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Drinking Water Treatment and Risk of Cancer Death in Wisconsin

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A case control study of drinking water treatment practices and female cancer mortality was conducted in Wisconsin. Cancer deaths for 1972-1977 from 28 Wisconsin counties and noncancer deaths matched to cancer deaths on age, year of death and county of residence, were compared for characteristics of drinking water supplied to their places of residence. Using logistic regression, estimates of relative risk associated with chlorinated water were examined allowing for the influence of indicators of water organics and the potential confounders of occupation, marital status and urbanicity. Only colon cancer appeared to be related significantly to chlorination in all models explored. A dose-response relationship was found between crude indicators of trihalomethane level (chlorination × organic contamination) and colon cancer death. The odds ratio for chlorinated surface water for colon cancer was 2.81 ($p < 0.01$); approximately half this risk was found for chlorinated ground water. Consequently, a case control study of colon cancer and drinking water quality utilizing newly diagnosed patients is being conducted in Wisconsin.

Introduction

In recent years, the human cancer risk associated with chronic, low-dose exposure to trihalomethanes (THMs) present in drinking water has been the ultimate concern of diverse research. [Trihalomethanes have the structure HCR_3, where R represents chlorine, bromine or iodine, or combinations thereof; the major THMs in drinking water are chloroform, bromodichloromethane, dibromochloromethane and tribromomethane (bromoform).] After the National Organics Reconnaissance Survey (NORS) documented the pervasiveness of THMs (particularly chloroform) in U.S. municipal water disinfected with chlorine (*1*), researchers in the field of water chemistry have sought to identify THM precursors to quantify reaction conditions which explain the variance in THM concentrations found in the finished water of different facilities. On the biological front, long-term rodent studies continue to show oncogenic effects following chronic chloroform ingestion (*2*). Preliminary epidemiologic studies of water quality and cancer mortality have associated some gastrointestinal and urinary tract cancers with presumed exposure to water likely to contain THMs.

As discussed in recent reviews (*3,4*), the epidemiologic studies vary in the specificity of exposure classification with respect to THMs. Since THM levels are unknown for the exposure period relevant to current cancer deaths (e.g., 15–20 years prior to disease onset to allow for latency), all exposure classification schemes are necessarily indirect and consequently rest on a set of assumptions. In the final analysis, it is the explicit or implicit model which holds the key to the assumptions inherent in a particular study, the biases introduced, the limitations and specificity, and the nature of the conclusions which may be drawn. This is a report of the epidemiologic model, methods and further results of the Wisconsin case control study of female gastrointestinal, urinary tract, brain, lung and breast cancer mortality and drinking water trihalomethanes. Previous analysis indicated that only colon cancer death was significantly associated with exposure to chlorine-dosed water (*5*). The odds ratio estimate of approximately 1.50

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did not appear to vary by chlorine dose level but was significantly modified by stratifying the sample on probable presence or absence of halogenatable organics in the water source. For the subsample with raw water affected by rural runoff, risks of 2.74, 3.60 and 3.30 for low, medium and high chlorine dose levels, respectively, were found. Since crude organic precursor indicators seemed to have a greater effect on colon cancer risk than dose level, an analysis based on crude organic levels of chlorinated water was conducted and is reported here.

Methods

Epidemiologic Model

For the investigation of Wisconsin female cancer mortality and water exposure, an attempt was made to make use of all historical water data on parameters shown by prior research to be relevant to THM formation. These water characteristic and treatment parameters, other factors related to THM exposure, and potential confounders with respect to water source and cancer mortality are included in the epidemiologic model presented in Figure 1. This model has guided the investigation and serves as a backdrop for the description of methods and analysis employed, and discussion of results.

Section I of the model pertains to raw water concentration of halogenatable organics, or THM precursors. Naturally occurring organics can be considered as a function of water source, with surface source and shallower wells likely to contain higher concentrations. Water color and turbidity are indirect indicators of "humus." Rural runoff which impinges on water source is considered the most important source of natural organics, while industrial discharge, municipal waste and air pollution are possible other sources of halogenated or halogenatable organics. It is important, too, to consider these conditions as possible sources of toxicants which potentiate or are potentiated by THMs.

Section II represents water treatment and reaction conditions known to influence THM formation. Chlorination dose has been shown to be an important predictor of THM concentration; both prechlorination, and post or one-step chlorination are considered here in addition to the total dose for the two procedures combined. Other factors include pH, water temperature, and purification procedures (coagulation, sedimentation, and filtration).

Actual THM exposure is represented in Section III, where amount of daily water consumption and chronicity of exposure to a particular source is considered. Information on THM exposure from sources other than drinking water is extremely limited. Calculations of "typical" uptake of chloroform (in mg/year) from water, food, and ambient air indicate that uptake from water is 2–3 times greater than that from the other sources (*6*). However, when minimum uptake is considered (lowest range for "reference man"), uptake from the atmosphere is ten times greater than that from water. One potential source which may be of importance for young age groups is that of chlorinated swimming pools, where THM levels of up to 1400 μg/l. have recently been detected (*7*).

At the next point in the model, Section IV, the

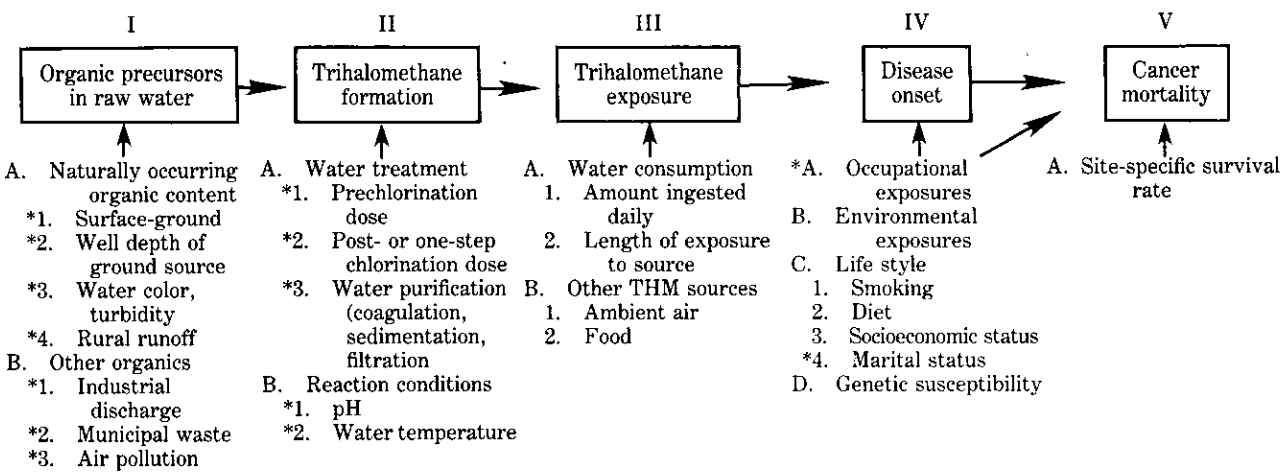

FIGURE 1. Epidemiologic model of trihalomethane exposure and cancer mortality. Data on the factors marked with an asterisk (*) were collected for this investigation.

influence of coexposures and confounders must be considered. Many factors, such as hazardous industrial exposures, may be related to both cancer incidence and living in areas served by chlorinated water. It is also possible that some of these factors act synergistically with THMs.

Since this study, as most reported to date, takes cancer death as the measured effect, it is important to consider causal and confounding factors related to cancer death. While influences on this section of the model (V) are largely unknown and unquantifiable, the assumptions and limitations so introduced by use of mortality data must be addressed.

Study Design

A case control study utilizing mortality data was conducted. The characteristics of water supplied to the usual place of residence (as listed on the death certificate) of cancer decedents were compared to that of noncancer decedents. In order to maximize the necessary assumption that the cases and controls were exposed to the water supply associated with the "usual place of residence" listed on the death certificate for 15–20 years before death, only counties with less than 10% population increases attributed to immigration over the past 20 years were included in the study. In addition, the study was restricted to females, and since females of this cohort of decedents (death years 1972–1977) were likely to have been homemakers, more exposure to the home water supply is likely.

The sample of white female cases and controls was obtained from computer tapes of abstracted death certificate data, provided by the Wisconsin Department of Health and Social Services, Bureau of Health Statistics. Only deaths from 28 of the 72 Wisconsin counties were considered. In addition to the criteria of low immigration rates mentioned above, counties had to have both chlorinated and unchlorinated municipal water supplies. Due to the lack of racial heterogeneity in most of Wisconsin, only white female deaths were included. Based on Wisconsin female cancer death rates, mortality data for six years were determined from sample-size tables (*8*) to be adequate for detecting a site-specific relative risk of 1.5 (at an error level of $\alpha = 0.05$, $\beta = 0.1$); 1972–1977 was the most current six-year period for which abstracted death certificate data were available.

Cases were defined as all white female deaths occurring 1972–1977 within the 28 study counties due to malignant neoplasms of the following sites: esophagus, stomach, colon, rectum, liver and intrahepatic bile ducts, pancreas, urinary bladder, kidney, lung, brain and breast. Each case was matched with a female noncancer death control on year of birth, county of residence and nearest birth date (day, month, year). After matching on death year and county, 95% of the cases were matched within the same year of birth as the control, 4.5% were matched within a three-year interval, and 0.5% within a six-year interval. For the majority of controls (70.93%), the cause of death was in the category of circulatory system disorders.

Several water variables were constructed for use in a statistical model, and the necessary data from all waterworks ($N = 202$) serving the 28 study counties were gathered. Individual exposure data were then assembled by assigning each case and control the values of the water variables for the particular waterworks which served the place of residence (city, town, or village) of the case or control recorded on the death certificate.

For each waterworks, data on type of water source (surface/ground), depth of ground source in feet, and use of purification procedures (coagulation, sedimentation, and filtration) were obtained from the 1970 Wisconsin Waterworks Survey report (based on data for the period 1960–1965). More detailed information on chlorination doseages used over the past 20 years (average daily dose in ppm) and the occurrence of several environmental factors influencing organic content of raw water (rural runoff, industrial discharge, air pollution, water with taste or color) were ascertained from a mail-back questionnaire sent personally to each water superintendent.

Data on the potential confounding factors of urban residence, occupation and marital status were based on death certificate information and assigned to each case and control. For urbanicity, community of residence was ranked into one of six population size categories on the basis of the 1960 census. Cases or controls with occupations considered high risk for each particular cancer site were given a score of one, otherwise zero. The marital status variable indicated married or not married.

To estimate the site-specific cancer risk associated with water supply, several statistical models were analyzed, using logistic regression. The distinct advantage of this technique lies in the ability to take factors into account which may confound the association of interest as well as allowing for the influence of factors related to the strength of the association (*9*). Thus, when variables for potential confounders are included in the logistic regression model, the estimated value of the regression coefficient for site-specific cancer deaths in relation to chlorination (a direct estimate of the odds ratio associated with the exposure) is considered to be adjusted for the other variables in the model (*10*).

The basic model (Model I) used to test the null hypothesis that cancer death is not associated with

chlorinated drinking water is specified in Eq. (1) with urbanicity, marital status and site-specific high risk occupation included as potentially confounding variables.

Risk of cancer death with chlorination, controlling for confounding variables:

$$\text{Log}\left[\frac{p\ (\text{chlorination})}{1-p\ (\text{chlorination})}\right] = \alpha + \beta D + \delta \mathbf{Z} \qquad (1)$$

where

D = Cancer death (yes = 1, no = 0)
Z_1 = Urbanicity (6 population categories)
Z_2 = Marital status (unmarried = 0, married = 1)
Z_3 = Cancer site-specific high risk occupation (yes = 1, no = 0)
Z_4 = Age (in years)
Z_5 = County chlorine exposure (%)

Since the variance in THM content of chlorinated water is expected to be a function of the presence of halogenatable organics, a more specific model [Model II, Eq. (2)] was tested which included terms for the presence of organic contamination, water purification and water source depth (surface or shallow well = 0, deep well > 150 ft = 1). The odds ratios for risk of cancer death and chlorination which result from this model are thus considered adjusted for confounding and exploratory variables.

Risk of cancer death with chlorination, controlling for confounding and explanatory variables:

$$\text{Log}\left[\frac{p\ (\text{chlorination})}{1-p\ (\text{chlorination})}\right] = \alpha + \beta D + \delta \mathbf{Z} + \gamma \mathbf{W} \qquad (2)$$

where

D, $\mathbf{Z}$ are as for Eq. (1),
W_1 = Organic contamination from any source (yes = 1, no = 0)
W_2 = Water purification (yes = 1, no = 0)
W_3 = Source depth (surface or wells < 150 ft = 0, > 150 ft = 1)

A third set of models [Model III, Eq. (3)] were used, which feature categorical chlorination-organic exposure variables. Under these models, risk estimates are calculated for categories expected to more closely approximate THM content.

Risk of cancer death with organic-chlorination exposure categories, controlling for confounding and explanatory variables:

$$\text{Log}\left[\frac{p\ (\times\ \text{exposure})}{1-p\ (\times\ \text{exposure})}\right] = \alpha + \beta D + \delta \mathbf{Z} + \gamma \mathbf{W} \qquad (3)$$

where

D, $\mathbf{W}$, $\mathbf{Z}$ are as above, and with the exposure categories given in Table 1.

Results

Water treatment for the 28 study counties is summarized in Table 2. Relevant correlations between water variables for raw water characteristics and treatment are given in Table 3. As expected, high chlorine dose is strongly and positively associated with point and nonpoint sources of organic contamination, surface source, and large population of community; and negatively associated with depth of ground source. Waterworks serving greater populations, or drawing surface or shallow water are more likely to report more sources of organic contamination. It is noteworthy, however, that chlorine dose and presence of organic contamination are also positively associated with water purification. Since purification may be expected to reduce THM content, it is important to consider these interrelationships.

The odds ratio estimates under model I and model II are given in Tables 4 and 5, respectively. Only colon cancer was significantly related to chlorinated water exposure under model I. When the water factor terms were included (model II), the odds ratio for brain cancer increased considerably and reached significance. These two sites were then examined for consistency and with regard to the scheme of THM formation using the more complex exposure variables under model III. The resulting odds ratio estimates are presented in Table 6.

For colon cancer, the greatest risk is seen with exposure to chlorinated surface water. In addition, chlorinated water with organic contamination carries a greater risk than chlorinated water with no organic contamination. The risk of purified chlorinated water and unpurified chlorinated water differed little. It is likely that the correlation between water purification and surface water may be responsible. Alternatively, various purification procedures, grouped together in this study, may differ in their ability to effect a change in final THM content. The

Table 1. Model specifications.

	Model	Exposure categories
A.	Point and non-point organic contamination × chlorination	Chlorinated water, organic contamination Chlorinated water, no organic contamination Unchlorinated water
B.	Water source × chlorination	Chlorinated water, surface source Chlorinated water, shallow well (≤ 150 ft) Chlorinated water, deep well (> 150 ft) Unchlorinated water
C.	Water purification × chlorination	Chlorinated, unpurified water Chlorinated, purified water Unchlorinated water

Table 2. Characteristics of water supplies: 202 waterworks.

Water variable	Percent of waterworks
Chlorine disinfection	47%
Filtration, purification, sedimentation	32%
Prechlorination	20%
Surface source	20%
Rural runoff	18%
Industrial discharge	12%
Air pollution	6%
Taste or odor problem	19%
Wind	12%
Sewage	7%
Average daily prechlorination dose, ppm	0-4.80
Average daily chlorination dose, ppm	0-6.00
Well depth, ft	40-1800

results for brain cancer are most striking when the chlorination × organic contamination exposure variable was used. The estimates with source depth × chlorination as exposure are neither consistent nor significant, and the estimates based on the third exposure variable, purification × chlorination, are barely significant.

Table 3. Correlations among water treatment and raw water characteristics of 202 waterworks serving the study sample of cases and controls.

	r[a]
Total average daily chlorination dose with:	
Purification	0.508
Surface source	0.521
Rural runoff	0.528
Industrial discharge	0.340
Air pollution	0.273
Taste, odor problems	0.513
Wind	0.311
Sewage	0.226
Total no. of sources of organic contamination	0.452
Urbanicity	0.459
Well depth of ground source	-0.261
Total no. of sources of organic contamination:	
Purification	0.557
Prechlorination	0.797
Surface source	0.770
Well depth	-0.301
Urbanicity	0.512
Surface source:	
Rural runoff	0.732
Industrial discharge	0.644
Air pollution	0.418
Taste and odor problems	0.744
Wind	0.418

[a]All $p < 0.01$

Table 4. Odds ratios for site-specific cancer death and chlorination (controlling for confounding variables, model I estimates).

Site	Chlorinated	Unchlorinated	Total	OR	Significance (p)
Esophagus	161	33	194	0.77	0.8
Stomach	699	211	910	1.45	0.2
Colon	2565	619	3184	1.43	<0.02
Rectum	601	177	778	1.47	0.2
Liver	569	169	738	1.13	0.7
Pancreas	1069	325	1394	1.21	0.4
Kidney	368	116	484	0.52	0.2
Bladder	358	100	458	1.24	0.6
Lung	569	169	738	1.13	0.7
Brain	312	116	428	2.29	0.1
Breast[a]	1424	391	1815	0.74	0.2

[a]3 years of data (1976-1978).

Table 5. Odds ratios for site specific cancer death and chlorination (controlling for confounding variables and organic contamination, source depth, and water purification; model II estimates).

Site	Chlorinated	Unchlorinated	Total	OR	Significance (p)
Esophagus	161	33	194	0.30	0.3
Stomach	699	211	910	1.30	0.4
Colon	2565	619	3184	1.46	<0.02
Rectum	601	177	778	1.59	0.2
Liver	569	169	738	1.29	0.5
Pancreas	1069	325	1394	1.52	0.2
Kidney	368	116	484	0.48	0.2
Bladder	358	100	458	1.40	0.5
Lung	569	169	738	0.87	0.6
Brain	312	116	428	4.71	<0.03
Breast	1424	391	1815	0.77	0.3

Table 6. Odds ratio (OR) estimates of cancer death by chlorination-organics categories (controlling for confounding and additional water variables; model III estimates).

Cancer	Category	N	OR	p
Colon	Exposure variable = organic contamination × chlorination			
	Chlorinated, organic contamination	1974	1.81	0.03
	Chlorinated, no organic contamination	253	1.41	0.03
	Unchlorinated	463		
	Total	2690		
	Exposure variable = source depth × chlorination			
	Chlorinated surface	1983	2.81	0.01
	Chlorinated shallow (≤ 150ft)	72	1.34	0.2
	Chlorinated deep (> 150 ft)	68	1.60	0.08
	Unchlorinated	367		
	Total	2490		
	Exposure variable = water purification × chlorination			
	Chlorinated, unpurified	350	1.52	0.05
	Chlorinated, purified	2021	1.75	0.01
	Unchlorinated	555		
	Total	2926		
Brain	Exposure variable = organic contamination × chlorination			
	Chlorinated, organic contamination	258	6.86	0.03
	Chlorinated, no organic contamination	27	2.53	0.2
	Unchlorinated	81		
	Total	366		
	Exposure variable = source depth × chlorination			
	Chlorinated surface	266	1.14	0.8
	Chlorinated shallow (≤ 150 ft)	10	1.06	0.9
	Chlorinated deep (> 150 ft)	8	1.60	0.6
	Unchlorinated	74		
	Total	358		
	Exposure variable = water purification × chlorination			
	Chlorinated, unpurified	33	4.41	0.04
	Chlorinated, purified	266	1.69	0.4
	Unchlorinated	97		
	Total	396		

Discussion

No site other than brain or colon cancer showed any significant association with chlorinated water, although elevated risks were generally seen for gastrointestinal and bladder cancer sites. While it appears that there are adequate numbers of cases and controls for all sites except esophagus, certain limitations of the death certificate approach may necessitate even larger samples. Misclassification error has been shown to reduce power (*11*); error of this type was introduced in this study when the

assumption that the water supplied to the usual residence was consumed over a 15–20 year period prior to death was not met (whether due to migration or simply not drinking tap water). With regard to the findings of other epidemiologic studies implicating bladder or rectum cancer, it is important to stress that this Wisconsin study is based on white female deaths only. While confounding due to smoking, alcohol, occupation and probable migration is of less concern for this homogeneous sample relative to a sample of males, the generalizability of results is restricted.

The lack of a consistent brain cancer risk under the various models indicates that the brain cancer-chlorination association is not substantive. The strong influence of the organic contamination variable (an indirect indicator for any point or nonpoint source of organics) and the lack of influence of surface water source suggest that ground water contamination with specific organic contaminants may be responsible for the pattern of risk found. Alternatively, the inconsistent relationship may be due to an unknown confounding factor that is positively associated with some of the ground water supplies in particular areas.

The evidence from this analysis for a colon cancer risk is stronger, but methodological limitations stemming from the use of death certificate and other indirect data preclude drawing causal interpretations. It is not likely that known confounding factors or bias introduced via nonrandom misclassification error can completely account for the estimated risks since such factors (e.g., vegetable consumption) would have to persist through the more complex categorization by organic levels of chlorinated water. Since no risk was found for breast cancer, which is known to be linked positively to higher socioeconomic status, it is not likely that this potential confounding factor influenced only the colon cancer relationship. Moreover, urbanicity was always used as a control variable, thus lessening concern with this important confounding factor. The result, then, may be cautiously viewed as suggestive of a colon cancer risk with exposure to water likely to contain chlorinated organics.

In view of the results of this study and similar findings recently reported (*12*), drinking water exposure warrants consideration as a possible cause of colon cancer. We are currently conducting an epidemiologic study in which the lifetime THM water exposure of Wisconsin colon cancer patients are compared to that of a group of controls, in order to test the hypothesis that exposure to THMs in drinking water carries significant risk of colon cancer, and to determine the magnitude of risk. The subordinate goals include the following:

1. Development of a valid measure to assess lifetime THM exposure. This involves the measurement of THMs in approximately 100 Wisconsin supplies from different waterworks and the characterization of these water supplies on parameters for which historic data exist (e.g., chlorine dose, prechlorination or not, surface or ground source, depth of ground source, pH, water purification procedures). Using statistical modelling procedures, these data will be used to determine how much of the final THM concentration can be explained, or predicted, by the parameters. An index of the significant factors, weighted by the magnitude of association with THM concentration, will result, whereby a THM level will be calculated for all Wisconsin water supplies for any past period for which data on the index factors exist. Then, in conjunction with the history of all water sources to which an individual was exposed, length of exposure in years and amount of tap water consumed, estimates of individual lifetime THM exposure will be derived.

2. Exploration of the relationship between colon cancer and the interaction of THM exposure with other exposures and personal characteristics. Recent experimental evidence suggests that a variety of compounds are capable of potentiating the biological effects of chloroform. The risk associated with THM exposure, for example, may be compounded among those exposed to alcohol or pesticides. The relationship may also differ by personal characteristics such as ethnic heritage, diet considerations, and age at exposure to chlorinated water.

3. Exploration of the relationship between colon cancer and other environmental contaminants. One of the main features of a case control study in which subjects are available for interview, is the ability to assemble complete residential histories (address × length of time). Consequently, the past proximity to potential environmental hazards such as chemical dumps, heavy pesticide/herbicide land saturation, industrial discharge and air pollution will be examined as risk factors for colon cancer.

It is hoped that this case control study will further clarify the role of chlorinated drinking water in human colon cancer incidence.

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