Haloacetic acids in drinking water and risk for stillbirth

W D King, L Dodds, A C Allen, B A Armson, D Fell, C Nimrod

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.

METHODS
Study subjects and data collection
A detailed description of subject accrual and exposure assessment has been previously published. 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

Six studies have examined the risk of intrauterine death, stillbirth, or miscarriage, in relation to exposure to trihalomethane levels. All but one have reported an increase in risk with THM exposure. 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. 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. 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.
Haloacetic acids and risk for stillbirth

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. Boiling water and home treatment devices were assumed to have a negligible effect on showering and bathing and has been described previously.

THM exposure incorporated water use behaviour (ingestion, swallowing and bathing) and has been described previously. THM exposure incorporated water use behaviour to exposure was lower (r = 0.68). 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 = 0.81). However, 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 = 0.81).

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 THM 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 brominated HAAs were not associated with stillbirth risk after adjustment for THMs.

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 brominated HAAs were not associated with stillbirth risk after adjustment for THMs.

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

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<tr>
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<th>Cases</th>
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<tr>
<td></td>
<td>25th</td>
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<td>Household (µg/l)</td>
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<td>Total exposure (µg/l/day)</td>
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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.

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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 between exposure in pregnancy to HAA compounds in drinking water and stillbirth risk after controlling for THM exposure.24 This measure thus introduced an analysis of the independent effects of THM and HAA exposures.

Although a relation between exposure to THMs and stillbirth risk 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.

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**REFERENCES**


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Committee on Publication Ethics Seminar 2005
Friday 11 March 2005, 9.30 am – 5 pm, BMA House, London

This year’s seminar will focus on COPE’s new Code of Conduct for Editors and interactive workshops on common ethical and editorial dilemmas. The seminar is for editors, authors, and all those interested in increasing the standard of publication ethics.

The Code aims to set a new basic standard for the ethical conduct of editors and sets out guidelines for quality and correct the record, standing by decisions made, ethics committee approval, consent for publication confidentiality of submitted material, guidance to authors, pursuing misconduct, relationship to publishers, owners, and advertisers, and conflict of interest. The code also creates a mechanism to refer a complaint to COPE if an editor has breached the code.

The seminar will include:

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- COPE’s new website—full text and keyword searching for COPE’s advice on specific issues, for example research misconduct, conflict of interest, and deception
- Interactive workshops—common ethical and editorial dilemmas for editors
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