

Disinfection Byproducts and Bladder Cancer

A Pooled Analysis

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Background: Exposure to disinfection byproducts in drinking water has been associated with an increased risk of bladder cancer. We pooled the primary data from 6 case-control studies of bladder cancer that used trihalomethanes as a marker of disinfection byproducts.

Methods: Two studies were included from the United States and one each from Canada, France, Italy, and Finland. Inclusion criteria were availability of detailed data on trihalomethane exposure and individual water consumption. The analysis included 2806 cases and 5254 controls, all of whom had measures of known exposure for at least 70% of the exposure window of 40 years before the interview. Cumulative exposure to trihalomethanes was estimated by combining individual year-by-year average trihalomethane level and daily tap water consumption.

Results: There was an adjusted odds ratio (OR) of 1.24 in men exposed to an average of more than 1 $\mu\text{g/L}$ (ppb) trihalomethanes compared with those who had lower or no exposure (95% confidence interval [CI] = 1.09–1.41). Estimated relative risks increased

with increasing exposure, with an OR of 1.44 (1.20–1.73) for exposure higher than 50 $\mu\text{g/L}$ (ppb). Similar results were found with other indices of trihalomethane exposure. Among women, trihalomethane exposure was not associated with bladder cancer risk (0.95; 0.76–1.20).

Conclusions: These findings strengthen the hypothesis that the risk of bladder cancer is increased with long-term exposure to disinfection byproducts at levels currently observed in many industrialized countries.

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Chlorination is a widely used and highly cost-effective technique for disinfection of drinking water, and has conferred important public health benefits. In 1974, the first reports were published on toxic byproducts produced by the reaction of chlorine with organic matter.^{1,2} Since that time, a number of epidemiologic studies have evaluated the cancer risk associated with this exposure. The initial studies, which were ecologic in design,^{3–7} suggested bladder as one of the cancer sites associated with chlorinated water intake. Case-control studies based on death certificates,^{8–10} as well as a cohort study,¹¹ strengthened these findings.

When the International Agency for Research on Cancer (IARC)¹² evaluated chlorinated drinking water as a potential human carcinogen in 1991, most of the available studies were ecologic or based on death certificate. These studies typically used cross-sectional estimates of exposure (usually around the time of death) and were limited in their ability to adjust for other risk factors. These methodologic limitations led the IARC to conclude that the evidence for the carcinogenicity of chlorinated drinking water in humans was limited (classified as “group 3”).

After this evaluation, several studies with improved exposure assessment at the individual level were published. Among them, the studies of bladder cancer reported positive associations with chlorination byproducts exposure.^{13–18} A recent metaanalysis of studies on bladder cancer with individual information on residence and water consumption re-

ported an increased risk in subjects with long-term consumption of chlorinated drinking water. The meta-odds ratios were higher among men than women.¹⁹

Recent evaluations by the IARC of single chlorination byproducts such as specific trihalomethanes and haloacetic acids^{20,21} concluded that the evidence for their carcinogenicity in humans is inadequate or limited. It was argued that although some studies had associated chlorinated drinking water intake with cancer, single compounds could not be evaluated using these studies because these compounds occur in mixtures. A recent report by the World Health Organization²² considered that the evidence was insufficient to determine whether the observed associations are causal or to determine which specific byproduct or other contaminants play a role.

We pooled the primary data from 6 case-control studies with individual-based exposure assessments conducted in 5 countries using trihalomethanes as a marker for the total mixture of chlorination byproducts. These studies evaluated the association between bladder cancer risk and exposure to chlorination byproducts.

METHODS

Studies

We obtained the primary data from 6 studies (Table 1) that met the following inclusion criteria: 1) case-control studies of incident bladder cancer, 2) availability of detailed long-term exposure assessment to trihalomethanes, and 3) accessibility to primary data. We identified the published studies through Medline searches. Unpublished studies were identified through personal contacts with research groups that had collaborated on another pooled analysis of bladder cancer.^{23–25} The pooled database included 2 studies from the United States,^{18,26} and one each from Canada,¹⁵ Finland,¹⁷ France,²⁷ and Italy (Porru, unpublished data, 2003) conducted between 1978 and 2000. Data on trihalomethanes from the

Finnish, French, and Italian studies had not been previously published. Detailed trihalomethane information was available for only part of a large U.S. study¹³ and that part was incorporated in the pooled analysis.²⁶ Data from an additional study from the United States¹⁴ were not accessible and were not included in this analysis. Overall results from this U.S. study are similar to those found in the pooled analysis, with a 2-fold relative risk found for both men and women for consumption of chlorinated drinking water for more than 34 years.

The principal investigators of the present pooling project and of the individual studies met and discussed the protocol, operational decisions for the analysis, and the results of this analysis.

Data

We extracted from the original databases exposure information and covariates that might be potential confounders or effect modifiers: age, sex, smoking status (never-smokers; ex-smokers, quitting 2 years before the interview; current smokers), duration of smoking, cigarettes smoked per day, ever worked in an a priori high-risk occupation,²⁸ coffee consumption, total fluid consumption, and socioeconomic status (as years of education). Education was categorized into 4 groups: primary school completed or less, some secondary education, secondary education completed, and higher education. We established common definitions and coding schemes for all variables. A separate occupational classification had to be used for the Canadian study and the high-risk occupations are therefore not identical to those used in the remaining 5 studies. We excluded subjects under 30 and over 80 years old ($n = 774$) from the pooled database, as well as patients with more than 2 years between diagnosis and interview ($n = 166$). The final pooled data set comprised 3419 cases and 6077 controls (Table 1). All cases included in the pooled analysis were histologically confirmed. Four stud-

TABLE 1. Description of the Studies Included in the Pooled Analysis

Study	Country	Cases		Controls		Source of Controls	Period of Enrollment
		No.	Percent of Total	No.	Percent of Total		
Porru*	Italy	123	4	150	3	Hospital	1997–2000
King, 1996 ¹⁵	Canada	696	20	1545	25	Population	1992–1994
Koivusalo, 1998 ¹⁷	Finland	759	22	1292	21	Population	1991–1992
Cantor, 1998 ¹⁸	USA	959	28	1768	29	Population	1986–1992
Cordier, 1993 ²⁷	France	567	17	666	11	Hospital	1984–1987
Lynch, 1989 ²⁶	USA	315	9	656	11	Population	1977–1978
All studies		3419		6077			

*Unpublished data, 2003.

ies enrolled population controls. The remaining 2 recruited hospital controls, either urologic controls (Porru, unpublished data, 2003) or patients from various wards diagnosed with osteoarticular, digestive, and heart diseases.²⁷ Controls were individually or frequency-matched to cases on age and geographic area.

Exposure Information

The approaches followed in individual studies to estimate past exposures were fairly similar, although the detail of information available in each study and the specific models applied for the extrapolation differed. In the 2 U.S. studies,^{18,26} the geometric means of contemporaneous trihalomethanes levels by water source and treatment were estimated, and levels were then extrapolated to past periods taking into account water source and treatment. In the French study,²⁷ information on water sources and treatments were collected retrospectively and trihalomethane mean levels were assigned to the different combinations of water sources and treatments as predicted by an experimental model using the same parameters. In the Canadian study,¹⁵ retrospective trihalomethane data were estimated from a predictive model based on raw water parameters, treatment, and current trihalomethane data. In the Italian study (Porru, unpublished data, 2003), average trihalomethane levels from recent years were applied retrospectively to past years. A different approach was followed in the Finnish study.¹⁷ Levels of mutagenicity in drinking water were estimated by an equation giving the level of mutagenicity on the basis of information on raw water quality (eg, permanganate consumption, pH, and color) and water treatment practices. A mutagenicity score was estimated for each person by calculating an individual estimate of historical exposure to drinking water mutagenicity.²⁹ Individual levels of trihalomethanes were then derived applying a trihalomethane mutagenicity correlation.

The exposure-related variables that we extracted from the 6 databases were amount of daily tap water consumption (water, coffee, tea, and other beverages prepared with water from the tap, expressed as liters per day) and yearly average trihalomethane level ($\mu\text{g/L}$). We created 2 exposure indices from these 2 variables: 1) average trihalomethane exposure ($\mu\text{g/L}$ or ppb) that was calculated as the sum of the year-by-year annual mean level in each residence, divided by the number of years with nonmissing data; and 2) cumulative exposure (mg) that was calculated as the product of average trihalomethane exposure and total tap water consumption. (A subject who reported drinking bottled water only would have zero cumulative exposure irrespective of average exposure.) Average exposure reflects uptake through all exposure routes (ingestion, inhalation, and skin absorption), whereas cumulative exposure is a better proxy for uptake through ingestion. The 2 exposure indices differ in 2 aspects: by the method of summarizing (average vs. cumulative), but also by the nature of exposure (tap water concentrations vs. ingestion multiplied by tap water concentrations). It should be noted, however, that none of the studies included information on routes of exposure and that the 2 exposure indices are correlated (Pearson correlation coefficient = 0.74).

Average trihalomethane levels by study ranged between 10 and 30 $\mu\text{g/L}$ with the exception of the smallest study (Porru, unpublished data, 2003) in which exposure levels were very low (Table 2). From the 4 studies that had available information on water source and chlorination status,^{15,18,26,27} we created variables for duration of exposure to chlorinated surface water, chlorinated groundwater, and unchlorinated water. For all exposure indices, we defined a common exposure window of 40 years, extending from 45 years to 5 years before the interview. A shorter time window

TABLE 2. Estimated Average Trihalomethane Levels ($\mu\text{g/L}$) and Range for All the Cases and Controls (Exposed and Unexposed) by Study*

Author	Cases			Controls		
	Average THM ($\mu\text{g/L}$)		Percent Exposed to $\leq 1 \mu\text{g/L}$	Average THM ($\mu\text{g/L}$)		Percent Exposed to $\leq 1 \mu\text{g/L}$
Mean (SD)	Range	Mean (SD)		Range		
Cantor ¹⁸	11.6 (19.7)	0.5–73.9	38	10.0 (18.3)	0.5–73.9	42
Cordier ²⁷	18.4 (21.9)	0–78.3	15	17.2 (21.2)	0–78.3	16
King ¹⁵	32.2 (23.3)	0–124.7	13	29.7 (23.0)	0–124.7	16
Koivusalo ¹⁷	23.5 (30.8)	0–130.0	49	21.5 (29.4)	0–130.0	52
Lynch ²⁶	14.8 (21.5)	0.5–73.9	40	10.3 (17.7)	0.5–73.9	51
Porru [†]	0.6 (0.8)	0–2.2	72	0.4 (0.7)	0–2.2	84

*For subjects for whom exposure information is available for at least 70% of the time over the 40-year period evaluated.

[†]Unpublished data, 2003.

SD, standard deviation.

was used for the French study because the earliest exposure data were available for 37 years before diagnosis.

Statistical Analysis

We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the different exposure indices. Most ORs were adjusted for study, age (continuous), sex (when not stratified), education, smoking status (never, ex-, and current smokers), ever worked in an *a priori* high-risk occupation,²⁸ and heavy coffee consumption (more than 5 cups of coffee a day). Models for average exposure were also adjusted for total fluid intake.

Information on smoking status was available for all studies, whereas detailed information on duration and intensity was available for 5 of 6 studies (all except Koivusalo¹⁷). Analyses of trihalomethane exposure in these 5 studies adjusting for smoking status, and, alternatively, for smoking status and pack-years of current smoking, indicated differences between the 2 sets of ORs only in the second decimal point.

Trihalomethane exposure variables were initially treated as categorical variables. We first estimated the risk for those ever-exposed compared with those never-exposed (average exposure equal to zero). The never-exposed group was much smaller than those exposed and also could be dissimilar to the remaining study population. Therefore, 3 alternative cutpoints for exposure were examined: 0.5, 1.0, and 1.5 $\mu\text{g/L}$ average trihalomethane. The 1.0- $\mu\text{g/L}$ average trihalomethane exposure cutoff corresponds approximately to the 15th percentile of the number of exposed subjects. A similar approach was followed for cumulative exposure, with the cutoff of 15 mg corresponding to the 15th percentile. Using these cutpoints guaranteed that exposure of the reference group was sufficiently low while allowing the inclusion of enough subjects from all studies in the reference group for the overall and sex-specific analyses.

To examine exposure-response, exposed subjects were grouped using quartiles as category boundaries. The pattern of the exposure-response relationship was also evaluated through a generalized additive model using a natural spline (3 degrees of freedom) for the continuous average exposure variable adjusting for study, age, sex, education, smoking status, ever worked in high-risk occupations, heavy coffee consumption, and total fluid intake.

All analyses evaluating trihalomethanes were limited to the 8060 subjects for whom estimates of exposure were available for at least 70% of the exposure window (2806 cases and 5254 controls). We calculated adjusted ORs for the main effects within individual studies and evaluated the heterogeneity of effects among studies through a metaanalysis.³⁰

RESULTS

Table 3 shows the distribution of covariates in the pooled study population. Eighty percent of cases and 70% of controls were men, and the median age at interview was 67 years. After adjusting for study, sex, and age, excess risks were found for ex- and current smokers, ever-worked in an *a priori* high-risk occupation, heavy coffee consumption, and above-median intakes of total fluids, tap water and nontap beverages. ORs for these covariates were similar between men and women except for occupation in which ORs were higher among men.

Exposure to trihalomethanes was associated with an excess relative risk among ever-exposed men (OR = 1.32; 95% CI = 1.10–1.59) (Table 4). Slightly lower ORs were obtained when the cutpoints for defining ever-exposed men were set at 0.5 $\mu\text{g/L}$ (1.23; 1.09–1.39), 1 $\mu\text{g/L}$ (1.24; 1.09–1.41), or 1.5 $\mu\text{g/L}$ (1.15; 1.03–1.28). The relative risk tended to increase with increasing exposure (Table 4). The pattern of exposure response was further evaluated using natural splines (Fig. 1) that also showed increasing risk with increasing exposures. Although not pronounced, an exposure-response was seen even when the analysis was limited to exposed persons. No association was found among women (for women with an average exposure higher than 1 $\mu\text{g/L}$: OR = 0.95; 95% CI = 0.76–1.20).

Cumulative exposure to trihalomethanes was associated with excess bladder cancer risk among men (Table 4). The OR in men ever exposed to trihalomethanes as compared with those never exposed was 1.30 (1.10–1.53). The risk was similar when including low-exposed men (0–15 mg trihalomethanes) in the reference group (1.30; 1.14–1.50). The OR for women ever exposed was 1.06 (0.77–1.45). An exposure-response trend was observed among men, with an OR of 1.50 for the highest quintile, corresponding to more than 1000 mg trihalomethanes during the 40-year exposure window. No exposure-response pattern was observed in women.

The overall OR did not depend on any single study, with only minor differences of the pooled relative risk estimates when each study was excluded in turn. Similar ORs for average exposure above 1 $\mu\text{g/L}$ were found for studies using hospital controls (OR = 1.15; 0.76–1.74) or population controls (1.19; 1.06–1.34). There was no observed heterogeneity of effects between studies for average trihalomethane exposure (Cochran's Q test for heterogeneity = 6.511, 4 df, $P = 0.164$), and the metaanalysis of study-specific relative risk estimates (Fig. 2A) gave the same OR as that obtained from the logistic regression adjusting for the study (Table 4). This evaluation was also done separately by sex and did not indicate the presence of heterogeneity in men (Fig. 2B) (Cochran's Q test for average trihalomethane exposure = 6.556, $P = 0.256$) or in women (Fig. 2C) (Cochran's Q test

TABLE 3. Characteristics of Cases and Controls in the Pooled Study Population*

	Cases (n = 3419) No. (%)	Controls (n = 6077) No. (%)	OR (95% CI) [†]
Sex			
Men	2727 (80)	4227 (70)	
Women	692 (20)	1850 (30)	
Age (yrs) [‡]			
≤67	1766 (52)	3415 (56)	
>67	1633 (48)	2662 (44)	
Smoking			
Never smoker [§]	642 (19)	2379 (39)	1.00
Ex-smoker	1334 (39)	2140 (35)	2.13 (1.89–2.40)
Current smoker	1422 (42)	1526 (25)	3.55 (3.14–4.00)
Worked in high-risk occupations			
Never [§]	2303 (67)	4276 (70)	1.00
Ever	653 (19)	851 (14)	1.30 (1.15–1.47)
Unclassifiable	463 (14)	950 (16)	1.45 (1.19–1.76)
Education			
≤Primary school [§]	699 (20)	1160 (19)	1.00
Some secondary	994 (29)	1405 (23)	1.15 (1.00–1.31)
Secondary completed	773 (23)	1546 (25)	0.95 (0.83–1.08)
>Secondary	657 (19)	1458 (24)	0.86 (0.73–1.00)
Other	296 (9)	508 (8)	0.85 (0.70–1.04)
Coffee (cups/day)			
0–5 [§]	2832 (83)	5234 (87)	1.00
>5	567 (17)	795 (13)	1.58 (1.39–1.79)
Total fluid consumption (L/day) [‡]			
≤2.4 [§]	1650 (49)	3019 (50)	1.00
>2.4	1694 (51)	2960 (50)	1.21 (1.11–1.33)
Tap water consumption(L/day) [‡]			
≤1.4 [§]	1756 (52)	3014 (50)	1.00
>1.4	1605 (48)	2983 (50)	1.20 (1.07–1.34)
Non-tap fluid consumption (L/day) [‡]			
≤0.9 [§]	1547 (46)	2978 (50)	1.00
>0.9	1797 (54)	3001 (50)	1.17 (1.06–1.30)

*Numbers do not always add to a total of 9496 because of missing information.

[†]OR from logistic regression adjusted for study, sex, and age.

[‡]Dichotomous at the median.

[§]Reference category.

= 5.113, $P = 0.276$). Similar results were obtained for cumulative exposure with a Cochran's Q test of 4.616, $P = 0.329$ for both sexes, and no heterogeneity in men or in women.

Duration of exposure to chlorinated surface water was associated with an increase in bladder cancer risk among men (Table 4). In the group with the longest exposure to chlorinated surface water (30–40 years), the OR was 1.62 (1.21–2.16) in relation to those never exposed. An increased risk was also found among subjects exposed to chlorinated

groundwater. Among women, no association was found for duration of exposure to chlorinated surface water.

We evaluated whether bladder cancer risk in men was associated with specific time windows of exposure. We evaluated 4 10-year periods within the 40-year exposure period, specifically 5 to 14 years before the interview, 15 to 24 years, 25 to 34 years, and 35 to 45 years. All periods of exposure were associated with an increased risk (Table 5). Because exposure between periods could be correlated, the same analysis was repeated adjusting for exposure in all other

TABLE 4. Association of Several Measures of Exposure to Disinfection Byproducts with Bladder Cancer, By Sex

	Men		Women		Both Sexes OR (95% CI) [†]
	Cases/ Controls*	OR (95% CI) [†]	Cases/ Controls*	OR (95% CI) [†]	
Average THM ($\mu\text{g/L}$)					
0 [‡]	328/605	1.00	94/221	1.00	1.00
>0	1798/2909	1.32 (1.10–1.59)	509/1415	0.85 (0.60–1.19)	1.18 (1.00–1.39)
0–1 [‡]	711/1365	1.00	189/506	1.00	1.00
>1	1415/2149	1.24 (1.09–1.41)	414/1130	0.95 (0.76–1.20)	1.18 (1.06–1.32)
0–1 [‡]	711/1365	1.00	189/506	1.00	1.00
>1–5	366/574	1.10 (0.92–1.31)	96/231	0.99 (0.72–1.36)	1.08 (0.93–1.26)
>5–25	314/499	1.26 (1.05–1.51)	97/309	0.86 (0.63–1.18)	1.15 (0.98–1.35)
>25–50	399/647	1.25 (1.04–1.50)	128/356	1.04 (0.76–1.43)	1.22 (1.04–1.42)
>50	336/429	1.44 (1.20–1.73)	93/234	0.93 (0.67–1.28)	1.31 (1.12–1.54)
<i>P value</i> [§]		<0.001		0.753	<0.001
Cumulative exposure to THMs (mg)					
0 [‡]	415/783	1.00	104/270	1.00	1.00
>0	1720/2739	1.30 (1.10–1.53)	502/1371	1.06 (0.77–1.45)	1.24 (1.07–1.44)
0–15 [‡]	632/1233	1.00	159/406	1.00	1.00
>15	1503/2289	1.30 (1.14–1.50)	447/1235	0.95 (0.74–1.23)	1.22 (1.08–1.38)
0–15 [‡]	632/1233	1.00	159/406	1.00	1.00
>15–50	333/532	1.22 (1.01–1.48)	87/243	0.92 (0.65–1.32)	1.14 (0.96–1.35)
>50–400	500/744	1.28 (1.08–1.51)	147/386	0.94 (0.70–1.27)	1.21 (1.04–1.39)
>400–1000	369/609	1.31 (1.09–1.58)	119/337	1.02 (0.74–1.41)	1.25 (1.07–1.47)
>1000	301/404	1.50 (1.22–1.85)	94/269	0.92 (0.65–1.30)	1.34 (1.12–1.59)
<i>P value</i> [§]		<0.001		0.818	<0.001
Duration of exposure to chlorinated surface water (years)					
0	252/537	1.00	58/163	1.00	1.00
>0–7	94/132	1.40 (1.02–1.94)	27/83	0.83 (0.47–1.47)	1.25 (0.95–1.64)
>7–15	96/173	1.01 (0.74–1.37)	36/68	1.24 (0.72–2.15)	1.09 (0.84–1.42)
>15–30	104/127	1.67 (1.22–2.29)	21/64	0.60 (0.32–1.12)	1.36 (1.03–1.79)
>30–40	146/158	1.62 (1.21–2.16)	32/67	1.08 (0.62–1.88)	1.50 (1.16–1.93)
<i>P value</i> [§]		<0.001		0.725	0.002
Exposed only to chlorinated ground water	470/717	1.23 (1.01–1.50)	131/316	1.04 (0.71–1.53)	1.20 (1.00–1.43)

*Numbers do not always add to 8060 because of missing information.

[†]OR from logistic regression adjusted for study, age, smoking status, ever worked in high-risk occupations, heavy coffee consumption (>5 cups/day) and education. (The analysis of both sexes combined is also adjusted for sex. The analysis of average exposure is also adjusted for total fluid intake.)

[‡]Reference category.

[§]Linear test for trend.

^{||}This reference group comprises subjects never exposed to chlorinated surface water and never exposed to chlorinated ground water.

periods. This analysis indicated that excess risks were associated with exposures that took place relatively early in life, at least 25 years before the interview.

Adjusting for smoking status, in addition to all other variables produced an OR for men who were ever exposed to an average of more than 1 $\mu\text{g/L}$ trihalomethanes of 1.24

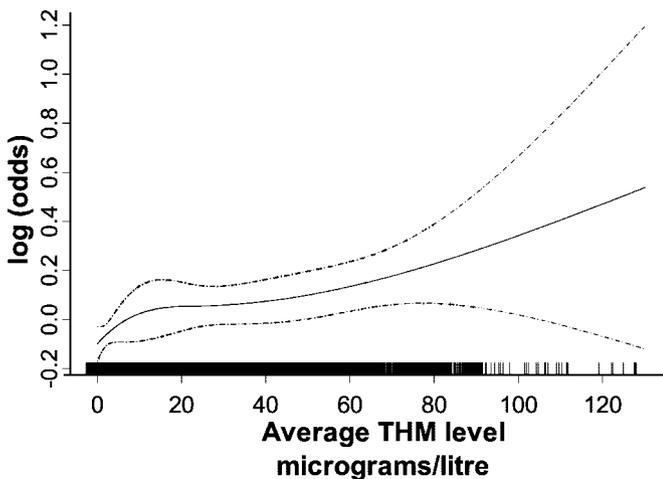


FIGURE 1. Log odds (solid line) and 95% confidence interval (dotted line) for average exposure to trihalomethanes ($\mu\text{g/L}$) and bladder cancer using a generalized additive model with a natural spline for THM exposure (3 degrees of freedom). Both sexes. The short vertical lines in the x-axis indicate the number of subjects by exposure level. The spline is adjusted for age, sex, center, tobacco consumption, high-risk occupation, education, total fluid consumption, and high coffee consumption. Analysis limited to subjects with 70% or more lifetime exposure information.

(1.09–1.41), compared with 1.30 (1.15–1.47) when adjusted for all variables except smoking. The OR among men never-smokers was 1.25 (0.92–1.69), indicating that confounding or residual confounding by smoking could not have produced the observed excess risk. There was no evidence of effect modification for smoking and trihalomethane exposure, with the OR for current smokers being 1.23 (0.99–1.52). Similarly, in women, no association with average trihalomethane exposure of more than 1 $\mu\text{g/L}$ was observed, regardless of smoking status (for never smokers: OR = 0.94; CI = 0.69–1.27; for current smokers: OR = 0.99; CI = 0.63–1.57). No differences were observed when subjects were stratified by occupation.

DISCUSSION

Trihalomethane exposure was found to be associated with an increased risk of bladder cancer among men, whereas among women, no association was observed with any of the exposure indices that we used. We found an association when comparing nonexposed and exposed men, as well as an exposure–response among exposed subjects. Although not devoid of methodologic difficulties, there are advantages to pooling and joint analysis of data from studies with individual estimates of exposures. The statistical power of the pooled dataset is considerably higher than that of the individual studies. The results from combined databases from many

independent studies could have a stronger impact on public health policy than those of individual studies.

Publication bias is a potential concern when pooling studies, although given the effort required to document disinfection byproduct levels, such studies are likely to be published regardless of results. Publication bias could not be formally tested because of the small number of studies and the inclusion of unpublished data.

A limitation of this pooled analysis is the use of trihalomethanes as the common estimate of exposure from all studies in the face of known and suspected differences among the studies. Trihalomethane exposure has been used as a marker of exposure to chlorination byproducts, which is a complex mixture of compounds with a variety of chemical and toxicologic properties. Trihalomethanes are the most prevalent chlorination byproducts, but the proportion of trihalomethanes compared with other contaminants could vary depending on factors such as raw water characteristics, temperature, and treatment practices. Consequently, the same level of trihalomethanes did not necessarily represent the same mixture in all studies. Even within studies, the same trihalomethane level could have been a surrogate for mixtures that varied across regions and over time. Another source of heterogeneity in exposure assessment came from the different exposure models. Three studies (those by Cantor,¹⁸ Lynch²⁶ and Porru, unpublished data, 2003) estimated past trihalomethane levels by extrapolating current or recent trihalomethane levels while taking into account source and type of treatment. The remaining 3 studies^{15,17,27} applied models to predict past trihalomethane levels on the basis of historical data on raw water parameters, water source, and treatment. The models applied in the French and the Canadian studies were similar, whereas the one of the Finnish study was based on totally different parameters. We found no cohort studies that estimated past trihalomethane levels.

The difference estimated in relative risk by sex was observed in 5 of the 6 studies, although differences between sexes were not pronounced. Among studies not included in the pooled data, some found a similar pattern,^{11,16} whereas one investigation reported higher relative risks in women¹³ and another¹⁴ reported no differences by sex. We had selected this latter study for inclusion in the pooled analysis, but the data were not accessible. Bladder cancer is much less common in women than in men, but given the large size of this pooled dataset and the observed trends, chance appears an unlikely explanation for our observation of a higher relative risk among men. Under scenarios of a causal relationship or biases with which we are familiar, these differences cannot be easily explained. Nondifferential misclassification, attenuating risk only among women and not men, seems unlikely, although we had no means of testing this.

Smoking and occupation are the most important risk factors for bladder cancer, and neither substantially con-

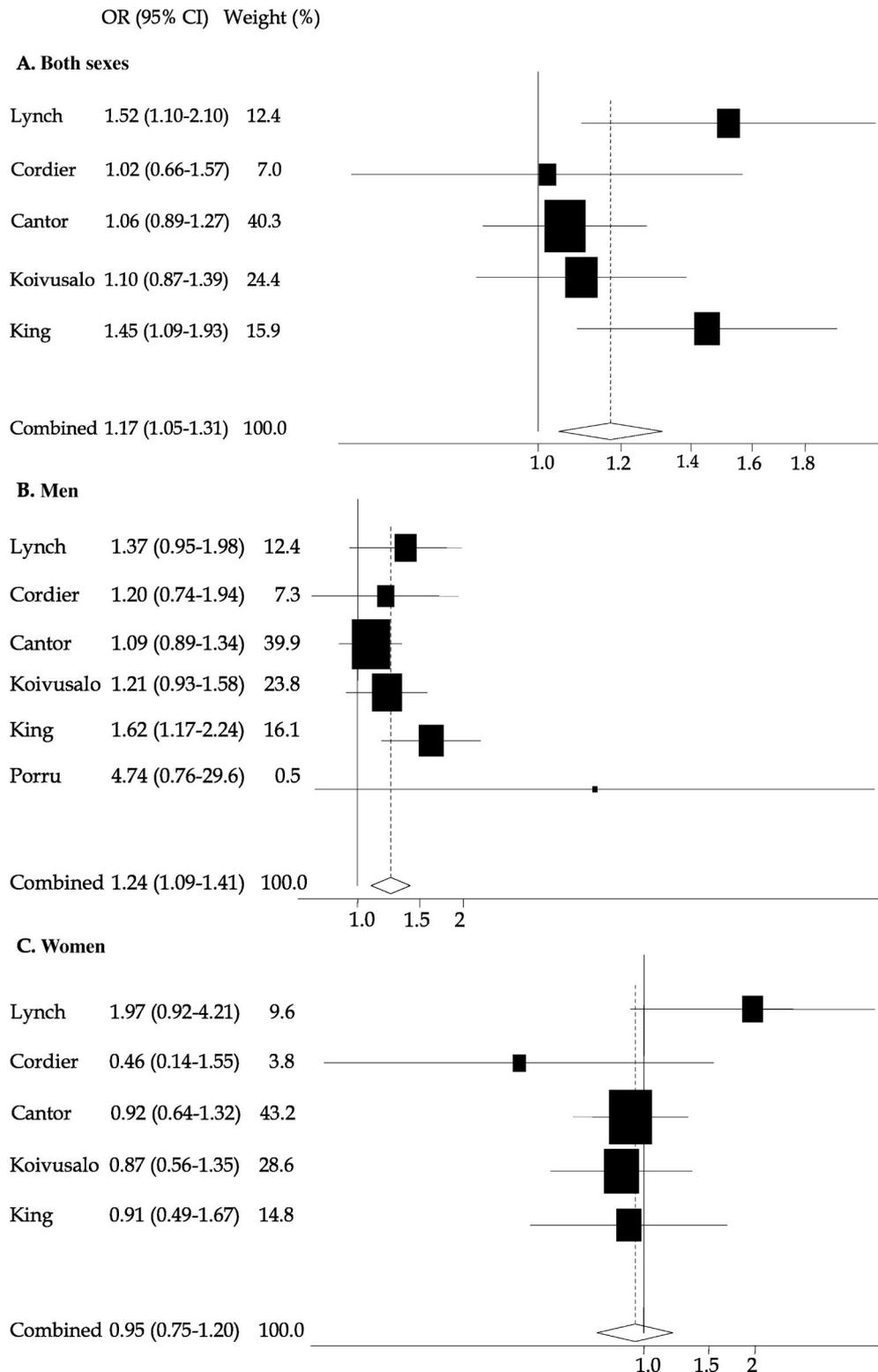


FIGURE 2. Metaanalysis of study-specific adjusted odds ratios for those with average exposure more than 1 $\mu\text{g/L}$ THM (compared with $\leq 1 \mu\text{g/L}$) in the 40-year exposure window, from a logistic regression adjusting by age, smoking status, ever worked in high-risk occupations, heavy coffee consumption, education, and total fluid intake. (A also adjusted for sex). For both sexes (A), men (B), women (C).

TABLE 5. Association of Average Exposure to Trihalomethanes Higher Than 1 $\mu\text{g/L}$ (Compared With ≤ 1 $\mu\text{g/L}$) With Bladder Cancer, Within Specific Time Windows of Exposures for Men

Time Window Before the Interview	OR (95% CI)*	OR (95% CI)* Adjusting for All Other Time Periods
5–14 years	1.15 (1.00–1.32)	1.05 (0.84–1.31)
15–24 years	1.19 (1.04–1.36)	0.92 (0.70–1.21)
25–34 years	1.29 (1.12–1.48)	1.22 (0.95–1.58)
35–45 years	1.24 (1.07–1.44)	1.13 (0.93–1.37)

*ORs are adjusted for sex, age, center, smoking status, education, ever worked in high-risk occupations, heavy coffee consumption (>5 cups/day), and total fluid intake. The analysis was conducted only among subjects with $\geq 70\%$ exposure information.

founded the association between trihalomethane exposure and bladder cancer in our analysis. Knowledge of occupational risk factors is, however, more limited in women than in men²⁸ and residual confounding from occupation could occur, particularly among women. There are no published data on the importance of exposure to disinfection byproducts at work, and it is therefore unknown to what extent differential commuting between sexes would affect results. Furthermore, the pooled analysis includes international data, and the flow of populations to and from work could differ by country.

Unpublished data from Iowa (Lynch, personal communication, 2003) indicate that water intake at work is approximately one third of that at home, and that subjects tended to be exposed to similar levels of trihalomethanes at work and home. In addition, exposure to volatile compounds in the mixture occurs mostly at home, because a large part of this uptake is through inhalation and dermal absorption that occur during bathing, showering, cleaning dishes, and so on.³¹ There is a sizable literature on the association of bladder cancer with diesel exhaust and other particulate matter air pollution, but it refers to workers exposed to high exposure levels of these compounds.²⁸ If air pollution were a confounder in our analysis, it is likely to be a weak one because any effect of air pollution on bladder cancer can be expected to be small. Comparisons between subjects never exposed to disinfection byproducts with those exposed are, in part, also comparisons between subjects living in different geographic areas. The main analyses of our study, however, are not based on never-ever comparisons but rather on exposure–response trends. These are not purely comparisons between subjects of urban versus rural residences. “Urban” areas, that is areas that use water with elevated levels of trihalomethanes and other chlorination byproducts, are frequently places as small as a few thousand inhabitants.

Adjustment for education as a measure of socioeconomic status did not make a difference for either sex, but this adjustment might not have adequately captured other socioeconomic correlates of exposure.

We did not have information in the pooled dataset on other potential bladder cancer risk factors that probably have a differential sex distribution such as use of hair dyes, urinary infections, analgesics, and diet.²⁸ However, their role as confounders of the association between trihalomethanes and bladder cancer in either sex seems improbable.

Biologic explanations for the observed sex difference should be considered, particularly because such differences in relation to a variety of outcomes have been observed in experimental animals.²⁰ Several authors have discussed the differences in bladder cancer risk between men and women, and several mechanisms have been proposed.³² These mechanisms could involve the role of sex hormones in the modulation of the enzymes that metabolize chlorination byproducts into reactive metabolites, factors such as voiding frequency and anatomic differences between the sexes, or the action of disinfection byproducts as hormone disruptors.^{33,34} Cytochrome P4502E1 (CYP2E1) is important in the metabolism of chloroform to active metabolites in humans^{35,36} and, in laboratory animals, appears to be regulated by sex hormones.³⁷ Pharmacokinetic studies in humans show that the activity of CYP2E1 could be higher in men than in women.^{38,39} The metabolism of brominated trihalomethanes is thought to involve a glutathione conjugation reaction leading either to formaldehyde or DNA-reactive intermediates through glutathione transferase-theta.⁴⁰ Several lines of evidence show that glutathione transferases are subject to regulation by thyroid and sex hormones.^{41–43} In the absence of more complete experimental data, the role of sex hormones in explaining sex differences in the effect of trihalomethanes remains a hypothesis. Only a few studies provide information on voiding frequency in population samples, most indicating that voiding frequency is higher in women than men^{44–47} and one study showing equal voiding frequency among men and women.⁴⁸ Furthermore, although biologically plausible, the importance of voiding frequency in bladder cancer risk has not been properly evaluated in epidemiologic studies.

No epidemiologic study has explicitly assessed routes of exposure other than ingestion of drinking water. Volatile compounds (trihalomethanes) enter the body not only through ingestion, but also through inhalation and dermal absorption. Recent estimates indicate that swimming, bathing, and showering are the main routes of uptake of chloroform, which is the most prevalent byproduct in most chlorinated water.³¹ Exposure to nonvolatile compounds (haloacetic acids, haloacetonitriles, and so on) is mainly through drinking water. We used 2 exposure indices, average and cumulative exposure, as proxies for different exposure routes. Average exposure was defined, a priori, as the best proxy for exposure through all

routes. Cumulative exposure was used as a proxy for exposure through ingestion because it was defined as the product of average exposure and amount of tap water consumed. The interpretation of the cumulative exposure index is more complicated because 1 of the 2 composite variables (fluid intake) defining this index could also be regarded as a confounding variable.^{28,49,50} The 2 exposure indices were, however, highly correlated and results were very similar.

This pooled analysis of 6 epidemiologic studies constitutes the most statistically robust analysis to date on disinfection byproducts and bladder cancer. We found an increased risk of bladder cancer and a dose-response pattern among men exposed to trihalomethanes at levels currently observed in many industrialized countries. The observed relative risks were modest but the attributable risk could be considerable, given that the potentially exposed population is large. The observed difference in risk by sex is puzzling. In view of growing evidence that exposure to disinfection byproducts is associated with cancer risk and other health effects, consideration should be given to a more strict control of contaminant levels in chlorinated drinking water through water treatments that reduce the formation of such byproducts without compromising the control of microbial contamination.

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Poetry and Epidemiology

INVOCATION FOR A METHODS CLASS

Tradition fails: which muse shall I invoke?
 Is poetry at odds with this, our field?
 Must we empiricists our songs revoke?
 But hear: need faith in intuition yield?
 For mechanism is a deadly curse
 Anathema to deeper rumination
 But inspiration underlined with verse
 Brings intuition in coordination.
 While blind statistics verge upon uncouth,
 A synergy of brains both right and left,
 Ensures that we steer closer to the truth
 With insights new, our thesis bright and deft:
 A partnership of qual' and quant' illuminates the dark;
 We bless the union, two are one: at last, a muse to hark.

—Daniel Westreich