MONOGRAPHS ON CHLORAMINE, CHLORAL AND CHLORAL HYDRATE, DICHLOROACETIC ACID, TRICHLOROACETIC ACID AND 3-CHLORO-4-(DICHLOROMETHYL)-5-HYDROXY-2(5*H*)-FURANONE

INTRODUCTION TO THE MONOGRAPHS ON CHLORAMINE, CHLORAL AND CHLORAL HYDRATE, DICHLOROACETIC ACID, TRICHLOROACETIC ACID AND 3-CHLORO-4-(DICHLOROMETHYL)-5-HYDROXY-2(5*H*)-FURANONE

Studies of Cancer in Humans

No specific studies on chlorinated drinking-water are available in the literature. However, a number of studies that address the risk of several cancers associated with drinking-water also evaluate the risk linked to chlorinated compounds, and are described below.

1. Cohort studies

Wilkins and Comstock (1981) (Tables 1 and 2) followed up 14 553 men and 16 227 women over 25 years of age, who were residents of Washington County, MD (USA), using data from a census conducted in 1963. Cancer incidence and mortality rates in 1963–75 were assessed in two subcohorts: people who were exposed to chlorinated surface water (average chloroform concentration, 107 μg/L) and those who used water from deep wells that had not been chlorinated. After adjusting for potential confounders, incidence rates were reported for several subsites of cancer. A slightly elevated but non-significant risk for urinary bladder cancer was observed for both men and women. There were no differences in risk for cancers of the kidney or liver between exposed and non-exposed cases, but a risk for liver cancer was suggested in women.

Koivusalo *et al*. (1997) (Tables 1 and 2) reported a historical cohort study of 621 431 persons in 56 towns in Finland with different water sources and practices of water treatment and thus different levels of exposure to chlorination by-products. The cohort was restricted to persons who, in 1970, were living in their town of birth. Information from 1970 onwards on occupation, migration, death, place of residence and water-pipe connection was obtained from Statistics Finland. Cancer incidence for 26 organ sites among these individuals in 1971–93 was ascertained by record linkage with the Finnish National Cancer Registry.

Table 1. Studies on the incidence of urinary bladder cancer associated with chlorinated drinking-water

Study	Population/end-point	No. of cases	Exposure		Risk estimate	Comments
Cohort studies						
Wilkins & Comstock (1981)	Residents of Washington County, MD, USA 30 780 persons (14 553 men, 16 227 women), ≥ 25 years of age, followed up 1963–75	52	Chlorinated surface water (average chloroform concentration, 107 µg/L) versus non-chlorinated deep wells	Men Women	RR (95% CI) 1.8 (0.8–4.8) 1.6 (0.5–6.3)	Adjusted for differences between cohorts in age, marital status, education, smoking history, church attendance, housing, persons per room
Doyle *et al.* (1997)	Iowa Women's Health Study (USA): 41 836 women aged 55–69 years, followed up 1986–93	42	1108 municipal water supplies (1979 and 1986–87) Chloroform concentration in 1986–87 (µg/L) < limit of detection 1–2 3–13 14–287 *p* for trend		 1.0 0.9 (0.4–2.0) 1.2 (0.6–2.7) 0.6 (0.3–1.6) 0.46	Adjusted for age, education, smoking, physical activity, fruit and vegetable intake, energy intake, body mass index and waist-to-hip ratio
Koivusalo *et al*. (1997)	Finland, incidence 1971–93 56 towns – 32% of country population	313 464 men 307 967 women	Estimates of mutagenic potency of drinking-water; 3000 net rev/L increase in average exposure to mutagenicity	Men Women	RR (95% CI) 1.03 (0.8–1.3) 1.5 (1.01–2.2)	Record-linkage study Adjusted for age, time-period, urbanization and social status. Cancers of ureter and urethra included

Table 1 (contd)

Study	Population/end-point	No. of cases	Exposure		Risk estimate	Comments
Case–control studies						
Cantor *et al*. (1987)	10 areas in the USA: Atlanta, Connecticut, Detroit, Iowa, New Jersey, New Mexico, New Orleans, Seattle, San Francisco, Utah Incidence, 1-year period starting December 1997	2805 5258 population controls (men and women)	Duration of consumption of chlorinated surface drinking-water in subjects with tap-water consumption above median (1.44 L/day)	*Years* 0 1–19 20–39 40–59 ≥ 60 0 1–19 20–39 40–59 ≥ 60	OR (95% CI) *Men* 1.0 1.1 (0.7–1.6) 1.1 (0.7–1.5) 1.2 (0.8–1.7) 1.2 (0.7–2.1) *p* for trend = 0.44 *Women* 1.0 1.8 (0.8–3.7) 1.5 (0.7–3.1) 2.2 (1.0–4.8) 3.2 (1.2–8.7) *p* for trend = 0.02	Adjusted for age, smoking habit, high-risk occupation, population size of usual residence and reporting centre
McGeehin *et al*. (1993)	Colorado, USA Incidence 1990–91	327 261 controls with other cancers excluding lung and colorectal cancer (men and women, all white)	Lifetime exposure to chlorinated water from individual histories of residence and water source	*Years* 0 1–10 11–20 21–30 > 30	OR (95% CI) 1.0 0.7 (0.4–1.3) 1.4 (0.8–2.5) 1.5 (0.8–2.9) 1.8 (1.1–2.9)	Adjusted for coffee consumption, smoking, tap-water intake, family history of bladder cancer, sex, medical history of bladder infection or kidney stone
Vena *et al*. (1993)	Western New York, USA Incidence, 1979–85	351 855 population controls (men, white)	Daily intake of tap-water	*No. of cups* 0–5 6–7 8–9 10–39	*Age < 65 years* 1.00 1.3 (0.7–2.4) 1.6 (0.9–3.0) 2.6 (1.5–4.5) *p* for trend < 0.001	Adjusted for age, education, cigarette smoking (pack–years), and coffee, carotene and non-tap-water intake

Table 1 (contd)

Study	Population/end-point	No. of cases	Exposure		Risk estimate	Comments
Vena *et al*. (1993) (contd)				*Age ≥ 65 years*		
				0–5	1.00	
				6–7	1.3 (0.8–2.1)	
				8–9	1.4 (0.8–2.5)	
				10–39	3.0 (1.8–5.0)	
					p for trend < 0.001	
King & Marrett (1996)	Ontario, Canada Incidence, September 1992–May 1994	696 1545 population controls (men and women)	Years of consumption of chlorinated surface drinking-water	*Years*		Adjusted for age, sex, log pack–years of smoking, current smoking, education and calorie intake
				0–9	1.0	
				10–19	1.04 (0.7–1.5)	
				20–34	1.2 (0.9–1.5)	
				≥ 35	1.4 (1.1–1.8)	
			Trihalomethane–years	Quartiles (µg/L–years)		
				0–583	1.0	
				584–1505	1.2 (0.9–1.6)	
				1506–1956	1.08 (0.8–1.4)	
				1957–6425	1.4 (1.1–1.9)	
			Level of trihalomethanes in water source	Level (µg/L)		
				0–24	1.0	
				25–74	1.4 (1.0–2.0)	
				≥ 75	1.7 (1.1–2.5)	
				p for trend	0.006	
Freedman *et al.* (1997)	Washington County, MD, USA Incidence, 1975–92	294 2326 population controls	Duration of residence with municipal water source	*Years* *Cases*	OR (95% CI)	Adjusted for age, sex, smoking and urbanicity
					Men	
				None 54	1.0	
				1–10 63	1.1 (0.6–1.9)	
				11–20 41	1.1 (0.6–1.9)	
				21–30 31	1.3 (0.7–2.5)	
				31–40 11	1.5 (0.6–3.3)	
				> 40 9	2.2 (0.8–5.1)	

Table 1 (contd)

Study	Population/end-point	No. of cases	Exposure		Risk estimate	Comments
Freedman *et al.* (1997) (contd)				*Years* *Cases* None 25 1–10 28 11–20 15 21–30 7 31–40 5 > 40 4	*Women* 1.0 0.7 (0.3–1.7) 0.7 (0.3–1.8) 0.6 (0.2–1.6) 0.7 (0.2–2.2) 0.6 (0.2–2.2)	
Cantor *et al.* (1998)	Iowa, USA Incidence, 1986–89	1123 bladder cancers 1983 population controls (men and women)	Total lifetime trihalomethanes (THM) estimated from lifetime residential histories, water utility survey and measurements of water samples	*THM (g)* ≤ 0.04 0.05–0.12 0.13–0.34 0.35–1.48 1.49–2.41 ≥ 2.42	*Men* 1.0 1.3 (1.0–1.7) 1.1 (0.8–1.5) 1.2 (0.9–1.6) 1.3 (0.8–2.0) 1.8 (1.2–2.7) *p* for trend = 0.05	Adjusted for age, study period, education, high-risk occupation and cigarette smoking (6 strata)
				≤ 0.04 0.05–0.12 0.13–0.34 0.35–1.48 1.49–2.41 ≥ 2.42	*Women* 1.0 1.2 (0.8–1.8) 0.9 (0.6–1.6) 1.0 (0.6–1.7) 0.9 (0.9–2.0) 0.6 (0.3–1.4) *p* for trend = 0.54	

Table 1 (contd)

Study	Population/end-point	No. of cases	Exposure		Risk estimate	Comments
Koivusalo *et al*. (1998)	Finland Incidence, 1991–92	732 914 population controls (men and women)	Mutagenic potency of drinking-water estimated from historical exposure at past residence, past water source and historical data on water quality and treatment	3000-net rev/L increase in average exposure to mutagenicity among subjects with ≥ 30 years of exposure	*Men* 1.2 (0.9–1.7) *Women* 1.2 (0.7–2.0)	Adjusted for age, smoking, socioeconomic status
				Tertiles of exposure among subjects with ≥ 30 years of exposure (net rev/L):		
				Non-exposed	*Men* (552 cases) 1.0	
				Low (1–999)	1.2 (0.8–1.6)	
				Medium (1000–2499)	0.97 (0.7–1.4)	
				High (≥ 2500)	1.4 (0.9–2.0)	
				Non-exposed	*Women* (180 cases) 1.0	
				Low (1–999)	1.2 (0.7–2.0)	
				Medium (1000–2499)	1.3 (0.7–2.4)	
				High (≥ 2500)	1.2 (0.6–2.2)	

RR, relative risk; CI, confidence interval; OR, odds ratio

Table 2. Cohort studies of cancer at other sites and chlorinated drinking-water

Reference	Population/follow-up	Exposure	Site and no. of cases		Relative risk (95% CI)	Comments
Wilkins & Comstock (1981)	Residents of Washington County, MD, USA 30 780 persons (14 553 men, 16 227 women) ≥ 25 years of age followed up 1963–75	Chlorinated surface water (average chloroform concentration, 107 µg/L) versus non-chlorinated deep wells	Liver Men Women Kidney Men Women	12 18 	 0.7 (0.2–3.5) 1.8 (0.6–6.8) 0.8 (0.3–2.7) 1.01 (0.3–6.0)	Adjusted for differences between cohorts in age, marital status, education, smoking history, church attendance, housing, persons per room
Doyle *et al.* (1997)	Iowa Women's Health Study (USA) 41 836 women aged 55–69 years, followed up 1986–93	1108 municipal water supplies (1979 and 1986–87) Chloroform concentration in 1986–87 (µg/L) < limit of detection 1–2 3–13 14–287 1–2 3–13 14–287 1–2 3–13 14–287	 Kidney Colon Rectum and anus 	 30 178 78 	 1.0 0.5 (0.2–1.6) 1.2 (0.5–3.1) 0.9 (0.3–2.3) 1.1 (0.7–1.7) 1.4 (0.9–2.2) 1.7 (1.1–2.5) 0.8 (0.4–1.5) 0.8 (0.4–1.5) 1.1 (0.6–1.9)	Adjusted for age, education, smoking, physical activity, fruit and vegetable intake, energy intake, BMI and waist-to-hip ratio *p* for trend = 0.82 *p* for trend < 0.01 *p* for trend = 0.89

Table 2 (contd)

Reference	Population/follow-up	Exposure	Site and no. of cases	Relative risk (95% CI)	Comments
Doyle *et al.* (1997) (contd)			Lung 143		
		1–2		1.2 (0.8–2.1)	
		3–13		1.8 (1.1–3.0)	
		14–287		1.6 (0.97–2.6)	*p* for trend = 0.025
			Melanoma 44		
		1–2		2.6 (0.99–6.6)	
		3–13		1.3 (0.4–4.0)	
		14–287		3.4 (1.3–8.6)	*p* for trend = 0.049
			All cancers 983		
		1–2		1.04 (0.9–1.3)	
		3–13		1.2 (1.03–1.5)	
		14–287		1.3 (1.1–1.5)	*p* for trend < 0.01
Koivusalo *et al*. (1997)	Finland 56 towns; 32% of Finnish population, 1971–93	Chlorinated/ unchlorinated water supplies; mutagenicity assessment	621 431 persons (307 967 women, 313 464 men)		Adjusted for age, time period, urbanization and social status. Cancers of the ureter and urethra included in bladder cancer
			Both sexes		
			Colon	0.9 (0.8–1.04)	
			Rectum	1.04 (0.9–1.3)	
			Oesophagus	1.4 (0.9–2.1)	
			Pancreas	1.01 (0.8–1.2)	
			Kidney	1.03 (0.8–1.3)	
			Brain and nervous system	1.00 (0.9–1.2)	
			Non-Hodkgin lymphoma	1.2 (0.9–1.5)	
			Leukaemia	1.04 (0.9–1.3)	
			Women		
			Colon	0.95 (0.8–1.9)	
			Rectum	1.4 (1.03–1.9)	
			Oesophagus	1.9 (1.02–3.5)	
			Breast	1.1 (1.01–1.2)	
			Pancreas	1.1 (0.8–1.5)	
			Kidney	1.03 (0.7–1.4)	
			Brain and nervous system	1.08 (0.9–1.4)	
			Non-Hodkgin lymphoma	1.4 (0.98–1.98)	
			Leukaemia	1.08 (0.8–1.5)	

Table 2 (contd)

Reference	Population/follow-up	Exposure	Site and no. of cases	Relative risk (95% CI)	Comments
Koivusalo *et al*. (1997) (contd)			*Men*		
			Colon	0.8 (0.7–1.04)	
			Rectum	0.9 (0.7–1.09)	
			Oesophagus	0.9 (0.5–1.7)	
			Prostate	0.97 (0.8–1.1)	
			Pancreas	0.9 (0.7–1.2)	
			Kidney	1.04 (0.8–1.4)	
			Brain and nervous system	0.9 (0.7–1.2)	
			Non-Hodkgin lymphoma	1.03 (0.8–1.4)	
			Leukaemia	1.02 (0.8–1.3)	

CI, confidence interval

Historical exposure estimates used information on past residence, past water source and historical data on water quality and treatment during the years 1955 and 1970. Exposure was expressed as estimates of mutagenic potency of drinking-water through regression models developed by Vartiainen *et al*. (1988), which used indicators of water quality and water treatment in the past (1986–87) to estimate mutagenic potency with the Ames test using *Salmonella typhimurium* strain TA100. Vartiainen *et al*. (1988) showed a correlation of 0.63 between the level of mutagenicity (TA100) and levels of trihalomethanes in water, but did not report on 3-chloro-4-(dichloromethyl)-5-hydroxy-2-(5*H*)-furanone (MX). Kronberg and Vartiainen (1988), however, reported that between 15 and 57% (mean, 33%) of the mutagenicity in 23 Finnish tap-water samples could be explained by MX. They also reported a correlation of 0.89 between the level of mutagenicity (TA100) in water and concentration of MX. Koivusalo *et al.* (1997) evaluated 24 cancer sites separately for men and women. Relative risks were calculated using a continuous variable for the mutagenicity level of a 3000-net revertants (rev)/L exposure. Significantly elevated risks were observed among women only for cancers of the urinary bladder, rectum and oesophagus. The relative risk for female breast cancer was 1.1 (95% CI, 1.01–1.22). No increased risk for colon cancer was shown in this study.

The Iowa Women's Health Study in the USA comprised a cohort of 41 836 women, aged 55–69 in 1986, followed up for cancer incidence through to 31 December 1993 (Doyle *et al*., 1997) (Tables 1 and 2). The source of drinking-water for each cohort member was assessed from a postal survey in 1989. After excluding women who reported having drunk municipal or private well-water for less than 10 years previously, 28 237 women were included in the analysis. Data on 252 municipal water supplies in 1979 and 856 municipal water systems in 1986–87 were used to assess exposure. All women who lived in the same community and reported drinking municipal water were assigned the same concentration of trihalomethanes, including chloroform. The concentrations of chloroform in 1986–87 were categorized as below the detection limit (reference) or 1–2, 3–13 and 14–287 μg/L. The incidences of a number of cancers were estimated in each category. Relative risks were adjusted for age, education, smoking status, pack–years of smoking, physical activity, all fruit and vegetable intake, total energy intake, body mass index and waist-to-hip ratio. In comparison with women who used groundwater sources, women drinking water from surface sources were at increased risk for colon cancer and all cancers combined, with a clear dose–response relationship. In addition, trends in risk were found for cancer of the lung (p for trend = 0.025) and melanoma (p for trend = 0.049).

2. Case–control studies

2.1 *Cancers of the urinary bladder* (Table 1)

Cantor *et al*. (1987) interviewed 2805 patients with urinary bladder cancer aged 21–84 years at the time of diagnosis and 5258 population-based controls in a case–control study in 10 geographical areas in the USA. Controls under the age of 65 years were selected by

random-digit dialling and controls over the age of 65 from rosters of the US Health Care Financing Agency. The cases were newly diagnosed and histologically confirmed during 1977–78. Cases and controls were frequency-matched on sex, age and geographical area. All subjects were administered a questionnaire at home by trained interviewers, which included questions on consumption of tap-water during a typical week 1 year before the interview. A lifetime history of residence and water sources was ascertained. A total of 1102 water utilities were visited, and utility personnel were interviewed; the water sources were then categorized for chlorination status (chlorination or no chlorination) during various periods. The residential histories of the subjects were linked with year-by-year data on water source and treatment. Logistic regression models with adjustment for sex, age, study area, smoking, high-risk occupation and population size were used with various indicators of water quality. Odds ratios for bladder cancer were elevated among those with both elevated intakes of drinking-water and long-term consumption of chlorinated surface water. Among subjects who had lived for 60 years or longer at residences supplied with chlorinated surface water, odds ratios for successive quintiles of tap-water ingestion were: 1.0 (≤ 0.8 L/day, referent), 0.8, 1.1, 1.7 and 2.0 (p for trend = 0.014). [Confidence intervals about the point estimates were not available.]

A population-based study of 327 histologically verified cases of urinary bladder cancer from the State Cancer Registry matched to 261 controls with other cancers was conducted in Colorado (USA) during 1990–91 (McGeehin *et al*., 1993). After physician approval, telephone interviews were carried out to obtain individual histories of residence and water source from living patients and controls; the response rates were 78% and 75%, respectively. These data were linked to data from water utilities and records of the Colorado Department of Health. The total lifetime concentration of trihalomethanes was calculated for each subject as a time-weighted mean from data for each water system in Colorado in 1989. The mean lifetime concentration was 616 µg/L for cases and 422 µg/L for controls ($p < 0.001$). Adjustment for potential confounders resulted in odds ratios that increased with years of exposure to chlorinated water. More than 34 years of exposure to chlorinated water, contrasted with no such exposure, was associated with increased risks in both nonsmokers (odds ratio, 2.9; 95% CI, 1.2–7.4) and smokers (odds ratio, 2.1; 95% CI, 1.1–3.8).

Vena *et al*. (1993) reported a case–control study among male residents of three counties in western New York State (USA). Cases were diagnosed during 1979–85 and were confirmed histologically. Physician approval was obtained for 972 cases. Of these, 719 were eligible according to inclusion criteria and 351 cases of transitional-cell bladder cancer were interviewed. Controls (aged 35–90 years) were residents of the same counties, were matched to individual cases by sex, age and neighbourhood of residence and were interviewed during the period of case ascertainment. All 850 were included in the bladder cancer study [response rates not indicated]. Usual dietary habits including consumption of tap-water and non-tap-water were ascertained for the year prior to diagnosis (cases) or interview (controls). Total tap-water consumption also included beverages prepared with tap-water. More than 70% of subjects spent more than 90% of their lives using a public source of tap-

water that historically had been treated with chlorine. The odds ratios for bladder cancer increased with increasing number of cups of tap-water consumed daily (p for trend < 0.001). There was an almost threefold increase for intake of more than 10 cups of tap-water daily compared with an intake of less than 5 cups per day. No excess risk was observed in subjects who had used the public water supply for more than 50 years compared with those who had used it for less than 50 years. [The Working Group noted that the non-exposed group included subjects with a lengthy exposure time to chlorinated drinking-water. This paper did not analyse associations with water source or level of trihalomethanes.]

King and Marrett (1996) reported a population-based case–control study of bladder cancer among residents of Ontario, Canada (excluding the north), aged 25–74 years. Cases diagnosed in the period 1 September 1992 to 1 May 1994 were identified from records of the Ontario Cancer Registry. After exclusions due to illness, death and lack of physician approval, 1262 patients were contacted out of 1694 eligible cases, and 927 cases completed a questionnaire (84%). Controls were selected by random-digit dialling. Of 2768 eligible controls, 2494 were contacted and 2118 completed the questionnaire (87%). The overall response rates were 73% for cases and 72% for controls. The period of exposure ascertainment extended from 1950 to 1990. Summer trihalomethane levels were estimated by modelling data from 1988–92 for 114 water-treatment plants. Predictors in the model were characteristics of the raw water (source, depth of intake pipe, temperature), pretreatment procedures (dose of chlorination, chloramination), treatments employed (coagulation, polyelectrolytes, activated carbon) and post-treatment procedures (dose of chlorination, dechlorination). Separate models were created for surface water with and without chlorination pretreatment and for groundwater sources. Information from subjects was collected by telephone, using a structured interview after they had received a mailed questionnaire. Items included demographic data, smoking history, usual diet, lifetime residence (with information on water source) and usual water consumption prior to diagnosis. Water exposures were estimated by linking residential histories with the relevant data on treatment plant by time and geographical area. After restricting the population for analysis to persons with 30 or more years of identified exposure, 696 cases of bladder cancer and 1545 controls remained. Analyses were adjusted for age, sex, smoking habit, education and calorie intake. Odds ratios increased up to 1.4 with increasing duration of use of a chlorinated surface water source. Results from another analysis, in which trihalomethane–years was used as the exposure variable, showed a similar increase in risk. In addition, among subjects with relatively homogeneous exposures for at least 30 years, a trend in risk with increasing trihalomethane levels was observed ($p = 0.006$).

Freedman *et al*. (1997) conducted a case–control study of bladder cancer among residents of Washington County, MD, USA. Cases were white residents reported to the local cancer registry between 1975 and 1992 ($n = 294$). All cases had been enumerated in a special county census conducted by the Johns Hopkins School of Public Health and Hygiene in 1975 ($n = 2326$). Controls, frequency-matched by age (± 5 years) and sex, were randomly selected from the 1975 census population. Data collected in the 1975 census included age, sex, ethnicity, years of schooling, smoking status, residence, source

of drinking-water and other variables. Duration of exposure to chlorinated surface water was derived from census information on the length of residence in a household supplied with municipal water at the time of the census. With minor exceptions, municipalities in Washington County, MD, had been supplied for at least 30 years with chlorinated surface water. Odds ratios were adjusted for age, sex, smoking history and a number of other potential confounding factors. The risk for bladder cancer was weakly associated with duration of exposure to municipal drinking-water.

Koivusalo *et al*. (1998) conducted a population-based case–control study in Finland of 732 cases of bladder cancer, 703 cases of kidney cancer and 914 controls. The cases were identified by the Finnish Cancer Registry from persons diagnosed in 1991–92. Controls, frequency-matched by age and sex to the case series, were randomly selected from the national population registry. The overall response rate (cases and controls) was 68% of those eligible. Information on several confounding factors (tobacco use, socioeconomic status, intake of coffee and other beverages, past urinary tract infections and urolithiasis, occupational history, weight, height) and water-source history was obtained through a questionnaire. Historical exposure estimates were made using the methods described above (Koivusalo *et al*., 1997). Exposure estimates covered the period 1950–87, and only persons with information on exposure for at least 30 years were included in the analysis. Using a continuous variable for the estimated level of mutagenicity through exposure to water, odds ratios were calculated for a 3000-net rev/L increase in average exposure between 1950 and 1987 in logistic regression models adjusted for age, sex, socioeconomic status and smoking habit. Overall, after adjustment for confounding, a small excess risk for bladder cancer was observed for an increase of 3000 net rev/L in men and women. In other analyses, subjects were placed in categories of exposure (low, 1–999 net rev/L; medium, 1000–2499 net rev/L; high, ≥ 2500 net rev/L) and risk was compared with unexposed individuals, but the odds ratios remained non-significant.

Cantor *et al.* (1998) reported a case–control study of bladder cancer among residents of Iowa (USA) aged 40–85 years. Patients with histologically confirmed bladder cancer were identified through the State Health Registry of Iowa, supplemented by a rapid reporting system, during 1986–89. Controls were frequency-matched to cases by 5-year age group and sex. Controls under 65 years of age were randomly selected from driver's licence listings, whereas controls aged 65 and older were selected from rosters of the US Health Care Financing Agency. When a case was deceased or incapable of responding (approximately 10%), a close family member or friend was invited to participate. Patients, controls and proxies completed a self-administered questionnaire on demographic data, smoking history, occupational history, further indicators of lifestyle and medical conditions and the frequency of consumption as an adult inside and outside the home of beverages containing tap-water and other beverages. Lifetime residential histories were recorded, and the water source at each location was identified. Missing information important to the analysis of drinking-water exposures was completed by telephone interview. All 280 Iowa water utilities that supplied at least 1000 persons were contacted for historical information, and at each utility an interviewer collected one or two samples from the clear well where the water

enters the distribution system or from nearby the system. The lifetime exposure to total trihalomethanes (g) and the lifetime average trihalomethane concentration (μg/L) were calculated for 1123 cases and 1983 controls. The logistic regression models included adjustment for age, study period, level of education, high-risk occupation and cigarette smoking. Odds ratios increased with increasing total lifetime dose of trihalomethanes for men but not women. Results for average lifetime dose of trihalomethanes followed similar patterns [data not shown in table].

2.2 *Colorectal cancer* (Table 3)

On the basis of their previous findings of an excess risk for mortality from colon cancer associated with exposure to chlorinated water supplies (Kanarek & Young, 1982), Young *et al*. (1987) conducted a case–control study of 347 incident cases of colon cancer and 639 cancer controls, excluding gastrointestinal and urinary tract cancers, identified in the Wisconsin Cancer Reporting System. A group of 611 population controls was selected from state driver's licence listings. White men and women in whom colon cancer had been diagnosed when they were aged 35–90 were considered to be eligible. The self-administered questionnaire gathered information on background variables, past water sources, water-drinking and bathing habits, home treatment of tap-water, and medical, occupational, social and lifestyle histories. Overall, 45% of the cases of colon cancer and 48% of controls participated in the study. After accounting for deaths, an overall response rate (all cases and controls) of 65% was achieved. The exposure of each study subject to trihalomethanes was estimated from an algorithm based on a survey of 81 Wisconsin water supplies, historical data from water facilities, the residential history of the subjects, data on individual water use and other information. Average estimated trihalomethane concentrations of 10–40 μg/L or > 40 μg/L at the place of residence in the years 1951, 1961, 1971 and 1981 were used as exposure estimates, and odds ratios were calculated for each of these years (reference category, < 10 μg/L trihalomethane). Using the population control series, no association of estimated exposure to trihalomethanes with risk for colon cancer was observed. Similar results were found when cancer controls were used. In addition, analyses were conducted using cumulative lifetime exposure to trihalomethanes over the past 30, the past 20 and the past 10 years. Regardless of the control group used in the analysis, results were consistent with the authors' conclusion that exposure to trihalomethanes is not associated with colon cancer in Wisconsin.

Hildesheim *et al.* (1998) reported results from a case–control study of colon and rectal cancer among residents of Iowa, USA, aged 40–85 years. Patients with histologically confirmed cancers of the colon and rectum were identified through the State Health Registry of Iowa during 1987; for the controls, the same mailed questionnaire and back-up telephone interview were used as those in the study of Cantor *et al.* (1998; see Section 2.1). The lifetime exposure to total trihalomethanes (g) and lifetime average trihalomethane concentrations (μg/L) were calculated for 560 colon cancer patients, 537 rectal cancer patients and 1983 controls from data on water samples and from interviews. About 15% of the patients

Table 3. Case–control studies of colorectal cancer and chlorinated drinking-water

Study	Population/end-point	No. of cases	Exposure		OR (95% CI)	Comments
Young *et al.* (1987)	Wisconsin, USA Incidence, 1951–81	347 colon cancer 639 other cancer controls 611 population controls Age, 35–90 years (both sexes)	Total trihalomethane concentration at place of residence (µg/L) in 1951	< 10 10–40 > 40	1.0 1.2 (0.6–2.3) 0.98 (0.4–2.3)	OR for colon cancer adjusted for sex, age and population size of place of residence. General population controls
			Cumulative total trihalomethane exposure (mg) over lifetime	< 100 100–300 > 300	1.0 1.1 (0.7–1.8) 0.7 (0.4–1.2)	
Hildesheim *et al.* (1998)	Iowa, USA Incidence, 1986–89	560 colon cancer 537 rectal cancer 1983 population controls Age, 40–85 years (both sexes)	Total lifetime trihalomethane (g)	≤ 0.04 0.05–0.12 0.13–0.34 0.35–1.48 1.49–2.41 ≥ 2.42	1.0 1.3 (1.0–1.6) 1.3 (0.9–1.8) 1.5 (1.1–2.1) 1.9 (1.2–3.0) 1.6 (1.0–2.6)	Rectal cancer Adjusted for age and sex *p* for trend = 0.08
			Lifetime average trihalomethane concentration (µg/L)	≤ 0.7 0.8–2.2 2.3–8.0 8.1–32.5 32.6–46.3 ≥ 46.4	1.0 1.05 (0.8–1.4) 1.2 (0.9–1.7) 1.2 (0.9–1.7) 1.7 (1.1–2.6) 1.7 (1.1–2.6)	Rectal cancer Adjusted for age and sex *p* for trend = 0.01
King *et al.* (2000)	Southern Ontario, Canada Incidence, 1992–94	767 colon cancer 661 rectal cancer 1545 population controls Age, 30–74 years (both sexes)	Consumption of chlorinated drinking-water (years)		*Men*	Colon cancer Adjusted for sex, age, education, body mass index and intake of energy, cholesterol, calcium, alcohol and coffee
				0–9 10–19 20–34 ≥ 35	1.0 1.7 (1.1–2.7) 1.3 (0.96–1.9) 1.5 (1.1–2.1)	
					Women	
				0–9 10–19 20–34 ≥ 35	1.0 0.6 (0.3–0.9) 0.9 (0.6–1.2) 0.7 (0.5–1.1)	

Table 3 (contd)

Study	Population/end-point	No. of cases	Exposure		OR (95% CI)	Comments
King *et al.* (2000) (contd)			Trihalomethane level (μg/L)		*Men*	
				0–24	1.0	
				25–74	1.5 (0.99–2.4)	
				≥ 75	1.9 (1.2–3.1)	
					p for trend = 0.005	
					Women	
				0–24	1.0	
				25–74	0.5 (0.3–0.8)	
				≥ 75	0.9 (0.5–1.7)	
					p for trend = 0.211	
			Exposure to trihalo-methanes ≥ 75 μg/L (years)		*Men*	
				0–9	1.0	
				10–19	1.1 (0.9–1.5)	
				20–34	1.5 (0.99–2.3)	
				≥ 35	2.1 (1.2–3.7)	
					Women	
				0–9	1.0	
				10–19	0.9 (0.7–1.3)	
				20–34	0.9 (0.5–1.6)	
				≥ 35	1.2 (0.6–2.4)	

OR, odds ratio; CI, confidence interval

were interviewed by proxy. The logistic regression models included adjustment for sex, age, study period, education, high-risk occupation and cigarette smoking. There was a suggestion of a trend of increasing risk for rectal cancer with lifetime concentration of trihalomethanes and for average lifetime dose of trihalomethanes. No such trend was observed for colon cancer.

King *et al*. (2000) reported a population-based case–control study of colon and rectal cancer among residents of Ontario, Canada, aged 30–74 years. Of 1722 cases of colon and 1530 cases of rectal cancer identified by the Ontario Cancer Registry from 1 September 1992 to 1 May 1994, physician consent to contact patients was obtained for 1338 cases of colon and 1169 cases of rectal cancer. Questionnaires were completed by 991 and 875 cases of colon and rectal cancer, respectively. Analyses were conducted on 767 cases of colon cancer, 661 cases of rectal cancer, and 1545 controls with information on exposure for at least 30 of the 40 years prior to diagnosis (cases) or completion of the questionnaire (controls). Selection and numbers of controls, interviews and exposure assessments were conducted as in King and Marrett (1996; described in Section 2.1). Risk for colon cancer was elevated among men exposed to water with high levels of trihalomethanes, but not among women. Among men with homogeneous exposures for at least 30 years, adjusted odds ratios were also elevated, with a clear exposure–response relationship. This effect was not observed in women. When the exposure metric was years of exposure to ≥ 75 μg/L trihalomethane, the odds ratios for colon cancer were again elevated in men only. There was no association of risk for rectal cancer in either sex with number of years of exposure to water containing elevated levels of trihalomethanes.

2.3 *Other cancer sites* (Table 4)

(*a*) *Kidney cancer*

Koivusalo *et al.* (1998) conducted a population-based case–control study in Finland of 732 cases of bladder cancer, 703 cases of kidney cancer and 914 controls (described in detail in Section 2.1). An exposure-related excess risk was observed among men only for a 3000 net rev/L increase in average exposure to chlorination by-products. No significant risk was observed when cases were placed in tertiles of exposure, although a weak association was suggested.

(*b*) *Brain cancer*

Cantor *et al.* (1999) reported a case–control study of brain cancer among residents of Iowa (USA), aged 40–85 years. Patients with histologically confirmed glioma were identified through the State Health Registry of Iowa during 1984–87; for the controls, the same mailed questionnaire and back-up telephone interview were used as those in the study of Cantor *et al.* (1998; see Section 2.1). The lifetime exposure to total trihalomethanes (g) and the lifetime average trihalomethane concentrations (μg/L) were calculated for 291 cases and 1983 controls from data on water samples and from interviews. Elevated risks were observed among men, but not women, with duration of exposure to

Table 4. Case–control studies of cancer at other sites and chlorinated drinking-water

Cancer site	Study	Population/ end-point	No. of cases	Exposure	OR (95% CI)	Comments
Kidney	Koivusalo *et al*. (1998)	Finland Incidence 1991–92	703 (386 men, 317 women) and 914 population controls (621 men, 293 women)	Mutagenicity assessment; 3000 net rev/L increase	≥ 30 years of estimable exposure Both sexes 1.3 (1.0–1.7) Women 1.1 (0.7–1.7) Men 1.5 (1.1–2.1)	Calculated for all those with at least 30 years of known exposure. Adjusted for age, smoking, socioeconomic status and sex
				Tertiles of exposure (net rev/L): Non-exposed Low (1–999) Medium (1000–2499) High (≥ 2500)	*Women* 1.0 0.9 (0.6–1.5) 1.3 (0.8–2.1) 1.1 (0.7–1.9)	
				Non-exposed Low Medium High	*Men* 1.0 1.2 (0.8–1.7) 1.3 (0.8–1.8) 1.6 (1.0–2.4)	
Brain	Cantor *et al*. (1999)	Residents of Iowa, USA, aged 40–85 years. Incidence 1984–87	291 glioma (155 men, 136 women) and 1983 population controls (1308 men, 675 women)	Chlorinated surface water. Water utilities surveyed, measurements of trihalomethanes, personal questionnaire for past exposure	*Both sexes* (years of exposure to ≥ 75 µg/L) 0 1.0 1–19 1.1 (0.8–1.6) 20–39 1.6 (1.0–2.6) ≥ 40 1.3 (0.8–2.3) *p* for trend = 0.1	Adjusted for sex, age, farming occupation and population size; 74.4% of cases had proxy respondents. Cases and controls with ≥ 70% of lifetime with known source selected. Excluded population better educated and more urban
					Women 0 1.0 1–19 1.0 (0.6–1.6) 20–39 1.6 (0.8–3.0) ≥ 40 0.7 (0.3–1.6) *p* for trend = 0.4	

Table 4 (contd)

Cancer site	Study	Population/ end-point	No. of cases	Exposure	OR (95% CI)	Comments
Brain (contd)	Cantor *et al*. (1999) (contd)				*Men*	
					0 1.0	
					1–19 1.3 (0.8–2.1)	
					20–39 1.7 (0.9–3.3)	
					≥ 40 2.5 (1.2–5.0)	
					p for trend = 0.04	
				Lifetime average trihalomethane concentration (µg/L)		
					Both sexes	
				≤ 0.7	1.0	
				0.8–2.2	0.9 (0.6–1.3)	
				2.3–32.5	0.9 (0.6–1.4)	
				≥ 32.6	1.1 (0.7–1.8)	
					p for trend = 0.3	
					Women	
				≤ 0.7	1.0	
				0.8–2.2	0.9 (0.5–1.5)	
				2.3–32.5	0.8 (0.5–1.5)	
				≥ 32.6	0.9 (0.4–1.8)	
					p for trend = 0.9	
					Men	
				≤ 0.7	1.0	
				0.8–2.2	0.9 (0.6–1.6)	
				2.3–32.5	1.0 (0.6–1.8)	
				≥ 32.6	1.4 (0.7–2.9)	
					p for trend = 0.04	

Table 4 (contd)

Cancer site	Study	Population/ end-point	No. of cases	Exposure	OR (95% CI)	Comments
Pancreas	Ijsselmuiden *et al.* (1992)	Washington County, MD, USA. Incidence 1975–89	101 (47 men, 54 women) 206 population controls (96 men, 110 women) All white	Chlorinated drinking-water, as of 1975 census. Non-municipal (chlorinated) Municipal (chlorinated)	1.0 2.2 (1.2–3.95)	Adjusted for age and current cigarette smoking. Non-municipal but chlorinated water used as baseline for odds ratios
	Kukkula & Löfroth (1997)	Turku area, Finland. Study base: 220 000 persons Incidence 1989–91	183 (71 men, 112 women); 360 matched controls	Residence in an area supplied by chlorinated drinking-water until 1981	*Exposure (years)* 0 0.33 (0.2–0.7) 1 0.54 (0.3–1.2) 5 0.66 (0.3–1.3) 10 0.53 (0.3–1.07) 15 0.32 (0.1–0.8) 20 0.20 (0.04–0.9)	No adjustment for confounders. OR calculated from exposure data of the discordant case–control set. Total trihalomethanes often > 200 µg/L at end of distribution system
Acute lymphocytic leukaemia	Infante-Rivard *et al.* (2001)	Quebec, Canada. Incidence 1980–93	491 aged 0–9 years and 491 population controls (boys and girls)	Trihalomethanes, metals (As, Cd, Cr, Pb, Zn) and nitrates in drinking-water. Municipality–exposure matrix based on historical data.		Adjusted for maternal age and level of schooling
				Water chlorinated	*Prenatal*	
				Part of the time	1.6 (0.7–3.7)	Baseline: never
				Always	0.8 (0.5–1.2)	
				Cumulative exposure (total trihalomethanes)		
				> 95th percentile	0.8 (0.4–1.8)	Baseline: ≤ 95th percentile
				25th–75th percentile	1.1 (0.8–1.7)	Baseline ≤ 24th percentile
				> 75% percentile	1.2 (0.7–1.8)	

Table 4 (contd)

Cancer site	Study	Population/ end-point	No. of cases	Exposure	OR (95% CI)	Comments
Acute lymphocytic leukaemia (contd)	Infante-Rivard *et al.* (2001) (contd)			Water chlorinated	*Postnatal*	
				Part of the time	1.4 (0.7–2.5)	Baseline: never
				Always	0.9 (0.6–1.3)	
				Cumulative exposure (total trihalomethanes)		
				> 95th percentile	1.5 (0.8–3.0)	Baseline: ≤ 95th percentile
				25th–75th percentile	1.1 (0.8–1.6)	Baseline ≤ 24th percentile
				> 75% percentile	0.9 (0.6–1.4)	
	Infante-Rivard *et al*. (2002)	Québec, Canada. Incidence 1980–83 Case-only study	161 cases from earlier study (2001)	*GSTT1*-null Total trihalomethanes > 95th percentile		Postnatal exposure
				Average	9.1 (1.4–57.8)	
				Cumulative	2.5 (0.6–10.5)	
				*CYP2E1*5* Total trihalomethanes ≥ 75th percentile		
				Average	4.1 (0.8–21.5)	
				Cumulative	5.96 (0.7–53.8)	

OR, odds ratio; CI, confidence interval

chlorinated surface waters with levels of trihalomethanes of about 75 µg/L. For lifetime average exposure to trihalomethanes, the odds ratio among men increased to 1.4 (95% CI, 0.7–2.9) for levels > 32.6 µg/L. Among women, there was no association of risk with average trihalomethane level.

(*c*) *Pancreatic cancer*

A population-based case–control study on pancreatic cancer was conducted in the Turku area, Finland (Kukkula & Löfroth, 1997). All 183 cases diagnosed during 1989–91 from a study base of approximately 220 000 persons were included in the study. Two random controls were selected for each case. Source of drinking-water (chlorinated or non-chlorinated) was identified for each subject for all residences in the last 20 years prior to diagnosis. Exposure to chlorinated drinking-water was not associated with risk for pancreatic cancer, with odds ratios ranging from 0.2 to 0.7 depending on the length of exposure. [The Working Group noted that the study did not provide information on individual water-drinking habits or on potential confounding factors, and that the exposure time window of 20 years prior to diagnosis is short.]

Ijsselmuiden *et al*. (1992) conducted a case–control study of pancreatic cancer among residents of Washington County, MD (USA). Cases were residents reported at the local cancer registry from 1975 to 1989. All cases had been enumerated in a special county census conducted by the Johns Hopkins School of Public Health and Hygiene in 1975. Information on pancreatic cancer was obtained from hospital records and death certificates. Controls were randomly selected from the 1975 census population. The total study population comprised 101 white cases and 206 white controls (participation rates above 95% for both groups). Data collected in the 1975 census included age, sex, race, years of schooling, smoking, residence, source of drinking-water and other variables. A small validation study indicated that the population in this county was relatively stable and that there were few changes in water sources between 1963 and 1975. Chlorinated municipal drinking-water was used as a source of drinking-water by 79% of cases and 63% of controls, yielding an odds ratio of 2.2 (95% CI, 1.2–3.95) adjusted for age and smoking, relative to users of private well-water. [The Working Group noted that the information collected in the census on residence and source of drinking-water was cross-sectional.]

(*d*) *Childhood leukaemia*

A population-based case–control study of 491 cases of acute lymphoblastic leukaemia cases aged 0–9 years in the Province of Québec, Canada, was reported by Infante-Rivard *et al*. (2001). Cases were diagnosed in 1980–93 and controls ($n = 491$) were selected from a population-based registry of children, individually matched to cases on age (within 24 months), sex and region of residence at the calendar date of diagnosis. Information was collected by telephone interview of parents on the child's residential history, including information on source of drinking-water. Data on drinking-water quality, with information on individual trihalomethane levels, were collected from municipal water supplies and from data held by the Ministry of Environment. Exposure indices were developed after

merging residential histories with historical data on water quality. Odds ratios were estimated by conditional logistic regression with adjustment for maternal age and level of schooling. During the prenatal period, as well as the postnatal period, no substantial increase in risk was observed; however, a small increase was shown during the postnatal period for cumulative exposure to trihalomethanes (above the 95th percentile).

Subsequently, Infante-Rivard *et al*. (2002) conducted a case–case analysis among a subset of 161 childhood cases of acute lymphocytic leukaemia from their earlier study (Infante-Rivard *et al*., 2001) for whom information on exposure was available as well as information on genotyping for polymorphisms in the *GSTT1* and *CYP2E1* genes that are involved in the metabolism of trihalomethanes. Risk was assessed for gene–exposure interaction. For *GSTT1*, 25 cases had the null genotype and 136 carried the normal allele. Twelve cases carried at least one *CYP2E1*5* allele and 125 were normal for the *CYP2E1* genotype. The risk for acute lymphoblastic leukaemia associated with average exposure to total trihalomethanes was elevated among children homozygous for *GSTT1* deletion (null genotype). An increase in risk was also suggested among children bearing the *CYP2E1*-null genotype. The authors noted in conclusion that this preliminary study shows suggestive but imprecise results which should be repeated.

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