SHORT REPORT

Haloacetic acids in drinking water and risk for stillbirth

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Occup Environ Med 2005;**62**:124–127. doi: 10.1136/oem.2004.013797

Background: Trihalomethanes (THMs) occurring in public drinking water sources have been investigated in several epidemiological studies of fetal death and results support a modest association. Other classes of disinfection by-products found in drinking water have not been investigated.

Aims: To investigate the effects of haloacetic acid (HAA) compounds in drinking water on stillbirth risk.

Methods: A population based case-control study was conducted in Nova Scotia and Eastern Ontario, Canada. Estimates of daily exposure to total and specific HAAs were based on household water samples and questionnaire information on water consumption at home and work.

Results: The analysis included 112 stillbirth cases and 398 live birth controls. In analysis without adjustment for total THM exposure, a relative risk greater than 2 was observed for an intermediate exposure category for total HAA and dichloroacetic acid measures. After adjustment for total THM exposure, the risk estimates for intermediate exposure categories were diminished, the relative risk associated with the highest category was in the direction of a protective effect, and all confidence intervals included the null value.

Conclusions: No association was observed between HAA exposures and stillbirth risk after controlling for THM exposures.

The reaction of chlorine used in water disinfection with organic material in source water results in the formation of several classes of chemical by-products. Trihalomethanes (THMs) generally occur in the highest concentrations and are regulated in North American water supplies.

Apart from THMs, several other classes of by-products are formed, including haloacetic acids, acetonitriles, chlorinated ketones, and chlorophenols.^{1–2} Haloacetic acids (HAAs) occur in the highest quantities after THMs and can often equal the total THM concentrations.³ Among specific disinfection by-products, chloroform is the predominate THM formed and dichloroacetic acid (DCAA) and trichloroacetic acid (TCAA) occur in the highest concentrations among HAAs.³ Regulations on HAA concentrations in public water supplies were recently introduced in the United States.⁴

Characteristics of the source water (for example, pH, temperature, concentration and properties of natural organic materials, and bromide ion concentration) and treatment (contact time, concentration of chlorine and residual chlorine) affect disinfection by-product formation.^{1–3–5–6} Water pH plays an important role in determining the relative concentration of different by-products. THM formation is maximised at a high pH and TCAA formation is maximised at a low pH. DCAA formation is essentially independent of the pH.⁷ Variation in the bromide ion concentration of source water is the primary determinant of the relative percentage of brominated by-products formed.^{1–3}

Six studies have examined the risk of intrauterine death, stillbirth, or miscarriage, in relation to exposure to trihalomethane levels.^{8–13} All but one have reported an increase in risk with THM exposure.⁷ Three studies have reported on the risk of intrauterine death associated with individual THM compounds and each reported higher risks with bromodichloromethane (BDCM) than the other THM compounds.^{10–13–14} No studies have reported on fetal death and other classes of disinfection by-products.

Reviews of the state of evidence for a relation between disinfection by-products and adverse health events have cautioned that THMs are a proxy for disinfection by-product exposure and not necessarily the by-product of primary concern.^{15–19} These reviews have emphasised the need to investigate other by-product classes. This paper reports on the effects of HAA compounds in drinking water on stillbirth risk, controlling for THM exposures.

METHODS

Study subjects and data collection

A detailed description of subject accrual and exposure assessment has been previously published.¹³ Stillbirths and a random sample of live births occurring in Nova Scotia and Eastern Ontario, Canada, between 1999 and 2001 were identified through population based perinatal databases. Cases were women who had stillborn infants, defined as death of a fetus weighing 500 grams or more at delivery. Women whose pregnancy was terminated for a fetal anomaly were excluded. Approximately four times the number of controls as cases were randomly selected from the perinatal database in each province. Women were eligible to participate if they lived in the study area for at least the first five months of their pregnancy, delivered in the study area, and were resident in the study area at the time of recruitment.

Subjects completed a telephone interview that collected information on water consumption, and other water use behaviours. Residential tap water samples were collected from all subjects who lived in an area served by a public water supply. Water samples were collected in a 100 ml amber glass bottle and HAA analyses were accomplished via a gas chromatographic method. The water sample was timed to occur at approximately one year beyond the time when subjects were 4–5 months pregnant. Disinfection by-product levels were assumed to be zero for subjects served by a private well. If a subject had moved since the time when she was 4–5 months pregnant, a surrogate sample was collected from a public building close to the subject's former residence. The estimated by-product level for the distribution system corresponding to the subject's place of employment was used to assign the contribution of water consumption at work.

Abbreviations: BDCM, bromodichloromethane; DCAA, dichloroacetic acid; CI, confidence interval; HAA, haloacetic acid; RR, relative risk; TCAA, trichloroacetic acid; THM, trihalomethane

Main messages

- Trihalomethanes (THMs) occurring in public drinking water sources have been investigated in several epidemiological studies of fetal death and results support a modest association.
- Apart from trihalomethanes, several other classes of by-products are formed during water treatment.
- Among the classes of by-products formed, haloacetic acids (HAAs) are second in occurrence after THMs and can often equal the total THM concentrations.
- No association between HAA exposures and stillbirth risk was observed after controlling for THM exposures.

Measurement of exposure

The HAA measure was the sum of mass concentrations of nine haloacetic acid species. Exposure measures were also created for DCAA, TCAA, and total brominated HAAs. A measure representing the sum of brominated HAAs was created because the individual brominated compounds tended to occur in very low concentrations. Total exposure metrics were based on the product of volume of water consumed at home and work and HAA tap water level. Because they are non-volatile, showering and bathing are not important exposure routes for HAAs.^{20–21} Boiling water and home treatment devices were assumed to have a negligible effect on HAA concentration.^{22–23} The measure of subjects' total daily THM exposure incorporated water use behaviour (ingestion, showering and bathing) and has been described previously.¹³

Analyses

The odds ratio was used as an estimate of relative risk. Relative risks (RR) and 95% confidence intervals (CI) adjusted for potential confounders were calculated using logistic regression. Information on potential confounding factors included factors pertaining to past pregnancy history, information pertaining to the index pregnancy, information on jobs held during pregnancy, socioeconomic factors, and smoking during pregnancy. Potential confounders were entered into a multivariate model along with the total HAA exposure variable. Factors were kept in the model and considered confounders if the change in effect size for any category of total HAA was 10% or greater. This confounder model was used for each of the specific HAA exposures and in models adjusted for THM exposures.

Categorical representations of HAA exposures were based on a zero exposure group and tertiles of the control distribution.

Policy implications

- Among the two most prevalent classes of chlorination by-products, THMs display a stronger independent relation to stillbirth risk than HAAs, and therefore merit priority with respect to research aimed at understanding this relation and setting of allowable limits.

tribution of exposure. The THM measures were found in a previous analysis to follow a log linear pattern with stillbirth risk and were modelled as continuous variables in this analysis to overcome the potential for collinearity with HAA exposures.¹³ Analysis was conducted with and without adjustment for total THM exposure.

RESULTS

A letter inviting eligible subjects to participate was sent to 184 stillbirth cases and 580 live birth controls. Of these, a positive reply card was received by the study investigators from 61% of cases ($n=112$) and from 68% of controls ($n=398$).

Table 1 presents the distribution of HAA exposures for cases and controls. All distributions were positively skewed due to the high prevalence of zero HAA exposures. The median and 90th centile of household total HAA were similar for cases and controls. Among both cases and controls, more than 10% of subjects were exposed to total HAA in household water above 60 µg/l.

The occurrence of household HAA and THM tap water concentrations was highly correlated ($r=0.81$). However, the correlation between THM and HAA total exposure metrics, which also accounted for the contribution of water use behaviour to exposure was lower ($r=0.68$).

Table 2 presents the distribution of cases and controls for the total HAA exposure metrics and relative risks adjusted for potential confounders. In order to determine the effects of HAA exposures independent of THMs, relative risks were also estimated controlling for the continuous representation of total THM exposure.

In analyses adjusted for covariates not including other chlorination by-products, relative risks of greater than 2 were observed for an intermediate category of exposure for total HAA and DCAA measures. However, the pattern of risk was not consistent with a dose response, as for each measure, the relative risk associated with the highest category of exposure was lower and confidence intervals included the null value. After adjustment for total THM exposure, the risk estimates for intermediate exposure categories were diminished and all confidence intervals included the null value. TCAA and

Table 1 Cases and control distribution of household and total HAA exposures

	Cases				Controls			
	Centiles				Centiles			
	25th	50th	75th	90th	25th	50th	75th	90th
Household (µg/l)								
Total HAA	0.0	23.9	38.1	65.6	0.0	24.4	46.6	64.0
DCAA	0.0	7.7	19.5	32.0	0.0	7.0	24.0	36.0
TCAA	0.0	3.6	10.4	19.3	0.0	3.3	12.7	22.0
Brominated HAAs	0.0	1.1	5.2	12.4	0.0	0.0	4.0	9.2
Total exposure (µg/l/day)								
Total HAA	3.0	28.3	57.6	88.1	0.0	20.2	55.6	90.6
DCAA	0.0	8.2	23.5	41.1	0.0	7.1	25.8	47.5
TCAA	0.0	5.5	14.3	23.9	0.0	4.5	13.4	26.7
Brominated HAAs	0.0	2.8	7.7	14.3	0.0	1.6	6.2	13.1

Table 2 Relative risks (RR) and 95% confidence intervals (95% CI) for by-product total exposure measures and risk of stillbirth

Exposure	Cases n = 112	Controls n = 398	Adjusted RR (95% CI)*	THM adjusted RR (95% CI)†
Total HAA				
No exposure	27	116	1.00	1.00
Tertile 1 (lowest)	18	94	0.93 (0.46 to 1.89)	0.85 (0.41 to 1.74)
Tertile 2	40	94	2.35 (1.27 to 4.34)	1.91 (0.97 to 3.76)
Tertile 3	27	94	1.35 (0.70 to 2.63)	0.94 (0.41 to 2.18)
DCAA				
No exposure	30	127	1.00	1.00
Tertile 1 (lowest)	29	91	1.54 (0.82 to 2.88)	1.28 (0.67 to 2.46)
Tertile 2	30	90	1.99 (1.05 to 3.76)	1.45 (0.72 to 2.91)
Tertile 3	23	90	1.17 (0.60 to 2.31)	0.66 (0.28 to 1.56)
TCAA				
No exposure	32	127	1.00	1.00
Tertile 1 (lowest)	30	91	1.54 (0.83 to 2.87)	1.31 (0.69 to 2.51)
Tertile 2	19	90	1.13 (0.57 to 2.24)	0.87 (0.41 to 1.84)
Tertile 3	31	90	1.52 (0.82 to 2.83)	1.02 (0.48 to 2.20)
Brominated HAA				
No exposure	37	151	1.00	1.00
Tertile 1 (lowest)	19	83	1.15 (0.59 to 2.23)	1.03 (0.52 to 2.03)
Tertile 2	27	82	1.43 (0.77 to 2.66)	1.24 (0.65 to 2.37)
Tertile 3	29	82	1.60 (0.88 to 2.89)	1.29 (0.67 to 2.49)

*Adjusted for maternal age, province, income, occupation, and smoking during pregnancy.

†Adjusted for maternal age, province, income, occupation, smoking during pregnancy, and total THM exposure.

brominated HAA exposures were not associated with stillbirth risk in either THM adjusted or unadjusted analysis. The relative risks for total THM in these models (not presented), reflect risk estimates previously reported from these data.¹³

In a previous publication examining THM exposures and stillbirth risk, the strongest association among specific THMs was observed for bromodichloromethane.¹³ In the analysis of HAA exposures, similar results were observed when adjustment was made for BDCM exposures (not presented).

DISCUSSION

Investigations of the relation between disinfection by-products and reproductive outcomes have thus far focused on exposure to trihalomethanes. Haloacetic acids are common by-products of water disinfection and can occur in concentrations as high as THMs. We investigated the association between exposure in pregnancy to HAA compounds in drinking water and risk for a stillbirth and assessed the relation of HAA exposure after controlling for THM exposure. In the analysis of exposure to each HAA by-product without adjustment for THMs, a relative risk greater than 2 was observed for intermediate exposure categories for total HAA and DCAA measures. However, after adjustment for total THM exposure none of the HAA measures examined was associated with stillbirth risk.

Collinearity in the occurrence of different classes of disinfection by-products in household water supplies makes it difficult to determine the independent effects of specific by-products. Water use behaviours contribute different amounts of exposure for volatile and non-volatile by-products. In particular, our measure of total by-product exposure accounted for the large contribution of showering to an individual's THM exposure.²⁴ This measure thus introduced greater variability between a subject's THM and HAA exposure measures and facilitated an analysis of the independent effects of THM and HAA exposures.

The potential impact of low response rates (61% in cases and 68% in controls) on the validity of the study results has been discussed in a previous publication.¹³ Potential participants were unlikely to be aware of either the specific study hypothesis or the level of chlorination by-products in their water, and thus non-response was not likely to be related to exposure differentially among cases and controls.

Although a relation between exposure to THMs and intrauterine death is suggested in the epidemiological literature, causal mechanisms are not understood. THMs represent only one class of disinfection by-product, and other classes of by-product could be equally important in this relation. A relation between total THM and in particular BDCM and stillbirth risk was observed in our previous publication on this case-control study. The findings presented here focus on risk of stillbirth in relation to the next most prevalent class of disinfection by-products, HAAs, and exposure to this class of by-products was not found to be related to risk after controlling for THM or BDCM exposure.

ACKNOWLEDGEMENTS

This research was funded by the Toxic Substance Research Initiative, a research programme managed jointly by Health Canada and Environment Canada, and by the Canadian Chlorine Coordinating Committee. LD and BAA are supported by a Clinical Research Scholar Award from Dalhousie University.

We thank the study coordinators, Celine Zakos and Adelia Trenchard. We are grateful for assistance from the Reproductive Care Program of Nova Scotia, the Perinatal Partnership Program of Eastern and Southeastern Ontario, and the Analytical Services Unit of Queen's University. We thank all the participating physicians and hospitals.

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Accepted 12 May 2004

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