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Validation of trichloroacetic acid exposure via drinking water during pregnancy using a urinary TCAA biomarker

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ABSTRACT

Disinfection by-product (DBP) exposure during pregnancy may be related to reduced fetal growth, but the evidence is inconclusive and improved DBP exposure assessment is required. The authors conducted a nested exposure study on a subset ($n=39$) of pregnant women in the Born in Bradford cohort to assess validity of TCAA exposure assessment based on tap water sampling and self-reported water-use; water-use questionnaire validity; and use of a one-time urinary TCAA biomarker. TCAA levels in urine and home tap water supply were quantified, and water use was measured via a questionnaire and 7-day diary, at 28 weeks gestation. Diary and urine measures were repeated later in pregnancy ($n=14$). TCAA level in home tap water supply was not correlated with urinary TCAA (0.18, $P=0.29$). Cold unfiltered tap water intake at home measured by questionnaire was correlated with urinary TCAA (0.44, $P=0.007$), but correlation was stronger still for cold unfiltered tap water intake reported over the 3 days prior to urine sampling (0.60, $P<0.001$). For unemployed women TCAA ingestion at home, derived from tap water sampling and self-reported water-use, correlated strongly with urinary TCAA (0.78, $P<0.001$), but for employed women the correlation was weak (0.31, $P=0.20$). Results suggest individual tap water intake is most influential in determining TCAA exposure variability in this cohort, and that TCAA ingestion at home is a valid proxy for TCAA exposure for unemployed women but less satisfactory for employed women.

1. Introduction

During pregnancy exposure to disinfection by-products (DBPs) such as trihalomethanes (THMs) and haloacetic acids (HAAs) in public water supplies may be related to reduced fetal growth (Grellier et al., 2010; Nieuwenhuijsen et al., 2009). However because exposure assessment is difficult and prone to measurement error, and the effects seen are likely to be small, the evidence is inconsistent and inconclusive. Improved DBP exposure assessment is required, particularly addressing non-THM classes of DBPs such as HAAs, and use of biomarkers may allow advancement in this respect. HAAs are non-volatile and the predominant route for exposure is ingestion; with no significant contribution from inhalation and dermal absorption (Xu et al., 2002; Xu and Weisel 2003). TCAA is one of the most common HAAs found in chlorinated drinking water, and urinary TCAA has been validated as a biomarker for measuring TCAA exposure by ingestion of drinking water (Zhang et al., 2009). Incorporation of biomarkers into exposure assessment in epidemiological studies examining DBPs and fetal growth outcomes has occurred only recently, with two studies using urinary TCAA biomarkers (Costet et al., 2012; Zhou et al., 2012). Whilst there are knowledge gaps to address before we can fully rely upon or interpret urinary TCAA as an exposure biomarker, e.g. required number of samples and effectiveness of TCAA as a proxy for other DBPs (Savitz, 2012), as an integrated objective measure of exposure urinary TCAA may be a useful validation tool in epidemiological studies using existing exposure assessment methods based on DBP concentrations at the tap and individual water use.

We are investigating DBPs and fetal growth in the Born in Bradford (BiB) birth cohort. Exposure assessment comprises modelled area-level DBP concentrations combined with individual water-use data to estimate 'semi-individual' DBP exposure metrics. This paper presents a nested exposure validation study which

Abbreviations: BiB, Born in Bradford; CI, Confidence Interval; DBP, Disinfection by-product; FMU, First morning urine; ICC, Intra-class correlation coefficient; HAA, Haloacetic acid; TCAA, Trichloroacetic acid; THM, Trihalomethane.

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collected detailed individual-level exposure information, including urinary TCAA biomarkers and water use diaries as gold-standard measures, for a subset of women in the BiB cohort. The primary aim of this study was to evaluate the validity of TCAA exposure assessment, in order to improve interpretation of health-risk estimates in future epidemiological analyses. To achieve this we assessed correlation between urinary TCAA and TCAA exposure assessment based on tap water concentration and water-use questionnaire, and validity of a water-use questionnaire. The secondary aim was to assess correlation between repeated measures of both urinary TCAA and water use during the third trimester in order to evaluate exposure variability and adequacy of a one-time urinary TCAA biomarker to assess TCAA exposure during pregnancy.

2. Materials and methods

2.1. Recruitment

Born in Bradford (BiB) is a large, multi-ethnic birth cohort ($n=13,750$) in Bradford, UK, recruited 2007–2010. Pregnant women were recruited at 26–28 weeks gestation by BiB project workers, who informed them about the study, obtained written consent and conducted a baseline questionnaire including questions on tap water use, by interview (Raynor and Born in Bradford Collaborative Group, 2008). Recruitment for this nested study occurred in 2 phases, with 20 women recruited during February/March 2008, and 19 women during May 2008, and has been described in detail elsewhere (Smith et al., 2009). BiB and this nested study were reviewed and approved by the Bradford Research Ethics Committee. All subjects signed an informed consent form prior to participation.

2.2. Exposure assessment

Participants were supplied with a 7-day water-use diary (Diary 1) based on a diary used by Kaur et al. (2004), which they completed over 7 consecutive days commencing on average one day after completing the BiB baseline questionnaire. Tap water was sampled at each participant's home by the researcher. Participants collected a first morning urine (FMU) sample (Urine 1) three days after tap sampling to account for approximate TCAA half-life when comparing tap water and urine TCAA concentrations. Urinary TCAA measured in FMU samples has been validated as a biomarker for TCAA exposure by ingestion of drinking water, in a controlled direct exposure experiment in humans which demonstrated urinary TCAA concentration reflected TCAA ingestion (μg/day) (Zhang et al., 2009). Diary 1 recorded the same water exposures as the baseline questionnaire (daily intake at home, work/study and elsewhere of tap water, bottled water, tea, coffee and squash/cordial measured in mugs/glasses; water filtering habits; and daily frequency and duration of showering, bathing and swimming), additional tap water intakes and water-related activities, and potential DBP exposure modifiers (e.g. ventilation during showering/bathing). To assess potential exposure to chlorinated solvents (some of which metabolise to TCAA) the diary included questions on visiting/working in particular industries (dry cleaners, metal manufacturers, auto parts, textile production, paint production, printers), household members working in dry cleaning, and usage of various household products (correction fluid, carpet cleaner, stain removers, paint/varnish, thinners, adhesives, pesticides and disinfectants). No participant visited/worked in the industries listed during the diary week, or had a household member working in dry cleaning. Of 39 household products reported used, ingredient lists could be identified for 26 and none contained chlorinated solvents of interest. Fourteen participants (36%) repeated the study, providing a second urine sample (Urine 2) and completing a second diary (Diary 2). Tap water samples were analysed for TCAA, and urine samples were analysed for TCAA and creatinine (to adjust for diuresis)—detailed sampling and analytical methods provided in Appendices A and B. (shown in Supplementary Materials)

Water intakes at home, work, elsewhere and across all locations were calculated in L/day from both the questionnaire and the diary. Weekly duration (minutes per week) of showering, bathing and swimming were calculated from the questionnaire and diary. TCAA ingestion at home (μg/day) was calculated by multiplying home tap water TCAA concentration (μg/L) with tap water intakes at home (L/day), incorporating a 32% reduction in TCAA concentration for boiling (average of 2 and 5 min boiling tests (Krasner and Wright 2005; Ma, 2008; Wu et al., 2001)) applied to tea/coffee intake, and 64% reduction for filtering (average of all new/used pitcher and tap-mounted tests (Egorov et al., 2003; Levesque et al., 2006; Ma, 2008; Weinberg et al., 2006) applied to cold filtered tap water intake. Four metrics of TCAA ingestion at home were calculated based on (a) tap water intake at home from the questionnaire, (b) average tap water intake at home over 7 days of Diary 1, (c) average tap water intake at home over the 3 days of Diary 1 preceding urine sample collection, and (d) average tap water intake at home across 5 weekdays of Diary 1. TCAA ingestion was calculated at home only because data on TCAA in workplace tap water supplies were not available.

2.3. Statistical analysis

Spearman's correlations were calculated between urinary TCAA, and tap water intakes, tap TCAA concentration, and TCAA ingestion at home. Correlations between urinary TCAA and showering, bathing and swimming were also calculated to determine whether the relationship between urinary TCAA and ingestion is specific and is not seen with other sources, as would be expected. Agreement between questionnaire and Diary 1 was examined by mean difference between methods, intra-class correlation coefficient (ICC) and Spearman's correlation coefficient. Analyses were stratified by employment status, because employed women are potentially exposed to DBPs in tap water at work and other sources of TCAA. A Z-test (following Fisher's r to Z transformation) was used to test difference in correlation coefficients for employed versus unemployed women. William's T2-test (Steiger, 1980) was used to test difference in correlation coefficients using unadjusted and creatinine-adjusted urinary TCAA measures. For repeated measures we calculated Spearman's correlation and ICC. All ICCs were calculated as ICC (type A,1)

Table 1
Summary statistics for (a) TCAA in home tap water supply and (b) urinary TCAA (Urine 1) for pregnant women in a nested exposure study, BiB cohort, Bradford, UK, 2008.

		n[a]	Mean	95% CI for Mean	SD	Min	25th %ile	Median	75th %ile	Max
a) TCAA in home tap water supply (μg/L)	**All**	36[b]	11.3	10.1, 12.5	3.4	5.3	8.9	10.5	13.6	17.7
	Phase 1[c]	20	10.6	9.1, 12.1	3.2	5.3	8.5	10.2	12.8	17.5
	Phase 2[c]	16	12.2	10.3, 14.1	3.6	5.9	9.6	11.6	15.1	17.7
	Unemployed	17	11.4	9.5, 13.3	3.7	5.3	8.7	12.4	14.2	17.5
	Employed	19	11.2	9.6, 12.8	3.3	5.9	9.3	10.2	12.4	17.7
b) Urinary TCAA (nmol/L)	**All**	37[b]	37.1	28.9, 45.2	24.4	1.5	21.0	33.0	45.0	112.0
	Phase 1[c]	20	32.9	22.7, 43.2	21.9	1.5	18.3	31.0	41.3	86.0
	Phase 2[c]	17	42.0	28.1, 55.9	27.0	13.0	24.0	34.0	50.0	112.0
	Unemployed	17	38.5	27.3, 49.7	21.8	5.0	21.0	36.0	45.0	86.0
	Employed	20	35.9	23.2, 48.5	27.0	1.5	23.3	29.0	41.3	112.0
Creatinine-adjusted urinary TCAA (μmol/mol creatinine)	**All**	37[b]	4.9	3.4, 6.3	4.4	0.1	2.2	3.5	6.7	20.6
	Phase 1[c]	20	4.2	2.0, 6.3	4.6	0.1	2.1	2.6	4.2	20.6
	Phase 2[c]	17	5.7	3.6, 7.8	4.1	1.5	3.1	4.5	6.9	15.1
	Unemployed	17	3.7	2.5, 4.9	2.3	1.0	2.1	3.4	4.1	8.5
	Employed	20	5.9	3.3, 8.4	5.4	0.1	2.4	4.2	7.7	20.6

Abbreviations: BiB, Born in Bradford; CI, confidence interval; TCAA, trichloroacetic acid.

[a] *n* represents 1 sample, either (a) tap water or (b) urine, per woman enrolled in the study. For urinary TCAA, the statistics are for the initial Urine 1 sample only (Urine 2 samples are not included in this analysis).

[b] 37 Women had Urine 1 TCAA data, but only 36 women had data for TCAA in tap water.

[c] Recruitment and fieldwork for this nested validation study was carried out in 2 phases: during February/March 2008 (Phase 1), and during May 2008 (Phase 2). Statistics are calculated separately for each Phase to allow for any seasonal variation in TCAA in tap water.