makes free Cu(II) the most prevalent species in drinking water (Cuppett et al., 2006; Kiaune and Singhasemanon, 2011; Omur-Ozbek and Dietrich, 2011). Therefore, the main focus of this document will be on dissolved copper.

4.4 Aesthetic characteristics

Copper in water can be detected through taste or visual inspection (i.e., colouration). Taste thresholds for copper have ranged from 0.0035 to > 5 mg/L (Zacarias et al., 2001; Omur-Ozbek and Dietrich, 2011) and 0.4–0.8 mg/L (Cuppett et al., 2006); reported taste threshold values vary significantly due to different sensory test methods used, the concentrations of the metal tested, the type of water used, and the type of data analysis performed. The aesthetic properties of copper are affected by solubility, with soluble copper being more readily tasted than the particulate form (Cuppett et al., 2006). However, both Cu(I) and Cu(II) ions are equally detectable producing a weak bitter and salty taste and an astringent mouth feel (Omur-Ozbek and Dietrich, 2011). Omur-Ozbek and Dietrich (2011) estimated that 79% of the population would be able to taste copper at a concentration of 2 mg/L, while 72% would be able to taste it at 1 mg/L. The visual detection of copper in water is a function of light path through the water, deposited particles and the concentration of copper in water (Edwards et al., 2000). For example, 0.3 mg/L would be visible in a white bathtub at a distance of approximately 460 mm (18 inches) (typical observation distance), but 3 mg/L of copper would need to be present for the copper particulate to be noticeable in a glass of water.

5.0 Exposure

Canadians can be exposed to total copper via food, drinking water, air, soil and consumer products. For the general population, food is the major source of exposure (more than 90% of dietary intake), followed by drinking water (less than 10% of dietary intake) and copper-containing supplements (WHO, 2004; Sadhra et al., 2007; Cockell et al., 2008; de Romana et al., 2011; Shaligram and Campbell, 2013; Mauceri and Mishra, 2014; EFSA, 2015). However, drinking water can be a significant source of exposure if distributed through corroded pipes, especially in the case of infants fed formula (fortified, non-soy-based) reconstituted with water from such sources (Cockell et al., 2008; Chambers et al., 2010). Copper speciation in water

differs from that in food (NRC, 2000) and this can influence its solubility and bioavailability. In fact, in food, copper is covalently bound to macromolecules (IOM, 2001; OEHHA, 2008; Ceko et al., 2014). In contrast, copper occurs free or complexed with ligands in drinking water. Thus, copper in drinking water can readily reach the bloodstream, bypassing the liver processing. Consequently, the bioavailability of copper in drinking water ingested in a fasted state is considered greater than that in food (OEHHA, 2008; Mauceri and Mishra, 2014; Ellingsen et al., 2015).

5.1 Food

The Canadian Total Diet Study (TDS) is a Health Canada initiative that measures the dietary concentrations of different chemicals in food and uses these data to estimate dietary intakes for different age–sex groups of the Canadian population (Health Canada, 2009b). Based on the TDS, the average intakes of dietary copper were estimated between 1993 and 2007 for Canadians of all age groups in 7 cities (Montreal, Ottawa, St John’s, Vancouver, Winnipeg, Toronto, and Halifax). These estimates ($\mu\text{g}/\text{kg}$ bodyweight [bw] per day) were 40–91 for 0–6 months old, 36–57 for 6 months–4 years old, 36–48 for 5–11 years old, 19–35 for 12–19 years old, and 13–32 for 20 years old and above. Based on copper intake for male and female 20+ years of age, an adult Canadian weighing 70 kg would have a dietary exposure to copper of 910–2,240 $\mu\text{g}/\text{day}$.

Based on the data collected as part of the TDS conducted between 1993 and 2007, copper concentrations in common food items vary in Canada, with the highest concentrations being food in organ meats (offal) such as liver and kidney. Lower copper levels are found in milk (25–70 $\mu\text{g}/\text{kg}$), while infant milk formulas have concentrations of 650–850 $\mu\text{g}/\text{L}$, and human breast milk was reported to have 200–300 $\mu\text{g}/\text{L}$ (Lonnerdal, 1998; Bauerly et al., 2005). The World Health Organization (WHO) and the Food and Agricultural Organization (FAO) recommended a minimum of 35 μg Cu/100 kcal formula (liquid or powder) intended to be marketed in order to comply with normal nutritional requirements of infants. They also acknowledged that levels adjustment may be needed in regions with high copper levels (FAO and WHO, 2011).

Even if the copper content of human breast milk is lower than that of formula, this form of copper is highly bioavailable (Lonnerdal, 1996, 1998; Bauerly et al., 2005). In contrast, phytates (zinc and copper chelators found at high levels in soy-based infant formula) and soy proteins in infant formula reduce copper bioavailability (Gibson, 1994; NRC, 2000; IOM, 2001; WHO, 2004; EFSA, 2006, 2009; Stern et al., 2007; OEHHA, 2008; Collins and Klevay, 2011).

5.2 Water

Exposure to copper in drinking water can be properly assessed only by monitoring copper levels at the tap. This is because copper is present in tap water principally as a result of dissolution (corrosion) from components of distribution and household plumbing systems that contain copper. However, the concentration of copper is less variable both across a system and within an individual site (Kirmeyer et al., 1994; Schock et al., 1995), making the assessment of copper exposure from drinking water much less challenging than for lead. Monitoring of copper at the tap can be done using different sampling protocols; the selection of an appropriate protocol must take into consideration the desired objective, such as identifying sources of copper, effectively controlling corrosion or estimating exposure to copper.

5.2.1 Canadian exposure to copper from drinking water

Generally, across the provinces and territories, median copper levels at the tap were low (below 1 mg/L); however there are cases where high levels of copper release have been observed.

In Prince Edward Island, dissolved copper (filtered through a 0.45 µm filter prior to sample preservation) was measured in ground water, municipal central water supply plants, private central water systems, and private wells and stand-alone system. Data from 2013–2015 were analyzed. For municipal central water supply plants, 48% of samples were below the detection limit (0.005 mg/L), and for the samples above the detection limit (n=117), the median dissolved copper level was 0.03 mg/L, with a maximum reported value of 0.9 mg/L. For municipal central water supplies, the 95th percentile was 0.12 mg/L, and the 97th percentile was 0.19 mg/L. In private central water systems, 67% of samples were below the detection limit, and for those samples above the detection limit (n=13), the median dissolved copper level was 0.013 mg/L, with a maximum reported value of 0.044 mg/L. For private wells, and stand-alone systems, 27% of samples were below the detection limit, and for those samples above the detection limit (n=2798), the median dissolved copper level was 0.017 mg/L, with a maximum reported value of 1.8 mg/L.

In Newfoundland, for the 62 source water samples taken in 2013–2014, all were found to be above the detection limit, and the median total copper level was 0.0020 mg/L, with a range of 0.001–0.073 mg/L. For source water samples, the 95th percentile was 0.031 mg/L, and the 97th percentile was 0.033 mg/L. For the 1968 tap water samples reported from 2013–2014, 97% were above the detection limit. For the tap water samples above the detection limit (n=1905), the median total copper level was 0.035 mg/L, with a range of 0.001–2.5 mg/L. For tap water samples, the 95th percentile was 0.4 mg/L and the 97th percentile was 0.49 mg/L.

In Nova Scotia, for the 845 municipal treated water samples reported from 2005–2012, 73% of the total copper were above the detection limit of 0.002 mg/L. For the treated water samples above the detection limit, the median total copper level was 0.014 mg/L, with a range of 0.002–0.490 mg/L. The treated water samples 95th percentile was 0.12 mg/L, and the 97th percentile was 0.17 mg/L.

In New Brunswick, for copper samples from 2010–2015 the detection limit ranged from 0.000026 mg/L to 0.0004 mg/L. Samples are prepared by nitric acid preservation, and analyzed for dissolved plus dilute acid labile trace copper, which is approximate to a total copper sample. For raw water, 71% of total copper samples were below the detection limit; for samples above the detection limit (n=367) the median copper level was 0.006 mg/L with a maximum of 8.3 mg/L. For water treatment plant samples, all the total copper samples were above the detection limit (n=17), with a median of 0.029 mg/L and a maximum of 0.11 mg/L. For water treatment plant samples, the 95th percentile was 0.083 mg/L, and the 97th percentile was 0.094 mg/L. For the distribution system samples, 20% were below the detection limit; for samples above the detection limit (n=1129), the median copper level was 0.021 mg/L with a maximum of 3.1 mg/L. For distribution system samples, the 95th percentile was 0.48 mg/L, and the 97th percentile was 0.63 mg/L.

In Quebec, copper sampling is conducted at the tap following a five minute flush. Of the 17,863 reported total copper samples from 2012–2015, 12.5% were below the detection limit (0.001–0.01 mg/L), and 119 samples (0.7%) exceeded 1.0 mg/L. The median total copper concentration was 0.028 mg/L, and the maximum value detected was 15 mg/L.

In Manitoba, total copper samples from 2009–2015 were analysed, and the detection limit was reported as 0.001 mg/L. For raw water, 6% of samples were below the detection limit, and

for those samples above the detection limit (n=969), the median copper level was 0.003 mg/L, with a maximum of 0.94 mg/L. For raw water samples, the total copper 95th percentile was 0.03 mg/L, and the 97th percentile was 0.05 mg/L. For distributed water, all of the samples were above the detection limit, and the median copper level was 0.016 mg/L with a maximum reported level of 0.193 mg/L and minimum reported level of 0.002 mg/L (n=9). For distributed water samples, the 95th percentile was 0.133 mg/L, and the 97th percentile was 0.157 mg/L. For treated drinking water, 2% of the samples were below the detection limit, and for those samples above the detection limit (n=1026), the median copper level was 0.009 mg/L with a maximum of 0.8 mg/L. For treated water samples, the 95th percentile was 0.12 mg/L, and the 97th percentile was 0.19 mg/L. For untreated drinking water, 6% of the total copper samples were below the detection limit, and for those samples above the detection limit (n=165) the median copper level was 0.005 mg/L with a maximum of 0.62 mg/L. For disinfected drinking water samples, the 95th percentile was 0.08 mg/L, and the 97th percentile was 0.13 mg/L.

In Saskatchewan, of the 2423 total copper samples taken from distribution sites in 2005–2015, 90% were above the detection limit, with a median of 0.012 mg/L, and a range of 0.002–3.9 mg/L. The 95th percentile was 0.12 mg/L and the 97th percentile was 0.18 mg/L.

In Alberta, for dissolved copper samples from 2010–2015 the detection limit ranged from 0.002–0.003 mg/L. For raw water/entering the water treatment plant samples 43% were below the detection limit, and the median copper level was 0.005 mg/L with a maximum of 0.025 mg/L for those samples above the detection limit (n=131). For samples taken exiting the water treatment plant, 94% were below the detection limit, and the median copper level was 0.003 mg/L with a maximum of 0.17 mg/L for those samples above the detection limit (n=9). For water leaving the treatment plant, the 95th percentile was 0.105 mg/L, and the 97th percentile was 0.131 mg/L. For distribution system samples, 82% of samples were below the detection limit, and the median copper level was 0.004 mg/L, with a maximum of 0.147 mg/L for those samples above the detection limit (n=50). For distribution system samples, the 95th percentile was 0.047 mg/L, and the 97th percentile was 0.096 mg/L.

In British Columbia, for total copper samples from 2010–2015, 11% were below the detection limit (0.0002–0.005 mg/L). For those samples above the detection limit (n=473), the median copper level was 0.0077 mg/L, with a maximum reported value of 0.549 mg/L. The 95th percentile was 0.0824 mg/L, and the 97th percentile was 0.13 mg/L.

In the Yukon, samples from 2012–2015 taken from 20 communities were examined, and 19% of raw water and 10% of treated water total copper samples were below the detection limit (0.001–0.002 mg/L). For raw water samples above the detection limit (n=51), the median total copper level was 0.0029 mg/L, with a maximum reported value of 0.13 mg/L. For raw water samples, the total copper 95th percentile was 0.054 mg/L, and the 97th percentile was 0.09 mg/L. For treated water samples above the detection limit (n=26), the median total copper level was 0.003 mg/L, with a maximum reported value of 0.0712 mg/L. For treated water samples, the total copper 95th percentile was 0.067 mg/L, and the 97th percentile was 0.07 mg/L.

High Canadian household tap water copper levels have also been documented in the literature. In a 1985 study found that 50% of rural Nova Scotia homes had copper levels exceeding 1 mg/L. The 55 homes surveyed were all served by private wells in three different areas of bedrock (granite, quartzite, and limestone). The authors did not find the Langelier, Ryznar, or Aggressiveness indexes, chloride to sulphate mass ratio (CSMR), alkalinity, or pH to be good predictors of corrosion. They also noted that from house to house, there was a large degree of variation of metal (copper, lead, zinc) mobilization (Maessen et al., 1985).

5.2.2 *Sampling to assess copper exposure from drinking water*

Sampling protocols will differ, depending on the desired objective (i.e., identifying sources of copper, controlling corrosion, assessing compliance, estimating exposure to copper). As monitoring of copper at the tap can be done using different sampling protocols, it is important that the selected protocol be appropriate to meet the desired objective. Monitoring for typical exposure to total copper should be conducted at the consumer's tap, with priority given to identifying homes with new copper plumbing or supplied with water having low or unstable pH or situated near dead ends, as these are likely to have the highest copper concentrations. Daycare facilities should also be prioritized for monitoring, to ensure that the most sensitive population (i.e., bottle-fed infants) is captured. Sampling should be conducted at least once per year, with the number of sites to be monitored determined based on the size of the drinking water system and the water quality characteristics.

5.3 Air

The Canadian National Air Pollution Surveillance Program reported copper concentrations in fine ($PM_{2.5}$) particulates in 2014 (Environment Canada, 2014). 75.2% of samples exceeded the detection limit of 0.28–0.85 ng/m^3 , 14 samples were above 50 ng/m^3 and 7 were above 100 ng/m^3 . The mean was 3.4 ng/m^3 , the median was 1.2 ng/m^3 , the 75th percentile was 2.4 ng/m^3 , and the maximum was 430.3 ng/m^3 . Similar results were observed in a Health Canada study of indoor and outdoor air (n=3,000 sites in Edmonton, Halifax, Ottawa, Sault-Saint-Marie, and Windsor), where average concentrations of 2.9 ng/m^3 and medians < 2 ng/m^3 were reported (Health Canada, 2015). Indoor airborne copper concentrations of 8.2 ng/m^3 (range of 3.8–17.8) and 11.4 ng/m^3 (range of 3.9–56.9) were reported in 10 Canadian rural and urban homes ($PM_{2.5}$ filter), respectively (Rasmussen et al., 2006). Copper was shown to be mainly associated with the organic phase of house dust, increasing its bioavailability (Rasmussen et al., 2008). Based on these low concentrations of copper in ambient air, intake from air would be negligible compared with that from other media.

5.4 Consumer products

Canadian quantitative estimates of total copper exposure from consumer products are rather scarce. However, copper compounds, e.g., copper(II) acetate, carbonate, chloride, sulfate, are part of various medicinal products available in Canada, and can be consumed in oral natural therapy formulae at maximum doses of 0.7 mg/day for children 1–3 years of age, up to 8 mg/day for adults \geq 19 years of age (Health Canada, 2007). The use of copper IUDs may also result in daily exposure of about 80 μg copper and less, with decreasing levels after the first few weeks from insertion (IPCS, 1998; Gaetke et al., 2014; Ellingsen et al., 2015). Although amalgams have been pointed out as a source of copper, exposure from this source is considered minimal (IPCS, 1998).

5.5 Soil

Copper distribution in rocks and soil varies as a reflection of the mineralogy of parent material and proximity to anthropogenic sources. Total copper mean concentration in Canada was estimated at 20 mg/kg soil (range: 2–100 mg/kg), with lower levels in the Canadian Shield (11 mg/kg) and higher levels in the Cordilleran region (46 mg/kg) (CCME, 1999). Levels of 41–65 mg/kg were reported in Ontario parklands, 25 mg/kg in western Manitoba, and 17–19 mg/kg in rural Alberta. Street dusts in Halifax had levels of 87 mg/kg. Copper was measured in garden

soil (geometric mean [GM]: 12.3 mg/kg; 95th percentile: 19.4 mg/kg), house dust (GM: 170.7 mg/kg; 95th percentile: 489.0 mg/kg), and street dust (GM: 38.1 mg/kg; 95th percentile: 236.2 mg/kg) from 50, 48 and 45 residences in Ottawa, respectively (Rasmussen et al., 2001). Copper is used as a dietary supplement for farmed animals (Nicholson et al., 1999; Xiong et al., 2010) with some of the copper absorbed by the animal and the remainder excreted. The concentration of copper in manure has been reported in a study in China as 699.6 mg Cu/kg (pigs); 31.8 mg Cu/kg (cattle); 81.8 mg Cu/kg (chickens) and; 66.85 mg Cu/kg (sheep). In a study in England and Wales, 360 mg Cu/kg was found in pig manure, 80 mg Cu/kg in poultry manure and 50 mg Cu/kg in cattle manure. In a Canadian study examining run-off from manure compost windrows (containing a mixture of cattle manure and barley straw), the copper concentration in the compost ranged from 49 to 55 mg Cu/kg (Larney et al., 2014). Run-off from the manure was measured periodically over a 224 day period. On day 18 (first measurement), the copper concentration ranged from 0.3 to 0.62 mg/L. The copper concentration in run-off peaked at 0.78 mg/L on day 26. As the compost matured, the copper concentration significantly declined, and the copper concentration had decreased by 67% between days 26 and 40.

5.6 Blood and urine levels in the Canadian population

Copper levels in the blood and urine of Canadians are available from the Canadian Health Measures Survey (cycle 2) conducted by Statistics Canada, Health Canada and the Public Health Agency of Canada. As part of this cross-sectional study, health data and biological specimens were collected at 257 sites from 6,070 Canadians aged 3–79 years, distributed among six age groups (3–5, 6–11, 12–19, 20–39, 40–59 and 60–79 years). The geometric mean for whole blood copper concentration was 900 µg/L (95% confidence interval [CI] = 900–910 µg/L; $n = 6,070$), and the geometric mean for urinary copper concentration was 10 µg/L (95% CI = 10–11 µg/L; $n = 6,311$), for the total Canadian population aged 3–79 years (Health Canada, 2013).

A study conducted by the Government of the Northwest Territories and Health Canada between 1994 and 1999 found that the geometric mean for maternal and umbilical cord plasma copper concentrations for 523 women from arctic Canada was 2.1 mg/L (Butler Walker et al., 2006). Levels did not differ between ethnic groups.

5.7 Multi-route exposure

Based on the physical and chemical properties of copper, drinking water exposure through the dermal and inhalation routes is likely negligible. Exposure to copper in vapors while showering is not expected since it is non-volatile, and no reports on copper absorption by inhalation were found. Although the generation of mists during showering could allow for inhalation of copper in aerosol form, the typical multi-route assessment, which measures inhalation exposure to volatile chemicals from showering and bathing, would not accurately represent copper aerosols inhaled during a showering event. There is little information on the dermal absorption of copper; however, bathing and showering are not expected to be significant sources of exposure, as indicated in a risk assessment of dissolved trace metals in drinking water (Karim, 2011). As a result, dermal and inhalation exposure during showering and bathing are unlikely to contribute significantly to the total exposure to copper through drinking water.

6.0 Analytical methods

The United States Environmental Protection Agency (U.S. EPA) has several approved methods for measuring copper in drinking water:

- EPA 200.5 Rev 4.2 (U.S. EPA, 2003a)
- EPA 200.7 Rev 4.4 (U.S. EPA, 1994a)
- EPA 200.8 Rev 5.4 (U.S. EPA, 1994b)
- EPA 200.9 Rev 2.2 (U.S. EPA, 1994c)
- ASTM D1688-95A, ASTM D1688-02A, ASTM D1688-07A, D1688-12A (ASTM, 1995, 2002, 2007, 2012).
- ASTM D1688-95C, ASTM D1688-02C, ASTM D1688-07C, D1688-12C (ASTM, 1995, 2002, 2007, 2012).
- Hach 8026, Hach 10272 (Hach, 2014, 2016)
- SM 3111B (1992, 1995, 2005, 2012) and the online version of SM3111B (1999) (APHA et al., 1992, 1995, 1999, 2005, 2012)
- SM 3113B (1992, 1995, 2005, 2012) (APHA et al., 1992, 1995, 1999, 2004, 2005, 2010, 2012)
- SM 3120 B (1992, 1995, 1998, 2005, 2012) and the online version of SM 3120B (1999) (APHA et al., 1992, 1995, 1999, 2005, 2012).

The method detection limits (MDLs) for the methods listed above range between 0.02 and 500 µg/L. It should be noted, however, that MDLs are dependent on the sample matrix, instrumentation and selected operating conditions and will also vary between individual laboratories. In selecting an analytical method, consideration should be given to the water matrix to minimize the effect of interfering agents by using the prescribed sample pre-treatment or mitigation steps can help eliminate or decrease the effects of interfering agents.

ASTM D1688A, ASTM D1688C, EPA Rev 2.2, SM 3111B, SM 3113B are all atomic absorption based methods. The light source is specific to each element measured, as each metal has a characteristic absorption wavelength (APHA et al., 2012). ASTM D1688 uses an atomic absorption direct method, with a method range of 0.5–5 mg/L (ASTM, 1995, 2002, 2007, 2012); whereas ASTM D1688C uses an atomic absorption graphite furnace method, with a method range of 5–100 µg/L (ASTM, 1995, 2002, 2007, 2012). EPA 200.9 Rev 2.2 uses a graphite furnace atomic absorption method, with a method detection limit of 0.7 µg/L (U.S. EPA, 1994c). SM 3111B (1992, 1995, 2005, 2012) and the online version of SM 3111B (1999) use a flame atomic absorption spectrometry method, with an instrument detection limit of 0.01 mg/L (APHA et al., 1992, 1995, 1999, 2005, 2012). SM 3113B (1992, 1995, 2005, 2012) and the online version of SM 3113B (1999, 2004, 2010) use an electrothermal atomic absorption spectrometry method with an estimated detection level of 0.7 µg/L with an optimum concentration range of 5–100 µg/L (APHA et al., 1992, 1995, 1999, 2004, 2005, 2010, 2012). Flame atomic absorption is subject to several interferences primarily chemical interferences, where there is a lack of absorption by atoms because they are bound in molecules or they ionize in the flame. The electrothermal/graphite furnace method generally has detection levels 20 to 1000 times lower than flame based methods as a result of increased atom density within the furnace (APHA et al., 2012). However, the electrothermal/graphite furnace method is also subject to more interferences, including spectral, matrix and memory interferences (U.S. EPA, 1994c) and may require increased analysis time compared to flame based methods (APHA et al., 2012).

EPA 200.7 Rev 4.4 uses an inductively coupled plasma atomic emission spectroscopy (ICP-AES) method, with a method detection limit of 0.003 mg/L (U.S. EPA, 1994a). EPA 200.5 Rev 4.2 uses an axially viewed ICP-AES method, with a method detection limit of 0.3 µg/L and a calculated reporting limit of 0.7 µg/L (U.S. EPA, 2003a). EPA 200.8 Rev 5.4 uses an inductively coupled plasma mass spectroscopy (ICP-MS) method, with a method detection limit of 0.5 µg/L in scanning mode and 0.02 µg/L in selective ion monitoring mode (U.S. EPA, 1994b). SM 3120 B (1992, 1995, 1998, 2005, 2012) and the online version of SM 3120B (1999) use an inductively coupled plasma method, with an estimated detection level of 6 µg/L (APHA et al., 1992, 1995, 1999, 2005, 2012). Sources of interference can include matrix effects and isobaric elemental and polyatomic ion interferences. Generally, for both ICP-AES and ICP-MS methods, the presence of high dissolved solids in a sample may interfere with ion transmission, and interferences can occur when dissolved solids exceed 0.2% (w/v) (U.S. EPA, 1994b; APHA et al., 2012).

Determination of copper by the colorimetric methods Hach 8026 and 10272 rely on the complexation of Cu(I) with bicinchoninic acid. Hach 8026 has a method range of 0.04–5 mg/L (Hach, 2014), and Hach 10272 has a method detection limit of 0.06 mg/L (Hach, 2016). In the colorimetric method, the Cu(II) is chemically reduced to Cu(I), and the concentration is determined through spectrophotometry at 560 nm. There are a number of interfering agents for Hach 8026 (Al^{3+} , CN^- , Fe^{3+} , Ag^+ , hardness, $\text{pH} \leq 2$) and Hach 10272 (CN^- , Ag^+ , $\text{pH} \leq 2$) that can be mitigated through the use of a chelating agent or a prescribed pH adjustment.

The current practical quantitation limit (PQL) is 0.05 mg/L (U.S. EPA, 2009). In the second-six year review of existing national primary drinking water regulations, the U.S. EPA indicated that although the laboratory passing rate was high, there were insufficient or inconclusive performance evaluation and proficiency testing data for copper to justify lowering the PQL (U.S. EPA, 2009).

6.1 Sample preparation

The concentration of copper is much less variable than the concentration of lead, both across a system and within an individual site (Kirmeyer et al., 1994; Schock et al., 1995), making the analysis of total copper generally easier. Sample preparation to ensure that both the particulate and dissolved fractions of copper are capable of being detected is best practice, especially for diagnostic purposes. Generally, all methods listed above follow the same preservation steps, including the use of 0.15% nitric acid, a 16-hour holding time and the addition of hydrochloric acid for hot digestion when the sample turbidity is above 1 nephelometric turbidity unit (NTU). The standard acid preservation ($\text{pH} < 2$) has been shown to quantify total copper in water samples (U.S. EPA, 1994b; APHA et al., 2012). However, similarly to lead and other metals, when particles of copper are present in a sample, they may not be well dispersed and may settle to the bottom of the sampling bottle, resulting in turbidity below 1 NTU. As such, the current protocol may underestimate total copper in drinking water when particulate copper is present and best practice for the preservation step should be considered. Increasing the nitric acid strength to 2% for the preservation step may result in better recovery for most forms of particulate copper as has been observed with lead particulates (Haas et al., 2013; Triantafyllidou et al., 2013; Clark et al., 2014).

Best practice leading to a better estimation of total metals include ensuring that no aliquot or volume transfers occur prior to preservation or analysis, *in situ* sample preservation where feasible, maintaining a minimum holding time of 16 hours after preservation, thoroughly mixing the sample prior to analysis and taking the aliquot directly from the original sample bottle

(Cartier et al., 2013; Haas et al., 2013; Triantafyllidou et al., 2013). It is important to note that the addition of 2% nitric acid should be undertaken by qualified personnel and using appropriate precautions. To this end, if sampling is conducted by homeowners, the sample should only be acidified and held upon arrival at the laboratory.

7.0 Treatment technology

7.1 Municipal scale

Historically, copper release has been considered an aesthetic nuisance in the case of blue water or a financial nuisance in the case of pipe failure attributed to pitting corrosion/pinhole leaks. Copper levels in source water are typically very low, and copper is generally introduced into drinking water after it leaves the treatment plant. The treatment approach for copper is generally focused on corrosion control. The approaches used for corrosion control include water quality adjustments (e.g., pH, alkalinity) and the use of corrosion inhibitors. The selection of an appropriate strategy for minimizing copper at the tap and, thus copper exposure, will depend on many factors including the characteristics of the raw water supply and the type of corrosion (Health Canada, 2009c). Utilities should undertake pilot-scale or pipe rig studies to understand how water quality changes to control copper will affect various chemical constituents in the treated water (e.g., iron and manganese) as well as materials in the distribution system (e.g., scale stability, lead-bearing components).

Site-specific investigations can be a useful tool when copper exceedances are limited an individual building or neighbourhood. An investigation of a widespread and rapid copper plumbing failure (2 months after installation) in a German hospital, Fischer et al. (1992) found evidence of both uniform and pitting corrosion in copper pipes. Biofilm was also found layered between corrosion products and implicated as a contributing factor to copper release. The authors also found that the areas that experienced greater corrosion were in intensively branched, horizontal sections of the pipe network that experienced long stagnation times. Arnold et al. (2012) conducted a site-specific investigation at a newly built U.S. school where copper release exceeded 6 mg/L and blue water was observed. Through targeted investigations, a practical long-term treatment strategy (removal of natural organic matter [NOM]) was identified for the school.

7.1.1 Treatment considerations

Although copper levels in source water tend to be low, conventional water treatment technologies have been demonstrated both at the bench/pilot-scale as well as full scale to remove copper. Stover and Kincannon (1983) conducted bench/pilot scales treatability studies using raw groundwater (pH 6). pH adjustments using lime decreased copper from 0.1 mg/L to < 0.001 mg/L (at pH 9.1 and 9.9) and 0.008 (at pH 11.3). Activated carbon adsorption was shown to also decrease copper from 0.1 mg/L to < 0.001 mg/L (Stover and Kincannon, 1983). A survey of the performance of twelve water treatment plants in Colorado and California also provided some evidence of copper removal from source water (average influent concentration of 0.03 mg/L) through microstrainer (14%), clarifier (26%) and filtration (37%) steps, for an overall removal of 49% (Zemansky, 1974). A comparison of three granular activated carbon (GAC) filter media was conducted in a river water supplied water treatment plant in Southern Poland. The water treatment plant consisted of two parallel treatment trains prior to the GAC filters consisting of either pre-ozonation, coagulation, flocculation, sedimentation and rapid sand filtration; or pre-ozonation, coagulation, clarification/flocculation, rapid sand filtration and ozonation. The GAC

filters were followed by storage where final disinfection occurred. The water entering the GAC filters was pH 6.8, 0.2 NTU. The authors found that the copper concentration increased by 130-253% on the Chemvicon F-300 filter media and by 1965% on the Norit ROW 08 filter media over the course of the first year of operation (influent concentration not reported). On the third filter media (WG-12), adsorption of copper was irregular and some desorption (release) of copper was observed. (Dabioch et al., 2013). For public water systems, the U.S. EPA has identified point-of-use (POU) ion exchange (using cationic resins) and reverse osmosis (RO) as small systems (i.e., serving fewer than 10 000 people) compliance technologies for copper removal (U.S. EPA, 1998). These technologies are also relevant for residential-scale treatment (see section 7.). The alkalinity of finished water is affected by the use of the reverse osmosis process. This process removes sodium, sulphate, chloride, calcium and bicarbonate ions and results in finished water that is corrosive (Taylor and Wiesner, 1999). This underlines the importance of process adjustments such as addition of a base and aeration of the permeate stream to recover alkalinity prior to distribution.

7.1.2 Distribution system considerations

The National Plumbing Code of Canada (NPC) allows copper as an acceptable material for service lines and plumbing systems (NRCC, 2010), without respect to water quality. All provinces and territories use the NPC as the basis for their plumbing regulations. However, in certain water qualities, both soluble and particulate copper may be released into drinking water from copper plumbing pipes, copper service lines and copper in brass fittings used in both home plumbing systems and in distribution mains, to levels exceeding the proposed MAC.

7.2 Factors affecting uniform copper corrosion

Schock and Lytle (2011) report that for general uniform copper corrosion and copper release, the most important variables are pH, alkalinity, redox potential (ORP) and plumbing age. Several other factors can also influence uniform copper corrosion including the stagnation time of the water and flow in pipes, temperature and other water quality conditions as well as NOM and biofilms.

7.2.1 pH

The effect of pH on the solubility of the corrosion products formed during the corrosion process is often the key to understanding the concentration of metals at the tap. Typically, distributed water with higher pH decreases the solubility of the corrosion products formed in the distribution system. Copper corrosion increases rapidly as the pH drops below 6; in addition, uniform corrosion rates can be high at low pH values (below about pH 7), causing metal thinning. At higher pH values (above about pH 8), copper corrosion problems are almost always associated with non-uniform or pitting corrosion processes (Edwards et al., 1994a; Ferguson et al., 1996). Edwards et al. (1994b) found that for new copper surfaces exposed to simple solutions that contained bicarbonate, chloride, nitrate, perchlorate or sulphate, increasing the pH from 5.5 to 7.0, roughly halved corrosion rates, but that further increases in pH yielded only subtle changes. The prediction of copper levels in drinking water relies on the solubility and physical properties of the Cu(II) oxide, hydroxide and basic carbonate solids that comprise most scales in copper water systems (Schock et al., 1995). In the Cu(II) hydroxide model of Schock et al. (1995), a decrease in copper solubility with higher pH is evident. Above a pH of approximately 9.5, an upturn in solubility is predicted, caused by carbonate and hydroxide complexes increasing the solubility of Cu(II) hydroxide. Copper solids also age much more rapidly, transforming to

much less soluble Cu(II) hydroxide phases, at higher pH and higher temperatures (Hidmi et al., 1999). Copper solubility was found to be high in cold, high-alkalinity and high-sulphate groundwater up to about pH 7.9 (Edwards et al., 1994a).

7.2.2 Alkalinity

Alkalinity is a measure of the capacity of the water to neutralize acids and serves to control the buffer intensity of most water systems. Therefore, a minimum amount of alkalinity is necessary to provide a stable pH throughout the distribution system for corrosion control. Alkalinity is influenced by the presence of the conjugate bases of inorganic carbon (HCO_3^- and CO_3^{2-}), organic acids and OH^- ion and is expressed in mg CaCO_3/L (Edzwald and Tobiason, 2011). Alkalinity is generally used interchangeably with dissolved inorganic carbon (DIC). The relationship between alkalinity, pH and cuprosolvency is complex, with the form of the controlling copper solid playing a critical role. Hard, high alkalinity groundwaters are particularly aggressive toward copper materials (Schock and Lytle, 2011). For example, copper releases of 1.4 – 2.4 mg/L were observed in high alkalinity (273 CaCO_3 mg/L) and pH 7.4 water from tap water samples from relatively new copper plumbing (< 6 years old) in large buildings. The addition of orthophosphate at 3mg/L was sufficient to decrease copper release to below 1.3 mg/L (Grace et al., 2012). Similarly, Schock and Fox (2001) found that in a high alkalinity (280 mg CaCO_3/L), pH 7.3 water, the 90th percentile copper levels exceeded 1.63 mg/L. Edwards et al., (1999) found that a combination of low pH (< 7.8) and high alkalinity (> 74 mg CaCO_3/L) produced the worst-case 90th-percentile copper levels (Edwards et al., 1999). Laboratory and utility experience have demonstrated that copper corrosion releases are worse at higher alkalinity (Edwards et al., 1994b, 1996; Schock et al., 1995; Ferguson et al., 1996; Broo et al., 1998). These effects are likely due to the formation of soluble Cu(II) bicarbonate and carbonate complexes (Schock et al., 1995; Edwards et al., 1996) and in certain waters such as those that do not form insoluble malachite scale (Arnold et al., 2012). Both carbonate complexation and pH have a strong effect of on copper solubility in relatively new plumbing systems. Low alkalinity (< 25 mg CaCO_3/L) also proved to be problematic under utility experience (Schock et al., 1995). For high-alkalinity waters, the only practical solutions to reduced cuprosolvency are lime softening, removal of bicarbonate or addition of rather large amounts of orthophosphate (U.S. EPA, 2003b). Lower copper concentrations can be associated with higher alkalinity when the formation of the less soluble malachite and tenorite has been favoured (Schock et al., 1995; Edwards et al., 2002).

7.2.3 Redox potential

The importance of redox potential (ORP) lies mostly in defining the conditions under which Cu(II) ions are formed (i.e., high oxidizing potential). At lower redox potentials, copper will not be subject to corrosion or the formation of highly insoluble copper(I) oxide or hydroxide solids will occur, resulting in extremely low copper levels in the water (Schock et al., 1995; Ferguson et al., 1996). Many untreated groundwaters of neutral pH and high alkalinity fall into this category.

The rate of release of copper into the water is influenced by the level of oxidizing agents in the system, especially free chlorine. Even low levels (i.e., 0.2 mg/L) affect the oxidation and corrosion rate (Schock and Lytle, 2011). Reiber (1989) has shown that the chlorine effect is much more important than dissolved oxygen in normal drinking water situations.

Hypochlorous acid is the predominant form of free chlorine below pH 7.5 in drinking water and the dominant oxidant on the copper surface (Atlas et al., 1982; Reiber, 1987, 1989;

Hong and Macauley, 1998). Free chlorine residual was shown to increase the copper corrosion rate at lower pH (Atlas et al., 1982; Reiber, 1989). Conversely, free chlorine residual was shown to decrease the copper corrosion rate at pH 9.3 (Edwards and Ferguson, 1993; Edwards et al., 1999). However, Schock et al. (1995) concluded that free chlorine species would affect the equilibrium solubility of copper by stabilizing copper (II) solid phases, which results in a substantially higher level of copper release. The authors did not observe any direct effects of free chlorine on copper (II) solubility other than the change in valence state and, hence, the indirect change in potential of cuprosolvency.

Sometimes, copper levels in water that has been stagnant in the plumbing system can increase for as many as 48 to 72 hours, especially in relatively rare cases of blue water (Edwards et al., 2000). For this reason, an overnight standing sample is not necessarily representative of a worst-case scenario for exposure to copper (Schock et al., 1995). Conversely, the depletion of oxidants may decrease copper levels (Edwards et al., 1996; Schock and Lytle, 2011). The introduction of oxidative processes such as those for iron or manganese removal, or the initiation of disinfection after low-ORP conditions, could increase, decrease or have no effect on copper concentration depending on the circumstances.

Limited information has been reported in the literature about the effect of other disinfectants on copper. A bench-scale study by Rahman et al. (2007) examined the effect of three disinfectants (chlorine, chlorine dioxide, and chloramines) under two pH (7.2 and 8.5) and alkalinity (10 or 100 mg CaCO₃/L) conditions. The authors found that there was no significant difference in dissolved copper release for the disinfectant-free control compared to any of the disinfectants used in the study. Generally, the study found that the application of disinfectant lowered the copper release, with the lowest total copper release found under the pH 8.5, 10 mg CaCO₃/L and 1.0 mg Cl₂/L conditions. The authors suggested that the lower biomass (not assessed in the study) might explain part of the benefit to disinfectant, and that the long stagnation period (72 h) would result in low chlorine residuals. The authors also suggested that in the case of chlorine dioxide the presence of chlorite (a by-product) may have acted as a corrosion inhibitor.

Boyd et al. (2010) studied the effects of changing disinfectants from free chlorine to chloramines and vice versa on leaching rates of metals and concentrations of metals from lead, brass, and copper components in the distribution system. Local tap water was used and water quality parameters (disinfectant residual, pH, alkalinity, and orthophosphate concentration) were monitored and maintained. The authors conducted pipe loop testing using new copper tubing and bronze piping (as a surrogate for standard brass) with different galvanic couplings (copper-bronze, lead-bronze, and lead-copper couplings). Copper concentrations in unpassivated copper and bronze pipe loops were sensitive to free chlorine and chloramines but the effects were transient and not related to a specific disinfectant. A study assessed the leaching potential for several components tested under NSF/ANSI Standard 61 protocols with both chlorinated and chloraminated water. The study also tested these components using 28 waters (chlorinated and chloraminated) collected from utilities throughout the U.S. These utilities were also surveyed on copper and lead release issues. The authors found that neither chlorine nor chloramine was a dominant factor towards the leaching of copper under the test conditions for both the synthetic and utility waters. This mirrored the results from the utility survey that indicated few problems with copper (and lead) release when chloramines were used for secondary disinfection (Sandvig et al., 2012).

7.2.4 Pipe age and copper solubility

Copper release into the drinking water largely depends on the type of scale formed within the plumbing system and whether they are relatively thin and adherent films of corrosion products such as copper(I) oxide (cuprite, Cu_2O), copper(II) oxide (tenorite, CuO), or copper carbonate (malachite, $\text{Cu}_2(\text{OH})_2\text{CO}_3$) (Schock and Lytle, 2011). It can be assumed that at a given age, a corrosion product governs the release of copper into the drinking water. In uniform corrosion, solubility is highest for Cu(I) hydroxide [$\text{Cu}(\text{OH})_2$] and lowest for tenorite [CuO] and malachite [$\text{Cu}_2(\text{OH})_2\text{CO}_3$] (Schock et al., 1995). Similarly, Lagos et al. (2001) observed a linear relationship between pipe age and mean dissolved copper concentration in water. The more stable scales (malachite and tenorite) were also found to be the oldest and the least stable scale (langite), the youngest. Copper concentrations continue to decrease with the increasing age of plumbing materials, even after 10 or 20 years of service, when tenorite or malachite scales tend to predominate (Sharrett et al., 1982; Neuman, 1995; Edwards and McNeill, 2002). Sulphate and phosphate can decrease copper concentrations by forming bronchantite and copper(II) phosphate in the short term but, in the long term, they may prevent the formation of the stable tenorite and malachite scales (Edwards et al., 2002; Schock and Sandvig, 2009; Arnold et al., 2012).

7.2.5 Stagnation time, water age and flow

Long copper pipe of small diameter produces the greatest concentrations of copper upon stagnation (Kuch and Wagner, 1983; Ferguson et al., 1996). Copper behaviour is complex with respect to the stagnation of the water. Copper levels will initially increase upon stagnation of the water, but can subsequently decrease or increase, depending on the oxidant levels. Lytle and Schock (2000) showed that copper levels increased rapidly with the stagnation time of the water, but only until dissolved oxygen (DO) fell below 1 mg/L, after which they dropped significantly. Sorg et al. (1999) also observed that in softened water, copper concentrations increased to maximum levels of 4.4 and 6.8 mg/L after about 20–25 h of standing time, then dropped to 0.5 mg/L after 72–92 h. Peak concentrations corresponded to the time when the DO was reduced to 1 mg/L or less. In non-softened water, the maximum was reached in less than 8 h, because the DO decreased more rapidly in the pipe loop exposed to non-softened water. Typically, water in a conventional home has a water age of 1 day compared to green buildings, where water age has been found to range from 2.7 days (net-zero energy house), 8 days (in a LEED-Gold healthcare facility) and 1–6 months (net-zero office) (Rhoads et al., 2016). Increased water age has been associated with deterioration of water quality (loss of disinfectant residual, pH decrease) (Masters et al., 2015) as well as increases in microbial population (Masters et al., 2015; Rhoads et al., 2016) and could increase the propensity of water towards copper corrosion. As green building technology becomes more prevalent, consideration should be made for the implications of increased water age on water quality and corrosion.

High flow velocities can sometimes be associated with erosion corrosion or the mechanical removal of the protective scale (impingement attack) in copper pipes. Water flowing at high velocity, combined with corrosive water quality, can rapidly deteriorate pipe materials. For example, the combination of high Cl_2 , continuous flow velocity with low-pH and high-alkalinity is extremely aggressive toward copper (Sarver et al., 2011; Schock and Lytle, 2011).

7.2.6 Temperature

No simple relationship exists between temperature and corrosion processes, because temperature influences several water quality parameters, such as dissolved oxygen solubility, solution viscosity, diffusion rates, activity coefficients, enthalpies of reactions, compound

solubility, oxidation rates and biological activities (McNeill and Edwards, 2002). These parameters, in turn, influence the corrosion rate, the properties of the scales formed and the leaching of materials into the distribution system. In hot water systems of building plumbing, a high water temperature ($>60^{\circ}\text{C}$), in the presence of high flow velocity, is a factor in erosion corrosion (Ferguson et al., 1996). In a survey of the release of copper corrosion by-products into the drinking water of high-rise buildings and single-family homes in the Greater Vancouver Regional District, Singh and Mavinic (1991) noted that copper concentrations in water run through cold water taps were typically one-third of copper concentrations in water run through hot water taps. A laboratory experiment that compared copper release at 4, 20, 24 and 60°C in a soft, low alkalinity water showed higher copper release at 60°C , but little difference in copper release between 4°C and 24°C (Boulay and Edwards, 2001). However, copper hydroxide solubility was shown to decrease with increasing temperature (Edwards et al., 1996; Hidmi and Edwards, 1999). In a survey of 365 utilities under the U.S. EPA Lead and Copper Rule, no significant trend between temperature and copper levels was found (Dodrill and Edwards, 1995).

7.2.7 Chloride and sulphate

Chloride has traditionally been reported to be aggressive towards copper but has been found to be less detrimental for cuprosolvency than originally expected (Edwards et al., 1994b). High concentrations of chloride (71 mg/L) were shown to reduce the rate of copper corrosion at pH 7–8 (Edwards et al., 1994a, 1994b, 1996; Broo et al., 1997, 1999). Edwards and McNeill (2002) suggested that this dichotomy might be reconciled when long-term effects are considered instead of short-term effects: chloride increases copper corrosion rates over the short term. However, with aging, the copper surface becomes well protected by the corrosion products formed. Sulphate is a strong corrosion catalyst implicated in the pitting corrosion of copper (Schock, 1990; Edwards et al., 1994b; Ferguson et al., 1996; Berghult et al., 1999). Although sulphate was shown to decrease concentrations of copper in new copper materials, it was found that high sulphate concentrations resulted in higher copper levels in the experimental water once the copper material had aged (i.e., transitioned from copper(II) hydroxide to CuO) (Edwards et al., 2002). The authors concluded that this was due to the ability of sulphate to prevent the formation of the more stable and less soluble malachite and tenorite scales, supporting the hypothesis of Schock et al. (1995) that aqueous sulphate complexes are not likely to significantly influence cuprosolvency in potable water.

7.2.8 Natural organic matter

Research in copper plumbing pitting has indicated that some NOM may alleviate the propensity of a water to cause pitting attacks by promoting the formation of more protective scales (Campbell, 1954a, 1954b, 1971; Campbell and Turner, 1983; Edwards et al., 1994a; Korshin et al., 1996; Edwards and Sprague, 2001). However, NOM contains strong complexing groups and has been shown to increase the solubility of copper corrosion products (Korshin et al., 1996; Rehring and Edwards, 1996; Broo et al., 1998, 1999; Berghult et al., 1999, 2001; Edwards et al., 1999; Boulay and Edwards, 2001; Edwards and Sprague, 2001). Nevertheless, the significance of NOM to cuprosolvency relative to competing ligands has not been conclusively determined (Schock et al., 1995; Ferguson et al., 1996). A study found that NOM initially promoted pitting under certain narrow water quality and NOM concentration ranges. However, over long periods of time, a reduction in pitting at the higher NOM concentrations was observed (Korshin et al., 1996). Generally, the study concluded that NOM interacts with the

copper through sorption, increasing the rate of copper leaching and the dispersion of the corrosion scales.

Mechanistic work by Edwards and Sprague (2001) elucidated some of the complex and apparently contradictory effects of NOM on copper. NOM was shown to contribute to copper by-product release through complexation and/or colloid mobilisation. NOM can interfere with pipe ageing through promoting the formation of highly soluble copper(II) hydroxide, copper carbonate and copper-NOM complex formation and thus, prevent the formation of the more stable solid, malachite. Conversely, NOM can serve as a food source for bacteria, which in turn consumes dissolved oxygen, triggering re-deposition of copper onto the pipe in the presence of a suitable catalyst (e.g. chloride). In practice, Arnold et al. (2012) demonstrated, at the bench-scale, that NOM removal was a practical and effective method to decrease copper release in a school experiencing blue-water issues. NOM removal increased dissolved oxygen (and the corrosion rate) and subsequently increased scale formation. The authors suggested that in the absence of NOM, the corrosion rate increased, accelerating the natural ageing process. Visual inspection of the copper pipes revealed a blue-green solid, which is associated with the stable crystalline solid, malachite.

7.2.9 Microbiologically influenced corrosion

Microbiologically influenced corrosion (MIC) results from a reaction between the pipe material and organisms, their metabolic by-products, or both (Schock and Lytle, 2011). Microbial activity can affect pH, metal solubility, and the oxidation-reduction potential of the surrounding microenvironment. Biofilms are surface associated communities of bacteria and their interaction with copper surfaces is complex. Bacteria can interact with the surface in physically, metabolically, or as storage reservoir for released metals. As biofilms form on the surface, corrosive microenvironments can form, for example, the area under the biofilm becomes oxygen deprived (anaerobic) and can act as an anode to the neighbouring metallic surface (cathode), thereby driving a localised corrosion event (Javaherdashti, 2008). Acidic metabolic products can also create local pH decreases (Little et al., 1991) and create bulk water pH decreases (Davidson et al., 1996). Bacteria in a biofilm produce sticky exopolymeric substances (EPS) that tend to have a negative charge, providing a binding site for positively charged metals ions (Qin-qin et al., 2012). Specifically, biofilm has been shown to act as a reservoir for released copper (Davidson et al., 1996; Lehtola et al., 2006; Qin-qin et al., 2012; Payne et al., 2016), representing another potential source of copper exposure in a biofilm detachment event.

There have been several bench-scale studies, as well as autopsies of corroded copper plumbing, that have indicated a significant role for bacteria and biofilm in cuprosolvency. Dutkiewicz and Fallowfield (1998) found that copper exposed to *Agrobacterium* sp., isolated from a copper pipe biofilm found in Adelaide, Australia, increased copper release compared to a sterile control. In an Australian study, *Sphingomonas* spp. and *Acidovorax* sp. have been identified as species associated with corroding copper surfaces, and a species of *Acidovorax* has been observed to accumulate copper when grown in a laboratory setting on a copper-containing food source (Critchley et al., 2004). Conversely, other bacteria, *Stenotrophomonas maltophilia*, were observed to have protective effects on copper, which the authors hypothesized could be a result of the binding of the chloride ions to the EPS (Critchley et al., 2003).

Copper has antimicrobial properties (Grass et al., 2011), and in drinking water delayed biofilm formation on copper pipes has been observed when compared to polyethylene pipes. Although after 200 days there was a significant decrease in virus numbers on copper pipe biofilm, there was no significant difference in microbial numbers (Lehtola et al., 2004). Biofilms

have also been implied as causative or contributing agents to both blue water events (Arens et al., 1996; Critchley et al., 2004) and pitting corrosion (Fischer et al., 1992; Reyes et al., 2008; Burleigh et al., 2014).

7.3 Blue water events

Copper dissolution can cause blue or green water events and are frequently characterized by a fine dispersion of copper corrosion products. Particulate copper appears light blue as a copper hydroxide and black as copper sulphide. Visual perception of a blue water issue is challenging as the coloured water can be flushed away through the first flush of a toilet or tap. The distance of the observer from the coloured water also affects the perception, with 0.3 mg/L visible at the typical observation distance from a bathtub, but 3 mg/L would need to present for the copper particulate to be noticeable in a glass of water (Edwards et al., 2000).

No single cause has been identified for blue water events; they are thought to result from a combination of microbial activity and certain water quality conditions. Critchley et al. (2004) successfully induced blue water in a laboratory setting by inoculating copper pipe rigs with non-sterile copper corrosion extracts, although the water used was not representative of drinking water. The authors noted a nine week lag time before blue water was apparent suggesting that there is an initial establishment phase to initiate this type of corrosion. Previously, Arens et al. (1996) investigated a blue water event in recently commissioned copper pipes. MIC was suspected as the causative agent and Arens et al. (1996) found that various food sources (e.g., sealing putty) increased microbial activity and copper release. Arnold et al. (2012) also reported blue water and elevated copper (>6 mg/L) in new copper plumbing, in a high alkalinity (200 mg CaCO₃/L), pH 7.15-7.4 water. NOM removal provided long-term copper stability through accelerated pipe ageing.

7.4 Brass alloys

Brasses are, basically, alloys of copper and zinc, with other minor constituents, such as lead. Brass dezincification is thought to be either a selective leaching of zinc or a multi-stage process through which zinc and copper are leached through uniform corrosion and copper is redeposited, creating a net effect of zinc leaching and both mechanisms leave behind a porous weakened copper surface (Lytle and Schock, 1996; Sarver et al., 2011). Zinc oxide corrosion products can build-up forming a “meringue” structure that restricts flow, which can subsequently cause leaks and bursts. Brasses are particularly vulnerable to dezincification in low alkalinity, high chloride water (Sarver et al., 2011). Ideally, brass used in premise plumbing should be low zinc to help make the brass dezincification resistant. However, it should also be noted that in cross-linked polyethylene (PEX) plumbing systems, higher zinc content brass (yellow brass) fittings are frequently used. There have been widespread plumbing failures associated with PEX and dezincification of brass fittings documented in North America (U.S. District Court, 2011; Ontario Superior Court of Justice, 2011; Superior Court Province of Quebec, 2011). In addition to the financial ramifications of brass corrosion, other metals are also released, including copper. Lytle and Schock (1996) demonstrated that the composition of the brass alloy was a significant factor in the amount of copper released and that small changes in pH were a strong influence on copper release. A pH 8.5 and 7, with red brasses (low zinc) released more copper than yellow brasses (high zinc) and some red brasses released similar copper levels as pure copper. Brasses at pH 7 released more copper than at pH 8.5. It should also be noted that at pH 7, the copper releases were more sporadic. In practice brass can represent a significant source of copper release. A cluster of Southern California homes with all plastic plumbing, brass fittings were the

major source of copper release with medians ranging from 85-185 µg/L over the course of three sampling events.

7.5 Pitting corrosion

Pitting corrosion is a form of non-uniform corrosion in all types of copper pipe and tubing and can ultimately lead to pinhole leaks, a costly plumbing failure (Scardina et al., 2008). Pitting corrosion can occur where a localised corrosion cell forms as a result of several mechanisms such as a differential in pH or oxygen on the pipe surface. In the localised corrosion cell, the cathodic area is protected, and the anodic area is oxidized, electrons are released, and copper is depleted, creating a pit. The pit can ultimately breach the wall of the copper, creating a small pinhole. If unfavorable water quality conditions occur prior to the formation of the protective scale, then a serious pitting corrosion may occur (Schock and Lytle, 2011). The causal pit initiation mechanism could be a result of one or a combination of several factors including surface imperfections, carbon residues from manufacturing, soldering flux, unfavourable water quality or microbiological activity. There are certain water quality, microbiological and flow conditions that appear to induce or propagate pits and include: waters with high pH, low alkalinity, the presence of chloride (Lytle and Schock, 2008; Lytle and Nadagouda, 2010) and sulphides (Jacobs et al., 1998; Jacobs and Edwards, 2000); chlorine, high pH, low alkalinity (Sarver et al., 2011); the presence of some biofilms (Fischer et al., 1992; Reyes et al., 2008; Burleigh et al., 2014); pipe configuration (Fisher et al., 1992) and high water velocity (Custalow, 2009). Lytle and Schock (2011) describe the three types of copper pitting (based on chemistry and physical features): cold-water (type I), hot-water (type II) and soft-water (type III) as well as conditions typically associated with each type. It is important to note that sulphate and chloride are typically associated in one way or another to all forms of pitting although the relative importance of chloride versus sulfate in copper pitting corrosion is still a subject of debate (Schock and Lytle, 2011).

In bench-scale experiments, the addition of 3 mg PO₄/L or increasing DIC to 50 mg/L (from 5–25 mg/L) was effective in preventing pit initiation at pH 9 (Lytle and Schock, 2008). It has been theorised that phosphate may displace other anions from the anode and compete for binding sites with Cu²⁺ to form a relatively stable scale and that alkalinity decreases pit initiation by either, limiting pH differentials on the surface or by forming copper carbonates and decreasing precipitation on the surface. Ha and Scully (2013) suggested that phosphate (as Na₂HPO₄) addition inhibits pit initiation through increasing passivation and suppressing the dissolution of copper. Lytle and Nadagouda (2010) analysed the elemental composition of copper pits taken from in-home plumbing and found that chloride was concentrated in the floor of the pits as well as in cracks or imperfections near the surface, suggesting that chloride plays an important role in the propagation of pits. Although the presence of chloride has been demonstrated to play a fundamental role in pit initiation, Edwards et al (1994a) hypothesized that given longer exposures (with greater scale formation) that chloride could potentially have a protective effect. Sulphides have been shown to be significant factors in inducing copper corrosion and have been associated with pitting at pH 9.2 (Jacobs and Edwards, 2000).

Burleigh et al. (2014) evaluated copper pitting in copper tubing from multiple cold water lines in Santa Fe, New Mexico and found evidence of Actinobacteria deep inside the pits. The authors suggested that Actinobacteria role in copper pitting could be through either the excretion of an acidic metabolic product or using copper as an energy source (Burleigh et al., 2014). Reyes et al (2008) compared two communities in Chile, one rural (pH 6.2, CaCO₃ = 63 mg/L, no chlorine) and one urban (pH = 6.9, CaCO₃ = 98 mg/L, chlorinated), and although the two

communities had similar water quality they had different stagnant copper levels. The rural homes had stagnant copper levels of 5 mg/L compared to the urban homes where stagnant copper levels were 0.4 mg/L. When investigating the copper release in rural homes, the authors found that only one quarter of the copper release could be attributed to water quality factors and the microbiological component was suspected as another causal agent of copper release. In the rural homes pipes with biofilm, surface pitting was observed; whereas in the absence of bacterial biofilms no pitting was observed. High water velocity have also been demonstrated to increase pitting in high pH chlorinated waters (Custalow, 2009) and are likely a result of the continuous resupply of oxidants to the cathodic regions of a localised corrosion cell (Sarver et al., 2011). Leaking pipes present an additional health risk as they could lead to mould growth (Scardina et al., 2008), affecting indoor air quality (Health Canada, 2016).

7.6 Impact of treatment and/or water quality changes on copper release

Distribution system deposits and corrosion scales lie in delicate balance with the aqueous environment and utilities should be aware that changes in water quality can affect the stability of distribution system scale. Some treatment technologies can increase copper in drinking water by changing water quality parameters that impact copper release. Changing water treatment to address one issue, could inadvertently negatively impact another water treatment objective. For example, switching from a sulphate to chloride containing coagulant has been shown to increase CSMR and exacerbate lead release in premise plumbing material (Edwards and Triantafyllidou, 2010).

In the anion exchange process, when removing contaminants such as uranium, freshly regenerated ion exchange resin removes bicarbonate ions. This causes reductions in pH and total alkalinity during the initial 100 bed volumes (BVs) of a run and may require raising the pH of the treated water at the beginning of a run to avoid corrosion (Clifford, 1999; Wang et al., 2010; Clifford et al., 2011). Similarly, frequent regeneration of an ion exchange resin can have an impact on corrosion. In a case study in Maine, frequent regeneration of the ion exchange resin was required to reduce the levels of uranium in the waste stream (residuals). This resulted in a significant and continual decrease of pH and subsequent leaching of copper and lead into the drinking water (Lowry, 2009, 2010). Since reverse osmosis (RO) continually and completely removes alkalinity in water, it will continually lower the pH of treated water and increase its corrosivity. Therefore, the product water pH must be adjusted to avoid corrosion issues in the distribution system such as the leaching of lead and copper (Schock and Lytle, 2011; U.S. EPA, 2012). Additionally, changing from lime softening, which balances hardness and alkalinity with a high pH, to ion exchange softening can leave a high alkalinity, which is corrosive to copper (Schock and Lytle, 2011).

Similarly changes to finished water to address corrosion concerns can cause other unintended changes in the distribution system. For example, raising pH in finished water to greater than 9 in order to decrease copper release from premise plumbing, would precipitate dissolved manganese in the treated water, which could lead to unwanted aesthetic issues.

Additionally, it is important to consider that distribution system deposits are susceptible to changes in water quality. Distribution system deposits are comprised of the underlying corroded material (e.g. cast iron) as well as the accumulated trace inorganics that have accumulated over the service life of the water main. Friedman et al. (2010) found that trace inorganic contaminants (including barium lead nickel, vanadium, arsenic, radium, chromium and uranium) had accumulated in manganese deposits in distribution systems. Gerke et al. (2016) reported copper accumulation in both chlorinated and chloraminated distribution system

manganese deposits. The stability of deposited inorganics is dependent upon maintaining stable water quality conditions (e.g., pH, ORP, corrosion control), as well as avoiding the uncontrolled blending of source water (ground and surface), and the uncontrolled blending of chlorinated and chloraminated water (Friedman et al., 2010).

Before changing water quality to achieve a new treatment goal, such as corrosion control, utilities should undertake pilot-scale studies to understand how a proposed water quality amendment will affect various components of their distribution system.

7.7 Mitigation of copper release

The selection of a mitigation strategy for copper should take into consideration other metals present since different strategies, including water quality adjustments, may impact various metals differently. The use of test pipe-rigs under site specific water quality conditions is recommended, as the testing process can be helpful in selecting an effective corrosion control strategy and aid in anticipating unintended impacts. Generally, the level of trace metals increases upon stagnation of the water but may vary according to water quality. For example, in standing water in plumbing systems where oxidants are present, copper levels can increase for up to 48 to 72 hours. As such, flushing the water present in the plumbing system can significantly reduce the levels of copper and is, therefore, considered a mitigation strategy. However, flushing the cold water tap may not be sufficient to reduce the levels of copper (Singh and Mavinic, 1991; Murphy, 1993; Barn et al., 2014). Periodic flushing throughout the day and extensive flushing following long stagnation periods (vacation periods, weekends) may therefore be advisable to provide suitable water quality throughout the day.

Reducing exposure to copper can also be achieved, as an interim measure, by the use of drinking water treatment devices. It must be noted that in situations where high levels of copper occur, drinking water treatment devices may have reduced capacity and require more frequent replacement of the filter.

7.7.1 Alkalinity and pH

Copper solubility is strongly influenced by both alkalinity (through carbonate complexation) and pH, for relatively new plumbing systems (Edwards et al., 1994b; Dodrill and Edwards, 1995). However, it was also noted that high alkalinity groundwaters are aggressive toward copper materials (Schock et al., 1995; Vik et al., 1996; Schock and Lytle, 2011).

The adjustment of pH at the water treatment plant is the most common method used for reducing corrosion in drinking water distribution systems and leaching of contaminants, such as copper, in the distributed water. Raising the pH is an effective method for reducing copper corrosion and thus, minimizing copper levels in drinking water. Generally, uniform corrosion of copper is best controlled at $\text{pH} > 7$, depending on alkalinity (Schock and Lytle, 2011). Treatment chemicals used for adjusting pH include caustic soda, potash, lime and sulfuric acid. Minimal pH adjustment can also be achieved using CO_2 , with either sodium carbonate (Na_2CO_3) or sodium bicarbonate (NaHCO_3); however, this combination primarily adjusts alkalinity. Aeration is a non-chemical treatment method that introduces air in the water, removing CO_2 and resulting in a pH increase. Another method of adjusting pH is the use of limestone contactors: water flows through a bed of crushed limestone, dissolving the limestone and causing the pH (as well as alkalinity and calcium level) to increase. These last two methods offer less precise control of the pH adjustment. A combination of lime or caustic soda and carbon dioxide offers more precise control, as it allows the pH and alkalinity of the water to be independently adjusted (Schock, 1999).

Alkalinity, in combination with pH, serves to control the buffer intensity of most water systems. Therefore, sufficient alkalinity is necessary to provide a stable pH throughout the distribution system for corrosion control of copper (and other metals such as lead). Alkalinity can improve the buffering capacity at a given pH. Raising or lowering the pH can substantially increase the buffering capacity of the water as seen in buffer intensity plots developed by Schock and Lytle (2011). This was demonstrated in practice by Clement et al. (1998) in a field study in Concord, New Hampshire, where minor adjustments in pH and alkalinity resulted in greater pH stability in the distribution system and improved corrosion control. In very low alkalinity waters, adjustment of the alkalinity can be achieved by adding carbonate ion with either Na_2CO_3 or NaHCO_3 . As stated previously, these chemicals are also used to adjust pH because they also contribute carbonate (CO_3^{2-}) or bicarbonate (HCO_3^-) ions. It is important to note that the number of carbonate ions available is a complex function of pH, temperature, and other water quality parameters (Schock, 1999).

7.7.2 Addition of corrosion inhibitors

Phosphate- and silicate-based corrosion inhibitors are typically used for corrosion control in drinking water. The most commonly used inhibitors are phosphate corrosion inhibitors with or without zinc, which include orthophosphate or polyphosphate (typically, blended polyphosphates). Silicate corrosion inhibitors (i.e. sodium silicates) have also been used for corrosion control. The success of corrosion inhibitors is often based on pilot- or bench-scale testing and depends on both the water quality and the conditions prevailing in the distribution system. The effectiveness of corrosion inhibitors is largely dependent on maintaining a residual of the inhibitor throughout the distribution system and on the pH and alkalinity of the water. Measuring the concentration of inhibitors within the distribution system is part of good corrosion control practice. Generally, direct correlations between the residual concentration of inhibitors in the distribution system and the levels of metals, including copper at the tap are not possible.

Health Canada recommends that water utilities choose drinking water additives, such as corrosion inhibitors, that have been certified as conforming to the applicable NSF/ANSI health-based standard. Phosphate- and silicate-based corrosion inhibitors are included in NSF/ANSI Standard 60, Drinking Water Treatment Chemicals—Health Effects (NSF International, 2015a). These standards have been designed to safeguard drinking water by ensuring that additives meet minimum health effects requirements and thus are safe for use in drinking water.

7.7.2.1 Phosphate-based inhibitors

Orthophosphate and zinc orthophosphate are the inhibitors most often reported in the literature as being successful in reducing copper levels in drinking water (Bancroft, 1988; Reiber, 1989; Boffardi, 1993; Johnson et al., 1993; Dodrill and Edwards, 1995; Rezania and Anderl, 1995, 1997; Schock et al., 1995; Boireau et al., 1997; MacQuarrie et al., 1997; Churchill et al., 2000; Schock and Fox, 2001; Becker, 2002; Dudi, 2004; Kirmeyer et al., 2004). Orthophosphate is generally used for lead control when pH control or pH and alkalinity adjustment are not sufficient to control corrosion (Vik et al., 1996), and the effects on copper are secondary considerations.

Some authors have reported that the use of orthophosphate may reduce copper levels in the short term, but that in the long term the formation of more stable scales such as malachite and tenorite may be prevented (Schock and Clement, 1998; Edwards et al., 2001; Cantor et al., 2003; Schock and Sandvig, 2009). There is evidence that ineffective treatment for copper with phosphate was successful when higher dosages were applied or when pH and orthophosphate

dosages were optimized (Schock et al., 1996; Schock and Fox, 2001). Schock and Fox (2001) demonstrated successful copper control in high-alkalinity water with orthophosphate when pH and alkalinity adjustments were not successful. Similarly, Grace et al. (2012) found that orthophosphate dosed at 3 mg/L effectively decreased copper levels below 1.3 mg/L from 1.4–2.4 mg/L in a high alkalinity (273 mg/L) neutral pH (7.4) water. Bench-scale results also indicated that a pH increase to 8.4 may also have been successful; however due to the high alkalinity of the water this option was not selected over concerns of calcium carbonate deposition on distribution system components (Grace et al., 2012).

A survey of 365 water utilities under the U.S. EPA Lead and Copper Rule also revealed that utilities using orthophosphate had significantly lower copper levels only when pH was below 7.8 and alkalinity was below 74 mg CaCO₃/L as (Dodrill and Edwards, 1995). Limited data are available on the impact of polyphosphate on copper solubility. Generally, polyphosphates increase the corrosion rate of copper (Vik et al., 1996). In a case study, Cantor et al. (2000) reported that the use of a polyphosphate blend, at one of the three utilities studied, increased copper levels at the tap. In a copper pipe rig study, Edwards et al. (2002) reported that although polyphosphate generally reduced soluble copper concentrations, they also significantly increased them at pH 7.2 and alkalinity of 300 mg CaCO₃/L since polyphosphates hinder the formation of the more stable malachite scales.

McNeill and Edwards (2004) used bench-scale experiments to compare the performance of orthophosphate, polyphosphate and zinc orthophosphate. Orthophosphate addition (1 mg/L) was associated with decreased soluble copper release, although no difference was observed for particulate release compared to the control. Polyphosphate addition (1 mg/L) decreased soluble copper release compared to orthophosphate, but increased particulate copper release. Zinc orthophosphate addition decreased soluble copper release but increased particulate copper release, compared to orthophosphate, except at pH 9.5. Additionally, particulate copper release increased with pipe age in zinc orthophosphate treated copper pipes. The comparison of phosphate corrosion inhibitors highlights the importance of using site-specific water quality as well as pilot testing and/or pipe rigs in selecting an appropriate corrosion inhibitor for a given water system. It should also be noted that phosphate can decrease copper concentrations by forming copper(II) phosphate but may also prevent the formation of the more stable tenorite and malachite scales (Edwards et al., 2002; Arnold et al., 2012).

7.7.2.2 Silicate-based inhibitors

Only limited data are available on the impact of sodium silicate on copper solubility. As sodium silicate is a basic compound, it is always associated with an increase in pH, making it difficult to attribute reductions in copper concentrations to sodium silicate alone when an increase in pH may also result in a decrease in copper concentrations. A study conducted by Schock (2005) in a medium-sized utility was able to solve problems from iron in source water as well as lead and copper leaching in the plumbing system. The problems were solved simultaneously through the addition of sodium silicate with chlorination. Sodium silicate was added to the three wells that contained elevated levels of iron and manganese and that serviced homes containing lead service lines. A fourth well required only chlorination and pH adjustment with sodium hydroxide. At the three wells, an initial silicate dose of 25–30 mg/L increased the pH from 6.3 to 7.5 and immediately resulted in 55% and 87% reductions in lead and copper levels, respectively. An increase in the silicate dose to 45–55 mg/L increased the pH to 7.5 and resulted in an even greater reduction in the lead and copper levels (0.002 mg/L and 0.27 mg/L, respectively).

Lintereur et al. (2011) compared three different sodium silicate dosages (3 mg/L, 6 mg/L, and 12 mg/L) and found that sodium silicate decreased copper release compared to the control (i.e., no treatment) and pH increase control. The decrease appeared to be dose dependant, with the lowest copper releases observed at the highest doses of sodium silicate. Additionally, scale analysis revealed a silicate-copper scale on coupons retrieved from the silicate treated systems, providing evidence that a silicate scale is at least partly responsible for the inhibitory action of sodium silicates. Woszczyński et al. (2015) found that sodium silicates (18 mg-Si/L, pH 7.3 and pH 6.3) did not control copper when compared to treatment by phosphate (0.8 mg-PO₄/L, pH 7.3). The authors noted that silicate performance was affected by pH and suggested that water quality conditions could affect sodium silicate performance

7.7.3 *Mitigation of blue water events*

Blue water remains a poorly understood phenomenon, and there is limited guidance on its management. Short term management strategies include identified heat-shock (> 60°C) (Arens et al., 1996) or a one-time super chlorination Edwards et al. (2000), although the blue water could reoccur. Arnold et al. (2012) found that NOM removal through GAC provided a practical long-term solution for a blue water issue.

Sequestering agents, such as polyphosphate, will mask the copper release, improving the aesthetic quality without decreasing copper levels and may, in some cases, increase copper levels. Cantor et al. (2000) reported on an incident in Wisconsin, where polyphosphates were used to sequester iron in one of three communities with a hard, high alkalinity groundwater. Subsequent to this treatment, copper related illness were reported to and confirmed by the Wisconsin Department of Health and Family Services (Knobeloch et al., 1994). The highest copper levels (up to 5 mg/L) were found in new and newly remodeled homes and the levels decreased over time once polyphosphate was no longer dosed (Cantor et al., 2000). Generally, the use of sequestering agents is not recommended for mitigating copper release.

7.7.4 *Mitigation of copper pitting and dezincification*

Given the variety of water quality, microbiological and flow condition factors that can affect the propensity towards copper pitting, utilities should consider using the tools such as those found in Sarver et al. (2011). These tools help utilities avoid or mitigate copper pitting and address key water quality changes including the removal of NOM, phosphate, silicate as well as waters with chlorine, high pH or low alkalinity. In addition, utilities should conduct pilot-testing to evaluate their particular water quality and any proposed or potential changes to water quality to both diagnose a problem and to identify workable solutions (Lytle and Schock, 2008; Lytle et al., 2012). A low-cost pipe-loop system is described in Lytle et al. (2012) and could serve as an evaluative tool for utilities.

The water quality conditions associated with a tendency towards dezincification are not as clearly characterized when compared to the copper pitting phenomenon. However, high alkalinity low chloride water is associated with decreased dezincification (Sarver et al., 2011). Lytle and Schock (1996) found that orthophosphate did not provide a clear benefit at pH 7 and 8.5 although they suggested that orthophosphate might be more effective for copper leaching from brass at pH 6.5 (Lytle and Schock, 1996). Sarver et al. (2011) suggested that utilities determine the aggressiveness of their particular water quality towards brass alloys and communicate this information to stakeholders (consumers and developers), and encourage the use of dezincification resistant brass alloys.

7.8 Impact of copper ions on lead release

Copper has also been observed to play a role in lead release in downstream plumbing. Clark et al. (2015) observed copper deposition onto lead surfaces in certain water conditions significantly increased lead release. The copper deposits were hypothesized to act as small galvanic connections on the lead surface. The solubility of copper directly correlated to copper deposition and release of lead. Based on bench-scale experiments, Hu et al. (2012) deduced that between 37- 92% of the Cu^{2+} in chloraminated water and 62-91% of Cu^{2+} in chlorinated water accumulated on new lead pipe under stagnation conditions. Copper deposition was also observed to be affected by flow and stagnant conditions, as lead release was greatest from the chlorinated system under flow-through conditions; whereas lead release was greatest from the chloraminated system under stagnant conditions. Although, the specific water quality and flow conditions that exacerbate the effects of copper deposition still require further investigation, the role of copper deposition on lead release could be a significant consideration when upstream copper tubing is followed by lead bearing materials, such as in the case of partial lead service line replacements.

7.9 Residential scale

It is not generally recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. However, as the primary source of copper in drinking water is the leaching from plumbing and distribution system components, a private residential drinking water treatment device is the best option for reducing copper concentrations in drinking water at the tap. However, the use of such devices should not be considered to be a permanent solution.

Before a treatment device is installed, the water should be tested to determine general water chemistry and to verify the concentration of copper. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Products that use adsorption technology can lose removal capacity through usage and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the adsorption media in their treatment device as per the manufacturer's recommendations and service the device when required.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF/ANSI drinking water treatment unit standard(s). These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2016):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- Bureau de normalisation du Québec (www.bnq.qc.ca – available in French only);
- Truesdail Laboratories (www.truesdail.com); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained directly from the SCC (2016).

Drinking water treatment devices can be installed at the faucet (POU) or at the location where water enters the home (point-of-entry or POE) in residential settings to reduce contaminant concentrations. POU systems are preferred for the removal of copper, as copper levels may increase in the plumbing system and because exposure to the contaminants from drinking water is a concern only if the contaminants are ingested (i.e., inhalation and dermal absorption are not significant routes of exposure). As such, POU treatment devices installed at individual drinking water taps are considered to be the best approach to reduce concentrations to safe levels immediately before consumption or for preparation of food or beverages.

A number of certified residential treatment devices are available that can remove copper from drinking water to below the proposed MAC of 2 mg/L. Adsorption (i.e., carbon block/resin), RO and distillation technologies are effective treatment technologies at the residential scale for the removal of copper at the tap. Certified residential treatment devices using adsorption, RO and distillation are currently available for the reduction of copper in drinking water.

For a drinking water treatment device to be certified to NSF/ANSI Standard 53 (Drinking Water Treatment Units—Health Effects) for the removal of copper, the device must be capable of reducing an influent copper concentration of 3 mg/L to a maximum final (effluent) copper concentration of less than 1.3 mg/L (NSF/ANSI, 2015b). Treatment devices that are certified to remove copper under NSF/ANSI Standard 53 are generally based on activated carbon adsorption technology.

RO systems certified to NSF/ANSI Standard 58 (Reverse Osmosis Drinking Water Treatment Systems) may also be certified for the reduction of copper to achieve a final concentration below 1.3 mg/L (NSF/ANSI, 2015c). RO systems certified to this standard are intended for POU installation only. This is because water treated by an RO system may be corrosive to internal plumbing components. RO requires larger quantities of influent water to obtain the required volume of drinking water, because these systems reject part of the influent water. A consumer may need to pretreat the influent water to reduce fouling and extend the service life of the membrane.

Distillation systems certified to NSF/ANSI Standard 62 (Drinking Water Distillation Systems) can also be certified for the reduction of copper to achieve a final concentration below 1.3 mg/L (NSF/ANSI, 2015d). Distillation systems that would be certified to this standard are also intended for POU installation, for the same reasons described above. The distillation process is effective for the reduction of copper, but requires an electrical energy input.

Health Canada strongly recommends that any components used in these treatment systems be certified to NSF/ANSI Standard 61- Drinking Water System Components Health Effects (NSF/ANSI, 2016a) and NSF/ANSI Standard 372 – Drinking Water Systems Components Lead Content (NSF/ANSI, 2016b).

8.0 Toxicokinetics

The toxicokinetics, storage and handling of copper are regulated by homeostatic mechanisms (Petris et al., 1996; Peña et al., 1999).

8.1 Absorption

In humans, dietary Cu(II) is mainly absorbed from the upper gastrointestinal (GI) tract after oral exposure, with maximum absorption occurring within 1-3 hours of exposure (Linder, 1991; Lonnerdal, 1996; Tapiero et al., 2003; Stern et al., 2007; Shike, 2009; Corkins, 2011).

Studies on copper absorption in humans are limited; mean absorption rates of 50–55% (range, 12–60%) have been reported for normal copper intakes (0.6–1.6 mg/day) from mixed diets, as was a theoretical maximum absorptive capacity of 63–75% (Turnlund et al., 1989; Wapnir, 1998; NRC, 2000; Tapiero et al., 2003; Turnlund et al., 2005; Klevay, 2010; Collins and Klevay, 2011; EFSA, 2015; Ellingsen et al., 2015). However, with typical diets in developed countries, copper absorption is considered to average 30–40% (Wapnir, 1998). Dietary Cu(II) absorption is modulated by several factors, including an individual's copper status and intake, age, the amount of metal in the GI tract, the valence state, and the presence of other dietary factors or (essential and nonessential) competing metals (Turnlund et al., 1989; Wapnir, 1998; NRC, 2000; EFSA, 2006; Stern et al., 2007; van den Berghe and Klomp, 2009; Stern, 2010; Collins and Klevay, 2011; de Romana et al., 2011; Gaetke et al., 2014). Although limited, human studies using different methodologies (e.g., fecal copper excretion, ⁶⁵Cu retention) have demonstrated that absorption rates vary inversely with dietary copper intake. More specifically, absorption rates higher than 50% have been reported with copper intakes below 1 mg/day whereas absorption rates less than 20% have been reported with copper intakes above 5 mg/day (Turnlund et al., 1989, 1998; Stern et al., 2007). In contrast, copper retention (or balance) increases with increasing dietary intakes. For example, an increase in copper retention from 0.06 mg/day when dietary intake was 1.6 mg/day to 0.67 mg/day with dietary intake of 7.8 mg/day was reported. However, the amount retained decreases with time, suggesting restoration of normal balance over time (Turnlund et al., 2005).

The solubility of Cu(II) complexes influences their bioavailabilities (OEHHA, 2008; Mauceri and Mishra, 2014; EFSA, 2015). This was observed in a study by Lind and Glynn (1999) in which high levels of Cu(II) were measured in the blood of rats given copper in deionized water as compared to rats given a fulvic acid mixture in infant formula. Furthermore, developmental stage has been reported to influence Cu(II) absorption, with higher intestinal absorption anticipated in neonates (Lonnerdal, 1998; Bauerly et al., 2005; Collins and Klevay, 2011). This may be explained by immature digestive and homeostatic copper mechanisms (WHO, 2004; Araya et al., 2005a; Collins and Klevay, 2011). Finally, it has been suggested that Cu(II) absorption increases during pregnancy and cancer (Tapiero et al., 2003).

8.2 Distribution

Upon release from the GI tract, Cu(II) is immediately bound to either albumin, transcuprein, or low-molecular weight molecules (e.g., peptides and amino acids, especially histidine) before it reaches the hepatic portal circulation (Linder, 1991; IPCS, 1998; Linder, 2002; Talcott, 2013; Ellingsen et al., 2015). During this first pass, around 40% of copper is taken up by the liver (Gaetke et al., 2014; Pal, 2014; EFSA, 2015). Cu(II) then reaches the post-hepatic circulation bound to ceruloplasmin (Cp) for distribution throughout the body. Hence, under human physiological conditions, plasma copper is usually viewed in two pools, one covalently bound to Cp (about 75–98% of plasma copper) and the remainder (about 7% or less), also known as 'free copper', which is loosely bound to albumin and low-molecular weight molecules (IPCS, 1998; Bradberry, 2007; Montes et al., 2014; Ellingsen et al., 2015). Cp is a ferroxidase synthesized and bound to copper within the liver, for the delivery of the nutrient to peripheral tissues (OEHHA, 2008; Shike, 2009; Montes et al., 2014). Consequently, increases in copper and Cp parallel one another (Turnlund et al., 2004). Moreover, Cp is an acute phase protein that levels and activity can be increased by hormone replacement therapy (e.g., oral contraceptives, steroid hormones), response to several physiological alterations (e.g., inflammation, some non-specific diseases, some cancers, pregnancy and other hormonal perturbations) and smoking

(Kehoe et al., 2000; Turnlund et al., 2004; Shike, 2009; Collins and Klevay, 2011). There is a well-documented sex difference in Cp levels and activity with women exhibiting higher levels (Kehoe et al., 2000).

“Free copper” mostly includes free Cu(I) and Cu(II) and, to a lesser extent, complexes of these ions with labile ligands, in body fluids (Donnelly et al., 2007). In addition, ‘free copper’ constitutes the bulk of the exchangeable copper pool in blood plasma and (presumably) interstitial fluid which levels have been estimated around 2×10^{-16} M or 43 ± 30 mg (Linder, 2001; Harvey et al., 2005). Its levels are tightly controlled by homeostatic mechanisms (IOM, 2001; Bertinato and L'Abbe, 2004; Cockell et al., 2008; Collins and Klevay, 2011) and very low within cells (Rae et al., 1999; Rosenzweig, 2001; Prohaska, 2008; Boal and Rosenzweig, 2009; Kaplan and Lutsenko, 2009; Brewer, 2010). Some of these mechanisms are materialized by: transporters such as ATP7A, ATP7B (Kim et al., 2008; Qian et al., 2012; Montes et al., 2014), storage proteins such as metallothionein (Tapia et al., 2004) and chaperones such as copper chaperone for superoxide dismutase (SOD), cytochrome c oxidase copper chaperone (COX17) and ATOX1 (Shike, 2009; Bertinato et al., 2010; Boveris et al., 2012; Talcott, 2013).

Thus, copper is distributed to all tissues (including the liver) as Cu(II)-Cp bound and a volume of distribution of 1.95L/kg has been estimated in healthy individuals (OEHHA, 2008; Shike, 2009; Montes et al., 2014). The average total body content of copper is about 110 mg (range, 50-150 mg) (Turnlund et al., 2005), with approximately 50% being found in muscle and bone; however, its highest concentrations are found in the liver (about $40 \mu\text{g/g}$ dry weight or 8-10% of the body's total content) and the brain (about $5 \mu\text{g/g}$) (Prohaska, 1990; Turnlund, 1998; Gaggelli et al., 2006; Gurusamy and Davidson, 2007; Madsen and Gitlin, 2007; Collins and Klevay, 2011; Kumar et al., 2015). It is noteworthy that in humans of all ages, there are documented sex differences in plasma copper levels. Women, particularly those taking estrogens, have higher plasma levels (Ellingsen et al., 2015). In humans, fetal copper levels increase during gestation, reaching their maximum around the third trimester ($13\text{-}1,218 \mu\text{g/g}$ wet weight), then decline with age (Zlotkin et al., 1995; Lonnerdal, 1996; Bauerly et al., 2005; Michaluk and Kochman, 2007). Quantitative estimates of copper in infant livers are quite variable. Hepatic levels above 90% of the total body copper ($4\text{-}5 \text{ mg/kg bw}$) have been reported for neonates (WHO, 1996). In contrast, in one study, neonatal levels similar to adults were reported, while in another, neonatal to adult ratios as high as 16:1 were suggested (EFSA, 2015 and references therein).

8.3 Metabolism

Copper metabolism involves all the processes implicated during its absorption, distribution, biotransformation and utilization by cells within the body. The intestines and liver are the key metabolic organs and steps within each of them could be considered as pre-systemic and post-systemic metabolism, respectively.

8.3.1 Pre-systemic metabolism

In mammals, ingested Cu(II) is first reduced to Cu(I) by enterocyte metalloreductases for either storage by metallothionein (MT), use by intestinal enzymes or blood absorption (by the transporter affected by Menkes disease). Upon leaving the gut, Cu(I) is reoxidized to Cu(II), bound to albumin, and then secreted into the portal circulation (Peña et al., 1999; Shike, 2009; Ellingsen et al., 2015).

8.3.2 *Post-systemic metabolism*

The liver plays a key role in storage, uptake regulation and biliary excretion (Talcott, 2013; Ellingsen et al., 2015). When Cu(II)-albumin enters hepatocytes, it is first reduced to Cu(I). The latter is further complexed by glutathione (GSH) before being incorporated as Cu(I)-GSH complex into either MT (for storage) or various copper chaperones. Later, these chaperones transfer copper to Cp or the numerous copper-requiring nascent apo-proteins within the hepatocytic cytoplasm and subcellular compartments. However, the most significant of these hepatic copper metabolism pathways is the transfer of copper from a chaperone to ATPase7B (the transporter affected in Wilson's disease) with further coupling to Cp. The Cu(II)-Cp complex is then either excreted into the bile or secreted into systemic circulation (IPCS, 1998; Roelofsen et al., 2000; Linder, 2002; Bradberry, 2007; de Romana et al., 2011; Boveris et al., 2012; Gitlin, 2014).

8.4 **Elimination**

In humans, absorbed copper is primarily excreted from the body by feces (up to 98% or ~2,500 µg/day), and, to a lesser extent, through urine, sweat, menses, and hair (Turnlund et al., 1990; Wijmenga and Klomp, 2004; Stern et al., 2007; Mauceri and Mishra, 2014). Biliary copper excretion accounts for almost all of the fecal copper and is proportional to dietary copper to some degree (Linder, 1991; Turnlund et al., 1998; Harvey et al., 2005; Stern et al., 2007). It represents the main mechanism of regulating total body copper (Scott and Turnlund, 1994; Turnlund, 1998; Miller et al., 2006; van den Berghe and Klomp, 2009). 12-days averaged daily fecal excretion of 100% (1.6 mg/day) and 91% (7.1 mg/day) have been reported in 9 men after 18-day exposure to low (1.6 mg/day) and high (7.8 mg/day) dietary intakes, respectively (Turnlund et al., 2005). It is noteworthy that, in contrast, intravenous infusion of 460 µg ⁶³Cu resulted in significantly higher ($p < 0.05$) excretion (46%) during high intakes than during low intakes (27%; standard error = 2.3) (Turnlund et al., 2005).

Quantitative estimates of urinary excretion are scarce. However, excretion increases with increasing intakes (Turnlund et al., 2004, 2005) and average levels lower than 3% are generally reported (WHO, 1996; Turnlund et al., 2004, 2005). Turnlund et al. (2004, 2005) reported average urinary excretion for 9 men of 26 µg/day and 20 µg/day (range, 18.5–30.9; standard error on the means = 3.3) during high (7.8 mg/day) and low (1.6 mg/day) intake period, respectively. Even if the authors didn't estimate daily losses in hair, they found significantly increased hair concentrations (mean ± standard deviation [SD]) during periods of high copper dietary intakes as compared to low intakes: from 9.2 ± 3.1 to 21.1 ± 5.9 µg/g hair (range, 3–40 µg/g hair), as measured on the 15th day of a 18-day exposure period (Turnlund et al., 2004, 2005). These levels were not significantly different between subjects (Turnlund et al., 2004). Linder (1991) has estimated a total daily excretion from hair, nails, skin, and sweat of 200 µg in adults. A half-life of 2–5 weeks was estimated for copper in healthy adults following oral administration (Ellingsen et al., 2007). Biliary excretion is limited in early life due to a poorly developed biliary transport system at the time of birth. Excretory losses of 50 µg/kg bw per day have been estimated for infants (Aggett, 1999).

9.0 Health effects

9.1 Effects in humans

9.1.1 Essentiality

Copper is an essential element. Its ability to cycle between the oxidized (Cu(II)) and reduced (Cu(I)) forms provides the catalytic properties of various metalloenzymes that are necessary for metabolism (e.g., of glucose) and cellular respiration (e.g., SOD, cytochrome c oxidase) (IOM, 2001; Bertinato and L'Abbe, 2004; Gitlin, 2014). Moreover, copper plays a role in many physiological processes including neurological, immunological, connective tissues formation, thermal regulation and erythropoiesis (Tapiero et al., 2003; Stern et al., 2007; Gambling et al., 2011).

Copper deficiency can lead to abnormalities of these systems; cases of copper deficiency have been reported in premature infants fed unfortified milk formulas, in severely malnourished infants with chronic diarrhea, and in patients receiving chronic parenteral nutrition without copper supplementation (IOM, 2001). Copper deficiency is characterized by anemia, leukopenia, neutropenia, neurological and bone abnormalities, among other symptoms. Deficiency is not expected in the Canadian population, as food is the main source of intake, and the Canadian TDS (Health Canada, 2011) shows that the population is meeting the recommended daily allowances (RDAs) established by the Institute of Medicine (IOM, 2001) and Health Canada (2010). The RDA is “the average daily intake level sufficient to meet the nutrient requirements of 97.5% of the apparently healthy population of a given sex and age” (de Romana et al., 2011). RDAs for copper have been established at 900 µg/day for adults (19–70+ year-old) of both genders and 340–890 µg/day for children (1 to ≤ 18 years old) (IOM, 2001; Health Canada, 2010). No RDA was established for infants, but adequate intakes of 200 µg/day for 0–6 month-olds and 220 µg per/day for 7–12 month-olds were established based on copper levels in human milk (200–250 µg/L).

Due to the potential for adverse health effects from ingestion of high amounts of copper, tolerable upper intake levels (ULs) have been estimated at 1,000 µg/day for 1–3 year-olds, 3,000 µg/day for 4–8 year-olds, 5,000 µg/day for 9–13 year-olds, 8,000 µg/day for 14–18 year-olds, 10,000 µg/day for those ≥19 year-olds, and 8,000–10,000 µg/day for pregnant and lactating women (IOM, 2001). The ULs were based on absence of liver or GI effects in a small and poorly detailed 12-week double-blind study of back-pain management in seven human adults (Pratt et al., 1985), indicating no adverse effects of diets contributing 10 mg/day of copper, as the gluconate salt.

9.1.2 Copper toxicity syndromes

Copper dyshomeostasis can cause adverse health effects including conditions resulting from inherited metabolic disorders such as Menkes' disease (MKD) and Wilson's disease (WD) (Cockell et al., 2008; Govindaraju et al., 2013; Gaetke et al., 2014; Jazvinscak Jembrek et al., 2014).

MKD, a rare X-linked recessive disorder, results from a mutation on the gene encoding ATP7A translocase. Symptoms in patients with MKD are consistent with those of a severe copper deficiency. Thus, MKD (and its milder variant occipital horn syndrome [OHS]) is characterized by reduced systemic Cu(II) absorption from the gut and blood-brain barrier, excessive copper accumulation in gut mucosa, low serum copper and Cp levels and low copper levels in liver and brain (NRC, 2000; Shike, 2009; Montes et al., 2014; Ellingsen et al., 2015).

Most MKD patients die during early childhood (within their first 10 years, usually before three years of age) while OHS patients may live longer (Kaler, 1998; Camakaris et al., 1999; Schaefer and Gitlin, 1999).

WD (an hepatolenticular degeneration) is a monogenic autosomal recessive disorder that results from one mutation, among over 500 identified, in the gene encoding ATP7B translocase (Harris and Gitlin, 1996; Schilsky, 1996; Shike, 2009; Boveris et al., 2012; Bandmann et al., 2015; Ellingsen et al., 2015; Kumar et al., 2015). WD is characterized by impaired biliary excretion of excess copper, deficient efflux of copper from cells, impaired ceruloplasmin synthesis, which results in copper accumulation in certain tissues (particularly the liver, brain and kidneys). Consequently, WD patients frequently experience liver failure (e.g., disease, cirrhosis) and a variety of neuropsychiatric/behavioral symptoms (Das and Ray, 2006; Machado et al., 2008; Shike, 2009; Montes et al., 2014). Usually, liver dysfunction occurs in the first decade of life and neurological dysfunction in the second (Ala et al., 2007). WD patients are normally under medical supervision. Heterozygous carriers of the defective WD gene have been speculated to be sensitive populations, but evidence for this, other than increased hepatic copper levels, is lacking (IPCS, 1998; NRC, 2000; WHO, 2004).

Other extremely rare but well documented childhood copper toxicosis conditions are: Indian childhood cirrhosis (ICC, a condition primarily affecting children under 5 years old), endemic Tyrolean infantile cirrhosis (TIC), and idiopathic copper toxicosis (ICT) (Madsen and Gitlin, 2007; Pal, 2014). These diseases are characterized by extremely high copper concentrations in the liver during early childhood, leading to liver enlargement, pericellular fibrosis, necrosis, and even death (Muller et al., 1996; Tanner, 1998; Johncilla and Mitchell, 2011). However, the etiology of these syndromes seems more complex, potentially involving, in addition to genetic components, environmental factors (e.g., very high copper intakes) (Olivares and Uauy, 1996; Scheinberg and Sternlieb, 1996; ATSDR, 2004; OEHHA, 2008; Shike, 2009; Ellingsen et al., 2007, 2015). Finally, individuals with glucose-6-phosphate dehydrogenase deficiencies may be sensitive to haemolytic anemia in response to copper overexposure (OEHHA, 2008).

9.1.3 Case reports

There are several reports of ingested copper poisoning with the main targets including the GI tract, liver, kidneys and haematopoietic/central nervous systems (IPCS, 1998; NRC, 2000).

During 1992 and 1993, the Wisconsin Division of Health investigated cases of gastrointestinal upsets thought to be related to copper in drinking water. They concluded that the symptoms occurred most frequently in infants and children and among residents of newly constructed or renovated homes (Knobeloch et al., 1994). In adults, anecdotal reports suggest that the immediate symptoms following the consumption of contaminated beverages or drinking water include a metallic taste and GI disruption (e.g., nausea and epigastric pain and vomiting combined, diarrhea), usually occurring like symptoms of food poisoning, within 15–60 minutes, and at concentrations as low as 3–4 mg Cu(II)/L drinking water. Nausea and vomiting (generally not persistent) are usually more common than diarrhea. Anorexia, headache, dizziness, hypotension and shock have also been reported. Delayed symptoms, at higher doses, include anemia, hemoglobinuria, jaundice, liver and renal failure, and even death. Histological findings upon autopsy include kidney lesions (e.g., glomeruli congestion, necrosis) and gastric mucosa erosions (Wyllie, 1957; Spitalny et al., 1984; Mehta et al., 1985; Gulliver, 1991; Araya et al., 2001). Rhabdomyolysis (muscle injury) has also been reported (Jantsch et al., 1984; Takeda et al., 2000).

In children, limited data indicate similar effects. Indeed, case reports have attributed adverse effects (e.g., diarrhea and weight loss) to levels ranging from 0.22 to 1.0 mg Cu(II)/L drinking water (Stenhammar, 1999) or 1.0 to 6.5 mg Cu(II)/L drinking water (Berg et al., 1981). Also, neonates and infants appear to be more sensitive due to their enhanced intestinal absorption and immature hepatobiliary system (Collins and Klevay, 2011).

Finally, there are few case reports of chronic exposure. According to the available data, chronic ingestion of excessive copper may cause GI effects in infants, and liver and renal failure in adults (O'Donohue et al., 1993, 1999; Stenhammar, 1999; Cech et al., 2006; Stern et al., 2007).

9.1.4 Short-term exposure

Gastrointestinal symptoms, usually defined in most studies as the occurrence of one or more outcome symptoms of nausea, epigastric pain, vomiting, or diarrhea, have been identified as primary effects from short-term exposure to ingested Cu(II). Nausea is the earliest (occurring within 15 minutes to one hour) and most frequent symptom and is transient (Pizarro et al., 1999a; Pizarro et al., 1999b; Araya et al., 2001; Olivares et al., 1998; 2001).

In a double-blind randomized prospective study consisting of sixty healthy Chilean women (15/group), acute GI effects from ingested copper were identified by (Pizarro et al., 1999b) following a two-week-exposure to drinking water with at least 3 mg Cu(II)/L (as copper sulphate). In this study, GI effects (nausea, abdominal pain, or vomiting) were significantly increased (overall $\chi^2 = 11.3$, $p < 0.01$) but not diarrhea. Although thresholds for specific symptoms could not be derived, nausea was identified as a good indicator for the effects evaluation. Also, there was a range of sensitivity among subjects and most symptoms disappeared when the exposure ceased. Therefore, a lowest observed adverse effect level (LOAEL) of 3 mg Cu(II)/L based on nausea, abdominal pain, and vomiting combined can be identified from this study.

With nausea identified as the earliest symptom of GI effects, several efforts were conducted to estimate a dose threshold. Olivares et al. (2001) used a randomized, Latin square design to administer 0, 2, 4, 6, 8, 10, or 12 mg Cu(II)/L purified water or orange-flavored drink, as copper sulphate, to apparently healthy Chilean adults. In this study, the subjects (47–61/group) received, after an overnight fast, a fixed volume of 200 mL of the solution, during a 1-hour session, once per week, for a theoretical maximum of 12 weeks. This resulted in exposure dose of 0, 0.4, 0.8, 1.2, 1.6, 2 and 2.4 mg Cu(II), respectively. There were no age- or gender-related differences between the groups and no observed response up to 0.4 mg (= no observed adverse effect level [NOAEL] based on nausea). However, mild nausea shortly after ingestion was most frequently reported, starting at 0.8 mg Cu(II), then plateauing at 1.6–2.4 mg. The vomiting incidence, which first appeared at 1.2 mg, was low (11.5%), with a two-fold increase between 2 and 2.4 mg. The concomitant occurrence of nausea and vomiting was less frequent, with the highest incidence at 2.4 mg (12% of subjects). Diarrhea and abdominal cramps were rare within the range of concentrations studied. Because a range of sensitivity had been reported earlier (Pizarro et al., 1999b), the authors used a benchmark dose (BMD) approach to derive the lower bound on the 95% confidence interval (CI) on the drinking water concentration that would produce a response in 5% of the population (BMDL₀₅). The resulting BMDL₀₅ were 0.4 mg Cu(II) (2 mg/L) and 0.84 mg Cu(II) (4.2 mg/L) for apparent and confirmed cases of nausea, respectively. The BMDL₀₅ for apparent cases of nausea is very close to the NOAEL of 0.4 mg Cu(II) based on nausea; the LOAEL based on nausea was 0.8 mg Cu(II), which was also the NOAEL for vomiting.

The same group of investigators reported on a prospective, double-blind controlled multi-site (Chile, Northern Ireland and United States) phase I study in apparently healthy adult volunteers, also designed to determine the nausea threshold (Araya et al., 2001). After an overnight fast, subjects (179/group) were randomly given 0, 0.4, 0.8, 1.2, or 1.6 mg Cu(II) (as copper sulphate salt) in a bolus of 200 mL distilled-deionized water (equivalent to 0, 2, 4, 6, or 8 mg Cu(II)/L) once per week over five consecutive weeks. The results also suggested that women may be more sensitive. As copper dose increased, female subjects reported significantly more occurrences of nausea and GI symptoms than male subjects (odds relative to males, 2.66, $p < 0.004$; and 1.68, $p < 0.05$, respectively). Nausea, which was transient, was the most prevalent symptom (average prevalence = 27.3% among all subjects) and was frequently reported within the first fifteen minutes. Also, there was a clear dose-response to (1) combined positive GI symptoms (nausea, vomiting, diarrhea or abdominal pain) and (2) nausea alone. Statistically significant greater reporting of effects occurred at 1.2 and 1.6 mg Cu(II). Unlike abdominal pain and diarrhea, nausea and GI symptoms as a whole were strongly predicted by Cu(II) concentrations, with incidences significantly increasing ($P < 0.0001$) with increasing concentrations (odds of 0.66; 3.53, 7.67, and 17.15 for nausea and 0.87, 1.83, 3.54, and 7.29 for GI symptoms, for 2, 4, 6, and 8 mg/L, respectively; $p < 0.0001$). Both nausea and other GI symptoms were significantly increased ($p < 0.002$) at 1.2 mg Cu(II) but not at 0.8 mg Cu(II) (LOAEL and NOAEL, respectively). The performed dose-response modeling determined that the BMDL₀₅ for nausea alone was 0.7–0.8 mg Cu(II) (3.5–4 mg/L). The upper bound of this latter range is similar to the NOAEL of 0.8 mg based on nausea and other GI symptoms. Overall, the findings (nausea occurrence, no correlation with diarrhea and a LOAEL ≥ 3 mg Cu(II)/L) were consistent with that from Olivares et al. (2001) and Pizarro et al. (1999b).

The above phase I results from Araya et al. (2001), in which copper was delivered in distilled-deionized water, were confirmed in the phase II of this study (Araya et al., 2003a) in another multi-sites double-blind study in 269 adult women receiving Cu(II) sulphate in 200 mL bottled natural spring water, once per week, for 11 consecutive weeks. In this study, a 3×3 two-way factorial design was used to administered to the subjects (58 to 73/site) 0.4, 0.8, 1.2 mg Cu(II) as the sulphate salt in 100, 150 and 200 mL of water. The 0 and 1.6 mg Cu(II) doses were added at the 200 mL level. It is worth noting here that, all the other short-term studies used a constant dosing volume of 200 mL. The results from (Araya et al., 2003a) showed that both the copper dose ($p = 0.0001$) and the volume of water ($p = 0.032$) significantly contribute to the nausea incidence. The latter increased with increase in copper dose, and decrease in water volume. In addition, a benchmark dose (BMD) analysis was performed for nausea incidence for the 200 mL bolus dose. The calculated BMD for a 10% response was 0.94 mg Cu(II) (4.8 mg/L; $p = 0.94$) and the corresponding BMDL₁₀ was 0.84 mg Cu(II) (4.2 mg/L). The BMDL₁₀ is very close to the NOAEL of 0.8 mg Cu (II) (4 mg/L); this NOAEL identified for women is also the same as the NOAEL based on nausea and other GI symptoms identified for both men and women in the phase I of the study by Araya et al. (2001).

Overall, from the above short-term studies, the lowest effect level identified is a BMDL₀₅ of 0.7 mg (or 3.5 mg/L) based on nausea alone and non-continuous exposure (Araya et al., 2001).

9.1.5 Long-term exposure

Chronic copper toxicity is usually observed in patients with Wilson's disease, hemochromatosis and infantile cirrhosis (Olivares et al., 1998; Mauceri and Mishra, 2014). While WD involves more than simple accumulation of copper, it is likely that some of the

typical WD symptoms are related to long-term exposure to excessive copper (see section 9.1.2). However, the current evidence, mostly from mechanistic data, as well as limited case and clinical studies, indicates that in the general population, chronic exposure to very high levels, above those associated with GI illnesses, may lead to liver and renal damage (O'Donohue et al., 1993; IPCS, 1998; O'Donohue et al., 1999; Pizarro et al., 1999b; Stenhammar, 1999; Stern et al., 2007).

9.1.5.1 Gastrointestinal effects

Araya et al. (2004) conducted a randomized, double-blind, two-month-community-based study on 1365 apparently healthy adults (327 to 355/test group) receiving up to 6 mg Cu(II)/L. Copper-containing water was used for drinking and the preparation of other beverages (e.g., tea, coffee, infusions, and soups) and mean fluid consumption was 1.5 L/day. Unlike the previous findings from short-term exposure (Pizarro et al., 1999b; Araya et al., 2001, 2003a; Olivares et al., 2001), abdominal pain and nausea were most prevalent and symptoms reporting significantly decreased over time for both sexes, suggesting an adaptive response. However, more importantly, a LOAEL of 6 mg Cu(II) (4 mg/L) was identified in women, the most sensitive population. This LOAEL which was no longer valid by week 4, is similar to the BMDL₀₅ of 4 mg/L, based on nausea, identified previously for short-term exposure (Araya et al., 2001, 2003a; Olivares et al., 2001). Also, as with the short-term studies, the symptom risks were positively associated with copper concentration and the female sex, and negatively related to time. In fact, the risk of GI effects was significantly higher in female during the first week, but this was no longer the case by week 4. Overall, the authors found that Cu(II) concentration and dosing volume were the main determinants of the response, the applied dose and vehicle being less important.

A prospective study by Olivares et al. (1998) showed that infants who continuously received up to 31.48 µmol Cu(II)/L drinking water as copper sulphate (i.e., 2 mg/L) during the last nine months of their first year of life remained asymptomatic, grew normally, and did not present with significant increased risk of diarrhea when compared to those receiving less than 1.57 µmol Cu(II)/L (i.e., less than 0.1 mg/L). The main goal of this study was to verify the tolerance and safety of chronic exposure of infants to the previous provisional guideline value (WHO, 1993) for the general population. This placebo-controlled study randomly assigned 128 apparently healthy Chilean infants (3 months of age), from the same socioeconomic level and weighing more than 2 kg at birth, to receive, drinking water with either 1.57 µmol Cu(II)/L or 31.48 µmol Cu(II)/L, daily for 9 months. Breast-fed infants were exclusively breast-fed until at least 6 months of age and those given formula were partially or totally weaned from the breast by 3 months of age. More specifically, the 3-month olds infants were divided into four groups at the beginning of the study as follows: 1) group 1: formula-fed infants receiving 31.48 µmol Cu(II)/L (n = 56); 2) group 2: formula-fed infants receiving 1.57 µmol Cu(II)/L (n = 27); 3) group 3: breast-fed infants receiving 31.48 µmol Cu(II)/L (n = 24); and 4) group 4: breast-fed infants receiving 1.57 µmol Cu(II)/L water (n = 21). Mothers of breast-fed infants (groups 3 and 4) also received water with the corresponding Cu(II) levels. Thus, two litres of drinking water were prepared for consumption daily, by the mothers, either from a fresh copper sulphate-containing standard solution (0.8 g Cu (II)/L) for the exposed groups (1 and 3), or from an equivalent volume of placebo for the non-exposed groups (2 and 4). This placebo was not clearly defined except that it was organoleptically identical to the copper-based solution. The water for daily consumption was used for drinking, in preparation of meals, and in preparations (by dilution) of the powdered cow's milk and the powdered cow's milk-based formula. The latter was fortified

with 7.87 μmol copper/L. Any additional water needed was prepared as per the same approach. Formula-fed infants started receiving solid food at 3 months of age whilst breast-fed infants began weaning and receiving unfortified cow's milk formula and solid food at 6 months of age. Although breast milk Cu(II) was not considered when calculating total intake, dietary copper from foods, milk formula and water used for meals and formula preparation was. During the study, a field worker visited each home weekly, recording water intake, GI, respiratory, and other illnesses, as recalled by mothers. Each infant also underwent monthly clinical and anthropometric evaluations. Overall, chronic ingestion of up to 31.48 μmol Cu/L by infants (in their formula [F], foods and drinking water), from three months to one year old, did not result in any acute or chronic effects. Specifically, there were no differences in morbidity episodes (i.e., diarrhea and respiratory infections) among the four studied groups, as indicated by the performed analyses. At 9 months, there was a significant difference in Cp activity between the Cu(II) exposed subjects (groups 1 and 3) as compared to the unexposed (groups 2 and 4) (350 ± 85 mg/L vs. 322 ± 75 mg/L; $F = 5.42$; $p = 0.02$), which was more pronounced in the breast-fed groups (groups 3 and 4). However, the overall copper status (based on serum copper levels, Cp protein levels or activity, erythrocyte Cu/Zn-SOD, erythrocyte metallothionein) of the infants did not significantly change at 6, 9, and 12 months of age. Also, no significant differences were found in the liver function (based on bilirubin, SGOT, serum glutamic pyruvic transaminase, and gamma glutamyl transferase [GGT]) among the infants at 6, 9, and 12 months of age. The authors reported the results for 3 time points (4 to 6 months, 6 to 9 months and 9 to 12 months). But as discussed earlier (section 9.1.3), infants are at increased risk of copper exposure during their first 6 months of life, when their hepatobiliary system is still immature. Since no toxic effect was reported for the entire studied period, results from the highest exposure window, months 4 to 6 (equivalent to a 4-month exposure), will be considered. According to the authors, for this exposure window, the corresponding figures for total daily intakes (mean \pm SD) were: 318.7 ± 107.3 $\mu\text{g}/\text{kg}$ bw per day (group 1); 122.7 ± 107.4 $\mu\text{g}/\text{kg}$ bw per day (group 2); 52.2 ± 48.5 $\mu\text{g}/\text{kg}$ bw per day (group 3); 37.8 ± 36.7 $\mu\text{g}/\text{kg}$ bw per day (group 4).

9.1.5.2 Liver and renal effects

Liver toxicity from copper overexposure has mostly been studied and reported in sensitive populations (e.g., WD, childhood cirrhosis syndromes); however, there have been a few reports studying individuals from the general population. Indeed, a significant transient increase in liver enzyme activities (glutamic-oxaloacetic aminotransferase (GOT), glutamic-pyruvic transaminase (GPT) and gamma glutamyl transferase (GGT); ANOVA p-value < 0.01) was observed in a prospective controlled trial in apparently healthy Chilean adults ($n = 87$, with serum Cp levels below the 0.05 and above the 0.95 quantiles of the distribution curve) receiving 10 mg Cu(II)/day (0.17 mg/kg bw per day assuming an average 60-kg adult) (as sulphate salt) in capsules for 60 days (Araya et al., 2005b). However, not only were the results within normal clinical ranges, but the participants remained asymptomatic and the increased liver enzyme activities ceased one year after the termination of the study.

In a double-blind study by Pratt et al. (1985), there was no evidence of liver or GI effects in seven adult humans supplemented with 10 mg Cu/day (0.08 mg/kg bw twice a day) as gluconate salt in capsules for 12 weeks. Furthermore, no significant changes were reported in: (1) hair, serum and urine copper levels; (2) hematocrit, serum triglycerides and cholesterol; and (3) serum enzymes such as alkaline phosphatase (AP), GGT, GOT and lactate dehydrogenase (LDH).

A European multi-sites, double-blind, placebo-controlled, food-trial also found no association between liver function and copper supplementation (in sequence: 0.05 mg/kg bw per day as copper sulfate salt, and 0.12 mg/kg bw per day as copper amino acid chelates) for 6 weeks (O'Connor et al., 2003).

No significant changes in indicators of liver function (aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT) were observed in adults who ingested up to 6 mg Cu(II)/L (0.10 mg/kg bw per day for an average 60-kg adult) as the sulphate salt for two months (Araya et al., 2003b).

Long-term exposure of infants and young children to drinking water containing copper was not associated with a significant increase in the prevalence of liver disease (Fewtrell et al., 1996; Olivares et al., 1998; Zietz et al., 2003a).

9.1.5.3 Biochemical effects

In general, the results of studies that lasted less than 3 months showed that copper supplementation did not alter the indexes of its status. Thus, no significant changes in markers of copper status (serum, erythrocyte, and mononuclear cell copper concentrations; serum Cp; non-Cp-bound copper pool; SOD activity) were detected in healthy adults given either up to 6 mg Cu(II)/L as the sulphate (~ 0.20 mg/kg bw per day for 2 L water/day) (Araya et al., 2003b, 2004; Mendez et al., 2004), tablets of 10 mg/day (0.17 mg/kg bw per day) copper sulphate for two months (Mendez et al., 2004), or diet supplemented with up to 6 mg Cu(II)/day (0.09 mg/kg bw per day) as the sulphate salt or amino acid chelates (Kehoe et al., 2000; Turnlund et al., 2004). However, some changes observed after supplementation for a longer period of time may suggest an adverse effect of high copper intake. Thus, a study was conducted in 9 men to determine the long-term effects of high copper intake (Turnlund et al., 2004). After a 5-month supplementation with up to 7.8 mg Cu(II)/day (0.11 mg/kg bw per day for an average 70-kg adult), changes were observed in several function markers. Indeed, for the immune function, there were significant decreases ($p < 0.05$) in the percentage of circulating neutrophils, serum interleukin 2R, and the antibody titer against the Beijing strain of influenza. For the antioxidant defense, the urinary thiobarbituric acid reactive substances (TBARS), an indirect measure of oxidative damage, was significantly higher ($p < 0.05$). Additionally, small but significant changes were observed in some indexes of copper status (e.g., Cp activity and SOD activity), although concentrations of plasma copper and Cp did not change (Turnlund et al., 2004).

In conclusion, for exposure less than 3 months, the results were negative. Indeed, adults supplementation with up to 0.17 mg/kg bw per day did not significantly alter the indices of liver damage (O'Connor et al., 2003; Araya et al., 2005b) or copper status (Kehoe et al., 2000; Mendez et al., 2004; Turnlund et al., 2004); the same picture was observed after long-term exposure to drinking water with up to 0.2 mg/kg bw per day (Araya et al., 2003b; Araya et al., 2004; Mendez et al., 2004). However, for exposure above 5 months, the results suggest adverse effect of high copper intake over longer period of time (Turnlund et al., 2004). Therefore, given the paucity of chronic exposure studies, perhaps such data (Turnlund et al., 2004) and the symptoms experienced by WD patients could shed light on the types of adverse effects that might be expected from chronic copper overexposure.

9.1.5.4 Neurotoxicity

Copper-enzymes play an essential role in neurological functions. Multiple reviews have reported conflicting results on the association between copper exposure and neurodegenerative conditions such as Alzheimer's disease (AD) and Parkinson's disease (Bush et al., 2003; Squitti

et al., 2006; Rivera-Mancia et al., 2010; Tiffany-Castiglioni et al., 2011; Montes et al., 2014; Pal et al., 2014). For example, two case-control studies in Italy have found that serum copper levels were significantly higher in AD patients compared to age or sex-matched controls (P-value < 0.001) and correlated with lower neuropsychological scores; however, the copper serum levels reported were within normal range (Squitti et al., 2002; Brenner, 2003). Also, senile plaques and neuropils of the amygdala of 9 AD patients were found to contain significantly higher levels of copper compared with neuropils of the amygdala of 5 control subjects (P-value < 0.05) (Lovell et al., 1998) and compared with non-plaque regions of 2 AD patients. However, copper levels also correlated with those of zinc (Miller et al., 2006).

Other studies have not supported the above results. For example, copper levels in cerebrospinal fluid and serum were not significantly different between Alzheimer's disease patients (n = 26) and matched controls (n = 28) (Molina et al., 1998). In another study, patients with lower plasma copper had a significantly poorer performance on the AD's Assessment Scale-cognitive subscale compared with patients with higher plasma copper (ANOVA p-value < 0.001; all patients (n = 32) had normal plasma copper levels) (Pajonk et al., 2005). Finally, higher levels of AD biomarkers were correlated with lower plasma copper levels among AD patients (Mann-Whitney p-value = 0.03, total n = 29) (Kessler et al., 2006).

In conclusion, from the above results, it appears that the specific role of copper in neurodegenerative diseases, which are multifactorial, remains unclear.

9.1.6 Carcinogenicity

Numerous epidemiological studies have investigated the association between copper status or intake, serum copper and various types of cancers. In general, the evidence of the carcinogenicity of copper is inconclusive and there is no clear or substantiated evidence of an aetiological role of the nutrient in the cancer development in humans.

A case-control study in France (Senesse et al., 2004) found an increase in the odds of colorectal cancer in the highest quartile of copper intake compared to the lowest quartile (odds ratio [OR] = 2.4, 95% CI 1.3–4.6, p-value < 0.01). Another case-control study nested within a large Dutch chronic diseases cohort (n > 10,000) found an increased risk of death from cancer (OR = 3.7, 95% CI 1.5–9.1) in participants with serum copper > 1.4 mg/L compared to 1.1–1.4 mg/L after adjusting for BMI, cholesterol, education and blood pressure; however, important cofactors were not adjusted for (Kok et al., 1988). Furthermore, a nested case-control study (n = 133 cases, 241 controls) of a worker cohort (n = 5,000) in Washington also found an increased risk of cancer in subjects with serum copper at 126–276 µg/dL compared with those having 43–92 µg/dL (OR = 2.4, 95% CI 1.1–5.1). However, according to the authors, the findings rather suggested that increased serum copper was a consequence of the disease state, i.e., cancer (Coates et al., 1989). Finally, a nested case-cohort study from a random sample of cases (n = 46) from a cohort of English women found an increased odds of breast cancer (OR 3.2, 95% CI 1.1–9.4) for women with plasma copper above 1.3 mg/L compared to 1.0–1.2 mg/L after adjusting for age, weight, and family history; however, there was no dose-response and other factors could explain the association (Overvad et al., 1993). Moreover, many case-control studies have not supported associations between copper intake or serum levels and the risk of breast or oesophageal cancers (Cavallo et al., 1991; Dabek et al., 1992; Prasad et al., 1992). Furthermore, no association between copper intake and lung cancer was observed in a retrospective cohort study (Mahabir et al., 2010). In a cohort study of associations between multiple antioxidants and cancers in women, the risks of non-Hodgkin's lymphoma, diffuse large B-cell lymphoma or

follicular lymphoma were not increased in participants with higher copper intake (Thompson et al., 2010).

In conclusion, the results from the above studies are equivocal since (1) individual exposure was poorly characterized and (2) increased serum copper concentrations might be related to alterations in copper handling as a result of disease state (cancer in this case). In addition, as has been mentioned earlier, more than 90% of serum copper is normally bound to Cp. The latter is an acute phase protein whose levels increase during stress (see section 8.2).

9.1.7 Genotoxicity

In general, copper is not expected to be genotoxic with normal intakes. However, increases in genotoxicity and oxidative damage have been shown in patients suffering from copper dyshomeostasis conditions (NRC, 2000). For example, DNA damage was observed in hepatocytes from patients with Indian Childhood Cirrhosis, and this was postulated to result from excessive accumulation of copper in the nucleus, leading to the production of free radicals (Prasad et al., 1996). Also, bulky DNA adducts (vs. 8-hydroxydeoxyguanosine adducts) were observed in the livers of Wilson's disease patients (Carmichael et al., 1995). Moreover, a 6-week-double-blind crossover trial (n = 15–17) found no significant differences in leucocyte DNA damage (Comet assay) in participants supplemented with 3 mg/day copper sulphate or 3 or 6 mg/day copper glycine chelates compared with the placebos (*t-test* p-value > 0.05) (O'Connor et al., 2003).

9.1.8 Developmental and reproductive toxicity

There is no convincing evidence of reproductive or developmental toxicity in humans related to oral copper intake (IPCS, 1998; NRC, 2000; EFSA, 2006; Heinemann et al., 2015). However, it should be noted that women with untreated WD frequently experience spontaneous abortions (NRC, 2000).

9.2 Effects on experimental animals

Copper toxicity varies between animal and chemical species, and target organs are primarily those involved in the absorption and excretion of the metal (i.e., liver, kidneys, forestomach). Liver and kidney toxicities were the main endpoints reported in young rodents exposed to high copper doses for short/sub-chronic durations, and recoveries suggestive of physiological adaptations to high copper intake have been observed in rats (Haywood, 1980, 1985; Haywood and Loughran, 1985; Haywood et al., 1985a, 1985b; Fuentealba and Haywood, 1988; Fuentealba et al., 1989a, 1989b). Effects on the central nervous system have also been observed; however, the body of evidence for these effects is weak and inconclusive. Exposure to high levels of copper via drinking water appears to be more toxic than via the diet, and rats were generally more sensitive than mice. Copper salts, and particularly Cu(II) sulphate, were commonly used and the toxicity is attributed to the ionic form. No quality study of chronic duration was found.

9.2.1 Acute toxicity

Oral lethal doses (LD₅₀) of 15–1600 mg Cu/kg bw have been reported for different forms of copper across different species; for example, in rats, the LD₅₀ is 120–300 mg/kg bw for Cu(II) sulphate and 15–90 mg/kg bw for Cu(II) chloride (Stern et al., 2007; OEHHA, 2008; Ellingsen et al., 2015). Death is usually preceded by bleeding of the stomach, cardiovascular dysfunctions, and paralysis (IPCS, 1998). The stomach being the primary site for the emetic response,

vomiting is induced within a few minutes in Beagle and Mongrel dogs and ferrets exposed to aqueous solution of Cu(II) sulphate (WHO, 2004). Most studies using vomiting as an indicator may not have observed a response in mouse and rat at levels that might be comparable to those eliciting a response in other species; it is important to note, however, that rats and mice do not vomit (Horn et al., 2013). Soluble salts (e.g., Cu(II) sulphate) generally elicit greater responses than insoluble forms, and rodents were reported to be more sensitive than ferrets, sheep, dogs and cats (IPCS, 1998; WHO, 2004).

9.2.2 Short-term and sub-chronic toxicity

9.2.2.1 Liver effects

Liver inflammation (i.e., multifocal hepatitis, accumulation of macrophages, increased liver enzyme activity in the serum) and necrosis of hepatocytes have been observed in young (~6–10 weeks of age) and adults F344 rats of both sexes ingesting 1,500–16,000 ppm Cu(II) sulphate in feed for 2–18 weeks (Hebert et al., 1993; NTP, 1993; Fuentealba et al., 2000; Aburto et al., 2001). Effects were more pronounced in both male and young rats. Moreover, alterations in the integrity and size of lysosomes, endoplasmic reticulum, mitochondria, and nucleus have been observed in rats fed 1,500 mg Cu/kg feed for 16 weeks (Fuentealba and Haywood, 1988).

No evidence of copper toxicity or liver damage was observed in infant rhesus monkeys administered 6.6 mg Cu(II) sulphate/L (900 µg/kg bw per day, n = 5) until 5 months of age; however, increased number of K upffer cells were observed in the liver, suggestive of inflammation (Araya et al., 2005a). Moreover, no clinical, biochemical, or histological evidence of liver damage were observed in newborn or adults capuchin monkeys (2 females, 2 males each) exposed for 36 months to, 5.5 mg and 7.5 mg Cu(II) gluconate/kg per day, respectively; however, an increase in inflammatory genes (e.g., HGF, TGF  and NF B) was found (Araya et al., 2012). Finally, no adverse effects were noted in Beagle dogs fed with Cu(II) gluconate at levels up to 8.4 mg/kg bw per day for 6 to 12 months, and the slight liver function changes observed at the highest dose were reversed after stopping the exposure (NRC, 2000).

9.2.2.2 Kidney effects

Increases in cytoplasmic protein droplets were observed in the renal convoluted tubules of male rats given water containing 300 ppm Cu(II) sulphate for 2 weeks (Hebert et al., 1993; NTP, 1993). Similar effects were observed in rats receiving feed with 2,000 ppm Cu(II) sulphate and more for 2–15 weeks (Haywood, 1980; Hebert et al., 1993; NTP, 1993). The effects were more pronounced in males.

9.2.2.3 Other effects

Hyperplasia and hyperkeratosis of the forestomach's limiting ridge mucosa were observed in both sexes of rats and mice at doses of 2,000 ppm Cu(II) sulphate and more in food for 2–13 weeks, with rats being more sensitive (Hebert et al., 1993; NTP, 1993). Symptoms varied from oedema and inflammation in the stroma to papilliferous ridge with expansions of the stromal core and the squamous mucosa in severely affected rats.

Bone marrow cell depletion, decreased spleen and bone marrow hematopoiesis, transient changes in haematological parameters, organ damages, and death have been observed in rats consuming high doses of copper (over 2,000 ppm) (NTP, 1993; Bertinato et al., 2010).

9.2.3 Carcinogenicity

Copper has not been shown to be carcinogenic in animals. Indeed, the limited available data does not suggest that copper or its salts are carcinogenic in animals with normal copper homeostasis. Specifically, the available data have several weaknesses that hinder any adequate assessment such as: ‘dated studies, small group sizes, single oral-dose tested; limited extent of histopathological examination, inadequate reports’ (NRC, 2000; EFSA, 2006; Abe et al., 2008; OEHHA, 2008). No chronic/cancer inhalation studies in animals were identified. However, the data for the Long-Evans cinnamon (LEC) rat, a model for Wilson disease, support the hypothesis that copper-induced cirrhosis can be an aetiological factor in hepatic cancer (NRC, 2000).

9.2.4 Genotoxicity

Although some positive responses have been observed in the Mutatox and SOS Chromotest assays (Codina et al., 1995), copper is generally not genotoxic. Moreover, microbial mutation assays with different copper salts were negative. Indeed, no mutations were induced by Cu(II) sulphate in the TA98, TA 100, TA102, TA1535 or TA1537 strains of *S. Typhimurium* (Moriya et al., 1983). Also, no mutations were induced by Cu(II) gluconate in the Ames test or by Cu(II) chloride in *E. coli* WP2 with or without microsomal activation (Wong, 1988; Hujita et al., 1998).

9.2.5 Neurotoxicity

There is some evidence for a relationship between copper exposure and neurotoxicity. For example, lower anti-oxidative activity and alterations in dopamine kinetics were observed in the brains of rats exposed to high levels of copper (1 g Cu/L, or 46 mg Cu/kg bw) via drinking water for 1–11 months (De Vries et al., 1986; Ozcelik and Uzun, 2009) and both alterations in amyloid-beta protein processing and learning impairment were observed in mouse and rabbit models of AD chronically exposed to copper (Sparks and Schreurs, 2003; Kitazawa et al., 2009). However, no increased neurological sensitivities were identified in LEC rats and in Bedlington terriers, genetic animal models for copper toxicosis (NRC, 2000; Pal et al., 2013), and no neurobehavioral manifestations were observed in rats exposed to 1 ppm Cu(II) sulphate in their drinking water for 6 weeks (Fujiwara et al., 2006)(Fujiwara et al., 2006). Hence, the results for neurotoxicity are equivocal and adverse effects were only observed following exposure to very high doses and/or with the use of animals with genetic anomalies.

9.2.6 Reproductive and developmental toxicity

Some studies have reported changes in testes, seminal vesicles, uteri and ovaries in rats, mice, and bank voles after exposure to high levels of copper (27–200 mg/kg bw per day) (EFSA, 2006; Roychoudhury et al., 2015). Despite that there were some reports of teratogenicity and fetolethality following ingestion of copper at high doses (above 80–390 mg/kg bw), these outcomes were attributed to dam toxicity (IPCS, 1998; NRC, 2000; EFSA, 2006). Moreover, no adverse effects were reported for any of the reproductive parameters studied in rats and mice of either sex exposed to Cu(II) sulphate (up to 8,000 mg/kg of feed or 140 mg/kg bw) for 13 weeks (NTP, 1993).

9.3 Mode of action

Copper exerts its toxicity via two main pathways: The neuronal pathway in the case of GI effects, and the cellular toxicity pathway (especially oxidative stress) for the other adverse

effects. In order to manifest toxic effects, copper must be in its free ionic form or free copper. The following sections briefly describe the proposed mode of action for copper-induced toxicity.

9.3.1 *Gastrointestinal effects*

Copper exerts its GI tract toxicity by direct irritation of the stomach, activating the release of serotonin by enterochromaffin cells (NRC, 2000; Bradberry, 2007; OEHHA, 2008). The mode of action of this neuromuscular response is a reflex mechanism mediated by the central nervous system. As part of a study involving several emetic agents, Bhandari and Andrews (1991) concluded that copper sulfate causes emesis through GI chemoreceptors in the vagal nerve afferents and that this process most likely involves activation of 5-hydroxytryptamine-4 receptors in some manner. These receptors are receptor subtypes that respond to serotonin. Serotonin can sensitize gastric mucosa parasympathetic nerve endings, activating the vomit centre in the brain. The latter mediates efferent signaling messages to the GI tract, initiating a response (OEHHA, 2008). Stomach infusion with copper sulphate solution resulted in vomiting in 7/9 ferrets as compared to 1/9 animals with duodenum infusion with similar solution (Makale and King, 1992). Dogs with severed vagus and sympathetic gastric nerves showed impaired emetic response (Fukui et al., 1994). The latter is modulated by many factors such as: individual sensitivity, copper form, and the nature of gastric content. Adaptation in the response has also been demonstrated (NRC, 2000). Since the GI responses of copper are related to portal of entry effects, the appropriate metric for risk assessment is the concentration.

9.3.2 *Other adverse effects*

Cellular toxicity is the main and most studied mode of action by which copper exerts its other adverse effects (Gaetke and Chow, 2003; Gaetke et al., 2014). Several mechanisms have been proposed to explain copper-induced cellular toxicity. However, oxidative damage to membranes and biological macromolecules is the most studied and consistent of them (Bremner, 1998; Gaetke and Chow, 2003; Jomova and Valko, 2011; Mauceri and Mishra, 2014). Free copper has been identified as the toxic moiety leading to oxidative stress (EFSA, 2006; Bertinato et al., 2010; Stern, 2010; Montes et al., 2014). Both Cu(I) and Cu(II) ions possess redox potential and can catalyze the production of reactive oxygen species (ROS), especially the hydroxyl radical (OH^\bullet). However, in order to exert its cytotoxicity, the Cu(II) ion must be reduced (e.g., by GSH or ascorbate) to the Cu(I) ion (EFSA, 2006; Bertinato et al., 2010; Stern, 2010; Formigari et al., 2013; Montes et al., 2014) which can catalyze the formation of OH^\bullet from hydrogen peroxide (H_2O_2) via a Haber-Weiss driven Fenton reaction (Bremner, 1998; Bradberry, 2007; Bertinato et al., 2010; Stern, 2010; Formigari et al., 2013; Gaetke et al., 2014; Jazvinscak Jembrek et al., 2014; Montes et al., 2014). Indeed, copper-induced oxidative stress involves the formation of the extremely reactive hydroxyl radical (OH^\bullet) which is capable of initiating one of the three main cellular events most frequently reported (Gaetke et al., 2014; Jazvinscak Jembrek et al., 2014). The first event, the peroxidation of membrane lipids, is the consequence of a hydrogen abstraction from an unsaturated fatty acid by the hydroxyl radical, leading to a lipid radical. One consequence of this process is the breakdown of hepatic lysosome membranes (Burkitt, 2001; Letelier et al., 2010; Gaetke et al., 2014). The second key event, the oxidation of proteins, results from a hydrogen abstraction from an amino-bearing carbon by OH^\bullet , to form a carbon-centered protein radical. This leads to, for example, the deactivation of enzymes. The third key event, DNA damage, is the consequence of the DNA strands breaks and oxidation of bases by OH^\bullet , leading for example to mutations (Gaetke and Chow, 2003; Jomova and Valko, 2011; Gaetke et al., 2014). These key oxidation events can lead to inflammation and cell death (Yoshida et al.,

1993; NRC, 2000; Jomova and Valko, 2011; Formigari et al., 2013; Gaetke et al., 2014) which potentially explain copper's toxic effects as well as the molecular and morphological alterations observed in the liver, kidney, brain, and red blood cells at high doses in animal studies (Eskici and Axelsen, 2012; Shaligram and Campbell, 2013; Jazvinscak Jembrek et al., 2014). Also, since copper-induced ROS is time and dose-dependent, this mode of action has long been proposed to explain the liver toxicity induced by the metal (Formigari et al., 2013). In addition, the current evidence suggests that the hepatic mitochondrion is an important target in copper-induced liver oxidative damage (Jiménez Del Río and Vélez-Pardo, 2004; EFSA, 2006; Kawakami et al., 2008; Paris et al., 2009; Tardito et al., 2011; Formigari et al., 2013; Gaetke et al., 2014).

Thus, data from experimental studies support the ROS-induced oxidative damage as the mode of action of copper toxicity. For example, lipid peroxidation, protein oxidation, decline in the mitochondrial membrane potential, and mitochondrial expulsion of cytochrome c, all preceding cell death, were reported following exposure to excess copper (Kumar et al., 2015). Also, rats fed high levels of dietary copper exhibited increased peroxidation of the mitochondrial membrane lipids as measured by increased levels of conjugated dienes and TBARS (Sokol et al., 1990). In addition, the formation of hydroxyl radical has been measured in bile of rats dosed with copper and ascorbic acid (Kadiiska et al., 1992).

Furthermore, neurotoxic endpoints observed at high doses could be explained by the production of ROS, such as release of a hydroxyl radical, a by-product of the monoamine oxidase metabolism (Eskici and Axelsen, 2012; Formigari et al., 2013; Govindaraju et al., 2013; Shaligram and Campbell, 2013; Zhao et al., 2013; Gaetke et al., 2014; Jazvinscak Jembrek et al., 2014; Montes et al., 2014). Also, the depletion of GSH reductase (which also depends on NADPH) and generation of hydroxyl radicals could also lead to haemolytic effects (IPCS, 1998; Grass et al., 2011). Furthermore, the methaemoglobinemia often observed in cases of acute copper poisoning may be a consequence of the direct oxidization of the haem iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form by copper (IPCS, 1998; Bradberry, 2007).

Other modes of action such as the direct interaction of copper with essential macromolecules and the displacement of cofactors from metalloenzymes have also been proposed. Thus, being a component of many metalloenzymes, it is also likely that high concentrations of copper can affect proteins containing sulfhydryl groups by directly interacting with macromolecules (e.g., DNA, biological membranes, proteins, etc.). The irreversible and non-specific binding of copper to sulfhydryl groups can alter the structure of macromolecules (e.g., GSH, monooxygenases, etc.) and inactivate them. This mode of action has been proposed to explain the haemolytic anemia and methaemoglobinemia observed following acute copper sulphate poisoning. Copper can enter red blood cells, where it can bind to sulfhydryl groups and inactivate glucose-6-phosphate dehydrogenase, which is essential for generating NADPH, an intermediate in the electron transfer chain (Pamp et al., 2005).

10.0 Classification and assessment

The current data are insufficient to classify copper with respect to carcinogenicity. The U.S. EPA (1988) has classified copper in Group D, not classifiable with respect to its carcinogenic risk to humans. The International Agency for Research on Cancer has not classified copper and its soluble salt (e.g., sulphate, chloride) with respect to carcinogenicity.

10.1 Non-cancer risk assessment

Copper is an essential element involved in many biological processes (e.g., as a component of metalloenzymes), however, both copper deficiency and overexposure can result in adverse effects. As discussed in section 9.1.1, copper deficiency and overexposure are rare in healthy Canadians consuming a balanced diet since homeostatic mechanisms regulate nutrient levels (Health Canada, 2011).

The health effects from copper exposure may be influenced by the medium of exposure. Copper in food is subject to liver's first-pass effect which can potentially reduce the systemic dose; free copper, the toxic moiety of concern in drinking water, may not be subject to such an effect which may significantly increase the internal dose (Brewer, 2009, 2014).

The database of human studies on health effects associated with ingested copper is large and contains adequate data for determining an acceptable concentration in drinking water. In general, short-term exposures results in GI tract effects, usually observed at copper levels greater than 3 mg/L water (see sections 9.1.3 and 9.1.4). Also, when considering the current evidence (mainly from animal and mechanistic studies) it appears that the primary effect from chronic overexposure is metal accumulation in the liver and kidneys, potentially leading to structural and biochemical damage (Linder and Hazegh-Azam, 1996; IPCS, 1998; Tapiero et al., 2003; Cockell et al., 2008).

Several randomized controlled studies have investigated the adverse health effects of copper exposure, although mostly in adults; the results from these studies indicate that short-term oral exposure to copper in drinking water while in a fasted state leads to GI effects (usually nausea, epigastric pain and vomiting combined, and diarrhea), which although transient, are the most sensitive clinical endpoints (Pizarro et al., 1999b; Araya et al., 2001, 2003a; Olivares et al., 2001). Nausea was the most frequently reported symptom generally occurring within 15 minutes following exposure; diarrhea was less frequently reported within the range of studied doses and women appeared to be more sensitive. In addition, the observed GI effects were found to disappear when exposure ceased suggesting an adaptive response with time (Araya et al., 2004). Furthermore, the results indicate that the concentration of copper (i.e., the bolus dose in water on an empty stomach divided by the dosing volume) is the primary determinant of the incidence of nausea (Araya et al., 2001, 2003a) and thus, with support from the data on the mode of action, is considered as the most appropriate dose metric for risk assessment. It is noteworthy, however, that although the above studies (except Araya et al., 2004) were conducted for up to 12 weeks, the exposure was not continuous and copper was consistently administered via single bolus dosing (using tap or distilled-deionized water) for short time periods (i.e., once/week) which may not accurately reflect the typical chronic low-dose drinking water exposure.

Although the long-term exposure to copper has not been extensively studied, limited results suggest an effect of time. Indeed, available data from drinking water exposure of adults for less than 3 months confirmed the results from short-term exposure studies (Araya et al., 2004). However, the results from adult supplementation studies suggest adverse health effects following exposure to high levels intakes over longer periods of time (over 5 months; Turnlund et al., 2004).

Subgroups identified as being vulnerable to chronic copper overexposure are individuals with copper-metabolism-related genetic disorders (such as WD patients), individuals with glucose-6-phosphate dehydrogenase deficiencies, children with childhood cirrhosis syndromes (ICC, ICT and TIC), and infants (less than one year-old). Of these subgroups, infants are considered the most vulnerable since they are likely to have the highest exposure due to the immaturity of their hepatobiliary system and their higher rates of copper absorption.

A randomized prospective study by Olivares et al. (1998) investigated the effects of copper exposure in breast- and formula-fed infants (3 to 12 months old) who ingested drinking water with high (31.48 µmol Cu(II)/L or 2 mg/L) or low (less than 1.57 µmol Cu(II)/L or 0.1 mg/L) copper levels (as Cu (II) sulphate) for nine months via different means of consumption (e.g., food, formula, drinking water). Clinical and biochemical findings were recorded at six, nine and twelve months of age. Both over the course of the study and upon study termination, the subjects presented no acute (i.e., cases of diarrhea or respiratory symptom) or chronic (i.e., differences in markers of liver function) clinical effects following exposure to drinking water containing 2 mg/L of copper (corresponding to a mean ± SD daily intake of 318.7 ± 107.3 µg/kg bw per day) when compared to controls.

The Olivares et al. (1998) study has been chosen as the critical study for deriving a proposed MAC since it was conducted in infants, involved continuous exposure to Cu(II) via drinking water for a longer period than studies in adults (usually up to three months), and took into account several temporal windows, including infants 4–6 months when the hepatobiliary system is still immature and gut absorption is greatest. Since formula-fed infants are expected to have the highest exposure to copper, the upper bound of the NOAEL, based on GI effects and liver function, for the formula-fed exposure sub-group (mean ± SD = 318.7 ± 107.3 µg/kg bw per day, experienced by 56 infants aged 4–6 months) was chosen as the point of departure; this upper bound dose (i.e., 426 µg/kg bw per day) represents the highest dose administered where no adverse effects were observed.

Although there are some uncertainties in the database for copper toxicity (including limited data on copper exposure in infants aged less than 6 months, limited data on the degree of variability in copper absorption among early age groups, as well as a lack of chronic exposure studies), the point of departure identified from Olivares et al. (1998) is considered conservative since no symptoms of copper toxicity were observed at this dose over the entire duration of the study (9 months); furthermore, due to the homeostatic regulation of copper absorption and excretion, the absorption of copper has been shown to decline as exposure to dietary copper increases (see section 8.1). As a result, an uncertainty factor accounting for database deficiencies is not warranted and thus 426 µg/kg bw per day is identified as the tolerable daily intake (TDI) for free copper.

A proposed MAC for total copper can be calculated as follows:

$$\begin{aligned} \text{MAC} &= \frac{426 \mu\text{g/kg bw per day} \times 7 \text{ kg} \times 0.5}{0.75 \text{ L/day}} \\ &= 1988 \mu\text{g/L} \\ &\approx 2000 \mu\text{g/L (2 mg/L)} \quad [\text{rounded}] \end{aligned}$$

where:

- 426 µg/kg bw per day is the TDI based on gastro-intestinal effects and liver function in formula-fed infants in the 9-month study by Olivares et al. (1998);
- 7 kg is the average body weight of an infant (0–6 months) (Health Canada, 1994);
- 0.5 is the allocation factor estimated for drinking water. Given that formula represents the total diet in non-breast fed infants for the first few months of life, both drinking water and formula represent the main sources of exposure and contributions from other sources are not expected to be significant for this age group (WHO, 1996). Thus allocating 50%

source contribution to drinking water is deemed appropriate since only two principal sources of exposure have been identified (Krishnan and Carrier, 2013) and the data for these exposure sources is highly variable; and

- 0.75 L/day is the estimated daily volume of tap water consumed by a bottle-fed infant in the 0–6 month age group (Health Canada, 1994).

The proposed MAC is considered to be protective of both short-term effects (i.e., GI effects) as well as longer-term effects (including potential effects in the liver and kidneys).

10.2 International considerations

This section presents drinking water guidelines and standards from other national and international organizations. Variations in these limits can be attributed to the age of the assessments or to differing policies and approaches, including the choice of key study and the use of different consumption rates, body weights and allocation factors.

The WHO (1993) set a provisional health-based guideline value of 2 mg/L for copper in drinking water from a provisional maximum tolerable daily intake (PMTDI) of 0.5 mg/kg proposed by JECFA in 1982 and an allocation factor of 10% of the PMTDI to drinking water. The PMTDI was based on liver toxicity, observed in an industry-funded study in dog (Shanaman et al., 1972) and the guideline was deemed provisional due to the uncertainties related to copper toxicity in humans (WHO, 1996). However, from an assessment conducted in 2003, the WHO maintained the value of 2 mg/L stated that it was based ‘to be protective against acute GI effects of copper and provide an adequate margin of safety in population with normal copper homeostasis’ (WHO, 2011). In 2004, the guideline value of 2 mg/L was confirmed, but was no longer provisional based on (Olivares et al., 1998, 2001; Pizarro et al., 1999b, 2001; Araya et al., 2001; Zietz et al., 2003b).

The U.S. Environmental Protection Agency (U.S. EPA, 1991) has set the maximum contaminant level goal (MCLG) and maximum contaminant level (MCL) for copper in drinking water at 1.3 mg/L. The U.S. EPA’s MCLG for copper was based on adverse gastrointestinal tract effects following acute exposure and was derived from a case study of nurses who consumed an alcoholic beverage that was stored in copper containers (Wyllie, 1957). A secondary Maximum Contaminant Level (SMCL) for copper has been established at 1 mg/L based on aesthetic considerations (taste and blue/green staining). However, the U.S. EPA regulates levels of copper through the Lead and Copper Rule (U.S. EPA, 1991, 2000), a treatment based rule, which established an action level of 1.3 mg/L for copper in drinking water. Large water systems (with more than 50,000 connections), unless determined to be non-corrosive, are required to install “optimal corrosion control treatment” and meet specified water quality operating limits requirements. If the 90th percentile of copper concentrations in samples taken at customer taps at sites distributed with a specified prioritization (first-draw samples that have stagnated for at least 6 hours) exceeds the action level of 1.3 mg/L, the system must undertake a number of additional actions to control corrosion and provide public education. The number of sites, frequency of monitoring and scope of required actions vary with system size. Currently, a major revision of the Lead and Copper Rule is under way, but is not expected to be finalized until after 2017.

The California EPA (OEHHA, 2008) has developed a non-regulatory public health goal of 0.3 mg/L for copper in drinking water, based on infants as a sensitive population and is “believed adequate to protect against any adverse acute or chronic effects” from copper exposure. This goal was based on the absence of an adverse effect in the Olivares et al. (1998)

clinical study of infants exposed to copper in drinking water, and took into consideration “data from other studies on GI effects as the key endpoint” .

The Australian Drinking Water Guidelines has set two levels for copper: 1 mg/L for aesthetics to prevent taste and staining problems; and 2 mg/L to prevent health issues (NHMRC, 2011).

11.0 Rationale

Copper is an essential nutrient that occurs naturally in the Earth’s crust, either in mineral deposits or, less frequently, in its metallic form. The U.S National Academy of Medicine (formerly called the Institute of Medicine) has established both recommended daily intakes and tolerable upper intake levels for copper.

Copper is used in a wide range of products, including as a result of it being a component of bronze and brass, and is considered by the National Plumbing Code of Canada to be an acceptable material for service lines and plumbing systems. The main anthropogenic sources of copper in the environment include mining, agricultural run-off, waste management and water treatment.

Canadians are mainly exposed to copper through the ingestion of food, drinking water and nutritional supplements. International agencies have determined that the data available on copper are not sufficient to classify it with respect to carcinogenicity. Health effects can be associated with both copper deficiency, and to exposure to copper at levels much higher than the recommended daily intake. Copper deficiency is not considered to be a concern in Canada.

A maximum acceptable concentration (MAC) of 2 mg/L (2000 µg/L) is proposed for total copper in drinking water. The proposed MAC is considered to be protective of both short-term effects (i.e., GI effects) as well as longer-term effects (including potential effects in the liver and kidneys). The proposed MAC is achievable by available treatment technology and measurable by available analytical methods. However, because copper is generally found in drinking water as a result of leaching in the distribution and plumbing systems, strategies for reducing exposure to copper from drinking water should focus on corrosion control through approaches such as water quality adjustments and the use of corrosion inhibitors.

As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change to the guideline that it deems necessary.

12.0 References

- Abe, M., Suzuki, N., Yoshida, M., Usuda, K., Furukawa, S., Juneja, L.R., Okubo, T. and Nakae, D. (2008). Possible carcinogenic risks of copper gluconate and their prevention by co-administered green tea catechins evaluated by a rat medium-term multi-organ carcinogenicity bioassay protocol. *Food Chem.Toxicol.*, 46(5): 1760–1770.
- Aburto, E.M., Cribb, A.E., Fuentealba, I.C., Ikede, B.O., Kibenge, F.S. and Markham, F. (2001). Morphological and biochemical assessment of the liver response to excess dietary copper in fischer 344 rats. *Can. J. Vet. Res.*, 65(2): 97–103.
- Aggett, P.J. (1999). An overview of the metabolism of copper. *Eur. J. Med. Res.* 4: 214–216. [As cited in EFSA, 2006].
- Ala, A., Walker, A.P., Ashkan, K., Dooley, J.S. and Schilsky, M.L. (2007). Wilson's disease. *The Lancet*, 369(9559): 397–408.

APHA, AWWA and WEF (1992). Standard methods for the examination of water and wastewater. 18th edition supplement. American Public Health Association, American Water Works Association, and Water Environment Federation, Washington, DC.

APHA, AWWA and WEF (1995). Standard methods for the examination of water and wastewater. 19th edition. Association, American Water Works Association, and Water Environment Federation, Washington, DC.

APHA, AWWA and WEF (1999). Standard methods for the examination of water and wastewater. online. American Public Health Association, American Water Works Association, and Water Environment Federation, Washington, DC.

APHA, AWWA and WEF (2004). Standard methods for the examination of water and wastewater. online. American Public Health Association, American Water Works Association, and Water Environment Federation, Washington, DC.

APHA, AWWA and WEF (2005). Standard methods for the examination of water and wastewater. 21st edition. American Public Health Association, American Water Works Association, and Water Environment Federation, Washington, DC.

APHA, AWWA and WEF (2010). Standard methods for the examination of water and wastewater. online. American Public Health Association, American Water Works Association, and Water Environment Federation, Washington, DC.

APHA, AWWA and WEF (2012). Standard methods for the examination of water and wastewater. 22nd edition. American Public Health Association, American Water Works Association, and Water Environment Federation, Washington, DC.

Araya, M., McGoldrick, M.C., Klevay, L.M., Strain, J.J., Robson, P., Nielsen, F., Olivares, M., Pizarro, F., Johnson, L.A. and Poirier, K.A. (2001). Determination of an acute no-observed-adverse-effect level (NOAEL) for copper in water. *Regul. Toxicol. Pharmacol.*, 34(2): 137–145.

Araya, M., Chen, B., Klevay, L.M., Strain, J.J., Johnson, L., Robson, P., Shi, W., Nielsen, F., Zhu, H., Olivares, M., Pizarro, F. and Haber, L.T. (2003a). Confirmation of an acute no-observed-adverse-effect and low-observed-adverse-effect level for copper in bottled drinking water in a multi-site international study. *Regul. Toxicol. Pharmacol.*, 38(3): 389–399.

Araya, M., Olivares, M., Pizarro, F., Gonzalez, M., Speisky, H. and Uauy, R. (2003b). Gastrointestinal symptoms and blood indicators of copper load in apparently healthy adults undergoing controlled copper exposure. *Am. J. Clin. Nutr.*, 77(3): 646–650.

Araya, M., Olivares, M., Pizarro, F., Llanos, A., Figueroa, G. and Uauy, R. (2004). Community-based randomized double-blind study of gastrointestinal effects and copper exposure in drinking water. *Environ. Health Perspect.*, 112(10): 1068–1073.

Araya, M., Kelleher, S.L., Arredondo, M.A., Sierralta, W., Vial, M.T., Uauy, R. and Lonnerdal, B. (2005a). Effects of chronic copper exposure during early life in rhesus monkeys. *Am. J. Clin. Nutr.*, 81(5): 1065–1071.

Araya, M., Olivares, M., Pizarro, F., Mendez, M.A., Gonzalez, M. and Uauy, R. (2005b). Supplementing copper at the upper level of the adult dietary recommended intake induces detectable but transient changes in healthy adults. *J. Nutr.*, 135(10): 2367–2371.

Araya, M., Núñez, H., Pavez, L., Arredondo, M., Méndez, M., Cisternas, F., Pizarro, F., Sierralta, W., Uauy, R. and González, M. (2012). Administration of high doses of copper to capuchin monkeys does not cause liver damage but induces transcriptional activation of hepatic proliferative responses. *J. Nutr.*, 142(2): 233–237.

Arens, P., Tuschewitzki, G-J., Follner, H., Jacobi, H., and Leuner, S. (1996). Experiments for stimulating microbiologically induced corrosion of copper pipes in a cold-water plumbing system. *Materials and Corrosion*, 47: 96–102.

- Arnold, R.B., Griffin, A. and Edwards, M. (2012). Controlling copper corrosion in new construction by organic matter removal. *J. Am. Water Works Assoc.*, 104(5): E310-E317.
- ASTM (1995). ASTM D1688-95 Standard test methods for copper in water. ASTM International, West Conshohocken, Pennsylvania.
- ASTM (2002). ASTM D1688-02 Standard test method for copper in water. ASTM International, West Conshohocken, Pennsylvania.
- ASTM (2007). ASTM D1688-07 Standard test method for copper in water. ASTM International, West Conshohocken, Pennsylvania.
- ASTM (2012). ASTM D1688-12 Standard test method for copper in water. ASTM International, West Conshohocken, Pennsylvania.
- Atlas, D., Coombs, J. and Zajcek, O.T. (1982). The corrosion of copper by chlorinated drinking waters. *Water Res.*, 16: 693–698.
- ATSDR (2004). Toxicological profile for copper. Agency for Toxic Substances and Disease Registry. U.S. Department of Health and Human Services. Public Health Service. Atlanta, Georgia.
- Bancroft, D.A. (1988). Corrosion control program in Danvers, Massachusetts. *J. N. Engl. Water Works Assoc.*, 102(3): 163–171.
- Bandmann, O., Weiss, K.H. and Kaler, S.G. (2015). Wilson's disease and other neurological copper disorders. *Lancet Neurol.*, 14(1): 103–113.
- Barceloux, D.G. (1999). Copper. *J. Toxicol. Clin. Toxicol.*, 37(2): 217–230.
- Barn, P., Nicol, A.M., Struck, S., Dosanjh, S., Li, R. and Kosatsky, T. (2014). Investigating elevated copper and lead levels in school drinking water. *Environ. Health Rev.*, 56(4): 96–102.
- Bauerly, K.A., Kelleher, S.L. and Lonnerdal, B. (2005). Effects of copper supplementation on copper absorption, tissue distribution, and copper transporter expression in an infant rat model. *Am. J. Physiol. Gastrointest. Liver Physiol.*, 288(5): G1007–14.
- Becker, A. (2002). The effect of corrosion inhibitors in drinking water installations of copper. *Mater. Corros.*, 53: 560–567.
- Berg, R., Lundh, S., Jansson, G. and Rappe, A. (1981). Copper contamination of drinking water as a cause of diarrhea in children. *Halsovardskontakt* 1:6-10. [as cited in OEHHA, 2008]
- Berghult, B., Hedberg, T. and Broo, A.E. (1999). Drinking water distribution: corrosion control in Swedish municipalities. *J. Water Supply Res. Technol. – Aqua*, 48(2): 44–52.
- Berghult, B., Broo, A.E. and Hedberg, T. (2001). Corrosion control measures in Sweden and the effect of succession order. *Water Sci. Technol. Water Supply*, 1(3): 47–58
- Bertinato, J. and L'Abbe, M.R. (2004). Maintaining copper homeostasis: Regulation of copper-trafficking proteins in response to copper deficiency or overload. *J. Nutr. Biochem.*, 15(6): 316–322.
- Bertinato, J., Sherrard, L. and Plouffe, L.J. (2010). Decreased erythrocyte CCS content is a biomarker of copper overload in rats. *Int. J. Mol. Sci.*, 11(7): 2624–2635.
- Bhandari, P. and Andrews, P.L. (1991). Preliminary evidence for the involvement of the putative 5-HT₄ receptor in zacopride- and copper sulphate-induced vomiting in the ferret. *Eur. J. Pharmacol.*, 204(3): 273–280.
- Boal, A.K. and Rosenzweig, A.C. (2009). Structural biology of copper trafficking. *Chem. Rev.*, 109(10): 4760–4779.

- Boffardi, B.P. (1993). The chemistry of polyphosphate. *Mater. Perform.*, 8: 50–53
- Boireau, A., Benezet-Toulze, M., Randon, G. and Cavard, J. (1997). Limitation de la solubilisation du plomb par ajout de produit filmogène. Transposition d'une étude sur pilote à un réseau réel. *Tech. Sci. Meth. Gen. Urbain Gen. Rural*, 92(5): 63–72.
- Boulay, N. and Edwards, M. (2001). Role of temperature, chlorine, and organic matter in copper corrosion byproduct release in soft water. *Water Res.*, 35(3): 683–690.
- Boveris, A., Musacco-Sebio, R., Ferrarotti, N., Saporito-Magrina, C., Torti, H., Massot, F. and Repetto, M.G. (2012). The acute toxicity of iron and copper: Biomolecule oxidation and oxidative damage in rat liver. *J. Inorg. Biochem.*, 116: 63–69.
- Boyd, G.R., McFadden, M.S., Reiber, S.H., Sandvig, A.M., Korshin, G.V., Giani, R. and Frenkel, A.I. (2010). Effects of changing disinfectants on distribution system lead and copper release: Part 2—research results. Water Research Foundation, Denver, Colorado.
- Bradberry, S. (2007). Copper. Poisoning part 2 of 3. *Medicine*, 35(11): 608.
- Bremer, P., Webster, B.J. and Wells, D.B. (2001). Biocorrosion of copper in potable water. *J. Am. Water Works Assoc.*, 93(8): 82–91.
- Bremner, I. (1998). Manifestations of copper excess. *Am. J. Clin. Nutr.*, 67(5 Suppl): 1069S-1073S.
- Brenner, I.B. and Zander, A.T. (2000). Axially and radially viewed inductively coupled plasmas – a critical review. *Spectrochimica Acta Part B: Atomic Spectroscopy*, 55(8): 1195–1240.
- Brenner, S. (2003). Elevation of serum copper levels in Alzheimer's disease. *Neurology*, 60(9): 1559; author 1559.
- Brewer, G.J. (2009). The risks of copper toxicity contributing to cognitive decline in the aging population and to Alzheimer's disease. *J. Am. Coll. Nutr.*, 28(3): 238–242.
- Brewer, G.J. (2010). Copper toxicity in the general population. *Clin. Neurophysiol.*, 121(4): 459-460.
- Brewer, G.J. (2014). Alzheimer's disease causation by copper toxicity and treatment with zinc. *Front. Aging Neurosci.*, 6: 92.
- British Geological Survey (2016). World mineral production 2010-2014. Natural Environmental Research Council (NERC). ISBN 978-0-85272-856-7 (print version). ISBN 978-0-85272-857-4 (website version).
- Broo, A.E., Berghult, B. and Hedberg, T. (1997). Copper corrosion in drinking water distribution systems—The influence of water quality. *Corros. Sci.*, 39(6): 1119–1132.
- Broo, A.E., Berghult, B. and Hedberg, T. (1998). Copper corrosion in water distribution systems—The influence of natural organic matter (NOM) on the solubility of copper corrosion products. *Corros. Sci.*, 40(9): 1479–1489.
- Broo, A.E., Berghult, B. and Hedberg, T. (1999). Drinking water distribution—The effect of natural organic matter (NOM) on the corrosion of iron and copper. *Water Sci. Technol.*, 40(9): 17–24.
- Burkitt, M.J. (2001). A critical overview of the chemistry of copper-dependent low density lipoprotein oxidation: Roles of lipid hydroperoxides, alpha-tocopherol, thiols, and ceruloplasmin. *Arch. Biochem. Biophys.*, 394(1): 117–135.
- Burleigh, T.D., Gierke, C.G., Fredy, N. and Boston, P.J. (2014). Copper tube pitting in Sante Fe municipal water caused by microbial induced corrosion. *Materials*, 7:4321–4334.
- Bush, A.I., Masters, C.L. and Tanzi, R.E. (2003). Copper, beta-amyloid, and Alzheimer's disease: Tapping a sensitive connection. *Proc. Natl. Acad. Sci. U. S. A.*, 100(20): 11193–11194.

Butler Walker, J., Houseman, J., Seddon, L., McMullen, E., Tofflemire, K., Mills, C., Corriveau, A., Weber, J., LeBlanc, A., Walker, M., Donaldson, S.G. and Van Oostdam, J. (2006). Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in arctic Canada. *Environ. Res.*, 100(3): 295–318.

Camakaris, J., Voskoboinik, I. and Mercer, J.F. (1999). Molecular mechanisms of copper homeostasis. *Biochem. Biophys. Res. Commun.*, 261(2): 225–232.

Campbell, H.S. (1954a). The influence of the composition of supply waters, especially of traces of natural inhibitor on pitting corrosion of copper water pipes. *Proc. Soc. Water Treat. Exam.*, 3: 100–117.

Campbell, H.S. (1954b). A natural inhibitor of pitting corrosion of copper in tap waters. *J. Appl. Chem.*, 4: 633–647.

Campbell, H.S. (1971). Corrosion, water composition and water treatment. *Proc. Soc. Water Treat. Exam.*, 20: 11–34.

Campbell, H.S. and Turner, M.E.D. (1983). The influence of trace organics on scale formation and corrosion. *J. Inst. Water Eng. Sci.*, 37(1): 55–72.

Cantor, A.F., Denig-Chakroff, D., Vela, R.R., Oleinik, M.G. and Lynch, D.L. (2000). Use of polyphosphate in corrosion control. *J. Am. Water Works Assoc.*, 92(2): 95–102.

Cantor, A.F., Park, J.K. and Vaiyavatjamai, P. (2003). Effect of chlorine on corrosion. *J. Am. Water Works Assoc.*, 95(5): 112–123.

Carmichael, P.L., Hewer, A., Osborne, M.R., Strain, A.J. and Phillips, D.H. (1995). Detection of bulky DNA lesions in the liver of patients with Wilson's disease and primary haemochromatosis. *Mutat. Res.*, 326(2): 235–243.

Cartier, C., Doré, E., Laroche, L., Nour, S., Edwards, M. and Prévost, M. (2013). Impact of treatment on Pb release from full and partially replaced lead service lines (LSLs). *Water Res.*, 47(2): 661–671.

Cavallo, F., Gerber, M., Marubini, E., Richardson, S., Barbieri, A., Costa, A., DeCarli, H. and Pujol, A. (1991). Zinc and copper in breast cancer: A joint study in Northern Italy and Southern France. *Cancer*, 67: 738–745. [as cited in IPCS, 1998].

CCME (1999). Copper. Canadian soil quality guidelines for the protection of environmental and human health. Canadian environmental quality guidelines. Canadian Council of Ministers of the Environment.

Cech, I., Smolensky, M.H., Afshar, M., Broyles, G., Barczyk, M., Burau, K. and Emery, R. (2006). Lead and copper in drinking water fountains--information for physicians. *South. Med. J.*, 99(2): 137–142.

Ceko, M.J., Aitken, J.B. and Harris, H.H. (2014). Speciation of copper in a range of food types by X-ray absorption spectroscopy. *Food Chem.*, 164: 50–54.

Chambers, A., Krewski, D., Birkett, N., Plunkett, L., Hertzberg, R., Danzeisen, R., Aggett, P.J., Starr, T.B., Baker, S., Dourson, M., Jones, P., Keen, C.L., Meek, B., Schoeny, R. and Slob, W. (2010). An exposure-response curve for copper excess and deficiency. *J. Toxicol. Environ. Health B Crit. Rev.*, 13(7–8): 546–578.

Churchill, D.M., Mavinic, D.S., Neden, D.G. and MacQuarrie, D.M. (2000). The effect of zinc orthophosphate and pH-alkalinity adjustment on metal levels leached into drinking water. *Can. J. Civil Eng.*, 27(6): 33–43.

Clark, B., Masters, S. and Edward, M. (2014). Profile sampling to characterize particulate lead risks in potable water. *Environ. Sci. Technol.*, 48(12): 6836–6843. doi: 10.1021/es501342j

Clark, B., St. Clair, J. and Edwards, M. (2015). Copper deposition corrosion elevates lead release to potable water. *J. Am. Water Works Assoc.*, 107(11): E627–E637.

Clement, J.A., Daly, W.J., Shorney, H.J., and Capuzzi, A.J., (1998). An innovative approach to understanding and improving distribution system water quality. In: Proceedings of the 1998 AWWA Water Quality Technology Conference, San Diego, CA. American Water Works Association, Denver, Colorado.

- Clifford, D.A. (1999). Ion exchange and inorganic adsorption. Chapter 9 in: Letterman, R.D.(ed). Water quality and treatment: a handbook of community water supplies. 5th edition American Water Works Association. Denver, Colorado. McGraw-Hill, New York, New York.
- Clifford, D., Sorg, T. and Ghurye, G. (2011). Ion exchange and adsorption of inorganic contaminants. Chapter 12 in: Edzwald, J.K. (ed.). Water quality and treatment: a handbook of community water supplies. 6th edition. American Water Works Association, Denver, Colorado. McGraw-Hill, New York, New York.
- Coates, R.J., Weiss, N.S., Daling, J.R., Rettmer, R.L. and Warnick, G.R. (1989). Cancer risk in relation to serum copper levels. *Cancer Res.*, 49(15): 4353–4356.
- Cockell, K.A., Bertinato, J. and L'Abbe, M.R. (2008). Regulatory frameworks for copper considering chronic exposures of the population. *Am. J. Clin. Nutr.*, 88(3): 863S–866S.
- Codina, J.C., Perez-Torrente, C., Perez-Garcia, A., Cazorla, F.M. and de Vicente, A. (1995). Comparison of microbial tests for the detection of heavy metal genotoxicity. *Arch. Environ. Contam. Toxicol.*, 29(2): 260–265.
- Collins, J.F. and Klevay, L.M. (2011). Copper. *Adv. Nutr.*, 2(6): 520–522.
- Corkins, M.R. (2011). Copper metabolism and pediatric cholestasis. *Curr. Opin. Clin. Nutr. Metab. Care*, 14(6): 642–646.
- Critchley, M.M., Cromar, N.J., McClure, N.C. and Fallowfield, H.J. (2003). The influence of the chemical composition of drinking water on cuprosolvency by biofilm bacteria. *J. of Appl. Microbiol.*, 94:501–507.
- Critchley, M., Pasetto, R. and O'Halloran, R.J. (2004). Microbiological influences in 'blue water' copper corrosion. *J. of Appl. Microbiol.*, 97:590–597.
- Cuppett, J.D., Duncan, S.E. and Dietrich, A.M. (2006). Evaluation of copper speciation and water quality factors that affect aqueous copper tasting response. *Chem. Senses*, 31(7): 689–697.
- Custalow, B.D. (2009). Influences of water chemistry and flow conditions on non-uniform corrosion in copper tube. Virginia Polytechnic Institute and State University, Blacksburg, VA (Master's thesis).
- Dabek, J.T., Hyvonen-Dabek, M., Harkonen, M. and Adlercreutz, H. (1992). Evidence for increased non-ceruloplasmin copper in early-stage human breast cancer serum. *Nutr Cancer*, 17: 195–201. [as cited in IPCS, 1998].
- Dabioch, M., Storek, R., Kita, A., Janoska, P., Pytlakowska, K., Zerzucha, P. and Sitko, R. (2013). A study on adsorption of metals by activated carbon I a large-scale(municipal) process of surface water purification. *Central European Journal of Chemistry*, 11(5):742–753.
- Das, S.K. and Ray, K. (2006). Wilson's disease: An update. *Nat. Clin. Pract. Neurol.*, 2(9): 482–493.
- Davidson, D., Beheshti, B. and Mittelman, M.W. (1996). Effects of arthrobacter sp., acidovorax delafieldii, and bacillus megaterium colonisation on copper solvency in a laboratory setting. *Biofouling*, 9(4):279–292.
- de Romana, D.L., Olivares, M., Uauy, R. and Araya, M. (2011). Risks and benefits of copper in light of new insights of copper homeostasis. *J. Trace Elem. Med. Biol.*, 25(1): 3–13.
- De Vries, D.J., Sewell, R.B. and Beart, P.M. (1986). Effects of copper on dopaminergic function in the rat corpus striatum. *Exp. Neurol.*, 91(3): 546–558.
- Dodrill, D.M. and Edwards, M. (1995). Corrosion control on the basis of utility experience. *J. Am. Water Works Assoc.*, 87(7): 74–85.
- Donnelly, P.S., Xiao, Z. and Wedd, A.G. (2007). Copper and Alzheimer's disease. *Bioinorganic chemistry / biocatalysis and biotransformation. Curr. Opin. Chem. Biol.*, 11(2): 128–133.

- Dudi, A. (2004). Galvanic corrosion of lead bearing plumbing devices. In: Reconsidering lead corrosion in drinking water: Product testing, direct chloramine attack and galvanic corrosion. Faculty of the Virginia Polytechnic Institute and State University, Blacksburg, VA. pp. 69–105 (Master's Thesis).
- Dudi, A., Schock, M., Murray, N. and Edwards, M. (2005). Lead leaching from inline brass devices: a critical evaluation of the existing standard. *J. Am. Water Works Assoc.*, 97(8): 66–78.
- Dutkiewicz, C. and Fallowfield, H. (1998). Assessment of microbial involvement in the elevation of copper levels in drinking water. *J. Appl. Microbiol.*, 85:597-602.
- Edwards, M. and Ferguson, J.F. (1993). Accelerated testing of copper corrosion. *J. Am. Water Works Assoc.*, 85(10): 105–113.
- Edwards, M. and McNeill, L.S. (2002). Effect of phosphate inhibitors on lead release from pipes. *J. Am. Water Works Assoc.*, 94(1): 79–90.
- Edwards, M. and Sprague, N. (2001). Organic matter and copper corrosion by-product release: a mechanistic study. *Corros. Sci.*, 43(1): 1–18.
- Edwards, M. and Triantafyllidou, S. (2010). Chloride-to-sulphate mass ratio and lead leaching to water. *J. Am. Water Works Assoc.*, 99(7): 96–109.
- Edwards, M., Ferguson, J.F. and Reiber, S.H. (1994a). The pitting corrosion of copper. *J. Am. Water Works Assoc.*, 86(7): 74–90.
- Edwards, M., Meyer, T.E. and Rehring, J.P. (1994b). Effect of selected anions on copper corrosion rates. *J. Am. Water Works Assoc.*, 86(12): 73–81.
- Edwards, M., Schock, M.R. and Meyer, T.E. (1996). Alkalinity, pH, and copper corrosion by-product release. *J. Am. Water Works Assoc.*, 88(3): 81–94.
- Edwards, M., Jacobs, S. and Dodrill, D.M. (1999). Desktop guidance for mitigating Pb and Cu corrosion by-products. *J. Am. Water Works Assoc.*, 91(5): 66–77.
- Edwards, M., Jacobs, S. and Taylor, R.J. (2000). The blue water phenomenon. *J. Am. Water Works Assoc.*, 92(7): 72–82.
- Edwards, M., Powers, K., Hidmi, L. and Schock, M.R. (2001). The role of pipe ageing in copper corrosion by-product release. *Water Sci. Tech.*, 1(3):25–32.
- Edwards, M., Hidmi, L. and Gladwell, D. (2002). Phosphate inhibition of soluble copper corrosion by-product release. *Corros. Sci.*, 44(5): 1057–1071.
- Edzwald, J.K. and Tobiason, J.E. (2011). Chemical principles, source water composition, and watershed protection. Chapter 3 in: *Water quality and treatment: A handbook on drinking water*, 6th edition. Edzwald, J.K. (ed.). American Water Works Association, Denver, Colorado; McGraw-Hill, New York, New York.
- EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food. Scientific panel on dietetic products, nutrition and allergies. European Food Safety Authority. ISBN: 92-9199-014-0.
- EFSA (2009). Scientific opinion of the panel on food additives and nutrient sources added to food on copper(II) oxide as a source of copper added for nutritional purposes to food supplements following a request from the European commission. *EFSA Journal*, 1089:1–15.
- EFSA (2015). EFSA NDA panel (EFSA panel on dietetic products, nutrition and allergies). scientific opinion on dietary reference values for copper. *EFSA journal*, 13(10): 4253, 51 pp.

- Ellingsen, D.G., Horn, N. and Aaseth, J. (2007). Chapter 26 - essential metals: Assessing risks from deficiency and toxicity. In: Handbook on the toxicology of metals. Nordberg, G.F., Fowler, B.A., Nordberg, M. and Friberg, L.T. (eds.). 3rd. Academy Press, San Diego, pp. 163–176.
- Ellingsen, D.G., Møller, L.B. and Aaseth, J. (2015). Chapter 35 - copper. In: Handbook on the toxicology of metals (fourth edition). Nordberg, G.F.N.A.F. (ed.). 3rd edition. Academic Press, San Diego, California. pp. 765–786.
- Environment Canada (2014). National air pollution surveillance network (NAPS) monitoring results: NAPS quality assured data products.
- Eskici, G. and Axelsen, P.H. (2012). Copper and oxidative stress in the pathogenesis of Alzheimer's disease. *Biochemistry*, 51(32): 6289–6311.
- FAO and WHO (2011). Standard for infant formula and formulas for special medical purposes intended for infants. CODEX STAN 72-1981. formerly CAC/RS 72-1972. Adopted as a Worldwide Standard in 1981. Amendment: 1983, 1985, 1987, 2011 and 2015. Revision: 2007. Codex Alimentarius. Food and Agriculture Organization of the United Nations. World Health Organization.
- Ferguson, J.F., Franqué, O.V. and Schock, M.R. (1996). Corrosion of copper in potable water systems. In: Internal corrosion of water distribution systems. 2nd edition. American Water Works Association Research Foundation and DVGW Technologiezentrum Wasser. Denver, Colorado. pp. 231–268.
- Fewtrell, L., Kay, D., Jones, F., Baker, A. and Mowat, A. (1996). Copper in drinking water--an investigation into possible health effects. *Public Health*, 110(3): 175–177.
- Fischer, W., Paradies, H.H., Wagner, D. and Hänßel, I. (1992). Copper deterioration in a water distribution system of a county hospital in Germany caused by microbially induced corrosion- I. Description of the problem. *Werkstoffe und Korrosion*, 43:56–62.
- Formigari, A., Gregianin, E. and Irato, P. (2013). The effect of zinc and the role of p53 in copper-induced cellular stress responses. *J. Appl. Toxicol.*, 33(7): 527–536.
- Friedman, M.J., Hill, A.S., Reiber, S.H., Valentine, R.L., Larsen, G., Young, A., Korshin, G.V. and Peng, C-Y. (2010). Assessment of inorganics accumulation in drinking water system scales and sediments. Water Research Foundation and United States Environmental Protection Agency. Denver, Colorado.
- Fuentealba, I. and Haywood, S. (1988). Cellular mechanisms of toxicity and tolerance in the copper-loaded rat. I. ultrastructural changes in the liver. *Liver*, 8(6): 372–380.
- Fuentealba, I., Haywood, S. and Foster, J. (1989a). Cellular mechanisms of toxicity and tolerance in the copper-loaded rat. II. pathogenesis of copper toxicity in the liver. *Exp. Mol. Pathol.*, 50(1): 26–37.
- Fuentealba, I.C., Haywood, S. and Foster, J. (1989b). Cellular mechanisms of toxicity and tolerance in the copper-loaded rat. III. ultrastructural changes and copper localization in the kidney. *Br. J. Exp. Pathol.*, 70(5): 543–556.
- Fuentealba, I.C., Mullins, J.E., Aburto, E.M., Lau, J.C. and Cherian, G.M. (2000). Effect of age and sex on liver damage due to excess dietary copper in fischer 344 rats. *J. Toxicol. Clin. Toxicol.*, 38(7): 709–717.
- Fujiwara, N., Iso, H., Kitanaka, N., Kitanaka, J., Eguchi, H., Ookawara, T., Ozawa, K., Shimoda, S., Yoshihara, D., Takemura, M. and Suzuki, K. (2006). Effects of copper metabolism on neurological functions in wistar and Wilson's disease model rats. *Biochem. Biophys. Res. Commun.*, 349(3): 1079–1086.
- Fukui, H., Yamamoto, M., Sasaki, S. and Sato, S. (1994). Possible involvement of peripheral 5-HT₄ receptors in copper sulfate-induced vomiting in dogs. *Eur. J. Pharmacol.*, 257(1–2): 47–52.
- Gaetke, L.M. and Chow, C.K. (2003). Copper toxicity, oxidative stress, and antioxidant nutrients. *Toxicology*, 189(1–2): 147–163.

- Gaetke, L.M., Chow-Johnson, H.S. and Chow, C.K. (2014). Copper: Toxicological relevance and mechanisms. *Arch. Toxicol.*, 88(11): 1929–1938.
- Gaggelli, E., Kozlowski, H., Valensin, D. and Valensin, G. (2006). Copper homeostasis and neurodegenerative disorders (Alzheimer's, prion, and Parkinson's diseases and amyotrophic lateral sclerosis). *Chem. Rev.*, 106(6): 1995–2044.
- Gambling, L., Kennedy, C. and McArdle, H.J. (2011). Iron and copper in fetal development. *Semin. Cell Dev. Biol.*, 22(6): 637–644.
- Georgopoulos, P.G., Roy, A., Yonone-Lioy, M.J., Opiekun, R.E. and Lioy, P.J. (2001). Environmental copper: Its dynamics and human exposure issues. *J. Toxicol. Environ. Health B Crit. Rev.*, 4(4): 341–394.
- Gerke, T.L., Little, B.J. and Maynard, B. (2016). Manganese deposition in drinking water distribution systems. *Science of the Total Environment*, 541:184–193.
- Gibson, R.S. (1994). Content and bioavailability of trace elements in vegetarian diets. *Am. J. Clin. Nutr.*, 59(5 Suppl): 1223S–1232S.
- Gitlin, J.D. (2014). Copper homeostasis: Specialized functions of the late secretory pathway. *Dev. Cell.*, 29(6): 631–632.
- Govindaraju, M., Shekar, H.S., Sateesha, S.B., Vasudeva Raju, P., Sambasiva Rao, K.R., Rao, K.S.J. and Rajamma, A.J. (2013). Copper interactions with DNA of chromatin and its role in neurodegenerative disorders. *J. Pharm. Anal.*, 3(5): 354–359.
- Grace, S., Lytle, D.A. and Goltz, M.N. (2012). Control of new copper corrosion in high-alkalinity drinking water. *J. Am. Water Works Assoc.* 104(1), E15–E25.
- Grass, G., Rensing, C. and Solioz, M. (2011). Metallic copper as an antimicrobial surface. *Appl. Env. Microbiol.*, 77(5): 1541–1547.
- Gulliver, J.M. (1991). A fatal copper sulfate poisoning. *J. Anal. Toxicol.*, 15(6): 341–342.
- Gurusamy, K. and Davidson, B.R. (2007). Trace element concentration in metastatic liver disease – A systematic review. *J. Trace Elem. Med. Biol.*, 21(3): 169–177.
- Ha, H.M. and Scully, J.R. (2013). Effects of phosphate on pit stabilization and propagation in copper in synthetic potable waters. *Corrosion*, 69(7): 703–718.
- Haas, C., Koch, L., Kelty, K., Lytle, D. and Triantafyllidou, S. (2013). Effectiveness of the preservation protocol within the Environmental Protection Agency (EPA) Method 200.8 for soluble and particulate lead recovery in drinking water. U.S. Environmental Protection Agency, Washington, D.C. (EPA/600/R-13/222).
- Hach (2014). Hach 8026 (CuVer2). Bicinchoninate Method. 9th Edition. Hach Company, Loveland, Colorado.
- Hach (2016). Hach 10272 Copper Bicinchoninate Method. 5th Edition. Hach Company, Loveland, Colorado.
- Harris, Z.L. and Gitlin, J.D. (1996). Genetic and molecular basis for copper toxicity. *Am. J. Clin. Nutr.*, 63(5): 836S–841S.
- Harvey, L.J., Dainty, J.R., Hollands, W.J., Bull, V.J., Beattie, J.H., Venelinov, T.I., Hoogewerff, J.A., Davies, I.M. and Fairweather-Tait, S.J. (2005). Use of mathematical modeling to study copper metabolism in humans. *Am. J. Clin. Nutr.*, 81(4): 807–813.
- Haywood, S. (1980). The effect of excess dietary copper on the liver and kidney of the male rat. *J. Comp. Pathol.*, 90(2): 217–232.

- Haywood, S. (1985). Copper toxicosis and tolerance in the rat: I. Changes in copper content of the liver and kidney. *J. Pathol.*, 145(2): 149–158.
- Haywood, S. and Loughran, M. (1985). Copper toxicosis and tolerance in the rat: II. Tolerance--a liver protective adaptation. *Liver*, 5(5): 267–275.
- Haywood, S., Loughran, M. and Batt, R.M. (1985a). Copper toxicosis and tolerance in the rat: III. Intracellular localization of copper in the liver and kidney. *Exp. Mol. Pathol.*, 43(2): 209–219.
- Haywood, S., Trafford, J. and Loughran, M. (1985b). Copper toxicosis and tolerance in the rat: IV. Renal tubular excretion of copper. *Br. J. Exp. Pathol.*, 66(6): 699–707.
- Health Canada (1994). Human health assessment for priority substances. Canadian Environmental Protection Act. Available at: www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/approach/approach-eng.pdf
- Health Canada (2007). Copper. Natural Health Products Ingredients Database, Natural Health Products Directorate, Ottawa, Ontario.
- Health Canada (2009a). Copper pesticides. Proposed re-evaluation decision. Pest Management Regulatory Agency. PRVD 2009-04.
- Health Canada (2009b). Canadian total diet study. Health Products and Food Branch, Health Canada, Ottawa, Ontario. Available at: www.canada.ca/en/health-canada/services/food-nutrition/food-nutrition-surveillance/canadian-total-diet-study.html.
- Health Canada (2009c). Guidance on controlling corrosion in drinking water distribution systems. Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario
- Health Canada (2010). Dietary reference intakes tables. Health Products and Food Branch. Available at: www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index-eng.php
- Health Canada (2011). Average dietary intakes ($\mu\text{g}/\text{kg}$ bw/day) of trace elements for Canadians in different age/sex groups for total diet study from 1993 to 1996. Available at: www.canada.ca/en/health-canada/services/food-nutrition/food-nutrition-surveillance/canadian-total-diet-study/dietary-intakes-contaminants-other-chemicals-different-sex-groups-canadians/average-dietary-intakes-day-trace-elements-canadians-different-sex-groups-total-diet-study-1993-1996.html
- Health Canada (2013). Second report on human biomonitoring of environmental chemicals in Canada. Available at: www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/second-report-human-biomonitoring-environmental-chemicals-canada-health-canada-2013.html
- Health Canada (2015). Personal communication with T. Shin. Healthy Environments and Consumer Safety Branch.
- Health Canada (2016). Residential indoor air quality guideline: moulds . Available at: <http://healthycanadians.gc.ca/publications/healthy-living-vie-saine/mould-moisissure/alt/mould-moisissures-eng.pdf>.
- Hebert, C.D., Elwell, M.R., Travlos, G.S., Fitz, C.J. and Bucher, J.R. (1993). Subchronic toxicity of cupric sulfate administered in drinking water and feed to rats and mice. *Fundam. Appl. Toxicol.*, 21(4): 461–475.
- Heinemann, K., Reed, S., Moehner, S. and Do Minh, T. (2015). Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European active surveillance study on intrauterine devices. *Contraception*, 91(4): 274–279.
- Hidmi, L. and Edwards, M. (1999). Role of temperature and pH in $\text{Cu}(\text{OH})_2$ solubility. *Environ. Sci. Technol.*, 33(15): 2607–2610.
- Hong, P.K.A. and Macauley, Y. (1998). Corrosion and leaching of copper tubing exposed to chlorinated drinking water. *Water Air Soil Pollut.*, 108(3–4): 457–471.

Horn, C.C., Kimball, B.A., Wang, H., Kaus, J., Dienel, S., Nagy, A., Gathright, G.R., Yates, B.J. and Andrews, P.L. (2013). Why can't rodents vomit? A comparative behavioral, anatomical, and physiological study. *PLoS One*, 8(4): 1–16.

Hu, J., Gan, F., Triantafyllidou, S., Nguyen, C.K. and Edwards, M.A. (2012). Copper-induced metal release from lead pipe in drinking water. *Corrosion*, 68(11):1037–1048.

Hujita, H., Nakano, M. and Sasaki, M. (1998). Mutagenicity of food additives in the Ames Salmonella/microsome assay. Tokyo Metropolitan Research Laboratory of Public Health Annual Reports, 39, pp. 343–350. [cited in Abe et al., 2008].

Ingle, A.P., Duran, N. and Rai, M. (2014). Bioactivity, mechanism of action, and cytotoxicity of copper-based nanoparticles: A review. *Appl. Microbiol. Biotechnol.*, 98(3): 1001–1009.

IOM (2001). Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Food and Nutrition Board, Institute of Medicine. National Academy Press, Washington, DC, USA, 797 pp.

IPCS (1998). Environmental Health Criteria 200: Copper. International Programme on Chemical Safety. World Health Organization, Geneva.

Jacobs, S. and Edwards, M. (2000). Sulfide scale catalysis of copper corrosion. *Wat. Res.*, 34(10): 2798–2808

Jacobs, S., Reiber, S. and Edwards, M. (1998). Sulfide-induced copper corrosion, *J. Am. Water Works Assoc.*, 90(7): 62–73.

Jantsch, W., Kulig, K. and Rumack, B.H. (1984). Massive copper sulfate ingestion resulting in hepatotoxicity. *J. Toxicol. Clin. Toxicol.*, 22(6): 585–588.

Javaherdashti, R. (2008). Chapter 4: Microbiologically influenced corrosion (MIC). In: *Microbiologically Influenced Corrosion*. 1st edition. Springer-Verlag London Limited.

Jazvinscak Jembrek, M., Vlainic, J., Radovanovic, V., Erhardt, J. and Orsolich, N. (2014). Effects of copper overload in P19 neurons: Impairment of glutathione redox homeostasis and crosstalk between caspase and calpain protease systems in ROS-induced apoptosis. *Biometals*, 27(6): 1303–1322.

Jiménez Del Río, M. and Vélez-Pardo, C. (2004). Transition metal-induced apoptosis in lymphocytes via hydroxyl radical generation, mitochondria dysfunction, and caspase-3 activation: An in vitro model for neurodegeneration. *Arch. Med. Res.*, 35(3): 185–193.

Johncilla, M. and Mitchell, K.A. (2011). Pathology of the liver in copper overload. *Semin. Liver Dis.*, 31(3): 239–244.

Johnson, B., Yorton, R., Tran, T. and Kim, J. (1993). Evaluation of corrosion control alternatives to meet the Lead and Copper Rule for eastern Massachusetts. *J. N. Engl. Water Works Assoc.*, 107(3): 24–45.

Jomova, K. and Valko, M. (2011). Advances in metal-induced oxidative stress and human disease. *Toxicology*, 283(2–3): 65–87.

Kadiiska, M.B., Hanna, P.M., Hernandez, L. and Mason, R.P. (1992). In vivo evidence of hydroxyl radical formation after acute copper and ascorbic acid intake: Electron spin resonance spin-trapping investigation. *Mol. Pharmacol.*, 42(4): 723–729.

Kaler, S.G. (1998). Metabolic and molecular bases of Menkes disease and occipital horn syndrome. *Pediatr. Dev. Pathol.*, 1(1): 85–98.

Kaplan, J.H. and Lutsenko, S. (2009). Copper transport in mammalian cells: Special care for a metal with special needs. *J. Biol. Chem.*, 284(38): 25461–25465.

- Karim, Z. (2011). Risk assessment of dissolved trace metals in drinking water of Karachi, Pakistan. *Bull. Environ. Contam. Toxicol.*, 86(6): 676–678.
- Kawakami, M., Inagawa, R., Hosokawa, T., Saito, T. and Kurasaki, M. (2008). Mechanism of apoptosis induced by copper in PC12 cells. *Food Chem. Toxicol.*, 46(6): 2157–2164.
- Kehoe, C.A., Turley, E., Bonham, M.P., O'Connor, J.M., McKeown, A., Faughnan, M.S., Coulter, J.S., Gilmore, W.S., Howard, A.N. and Strain, J.J. (2000). Response of putative indices of copper status to copper supplementation in human subjects. *Br. J. Nutr.*, 84(2): 151–156.
- Kirmeyer, G., Sandvig, A.M., Pierson, G.L. and Neff, C.H. (1994). Development of a pipe loop protocol for lead control. Water Research Foundation, Denver, Colorado. Awwa Research Foundation Report #90650.
- Kessler, H., Pajonk, F.G., Meisser, P., Schneider-Axmann, T., Hoffmann, K.H., Supprian, T., Herrmann, W., Obeid, R., Multhaup, G., Falkai, P. and Bayer, T.A. (2006). Cerebrospinal fluid diagnostic markers correlate with lower plasma copper and ceruloplasmin in patients with Alzheimer's disease. *J. Neural Transm. (Vienna)*, 113(11): 1763–1769.
- Kiaune, L. and Singhasemanon, N. (2011). Pesticidal copper (I) oxide: Environmental fate and aquatic toxicity. In: *Reviews of environmental contamination and toxicology*. volume 213. chap.1. Whitacre, D.M. (ed.). Springer, pp. 1–26.
- Kieber, R.J., Skrabal, S.A., Smith, C. and Willey, J.D. (2004). Redox speciation of copper in rainwater: Temporal variability and atmospheric deposition. *Environ. Sci. Technol.*, 38(13): 3587–3594.
- Kim, B.E., Nevitt, T. and Thiele, D.J. (2008). Mechanisms for copper acquisition, distribution and regulation. *Nat. Chem. Biol.*, 4(3): 176–185.
- Kimbrough, D.E. (2001). Brass corrosion and the LCR monitoring program. *J. Am. Water Works Assoc.*, 93(2): 81–91.
- Kimbrough, D.E. (2007). Brass corrosion as a source of lead and copper in traditional and all-plastic distribution systems. *J. Am. Water Works Assoc.*, 99(8): 70–76.
- Kimbrough, D.E. (2009). Source identification of copper, lead, nickel, and zinc loading in wastewater reclamation plant influents from corrosion of brass in plumbing fixtures. *Environmental Pollution*, 157:1310–1316.
- Kirmeyer, G., Murphy, B., Sandvig, A., Korshin, G., Shaha, B., Fabricino, M. and Burlingame, G. (2004). Post-optimization lead and copper control monitoring strategies. Awwa Research Foundation, Denver, Colorado.
- Kitazawa, M., Cheng, D. and Laferla, F.M. (2009). Chronic copper exposure exacerbates both amyloid and tau pathology and selectively dysregulates cdk5 in a mouse model of AD. *J. Neurochem.*, 108(6): 1550–1560.
- Klevay, L.M. (2010). Copper. In: *Encyclopedia of dietary supplements*. pp. 175–184.
- Knobeloch, L., Ziarnik, M., Howard, J., Theis, B., Farmer, D., Anerson, H. and Proctor, M. (1994). Gastrointestinal upsets associated with ingestion of copper-contaminated water. *Env. Health Persp.* 102(11):958–961.
- Kok, F.J., Van Duijn, C.M., Hofman, A., Van der Voet, G.B., De Wolff, F.A., Paays, C.H. and Valkenburg, H.A. (1988). Serum copper and zinc and the risk of death from cancer and cardiovascular disease. *Am. J. Epidemiol.*, 128(2): 352–359.
- Korshin, G.V., Pery, S.A.L. and Ferguson, J.F. (1996). Influence of NOM on copper corrosion. *J. Am. Water Works Assoc.*, 88(7): 36–47.
- Krishnan, K., Carrier, R. (2013). The use of exposure source allocation factor in the risk assessment of drinking-water contaminants. *J. Toxicol. Environ. Health B Crit. Rev.*, 16(1):39–51.

- Kuch, A. and Wagner, I. (1983). A mass transfer model to describe lead concentrations in drinking water. *Water Supply*, 17(10): 1330–1307.
- Kumar, V., Kalita, J., Misra, U.K. and Bora, H.K. (2015). A study of dose response and organ susceptibility of copper toxicity in a rat model. *J. Trace Elem. Med. Biol.*, 29: 269–274.
- Larney, F.J., Olson, A.F., Miller, J.J. and Tovell, B.C. (2014). Soluble salts, copper, zinc and solids constituents in surface runoff from cattle manure compost windrows. *Can. J. Soil Sci.*, 94:515–527.
- Lagos, G.E., Cuadrado, C.A. and Letelier, V. (2001). Aging of copper pipes by drinking water. *J. Am. Water Works Assoc.* 93(11): 94–103.
- Lehtola, M.J., Miettinen, I.T., Keinänen, Kekki, T.K., Laine, O., Hirvonen, A., Vartiainen, T. and Martikainen, P.J. (2004). Microbiology, chemistry and biofilm development in a pilot drinking water distribution system with copper and plastic pipes. *Water Research*, 38: 3769–3779.
- Lehtola, M.J., Laxander, M., Miettinen, I.T., Hirvonen, A., Vartiainen, T. and Martikainen, (2006). The effects of changing water flow velocity on the formation of biofilms and water quality in pilot distribution system consisting of copper or polyethylene pipes. *Water Research*, 40:2151–2160.
- Letelier, M.E., Sanchez-Jofre, S., Peredo-Silva, L., Cortes-Troncoso, J. and Aracena-Parks, P. (2010). Mechanisms underlying iron and copper ions toxicity in biological systems: Pro-oxidant activity and protein-binding effects. *Chem. Biol. Interact.*, 188(1): 220–227.
- Lide, D.R. (1993). *CRC Handbook of Chemistry and Physics*, 73rd ed. CRC Press, Boca Raton, Florida.
- Lind, Y. and Glynn, A.W. (1999). Intestinal absorption of copper from drinking water containing fulvic acids and an infant formula mixture studied in a suckling rat model. *Biometals*, 12(2): 181–187.
- Linder, M.C. (1991). *Biochemistry of copper*. Plenum Press, New York, New York.
- Linder, M.C. (2001). Copper and genomic stability in mammals. *Mutat. Res.*, 475(1–2): 141–152.
- Linder, M.C. (2002). Biochemistry and molecular biology of copper in mammals. *Handbook of Copper Pharmacology and Toxicology*. Edited by Massaro, E.J. and Totowa, N.J. Humana Press, 3–32.
- Linder, M.C. and Hazegh-Azam, M. (1996). Copper biochemistry and molecular biology. *Am. J. Clin. Nutr.*, 63(5): 797S–811S.
- Lintereur, P.A., Duranceau, S.J. and Taylor, J.S. (2011). Sodium silicate impacts on copper release in a potable water comprised of ground, surface and desalted sea water supplies. *Desalination and Water Treatment*, 30:348–360.
- Little, B., Wagner, P. and Mansfeld, F. (1991). Microbially influence corrosion of metals and alloys. *International Materials Reviews*, 36(6):253–272.
- Lonnerdal, B. (1996). Bioavailability of copper. *Am. J. Clin. Nutr.*, 63(5): 821S–829S.
- Lonnerdal, B. (1998). Copper nutrition during infancy and childhood. *Am. J. Clin. Nutr.*, 67(5 Suppl): 1046S–1053S.
- Lovell, M.A., Robertson, J.D., Teesdale, W.J., Campbell, J.L. and Markesbery, W.R. (1998). Copper, iron and zinc in Alzheimer's disease senile plaques. *J. Neurol. Sci.*, 158(1): 47–52.
- Lowry, J. (2009). Lakhurst Acres, ME: Compliance issues engineering problems and solutions. U.S. EPA Sixth annual drinking water workshop: Small drinking water system challenges and solutions. August 4-6. Cincinnati, Ohio.
- Lowry, J., (2010). Corrosion control with air stripping. American water work association. Inorganic contaminants workshop, Denver, Colorado.

- Lytle, D.A. and Nadagouda, M.N. (2010). A comprehensive investigation of copper pitting corrosion in a drinking water distribution system. *Corrosion Science*, 52:1927–1938.
- Lytle, D.A. and Schock, M.R. (1996). Stagnation time, composition, pH, and orthophosphate effects on metal leaching from brass. Office of Research and Development. U.S. EPA, Cincinnati, OH. EPA.600.R-96.103
- Lytle, D.A. and Schock, M.R. (2000). Impact of stagnation time on metal dissolution from plumbing materials in drinking water *Journal of Water Supply Research and Technology-AQUA*, 49(5):243–257.
- Lytle, D.A. and Schock, M.R. (2008). Pitting corrosion of copper in waters with high pH and low alkalinity. *J. Am Water Works Assoc.*, 100(3): 115–129.
- Lytle, D.A., Williams, D. and White, C. (2012). A simple approach to assessing copper pitting corrosion tendencies and developing control strategies. *J Water Supply: Research and Technology – AQUA*, 63(3): 164–175.
- Machado, A.A., Deguti, M.M., Genschel, J., Cancado, E.L., Bochow, B., Schmidt, H. and Barbosa, E.R. (2008). Neurological manifestations and ATP7B mutations in Wilson's disease. *Parkinsonism Relat. Disord.*, 14(3): 246–249.
- MacQuarrie, D.M., Mavinic, D.S. and Neden, D.G. (1997). Greater Vancouver Water District drinking water corrosion inhibitor testing. *Can. J. Civil Eng.*, 24(1): 34–52.
- Madsen, E. and Gitlin, J.D. (2007). Copper and iron disorders of the brain. *Annu. Rev. Neurosci.*, 30: 317–337.
- Maessen, O., Freedman, B. and McCurdy, R. (1985). Metal mobilization in home well water systems in Nova Scotia. *J. Am. Water Works Assoc.*, 77(6):73–80.
- Mahabir, S., Forman, M.R., Dong, Y.Q., Park, Y., Hollenbeck, A. and Schatzkin, A. (2010). Mineral intake and lung cancer risk in the NIH-American association of retired persons diet and health study. *Cancer Epidemiol. Biomarkers Prev.*, 19(8): 1976–1983.
- Makale, M.T. and King, G.L. (1992). Surgical and pharmacological dissociation of cardiovascular and emetic responses to intragastric CuSO₄. *Am. J. Physiol.*, 263(2 Pt 2): R284–291.
- Masters, S., Wang, H., Pruden, A. and Edwards, M.A. (2015). Redox gradients in distribution systems influence water quality, corrosion, and microbial ecology. *Water Research*, 68:140–149.
- Mauceri, C. and Mishra, S. (2014). Copper. Chapter 18 in: *Health effects of metals and related substances in drinking water*. Ferrante, M., Conti, O., G., Rasic-Milutinovic, Z. and Jovanovic, D. (eds.). IWA Publishing, Alliance House, London, UK, pp. 50–52.
- McNeill, L.S. and Edwards, M. (2002). Phosphate inhibitor use at U.S. utilities. *J. Am. Water Works Assoc.*, 94(7): 57–63.
- McNeill, L.S. and Edwards, M. (2004). Importance of Pb and Cu particulate species for corrosion control. *J. Environ. Eng.*, 130(2):136–144.
- Mehta, A., Patney, N.L., Bhati, D.P. and Singh, S.P. (1985). Copper sulphate poisoning--its impact on kidneys. *J. Indian Med. Assoc.*, 83(4): 108–110.
- Mendez, M.A., Araya, M., Olivares, M., Pizarro, F. and Gonzalez, M. (2004). Sex and ceruloplasmin modulate the response to copper exposure in healthy individuals. *Environ. Health Perspect.*, 112(17): 1654–1657.
- Michaluk, A. and Kochman, K. (2007). Involvement of copper in female reproduction. *Reprod. Biol.*, 7(3): 193–205.
- Miller, L.M., Wang, Q., Telivala, T.P., Smith, R.J., Lanzirrotti, A. and Miklossy, J. (2006). Synchrotron-based infrared and X-ray imaging shows focalized accumulation of cu and zn co-localized with beta-amyloid deposits in Alzheimer's disease. *J. Struct. Biol.*, 155(1): 30–37.

- Molina, J.A., Jimenez-Jimenez, F.J., Aguilar, M.V., Meseguer, I., Mateos-Vega, C.J., Gonzalez-Munoz, M.J., de Bustos, F., Porta, J., Orti-Pareja, M., Zurdo, M., Barrios, E. and Martinez-Para, M.C. (1998). Cerebrospinal fluid levels of transition metals in patients with Alzheimer's disease. *J. Neural Transm. (Vienna)*, 105(4–5): 479–488.
- Montes, S., Rivera-Mancia, S., Diaz-Ruiz, A., Tristan-Lopez, L. and Rios, C. (2014). Copper and copper proteins in Parkinson's disease. *Oxid. Med. Cell. Longev.*, 2014: 147251.
- Moriya, M., Ohta, T., Watanabe, K., Miyazawa, T., Kato, K. and Shirasu, Y. (1983). Further mutagenicity studies on pesticides in bacterial reversion assay systems. *Mutat. Res.*, 116(3–4): 185–216.
- Muller, T., Feichtinger, H., Berger, H. and Muller, W. (1996). Endemic Tyrolean infantile cirrhosis: An ecogenetic disorder. *Lancet*, 347(9005): 877–880.
- Murphy, E.A. (1993). Effectiveness of flushing on reducing lead and copper levels in school drinking water. *Environ. Health Perspect.*, 101(3): 240–241.
- Neuman, W.E. (1995). AWWC experience with zinc orthophosphate treatment. *J. N. Engl. Water Works Assoc.*, 109: 57–60.
- Nicholson, F.A., Chambers, B.J., Williams, J.R. and Unwin, R.J. (1999). Heavy metal contents of livestock feeds and animal manures in England and Wales. *Biores. Tech.*, 70:23–31.
- NHMRC (2011). Australian drinking water guidelines. Paper 6: National water quality management strategy. Version 3.1, updated march 2015. National Health and Medical Research Council, National Resource Management Ministerial Council, Commonwealth of Australia, Canberra. ISBN online: 1864965118.
- NRC (2000). Copper in drinking water. National Research Council. National Academy Press. Washington, DC.
- NRCC (2010). National Plumbing Code. National Research Council of Canada, Ottawa, Ontario.
- NSF International (2015a). NSF/ANSI Standard 60: Drinking water treatment chemicals—health effects. NSF International, Ann Arbor, Michigan.
- NSF International (2015b). NSF/ANSI Standard 53: Drinking water treatments units—Health effects. NSF International, Ann Arbor, Michigan.
- NSF International (2015c). NSF/ANSI Standard 58: Reverse osmosis drinking water treatment systems. NSF International, Ann Arbor, Michigan.
- NSF International (2015d). NSF/ANSI Standard 62: Drinking water distillation systems. NSF International, Ann Arbor, Michigan.
- NSF International (2016a). NSF/ANSI Standard 61: Drinking water system components—health effects. NSF International, Ann Arbor, Michigan.
- NSF International (2016b). NSF/ANSI Standard 372: Drinking water system components—lead content. NSF International, Ann Arbor, Michigan.
- NTP (1993). NTP Technical report on toxicity studies of cupric sulfate (CAS No. 7758-99-8) administered in drinking water and feed to F344/N rats and B6C3F1 mice. National Toxicology Program, National Institute of Health. Report No. 29 .
- O'Connor, J.M., Bonham, M.P., Turley, E., McKeown, A., McKelvey-Martin, V.J., Gilmore, W.S. and Strain, J.J. (2003). Copper supplementation has no effect on markers of DNA damage and liver function in healthy adults (FOODCUE project). *Ann. Nutr. Metab.*, 47(5): 201–206.
- O'Donohue, J., Reid, M.A., Varghese, A., Portmann, B. and Williams, R. (1993). Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. *Eur. J. Gastroenterol. Hepatol.*, 5: 561–562.

O'Donohue, J., Reid, M., Varghese, A., Portmann, B. and Williams, R. (1999). A case of adult chronic copper self-intoxication resulting in cirrhosis. *Eur. J. Med. Res.*, 4(6): 252.

OEHHA (2008). Public Health Goal for Copper in Drinking Water. Office of Environmental Health Hazard Assessment (OEHHA). California Environmental Protection Agency. Available at: https://oehha.ca.gov/media/downloads/water/chemicals/phg/copperphg020808_0.pdf

Oliphant, R.J. and Schock, M.R. (1996). Chapter 6: Copper alloys and solders. In: Internal corrosion of water distribution systems. 2nd edition. American Water Works Association Research Foundation and DVGW-Technologiezentrum Wasser, Denver, Colorado. pp.269–312.

Olivares, M. and Uauy, R. (1996). Copper as an essential nutrient. *Am. J. Clin. Nutr.*, 63(5): 791S–796S.

Olivares, M., Pizarro, F., Speisky, H., Lonnerdal, B. and Uauy, R. (1998). Copper in infant nutrition: Safety of world health organization provisional guideline value for copper content of drinking water. *J. Pediatr. Gastroenterol. Nutr.*, 26(3): 251–257.

Olivares, M., Araya, M., Pizarro, F. and Uauy, R. (2001). Nausea threshold in apparently healthy individuals who drink fluids containing graded concentrations of copper. *Regul. Toxicol. Pharmacol.*, 33(3): 271–275.

Omur-Ozbek, P. and Dietrich, A.M. (2011). Retronasal perception and flavour thresholds of iron and copper in drinking water. *J. Water. Health.*, 9(1): 1–9.

Ontario Superior Court of Justice. (2011) . Nicholas Rosati and Anthony Bellissimo and IPEX USA LLC and IPEX Inc. Proceeding Under the Class Proceedings Act, 1992. CV-09-13459. November 29, 2011.

Overvad, K., Wang, D.Y., Olsen, J., Allen, D.S., Thorling, E.B., Bulbrook, R.D. and Hayward, J.L. (1993). Copper in human mammary carcinogenesis: A case-cohort study. *Am. J. Epidemiol.*, 137(4): 409–414.

Ozcelik, D. and Uzun, H. (2009). Copper intoxication; antioxidant defenses and oxidative damage in rat brain. *Biol. Trace Elem. Res.*, 127(1): 45–52.

Pajonk, F.G., Kessler, H., Supprian, T., Hamzei, P., Bach, D., Schweickhardt, J., Herrmann, W., Obeid, R., Simons, A., Falkai, P., Multhaup, G. and Bayer, T.A. (2005). Cognitive decline correlates with low plasma concentrations of copper in patients with mild to moderate Alzheimer's disease. *J. Alzheimer's Dis.*, 8(1): 23–27.

Pal, A. (2014). Copper toxicity induced hepatocerebral and neurodegenerative diseases: An urgent need for prognostic biomarkers. *Neurotoxicology*, 40: 97–101.

Pal, A., Badyal, R.K., Vasishta, R.K., Attri, S.V., Thapa, B.R. and Prasad, R. (2013). Biochemical, histological, and memory impairment effects of chronic copper toxicity: A model for non-Wilsonian brain copper toxicosis in wistar rat. *Biol. Trace Elem. Res.*, 153(1–3): 257–268.

Pal, A., Jayamani, J. and Prasad, R. (2014). An urgent need to reassess the safe levels of copper in the drinking water: Lessons from studies on healthy animals harboring no genetic deficits. *Neurotoxicology*, 44: 58–60.

Pamp, K., Bramey, T., Kirsch, M., De Groot, H. and Petrat, F. (2005). NAD(H) enhances the cu(II)-mediated inactivation of lactate dehydrogenase by increasing the accessibility of sulfhydryl groups. *Free Radic. Res.*, 39(1): 31–40.

Paris, I., Perez-Pastene, C., Couve, E., Caviedes, P., Ledoux, S. and Segura-Aguilar, J. (2009). Copper dopamine complex induces mitochondrial autophagy preceding caspase-independent apoptotic cell death. *J. Biol. Chem.*, 284(20): 13306–13315.

Park, H.J., Nguyen, T.T., Yoon, J. and Lee, C. (2012). Role of reactive oxygen species in *Escherichia coli* inactivation by cupric ion. *Environ. Sci. Technol.*, 46(20): 11299–11304.

Payne, S.J., Piorkowski, G.S., Truelstrup Hansen, L. and Gagnon, G.A. (2016). Impact of zinc orthophosphate on simulated drinking water biofilms influenced by lead and copper, *J. Environ. Eng.*, 142(2).

- Peña, M.M.O., Lee, J. and Thiele, D.J. (1999). A delicate balance: Homeostatic control of copper uptake and distribution. *The Journal of Nutrition*, 129(7): 1251–1260.
- Petris, M.J., Mercer, J.F., Culvenor, J.G., Lockhart, P., Gleeson, P.A. and Camakaris, J. (1996). Ligand-regulated transport of the Menkes copper P-type ATPase efflux pump from the Golgi apparatus to the plasma membrane: A novel mechanism of regulated trafficking. *EMBO J.*, 15(22): 6084–6095.
- Pizarro, F., Olivares, M., Gidi, V. and Araya, M. (1999a). The gastrointestinal tract and acute effects of copper in drinking water and beverages. *Rev. Environ. Health*, 14(4): 231–238.
- Pizarro, F., Olivares, M., Uauy, R., Contreras, P., Rebelo, A. and Gidi, V. (1999b). Acute gastrointestinal effects of graded levels of copper in drinking water. *Environ. Health Perspect.*, 107(2): 117–121.
- Pizarro, F., Olivares, M., Araya, M., Gidi, V. and Uauy, R. (2001). Gastrointestinal effects associated with soluble and insoluble copper in drinking water. *Environ. Health Perspect.*, 109(9): 949–952.
- Prasad, M.P.R., Krishna, T.P., Pasricha, S., Krishnaswamy, K. and Quereshi, M.A. (1992). Esophageal cancer and diet a case-control study. *Nutr. Cancer*, 18: 85–93. [as cited in IPCS, 1998].
- Prasad, R., Kaur, G., Nath, R. and Walia, B.N. (1996). Molecular basis of pathophysiology of Indian childhood cirrhosis: Role of nuclear copper accumulation in liver. *Mol. Cell. Biochem.*, 156(1): 25–30.
- Pratt, W.B., Omdahl, J.L. and Sorenson, J.R. (1985). Lack of effects of copper gluconate supplementation. *Am. J. Clin. Nutr.*, 42(4): 681–682.
- Prohaska, J.R. (1990). Development of copper deficiency in neonatal mice. *J. Nutr. Biochem.*, 1(8): 415–419.
- Prohaska, J.R. (2008). Role of copper transporters in copper homeostasis. *Am. J. Clin. Nutr.*, 88(3): 826S–829S.
- Qian, Y., Zheng, Y., Taylor, R. and Tiffany-Castiglioni, E. (2012). Involvement of the molecular chaperone Hspa5 in copper homeostasis in astrocytes. *Brain Res.*, 1447: 9–19.
- Qin-qin, T., Zhi-rong, L., Ying, D. and Xin-xing, Z. (2012). Biosorption properties of extracellular polymeric substances towards Zn (II) and Cu (II). *Desalination and Water Treatment*, 45(1–3): 40–47.
- Rae, T.D., Schmidt, P.J., Pufahl, R.A., Culotta, V.C. and O'Halloran, T.V. (1999). Undetectable intracellular free copper: The requirement of a copper chaperone for superoxide dismutase. *Science*, 284(5415): 805–808.
- Rahman, S., McDonald, B.C. and Gagnon, G.A. (2007). Impact of secondary disinfectants on copper corrosion under stagnation conditions. *Journal of Environmental Engineering*, 133(2): 180–185.
- Rasmussen, P.E., Beauchemin, S., Nugent, M., Dugandzic, R., Lanouette, M. and Chénier, M. (2008). Influence of matrix composition on the bioaccessibility of copper, zinc, and nickel in urban residential dust and soil. *Hum. Ecol. Risk Assess.* 14(2): 351–371.
- Rasmussen, P.E., Dugandzic, R., Hassan, N., Murimboh, J. and Grégoire, D.C. (2006). Challenges in quantifying airborne metal concentrations in residential environments. *Can. J. Anal. Sci. Spectrosc.*, 51(1): 2–8.
- Rasmussen, P.E., Subramanian, K.S. and Jessiman, B.J. (2001). A multi-element profile of housedust in relation to exterior dust and soils in the city of Ottawa, Canada. *Sci. Total Environ.*, 267(1–3): 125–140.
- Rehring, J.P. and Edwards, M. (1996). Copper corrosion in potable water systems: impacts of natural organic matter and water treatment processes. *Corrosion*, 52(4): 301–317.
- Reiber, S.H. (1989). Copper plumbing surfaces: an electrochemical study. *J. Am. Water Works Assoc.*, 87(7): 114.
- Reiber, S., Poulsam, S., Perry, S.A.L., Edwards, M.A., Patel, S. and Dodrill, D.M. (1997). A general framework for corrosion control based on utility experience, AWWA Research Foundation and American Water Works Association, Denver, Colorado.

- Reyes, A., Letelier, M.V., De la Igledia, R., González, B., Lagos, G. (2008). Microbiologically induced corrosion of copper pipes in low-pH water. *International Biodeterioration & Biodegradation*, 61:135–141.
- Rezania, L.W. and Anderl, W.H. (1995). Copper corrosion and iron removal plants. The Minnesota experience. In: *Proceedings of the 1995 AWWA Water Quality Technology Conference*, New Orleans, LA. American Water Works Association, Denver, Colorado.
- Rezania, L.W. and Anderl, W.H. (1997). Corrosion control for high DIC groundwater phosphate or bust. In: *Proceedings of the 1997 AWWA Annual Conference*, Atlanta, GA. American Water Works Association, Denver, Colorado.
- Rhoads, W.J., Pruden, A., and Edwards, M.A. (2016). Survey of green building water systems reveals elevated water age and water quality concerns. *Environmental Science Water Research & Technology*, 2:164–173.
- Riedel, G.F. (2008). Copper. In: *Encyclopedia of ecology*. volume 1 A-C. Jorgensen, S.E. and Fath, B.D. (eds.). pp. 778–783.
- Rivera-Mancia, S., Perez-Neri, I., Rios, C., Tristan-Lopez, L., Rivera-Espinosa, L. and Montes, S. (2010). The transition metals copper and iron in neurodegenerative diseases. *Chem. Biol. Interact.*, 186(2): 184–199.
- Roelofsen, H., Wolters, H., Van Luyn, M.J.A., Miura, N., Kuipers, F. and Vonk, R.J. (2000). Copper-induced apical trafficking of ATP7B in polarized hepatoma cells provides a mechanism for biliary copper excretion. *Gastroenterology*, 119(3): 782–793.
- Rosenzweig, A.C. (2001). Copper delivery by metallochaperone proteins. *Acc. Chem. Res.*, 34(2): 119–128.
- Roychoudhury, S., Nath, S., Massanyi, P., Stawarz, R., Kacaniova, M. and Kolesarova, A. (2015). Copper induced changes in reproductive functions: Review of in vivo and in vitro effects. *Physiol. Res.*, 65(1):11–22.
- Sadhra, S.S., Wheatley, A.D. and Cross, H.J. (2007). Dietary exposure to copper in the European union and its assessment for EU regulatory risk assessment. *Sci. Total Environ.*, 374(2–3): 223–234.
- Sandvig, A., Martel, K., Beggs, K., Jaffe Murray, A., Greiner, P., Kneen, K., McLellan, C., Bennet, D. and Terrell, J. (2012). Is NSF 61 relevant for chloraminating utilities? Water Research Foundation, Denver, Colorado (Water Research Foundation Project No. 4243).
- Sarver, E., Zhang, Y. and Edwards, M. (2011). Copper pitting and brass dezincification: chemical and physical effects. Water Research Foundation, Denver, Colorado.
- Scardina, P., Edwards, M., Bosch, D.J., Loganathan, G.V. and Dwyer, S.K. (2008). Assessment of non-uniform corrosion in copper piping. Water Research Foundation, Denver, Colorado.
- Schaefer, M. and Gitlin, J.D. (1999). Genetic disorders of membrane transport. IV. Wilson's disease and Menkes disease. *Am. J. Physiol.*, 276(2 Pt 1): G311–G314.
- Scheinberg, I.H. and Sternlieb, I. (1996). Wilson disease and idiopathic copper toxicosis. *Am. J. Clin. Nutr.*, 63(5): 842S–845S.
- Schilsky, M.L. (1996). Wilson disease: Genetic basis of copper toxicity and natural history. *Semin. Liver Dis.*, 16(1): 83–95.
- Schock, M.R. (1990). Causes of temporal variability of lead in domestic plumbing systems. *Environ. Monit. Assess.*, 15(1): 59–82.
- Schock, M.R. (1999). Chapter 17: Internal corrosion and deposition control. In: Letterman, R.D. (ed.), *Water quality and treatment: a handbook on drinking water*. 5th edition. McGraw Hill and American Water Works Association, Denver, Colorado. pp. 87–88.

- Schock, M.R. (2005). Distribution systems as reservoirs and reactors for inorganic contaminants. In: Distribution system water quality challenges in the 21st century: a strategic guide. American Water Works Association, Denver, Colorado.
- Schock, M.R. and Clement, J.A. (1998). Lead and copper control with non-zinc orthophosphate. *J. N. Engl. Water Works Assoc.*, 112(1): 20–33
- Schock, M.R. and Fox, J.C. (2001). Solving copper corrosion problems while maintaining lead control in a high alkalinity water using orthophosphate. In: Proceedings of the 2001 AWWA Annual Conference, Washington, DC. American Water Works Association, Denver, Colorado.
- Schock, M.R. and Lytle, D. (2011). Chapter 20: Internal corrosion and deposition control. In: J.K. Edzwald (ed.), *Water quality and treatment: a handbook on drinking water*. 6th edition. McGraw Hill and American Water Works Association, Denver, Colorado.
- Schock, M.R. and Neff, C.H. (1988). Trace metal contamination from brass fittings. *J. Am. Water Works Assoc.*, 80(11): 47–56.
- Schock, M.R. and Sandvig, A.M. (2009). Long-term effects of orthophosphate treatment on copper concentration. *J. Am. Water Works Assoc.*, 101(7): 71–82.
- Schock, M.R., Lytle, D.A. and Clement, J.A. (1995). Effect of pH, DIC, orthophosphate, and sulfate on drinking water cuprosolvency. U.S. Environmental Protection Agency, Cincinnati, OH (Report No. EPA/600/R-95/085).
- Schock, M.R., Wagner, I. and Oliphant, R.J. (1996). Corrosion and solubility of lead in drinking water. In: *Internal corrosion of water distribution systems*. 2nd edition. American Water Works Association Research Foundation and DVGW Technologiezentrum Wasser, Denver, Colorado. pp. 131–230.
- Scott, K.C. and Turnlund, J.R. (1994). A compartmental model of zinc metabolism in adult men used to study effects of three levels of dietary copper. *Am. J. Physiol.*, 267(1 Pt 1): E165–173.
- Senesse, P., Meance, S., Cottet, V., Faivre, J. and Boutron-Ruault, M. (2004). High dietary iron and copper and risk of colorectal cancer: A case-control study in burgundy, France. *Nutr. Cancer*, 49(1): 66–71.
- Shaligram, S. and Campbell, A. (2013). Toxicity of copper salts is dependent on solubility profile and cell type tested. *Toxicol. in Vitro.*, 27(2): 844–851.
- Shanaman et al. (1972). [as cited by WHO,1993].
- Sharrett, A.R., Carter, A.P., Orheim, R.M. and Feinleib, M. (1982). Daily intake of lead, cadmium, copper, and zinc from drinking water: the Seattle study of trace metal exposure. *Environ. Res.*, 28: 456–475.
- Shike, M. (2009). Copper in parenteral nutrition. *Gastroenterology*, 137(5 Suppl): S13–S17.
- Singh, I. and Mavinic, D.S. (1991). Significance of building and plumbing specifics on trace metal concentrations in drinking water. *Can. J. Civil Eng.*, 18(6): 893–903.
- Sokol, R.J., Devereaux, M., Mierau, G.W., Hambidge, K.M. and Shikes, R.H. (1990). Oxidant injury to hepatic mitochondrial lipids in rats with dietary copper overload. Modification by vitamin E deficiency. *Gastroenterology*, 99(4):1061–1071.
- Sorg, T.J., Schock, M.R. and Lytle, D.A. (1999). Ion exchange softening: effects on metal concentrations. *J. Am. Water Works Assoc.*, 91(8): 85–97.
- Sparks, D.L. and Schreurs, B.G. (2003). Trace amounts of copper in water induce beta-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.*, 100(19): 11065–11069.
- Spitalny, K.C., Brondum, J., Vogt, R.L., Sargent, H.E. and Kappel, S. (1984). Drinking-water-induced copper intoxication in a Vermont family. *Pediatrics*, 74(6): 1103–1106.

- Squitti, R., Lupoi, D., Pasqualetti, P., Dal Forno, G., Vernieri, F., Chiovenda, P., Rossi, L., Cortesi, M., Cassetta, E. and Rossini, P.M. (2002). Elevation of serum copper levels in Alzheimer's disease. *Neurology*, 59(8): 1153–1161.
- Squitti, R., Barbati, G., Rossi, L., Ventriglia, M., Dal Forno, G., Cesaretti, S., Moffa, F., Caridi, I., Cassetta, E., Pasqualetti, P., Calabrese, L., Lupoi, D. and Rossini, P.M. (2006). Excess of nonceruloplasmin serum copper in AD correlates with MMSE, CSF [beta]-amyloid, and h-tau. *Neurology*, 67(1): 76–82.
- SCC (2016). Standards Council of Canada. Available at: www.scc.ca.
- Stenhammar, L. (1999). Diarrhoea following contamination of drinking water with copper. *Eur. J. Med. Res.*, 4(6): 217–218.
- Stern, B.R. (2010). Essentiality and toxicity in copper health risk assessment: Overview, update and regulatory considerations. *J. Toxicol. Environ. Health A*, 73(2): 114–127.
- Stern, B.R., Solioz, M., Krewski, D., Aggett, P., Aw, T.C., Baker, S., Crump, K., Dourson, M., Haber, L., Hertzberg, R., Keen, C., Meek, B., Rudenko, L., Schoeny, R., Slob, W. and Starr, T. (2007). Copper and human health: Biochemistry, genetics, and strategies for modeling dose-response relationships. *J. Toxicol. Environ. Health B Crit. Rev.*, 10(3): 157–222.
- Stewart, J.H., Macintosh, D., Allen, J. and McCarthy, J. (2012). Chapter 11 - germanium, tin, and copper. In: Patty's toxicology, sixth edition. volume 1, Bingham, E. and Cochrane, B. (eds.). John Wiley & Sons, Inc., pp. 355–380.
- Stover, E.L. and Kincannon, D.F. (1983). Contaminated groundwater treatability- a case study. *J. Am. Water Works Assoc.*, 75(6): 292–298.
- Superior Court, Province of Quebec (2011). Karen Cooke and Terry Cooke and Coopérative d'Habitation Lézarts and Stéphane Morissette v. Ipex Inv. Judgment on a motion for approval of a settlement Article 1025 of the Code of Civil Procedure. No. 200-06-000121-098. District of Quebec City. December 9.
- Takeda, T., Yukioka, T. and Shimazaki, S. (2000). Cupric sulfate intoxication with rhabdomyolysis, treated with chelating agents and blood purification. *Intern. Med.*, 39(3): 253–255.
- Talcott, P.A. (2013). Copper. Chapter 41 in: Small animal toxicology. Peterson, M. E., Talcott, P.A. (eds.), 3rd ed.
- Tanner, M.S. (1998). Role of copper in Indian childhood cirrhosis. *Am. J. Clin. Nutr.*, 67(5 Suppl): 1074S–1081S.
- Tapia, L., Gonzalez-Aguero, M., Cisternas, M.F., Suazo, M., Cambiazo, V., Uauy, R. and Gonzalez, M. (2004). Metallothionein is crucial for safe intracellular copper storage and cell survival at normal and supra-physiological exposure levels. *Biochem. J.*, 378(Pt 2): 617–624.
- Tapiero, H., Townsend, D.M. and Tew, K.D. (2003). Trace elements in human physiology and pathology. copper. *Biomed. Pharmacother.*, 57(9): 386–398.
- Tardito, S., Bassanetti, I., Bignardi, C., Elviri, L., Tegoni, M., Mucchino, C., Bussolati, O., Franchi-Gazzola, R. and Marchio, L. (2011). Copper binding agents acting as copper ionophores lead to caspase inhibition and paraptotic cell death in human cancer cells. *J. Am. Chem. Soc.*, 133(16): 6235–6242.
- Taylor, J.S. and Wiesner, M. (1999). Membranes. Chapter 11 in: Letterman, R.D.(ed). Water quality and treatment: a handbook of community water supplies, 5th edition American Water Works Association. Denver, Colorado. McGraw-Hill, New York, New York.
- Thompson, C.A., Habermann, T.M., Wang, A.H., Vierkant, R.A., Folsom, A.R., Ross, J.A. and Cerhan, J.R. (2010). Antioxidant intake from fruits, vegetables and other sources and risk of non-Hodgkin's lymphoma: The Iowa women's health study. *Int. J. Cancer*, 126(4): 992–1003.
- Tiffany-Castiglioni, E., Hong, S. and Qian, Y. (2011). Copper handling by astrocytes: Insights into neurodegenerative diseases. *Int. J. Dev. Neurosci.*, 29(8): 811–818.

- Triantafyllidou, S., Nguyen, K., Zhang, Y. and Edwards, M. (2013). Lead (Pb) quantification in potable water samples: implications for regulatory compliance and assessment of human exposure. *Environ. Monit. Assess.*, 185: 1355–1365. doi: 10.1007/s10661-012-2637-6
- Turnlund, J.R. (1998). Human whole-body copper metabolism. *Am. J. Clin. Nutr.*, 67(5 Suppl): 960S–964S.
- Turnlund, J.R., Keyes, W.R., Anderson, H.L. and Acord, L.L. (1989). Copper absorption and retention in young men at three levels of dietary copper by use of the stable isotope ⁶⁵Cu. *Am. J. Clin. Nutr.*, 49(5): 870–878.
- Turnlund, J.R., Keen, C.L. and Smith, R.G. (1990). Copper status and urinary and salivary copper in young men at three levels of dietary copper. *Am. J. Clin. Nutr.*, 51(4): 658–664.
- Turnlund, J.R., Keyes, W.R., Peiffer, G.L. and Scott, K.C. (1998). Copper absorption, excretion, and retention by young men consuming low dietary copper determined by using the stable isotope ⁶⁵Cu. *Am. J. Clin. Nutr.*, 67(6): 1219–1225.
- Turnlund, J.R., Jacob, R.A., Keen, C.L., Strain, J.J., Kelley, D.S., Domek, J.M., Keyes, W.R., Ensunsa, J.L., Lykkesfeldt, J. and Coulter, J. (2004). Long-term high copper intake: Effects on indexes of copper status, antioxidant status, and immune function in young men. *Am. J. Clin. Nutr.*, 79(6): 1037–1044.
- Turnlund, J.R., Keyes, W.R., Kim, S.K. and Domek, J.M. (2005). Long-term high copper intake: Effects on copper absorption, retention, and homeostasis in men. *Am. J. Clin. Nutr.*, 81(4): 822–828.
- U.S. EPA (1988). Chemical assessment summary for copper; CASRN 7440-50-8.. Integrated Risk Information System (IRIS). National Center for Environmental Assessment. U.S. Environmental Protection Agency.
- U.S. EPA (1991). Maximum contaminant level goals and national primary drinking water regulation for lead and copper; final rule. U.S. Environmental Protection Agency. *Fed Reg* 56 (110): 26460–26464. June.
- U.S. EPA (1994a). Method 200.9 rev. 2.2 determination of trace elements by stabilized temperature graphite furnace atomic absorption. Environmental Monitoring Systems Laboratory, Office of Research and Development, Cincinnati, Ohio.
- U.S. EPA (1994b). Method 200.8 rev 5.4 determination of trace elements in waters and wastes by inductively coupled plasma - mass spectrometry. Environmental Monitoring Systems Laboratory, Office of Research and Development, Cincinnati, Ohio.
- U.S. EPA (1994c). Method 200.7 rev. 4.4 determination of metals and trace elements in water and wastes by inductively coupled plasma-atomic emission spectrometry. Environmental Monitoring Systems Laboratory, Office of Research and Development, Cincinnati, Ohio.
- U.S. EPA (1998). Small system compliance technology list for the non-microbial contaminants regulated before 1996. Office of Water, U.S. Environmental Protection Agency, Washington, DC. (EPA 815-R-98-002).
- U.S. EPA (2000). 40 CFR Parts 141 and 142, National Primary Drinking Water Regulations for Lead and Copper; Final Rules. U.S. Environmental Protection Agency, Washington, DC.
- U.S. EPA (2003a). Method 200.5 rev 4.2 determination of trace elements in drinking water by axially viewed inductively coupled plasma-atomic energy emission spectrometry. National Exposure Research Laboratory, Office of Research and Development, Cincinnati, Ohio.
- U.S. EPA (2003b). Revised guidance manual for selecting lead and copper control strategies. U.S. Environmental Protection Agency, Washington, DC. (Report No. EPA-816-R-03-001).
- U.S. EPA (2009). National Primary Drinking Water Regulations. U.S. Environmental Protection Agency, Washington, DC. Available at: www.epa.gov/ground-water-and-drinking-water/table-regulated-drinking-water-contaminants

- U.S. EPA (2012). Radionuclides in drinking water, compliance options: Treatment technology descriptions. U.S. Environmental Protection Agency. Available at: <http://cfpub.epa.gov/safewater/radionuclides/radionuclides.cfm>
- U.S. District Court (2011). Order certifying class for settlement and approving class action settlement. Case no. 09-MD-2098. In re: Kitec Plumbing system products liability litigation.. Northern District of Texas, Dallas Division.. November.
- van den Berghe, P.V. and Klomp, L.W. (2009). New developments in the regulation of intestinal copper absorption. *Nutr. Rev.*, 67(11): 658-672.
- Vik, E.A., Ryder, R.A., Wagner, I. and Ferguson, J.F. (1996). Mitigation of corrosion effects. In: Internal corrosion of water distribution systems. 2nd edition. American Water Works Association Research Foundation and DVGW Technologiezentrum Wasser, Denver, Colorado. pp. 389-444.
- Wapnir, R.A. (1998). Copper absorption and bioavailability. *Am. J. Clin. Nutr.*, 67(5 Suppl): 1054S-1060S.
- WHO (1993). Guidelines for drinking-water quality. World Health Organization, Geneva, Switzerland. 2nd edition.
- WHO (1996). Guidelines for drinking-water quality, 2nd ed. Volume 2: Health criteria and other supporting information. World Health Organization, Geneva, Switzerland, pp. 219-226.
- WHO (1998). Guidelines for drinking-water quality, 2nd ed. Addendum to volume 2: Health criteria and other supporting information. World Health Organization, Geneva, Switzerland.
- WHO (2004). Copper in drinking-water. background document for development of WHO guidelines for drinking-water quality. World Health Organization, Geneva, Switzerland.
- WHO (2011). Guidelines for drinking-water quality, 4th ed. World Health Organization, Geneva, Switzerland. ISBN 978 92 4 154815 1.
- Wijmenga, C. and Klomp, L.W. (2004). Molecular regulation of copper excretion in the liver. *Proc. Nutr. Soc.*, 63(1): 31-39.
- Wong, P.K. (1988). Mutagenicity of heavy metals. *Bull. Environ. Contam. Toxicol.*, 40(4): 597-603.
- Woszczynski, M., Bergese, J., Payne, S.J. and Gagnon, G.A. (2015). Comparison of sodium silicate and phosphate for controlling lead release from copper pipe rigs. *Canadian Journal of Civil Engineering*, 42: 953-959.
- Wyllie, J. (1957). Copper poisoning at a cocktail party. *Am. J. Publ. Health*, 47: 617.
- Xiong, X., Yanxia, L., Wei, L., Chunye, L., Wei, H. and Ming, Y. (2010). Copper content in animal manures and potential risk of soil copper pollution with animal manure use in agriculture. *Resour. Conserv. Recy.*, 54:985-990.
- Yang, H.J., He, S.Y. and Tuan, H.Y. (2014). Self-seeded growth of five-fold twinned copper nanowires: Mechanistic study, characterization, and SERS applications. *Langmuir*, 30(2): 602-610.
- Yoshida, Y., Furuta, S. and Niki, E. (1993). Effects of metal chelating agents on the oxidation of lipids induced by copper and iron. *Biochim. Biophys. Acta*, 1210(1): 81-88.
- Zacarias, I., Yanez, C.G., Araya, M., Oraka, C., Olivares, M. and Uauy, R. (2001). Determination of the taste threshold of copper in water. *Chem. Senses*, 26(1): 85-89.
- Zemansky, G.M. (1974). Removal of trace metals during conventional water treatment. *J. Am. Water Works Assoc.* 66(10), 606-609.
- Zhao, L., Wang, J., Wang, Y. and Fa, X. (2013). Apigenin attenuates copper-mediated β -amyloid neurotoxicity through antioxidation, mitochondrion protection and MAPK signal inactivation in an AD cell model. *Brain Res.*, 1492: 33-45.

Zietz, B.P., de Vergara, J.D. and Dunkelberg, H. (2003a). Copper concentrations in tap water and possible effects on infant's health--results of a study in Lower Saxony, Germany. *Environ. Res.*, 92(2): 129–138.

Zietz, B.P., Dieter, H.H., Lakomek, M., Schneider, H., Kessler-Gaedtke, B. and Dunkelberg, H. (2003b). Epidemiological investigation on chronic copper toxicity to children exposed via the public drinking water supply. *Sci. Total Environ.*, 302(1–3): 127–144.

Zlotkin, S.H., Atkinson, S. and Lockitch, G. (1995). Trace elements in nutrition for premature infants. *Clin. Perinatol.*, 22(1): 223–240.

Appendix A: List of Acronyms

AD	Alzheimer's disease
ANSI	American National Standards Institute
AO	aesthetic objective
BMD	benchmark dose
BMDL ₀₅	95% lower confidence limit on the benchmark dose for a 5% change in effect
BMDL ₁₀	95% lower confidence limit on the benchmark dose for a 10% change in effect
bw	body weight
CAS	Chemical Abstracts Service
Cp	caeruloplasmin
Cu	copper
CSMR	chloride to sulphate mass ratio
Cu(I)	cuprous ion
Cu(II)	cupric ion
DIC	dissolved inorganic carbonate
DNA	deoxyribonucleic acid
DO	dissolved oxygen
EPA	Environmental Protection Agency (U.S.)
EPS	exopolymeric substances
GAC	granular activated carbon
GGT	gamma glutamyl transferase
GI	gastrointestinal
GM	geometric mean
GOT	glutamic-oxaloacetic aminotransferase
ICT	idiopathic copper toxicosis
IUDs	intrauterine devices
LOAEL	lowest observed adverse effect level
MAC	maximum acceptable concentration
MT	metallothionein
MDL	method detection limit
MIC	microbiologically influenced corrosion
MKD	Menkes' disease
NOAEL	no observed adverse effect level
NOM	natural organic matter
NPC	National Plumbing Code of Canada
NSF	NSF International
NTU	nephelometric turbidity unit
OHS	occipital horn syndrome
ORP	redox potential
PEX	cross-linked polyethylene
POU	point of use (device)
PQL	practical quantitation limit
RDA	recommended daily allowance
RO	reverse osmosis
SD	standard deviation
SOD	superoxide dismutase

TBARS	thiobarbituric acid reactive substances
TDS	total diet study
TIC	Tyrolean infantile cirrhosis
WD	Wilson's disease
WHO	World Health Organization

Appendix B: Provincial and territorial anticipated impacts

Please note that this information is not available in both official languages because the source of the information is not subject to the Official Languages Act.

Prince Edward Island

Based on available data, no impact is anticipated.

Newfoundland and Labrador

The Province of Newfoundland and Labrador is responsible for extensive monitoring for inorganic parameters including copper in the province. Copper monitoring is conducted semi-annually for all public water supplies in the province, and quarterly for populations larger than 5,000. pH in the province is typically low and below the guideline of 6.5–8.5. There are typically greater than 300 pH exceedances in the province annually. As discussed in the technical document, the low pH in the province causes issues with corrosion and can affect the copper concentration levels in drinking water.

There are 4 communities that may not meet the new proposed MAC of 2.0 mg/L. There are currently 16 communities that occasionally exceed the existing AO of 1.0 mg/L. There could be a moderate cost of implementing the proposed guideline for copper in Newfoundland and Labrador. Due to naturally low pH issues experienced by many water systems in the province, prevention of corrosion in household plumbing will require some communities to install pH adjustment systems or upgrade their existing pH adjustment systems to maintain appropriate pH levels within the distribution system. Water pH in some communities is so low, that even with treatment, it would be difficult to dose enough chemical to meet both pH and copper guidelines. Due to this, new treatment systems and/or significant upgrades may be required to a number of existing systems. The province will continue to monitor for copper and pH at the current frequency, and to assist communities in ensuring their pH adjustment systems are working effectively to increase pH levels and keep corrosion control measures in place.

Nova Scotia

Health Canada proposes to establish a maximum acceptable concentration (MAC) of 2 mg/L for total copper in drinking water while maintaining the existing aesthetic objective of 1 mg/L.

Available data suggests that utilities will not be impacted as a result of the proposed reduction; however, this data represents flushed samples collected from the distribution system and is not representative of total copper concentrations at the customer's tap. Existing data prevents an accurate determination of the true impact. The widespread use of copper in plumbing and distribution system components coupled with the lack of enforceable corrosion control program requirements likely result in consumer exposures to copper that are above the concentrations currently reported by utilities.

For Nova Scotia, the revised guideline will require the development and enforcement of copper sampling protocols in addition to clear requirements for corrosion control programs. This will likely result in challenges for the utilities and the Inspection, Compliance, and Enforcement Division of Nova Scotia Environment. Specific challenges are likely to include: lack of willing participants; access for sample collection; and increased costs for laboratory analysis.

New Brunswick

New Brunswick is supportive of a copper guideline that is protective of public health. Based on historical drinking water quality results for both regulated municipal and crown systems, as well as private wells, there is no evidence that this guideline will cause any significant immediate impacts. However, copper is not a regulated parameter in New Brunswick as there is no health based guideline. For the most part, water quality data for regulated drinking water systems has been obtained from samples and taken at the same time and location as other Inorganic parameters as part of regular compliance monitoring. The true impact of this guideline will not be known until sampling and monitoring protocols and approaches are updated to align with the recommendations of the guideline.

Quebec

Au Québec, de 2012 à 2015, 17 863 analyses de cuivre ont été réalisées dans le cadre du Règlement sur la qualité de l'eau potable, dans l'eau d'un total de 3049 réseaux de distribution. Les responsables de tous les réseaux assujettis au Règlement doivent réaliser annuellement le contrôle du cuivre dans l'eau potable distribuée. Durant la période de 2012 à 2015, 119 (0,7 %) des analyses réalisées ont présenté un résultat supérieur à la norme québécoise pour le cuivre dans l'eau potable établie à 1,0 mg/L, pour 70 réseaux de distribution distincts (2 %). La concentration maximale mesurée a atteint 15 mg/L. La révision proposée de la recommandation sur le cuivre dans l'eau potable n'aurait pas d'impact pour les réseaux de distribution du Québec étant donné que la norme québécoise est plus sévère que la concentration maximale acceptable proposée dans le document.

Ontario

The proposed *Guideline for Canadian Drinking Water Quality* for copper of 2 mg/L and an aesthetic objective of 1 mg/L will have minimal impact in Ontario. Ontario currently has an aesthetic objective of 1 mg/L for copper. The health guideline value for copper will be appropriate to assess the health impacts of the occasional exceedance of the aesthetic objective for copper.

Manitoba

A review of available public and semi-public water system data does not provide a clear picture of potential impacts of the proposed change to the Canadian guideline for copper in drinking water from an aesthetic objective of ≤ 1 mg/L to a maximum acceptable concentration (MAC) of 2 mg/L and an aesthetic objective of 1 mg/L. Manitoba water systems have historically been monitoring for metals, including copper, at water treatment plants. The proposed guideline requires that copper samples be drawn at the consumer's tap, which takes into consideration the effects of the main distribution system and individual home plumbing systems. Sampling at the consumer's tap would represent a significant change for Manitoba water systems. This would likely be the most significant impact from a cost perspective as well.

Saskatchewan

The Water Security Agency (WSA) has reviewed the proposed guideline document for copper in drinking water and agrees with the proposed MAC of 2 mg/L and aesthetic objective of 1 mg/L for total copper in drinking water. Drinking water data of 3512 samples collected in the last 10 years (2006 to present) from the distribution systems of municipalities regulated by the

WSA showed that total copper levels exceeded the proposed MAC and aesthetic objective in only 8 sampling locations or distribution systems of communities in the province. The WSA notes that copper in drinking water mainly results from the corrosion of copper containing pipes and fittings in the distribution and plumbing systems and based on the chemistry of water. An analysis of total copper levels in source water in the database showed that the copper levels are very low/insignificant to cause any exceedances in finished water. Some of the municipalities in Saskatchewan continue to replace the aged service lines and plumbing systems, and others have some form of replacement programs including providing an incentive to home owners to replace their aged service lines from the curb stop to the building entry. The WSA follows the corrosion control guidance document of Health Canada in dealing with exceedances of parameters such as copper and lead in the distribution system and encourages the waterworks owner to replace the service lines where related exceedances occur. The communities regulated by the WSA continue to monitor copper levels in the distribution systems as per monitoring requirements specified in the provincial document “Municipal Drinking Water Quality Monitoring Guidelines - EPB 202” and in accordance with operational permit conditions. Since studies showed that many of the water treatment systems including conventional water treatment filtration systems are effective in removing copper, and since these type of treatment systems are in existence and/or are being increasingly adopted for use in WTPs in the province the WSA believes and expects that the new standard for Total Copper will have a minimal or no impacts including cost to municipal and other regulated waterworks in the province. The WSA will also work with the affected municipalities in the province to have an improved monitoring of pH/ or alkalinity levels at the water treatment plant and the use of corrosion inhibitors, if necessary so as to minimize the copper level in the distribution system.

Alberta

Based on available data, no impact is anticipated.

British Columbia

The proposed change to the copper guidelines to maintain the aesthetic objective (AO) at 1.0 mg/L as well as the addition of a maximum acceptable concentration (MAC) of 2.0 mg/L based on studies citing an association between long term exposure to copper and liver and kidney effects is anticipated to have some notable shifts in how copper in drinking water is measured. Similar to lead, a notable impact of the new MAC will be the shift in focus from centralized sampling to point of consumption based programs. Sampling of buildings, particularly high risk institutions such as schools and daycares, will remain a cost pressure. Questions of whether this is responsibility of water suppliers or building owners will be raised.

Given that the data on water concentrations reported in section 5.2 shows very few exceedances of the MAC, it is anticipated the proposed change in the guideline will have little impact on the water delivered by water supply systems. However, as leaching from fixtures within individual buildings is likely the most significant contributor to copper concentration in water, it is therefore difficult to anticipate copper concentrations delivered at individual taps, as this will vary from building to building, depending on plumbing, and system to system, depending on how corrosive water is.

The proposed addition of a maximum acceptable concentration will also mean significantly different messaging from what health officials have historically given regarding copper. It will also require the need for clear and meaningful advice to those that have been

consuming water sources that exceed the proposed MAC, who have previously been told that elevated copper is merely an aesthetic concern.

Yukon

It is not possible to quantify the impact of the proposed technical document and MAC for copper at this point in time for Yukon. The Yukon drinking water regulatory framework is primarily focused on water treatment and provision of safe drinking water as it leaves the water treatment plant to the distribution system. Provisions of the Drinking Water Regulation specify specific monitoring requirements for raw and treated water (at the point of water leaving the plant). While there is a requirement for monitoring of free chlorine, total coliforms and *E.coli* within the distribution system, there are currently no specific requirements for routine monitoring of other parameters.

Environmental Health Services (EHS) regulatory mandate extends to curb stop for large public drinking water systems. Routine compliance monitoring and regulatory requirements for large public drinking water system owners beyond this point is not within the current mandate. Further policy development would be needed to incorporate testing at the tap. Currently all Yukon large public drinking water systems meet the proposed MAC for copper entering the distribution system. EHS will be doing policy development in terms of monitoring of the distribution system for copper and other metals over the next few months.

Northwest Territories

No impact paragraph has been provided by the territory.

Nunavut

No impact paragraph has been provided by the territory.