Chlorination by-products (CBPs) in drinking water and adverse pregnancy outcomes in Italy

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ABSTRACT

Chlorination by-products (CBPs) in drinking water have been associated with an increased risk of adverse pregnancy outcomes, including small for gestational age at term (term-SGA) and preterm delivery. Epidemiological evidence is weakened by a generally inaccurate exposure assessment, often at an ecological level.

A case control study with incident cases was performed in nine Italian towns between October 1999 and September 2000. A total of 1,194 subjects were enrolled: 343 preterm births (26th–37th not completed week of pregnancy), 239 term-SGA (from 37th completed week, and weight less than the lowest 10th percentile) and 612 controls. Exposure was assessed both by applying a questionnaire on mothers' personal habits during pregnancy and by water sampling directly at mothers' homes.

Levels of trihalomethanes (THMs) were low (median: 1.10 μg l^{-1}), while chlorite and chlorate concentrations were relatively high (median: 216.5 μg l^{-1} for chlorites and 76.5 μg l^{-1} for chlorates). Preterm birth showed no association with CBPs, while term-SGA, when chlorite levels ≥200 μg l^{-1} combined with low and high levels of inhalation exposure are considered, suggested a dose-response relationship (adjusted-Odds Ratios (ORs): 1.52, 95%CI: 0.91–2.54 and 1.70, 95%CI: 0.97–3.0, respectively). A weak association with high exposure levels of either THMs (≥30 μg l^{-1}), or chlorite or chlorate (≥200 μg l^{-1}) was also found (adjusted-OR: 1.38, 95%CI: 0.92–2.07). Chlorine dioxide treatment is widespread in Italy; therefore, chlorite levels should be regularly and carefully monitored and their potential effects on pregnancy further evaluated and better understood.

Key words | chlorination by-products, drinking water, exposure assessment, preterm delivery, small for gestational age

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INTRODUCTION

Drinking water disinfection with chlorine and related compounds is commonly applied worldwide because of its low costs and ease of use. However, water chlorination can form different disinfection by-products (chlorination by-products or CBPs) potentially dangerous for human health (Rook 1974, 1977; Aggazzotti and Predieri 1986;

IARC 1991; WHO 1996). Trihalomethanes (THMs), such as chloroform, dichlorobromomethane, dibromochloromethane and bromoform, are the most studied by-products and are considered as an index of the total amount of halogenated CBPs when chlorine or sodium hypochlorite are involved in the treatment. Some 780 other by-products have been identified, including halogenated acetonitriles, acetic acids, aldehydes, chlorophenols and chloroacetones (Steven *et al*. 1987; IARC 1991; WHO 1996). As opposed to sodium hypochlorite use, disinfection with chlorine dioxide forms low amounts of THMs but produces other CBPs, mainly chlorite and chlorate, which are able to induce oxidative stress and alteration in haematological parameters in animals (WHO 1996; IPCS 2000; USEPA 2000; Chang *et al*. 2001; OEHHA 2002).

Studies on laboratory animals have reported both reproductive and foetal development toxicity associated with CBPs exposure (Keen *et al*. 1992; Klinefelter *et al*. 1995; WHO 1996; IPCS 2000; USEPA 2000; Bielmeier *et al*. 2001; Christian *et al*. 2001*a*, *b*; Veeramachaneni *et al*. 2001; OEHHA 2002). An association between chlorinated drinking water exposure and adverse pregnancy outcomes, such as miscarriage, intrauterine growth retardation, stillbirth, preterm delivery, birth defects, small for gestational age and low birth weight has been suggested by a number of population-based epidemiological studies, although with conflicting results (Tuthill *et al*. 1982; Kramer *et al*. 1992; Swan *et al*. 1992, 1998; Windham *et al*. 1992; Aschengrau *et al*. 1993; Bove *et al*. 1995; Savitz *et al*. 1995; Kanitz *et al*. 1996; Gallagher *et al*. 1998; Waller *et al*. 1998; Dodds *et al*. 1999; Dodds and King 2001; Klotz and Pyrch 1999; Magnus *et al*. 1999; Kallen and Robert 2000; King *et al*. 2000; Yang *et al*. 2000; Jaakkola *et al*. 2001; Cedergren *et al*. 2002; Hwang *et al*. 2002).

Most studies have taken into account exposure to drinking water treated with chlorine or hypochlorite, while treatment with chlorine dioxide has been addressed in few studies. In these investigations an association has been suggested with: the occurrence of prematurity as assessed by the physician (Tuthill *et al*. 1982); with somatic parameters at birth (small body length and cranial circumference) and neonatal jaundice (Kanitz *et al*. 1996); and with congenital cardiac defects (Cedergren *et al*. 2002). In contrast, a study carried out in Sweden did not find any effect on several pregnancy outcomes in subjects living in areas supplied by chlorine dioxide-treated drinking waters (Kallen and Robert *et al*. 2000).

On the whole, in all these studies the epidemiological evidence is weakened by methodological limitations. In particular, CBPs exposure assessment is often ecological and residual confounding due to unmeasured personal characteristics, such as alcohol intake, smoking habits and exposure to environmental tobacco smoke, may be present. Moreover, in many studies personal habits influencing not only oral, but also inhalation and dermal exposure to CBPs were not adequately addressed. As a matter of fact, CBPs can be ingested, can enter the body through the skin when taking a bath or swimming in a pool and/or be inhaled; some CBPs such as THMs, are volatile, and some others, even though not volatile, could spread as an aerosol when taking a shower (Reif *et al*. 1996; Swan and Waller 1998; Nieuwenhuijsen *et al*. 2000; Graves *et al*. 2001; Bove *et al*. 2002).

Chlorine dioxide treatment is widespread in Italy, and reproductive and developmental effects of chlorite and chlorate have not been fully investigated up to now. In order to evaluate the association between exposure to both THMs and chlorite or chlorate during the last trimester of pregnancy and pregnancy outcomes such as preterm delivery and small for gestational age at term (term-SGA), we carried out a multicentre case-control study with incident cases. Personal exposure to CBPs was assessed by drinking water sampling at subjects' homes and by collecting information both on personal factors influencing CBPs exposure and on a number of potential confounding factors or effect modifiers.

METHODS

This study was carried out between October 1999 and September 2000 in public obstetric clinics of nine Italian cities (Genoa, Udine, Modena, Parma, Siena, Rome, L'Aquila, Naples and Catania). Almost all deliveries in Italy occur in hospital. While in Genoa, Rome, Naples and Catania the clinics involved in the study covered from

40 to 60% of total births in the surrounding municipal areas in the period, in Udine, Modena, Parma, Siena and L'Aquila the coverage was nearly 100%.

Case definition and recruitment

We studied preterm delivery and small for gestational age at term (term-SGA) children born from mothers who were of Caucasian race, Italian citizens and resident in the nine cities and surrounding areas. Only livebirths were included. Eligible preterm cases were singleton children born between the 26th and 37th not completed week of pregnancy. Term-SGA cases were born from the 37th completed week and weighed under the lowest 10th percentile of weight according to standard values defined by the Italian Society of Paediatrics (Gagliardi *et al*. 1999). Newborns with congenital malformations and chromosomal abnormalities evident at birth were excluded. Controls were enrolled among singleton babies born in the same hospitals within a few days (the same day or the day after) after the cases delivery with a gestational age >37th completed week and a weight ≥10th percentile. The same exclusion criteria were applied to controls.

Subjects were recruited during their hospital stay just after delivery. Interviewers contacted the mothers and those willing to take part in the study signed a written informed consent and agreed to fill in a questionnaire and to provide a water sample from their home. Overall, 1,713 subjects (96% of those eligible) filled in the questionnaire. Due to financial constraints two of each three subjects were asked to provide a water sample regardless of the characteristics of water sources and disinfection treatment: 1,194 mothers (69.7%) provided a water sample from their home. This paper deals with this subset of subjects.

Data collection

Before hospital discharge, mothers received and filled in a structured questionnaire which had been validated in a previous study (Barbone *et al*. 2002). The questionnaire referred to the last trimester of pregnancy and included four parts. The first part was designed to collect information on socio-demographic characteristics of the respondent woman. The second part gathered information on house location, type of water supply (public water system or private well) and drinking water treatments. The third part assessed the woman's lifestyle during the last trimester of pregnancy. Alcohol consumption, cigarette smoking habits and environmental tobacco smoke exposure (one or more smokers at home) were investigated to control for potential confounding. In this section additional questions referred to personal habits related to exposure to CBPs in drinking water, such as kind of water (bottled or tap water, or both) and water-based beverages (tea, camomile tea, herb tea, etc.) usually drunk. In addition, consumption of wine and spirits was recorded. In the same section of the questionnaire time spent cooking foods every day and frequency and duration of showers and baths were investigated, as these habits are involved in exposure to CBPs by inhalation (Weisel *et al*. 1999; Backer *et al*. 2000; Lynberg *et al*. 2001). Also type and frequency of sports activities such as swimming pool attendance was investigated, as it is well known that CBPs are present, sometimes at appreciable levels, in swimming pool water and air (Aggazzotti *et al*. 1990, 1993, 1995, 1998). In the fourth part of the questionnaire, history of present and past pregnancies and the woman's health status were ascertained and validated against medical records which were considered as the gold standard.

Water sampling and analyses

Water samples were collected at women's homes within a few days of delivery by trained members of the study group. Total and individual THMs (chloroform, dichlorobromomethane, dibromochloromethane, bromoform) were measured in each sample ($n = 1{,}194$), while chlorite and chlorate were investigated in water samples treated with chlorine dioxide or both chlorine and chlorine dioxide (893 samples, corresponding to 74.8% of the total).

Methods of sampling were standardized and an inter-laboratory quality control was carried out among the five laboratories involved in the study. Water sampling for THMs analyses is reported elsewhere (Aggazzotti *et al*.

1990, 1993, 1995, 1998). Water sampling for chlorite and chlorate analyses was performed by filling 250 ml opaque dark bottles, then by gurgling an inert gas (helium, argon, nitrogen) for 3–5 minutes and adding ethylenediamine in order to reach the concentration of 50 ml l^{-1}. Samples were kept refrigerated until they were analysed (at a maximum of 7 days after). The head-space gas chromatographic technique was employed for THMs, and values of total THMs were reported as the sum of the single species concentrations. Since the analysis of dichlorobromomethane is the most sensitive, a level of dichlorobromomethane of 0.01 μg l^{-1} was considered as the lowest detectable concentration for THMs. Chlorite and chlorate analysis was performed by ion chromatography: the limit of detection was 20 μg l^{-1} (Castello *et al*. 1986; *Standard Methods* 1998).

Statistical analyses

Statistical analyses were performed with SPSS 10.0 for Windows (SPSS 2000). Cases and controls were compared by socio-demographic characteristics, personal habits and women's health status, computing odds ratios (ORs) and their 95% confidence intervals (95% CI) using a univariate logistic regression. The CBPs concentrations were compared using the Mann Whitney U test.

The association between exposure to CPBs and preterm delivery or term-SGA was evaluated by multivariate logistic models. Exposure to CBPs was defined taking into account concentrations in drinking water, tap water consumption (yes/no) and inhalation exposure (classified as 'high' when showering/bathing frequency is at least daily, and 'low' when it is less frequent). The cut-off values for CBPs exposure levels were based on detection limits, on the value of 10 μg l^{-1} for THMs and on limits set up by the Italian law on drinking water (30 μg l^{-1} for THMs and 200 μg l^{-1} for chlorite) (DPR n.236 1988; WHO 1996; DL n.32 2001). The value of 200 μg l^{-1} was chosen for chlorate also according to the results of some toxicological studies (OEHHA 2002). As few subjects consumed tap water, and most of them were included in the category characterized by low concentrations of CBPs, it was not possible to create a composite exposure variable considering CBPs levels, tap water consumption and inhalation exposure at the same time. Therefore two composite exposure variables were created: one was based on CBPs levels and tap water consumption, and the other was based on CBPs levels and inhalation exposure.

The multivariate analyses were carried out adjusting for those variables significantly associated in univariate analyses: mother's education and smoking, tap water-based beverages intake, sex of the child and type of drinking water usually consumed (when not included in the composite exposure variable) for term-SGA analysis; and smoking, home cooking and type of drinking water usually consumed for preterm study. When adjusting for exposure to tobacco smoke, only active smoking (yes/no) was considered, as active and passive smoking exposures were highly correlated.

RESULTS

A total of 582 cases (343 preterm deliveries and 239 term-SGA cases) and 612 controls completed the questionnaire and provided water samples. On the whole, few women used to drink tap water only (13.5%); however, many subjects (69.7%) used to drink water-based beverages such as tea, herbal tea, camomile tea, surrogate coffee, and drinks prepared with powders. Of the mothers, 25.2% were resident in areas supplied by drinking water treated with chlorine, 56.1% in areas supplied by drinking water treated with chlorine dioxide and 18.7% in areas where both treatments were used. No differences between cases and controls according to water treatment were observed.

Table 1 shows the distribution of some of the variables derived from the questionnaire. Term-SGA cases were significantly associated with female sex, low level of education (primary versus high school degree), number of cigarettes smoked during pregnancy and exposure to environmental tobacco smoke at home (when more than two smokers were present). With regard to water use, a moderate protective effect related to water-based beverages intake appeared, but no associations with tap water and total liquid intake (glasses/weeks) were

Table 1 | Distribution of selected characteristics among cases and controls derived from a questionnaire reporting information about the last trimester of pregnancy

	Cases						Controls
	Term-SGA† (*n*=239)			Preterm (*n*=343)			*n*=612
	N (%)	OR*	95% CI	N (%)	OR*	95% CI	N (%)
Child's sex							
Male	100 (42)	1	—	181 (53)	1	—	310 (51)
Female	139 (58)	1.44	1.06–1.95	162 (47)	0.91	0.70–1.19	302 (49)
Mother's age (years)							
≤20	8 (3)	1.90	0.73–4.95	7 (2)	1.24	0.46–3.33	10 (2)
21–30	97 (41)	1	—	130 (38)	1	—	230 (37)
31–40	127 (53)	0.84	0.61–1.15	194 (57)	0.96	0.72–1.26	359 (59)
>40	6 (3)	1.42	0.50–4.02	11 (3)	1.61	0.67–3.89	10 (2)
Missing	1			1			3
Education							
Primary school	12 (5)	3.10	1.31–7.38	7 (2)	1.26	0.47–3.36	10 (2)
Middle school	61 (26)	0.96	0.67–1.38	90 (26)	0.99	0.72–1.36	164 (27)
High school	116 (50)	1	—	167 (49)	1	—	300 (49)
University	34 (15)	0.83	0.53–1.29	58 (17)	0.98	0.68–1.43	106 (17)
Other	10 (4)	0.89	0.42–1.89	19 (6)	1.18	0.64–2.16	29 (5)
Missing	6			2			3
Cigarettes (n day^{-1}) during pregnancy							
0	170 (73)	1	—	275 (81)	1	—	519 (86)
1–9	40 (17)	1.97	1.28–3.04	48 (14)	1.46	0.98–2.19	62 (10)
≥10	23 (10)	3.34	1.80–6.19	17 (5)	1.53	0.79–2.94	21 (4)
Missing	6			3			10
Environmental tobacco smoke at home							
No	142 (61)	1	—	219 (64)	1	—	395 (65)
1 smoker	78 (33)	1.15	0.83–1.59	108 (32)	1.03	0.77–1.37	189 (31)
2 smokers	7 (3)	1.22	0.49–3.02	7 (2)	0.79	0.32–1.95	16 (3)
>2 smokers	7 (3)	3.89	1.19–7.79	6 (2)	2.16	0.65–7.17	5 (1)
Missing	5			3			7

Table 1 | *Continued*

	Cases						Controls *n*=612
	Term-SGA† (*n*=239)			Preterm (*n*=343)			
	N (%)	OR*	95% CI	N (%)	OR*	95% CI	N (%)
Alcohol intake (wine, beer and spirits; glasses per day)							
≤2 glasses per day	221 (97)	1	—	330 (98)	1	—	581 (97)
>2 glasses per day	7 (3)	0.92	0.38–2.21	8 (2)	0.71	0.31–1.62	20 (3)
Missing	11			5			11
Coffee-cappuccino intake (cups per week)							
None	32(15)	1	—	51(16)	1	—	101(18)
1–7	65(31)	1.40	0.86–2.30	89(28)	1.21	0.79–1.85	146 (26)
8–35	107 (51)	1.17	0.74–1.84	166 (52)	1.14	0.77–1.68	289 (52)
>35	6 (3)	0.95	0.35–2.56	14 (4)	1.39	0.65–2.97	20 (4)
Missing	29			23			56
Drinking water usually consumed							
Bottled mineral water	188 (80)	1	—	273 (80)	1	—	485 (80)
Both	8 (4)	0.46	0.21–0.99	24 (7)	0.95	0.56–1.59	45 (7)
Tap water	38 (16)	1.24	0.81–1.89	44 (13)	0.99	0.66–1.47	79 (13)
Missing	5			2			3
Tap water intake (glasses per week)							
None	164 (78)	1	—	242 (75)	1	—	416 (74)
1–7	8 (4)	0.60	0.27–1.32	20 (7)	1.01	0.57–1.80	34 (6)
8–35	20 (9)	0.76	0.44–1.29	30 (9)	0.77	0.49–1.22	67 (12)
>35	19 (9)	1.02	0.55–1.80	30 (9)	1.10	0.68–1.78	47 (8)
Missing	28			21			48
Water-based beverages*> (glasses per week)							
None	89 (42)	1	—	102 (32)	1	—	171 (30)
1–7	89 (42)	0.60	0.42–0.85	172 (53)	1.01	0.74–1.37	286 (51)
8–35	27 (13)	0.50	0.30–0.82	41 (13)	0.66	0.43–1.02	104 (18)
>35	6 (3)	2.89	0.79–10.48	7 (2)	2.93	0.84–10.27	4 (1)
Missing	28			21			47

Table 1 | *Continued*

	Cases						Controls *n*=612
	Term-SGA† (*n*=239)			Preterm (*n*=343)			
	N (%)	OR*	95% CI	N (%)	OR*	95% CI	N (%)
Total liquid intake (glasses per week)							
≤35	23 (11)	1	—	32 (10)	1	—	53 (9)
>35	188 (89)	0.79	0.47–1.33	305 (90)	0.92	0.58–1.46	547 (91)
Missing	28			6			12
Home cooking							
No	12 (5)	1	—	40 (12)	1	—	40 (7)
Yes	222 (95)	1.30	0.67–2.53	302 (88)	0.53	0.33–0.84	568 (93)
Missing	5			1			4
Bathing and/or showering							
<3 per week	27 (12)	1	—	58 (17)	1	—	85 (14)
3–6 per week	10 1 (44)	1.12	0.68–1.82	162 (48)	0.83	0.57–1.23	285 (47)
Daily	103 (44)	1.40	0.85–2.28	116 (35)	0.73	0.49–1.10	232 (39)
Missing	8			7			10
Attending indoor swimming pool							
Never	226 (98)	1	—	328 (96)	1	—	574 (95)
Once a week or more	5 (2)	0.40	0.15–1.03	13 (4)	0.71	0.37–1.38	32 (5)
Missing	8			2			6

*OR are calculated by univariate analyses; †small for gestational age at term; *tea, herbal tea, camomile tea, surrogate coffee, infusions, drink prepared with powders.

observed. A weak protective effect was observed in women (only eight subjects) who used to drink both tap and bottled mineral water. When considering personal habits related to inhalation exposure to CBPs, neither home cooking, nor bathing and/or showering or attending an indoor swimming pool were significantly associated with term-SGA. Preterm delivery was not significantly associated with any variable except for a protective effect related to home cooking: this is probably due to the fact that women with preterm delivery are less likely to be involved in housework.

Levels of THMs, chlorite and chlorate are reported in Table 2. On the whole, levels of THMs were below the detection limit in 22.5% of the samples, and their concentrations appeared very low. Among THMs chloroform was the most represented substance; however, due to the low levels of each compound, only the total amount of THMs was considered. About 7% of the samples showed

Table 2 | Levels of THMs, chlorites and chlorates in drinking water samples collected at homes of cases and controls

	No. of samples	Samples with detectable concentrations*				
		N (%)	Mean	95% CI	Median	Range
THM ($\mu g\ l^{-1}$)						
Cases						
Term-SGA†	237	181 (76)	2.91	2.23–3.59	1.02	0.01–26.89
Preterm	342	261 (76)	3.09	2.44–3.74	1.24	0.01–41.52
Controls	606	477 (79)	3.41	2.86–3.96	1.10	0.01–54.55
Chlorites ($\mu g\ l^{-1}$)						
Cases						
Term-SGA†	177	89 (50)	320.44	255.14–385.74	250.00	20–2000
Preterm	251	113 (45)	278.32	232.60–324.04	177.00	20–1212.70
Controls	458	198 (43)	312.65	272.05–353.25	216.50	20–1665
Chlorates ($\mu g\ l^{-1}$)						
Cases						
Term-SGA†	177	68 (38)	150.49	101.34–199.64	72.00	20–1000
Preterm	249	81 (32)	154.47	108.13–200.81	76.20	20–1162
Controls	456	154 (34)	153.55	116.76–190.34	76.50	20–1500

†Small for gestational age at term.
*Not detectable as <0.01 $\mu g\ l^{-1}$ for THMs.
Not detectable as <20 $\mu g\ l^{-1}$ for chlorites/chlorates.

concentrations higher than 10 $\mu g\ l^{-1}$, and only 0.5% had levels of THMs higher than 30 $\mu g\ l^{-1}$, the limit set up in Italian law (DPR n.236 1988). Chlorite and chlorate, the main disinfection by-products derived from treatment with chlorine dioxide, were detected in 45% and 34% of the analysed samples, respectively. Sometimes concentrations were very high: 24% of the samples for chlorite and 6.2% for chlorate had concentrations higher than 200 $\mu g\ l^{-1}$, the limit set in Italian law for chlorite (DL n.32 2001). Moreover, 3.6% for chlorite and 0.7% for chlorate showed levels higher than 1,000 $\mu g\ l^{-1}$. No differences appeared between cases and controls either in the percentages of positive samples for THMs (76 vs. 79%), chlorite (47 vs. 43%) and chlorate (35 vs. 34%), or in the mean values among positive samples (3.0 $\mu g\ l^{-1}$ vs. 3.4 $\mu g\ l^{-1}$ for THMs, 294.3 $\mu g\ l^{-1}$ vs. 312.6 $\mu g\ l^{-1}$ for chlorite, 150.5 $\mu g\ l^{-1}$ vs. 153.5 $\mu g\ l^{-1}$ for chlorate).

In order to assess an association, if any, between exposure to CBPs and the investigated outcomes taking into account multiple ways of exposure and potential confounders, a multivariate logistic analysis was performed. With regard to CBPs values, three exposure categories were built based on the detection limit and the value of 10 $\mu g\ l^{-1}$ for THMs. Also for chlorite and

chlorate three categories were built: the detection limit, the limit set up in Italian law (chlorite) and a value calculated from toxicological studies (chlorate) were chosen as cut-off values (WHO 1996; DL n.32 2001; OEHHA 2002). With regard to term-SGA analysis, sex, education, water-based beverages intake, type of water usually drunk, active smoking (yes/no) were adjusted for, while for preterm delivery type of water usually drunk, active smoking (yes/no) and home cooking only were included in the model.

THMs exposure was not significantly associated with either term-SGA or preterm birth. For subjects exposed to THMs concentrations higher than 10 μg l^{-1}, tap water consumers and at high inhalation exposure level (frequency of bathing/showering at least daily) adjusted ORs were 0.63 (95%CI: 0.31–1.28) for term-SGA and 0.73 (95%CI: 0.56–1.35) for preterm birth with respect to mothers at lower exposure levels. These results are probably due to the very low THM concentrations measured in most of the samples.

The relationship between chlorite and chlorate exposure and term-SGA is reported in Table 3. The risk of term-SGA delivery appeared to increase, even though the association is not statistically significant, with increasing values of chlorite regardless of tap water consumption. However, when the mother's actual tap water consumption was taken into consideration, the association disappeared. In contrast, when the inhalation exposure status was considered, the risk increased according to the levels of chlorite.

With reference to women exposed to chlorite under the limit of detection or to chlorite ranging between 20 and 199 μg l^{-1} and at low inhalation exposure, the risk of term-SGA expressed as adjusted OR (95%CI), was 1.10 (0.58–2.11) when chlorite ranged between 20 and 199 μg l^{-1} and bathing/showering was at least daily, 1.52 (0.91–2.54) when chlorite was ≥200 μg l^{-1} and at low inhalation exposure, and 1.70 (0.97–3.0) when both chlorite level and inhalation exposure were high. The analyses carried out on chlorate exposure do not show significant results: note the small numbers of subjects exposed to high concentrations both by ingestion and inhalation.

An overall exposure to high levels of CBPs in drinking water (THMs ≥30 μg l^{-1}, chlorites ≥200 μg l^{-1} or chlorates ≥200 μg l^{-1}) involved a subset of 59 term-SGA cases (24.9%) and 113 controls (18.6%); when this exposure was used as a dichotomous, independent variable, and after adjusting for the same factors as before, a weak association was found (adjusted OR = 1.38, 95%CI: 0.92–2.07).

Preterm birth was not associated either with any level of exposure to chlorite or chlorate, or with the overall exposure to high levels of CBPs in drinking water as previously defined (adjusted OR = 0.84, 95%CI: 0.59–1.19).

DISCUSSION

The main aim of this study was to attempt a more accurate evaluation of the exposure to CBPs in drinking water at the individual level both by applying a questionnaire on personal habits and by collecting water samples at subjects' homes within a few days of delivery. Sampling at home addresses the problem of misclassification due to spatial variability in CBPs content related to the distance of the residences from the disinfection plant, and attempts to reduce the problem of temporal variability with respect to routine data which are collected only quarterly. Residual misclassification could also be present since only one sample was collected in each subject's home. However among the Italian water supplies spatial variability is more important than temporal variability as few waterworks involved in this study (5 out of 92) are supplied with surface waters with unstable chemical physical characteristics. Moreover, in this way we had the opportunity to analyse CBPs, such as chlorite and chlorate, not routinely investigated.

In our study 74.8% of the subjects were living in areas where drinking water was treated with chlorine dioxide and with both chlorine and chlorine dioxide. The main CBPs were therefore chlorite and chlorate, which showed high concentrations in several samples. In 24% of the samples levels of chlorite were higher than 200 μg l^{-1}, which is the limit set by Italian law coming in force in December 2006 (DL n.32 2001). In contrast levels of

Table 3 | Association between levels of chlorination by-products (CBPs) and small for gestational age at term (term-SGA)

	Cases N (%)	Controls N (%)	OR 95% CI (crude)		OR 95% CI (adjusted)	
Chlorites ($\mu g\ l^{-1}$)						
House water sample level regardless of tap drinking water consumption†						
<20	88 (50)	260 (57)	1	—	1	—
20–199	34 (19)	94 (20)	1.02	0.64–1.62	1.12	0 .67–1.80
≥200	55 (31)	104 (23)	1.71	1.15–2.55	1.32	0.85–2.11
House water sample level and tap water consumer status*						
<20 or non consumer	166 (94)	419 (92)	1	—	1	—
20–199, consumer	2 (1)	14 (3)	0.35	0.10–1.12	0.29	0.05–1.52
≥200, consumer	8 (5)	24 (5)	1.07	0.5–2.22	0.63	0.20–2.00
House water sample level and inhalation exposure status‡†						
<20 or 20–199 and at lower inhalation exposure level	108 (60)	310 (70)	1	—	1	—
20–199 and at higher inhalation exposure level	15 (8)	39 (9)	1.10	0.58–2.08	1.10	0.58–2.11
≥200, and at lower inhalation exposure level	33 (18)	57 (13)	1.66	1.03–2.67	1.52	0.91–2.54
≥200, and at higher inhalation exposure level	26 (14)	39 (8)	1.91	1.11–3.30	1.70	0.97–3.00
Chlorates ($\mu g\ l^{-1}$)						
House water sample level regardless of tap drinking water consumption†						
<20	109 (62)	302 (66)	1	—	1	—
20–200	55 (31)	130 (28)	1.11	0.76–1.47	0.98	0.64–1.52
≥200	13 (7)	25 (6)	1.38	0.68–2. 81	1.19	0.54–2.62
House water sample level and tap water consumer status*						
<20 or non consumer	170 (97)	432 (95)	1	—	1	—
20–200, consumer	4 (2)	19 (4)	0.63	0.30–1.47	0.37	0.09–1.61
≥200, consumer	2 (1)	5 (1)	0.81	0.16–4.04	0.30	0.03–3.42
House water sample level and inhalation exposure status‡†						
<20 or 20–199 and at lower inhalation exposure level	143 (79)	365 (82)	1	—	1	—
20–199 and at higher inhalation exposure level	27 (15)	56 (13)	1.23	0.75–2.02	1.25	0.75–210
≥200, and at lower inhalation exposure level	8 (4)	15 (3)	1.36	0.56–3.28	1.12	0.44–2.84
≥200, and at higher inhalation exposure level	4 (3)	9 (2)	1.13	0.34–3.74	1.21	0 .34–4.26

‡Inhalation exposure is classified as lower if bathing/showering is '<3 per week or 3–6 per week', all others are at higher lever of inhalation exposure.
†OR are adjusted for sex of the newborn, education, mother smoking, water-based beverages, type of water drunk; *OR are adjusted for sex of the newborn, education, mother smoking, water-based beverages.

THMs were very low, and 0.5% of samples showed concentrations higher than 30 μg l^{-1}, which is the limit set by present Italian law (DPR n.236 1988).

The questionnaire gave information on individual habits influencing CBPs exposure by multiple routes, and also on potential confounders such as smoking habits, exposure to environmental tobacco smoke and alcohol intake. With regard to tap water intake, in our study only 13.5% of the sample used to drink municipal tap water, even though many subjects (69.7%) drank water-based beverages. It should be noted that bottled mineral water in Italy is spring mineral water bottled directly without any disinfection treatment and therefore is CBPs free. With regard to inhalation and dermal exposure, bathing and/or showering were daily habits for about 38% of the subjects, while only 4.2% attended an indoor swimming pool during pregnancy. The importance of these ways of exposure to CBPs is stressed by some studies which observed that the highest levels of THMs were found in blood and alveolar air of subjects who had taken a shower (Weisel *et al*. 1999; Backer *et al*. 2000; Lynberg *et al*. 2001), while other studies have evaluated the intake, uptake and elimination of THMs in swimmers (Aggazzotti *et al*. 1990, 1993, 1995, 1998). Inhalation by home cooking appeared be a method of exposure for most subjects (91.5%).

In the multivariate logistic regression THMs exposure was not significantly associated with either term-SGA or preterm birth; THMs concentrations in drinking water were negligible in most samples. In contrast, while chlorite concentration did not show an association with preterm delivery, it was apparent for term-SGA newborns, suggesting a dose-response relationship. When chlorite level was higher than 200 μg l^{-1} and the frequency of bathing/showering was at least daily, an OR equal to 1.70 (95% CI: 0.97–3.0) was found after adjusting for sex of the newborn, mother's education, water-based beverages intake, type of water usually drunk and active smoking.

In this study few women consumed tap water, therefore inhalation was the main exposure route to CBPs; however our findings suggesting an increased risk of term-SGA when subjects are exposed to chlorite via inhalation are surprising, as these inorganic compounds, in contrast to THMs, are not considered volatile. One explanation of this situation could be the presence of chlorite or chlorate as aerosols in shower vapours. An alternative explanation is that chlorite could act as a proxy for other CBPs formed by chlorine dioxide treatment or as a proxy of residual chlorine dioxide itself (IPCS 2000).

Chlorite and chlorate are the main CBPs derived from chlorine dioxide drinking water treatment; up to now their reproductive and developmental effects have not been investigated in epidemiological studies, as the few studies carried out considered water treatment only, and not single CBPs levels (Tuthill *et al*. 1982; Kanitz *et al*. 1996; Kallen and Robert 2000; Cedergren *et al*. 2002). Living in areas supplied by drinking waters treated with chlorine dioxide was significantly associated with small somatic parameters such as body length and cranial circumference, and a borderline association became evident with low body weight (adjusted OR: 5.9; 95%CI: 0.8–14.9) in a study carried out in Italy (Kanitz *et al*. 1996). This association was not observed in a study performed in Sweden (Kallen and Robert 2000). Reproductive and developmental effects of chlorite and chlorate have been studied in animal toxicological work: despite some inconsistencies an adverse developmental effect was observed in rats, mainly for chlorite (WHO 1996; IPCS 2000; USEPA 2000; OEHHA 2002).

The association between chlorite and term-SGA may have several possible explanations. First, the direct action of high levels of chlorite could cause developmental effects in newborns. However, other studies are needed on this subject in different populations and areas. Second, chlorite could be representative of other CBPs formed by chlorine dioxide or of residuals of chlorine dioxide itself. Lastly, the association could be affected by confounding due to some true determinant of term-SGA. Identification of such an unknown confounder is speculative. We adjusted our results for several personal habits; however, there may be other unknown environmental, behavioural or socio-economic factors, which might be involved in the occurrence of term-SGA and present in areas where drinking water treatments form high levels of CBPs, as suggested by the association with an overall marker of high exposure to chlorite, chlorate or THMs.

CONCLUSIONS

In our study THMs concentrations in drinking water were negligible in most samples and no significant association between THMs exposure and either term-SGA or preterm birth was observed. In contrast, high levels of chlorite were observed and an association with term-SGA newborns was disclosed.

Despite the lack of clear evidence of a causal association between chlorite levels in drinking water and reproductive outcomes, our study raises some concern because of the high levels of chlorite and chlorate frequently measured. As most water utilities, at least in Italy, are adopting chlorine dioxide as the main water disinfection treatment in order to reduce the amount of THMs, chlorite and chlorate will become the most widespread CBPs in drinking water. For this reason their levels should be regularly and carefully monitored and their potential effects on human health further evaluated and better understood.

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ABBREVIATIONS

CBPs	chlorination by-products
term-SGA	small for gestational age at term
THMs	trihalomethanes
OR	odds ratio
95%CI	95% confidence interval

NOTE

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