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Benzotriazoles and benzothiazoles in paired maternal urine and amniotic fluid samples from Tianjin, China

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HIGHLIGHTS

- TTR and BTH were detected in amniotic fluid with detection rates (DRs) of more than 50%.
- Mothers and fetuses in Tianjin can be frequently exposed to BTRs and BTHs.
- DRs and concentrations of BTRs and BTHs in amniotic fluid were lower than those found in maternal urine.
- No significant correlations were observed in paired maternal urine and amniotic fluid for BTRs and BTHs.

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ABSTRACT

Benzotriazoles (BTRs) and benzothiazoles (BTHs) are two groups of heterocyclic compounds that are widely detected in the environment. In this study, the levels of BTRs and BTHs in 79 paired maternal urine and amniotic fluid samples from Tianjin were investigated. BTRs were detected in most maternal urine samples, with a median concentration of ∑BTRs of 0.88 ng/mL. BTH was detected in all maternal urine samples, with a median concentration of 1.35 ng/mL. Tolyltriazole (TTR, i.e., the sum of 4-methyl-1H-benzotriazole and 5-methyl-1H-benzotriazole) and BTH were detected in amniotic fluid with detection rates (DRs) > 50% and median concentrations of 0.026 and 0.61 ng/mL, respectively. The median concentrations of ∑BTRs and ∑BTHs (0.026 and 0.72 ng/mL) in amniotic fluid were lower than those in maternal urine. The median ratio of the ∑BTRs concentrations in amniotic fluid to those in maternal urine was 0.030, with a range of 0.017–1.82, while the median value for TTR, BTH and 5-Cl-1H-BTR were 0.12, 0.46, and 1.43, respectively. This indicates greater distribution in fetal excretion to 5-Cl-1H-BTR than BTH and TTR. The concentrations of ∑BTRs in maternal urine exhibited significant distribution differences ($p < 0.05$) with respect to some parameters, including maternal age, gestational week, gravidity, parity, and fetal weight. However, no significant correlations ($p > 0.05$) were observed in target compounds in amniotic fluid for the epidemiological factors assessed herein. The geometric means of the estimated daily intakes were 1.15 (0.052–7.66) μg/day and 1.92 (0.027–6.64) μg/day for ∑BTRs and ∑BTHs in present study, which are lower than those reported in previous study.

1. Introduction

Benzotriazoles (BTRs) and benzothiazoles (BTHs) are nitrogen-containing heterocyclic compounds. Due to their antiseptic properties and effects on light absorption and crosslinking, BTRs and BTHs have been widely used as organic corrosion inhibitors in a variety of consumer and industrial products (Deona et al., 1998; Cancilla et al., 2003). BTRs are also used as ultraviolet-absorbing antifreezing agents, dishwashing detergents, and antifogging agents (Wang et al., 2013). Benzothiazole (BTH) and its derivatives are commonly used in rubber products to accelerate the vulcanization of rubber and improve mechanical strength (Llompart et al., 2013). The output of BTHs was reported up to 450 t in 1993, and the

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yield of BTRs was at least 9000 t in 1999 (Hart et al., 2004).

Due to their increasing application, BTRs and BTHs have been widely detected in the environment, e.g., sewage from wastewater treatment plants, surface water, groundwater, sediment, drinking water, indoor air, and house dust (Walter et al., 2006; Wolschke et al., 2011; Zhang et al., 2011; Wang et al., 2013, 2016; Kong et al., 2015; Xue et al., 2016), posing exposure risks to ecosystems and humans. Toxicity studies have revealed that BTRs are phytotoxic, potentially carcinogenic and mutagenic, and estrogenic (Joseph et al., 1985; Harris et al., 2007; He et al., 2012). Accordingly, some countries have issued standards and regulations on these heterocyclic compounds to reduce their adverse effects. In 2000, 1H-benzotriazole (1H-BTR) was listed as a suspected human carcinogen by the Dutch Expert Committee on Occupational Standards (HCN, 2000) and was classified as an emerging contaminant by the United States Environmental Protection Agency in 2008 (Richardson, 2008). The allowable concentrations of 1H-BTR and 5-chloro-1H-benzotriazole (5-Cl-1H-BTR) in drinking water were limited to less than 20 ng/L in Denmark (Nielsen and Ladefoged, 2013), while the concentration of tolyltriazole (TTR, the sum of 4-methyl-1H-benzotriazole (4-Me-1H-BTR) and 5-methyl-1H-benzotriazole (5-Me-1H-BTR)), in drinking water was restricted to less than 7 ng/L by the Australian Government (AGWR, 2008).

Until now, there have been limited studies on human exposure to BTRs and BTHs around the world. BTRs and BTHs have been detected in human urine from the USA, China, Japan, India, Greece, Vietnam, and Korea and in human adipose tissue from the USA, demonstrating that BTRs and BTHs are widespread in the human body (Asimakopoulos et al., 2013a,b; Wang et al., 2015). Urine samples have been used as biomarkers of human exposure to BTRs and BTHs due to the simplicity of urine sampling. Due to their polar structures, both BTRs and BTHs have high water solubility that ranges from 3069 ng/mL (4-Me-1H-BTR) to 22,600 ng/mL (1-hydroxy-benzotriazole (1-OH-BTR)) (Asimakopoulos et al., 2013a). In a survey of urine samples from seven countries, BTH was found in higher concentrations than the other BTH derivatives, while BTR and TTR were found at low detection rates (DRs) (Asimakopoulos et al., 2013b). Overall, the geometric means (GMs) of the concentrations of $\sum$BTRs in different countries ranged from 0.40 to 2.10 ng/mL with DRs from 12.0 to 76.4%, while the GMs of the concentrations of $\sum$BTHs ranged from 2.80 to 10.7 ng/mL with DRs from 40.0 to 100% (Asimakopoulos et al., 2013b).

Amniotic fluid is derived from the urine, gastrointestinal tract, and umbilical cord of fetuses in the third trimester of pregnancy (Underwood et al., 2005); hence, it is an important matrix that reflects the prenatal exposure of fetuses to chemicals. Several organic contaminants (i.e., poly- and perfluoroalkyl substances, phthalate metabolites, and perchlorate) have been reported in amniotic fluid (Blount et al., 2009; Huang et al., 2009; Jensen et al., 2012; Zhang et al., 2013), revealing extensive prenatal exposure of fetuses to chemical contaminants. Simultaneous biomonitoring of BTRs and BTHs in paired maternal urine and amniotic fluid samples allows an understanding of the distribution of these kind of compounds between the two matrices. Moreover, a significant correlation between the levels of target chemicals in maternal urine and amniotic fluid can indicate the potential of using the urine concentration as a biomarker for the prenatal exposure of fetuses. However, the relationship between the chemical concentrations in maternal urine and amniotic fluid has been seldom reported. Animal studies using rats revealed an exponential relationship between maternal urinary mono-2-ethylhexyl phthalate (MEHP) levels and those in amniotic fluid (Calafat et al., 2006). Significant correlations were also found between maternal urine and amniotic fluid concentrations of organic contaminants, such as phthalate metabolites and perchlorate, in humans (Huang et al., 2009; Blount et al., 2009). To the best of our knowledge, exposure of pregnant women and fetuses to BTRs and BTHs has never been documented, and the relationship between the levels of BTRs and BTHs in maternal urine and amniotic fluid has not been previously assessed.

In this study, 79 paired maternal urine and amniotic fluid samples were collected from Tianjin, China. The aims of this study were 1) to investigate the concentration profiles of 4 common BTRs (i.e., 1H-BTR, 5-Cl-1H-BTR, TTR, and 1-OH-BTR) and 4 BTHs (i.e., BTH, 2-hydroxy-benzothiazole (2-OH-BTH), 2-chloro-benzothiazole (2-Cl-BTH), and 2-amino-benzothiazole (2-NH_2-BTH)) in paired maternal urine and amniotic fluid samples from individual pregnant women from Tianjin; 2) to assess the relationships between the concentrations of these heterocyclic compounds and select epidemiological parameters; and 3) to elucidate the distribution of BTR and BTH derivatives concentrations between maternal urine and amniotic fluid.

2. Materials and methods

2.1. Sample collection

Eighty-three maternal urine and 79 amniotic fluid samples (162 total samples), of which 79 were paired, were collected from Tianjin in October and November 2015. This research was approved by the Ethics Committee of Tianjin Central Hospital of Gynecology Obstetrics, and all the participants were informed for the research objectives, which was dispatched and collected together with the questionnaire. Maternal urine samples (~20 mL) were collected 2 h before delivery, and amniotic fluid samples (~3 mL) were collected during delivery. All the samples were stored at −20 °C prior to chemical analysis. Epidemiological parameters, including maternal age, weight before delivery, educational background, body mass index (BMI), gestational week, gravidity, parity, fetal weight and gender, were obtained by a questionnaire and are summarized in the Supplementary Information (SI) (Table S1).

2.2. Reagents and chemicals

All reagents used for the analysis of the target compounds were of trace analysis grade. 1-OH-BTR and 5-Cl-1H-BTR were purchased from Sigma-Aldrich (St. Louis, USA). 2-NH_2-BTH, 4-Me-1H-BTR and 5-Me-1H-BTR were purchased from Acros Organics (Morris Plains, USA). 1H-BTR, BTH, and 2-OH-BTH were purchased from Alfa Aesar (Karlsruhe, Germany). 2-Cl-BTH was purchased from Heowns Biochem (Tianjin, China). Benzotriazole-d_4 (D_4-BTR) and benzothiazole-d_4 (D_4-BTH) were purchased from CDN Isotopes (Pointe-Claire, Canada) and Toronto Research Chemicals (Toronto, Canada), respectively, and were used as internal standards for monitoring the quality of sample treatment and instrumental analysis. The purities of all analytical standards were higher than 95%. Oasis HLB cartridges (200 mg/6 mL) were purchased from Waters Company (Milford, USA). Methanol, ammonium acetate, Milli-Q water, and acetonitrile were purchased from CNW Technologies GmbH (Shanghai, China). Hydrochloric acid used as an acidity regulator was obtained from Tianjin Chemical Reagent Wholesale Company (Tianjin, China). β-Glucuronidase (100,000 Unit/mL) containing sulfatase (50,000 Unit/mL) was purchased from Sigma-Aldrich (St. Louis, USA). Select physicochemical properties of BTRs and BTHs are shown in Table S2.

2.3. Sample preparation

BTRs and BTHs in the two matrices were extracted via solid phase extraction (Asimakopoulos et al., 2013a). Briefly, 2 mL of each sample and 4 mL of 1 M ammonium acetate buffer (0.77 g of