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Total organic halogen (TOX) in human urine: A halogen-specific method for human exposure studies

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ABSTRACT

Disinfection by-products (DBPs) are a complex mixture of compounds unintentionally formed as a result of disinfection processes used to treat drinking water. Effects of long-term exposure to DBPs are mostly unknown and were the subject of recent epidemiological studies. However, most bioanalytical methods focus on a select few DBPs. In this study, a new comprehensive bioanalytical method has been developed that can quantify mixtures of organic halogenated compounds, including DBPs, in human urine as total organic chlorine (TOCl), total organic bromine (TOBr), and total organic iodine (TOI). The optimized method consists of urine dilution, adsorption to activated carbon, pyrolysis of activated carbon, absorption of gases in an aqueous solution, and halide analysis with ion chromatography and inductively coupled plasma-mass spectrometry. Spike recoveries for TOCl, TOBr, and TOI measurements ranged between 78% and 99%. Average TOCl, TOBr, and TOI concentrations in five urine samples from volunteers who consumed tap water were 1850, 82, and 21.0 μg/L as X^-, respectively. Volunteers who consumed spring water (control) had TOCl, TOBr, and TOI average concentrations in urine of 1090, 88, and 10.3 μg/L as X^-, respectively. TOCl and TOI in the urine samples from tap water consumers were higher than the control. However, TOBr was slightly lower in tap water urine samples compared to mineral water urine samples, indicating other sources of environmental exposure other than drinking water. A larger sample population that consumes tap water from different cities and mineral water is needed to determine TOCl, TOBr, and TOI exposure from drinking water.

Introduction

Water disinfection has been widely used around the world to protect human health against pathogens that cause water-borne diseases like cholera and typhoid. However, disinfectants can further react with other constituents found in natural waters (*i.e.*, natural organic matter, halide ions) and unintentionally form disinfection by-products (DBPs). While only a selected few DBPs are regulated or monitored worldwide, including trihalomethanes (THMs) and haloacetic acids (HAAs), they represent only a small fraction of DBPs formed in disinfected waters. Other classes of DBPs that have been found in disinfected waters include haloacetonitriles, haloacetamides, haloaldehydes, haloketones, halonitromethanes, iodinated-THMs, iodinated acids, halobenzoquinones, and nitrosamines (Brass et al., 1977; Cancho et al., 2000; Mitch and Sedlak, 2002;

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Choi and Valentine, 2002; Weinberg et al., 2002; Mitch et al., 2003; Plewa et al., 2004a, Plewa et al., 2004b; Koudjonou and Lebel, 2006; Krasner et al., 2006; Richardson et al., 2007, 2008; Zhao et al., 2008, 2010; Jones et al., 2011; Richardson, 2011; Allard et al., 2012; Chu et al., 2013; Ding et al., 2013; Linge et al., 2013; Bond et al., 2015; Jeong et al., 2015; Ioannou et al., 2016; Liew et al., 2016; Postigo et al., 2016; Zeng and Mitch, 2016a, 2016b). Although they are found at lower concentrations than THMs and HAAs, these other classes of DBPs have been found to be more cyto- and genotoxic using *in vitro* studies (Plewa et al., 2004a, 2004b; Muellner et al., 2007; Plewa et al., 2008a, 2008b book chapter; Jeong et al., 2015). Furthermore, it has been found that iodine containing DBPs (I-DBPs) are more toxic than bromine containing DBPs (Br-DBPs) and much more toxic than chlorine containing DBPs (Cl-DBPs) (Plewa et al., 2004b, 2008a, 2008b; Richardson et al., 2008 book chapter; Attene-Ramos et al., 2010; Yang et al., 2014).

However, adverse human health effects caused by chronic exposure to DBPs are not fully understood and have been the focus of epidemiologic and human exposure studies. Several studies have suggested an increased correlation between DBP exposure and adverse human health effects, including bladder cancer, colorectal cancer, and adverse birth outcomes (Swan et al., 1998; Waller et al., 1998; Nieuwenhuijsen et al., 2000, 2013; Villanueva et al., 2004, 2007; IARC, 2004; Bove et al., 2007; Costet et al., 2011; Grazuleviciene et al., 2011, 2013; Danileviciute et al., 2012; Jeong et al., 2012; Righi et al., 2012; Smith et al., 2016). Epidemiologic studies, however, are often limited by the lack of knowledge of specific DBP concentrations that individuals were exposed to. For example, because cancer has a ~20–30 year latency period, cancer epidemiologic studies often rely on older, archived THM data, which is typically the only DBP data available due to lack of regulation of other DBPs during that time. These data are usually population-based (provided as average data by the drinking water treatment plant or municipality), and are not based on individual exposures. As a result, exposure assessment is often limited and imperfect. Prospective studies, including adverse birth outcomes from drinking water exposure and asthma from swimming pool exposure, can have better exposure assessments, due to the possibility of sampling the drinking water or pool water over the course of the study and the possibility of collecting biological samples. However, human exposure studies have been limited primarily to measurements of THMs and HAAs in urine (Bader et al., 2004; Kogevinas et al., 2010; Cardador and Gallego, 2011; Gurzao et al., 2013; Smith et al., 2013; Charisiadis and Makris, 2014), blood (Erdinger et al., 2004; Ashley et al., 2005; Leavens et al., 2007; Font-Ribera et al., 2010; Kogevinas et al., 2010), and exhaled breath (Xu and Weisel, 2005a, 2005b; Font-Ribera et al., 2010; Kogevinas et al., 2010). In a recent study, total nitrosamines (TONO) and *N*-nitrosodimethylamine (NDMA) were quantified in urine from people who consumed ranitidine, a pharmaceutical used to treat gastroesophageal reflux disease and ulcers (Zeng and Mitch, 2016a, 2016b). Urinary NDMA concentrations increased significantly after consumption of ranitidine, which points to potential broader human health implications. Because drinking water is a complex mixture of DBPs, containing hundreds of DBPs beyond the regulated THMs and HAAs (Richardson, 2011), a comprehensive bioanalytical method is needed.

Total organic halogen (TOX) is a surrogate measurement used to comprehensively account for halogenated DBPs in finished drinking waters. This measurement includes *known* DBPs that we can measure, as well as *unknown* DBPs that are still unidentified. TOX measurement involves the adsorption of organic compounds onto activated carbon (AC) columns, pyrolysis of the AC in a furnace at 1000°C, and absorption of produced gases (*i.e.*, CO_2, HCl, HBr, HI, HF) into an aqueous solution that is titrated online specifically for halides. Because of the increasing concern of halogen-specific toxicity of DBPs ($I > Br \gg Cl$), TOX analysis has been further developed to distinguish between different halogenated species. Total organic chlorine (TOCl), total organic bromine (TOBr), and total organic iodine (TOI) are three measurements that pertain to the specific organic halogen, and the sum of all of these compounds is known as TOX. The halogen-specific analysis involves adsorption of the effluent gas onto an online ion chromatography (IC) column (Kristiana et al., 2015) or absorption into an aqueous solution that can be analyzed with IC (Echigo et al., 2000; Hua and Reckhow, 2006; Kristiana et al., 2009; Smith et al., 2010), inductively coupled plasma-mass spectrometry (ICP-MS) (Yang et al., 2014), or ultra performance liquid chromatography–electrospray ionization-mass spectrometry (UPLC–ESI-MS) (Gong and Zhang, 2013; Pan and Zhang, 2013).

Human urine is a complex mixture of urea, inorganic and organic salts, and organic compounds, with a range of total dissolved solids of 28.1 to 37.1 g/kg (Putnam, 1971). A comprehensive TOX measurement was previously carried out on 51 human urine samples from human subjects that lived in two cities in Sweden (Salkinojasalonen and Jokela, 1991). Results show a positive correlation between TOX measured in drinking water from six different sampling points and TOX measured in urine samples from human subjects that lived close to each drinking water sampling point. The findings suggest that TOX is possibly a good indicator for DBP exposure from disinfected treated waters. However, the TOX values measured did not distinguish between TOCl, TOBr, and TOI. Because it has been shown in comparative *in vitro* studies that toxicity is halogen-specific (Attene-Ramos et al., 2010; Plewa et al., 2004b), TOCl, TOBr, and TOI in urine could provide more insight between DBP exposure and adverse health outcomes in human exposure studies. In recent literature, an analytical method was developed to measure TOI, iodide, and iodate for various sample matrices, including urine (Gong and Zhang, 2013). The analytical method was not optimized for TOCl and TOBr in human urine samples.

The aim of this research was to develop a bioanalytical method that can comprehensively capture DBP exposure from disinfected treated waters in human populations. In this study, we tested different conditions, including the volume of urine, dilution of urine, number of AC columns, and composition of the absorption solution to accurately capture TOCl, TOBr, and TOI concentrations in human urine samples. This bioanalytical method will test TOCl, TOBr, and TOI in urine as potential DBP exposure biomarkers. This method could ultimately be used to assess adverse human health effects to exposure of halogenated DBPs and other environmental contaminants in human exposure or epidemiological studies.

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