Journal of Hazardous Materials 362 (2019) 451–457

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

First-trimester blood concentrations of drinking water trihalomethanes and neonatal neurobehavioral development in a Chinese birth cohort

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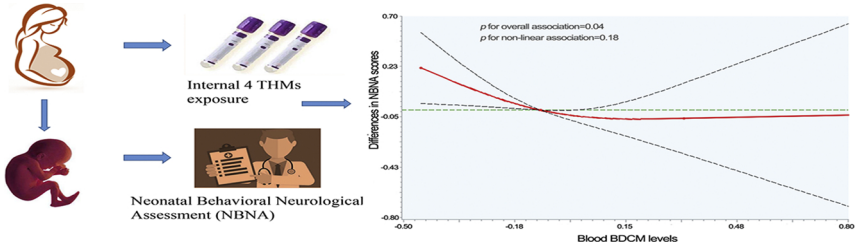
GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Behavioral neurological assessment
Blood trihalomethanes
Pregnancy
Epidemiology
Newborn

ABSTRACT

Toxicological evidence indicates that exposure to drinking water trihalomethanes (THMs) can impair neural development. However, no epidemiologic study to date has evaluated the relation of trihalomethanes exposure with neonatal neurobehavioral development. Here we aimed to evaluate if prenatal exposure to THMs during early pregnancy is associated with neonatal neurobehavioral development in 451 Chinese mother-child pairs. First trimester blood THMs [chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM)] were determined by solid phase micro-extraction gas chramatography. Neonatal neurobehavioral development was assessed using neonatal behavioral neurological assessment (NBNA) on the third day after birth. Multivariable linear regression models and restricted cubic spline models were constructed to evaluate the associations between blood THMs and neonatal neurological development scores. Blood concentrations of BDCM, whether modeled as continuous or categorical variables, were inversely associated with total NBNA score of newborns based on the multivariable linear regression. The association was further confirmed in the cubic spline model, and a linear dose-response relationship was observed. Stratified analysis showed that the inverse association between blood BDCM and total NBNA score was more evident in male infants than females. Our findings suggest that exposure to THMs during early pregnancy may be associated with impaired neonatal neurobehavioral development.

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https://doi.org/10.1016/j.jhazmat.2018.09.040
Received 18 March 2018; Received in revised form 11 September 2018; Accepted 12 September 2018
Available online 22 September 2018
0304-3894/

1. Introduction

Chlorination is commonly used in the world as an effective disinfectant to reduce the risk of water-born infectious disease and secure the safety of public water supply [1]. However, disinfection by-products (DBPs) can be produced in the process of disinfection as a consequence of the combination of chlorine and natural organic matter. Nowadays, more than 700 classes of DBPs are identified in chlorinated drinking water. Trihalomethanes (THMs), including chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM) and bromoform (TBM), account on average for 66% of the measured chlorinated DBP compounds [2]. THMs are lipophilic and volatile, and humans can be readily exposed to THMs in their daily water-use activities through ingestion, inhalation and dermal absorption (e.g., consumption, swimming and bathing) [3].Concentrations of THMs in blood are sensitive exposure biomarkers [4–6], which have been conformably detected in different populations, including specific vulnerable subgroups (e. g., pregnant women) [7,8].

Accumulating evidence indicates that exposure to THMs can induce neurotoxicity. Balster and Borzelleca [9] evaluated the behavioral toxicity of THMs in drinking water in adult mice, and found their operant behavior was affected by 100 mg/kg/day of TCM, BDCM and TBM and by 400 mg/kg/day of all 4 THMs with 60-day administration. Guariglia et al. [10] reported that prenatal and postnatal exposure to a combination of THMs and tetrachloroethylene caused an autistic like behavioral symptoms in CD-1 mice. Moser et al. [11] revealed that 6-month exposure to BDCM resulted in decreased body tone and axonopathy of the sciatic nerve in the midthigh region of treated rats. Studies from humans also suggested that THMs exposure may exert neurotoxicity. For instance, long-term occupational exposure to TCM was found to be associated with a variety of neurological disorders [12]; TBM was reported to cause central nervous system inhibitory by binding with human γ-aminobutyric acid receptor (GABA-R) [13]. Several epidemiological studies also reported that exposure to THMs was associated with central nervous system defects, such as neural tube defects (NTDs) [14–17]. In a latest Spanish cohort study, Villanueva et al. [18] found that total THMs and brominated THMs uptake though all routes (i.e., inhalation, absorption, or ingestion) during pregnancy was inversely associated with the cognitive score of children at 4–5 years of age. However, no study to date has assessed the association of prenatal exposure to drinking water THMs with neonates' neurobehavioral development, which can be used to predict neurodevelopmental outcomes of infants with high sensitivity and specificity [19,20].

Neonatal Behavioral Neurological Assessment (NBNA) is a valid tool to assess neurobehavioral development of neonates and has been widely used in many studies exploring the effect of exposure to environmental toxicants (e.g., lead, mercury, manganese) on neonatal neurological development [21–24]. Given that first trimester of gestation marks a critical period in neonatal development and vulnerable window of exposure [25,26], we conducted this cohort study to determine whether first-trimester exposure to high levels of drinking water THMs was associated with neonatal neurobehavioral development, using blood THMs concentrations as internal exposure biomarkers.

2. Materials and methods

2.1. Participants

The Medical Ethics Committee of Tongji Medical College approved this study. All recruited subjects were asked to finish written informed consents at enrollment. Mother-infant pairs in this study were participants recruited at the Maternal and Child Health Care Service Centre of Xiaonan District at Xiaogan City, Hubei Province, as part of an ongoing longitudinal study which was designed to examine the associations between prenatal environmental contaminants and birth outcomes. Eligible participants were those who were singleton pregnancy, < 14 week of gestation, permanently resident in Xiaogan District during pregnancy and had no history of psychiatric disorders and occupational exposure. From March 2015 to June 2016, 569 eligible mother-infant pairs were enrolled. Of them, 19 neonates were excluded because of severe condition (i.e., Down's syndrome, cleft palate, meningitis and severe neonatal jaundice) that may adversely affect neurodevelopment, and 99 did not perform the NBNA test because of unwillingness. Thus, a total of 451 mother-neonate pairs were finally retained in our current analysis.

2.2. Questionnaires

All participants were interviewed face-to-face during their clinic visits under the guidance of investigators who have been specifically trained. We collected information regarding demographic characteristics, dietary habit, marital status, medical history, occupational exposure, lifestyle factors (e.g., smoking status and drinking) and data of daily water-use activities (e.g., sources of drinking water, amount of tap-water consumption each day, use of boiled water, time since the last showering/bathing, frequency of showering/bathing and swimming habits).

2.3. Blood collection and analysis

A 5-mL venous blood was drawn from each subject on her first clinic visit during early pregnancy. After collection, we immediately shook the blood tubes to dissolve the anticoagulant. The blood samples sealed in an ice cooler were then transported to our laboratory and kept at 4 °C until determination of THMs within 14 days [27].

Blood levels of 4 THMs (i.e., TCM, BDCM, DBCM and TBM) were determined using the method of Headspace Solid Phase Micro-extraction Gas Chromatography (HS-SPME-GC), as previously described [28]. In short, a 3-mL whole blood sample was transferred to a 10-mL headspace vial. A SPME fiber was inserted into the headspace to facilitate extraction of THMs. At the same time, the samples were heated (26°C) and agitated (650 rpm) with a magnetic stirrer. Analytes were extracted on that fiber for 20 min and then determined with an electron capture detector. The average recoveries for the 4 THMs ranged from 82% to 114%, and the coefficient of variation (within-day and between-day variation) was < 10%. The limits of detection (LODs) for TCM, BDCM, DBCM and TBM were 1.90, 0.50, 0.70 and 2.00 ng/L, respectively. Values lower than the LODs were replaced with LOD/√2 for statistical analysis. All analyte levels in blank controls didn't exceed the LODs and thus considered as undetectable.

2.4. Outcome data collection

The infants' information, including delivery mode, gestational age and gender, were collected from the clinical birth records. Anthropometric data of the newborns, including body weight, birth length and head circumference were measured by trained staff according to a standard protocol [29].

NBNA test, formulated by Bao et al. [30] based on the method of Brazelton and Amiel-Tison, was used to assess behavioral neurological of newborns at their 3 days old (48 to 72 h after birth). It consists of five subgroups with a maximum score of 40, namely behavior, primary reflexes, active tone, passive tone and general assessment. Total NBNA score is the sum of five clusters mentioned above. The whole assessment process is completed within 10 min. Neonates with a total score higher than 37 are considered as well developed, less than 34 are considered as abnormal [21,22]. The NBNA test was conducted by two rigorous-trained examiners who had obtained corresponding certificates. There were no significant differences in test scores between the two examiners. They were not aware of the THMs exposure levels of the participants when NBNA assessments were performed.