INTRODUCTION TO THE *MONOGRAPHS* ON BROMOCHLOROACETIC ACID, DIBROMOACETIC ACID AND DIBROMOACETONITRILE

No epidemiological studies have evaluated exposure specifically to bromochloroacetic acid, dibromoacetic acid or dibromoacetonitrile in humans. Human exposure to these chemicals always occurs in mixtures with other disinfection by-products in chlorinated drinking-water and chlorinated water in swimming pools, which include more than 700 chemicals (Richardson *et al.*, 2007). The previous *Monograph* on drinking-water disinfectant by-products (IARC, 2004) reviewed the epidemiological studies published up to 2002. The current Working Group reviewed all of the data detailed below, although a formal evaluation on chlorinated drinking-water and disinfection by-products was not made at this time.

Chlorine is the most common disinfectant used worldwide, although others may also be used (i.e. ozone, chlorine dioxide and bromide in swimming pools). To deal with the complexity of the mixtures of chemicals in disinfected water, epidemiological studies conducted since the 1970s that evaluated the risk of chlorinated water and disinfection by-products for cancer used surrogates of exposure, which have evolved from duration of residence in a household supplied with chlorinated surface water and type and concentration of disinfectant to the quantification of levels of relevant by-products (e.g. chloroform and total trihalomethanes). However, although the more recent studies measured specific compounds (i.e. trihalomethanes), these are a proxy for a complex mixture in disinfected water, which includes bromochloroacetic acid, dibromoacetic acid and dibromoacetonitrile. The correlation between surrogates of disinfectant by-products and individual constituents in specific samples of treated water is complex and strongly depends on raw water quality and the type of treatment (including the disinfection processes). Brominated disinfection by-products, including bromochloroacetic acid, dibromoacetic acid and dibromoacetonitrile, tend to increase as the bromine content of the raw water increases (Kampioti & Stephanou, 2002). In general, trihalomethanes and haloacetic acids represent the two major classes of halogenated disinfection by-products on a weight basis, (Krasner *et al.*, 2006). Levels of total trihalomethanes are correlated with the total organic halide content when chlorine is used as the main disinfectant (Singer & Chang, 1989).

Several epidemiological studies have evaluated the risk of cancer associated with chlorinated drinking-water and disinfection by-products. They used a variety of methods

to assess exposure and indicators, generally through surrogates of exposure, such as duration of residence in a household supplied with chlorinated surface water, duration of exposure to chlorinated drinking-water, estimated lifetime level of trihalomethanes, amount of tap-water consumed, type of disinfectant or concentration of relevant by-products (e.g. total trihalomethanes).

The risk for cancer of the urinary bladder was reported in nine case–control studies (Cantor *et al.*, 1987; McGeehin *et al.*, 1993; Vena *et al.*, 1993; King & Marrett, 1996; Freedman *et al.*, 1997; Cantor *et al.*, 1998; Koivusalo *et al.*, 1998; Chevrier *et al.*, 2004; Bove *et al.*, 2007a; Villanueva *et al.*, 2007; Cantor *et al.*, 2010) and three cohort studies (Wilkins & Comstock, 1981; Doyle *et al.*, 1997; Koivusalo *et al.*, 1997). Positive and duration- or dose-dependent associations were reported in all case–control studies and reached statistical significance in all but three of them. One study (Cantor *et al.*, 2010) evaluated gene–environment interactions for glutathione *S*-transferase (GST) and cytochrome P450 (CYP) genes that metabolize disinfection by-products and found them to be statistically significant. A pooled analysis of six case–control studies (Villanueva *et al.*, 2004) showed that the risk for urinary bladder cancer among men increased with increasing exposure to trihalomethanes. The results from the cohort studies were inconsistent: studies reported elevated risks that were only statistically significant for women in one study (Koivusalo *et al.*, 1997) and no dose–response relationships were observed.

Other cancer sites have been evaluated in case–control and cohort studies. Increased risks were identified for cancers of the lung (Doyle *et al.*, 1997), melanoma (Doyle *et al.*, 1997), oesophagus (Koivusalo *et al.*, 1997) and breast (Koivusalo *et al.*, 1997) in cohort studies and cancers of the kidney (Koivusalo *et al.*, 1998), brain (Cantor *et al.*, 1999), melanoma (Nelemans *et al.*, 1994) and non-melanoma skin cancer (Karagas *et al.*, 2008) in case–control studies. These results either need to be replicated or were not statistically significant (non-melanoma skin cancer); there are also concerns about potential bias (melanoma). Findings were null for childhood leukaemia (one case–control study: Infante-Rivard *et al.*, 2001, 2002) and were contradictory for colorectal cancer in case–control (Young *et al.*, 1987; Hildesheim *et al.*, 1998; King *et al.*, 2000; Bove *et al.*, 2007b) and cohort (Doyle *et al.*, 1997; Koivusalo *et al.*, 1997) studies, pancreatic cancer (three case–control studies: Ijsselmuiden *et al.*, 1992; Kukkula & Löfroth, 1997; Do *et al.*, 2005) and different types of adult leukaemia (one case–control study: Kasim *et al.*, 2006).

Cancer in Humans

1. Cohort studies

See Table 1 and Table 2

Wilkins & Comstock (1981) identified increased risks for urinary bladder cancer in men and women and for liver cancer among women, but the risk estimates were not statistically significant, among users of chlorinated surface water versus those of non-chlorinated deep wells. Doyle *et al.* (1997) conducted a study among women only and found a significantly increased risk and a dose–response relationship with levels of chloroform for all cancers, melanoma, and cancers of the colon and lung. Koivusalo *et al.* (1997) identified a significantly increased risk among women for cancers of the urinary bladder, colon, oesophagus and breast with increasing mutagenicity of the water.

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

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Cohort					
Wilkins & Comstock (1981)	Residents of Washington County, MD, USA 30 780 persons (14 553 men, 16 227 women), ≥ 25 yr of age, followed up 1963–75; 52 cases	Chlorinated surface water (average chloroform concentration, 107 µg/L) vs non-chlorinated deep wells	Men Women	**Relative risk** 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 yr, followed up 1986–93; 42 cases	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, 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 revertants/L increase in average exposure to mutagenicity	Men Women	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
Case–control					
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-yr period starting December 1997; 2805 cases, 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/d)	**Duration (yr)** *Men* 0 1–19 20–39 40–59 ≥ 60 *P* for trend *Women* 0 1–19 20–39 40–59 ≥ 60 *P* for trend	**Odds ratio** 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) 0.44 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) 0.02	Adjusted for age, smoking habit, high-risk occupation, population size of usual residence, reporting centre

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
McGeehin *et al.* (1993)	Colorado, USA Incidence 1990–91; 327 cases, 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	**Duration (yr)** 0 1–10 11–20 21–30 > 30	 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 cases, 855 population controls; restricted to white males	Daily intake of tap-water	*No. of cups* 0–5 6–7 8–9 10–39 *P* for trend 0–5 6–7 8–9 10–39 *P* for trend	*Age < 65 yr* 1.00 1.3 (0.7–2.4) 1.6 (0.9–3.0) 2.6 (1.5–4.5) < 0.001 *Age ≥ 65 yr* 1.00 1.3 (0.8–2.1) 1.4 (0.8–2.5) 3.0 (1.8–5.0) < 0.001	Adjusted for age, education, cigarette smoking (pack–yr), and coffee, carotene and non-tap-water intake. [Overlaps with Bove *et al.* (2007a).]
King & Marrett (1996)	Ontario, Canada Incidence, September 1992–May 1994; 696 cases, 1545 population controls (men and women)	Consumption of chlorinated surface drinking-water	**Duration (yr)** 0–9 10–19 20–34 ≥ 35	 1.0 1.04 (0.7–1.5) 1.2 (0.9–1.5) 1.4 (1.1–1.8)	Adjusted for age, sex, log pack–yr of smoking, current smoking, education, calorie intake
		Trihalomethanes–yr	**Quartiles (µg/L–yr)** 0–583 584–1505 1506–1956 1957–6425	 1.0 1.2 (0.9–1.6) 1.08 (0.8–1.4) 1.4 (1.1–1.9)	
		Level of trihalomethanes in water source	**Level (µg/L)** 0–24 25–74 ≥ 75 *P* for trend	 1.0 1.4 (1.0–2.0) 1.7 (1.1–2.5) 0.006	

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Freedman *et al.* (1997)	Washington County, MD, USA Incidence, 1975–92; 294 cases, 2326 population controls	Duration of residence with municipal water source	**Duration (in yr)** *Men (cases)* 0 (54) 1–10 (63) 11–20 (41) 21–30 (31) 31–40 (11) > 40 (9) *Women (cases)* 0 (25) 1–10 (28) 11–20 (15) 21–30 (7) 31–40 (5) > 40 (4)	 1.0 1.1 (0.6–1.9) 1.1 (0.6–1.9) 1.3 (0.7–2.5) 1.5 (0.6–3.3) 2.2 (0.8–5.1) 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)	Adjusted for age, sex, smoking, urbanization
Cantor *et al.* (1998)	Iowa, USA Incidence, 1986–89; 1123 cases, 1983 population controls (men and women)	Total lifetime exposure to trihalomethanes (THM) estimated from lifetime residential histories, water utility survey and measurements of water samples	**THM (g)** *Men* ≤ 0.04 0.05–0.12 0.13–0.34 0.35–1.48 1.49–2.41 ≥ 2.42 *P* for trend *Women* ≤ 0.04 0.05–0.12 0.13–0.34 0.35–1.48 1.49–2.41 ≥ 2.42 *P* for trend	 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) 0.05 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) 0.54	Adjusted for age, study period, education, high-risk occupation, cigarette smoking (6 strata)

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Koivusalo *et al.* (1998)	Finland Incidence, 1991–92; 732 cases (552 men, 180 women), 914 population controls (621 men, 293 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 revertants/L increase in average exposure to mutagenicity among subjects with ≥ 30 yr 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 yr of exposure (net revertants/L)		
			Men		
			Unexposed	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)	
			Women		
			Unexposed	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)	

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Chevrier *et al.* (2004)	France Incidence, 1985–87; 281 cases (240 men, 41 women), 272 controls (233 men, 39 women)	Duration of exposure to ozonated water	*Men (231 cases)*		Adjusted for hospital, age, socioeconomic status, smoking status, coffee consumption, high-risk occupations, tap water consumption, average THM level
			0 yr	1.00	
			1–9 yr	0.58 (0.3–1.3)	
			10–30 yr	0.27 (0.1–0.6)	
			Women (38 cases)		
			0 yr	1.00	
			1–9 yr	0.40 (0.0–7.3)	
			10–30 yr	0.15 (0.0–2.7)	
		Average level of THM in a 30-yr exposure window from 5 to 35 yr before the interview; analysis restricted to subjects with known exposure of at least 70% of the exposure period.	*Men (231 cases)*		Adjusted for hospital, age, socioeconomic status, smoking status, coffee consumption, high-risk occupations, tap water consumption, duration of exposure to ozonated water
			< 1 µg/L	1.00	
			1–5 µg/L	1.32 (0.7–2.6)	
			6–50 µg/L	1.97 (0.8–5.2)	
			> 50 µg/L	3.73 (1.2–11)	
			Women (38 cases)		
			< 1 µg/L	-	
			1–5 µg/L	1.00	
			6–50 µg/L	1.97 (0.2–18)	
			> 50 µg/L	1.55 (0.1–32)	

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Villanueva *et al.* (2007)	Spain Incidence 1998–2001; 1219 cases (1067 men, 152 women), 1271 controls (1105 men, 166 women)	Average THM level in the residences from age 16 until the time of interview; analysis restricted to subjects with known exposure of at least 70% of the exposure window.	*Men (618 cases)*		Adjusted for age, smoking status, education, urbanization of longest residence until age 18 yr, overall quality of the interview, geographical area. [Overlaps with Cantor *et al.* (2010).]
			≤ 8 µg/L	1.00	
			> 8–26 µg/L	1.53 (0.95–2.48)	
			> 26–49 µg/L	2.34 (1.36–4.03)	
			> 49 µg/L	2.53 (1.23–5.20)	
			P for trend	< 0.01	
			Women (89 cases)		
			≤ 8 µg/L	1.00	
			> 8–26 µg/L	0.40 (0.13–1.27)	
			> 26–49 µg/L	1.14 (0.31–4.10)	
			> 49 µg/L	1.50 (0.26–8.61)	
			P for trend	0.61	
		Duration of chlorinated surface water in the residence from age 16 yr until the time of interview; analysis restricted to subjects with known exposure of at least 70% of the exposure window.	*Men (618 cases)*		
			0–3 yr	1.00	
			> 3–25 yr	2.26 (1.19–4.29)	
			> 25–30 yr	2.58 (1.33–5.01)	
			> 30 yr	2.21 (1.17–4.20)	
			P for trend	0.20	
			Women (89 cases)		
			0–3 yr	1.00	
			> 3–25 yr	2.72 (0.56–13.26)	
			> 25–30 yr	2.32 (0.44–12.13)	
			> 30 yr	2.33 (0.51–10.55)	
			P for trend	0.62	

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Cantor *et al.* (2010)	Spain Incidence 1998–2001; 680 cases (595 men, 85 women), 714 controls (622 men, 92 women)	Average THM level in the residences from age 16 yr until the time of interview; analysis restricted to subjects with known exposure of at least 70% of the exposure window.	*GSTT1 present (542 cases)*		Adjusted for age (continuous), sex, smoking status (never/ former/ current), size of the municipality of longest residence until 18 yr of age, education (3 strata), geographical area (6 strata), overall quality of interview. [Overlaps with Villanueva *et al.* (2007).]
			≤ 8 µg/L	1.0	
			> 8–26 µg/L	1.2 (0.7–1.9)	
			> 26–49 µg/L	2.0 (1.2–3.4)	
			> 49 µg/L	2.2 (1.1–4.3)	
			P for trend	0.0072	
			GSTT1 null (136 cases)		
			≤ 8 µg/L	1.0	
			> 8–26 µg/L	1.2 (0.5–2.5)	
			> 26–49 µg/L	1.2 (0.5–2.5)	
			> 49 µg/L	1.0 (0.4–2.5)	
			P for trend	0.28	
			GSTZ1 rs1046428 CT/TT (244 cases)		*P*-value for multiplicative interaction between THM level and: *GSTT1* polymorphism = 0.02; *GSTZ1* polymorphism = 0.02; *CYP2E1* polymorphism = 0.04
			≤ 8 µg/L	1.0	
			> 8–26 µg/L	1.4 (0.7–2.7)	
			> 26–49 µg/L	2.2 (1.1–4.2)	
			> 49 µg/L	2.9 (1.3–6-7)	
			P for trend	0.0043	
			GSTZ1 rs1046428 CC (405 cases)		
			≤ 8 µg/L	1.00	
			> 8–26 µg/L	1.1 (0.7–1.9)	
			> 26–49 µg/L	1.5 (0.9–2.7)	
			> 49 µg/L	1.3 (0.6–2.8)	
			P for trend	0.28	

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Cantor *et al.* (2010) Contd.			*CYP2E1 rs2031920 CC (590 cases)*		
			≤ 8 µg/L	1.0	
			> 8–26 µg/L	1.3 (0.8–2.0)	
			> 26–49 µg/L	2.1 (1.2–3.5)	
			> 49 µg/L	2.0 (1.0–4.1)	
			P for trend	0.014	
			CYP2E1 rs2031920 CT/TT (37 cases)		
			≤ 8 µg/L	1.0	
			> 8–26 µg/L	0.98 (0.4–2.5)	
			> 26–49 µg/L	1.1 (0.4–3.1)	
			> 49 µg/L	0.6 (0.1–2.7)	
			P for trend	0.33	

Table 1 (continued)

Study	Population/end-point	Exposure	Exposure categories	Risk estimate (95% CI)	Comments
Bove *et al.* (2007a)	Western New York, USA Incidence, 1979–85; 129 cases, 256 controls (all men)	THM level at the last residence around 20 yr after recruitment			Adjusted for daily tap-water consumption, age, cigarette smoking (pack–yr), carotene, water consumption from foods, dietary fibre, alcohol. [Overlaps with Vena *et al.* (1993).]
		Total THM			
		1st quartile	≤ 38.04 µg/L	1.00	
		2nd quartile	38.18–52.58 µg/L	1.43 (0.78–2.05)	
		3rd quartile	52.59–73.82 µg/L	1.93 (0.80–2.98)	
		4th quartile	74.10–351.73 µg/L	2.34 (1.01–3.66)	
		Chloroform			
		1st quartile	≤ 17.14 µg/L	1.00	
		2nd quartile	17.42–25.72 µg/L	1.79 (0.81–3.09)	
		3rd quartile	26.15–38.61 µg/L	1.76 (0.91–3.35)	
		4th quartile	38.46–192.52 µg/L	2.55 (1.25–4.66)	
		Bromodichloromethane			
		1st quartile	≤ 9.35 µg/L	1.00	
		2nd quartile	9.40–13.31 µg/L	1.89 (0.95–3.59)	
		3rd quartile	13.35–18.75 µg/L	2.20 (1.12–4.26)	
		4th quartile	18.80–78.93 µg/L	2.49 (1.19–4.48)	
		Dibromochloromethane			
		1st quartile	≤ 4.67 µg/L	1.00	
		2nd quartile	4.68–6.89 µg/L	1.29 (0.77–2.83)	
		3rd quartile	6.90–9.35 µg/L	1.34 (0.78–2.85)	
		4th quartile	9.37–35.62 µg/L	1.17 (0.84–3.03)	
		Bromoform			
		1st quartile	≤ 0.43 µg/L	1.00	
		2nd quartile	0.44–0.73 µg/L	2.12 (1.05–4.17)	
		3rd quartile	0.75–1.14 µg/L	2.34 (1.18–4.57)	
		4th quartile	1.16–41.88 µg/L	3.05 (1.51–5.69)	

CI, confidence interval; d, day or days; THM, trihalomethanes; vs, versus; yr, year or years

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

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

Table 2 (continued)

Reference	Population/follow-up	Exposure	Site (No. of subjects)	Relative risk (95% CI)	Comments
Doyle *et al.* (1997) Contd.			*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; 621 431 persons (307 967 women, 313 464 men)	Chlorinated/unchlorinated water supplies; mutagenicity assessment	*Both sexes*		Adjusted for age, time period, urbanization, social status; cancers of the ureter and urethra included
			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-Hodgkin 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-Hodgkin lymphoma	1.4 (0.98–1.98)	
			Leukaemia	1.08 (0.8–1.5)	

Table 2 (continued)

Reference	Population/follow-up	Exposure	Site (No. of subjects)	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-Hodgkin lymphoma	1.03 (0.8–1.4)	
			Leukaemia	1.02 (0.8–1.3)	

CI, confidence interval; vs, versus; yr, year or years

2. Case–control studies

2.1 Cancer of the urinary bladder

See Table 1

Seven case–control studies of urinary bladder cancer have been reviewed previously (IARC, 2004). Cantor *et al.* (1987) found increased odds ratios for bladder cancer among people with both elevated intakes of drinking-water and long-term consumption of chlorinated surface water. McGeehin *et al.* (1993) found odds ratios that increased with years of exposure to chlorinated water. In a study by Vena *et al.* (1993), the odds ratios for bladder cancer increased with increasing numbers of cups of tap-water consumed daily. 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 unexposed group included subjects with a long duration of exposure to chlorinated drinking-water. This paper did not analyse associations with the water source or the level of trihalomethanes.] King & Marrett (1996) reported odds ratios that increased with increasing duration of use of a chlorinated surface water source. Results for trihalomethanes–years 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 levels of trihalomethanes was observed (P = 0.006). Freedman *et al.* (1997) found that the risk for bladder cancer among men increased with duration of exposure to municipal drinking-water; but the associations were not statistically significant. Cantor *et al.* (1998) reported that odds ratios increased with increasing total lifetime dose of trihalomethanes for men but not for women. Results for average lifetime dose of trihalomethanes followed similar patterns. Koivusalo *et al.* (1998) identified a small, non-significant excess risk for bladder cancer for an increase in mutagenicity of 3000 net revertants/L in men and women. The odds ratio for categories of increasing exposure did not show a consistent exposure–response relationship.

Chevrier *et al.* (2004) analysed data from a hospital-based case–control study conducted in seven hospitals in France. Information on water source and treatment was collected retrospectively in the study areas and mean levels of trihalomethanes were assigned to the different combinations of water source and treatment as predicted by an experimental model. The risk for bladder cancer decreased as duration of exposure to ozonated water increased with a statistically significant dose–response relationship. [The Working Group noted that, in general, chlorinated by-products decrease as the level of ozonation increased.] The risk for bladder cancer increased with duration of exposure to chlorinated surface water and with the estimated trihalomethanes content of the water, but the dose–response relationship was not statistically significant. Results were similar among men and women.

The hospital-based case–control study conducted in Spain by Villanueva *et al.* (2007) evaluated lifetime exposure to trihalomethanes through different exposure situations involving ingestion, inhalation and dermal absorption. Study subjects were interviewed and provided individual information on water-related habits and residential history from birth. Levels of trihalomethanes, water source history and year when chlorination started in the study areas were ascertained through measurements from drinking-water samples and questionnaires to water companies and local authorities. Historical annual average level of trihalomethanes was calculated in the study municipalities and was linked to study subjects by year and municipality of residence (Villanueva *et al.*, 2006). Positive associations between lifetime exposure to trihalomethanes were observed among men and null associations were observed among women.

The combined influence of exposure to disinfectant by-products and genetic variants in the metabolic pathways of trihalomethanes was investigated in the Spanish study by Cantor *et al.* (2010). Polymorphisms in GST (*GSTT1*, *GSTZ1*) and CYP (*CYP2E1*) genes that are metabolizing enzymes of trihalomethanes were considered. Results showed that polymorphisms in these genes modified the disinfectant by-product-related risk for bladder cancer. Associations between trihalomethanes and bladder cancer were stronger among subjects who were *GSTT1*$^{+/+}$ or $^{+/-}$ versus *GSTT1* null, *GSTZ1* rs1046428 CT/TT versus CC, or *CYP2E1* rs2031920 CC versus CT/TT. Among the 195 cases and 192 controls with high-risk forms of *GSTT1* and *GSTZ1*, the odds ratios for quartiles 2, 3 and 4 of trihalomethanes were 1.5 (95% confidence interval [CI], 0.7–3.5), 3.4 (95% CI: 1.4–8.2) and 5.9 (95% CI: 1.8–19.0), respectively.

Bove *et al.* (2007a) re-analysed the population in the study by Vena *et al.* (1993) by including newly estimated indices of exposure to trihalomethanes. Assessment of exposure to disinfectant by-products was based on measurements of trihalomethanes in 1998–2003, which were assigned to study subjects by residence at time of interview (1979–85). A positive association was observed for total trihalomethanes, chloroform, bromodichloromethane, dibromochloromethane and bromoform. [The Working Group noted that there could be potential exposure misclassification due to the exposure assessment based on measurements of trihalomethanes conducted 20 years after the recruitment of study subjects.]

2.2 Cancer of the colorectum

See Table 3

Four case–control studies on colorectal cancer were reviewed previously (IARC, 2004). Cragle *et al.* (1985) reported a statistically significantly positive association with years of living in a residence with chlorinated versus non-chlorinated water. Young *et al.* (1987) concluded that exposure to trihalomethanes was not associated with colon cancer in the state of Wisconsin, USA. Hildesheim *et al.* (1998) reported an increased risk for rectal cancer with average lifetime dose of trihalomethanes. No such trend was observed for colon cancer. King *et al.* (2000) reported increased risks for colon cancer among men exposed to increasing levels of trihalomethanes and with increasing years of chlorinated drinking-water consumption. This effect was not observed in women. There was no association between the risk for rectal cancer and the number of years of exposure to water containing elevated levels of trihalomethanes in either sex.

Bove *et al.* (2007b) evaluated the risk for rectal cancer associated with exposure to total and specific trihalomethanes in a subset of the Upstate New York Diet Study (USA). Cases were identified from hospital pathology records and controls were identified from control groups of other cancer studies for five other unrelated sites (oral cavity, oesophagus, stomach, larynx, and lung). Measurements of trihalomethanes conducted from 1998 to 2003 for a separate independent study by Monroe County Department of Health were used to assign levels at the taps of study subjects in the last residence. The spatial patterns of trihalomethanes and individual measurements of tap-water consumption provided estimates of ingested trihalomethanes. Results indicated that the risk for rectal cancer did not increase with increasing levels of chloroform. Increasing odds ratios for rectal cancer were associated with increasing levels of bromoform consumed at the residence. Ingestion of chlorodibromomethane and bromodichloromethane was marginally associated with an increase in risk. [The use of cancer controls raises some concerns on potential selection bias. The exposure assessment based on non-contemporaneous measurements raises concerns on potential exposure misclassification.]

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

Study	Population/end-point	Exposure		Odds ratio (95% CI)	Comments
Young *et al.* (1987)	Wisconsin, USA Incidence, 1951–81; 347 colon cancer cases; 639 other cancer controls; 611 population controls; age, 35–90 yr (both sexes)	Total concentration of trihalomethanes at place of residence (μg/L) in 1951	< 10	1.0	Odds ratio for colon cancer adjusted for sex, age, population size of place of residence; general population controls
			10–40	1.2 (0.6–2.3)	
			> 40	0.98 (0.4–2.3)	
		Cumulative total exposure to trihalomethanes (mg) over lifetime	< 100	1.0	
			100–300	1.1 (0.7–1.8)	
			> 300	0.7 (0.4–1.2)	
Hildesheim *et al.* (1998)	Iowa, USA Incidence, 1986–89; 560 colon cancer cases; 537 rectal cancer cases; 1983 population controls; age, 40–85 yr (both sexes)	Total lifetime exposure to trihalomethanes (g)	≤ 0.04	1.0	Rectal cancer; adjusted for age, sex; *P* for trend = 0.08
			0.05–0.12	1.3 (1.0–1.6)	
			0.13–0.34	1.3 (0.9–1.8)	
			0.35–1.48	1.5 (1.1–2.1)	
			1.49–2.41	1.9 (1.2–3.0)	
			≥ 2.42	1.6 (1.0–2.6)	
		Lifetime average concentration of trihalomethanes (μg/L)	≤ 0.7	1.0	Rectal cancer; adjusted for age, sex; *P* for trend = 0.01
			0.8–2.2	1.05 (0.8–1.4)	
			2.3–8.0	1.2 (0.9–1.7)	
			8.1–32.5	1.2 (0.9–1.7)	
			32.6–46.3	1.7 (1.1–2.6)	
			≥ 46.4	1.7 (1.1–2.6)	

Table 3 (continued)

Study	Population/end-point	Exposure		Odds ratio (95% CI)	Comments
King *et al.* (2000)	Southern Ontario, Canada Incidence, 1992–94; 767 colon cancer cases; 661 rectal cancer cases; 1545 population controls; age, 30–74 yr (both sexes)	Consumption of chlorinated drinking-water (yr)		*Men*	Colon cancer; adjusted for sex, age, education, body mass index, intake of energy, cholesterol, calcium, alcohol, coffee
			0–9	1.0	
			10–19	1.7 (1.1–2.7)	
			20–34	1.3 (0.96–1.9)	
			≥ 35	1.5 (1.1–2.1)	
				Women	
			0–9	1.0	
			10–19	0.6 (0.3–0.9)	
			20–34	0.9 (0.6–1.2)	
			≥ 35	0.7 (0.5–1.1)	
		Level of trihalomethanes (μg/L)		*Men*	*P* for trend = 0.005
			0–24	1.0	
			25–74	1.5 (0.99–2.4)	
			≥ 75	1.9 (1.2–3.1)	
				Women	*P* for trend = 0.211
			0–24	1.0	
			25–74	0.5 (0.3–0.8)	
			≥ 75	0.9 (0.5–1.7)	
		Exposure to trihalomethanes ≥ 75 μg/L (yr)		*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)	
Bove *et al.* (2007b)	Western New York, USA Incidence, 1979–85; 128 rectal cancer cases, 253 controls (men)	Level of trihalomethanes at the residence approximately 20 yr after recruitment (1998–2003) weighted by the amount of tap-water consumed; bromoform (μg/d)	0.90–0.64	1.00	Adjusted for alcohol, β-carotene, total calories
			0.65–0.97	1.42 (0.73–2.74)	
			0.98–1.68	1.63 (0.85–2.69)	
			1.69–15.43	2.32 (1.22–4.39)	

CI, confidence interval; d, day or days; yr, year or years

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

Cancer site	Study	Population/end-point	Exposure	Odds ratio (95% CI)	Comments
Kidney	Koivusalo *et al.* (1998)	Finland Incidence 1991–92; 703 cases (386 men, 317 women), 914 population controls (621 men, 293 women)	Mutagenicity assessment; 3 000 net revertants/L increase	≥ 30 yr 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 yr of known exposure; adjusted for age, smoking, socioeconomic status, sex
			Tertiles of exposure (net revertants/L)		
				Women	
			Unexposed	1.0	
			Low (1–999)	0.9 (0.6–1.5)	
			Medium (1000–2499)	1.3 (0.8–2.1)	
			High (≥ 2500)	1.1 (0.7–1.9)	
				Men	
			Unexposed	1.0	
			Low	1.2 (0.8–1.7)	
			Medium	1.3 (0.8–1.8)	
			High	1.6 (1.0–2.4)	
Brain	Cantor *et al.* (1999)	Residents of Iowa, USA Incidence 1984–87; 291 glioma cases (155 men, 136 women); 1983 population controls (1308 men, 675 women); aged 40–85 yr	Chlorinated surface water; water utilities surveyed, measurements of trihalomethanes, personal questionnaire for past exposure; yr of exposure to ≥ 75 µg/L		Adjusted for sex, age, farming occupation, 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
				Both sexes	
			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	
				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 (continued)

Cancer site	Study	Population/end-point	Exposure	Odds ratio (95% CI)	Comments
	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 concentration of trihalomethanes (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	
				Both sexes	
			≤ 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	
Pancreas	Ijsselmuiden *et al.* (1992)	Washington County, MD, USA Incidence 1975–89; 101 cases (47 men, 54 women), 206 population controls (96 men, 110 women); all white	Chlorinated drinking-water, as of 1975 census		Adjusted for age, current cigarette smoking; non-municipal but chlorinated water used as baseline for odds ratios
			Non-municipal (chlorinated)	1.0	
			Municipal (chlorinated)	2.2 (1.2–3.95)	

Table 4 (continued)

Cancer site	Study	Population/end-point	Exposure	Odds ratio (95% CI)	Comments
	Kukkula & Löfroth (1997)	Turku area, Finland (220 000 persons) Incidence 1989–91; 183 cases (71 men, 112 women), 360 matched controls	Residence in an area supplied by chlorinated drinking-water until 1981 *Exposure (yr)* 0 1 5 10 15 20	 0.33 (0.2–0.7) 0.54 (0.3–1.2) 0.66 (0.3–1.3) 0.53 (0.3–1.07) 0.32 (0.1–0.8) 0.20 (0.04–0.9)	No adjustment for confounders; odds ratio calculated from exposure data of the discordant case–control set; total trihalomethanes often > 200 µg/L at end of distribution system
	Do *et al.* (2005)	Canada (provinces of Nova Scotia, Ontario, Manitoba, Saskatchewan, Alberta and British Columbia) Incidence 1994–1997; 576 cases (324 men, 252 women), 4105 matched controls (2066 men, 2039 women)	Total level of trihalomethanes (µg/L), for an exposure time window of 30 yr, ending 3 yr before the interview < 10 10–20 20–50 > 50 *P* for trend	 *Both sexes (476 cases)* 1.00 0.88 (0.67–1.17) 1.07 (0.83–1.39) 0.86 (0.58–1.28) 0.61	Adjusted for sex, age, province of recruitment, body mass index, per cent weight change, smoking, coffee, beer, alcohol, total fat intake, total energy intake

Table 4 (continued)

Cancer site	Study	Population/end-point	Exposure	Odds ratio (95% CI)	Comments
Acute lymphocytic leukaemia	Infante-Rivard *et al.* (2001)	Province of Québec, Canada Incidence 1980–93; 491 cases aged 0–9 yr, 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, level of education
			Water chlorination	*Prenatal*	
			Part of the time	1.6 (0.7–3.7)	
			Always	0.8 (0.5–1.2)	Baseline: never
			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)	
			Water chlorination	*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)	Province of Québec, Canada Incidence 1980–83; 161 cases from earlier study (2001)	*GSTT1*-null; total trihalomethanes > 95th percentile		Case-only study, 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)	

Table 4 (continued)

Cancer site	Study	Population/end-point	Exposure	Odds ratio (95% CI)	Comments
Leukaemia (adults); acute (myelocytic and lymphocytic), chronic (myelocytic, lymphocytic, and hairy cell), and non-specified leukaemia	Kasim *et al.* (2006)	Canada (provinces of Prince Edward Island, Nova Scotia, Ontario, Manitoba, Saskatchewan, Alberta, Newfoundland and British Columbia) Incidence 1994–97; 686 total leukaemia cases (421 men, 265 women), 91 chronic myelocytic leukaemia (48 men, 43 women), 161 acute myelocytic leukaemia (90 men, 71 women), 323 chronic lymphocytic leukaemia (217 men, 106 women), 23 acute lymphocytic leukaemia (13 men, 10 women), 48 hairy cell leukaemia (34 men, 14, women) and 3 240 controls (1 580 men, 1 660 women)	Duration of exposure to chlorinated surface water	*All leukaemia (686 cases)*	Adjusted alternately for age, gender, occupational exposure to benzene, ionizing radiation, body mass index, passive smoking, pack–yr of smoking, education
			Never exposed	1.00	
			1–28 yr	1.15 (0.88–1.51)	
			29–35 yr	1.02 (0.78–1.34)	
			> 35 yr	0.84 (0.63–1.97)	
			P for trend	0.07	
				Chronic myelocytic leukaemia (91 cases)	
			Never exposed	1.00	
			1–28 yr	1.86 (0.79–4.36)	
			29–35 yr	2.14 (0.92–4.94)	
			> 35 yr	2.20 (0.93–5.23)	
			P for trend	0.09	
				Acute myelocytic leukaemia (161 cases)	
			Never exposed	1.00	
			1–28 yr	1.48 (0.85–2.59)	
			29–35 yr	1.45 (0.84–2.50)	
			> 35 yr	1.09 (0.60–1.97)	
			P for trend	0.93	
				Chronic lymphocytic leukaemia (323 cases)	
			Never exposed	1.00	
			1–28 yr	1.10 (0.77–1.59)	
			29–35 yr	0.92 (0.64–1.31)	
			> 35 yr	0.69 (0.47–1.02)	
			P for trend	0.02	

Table 4 (continued)

Cancer site	Study	Population/end-point	Exposure	Odds ratio (95% CI)	Comments
	Kasim *et al.* (2006) Contd.		Total concentration of trihalomethanes in a 40-yr exposure window (analysis restricted to subjects with 30 or more yr of known level)	*All leukaemia (419 cases)*	Adjusted alternately for age, gender, occupational exposure to benzene, ionizing radiation, daily tap-water consumption, body mass index, passive smoking, pack–yr of smoking, education
				≤ 20 µg/L	1.00
				> 20–40 µg/L	0.80 (0.55–1.17)
				> 40 µg/L	0.90 (0.70–1.10)
				P for trend	0.14
				Chronic myelocytic leukaemia (56 cases)	
				≤ 20 µg/L	1.00
				> 20–40 µg/L	0.90 (0.32–2.58)
				> 40 µg/L	1.76 (1.01–3.10)
				P for trend	0.04
				Acute myelocytic leukaemia (96 cases)	
				≤ 20 µg/L	1.00
				> 20–40 µg/L	0.90 (0.42–1.80)
				> 40 µg/L	1.03 (0.68–1.60)
				P for trend	0.80
				Chronic lymphocytic leukaemia (199 cases)	
				≤ 20 µg/L	1.00
				> 20–40 µg/L	0.63 (0.36–1.10)
				> 40 µg/L	0.73 (0.51–0.97)
				P for trend	0.03

Table 4 (continued)

Cancer site	Study	Population/end-point	Exposure	Odds ratio (95% CI)	Comments
Melanoma	Nelemans *et al.* (1994)	the Netherlands, mideastern Incidence 1988–90; 128 cases, 168 controls (other types of malignancies); sex unspecified	Swimming in pools (vs not swimming or swimming only in lakes or fens) at different ages		Adjusted for age, gender, educational level, hair colour, freckling, tendency to burn, exposure to sun light
			< 15 yr (*n* = 73 cases)	2.20 (1.05–4.62)	
			15–25 yr (*n* = 76 cases)	2.46 (1.21–5.00)	
			> 25 yr (*n* = 84 cases)	1.01 (0.51–2.01)	
			Age at which swimming was learned (127 cases)		
			> 12 yr (or never)	1.00	
			9–12 yr	1.87 (0.91–3.78)	
			< 9 yr	2.22 (1.16–4.26)	
Skin cancer (basal-cell carcinoma and squamous-cell carcinoma)	Karagas *et al.* (2008)	New Hampshire (USA) Incidence 1993–95; 603 basal-cell carcinoma cases, 293 squamous-cell carcinoma cases, 540 controls	Water source and total level of trihalomethanes	*Basal-cell carcinoma (545 cases)*	Adjusted for age, gender, skin sensitivity to the sun (i.e. tendency to sunburn); further adjustment for toenail arsenic did not affect the results.
			Private	1.1 (0.7–1.8)	
			Public		
			< 1 µg/L	1.0 (referent)	
			≥ 1–20 µg/L	0.9 (0.6–1.5)	
			> 20–40 µg/L	1.1 (0.7–1.8)	
			> 40 µg/L	2.4 (0.9–6.7)	
				Squamous-cell carcinoma (266 cases)	
			Private	1.1 (0.6–1.9)	
			Public		
			< 1 µg/L	1.0 (referent)	
			≥ 1–20 µg/L	0.9 (0.5–1.6)	
			> 20–40 µg/L	1.3 (0.7–2.3)	
			> 40 µg/L	2.1 (0.7–7.0)	

CI, confidence interval; d, day or days; vs, versus; yr, year or years

2.3 Cancer at other sites

See Table 4

(a) Cancer of the kidney

Koivusalo *et al.* (1998) identified an exposure-related excess risk among men only for a 3000-net revertants/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) Cancer of the brain

Cantor *et al.* (1999) reported elevated risks among men, but not women, with duration of exposure to 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. There was no association with average levels of trihalomethanes among women.

(c) Cancer of the pancreas

Ijsselmuiden *et al.* (1992) classified subjects as users of chlorinated non-municipal or chlorinated municipal drinking-water, which yielded an odds ratio of 2.2 (95% CI: 1.2–3.95) for users of municipal water compared with those of non-municipal water. [The Working Group noted that the information collected in the census on residence and source of drinking-water was cross-sectional.] Kukkula & Löfroth (1997) found that 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 duration 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 before diagnosis was short.]

Do *et al.* (2005) reported results from a population-based case–control study derived from the National Enhanced Cancer Surveillance System of Canada. Study subjects were aged between 30 and 75 years. Cases were histologically confirmed and identified from six provincial cancer registries. Controls were frequency matched to the overall case group on age (5-year groups) and sex. Exposure to chlorination by-products was estimated by linking lifetime residential histories to two different databases containing information on levels of disinfectant by-products in municipal water supplies from routine surveys conducted in the past (back to 1962). A null association with exposure to trihalomethanes, bromodichloromethane or chloroform (all odds ratios, < 1.3) was observed for men and women separately and overall. Null findings were also obtained assuming a latency period for pancreatic cancer induction of 3, 8 or 13 years.

(d) Childhood leukaemia

Infante-Rivard *et al.* (2001) reported no consistent associations for chlorinated water consumption or cumulative exposure to trihalomethanes during the prenatal period, as well as the postnatal period. Subsequently, Infante-Rivard *et al.* (2002) conducted a case–case analysis among persons for whom data were available on exposure and genotypes of *GSTT1* and *CYP2E1*, genes that are involved in the metabolism of trihalomethanes. The results identified different risks by genotype.

(e) Adult leukaemia

Kasim *et al.* (2006) conducted a population-based case–control study in Canada using data available in the Canadian National Enhanced Cancer Surveillance System. Cases were histologically confirmed leukaemia patients aged 20–74 years identified from eight provincial cancer registries. Controls were identified from population-based records and were age-/sex-frequency matched to cases. Eligible subjects were contacted and mailed questionnaires (response rates: 70%

of cases, 63% of controls). Personal residential histories and the main source of drinking-water were ascertained. Data on trihalomethanes were as collected from different routine monitoring surveys. Individual exposures were assigned by linking the subjects' residences to the data on trihalomethanes by time and geographical area. Individual exposures to disinfection by-products were estimated for the 40-year period before the interview. The analysis included subjects for whom water quality information was available for at least 30 years. Results differed among subtypes of leukaemia. Duration of exposure to chlorinated surface water was positively associated with chronic myelocytic leukaemia, negatively associated with acute lymphocitic, chronic lymphocytic and hairy-cell leukaemia, and was not associated with acute myelocytic or all leukaemia. None of the point estimates or *P*-values for linear trend was statistically significant. Risk for chronic myeloid leukaemia increased with concentration of total trihalomethanes. A protective effect was observed for chronic lymphoid leukaemia for the highest category of trihalomethane concentration (> 40 versus ≤ 20 µg/L).

(f) Melanoma and non-melanoma skin cancer

Nelemans *et al.* (1994) conducted a case–control study of melanoma and enrolled patients aged between 25 and 70 years identified from a population-based cancer registry that covers 95% of tumours in the mid-eastern part of the Netherlands. Controls were patients with urogenital cancers (65%), non-Hodgkin lymphomas (24%) and laryngeal carcinomas (11%). Study subjects were interviewed within 1 year after diagnosis, and the response rate was 80% among cases and 47% among controls. Information on aquatic leisure-time activities (age when they learned to swim, frequency of swimming in different type of pools) was collected. A physical examination was conducted to assess the skin, hair and eye colour, degree of freckling and number of naevi on the back. Swimming in pools before 15 years or between 15 and 25 years of age was associated with an increased risk for melanoma. Younger age at learning to swim was associated with higher odds ratios for melanoma. [Although the results are suggestive of a potential association, they should be interpreted cautiously because of potential recall bias and potential selection bias due to the low response rates among controls and the use of cancer controls. Although these analyses were adjusted for exposure to sunlight, potential residual confounding by ultraviolet radiation cannot be ruled out.]

Karagas *et al.* (2008) published a preliminary analysis on the risk for skin cancer associated with exposure to trihalomethanes in a population-based case–control study conducted in New Hampshire (USA). They used data obtained in a previous population-based case–control study of keratinocyte-derived malignancies (basal-cell carcinoma and squamous-cell carcinoma) originally designed to examine the effects of arsenic in drinking-water. The study comprised cases and controls aged 25–74 years (response rates: 83% of cases, 69% of controls). Participants completed a self-administered work and residential history calendar and provided information on water supply at lifetime residences together with other risk factors (e.g. sun exposure, smoking history) in a structured interview. Average levels of trihalomethanes were computed from samples taken from public water systems between 1984 and 1994 that were assigned by subjects' residence at their reference date (date of diagnosis of the cases and a comparable date for controls). Increased odds ratios were identified among those in the highest category of exposure to trihalomethanes, but results were not statistically significant and there was no exposure–response trend. [The Working Group noted that there was potential exposure misclassification from the use of average values for multiple water utilities and applying these values to a specific individual, which would limit the power to detect an effect.]

Table 5 Meta-analyses and pooled analysis of cancer and exposure to chlorinated drinking-water

Study	Population/end-point	No. of subjects	Exposure		Risk estimate	Comments
Meta-analyses						
Multiple cancer sites				Site (No. of studies)		
Morris *et al.* (1992)	Mortality and morbidity studies; individual-based information on exposure and covariates	10 case–control and 2 cohort studies	Consumers of drinking-water containing chlorination by-products vs non-consumers	Urinary bladder (n = 7)	1.21 (1.09–1.34)	
				Brain (n = 2)	1.29 (0.53–3.14)	
				Breast (n = 4)	1.18 (0.90–1.54)	
				Colon (n = 7)	1.11 (0.91–1.35)	
				Colorectal (n = 8)	1.15 (0.97–1.37)	
				Oesophagus (n = 5)	1.11 (0.85–1.45)	
				Kidney (n = 4)	1.16 (0.89–1.51)	
				Liver (n = 4)	1.15 (0.94–1.40)	
				Lung (n = 5)	1.01 (0.86–1.18)	
				Pancreas (n = 6)	1.05 (0.91–1.22)	
				Rectum (n = 6)	1.38 (1.01–1.87)	
				Stomach (n = 6)	1.14 (0.94–1.38)	
				All sites	1.15 (1.09–1.20)	
Urinary bladder cancer						
Villanueva *et al.* (2003)	Individual-based studies of incident bladder cancer cases including data on long-term patterns of water consumption; studies conducted in North America and Europe	6 case–control studies (6084 cases, 10 816 controls) and 2 cohort studies (124 cases)	Consumption of chlorinated drinking-water was associated with an increased risk	Ever exposure	*Men* 1.4 (1.1–1.9) *Women* 1.2 (0.7–1.8) *Both sexes*	These estimates are based on 5 studies
				20 yr	1.13 (1.08–1.20)	
				40 yr	1.27 (1.15–1.43)	
				60 yr	1.43 (1.27–1.72)	

Table 5 (continued)

Study	Population/end-point	No. of subjects	Exposure		Risk estimate	Comments
Colorectal cancer						
Rahman *et al.* (2010)	Case–control or cohort studies on colorectal cancer with an assessment of exposure to disinfectant by-products reporting relative risks or odds ratios	13 studies (10 case–control, 3 cohort)	Mixed exposure variables: chloroform levels, trihalomethanes levels, chlorine dose, duration of exposure to chlorinated water	Highest versus lowest exposure category		
				Colon cancer		
				Cohort studies	1.11 (0.73–1.70)	
				Case–control studies	1.33 (1.12–1.57)	
				All studies	1.27 (1.08–1.50)	
				Rectal cancer		
				Cohort studies	0.88 (0.57–1.35)	
				Case–control studies	1.40 (1.15–1.70)	
				All studies	1.30 (1.06–1.59)	
Pooled analysis						
Urinary bladder cancer						
Villanueva *et al.* (2003)	Case–control studies with incident bladder cancer cases with evaluation of personal long-term exposure to trihalomethanes	6 studies (2 from the USA, and 1 from Canada, Finland, France and Italy); analysis included 2806 cases and 5254 controls	Average trihalomethanes level in the residences from 45 to 5 yr before the interview, with known data of at least 70% of the exposure window	*Men (n = 2126)*		Adjusted for study, age, smoking status, ever worked in high-risk occupations, heavy coffee consumption (> 5 cups/d), education, total fluid intake
				≤ 1 µg/L	1.00	
				> 1–5 µg/L	1.10 (0.92–1.31)	
				> 5–25 µg/L	1.26 (1.05–1.51)	
				> 25–50 µg/L	1.25 (1.04–1.50)	
				> 50 µg/L	1.44 (1.20–1.73)	
				P for trend	< 0.001	
			Duration of exposure to chlorinated surface water (yr), with known data ofat least 70% of the exposure window	*Women (n = 603)*		Adjusted for study, age, smoking status, ever worked in high-risk occupations, heavy coffee consumption (> 5 cups/d), education
				≤ 1 µg/L	1.00	
				> 1–5 µg/L	0.99 (0.72–1.36)	
				> 5–25 µg/L	0.86 (0.63–1.18)	
				> 25–50 µg/L	1.04 (0.76–1.43)	
				> 50 µg/L	0.93 (0.67–1.28)	
				P for trend	0.753	

Table 5 (continued)

Study	Population/end-point	No. of subjects	Exposure		Risk estimate	Comments
Villanueva *et al.* (2003) Contd.				*Men (n = 692)*		
				0 yr	1.00	
				> 0–7 yr	1.40 (1.02–1.94)	
				> 7–15 yr	1.01 (0.74–1.37)	
				> 15–30 yr	1.67 (1.22–2.29)	
				> 30–40 yr	1.62 (1.21–2.16)	
				P for trend	< 0.001	
				Women (n = 174)		
				0 yr	1.00	
				> 0–7 yr	0.83 (0.47–1.47)	
				> 7–15 yr	1.24 (0.72–2.15)	
				> 15–30 yr	0.60 (0.32–1.12)	
				> 30–40 yr	1.08 (0.62–1.88)	
				P for trend	0.725	

CI, confidence interval; d, day or days; vs, versus; yr, year or years

3. Meta-analyses and pooled analyses

See Table 5

Morris *et al.* (1992) reviewed the literature on cancer mortality and morbidity for any cancer site related to exposure to chlorination by-products. Studies that identified morbidity or mortality and provided information on exposure and potential confounders at the individual level (i.e. case–control or cohort studies) were included in a meta-analysis. Two independent readers scored each paper for quality. Studies were scored on the basis of selection of subjects, measurement of and adjustment for confounding variables, exposure assessment and statistical analysis. These quality scores were used to conduct subanalyses using different subsets of studies. The odds ratios or relative risks for cancer among consumers of drinking-water containing chlorination by-products were identified for each of the selected studies. The meta-analysis showed a significant association for all cancers overall and specifically for cancers of the urinary bladder and rectum.

In a meta-analysis, Villanueva *et al.* (2003) evaluated individual consumption of chlorinated drinking-water and incident cases of urinary bladder cancer. They focused on epidemiological studies including incident cases and individual information on long-term patterns of water consumption. The studies used provided information on residential history obtained from individual interviews linked with water source. Summary risk estimates were provided for intermediate and long-term (> 40 years) consumption of chlorinated water, stratified by sex when possible. Results indicated that long-term consumption of chlorinated drinking-water was associated with an increased risk for bladder cancer, particularly in men. Ever consumption of chlorinated drinking-water was associated with an increased risk of bladder cancer in men and women. An estimate was calculated that summarized the slopes of dose–response analyses and a positive duration–response relationship was observed.

A pooled analysis by Villanueva *et al.* (2004) re-evaluated the risk for urinary bladder cancer from six case–control studies with available data [of seven eligible studies] that used trihalomethanes as a marker of exposure to disinfection by-products and included individual data on water consumption. The methodology used to evaluate long-term exposure to trihalomethanes differed among studies and a common 40-year exposure window was created, from 45 to 5 years before the interview. Cumulative exposure to trihalomethanes was estimated by combining individual year-by-year average levels of trihalomethanes and daily tap-water consumption. Among men, risk increased with increasing exposure to trihalomethanes.

Rahman *et al.* (2010) performed a meta-analysis of colorectal cancer and exposure to disinfection by-products. The authors conducted a literature search to identify case–control or cohort studies that reported relative risks or odds ratios (or data that allowed their estimation) and an assessment of exposure to disinfectant by-products. Relative risks or odds ratios comparing the highest exposure category with the lowest were extracted from studies that met the inclusion criteria and were pooled using random effects methods. The results show an increased risk for colon and rectal cancers. [The Working Group noted that this meta-analysis included studies with poor exposure assessment.]

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