Risk of Specific Birth Defects in Relation to Chlorination and the Amount of Natural Organic Matter in the Water Supply

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Received for publication July 6, 2001; accepted for publication April 17, 2002.

To assess the effect of water chlorination by-products on specific birth defects, the authors conducted a nationwide cross-sectional study of 285,631 Norwegian births in 1993–1998. Risks of birth defects according to four chlorination by-product exposure categories were compared on the basis of chlorination (yes/no) and level of water color (mg Pt/liter), representing the amount of natural organic matter: high (chlorination, ≤20), medium (chlorination, 10–19.9), and low (chlorination, <10) exposure, with no chlorination and low color (<10) as the reference category. In logistic regression analysis, the risks of any birth defect (adjusted odds ratio (OR) = 1.13, 95% confidence interval (CI): 1.01, 1.25) and of cardiac (adjusted OR = 1.37, 95% CI: 1.00, 1.89), respiratory system (adjusted OR = 1.89, 95% CI: 1.00, 3.58), and urinary tract (adjusted OR = 1.46, 95% CI: 1.00, 2.13) defects were significantly associated with exposure (medium and high combined). Regarding risk of specific birth defects, only that for ventricular septal defects was significantly elevated, with an exposure-response pattern, yielding adjusted odds ratios of 1.63 (95% CI: 1.02, 2.58) for the medium and 1.81 (95% CI: 1.05, 3.09) for the high exposure categories. Furthermore, risk of neural tube defects was related to high color (adjusted OR = 2.60, 95% CI: 1.30, 5.26). Am J Epidemiol 2002;156:374–82.

abnormalities; chlorine compounds; disinfection; water pollution, chemical; water purification

Abbreviations: CI, confidence interval; ICD-8, International Classification of Diseases, Eighth Revision; OR, odds ratio.

Chlorination has been widely and successfully used in water disinfection to reduce waterborne infections. In 1974, Rook showed that chlorination of water containing natural organic material results in production of some volatile halo- genated organic compounds, such as chloroform (1). Since then, many other chlorination by-products such as trihalomethanes, haloacetic acids, chlorophenols, chloral hydrate, and haloacetonitriles have been found, most resulting from the process of chlorination but also from chloramination, chlorine dioxide disinfection, and ozonation (2). Generally, the trihalomethanes are the most prevalent in chlorinated water. They might not be the most important from a public health point of view, because there is no direct evidence of their teratogenic effect (3).

Recent findings suggest that exposure to chlorination by-products increases the risk of birth defects (4–7). In 1995–1998, Magnus et al. studied the association between water chlorination and adverse pregnancy outcomes in Norway (8). This study of 141,081 newborns indicated an increased risk of any birth defect related to the use of chlorinated water with a high content of natural organic matter compared with nonchlorinated water with a low amount of organic matter. In particular, an association was found for neural tube defects and for urinary tract defects. We conducted a nationwide cross-sectional study of all births occurring in 1993–1998 to assess the effect of water chlorination by-products on specific birth defects, particularly defects of the neural tube and urinary tract. In addition, we elaborated the role of natural organic matter in nonchlorinated waters.

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MATERIALS AND METHODS

Study population

The source population comprised all 361,767 newborns registered by the Norwegian Medical Birth Registry from 1993 to 1998. We excluded 76,136 newborns because of insufficient information on chlorination practices or humic content of the water in the municipality in which the mother was living during pregnancy. Some of the municipalities were served by more than one waterworks. We focused on municipalities served with either chlorinated or nonchlorinated water, excluding those with both types of waterworks (100,955 infants). Therefore, the final study population included 184,676 infants.

Health outcomes

We assessed the effect of chlorination by-products on the risks of any birth defect and of five groups of defects, including neural tube, cardiac, respiratory system, urinary tract, and oral cleft defects, used in the Magnus et al. study of Norwegian births in 1993–1995 (8). In the present study with a larger study population, including births in 1993–1998, we also evaluated the most common specific birth defects, in particular those previously observed to be associated with chlorination: neural tube and urinary tract defects.

All births after the 16th week of gestation are compulsorily reported to the Norwegian Medical Birth Registry. During a child’s first week of life, a physician, most often a pediatrician, diagnoses the birth defects to be reported. As a result, birth defects diagnosed later in life are not included in the registry. The International Classification of Diseases, Eighth Revision (ICD-8) is used to code as many as three birth defects for each child. We included all birth defects with ICD-8 codes 740.0–759.9 as well as umbilical hernia (ICD-8 code 551.1) and ventral hernia (ICD-8 code 551.2). The following diagnoses were excluded because of poor reliability (8, 9): other anomalies of the nose (ICD-8 code 748.1), congenital hydrocele testis (ICD-8 code 752.4), clubfoot (ICD-8 codes 754.0–754.9), congenital dislocation of the hip (ICD-8 code 755.6), and other specified anomalies of muscle, tendon, and fascia (ICD-8 code 756.8).

Exposure assessment

Assessment of exposure was based on municipal-level water quality information on chlorination practices and the humic content of raw water and on the mother’s place of residence during pregnancy. Waterworks serving more than 100 persons must report to the National Institute of Public Health in Oslo, Norway. Each municipality was served by one or more waterworks, and the waterworks seldom serve those persons across the municipality’s borders. A total of 233 waterworks serving about 2.7 million people chlorinated their water, and 1,084 waterworks serving about 1.0 million people did not.

The main hypothesis of our study was that exposure to chlorination by-products in tap water increases the risk of birth defects. This exposure was expected to be more likely in municipalities whose waterworks chlorinate the water with dissolved organic compounds. We divided waterworks according to their use of chlorination disinfection and by water color (in mg Pt/liter) as a quantitative measure of the dissolved organic compounds. Water color is highly correlated with the concentration of dissolved organic compounds \((r = 0.817, n = 634)\) (10). The color number is recorded routinely by most of the waterworks. About 28 percent of the municipalities have one waterworks only, 26 percent have two, 16 percent have three, and 30 percent have more than three. For municipalities with more than one waterworks, we calculated the weighted mean color based on the fraction of the population served by each waterworks as a weighting factor. In the main analyses, we focused on municipalities in which all waterworks were either using chlorination or not using chlorination. We constructed exposure categories by using chlorination and three levels of color: low (0–9.9 mg Pt/liter), medium (10–19.9 mg Pt/liter), and high (≥20 mg Pt/liter). Low color with no chlorination constituted the reference category. Furthermore, we elaborated the effects of natural organic matter by using the three levels of color without chlorination.

Covariates

We used routine birth registry data to construct the following covariates: maternal age (<20, 20–34, ≥35 years) and parity (0, 1, 2, ≥3 previous deliveries). We received municipal-level data from the Norwegian Social Science Data services, which were used to construct two municipal-level indicators of socioeconomic status: centrality and population density. Centrality indicates urbanicity and geographic placement in relation to a regional center. Population density is a measure of the proportion of the urban population living in the municipality.

Statistical methods

We estimated the prevalence (percentage) of the birth defects (with 95 percent confidence intervals) based on a binomial distribution. We compared the risk of birth defects for three exposure categories (chlorination and low color, chlorination and medium color, chlorination and high color) with the unexposed reference category (no chlorination and low color). We used prevalence odds ratios as a measure of association, and we applied logistic regression analysis to estimate the adjusted odds ratios. Goodness of fit was assessed with likelihood ratio tests to determine whether a variable contributed significantly to the model. First, we fitted a full model with a complete set of covariates. To elaborate sources of confounding, we fitted models with different combinations of covariates and compared the effect estimates from models with and without the covariate of interest. To evaluate the potential role of residual confounding and effect modification, we systematically compared effect estimates on different levels of covariates. In the main analyses, we focused on municipalities in which all waterworks either used chlorination or did not use chlorination. In further analyses, we also included municipalities that had two types of waterworks, taking into account the fraction of the population served by different types.
adopted a similar approach in studying the independent effect of natural organic matter by using the following two exposure categories: no chlorination and medium color, no chlorination and high color; no chlorination and low color was used as the reference.

RESULTS

Of 184,676 livebirths in the study population, we identified 5,764 (3.12 percent) with the birth defects of interest. Table 1 displays the study population according to exposure categories. Compared with reference municipalities, the municipalities with chlorination were more central and had a higher population density. Table 2 compares the included, excluded, and total study populations.

Table 3 shows the prevalence of any birth defect, as well as its 95 percent confidence interval, for the main categories of water quality measures and covariates. The prevalence of any birth defect was lower in the reference category and in the chlorination and low-color category (2.77 and 2.08 percent, respectively) and higher in the chlorination and medium- and high-color categories (3.57 and 3.51 percent, respectively). However, prevalence also increased by color without chlorination.

Any birth defect

Consistent with our hypothesis, the risk of any birth defect was higher in the chlorination and medium-color (adjusted odds ratio (OR) = 1.11, 95 percent confidence interval (CI): 0.99, 1.24) and high-color (adjusted OR = 1.18, 95 percent CI: 1.02, 1.36) categories than in the reference category, showing an exposure-related increase (table 4). The adjusted odds ratios were 1.08 (95 percent CI: 0.97, 1.20) for medium color and 1.09 (95 percent CI: 0.94, 1.26) for high color.

Neural tube defects

We identified 138 livebirths (0.08 percent) with neural tube defects, including 46 (0.03 percent) anencephalus, 81 (0.04 percent) spina bifida, and 68 (0.04 percent) hydrocephalus cases. There was no consistent association of chlorination and color with the risk of neural tube defects (adjusted OR for combined medium and high exposure: 1.05, 95 percent CI: 0.54, 2.03). The risk was related to color without

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**TABLE 1. Characteristics of the population studied (n = 184,676) to determine a relation between specific birth defects and water chlorination,* according to categories of exposure,† Norway, 1993–1998**

<table>
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<th>Characteristic</th>
<th>Exposure category</th>
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* Some percentages do not total 100 because of rounding.
† Color (mg Pt/liter) level was used as a quantitative measure of the dissolved organic compounds in the water: low, 0–9.9; medium, 10–19.9; high, ≥20.
‡ Reference category.
§ Data were missing for 1,130 subjects.
¶ Urbanicity and geographic placement in relation to a regional center. A measure of the proportion of the urban population living in a municipality.
chlorination; the adjusted odds ratio was 2.60 (95 percent CI: 1.30, 5.26) in the high-color category. Of the specific neural tube defects, the adjusted odds ratios for spina bifida were 1.43 (95 percent CI: 0.58, 3.48) in the medium-color and 3.11 (95 percent CI: 1.22, 7.95) in the high-color categories. The risk of hydrocephalus was not consistently related to the level of color.

Cardiac defects

In the present study, 537 (0.29 percent) cardiac defects were identified. Table 4 shows that the risk of cardiac defects was slightly elevated, yielding adjusted odds ratios of 1.38 (95 percent CI: 0.99, 1.93) for the medium-exposure and 1.35 (95 percent CI: 0.89, 2.06) for the high-exposure categories. The estimate for the combined medium- and high-exposure category reached statistical significance (adjusted OR = 1.89, 95 percent CI: 1.00, 3.58). Estimates for specific defects are not presented in this paper because of small numbers, as shown in the second footnote of table 4. The risk of respiratory defects was not related to color in nonchlorinated water.

Respiratory system defects

We identified 192 infants (0.10 percent) with respiratory defects. The adjusted odds ratios for respiratory defects were 1.87 (95 percent CI: 0.96, 3.62) for medium exposure and 1.96 (95 percent CI: 0.89, 4.34) for high exposure to chlorinated humic water. The risk estimate for the combined medium- and high-exposure category reached statistical significance (adjusted OR = 1.89, 95 percent CI: 1.00, 3.58). Estimates for specific defects are not presented in this paper because of small numbers, as shown in the second footnote of table 4. The risk of respiratory defects was not related to color in nonchlorinated water.

Oral cleft defects

There were 343 (0.19 percent) oral cleft defects. The risk of these defects was related to neither chlorinated humic water nor color in nonchlorinated water. Table 4 presents the risk estimates for cleft palate, cleft lip, and cleft palate with cleft lip. None of the estimates reached statistical signifi-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included population</th>
<th>Excluded population</th>
<th>Total population</th>
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<td>(n = 184,676)</td>
<td>(n = 177,091)</td>
<td>(n = 361,767)</td>
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<td>No. %</td>
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<td>Maternal age (years)</td>
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<td>&lt;20</td>
<td>3,753 2.0</td>
<td>4,089 2.3</td>
<td>7,842 2.2</td>
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<td>20–34</td>
<td>153,352 83.0</td>
<td>149,195 84.2</td>
<td>302,547 83.6</td>
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<td>≥35</td>
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<td>23,807 13.4</td>
<td>51,378 14.2</td>
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<tr>
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<td>70,081 39.8</td>
<td>146,736 40.8</td>
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<tr>
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<td>65,085 35.5</td>
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<td>30,055 16.4</td>
<td>31,226 17.7</td>
<td>61,281 17.0</td>
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<td>Centrality‡</td>
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<td>49,165 28.4</td>
<td>101,475 28.4</td>
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<td>Medium</td>
<td>37,305 20.2</td>
<td>30,893 17.9</td>
<td>68,198 19.1</td>
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<tr>
<td>High</td>
<td>95,061 51.5</td>
<td>92,999 53.7</td>
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<td>Population density§</td>
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<td>61,846 34.9</td>
<td>117,534 32.5</td>
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<tr>
<td>3</td>
<td>100,861 54.6</td>
<td>94,793 53.5</td>
<td>195,654 54.1</td>
</tr>
</tbody>
</table>

* Some percentages do not total 100 because of rounding.
† Data were missing for 1,130 subjects.
‡ Urbanicity and geographic placement in relation to a regional center.
§ A measure of the proportion of the urban population living in a municipality.
There were 232 (0.13 percent) urinary tract defects in the study population. In the logistic regression models, we found a slightly increased risk of urinary tract defects, with adjusted odds ratios of 1.61 (95 percent CI: 0.94, 2.76) for the medium-exposure and 1.35 (95 percent CI: 0.65, 2.80) for the high-exposure categories. The risk estimate for the combined medium- and high-exposure category was 1.55 (95 percent CI: 0.92, 2.61). When we included the municipalities with a mixed type of waterworks, the adjusted odds ratio was 1.46 (95 percent CI: 1.00, 2.13). The risk of obstructive defects of the urinary tract, with adjusted odds ratios of 1.89 (95 percent CI: 0.81, 4.44) for medium exposure and 1.99 (95 percent CI: 0.66, 5.96) for high exposure, showed an exposure-related increase, although the estimates did not reach statistical significance (table 4). The risk of urinary tract defects was not related to color level in nonchlorinated water.

DISCUSSION

The results of the present study suggest that prenatal exposure to chlorinated water containing elevated levels of natural organic matter increases the risk of birth defects. The risks of cardiac, respiratory system, and urinary tract defects were higher in the exposed than in the reference group. The risks of several specific birth defects were elevated, but risk estimates for only ventral septal defects reached statistical significance. In the elaborative analyses, the risk of neural tube defects was related to color level, with an exposure-response pattern, but not to chlorinated humic water.
Validity of results

The Norwegian Medical Birth Registry provided health information on a large number of newborns, which made it possible to assess the effects of chlorination by-products on some of the most common specific birth defects. We excluded one half of the births because of insufficient water quality data. This exclusion was not likely to introduce selection bias; it was made on the municipality level, and the characteristics of the excluded municipalities and newborns did not differ substantially from those for the included municipalities and newborns, as shown in table 2.

A major limitation of this study was the ascertainment and classification of prenatal exposure to chlorination by-products, including the imprecision of using aggregate municipal measures to classify exposure at the individual level. Residential mobility also raised a potential problem concerning misclassification. Substantial variation in by-product concentrations over time adds another dimension of complexity. The main assumption was that women in municipalities with chlorinated water containing elevated levels of natural organic matter are exposed to chlorination by-products and that the magnitude of exposure is related to the amount of organic compounds in the water. We had no information on the quantities or sources of water that the women consumed, which decreased the accuracy of exposure assessment.

We were not able to take into account confounders such as alcohol consumption; cigarette smoking; vitamin use; or medication, pesticide, and genetic factors. There was no reason to suspect that these confounders were associated with water color or chlorination practices. Adjustment for centrality and population density not only adjusted indirectly for municipal differences in these behavior factors but also partly eliminated detection bias between urban hospitals and rural hospitals. To elaborate the residual confounding and potential effect modification, we systematically conducted stratified analyses by using different categories of exposure and other covariates. Because of reduced group sizes, this procedure was meaningful for only any birth defect and the five birth defect groups. The stratified analyses did not indicate any major confounding or effect modification.

Misclassification of the birth defects was also possible in the present study; diagnosis is difficult because of the rarity of each condition. In general, the birth defects might have been underreported because we did not include those diagnosed after 7 days of age. However, in the presence of a true association, random underreporting would weaken the observed association rather than introduce a spurious effect. In addition, residual confounding by unmeasured parameters such as environmental exposures, including air contaminants and occupational exposures, remains a possible explanation for our results.

Synthesis with previous knowledge

The present study and both previous studies from Massachusetts (4) and New Jersey (5) provide consistent evidence that exposure to chlorination by-products increases the risk of birth defects. All available studies suggest an increased risk of respiratory (4) and urinary tract (4) defects, but the findings are inconsistent for neural tube (4, 5), oral cleft (5, 6), and major cardiac (5, 6) defects. So far, very little is known about the relations between exposure and specific birth defects.

A case-control study in Massachusetts indicated that pregnant women using chlorinated surface water have an increased risk of birth defects, particularly respiratory and urinary tract defects, compared with women using chlorinated water (4). A cross-sectional study in New Jersey found that infants born to women exposed to trihalomethane levels of 80 µg/liter or more tended to have a higher risk of neural tube defects, major cardiac defects, and oral cleft defects than those born to women exposed to trihalomethane levels of 20 µg/liter or less (5). A retrospective cohort study in Nova Scotia provided little evidence that women exposed to trihalomethane levels of 100 µg/liter or more versus 0–49 µg/liter had an elevated risk of giving birth to infants with neural tube defects (6). In a population-based case-control study in New Jersey, the adjusted odds ratio of neural tube defects was 1.6 (95 percent CI: 0.9, 2.7) for the highest third compared with the lowest third of total trihalomethane exposure levels in the first month of pregnancy (7).

We were able to study nine of the most common specific birth defects as outcomes. Two, ventricular septal defect and obstructive defects of the urinary tract, were related to exposure to chlorinated water with a high amount of organic matter. One previous study has provided effect estimates for specific birth defects. Consistent with our results, Klots and Pyrch (11) found no significant association between exposure to chlorination by-products and risk of spina bifida. Interestingly, we found that the risk of spina bifida was related to high amounts of organic matter in nonchlorinated water.

A study of 21 Norwegian waterworks using chlorination reported exposure levels for chlorination by-products (12). The average concentration of total trihalomethanes was 9.4 µg/liter and of halogenated acetic acid was 14.6 µg/liter, which were relatively lower compared with concentrations reported in US (5, 7) and Canadian (6) drinking water sources, although the mean color was 22 mg Pt/liter for these selected Norwegian waterworks.

We studied a relatively large number of health outcomes, which may have influenced interpretation of our results. However, we considered the hypotheses of the effects on the a priori defined birth defect groups, which are independent and mutually exclusive and thus do not require multiple-inference procedures (13). Following a suggestion by Rothman and Greenland (13), we presented all single-inference procedures with point estimates and confidence intervals (or numbers of birth defects when too few to produce an estimate) rather than selected effect estimates from an unknown number of estimates. Each reported association should be considered in the light of previous epidemiologic and toxicologic evidence (14, 15). Our finding suggested a small effect of prenatal exposure to chlorination by-products on ventricular septal defects, one of the most homogeneous cardiac defect categories. This finding is consistent with toxicologic evidence of the effects of haloacetic acids and haloacetonitriles (16).

<table>
<thead>
<tr>
<th>Birth defect (no. and prevalence (%))</th>
<th>Exposure category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No chlorination, low color</td>
</tr>
<tr>
<td>Any birth defect (n = 5,764 (3.121))</td>
<td></td>
</tr>
<tr>
<td>No.</td>
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</tr>
<tr>
<td>Prevalence (%)</td>
<td>2.772</td>
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<td>OR‡</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI‡</td>
<td>0.97, 1.20</td>
</tr>
<tr>
<td>Neural tube defects (n = 138 (0.075))</td>
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<tr>
<td>No.</td>
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<tr>
<td>Prevalence (%)</td>
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<tr>
<td>OR</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.57, 2.19</td>
</tr>
<tr>
<td>Anencephalus (n = 46 (0.025))</td>
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<td>No.</td>
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<tr>
<td>Prevalence (%)</td>
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<tr>
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<tr>
<td>95% CI</td>
<td>0.38, 3.44</td>
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<td>Spina bifida (n = 81 (0.044))</td>
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</tr>
<tr>
<td>Adjusted OR</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.58, 3.48</td>
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<tr>
<td>Hydrocephalus (n = 68 (0.037))</td>
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<td>No.</td>
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<tr>
<td>Prevalence (%)</td>
<td>0.032</td>
</tr>
<tr>
<td>OR</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.63, 3.61</td>
</tr>
<tr>
<td>Cardiac defects (n = 537 (0.291))</td>
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<tr>
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<td>Prevalence (%)</td>
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<td>95% CI</td>
<td>0.98, 1.85</td>
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<td>Ventricular septal defects (n = 279 (0.151))</td>
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<td>Prevalence (%)</td>
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</tr>
<tr>
<td>Adjusted OR</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
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</tr>
<tr>
<td>Atrial septal defect (n = 73 (0.040))</td>
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</tr>
<tr>
<td>No.</td>
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</tr>
<tr>
<td>Prevalence (%)</td>
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<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.15, 1.34</td>
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Table continues
TABLE 4. Continued

<table>
<thead>
<tr>
<th>Birth defect† (no. and prevalence (%))</th>
<th>No chlorination, low color†</th>
<th>No chlorination, medium color</th>
<th>No chlorination, high color</th>
<th>Chlorination, low color</th>
<th>Chlorination, medium color</th>
<th>Chlorination, high color</th>
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<tr>
<td>Respiratory defects (n = 192 (0.104))</td>
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<td>0.052</td>
<td>0.039</td>
<td>0.069</td>
<td>0.150</td>
<td>0.131</td>
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<tr>
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<td>0.85</td>
<td>0.63</td>
<td>1.13</td>
<td>2.46</td>
<td>2.14</td>
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<tr>
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<td>0.54</td>
<td>0.96</td>
<td>1.87</td>
<td>1.96</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.34, 1.52</td>
<td>0.16, 1.79</td>
<td>0.45, 2.06</td>
<td>0.96, 3.62</td>
<td>0.89, 4.34</td>
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<td>Oral cleft defects (n = 343 (0.186))</td>
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<tr>
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<td>140</td>
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<td>0.195</td>
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<td>0.88</td>
<td>0.89</td>
<td>0.77</td>
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<tr>
<td>95% CI</td>
<td>0.48, 1.12</td>
<td>0.52, 1.57</td>
<td>0.64, 1.56</td>
<td>0.61, 1.39</td>
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<tr>
<td>Cleft palate (n = 95 (0.051))</td>
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<td>Prevalence (%)</td>
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<td>0.065</td>
<td>0.057</td>
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<tr>
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<tr>
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<tr>
<td>95% CI</td>
<td>0.54, 2.54</td>
<td>0.55, 4.01</td>
<td>0.60, 3.33</td>
<td>0.62, 3.03</td>
<td>0.35, 3.27</td>
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<tr>
<td>Cleft lip (n = 67 (0.036))</td>
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<td>4</td>
<td>5</td>
<td>33</td>
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<tr>
<td>Prevalence (%)</td>
<td>0.034</td>
<td>0.031</td>
<td>0.052</td>
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<td>0.050</td>
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<td>0.59</td>
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<td>0.90</td>
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<td>2.01</td>
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<tr>
<td>95% CI</td>
<td>0.31, 2.21</td>
<td>0.48, 4.65</td>
<td>0.28, 2.93</td>
<td>0.83, 5.14</td>
<td>0.63, 6.46</td>
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<tr>
<td>Cleft palate with cleft lip (n = 181 (0.098))</td>
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<td>29</td>
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<tr>
<td>Prevalence (%)</td>
<td>0.137</td>
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<td>0.078</td>
<td>0.118</td>
<td>0.080</td>
<td>0.091</td>
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<tr>
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<td>0.86</td>
<td>0.58</td>
<td>0.66</td>
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<tr>
<td>Adjusted OR</td>
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<td>0.55</td>
<td>0.79</td>
<td>0.55</td>
<td>0.58</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.31, 0.99</td>
<td>0.23, 1.28</td>
<td>0.43, 1.44</td>
<td>0.30, 0.98</td>
<td>0.26, 1.29</td>
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<tr>
<td>Urinary tract defects (n = 232 (0.126))</td>
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<td>No.</td>
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<td>16</td>
<td>129</td>
<td>12</td>
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<tr>
<td>Prevalence (%)</td>
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<td>0.109</td>
<td>0.130</td>
<td>0.065</td>
<td>0.157</td>
<td>0.121</td>
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<tr>
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<td>1.20</td>
<td>0.60</td>
<td>1.45</td>
<td>1.12</td>
</tr>
<tr>
<td>Adjusted OR</td>
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<td>1.25</td>
<td>0.70</td>
<td>1.61</td>
<td>1.35</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.61, 1.76</td>
<td>0.62, 2.51</td>
<td>0.35, 1.37</td>
<td>0.94, 2.76</td>
<td>0.65, 2.80</td>
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<tr>
<td>Obstructive urinary tract defects (n = 102 (0.052))</td>
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<td>No.</td>
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<td>9</td>
<td>61</td>
<td>6</td>
</tr>
<tr>
<td>Prevalence (%)</td>
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<td>0.031</td>
<td>0.026</td>
<td>0.037</td>
<td>0.074</td>
<td>0.061</td>
</tr>
<tr>
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<td>0.71</td>
<td>0.59</td>
<td>0.83</td>
<td>1.68</td>
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<td>1.02</td>
<td>1.89</td>
<td>1.99</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.28, 1.83</td>
<td>0.14, 2.65</td>
<td>0.37, 2.78</td>
<td>0.81, 4.44</td>
<td>0.66, 5.96</td>
<td></td>
</tr>
</tbody>
</table>

* Color (mg Pt/liter) level was used as a quantitative measure of the dissolved organic compounds in the water: low, 0–9.9; medium, 10–19.9; high, ≥20.
† Estimates not given for the following rare outcomes: encephalocele (n = 13), common truncus (n = 3), tetralogy of Fallot (n = 26), ostium atrioventriculare commune (n = 8), heart valve anomalies (n = 13), fibroelastosis cordis (n = 34), transposition of great vessels (n = 27), choanal atresia (n = 9), web of larynx (n = 3), congenital cystic lung (n = 4), renal agenesis (n = 30), cystic kidney disease (n = 41), exstrophy of the urinary bladder (n = 5), atresia and stenosis of the urethra and bladder neck (n = 11).
‡ Reference category.
§ OR, crude odds ratio; CI, confidence interval.
¶ Logistic regression analysis adjusted for maternal age, parity, centrality (urbanicity and geographic placement in relation to a regional center), population density (a measure of the proportion of the urban population living in a municipality), and municipality in which the mother lived during pregnancy.
The risk of neural tube defects was related to color level, with an exposure response pattern. Of the risk for specific birth defects, that for spina bifida showed a similar pattern. We did not have sufficient information on the quality of unchlorinated water to elaborate potential, specific causal agents. From previous literature, we know that nitrate levels are higher in humic waters and could increase the risk of neural tube defects (17, 18). In addition, hardness of water has been reported to be associated with the risk of neural tube defects, particularly anencephaly (19–22). Any known or unknown determinant of birth defects related to the amount of natural organic matter could be responsible for the observed association between color level and risk of neural tube defects. This problem was common in all previous studies assessing the effects of chlorination by-products on the risk of birth defects, because persons exposed to chlorination by-products were also exposed to substances in water with natural organic matter. Unlike in the previous study areas of the United States and Canada, Norwegian waterworks commonly distribute unchlorinated surface water with a relatively high content of natural organic matter. This unusual setting made it possible to assess the effect of organic matter independently from the effect of chlorination. Further studies should determine the role of different water quality parameters related to the content of natural organic matter.

Conclusion

In summary, the present study indicates that exposure to chlorinated surface waters with a high content of natural organic matter increases the risk of birth defects. The current body of evidence, including the present and five previous studies (4–8), suggests small effects on the risk of urinary tract, respiratory system, and major cardiac defects. The studies of neural tube and oral cleft defects are inconclusive, probably explained by qualitative geographic differences in the levels of natural organic matter or lower concentrations of chlorination by-products in Norwegian drinking water than in US and Canadian drinking water. Additionally, the risk of ventricular septal defects was found to be associated with exposure to chlorinated surface water containing natural organic matter. This type of information emphasizes the importance of focusing on specific birth defects rather than using broad categories of outcomes based on organ systems. The present findings also suggest that natural organic matter in nonchlorinated tap water contains substances that may increase the risk of congenital birth defects.

REFERENCES