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Drinking water disinfection by-products during pregnancy and child neuropsychological development in the INMA Spanish cohort study

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ABSTRACT

Background: Disinfection by-products (DBPs) constitute a complex mixture of prevalent chemicals in drinking water and there is evidence of neurotoxicity for some of them.

Objectives: We evaluated the association between estimates of DBP exposure during pregnancy and child neuropsychological outcomes at 1 and 4–5 years of age.

Methods: We conducted a population-based mother-child cohort study in Spain with recruitment at first trimester of gestation (INMA Project, 2003–2008). Neuropsychological development was measured at 1 year of age using the Bayley Scales of Infant Development and at 4–5 years with the McCarthy Scales of Children's Abilities. Modeled tap water concentrations of trihalomethanes (THM) were combined with personal ingestion, showering and bathing habits to estimate exposure as ingestion uptake, all route (showering, bathing, ingestion) uptake (μg/day) and crude levels (μg/l) in the residence. Chloroform, brominated THMs (bromodichloromethane, dibromochloromethane, bromoform) and total THMs (chloroform and brominated THMs) were analysed separately. Nine haloacetic acids levels were available in one of the areas. Linear regression was used to estimate associations in 1855 subjects adjusting for covariables.

Results: The median concentration of total THMs, chloroform, brominated THMs, total haloacetic acids, dichloroacetic acid, and trichloroacetic acid were, respectively 30.3 μg/L, 9.4 μg/L, 11.6 μg/L, 10.5 μg/L, 2.7 μg/L, and 3.1 μg/L. The associations between THM exposure and neuropsychological outcomes were null, except for total and brominated THM uptake though all routes and the general cognitive score at 4–5 years, with a decrease in −0.54 points (95%CI −1.03, −0.05) and −0.64 (95%CI −1.16, −0.12), respectively, for doubling total and brominated THM uptake. A positive association found between dichloroacetic acid and the mental score at 1 year did not persist at 4–5 years.

Conclusions: Minor associations observed between DBP exposure during gestation and child neuropsychological development at 1 year disappeared at 4–5 years. Although a suggestive association is identified for exposure to brominated THMs and the cognitive score at 4–5 years, chance cannot be ruled out.

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1. Introduction

Disinfection by-products (DBPs) are widespread chemicals in drinking water produced as undesired side effects of disinfection process, which is necessary to remove pathogens and prevent waterborne infections. Trihalomethanes (THMs) and haloacetic acids (HAAs) are the two classes at highest concentrations when the disinfectant used is chlorine-based (Richardson et al., 2007). Some DBPs, such as THMs are volatile and skin permeable and human exposure occur through different routes (ingestion, inhalation, skin contact) in activities involving water contact such as showering, bathing, swimming in pools, and intake of water and water-based fluids (Villanueva et al., 2015). On the contrary, HAAs are not volatile or skin permeable and incorporation is mainly through the ingestion route. Given the ubiquity of DBPs, the multiple routes involved and the potential adverse outcomes, DBPs constitute an environmental exposure of concern.

Trihalomethanes are a class of DBPs including chloroform, bromodichloromethane, dibromochloromethane and bromoform. The sum of these four is known as total THMs (TTHMs) and is regulated in the US and EU, among other countries, with a maximum contaminant level (MCL) of 80 μg/L and 100 μg/L, respectively (Villanueva et al., 2014). Haloacetic acids are a family of DBPs including 9 chemicals: monochloro-, dichloro-, trichloro-, monobromo-, dibromo-, tribromo-, bromochloro, bromodichloro, and dibromochloroacetic acids. The sum of monochloro-, dichloro-, trichloro-, monobromo-, and dibromoacetic acid is regulated in the US with a MCL of 60 μg/L (Villanueva et al., 2014). Other DBPs, up to more than 700, have been identified in drinking water, including haloacetonitriles, haloketones among others (Richardson et al., 2007). These occur at much lower concentrations, in the range of ng/l and are not regulated in drinking water (Villanueva et al., 2014).

Dichloroacetic acid is a HAA with extensive evidence of neurotoxicity in humans at high doses. Dichloroacetic salts were used as a drug to treat several metabolic, cardiovascular and cerebrovascular disorders in the past (Stacpoole et al., 1998). Peripheral neuropathy (extremity weakness, decreased nerve conduction velocity, ataxia, tremors) produced by dichloroacetate has been reported in humans (Kaufmann et al., 2006; Spruijt et al., 2001; Stacpoole et al., 1979). Mechanisms suggested by experimental studies in animals involve degeneration of spinal cord nerve fibers, myelin changes and gliosis, observed in rat brain and *in vitro* studies (Felitsyn et al., 2007; Moser et al., 1999). Other haloacetic acids have been shown to produce neurotoxicity in experimental studies, including trichloroacetic acid (neuroembryopathic effect in rats exposed during organogenesis) (Singh, 2006), dibromoacetic acid (neuromuscular toxicity in rats) (Moser et al., 2004), and monocloroacetic acid (neuronal cell death through oxidative stress *in vitro*) (Chen et al., 2013; Lu et al., 2015).

Chloroform used as a solvent has been classified as neurotoxic in humans (Grandjean and Landrigan, 2006) but there is no human evidence on neurotoxicity of chloroform or other THMs in drinking water. Autistic like behaviors have been observed in male mice after gestational and postnatal exposure to chloroform and bromoform in drinking water (Guariglia et al., 2011). However, no evidence of neurotoxicity or neurobehavioural effects on motor activity has been observed in other animal studies (Balster and Borzelleca, 1982; Moser et al., 2007). Experimental evidence in animals from other DBPs occurring at lower levels in drinking water also show effects in murine studies. Chloroacetonitrile crosses the placenta and fetal blood-brain barrier and induces oxidative stress and apoptotic neurodegeneration in fetal brain in mice (Ahmed et al., 2005). Dichloroacetonitrile induces oxidative stress and developmental apoptotic imbalance in mouse fetal brain (Esmat et al., 2012). Detrimental behavioral effects in mice exposed to chloral during the prenatal and early postnatal period but no association among adult animals have been shown (Kallman et al., 1984).

The developing brain and nervous system during gestation is particularly vulnerable to environmental insults, with potential long-term consequences (Grandjean and Landrigan, 2014). Small molecules such as chloroform cross the placenta and can reach the fetus in humans (Dowty et al., 1976), but there is no evidence on the transplacental transmission for other DBPs. Given the widespread character of DBP exposure and the existing evidence suggesting potential neurotoxicity, the evaluation of neurodevelopmental impacts of DBP exposure *in utero* is warranted. We specifically aim to evaluate the association between markers of DBP exposure during pregnancy and neuropsychological outcomes at 1 and 4–5 years of age in a population-based mother-child cohort study in Spain.

2. Methods

2.1. Study design and population

A mother-child cohort study was set up in 4 Spanish areas (Asturias, Gipuzkoa, Sabadell and Valencia) following a common protocol to constitute the INMA — INfancia y Medio Ambiente [Environment and Childhood] Project. For a detailed description of study areas see Supplemental Material. Study subjects were recruited at the first trimester of gestation and followed until delivery. Eligibility criteria for enrollment were maternal age 16 years or older, singleton pregnancy, planning to deliver at the study hospitals, being able to communicate in either of the official languages, and not having followed an assisted reproduction program (Guxens et al., 2012). The study sample was representative of the target population in terms of prenatal care attendance in the public health system (used by more than 80% of the pregnant women). From 45% to 98% of the eligible pregnant women agreed to participate and enrollment periods ranged from November 2003 in Valencia to February 2008 in Gipuzkoa (Guxens et al., 2012). Recruited subjects at the first trimester of gestation were 494 in Asturias, 638 in Gipuzkoa, 657 in Sabadell and 827 in Valencia. Follow-up occurred at the third trimester of gestation, delivery, 1 year and 4–5 years of age. From the initial sample at recruitment, 475 children (96%) in Asturias, 599 (94%) in Gipuzkoa, 583 (89%) in Sabadell and 708 (86%) in Valencia were included at the 1 year follow up and mothers confirmed informed consent to participate for their children. The follow up at 4–5 years included 2028 children (453 in Asturias, 505 in Gipuzkoa, 514 in Sabadell and 556 in Valencia). The study protocol was approved by the Institutional Ethical Committees of the participating centers, and all included mothers gave written and voluntary consent in each phase of the study prior participation. See Fig. S2 for more details on included and excluded subjects.

2.2. THM and HAA levels

Chlorine was the main disinfectant used for drinking water in all the study areas. Sampling locations were defined *a priori* to cover geographically the study areas (see Supplemental Material Fig. S1). Water samples were collected from the tap with no filtration or other treatments that could affect THM or HAA concentration. Sample collection in the different study areas was conducted by local study personnel, who was specifically trained to follow a standardized procedure (see Supplemental Material for details on Experimental THM and HAA analysis in tap water). The sampling strategy did not consider individual pregnancy periods but covered the period between the minimum and maximum conception dates of study subjects.

2.2.1. Trihalomethanes

Concentration of THMs was ascertained based on sampling campaigns and regulatory data from local authorities and water companies. Measurements were conducted at different time points: 2004–2008 (Asturias), 2006–2008 (Gipuzkoa), 2004–2006 (Sabadell), and 2004–2005 (Valencia). THMs were determined in 183 samples in Asturias (18 from our own sampling and 165 from regulatory measurements), 421 in Gipuzkoa (own sampling), 198 in Sabadell (148 own