Relation between trihalomethane compounds and birth defects

L Dodds, W D King

Abstract

***Objectives*—To evaluate the risk of birth defects relative to exposure to specific trihalomethanes in public water supplies.**

***Methods*—A retrospective cohort study was conducted based on data from a population based perinatal database in Nova Scotia, Canada and from the results of routine water monitoring tests. The cohort consisted of women who had a singleton birth in Nova Scotia between 1988 and 1995 and who lived in an area with a municipal water supply. The birth defects analyzed included neural tube defects, cardiovascular defects, cleft defects, and chromosomal abnormalities. Two of the four trihalomethane compounds occur in large enough concentrations to be analyzed (chloroform and bromodichloromethane (BDCM)).**

***Results*—Exposure to BDCM at concentrations of 20 µg/l or over was associated with an increased risk of neural tube defects (adjusted relative risk (RR) 2.5, 95% confidence interval (95% CI) 1.2 to 5.1) whereas exposure to chloroform was not. Exposure to BDCM of 20 µg/l and over was associated with decreased risks of cardiovascular anomalies (RR 0.3, 95% CI 0.2 to 0.7). There was a suggestion of an increased risk of chromosomal abnormalities associated with exposure to chloroform, and no evidence of any association between either trihalomethane compound and cleft defects.**

***Conclusions*—In this cohort, differences were found in the RR associated with exposure to chloroform and BDCM for each of the congenital anomalies under study. These findings point to the importance of examining specific byproduct compounds relative to risk for these birth outcomes and in particular implicate BDCM and other correlated disinfection byproducts in the aetiology of neural tube defects.**

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Several recent studies have focused on the effect of disinfection byproducts and reproductive outcomes. In Canada, guidelines for maximum total concentrations exist only for trihalomethanes, the most abundant of the byproducts.[1] Trihalomethanes are comprised of four compounds—chloroform, bromodichloromethane (BDCM), bromoform, and chlorodibromomethane. The relative concentrations of these compounds depend on variables primarily related to the water supply—such as pH, bromide ion concentration, temperature, and concentration of organic compounds in the water.[2]

Most of the previous research on the effects of disinfection byproducts and reproductive outcomes has focused on exposure to concentrations of total trihalomethanes. In a previous analysis, we did not find significantly increased risks of congenital anomalies related to total trihalomethanes,[3] although other investigators have noted an increased risk of neural tube defects, major cardiac defects, and oral cleft defects related to their total concentrations.[4 5]

Water disinfection can result in the formation of a complex mixture of chemicals, including trihalomethanes, haloacetic acids, and acetonitriles. The chemical classes formed during water disinfection and the proportional distribution of individual chemicals within a class vary between water distribution systems. Investigation of specific compounds has the potential to identify the compounds or a correlate of the compounds which is most strongly related to an increased health risk. In this study, we examine the effect of exposure of two trihalomethanes, chloroform and BDCM on the risk of congenital anomalies.

Subjects and methods

This was a retrospective cohort study which included singleton births among residents of Nova Scotia, Canada between 1988 and 1995, inclusive. The perinatal information used in this study was obtained from the Nova Scotia Atlee perinatal database. Information on exposure concentrations of trihalomethanes was obtained from the Nova Scotia Department of Environment from the results of routine monitoring. At each time and place, total trihalomethanes and the concentration of each of the individual compounds were measured. Bromoform and chlorodibromomethane were measured but occurred at very low concentrations. Thus, only chloroform and BDCM were evaluated in these analyses. A complete description of the methods has been published previously.[3]

The birth defects studied were those reported in other studies and included neural tube defects, major cardiac defects, cleft defects, and chromosomal abnormalities. Information in the perinatal database was abstracted from medical records and includes infant diagnoses among stillborn infants and live born infants up to the time of discharge from hospital after the birth. As well, information on congenital anomalies was obtained

Table 1 Cross classification of percentage of subjects living in areas with high concentrations of chloroform or bromodichloromethane (BDCM)

	Chloroform		
	<100 µg/l	*≥100 µg/l*	*Total*
BDCM:			
<20 µg/l	82.2	12.3	94.5
≥20 µg/l	3.3	2.2	5.5
Total	85.5	14.5	100

from pregnancy terminations for a prenatally diagnosed congenital anomaly. Exposure windows were determined by the time in gestation (or before) when exposure to a potential teratogen (or mutagen) might have the most profound effect. Average chloroform and BDCM concentrations from 1 month before conception and 1 month after were used for the analysis of neural tube defects, concentrations during the first 2 months of pregnancy were used for the analyses of cardiac defects and cleft defects, and the average concentrations 3 months before pregnancy were used for the analysis of chromosomal abnormalities.

Estimates of relative risks (RRs) and 95% confidence intervals (95% CIs) were obtained from Poisson regression models with SAS software. Potential confounders were selected from confounders noted in previous studies as well as their availability in the perinatal database. Maternal age, parity, maternal smoking, and neighbourhood family income were assessed for confounding and were retained in the model if the coefficient for either variable of exposure to trihalomethanes changed by 5% in the presence of the potential confounder. Separate models were developed for chloroform and for BDCM. However, for each congenital anomaly evaluated, the same confounders were included in the models for chloroform and for BDCM so that results could be compared among the same subset of women. The categories used for chloroform were <50 µg/l (the referent category), 50–74 µg/l, 75–99 µg/l, and 100 µg/l and over. Smaller categories of BDCM were created which reflected their lower concentration. These categories included: <5 µg/l (the referent category), 5–9 µg/l, 10–19 µg/l, and ≥20 µg/l. The categories of chloroform were identical to those used in previous analyses for chloroform and total trihalomethanes.[3 6] The categories of BDCM were also used in a previous analysis of this study population.[6] As there are no guidelines in Canada or elsewhere, to indicate unacceptable levels of exposure to BDCM, the categories were selected before the analyses based on logical cut off points.

Table 2 Crude and adjusted relative risks (RRs) of congenital anomalies related to exposure to bromodichloromethane (BDCM) and chloroform during pregnancy

Defects and anomalies	*Cases (births) n**	*Rate/1000*	*Crude RR (95% CI)*	*Adjusted RR (95% CI)*
Neural tube defects:				
BDCM (µg/l):				
<5	35 (26636)	1.3	1.0	1.0†
5–9	27 (13837)	2.0	1.5 (0.9 to 2.5)	1.4 (0.8 to 2.3)†
10–19	5 (5638)	0.9	0.7 (0.3 to 1.7)	0.6 (0.2 to 1.5)†
≥20	10 (2734)	3.7	2.8 (1.4 to 5.6)	2.5 (1.2 to 5.1)†
Chloroform(µg/l):				
<50	33 (18964)	1.7	1.0	1.0†
50–74	19 (16323)	1.2	0.7 (0.4 to 1.2)	0.7 (0.4 to 1.2)†
75–99	8 (6685)	1.2	0.7 (0.3 to 1.5)	0.7 (0.3 to 1.5)†
≥100	17 (6873)	2.5	1.4 (0.8 to 2.6)	1.2 (0.7 to 2.3)†
Cardiovascular anomalies:				
BDCM (µg/l):				
<5	258 (26977)	9.6	1.0	1.0†
5–9	125 (13653)	9.2	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)†
10–19	39 (5546)	7.0	0.7 (0.5 to 1.0)	0.7 (0.5 to 1.0)†
≥20	8 (2669)	3.0	0.3 (0.2 to 0.6)	0.3 (0.2 to 0.7)†
Chloroform (µg/l):				
<50	170 (19057)	8.9	1.0	1.0†
50–74	153 (16350)	9.4	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.3)†
75–99	60 (6550)	9.2	1.0 (0.8 to 1.4)	1.0 (0.8 to 1.4)†
≥100	47 (6888)	6.8	0.8 (0.6 to 1.1)	0.7 (0.5 to 1.0)†
Cleft defects:				
BDCM (µg/l):				
<5	50 (27426)	1.8	1.0	1.0‡
5–9	17 (13972)	1.2	0.7 (0.4 to 1.2)	0.7 (0.4 to 1.2)‡
10–19	12 (5723)	2.1	1.2 (0.6 to 2.2)	1.1 (0.6 to 2.1)‡
≥20	3 (2721)	1.1	0.6 (0.2 to 1.9)	0.6 (0.2 to 1.9)‡
Chloroform (µg/l):				
<50	28 (19351)	1.4	1.0	1.0‡
50–74	29 (16597)	1.7	1.2 (0.7 to 2.0)	1.2 (0.7 to 2.0)‡
75–99	9 (6696)	1.3	0.9 (0.4 to 2.0)	0.9 (0.4 to 2.0)‡
≥100	16 (7198)	2.2	1.5 (0.8 to 2.8)	1.5 (0.8 to 2.8)‡
Chromosomal abnormalities:				
BDCM (µg/l):				
<5	54 (26214)	2.1	1.0	1.0†
5–9	29 (14565)	2.0	1.0 (0.6 to 1.5)	1.0 (0.6 to 1.5)†
10–19	8 (5304)	1.5	0.7 (0.3 to 1.5)	0.7 (0.4 to 1.6)†
≥20	5 (2762)	1.8	0.9 (0.4 to 2.2)	0.9 (0.4 to 2.3)†
Chloroform (µg/l):				
<50	30 (19416)	1.5	1.0	1.0†
50–74	33 (16086)	2.1	1.3 (0.8 to 2.2)	1.3 (0.8 to 2.2)†
75–99	19 (6721)	2.8	1.8 (1.0 to 3.3)	1.9 (1.1 to 3.3)†
≥100	14 (6622)	2.1	1.4 (0.7 to 2.6)	1.4 (0.8 to 2.8)†

*Subjects with missing values for adjustment variables were excluded.
†Adjusted for maternal age and income level.
‡Adjusted for maternal age.

Results

The cohort included 49 842 residents of Nova Scotia who lived in an area with a municipal water supply and delivered an infant between 1988 and 1995. Women with unknown gestational age (n=913) were excluded as the assignment of chloroform or BDCM concentration depended on the exposure window defined by gestational age or last menstrual period.

In this study area, chloroform has been shown to be highly correlated with total trihalomethanes.[6] The BDCM was less correlated with total trihalomethanes (r=0.44), and represents another dimension of exposure to chlorination byproducts. Table 1 shows the concordance between subjects with exposure to high concentrations of BDCM and to chloroform. Less than half of the subjects living in areas where BDCM concentrations exceeded 20 µg/l also had chloroform concentrations of above 100 µg/l.

Table 2 shows the crude and adjusted RRs associated with exposure to BDCM and chloroform for each anomaly group. For neural tube defects, excess risk was only found at the highest level of exposure to BDCM and there was no evidence of a dose-response pattern with its increasing concentration. The adjusted RR at exposure to the highest concentration of BDCM (≥20 µg/l) relative to exposure to concentrations less than 5 µg/l was 2.5 (95% CI 1.2 to 5.1). The few cases in this category results in a fairly unstable point estimate, as indicated by the width of the 95% CI. There was no evidence of an association between chloroform and neural tube defects.

For cardiac defects, there was a significant reduction in risk associated with exposure to ⩾20 μg/l of BDCM (RR 0.3, 95% CI 0.2 to 0.7) and a trend of decreasing risk associated with increasing level of exposure. Also, there was a suggestion of decreased risk associated with exposure to ⩾100 μg/l chloroform (RR 0.7, 95% CI 0.5 to 1.0).

There were no apparent trends or significant associations between concentration of BDCM or chloroform and cleft defects. There is a stronger relation between chloroform and chromosomal abnormalities than between BDCM and chromosomal abnormalities. For women exposed to 75–99 μg/l chloroform, the RR was 1.9 (95% CI 1.1 to 3.3) for having an infant with a chromosomal abnormality. The RR at concentrations of ⩾100 μg/l of chloroform was 1.4 (95% CI 0.8 to 2.8).

Discussion

We found differences in the RR associated with exposure to chloroform and BDCM for each of the congenital anomalies under study. For neural tube defects, the risk seems to be increased with high exposure to BDCM but not chloroform. The lack of association reported in an earlier publication between total trihalomethane and neural tube defects is explained by the fact that the total is made up primarily of chloroform.[3]

Previous reports have analyzed the relation between total trihalomethanes and congenital anomalies with inconsistent results. Only one epidemiological study has examined the risk of congenital anomalies associated with individual trihalomethanes. Klotz and Pyrch examined the relation between the four trihalomethane compounds and neural tube defects.[5 7] They found that the unadjusted risk of neural tube defects was similar among women exposed to the highest category of chloroform and the highest category of total brominated trihalomethanes. The unadjusted odds ratio (OR) associated with the highest concentration of BDCM (⩾8 μg/l) was 1.3 (95% CI 0.7 to 2.4), which is comparable with the RR found in the current study for similar levels of exposure. In Nova Scotia, BDCM occurs at higher concentrations and we were able to analyze exposure to higher levels than those reported in New Jersey. Only at concentrations over 20 μg/l did we find significantly increased risks of neural tube defects.

A strength of this study was that it incorporated therapeutic pregnancy terminations for antenatally diagnosed congenital anomalies. In Nova Scotia, it is estimated that about 80% of neural tube defects are detected antenatally and the pregnancy is electively terminated. Thus, other than early spontaneous losses of pregnancies with a congenital anomaly, we were able to capture all congenital anomalies. In this study, the inability to capture early losses of pregnancies with a congenital anomaly does limit our understanding of the relation between trihalomethanes and congenital anomalies.

The biological mechanism to support (or refute) the findings from the current study are not well understood. Nieuwenhuijsen *et al*, recently reviewed the toxicological evidence related to chlorination byproducts and reproductive effects.[8] In their review, pregnancy loss and reduced fetal weight were the most consistent reproductive effects related to high doses of trihalomethanes in animals, but there was no evidence of teratogenic effects related to total trihalomethanes or individual compounds. Several halogenated acids have been shown to have teratogenic effects (resulting primarily in heart defects) when given in high doses to rats.[9 10]

The protective effect found for exposure to BDCM on cardiovascular defects is difficult to explain. It is unlikely that exposure above 20 μg/l of BDCM is actually related to decreased risk of cardiac defects. Alternative explanations include a chance finding—for example, type 1 error—or the possibility that BDCM is negatively correlated with the occurrence of non-brominated byproducts in this region which may increase the risk of cardiovascular defects.

The anomaly groups in this study may not reflect anomalies with a common aetiology. This may be particularly true for the group of major cardiac anomalies, which actually represents several cardiac conditions. Combining these to a single disease entity may dilute any true association between trihalomethanes and cardiac anomalies. It should be noted that the diagnoses of birth defects in this study were limited to those detectable before an infant is discharged from hospital after delivery. However, most major anomalies included in this study would be detectable at birth or shortly thereafter.

In this study, exposure levels were based on trihalomethane concentrations from sampling sites within the water distribution systems. Exposure to chlorination byproducts occurs through several different routes, including ingesting, dermal exposure, and inhalation.[11] As we did not have information on individual patterns of consumption, showering, or bathing, the assigned category of exposure may not accurately reflect the actual trihalomethane uptake.

The potential confounders used in this study were limited to those variables available in the perinatal database. None of the available potential confounders proved to be strong, and their effect on the RRs were minimal. Two previous studies of congenital anomalies and trihalomethanes had information on additional confounders not available in this study.[4 5] Bove *et al*[4] did not find that adjustment for maternal education, adequacy of prenatal care, or other water contaminants altered the ORs for any of the anomalies studied and unadjusted analyses were used. In a study of neural tube defects, the variables representing the month in which prenatal care began, exposure to pesticides, maternal asthma or allergies, and employment outside the home each altered the ORs by more than 10%, although when combined, the adjustment did not alter the OR.[5]

The findings presented in this paper focus on the relation between two of the most abundant

trihalomethanes and the risk of birth defects. Many other byproducts may be present in water supplies and these two trihalomethanes may represent markers for other disinfection byproducts. This is one of the first epidemiological studies to evaluate the effect of specific trihalomethanes on the occurrence of congenital anomalies. Although the results from this study require confirmation from other populations, it does seem likely that risk of congenital anomalies varies according to specific disinfection byproducts and according to the specific anomaly under study. The BDCM and disinfection byproducts which tend to occur in conjunction with this specific chemical may be particularly important in the aetiology of neural tube defects.

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