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The need for a reassessment of the safe upper limit of selenium in drinking water

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ABSTRACT

Results of recent epidemiologic studies suggest the need to reassess the safe upper limit in drinking water of selenium, a metalloid with both toxicological and nutritional properties. Observational and experimental human studies on health effects of organic selenium compounds consumed through diet or supplements, and of inorganic selenium consumed through drinking water, have shown that human toxicity may occur at much lower levels than previously surmised. Evidence indicates that the chemical form of selenium strongly influences its toxicity, and that its biological activity may differ in different species, emphasizing the importance of the few human studies on health effects of the specific selenium compounds found in drinking water. Epidemiologic studies that investigated the effects of selenate, an inorganic selenium species commonly found in drinking water, together with evidence of toxicity of inorganic selenium at low levels in from in vitro and animal studies, indicate that health risks may occur at exposures below the current European Union and World Health Organization upper limit and guideline of 10 and 40 μg/l, respectively, and suggest reduction to 1 μg/l in order to adequately protect human health. Although few drinking waters are currently known to have selenium concentrations exceeding this level, the public health importance of this issue should not be overlooked, and further epidemiologic research is critically needed in this area.

1. Introduction

The metalloid selenium has always generated strong interest and controversy among members of both the scientific community and the general public due to its complex toxicological and nutritional properties (Fan and Kizer, 1990; Fordyce, 2007; Navarro-Alarcon and Cabrera-Vique, 2008; Bergomi et al., 2009a, 2009b; Lee and Jeong, 2012). Much recent interest in selenium attended the results of a clinical trial (Clark et al., 1996) and a few observational cohort studies (Vinceti et al., 2000c) that suggested a cancer preventive effect. However, further and larger studies have failed to support such an effect (Lippman et al., 2009; Dennert et al., 2011; Algotar et al., in press).

The issue of toxicity of selenium in drinking water has attracted debate since the 1970s (Pletnikova, 1970; Lafond and Calabrese, 1979; Hammer, 1981; Alexander, 1993; Barron et al., 2009; Gore et al., 2010; Gilron, 2012). Reflective of this controversy, a range of different standards and guidelines have been adopted or proposed (ICAIR - Life Systems Inc., 1990; WHO, 1996, 2011a; European Council, 1998; Vinceti et al., 2009; OEHHA, 2010; Gilron, 2012; ANSES, 2012). As recently reviewed (OEHHA, 2010), in most cases (European Union, Canada, Australia, Japan, Thailand and New Zealand, and for bottled waters, the United States Food and Drug Administration), the upper limit has been set to 10 μg/l, with the exception of Russia, which has set a limit of 1 μg/l as selenium trioxide since 1970, the U.S. Environmental Protection Agency, which has set a limit of 50 μg/l and the California Environmental Protection Agency, which has set a limit of 30 μg/l. Recently a background document published by a World Health Organization (WHO) group suggested a guideline value of 40 μg/l for drinking water (WHO, 2011a), and this value was incorporated into the update of the WHO guidelines for drinking water quality (WHO, 2011b), though tempered by its definition as a "provisional guideline value because of uncertainties in the health database." However, the background document did not consider the

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most recent epidemiologic and laboratory literature on selenium toxicity, including that of the inorganic forms typical of drinking waters, and therefore appears to have missed key relevant information (WHO, 2011a). New data on the toxicity of both inorganic and organic selenium from both human and laboratory studies (Vinceti et al., 2009) make it timely and appropriate to reassess the safety of selenium in drinking water and the adequacy of current regulatory standards. In the present report, we aimed to re-evaluate the potential hazard of selenium to human health when administered through drinking water, as well as the adequacy of current and proposed environmental standards in this regard. We did not intend to undertake a comprehensive review of the overall issue of selenium toxicity, for which we refer to several reviews (Fordyce, 2005; Vinceti et al., 2009; Brozmanova et al., 2010; Valdiglesias et al., 2010; Nogueira and Rocha, 2011; Copat et al., 2012).

The establishment of a new standard for selenium in drinking water is uniquely complex. Selenium is both an essential trace mineral nutrient and potentially toxic, with its effect depending on its dose and chemical form (Aggett, 2010; Douron, 2010; Lee and Jeong, 2012). In this respect, selenium epitomizes Paracelsus' proverb, "*Dosis facit venenum*" ("It is the dose that makes the poison"). Unlike other trace elements such as manganese and chromium, which are also known to be both toxic and essential for human health depending on dose and chemical form, selenium has garnered strong attention from the public and scientific community as a potential antioxidant and anti-carcinogen. The discovery of several selenoproteins, some with antioxidant properties, starting with the identification of selenium-containing glutathione peroxidase in 1973 (Rotruck et al., 1973), and suggestions of anticancer activity from epidemiologic and laboratory studies (IPCS INCHEM, 1987), prompted study of selenium supplementation in clinical trials and large-scale use of selenium as a nutritional supplement by the public (Stranges et al., 2010a). However, a large body of biochemical studies in the past two decades has demonstrated that selenium itself is a pro-oxidant rather than an antioxidant element, and that selenium-induced enzymes such as the selenium-containing glutathione-peroxidases and other non-selenium containing enzymes have both pro-oxidant and anti-oxidant effects (Vinceti et al., 2009; Miller and Hontela, 2011; Nogueira and Rocha, 2011; Lee and Jeong, 2012; Medeiros et al., 2012). Moreover, selenium in the form of selenium sulfide has been recognized as a carcinogen (United States Environmental Protection Agency, 2009). Thus the issue of a standard for selenium involves grappling with a complex myriad of issues.

2. Chemical forms

A key issue that must be considered with regard to exposure standards is that the chemical forms of selenium differ as to their toxicity, biological activity and nutritional roles, with such marked differences as to make futile the identification of single selenium standard for public health and environmental purposes (Vinceti et al., 2009). For example, selenium is a recognized neurotoxin, with inorganic selenium appearing to be about 40 times more neurotoxic than organic selenium (Ammar and Couri, 1981). Similar differences in biological activity of inorganic and organic selenium compounds have been shown in several experimental settings (Vinson and Bose, 1987; Borella et al., 1996; Barbosa et al., 1998; Johnson et al., 2000; Tsunoda et al., 2000). The organic forms generally exhibit less toxicity compared with inorganic forms, and in a few instances even have opposite effects. However, some effects such as low-dose toxicity on metabolic cell activity and insulin-induced Akt phosphorylation have been observed regardless of the inorganic or organic nature of the selenium compound under study (Pinto et al., 2011). Overall, the available evidence clearly indicates the importance of considering the different selenium compounds and of selenium speciation, and this issue is currently attracting considerable interest in human studies (Michalke et al., 2009; Solovyev et al., in press).

The fact that the toxicity of different selenium species may differ so markedly also raises issues about suitability of biomarkers in reflecting the biologically relevant selenium exposure; for example, the inorganic forms tend to be more toxic to target cells such as motor neurons than organic species at comparable amounts of intake, despite the greater retention of the latter species (Panter et al., 1996; Kim and Mahan, 2001), thus posing complex issues concerning exposure assessment for this metalloid.

Thus public health standards for selenium should take into account chemical form, an issue that is particularly critical for a drinking water standard for selenium since selenium occurs almost entirely in inorganic form in drinking water (Vinceti et al., 2010; Kumar and Riyazuddin, 2011); in contrast, inorganic forms of selenium are not generally found in foods (Combs, 2001).

3. Human exposure

Selenium is found throughout the world in all environmental matrices including air, soil, foods and drinking waters. In drinking waters, selenium is generally found at relatively low concentrations, with a few exceptions in cases of environmental contamination. In underground and surface waters, selenium is commonly found at levels on the order of pg/l, rarely reaching or exceeding 1 μg/l (Fordyce, 2005; Hu et al., 2009; Kumar and Riyazuddin, 2011). In some exceptional areas of the world, selenium content in well water or more generally in underground waters used for human consumption may reach 10–20 μg/l, with some concentrations in the hundreds of μg/l (Wang et al., 1991; Alfthan et al., 1992; Conde and Sanz Alaejos, 1997; Dhillon and Dhillon, 2003; Hurtado-Jimenez and Gardea-Torresdey, 2007; Hudak, 2009; Gourcy et al., 2010; Kuisi and Abdel-Fattah, 2010; Barron et al., 2012). Mineral waters generally contain selenium at levels of a few ng/l (Yanardag and Orak, 2001; Ferri and Frasconi, 2006). Drinking water is not generally regarded as a nutritional source of the element (Alexander, 1993).

The source of selenium found in underground waters is usually geologic, though selenium may also be an anthropogenic contaminant, released from facilities such as coal plants, mines and some industrial facilities, and large-scale land contamination due to high-selenium agricultural drainage in the California Central Valley has occurred (Wu, 2004; Gao et al., 2007).

By far most selenium found in well water and underground water, and therefore in tap water, is in the inorganic form, generally as hexavalent selenium, selenate, in ordinary alkaline and oxidized conditions, and less abundantly as the tetravalent form, selenite (Kuisi and Abdel-Fattah, 2010; Vinceti et al., 2010; Kumar and Riyazuddin, 2011; Randhawa et al., 2012). This also appears to be true for surface waters (Hu et al., 2009). Technologies for removal of these inorganic selenium species from groundwaters are of considerable scientific interest (Mao et al., in press; Randhawa et al., 2012).

4. Toxicity of inorganic selenium: laboratory studies

A number of laboratory studies have contributed to elucidation of the cellular and molecular mechanisms of toxicity of inorganic selenium and the minimum levels of exposure at which toxicity may occur (Vinceti et al., 2009; Nogueira and Rocha, 2011; Lee and Jeong, 2012).

In a 1982 report, Chatterjee and Banerjee (1982) administered selenium as selenite in a culture of mammary glands from BALB/c female mice. Selenium concentrations of 10^{-8} and 10^{-7} M, i.e. 0.8–8 μg/l, were able to enhance the transformation frequency of the glands, both at the initiation and promotional stages, a process considered to be conductive to neoplastic transformation. Interestingly, higher selenium concentrations (10^{-6} and 10^{-5} M) inhibited the frequency of transformed glands.