

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

EPIDEMIOLOGICAL STUDIES OF CHLORINATED DRINKING WATER AND CANCER

Introduction

1. COC is asked to advise whether revision of the May 1999 COC statement³ on chlorinated water and cancer is required in the light of recent published epidemiological studies.^{1 2 4-14}

Background

2. In May 1999, COC published a statement³ on chlorinated drinking water and cancer (see Annex A). The statement noted that:

“In the United Kingdom, North America, and many other countries, chlorination has long been an important part of water treatment, intended to ensure that drinking-water contains no microbes hazardous to human health. In the mid-1970s, refinements in techniques of chemical analysis resulted in the detection in drinking-water of traces of chemicals formed when organic chemicals (such as those which may occur naturally in rivers, lakes, reservoirs and other water sources) are subjected to chlorination. In drinking-water, each of these chlorination byproducts (CBPs) is typically present at a concentration below 1 part per billion (1 µg/l). Some, however, such as the trihalomethanes (THMs, ie chloroform, bromodichloromethane, chlorodibromomethane and bromoform), are often present at concentrations between 10 and 100 µg/l. Numerous CBPs have been identified, but many have yet to be detected or characterised. Some CBPs, including some of the THMs, are known to be carcinogenic in laboratory mammals given doses far greater than human intakes from drinking-water. Some CBPs are genotoxic in test systems..... There have been many epidemiological investigations into the possible association between chlorination of drinking-water and cancer in humans and also many experimental studies regarding the mutagenicity and carcinogenicity of CBPs.....”

3. COC reviewed the published studies and concluded that:

“Overall, the further epidemiological studies fail to provide persuasive evidence of a consistent relationship between chlorinated drinking-water and cancer. It remains possible that there may be an association between chlorinated drinking water and cancer which is obscured by problems such as the difficulty of obtaining an adequate estimate of exposure to chlorination byproducts, misclassification of source of drinking-water (including the use of bottled water), failure to take adequate account of confounding factors (such as smoking status), and errors arising from non-participation of subjects. We therefore consider that efforts to minimise exposure to

chlorination byproducts remain appropriate, providing that they do not compromise the efficiency of disinfection of drinking-water.”

4. Thirteen further relevant epidemiological papers^{1 2 4-14} have been published since the 1999 COC statement. These were identified from a literature review of human studies conducted from 1998 to May 2007. The databases searched were MEDLINE and TOXLINE, using the terms: drinking water AND cancer, trihalomethane* AND cancer, chlorinated byproduct* AND cancer, chlorinated drinking water AND cancer. All these were combined. Sixty-four references were identified from which the 13 epidemiological papers were selected for full review. Six of the papers concern bladder cancer (three of these are pooled analyses or meta-analyses of overlapping sets of papers, most of which have already been considered by COC). One paper concerns colon and rectal cancers. Two papers concern childhood acute lymphoblastic leukaemia, and one concerns adult leukaemias. One each investigates brain cancer and pancreatic cancer. A retrospective cohort study examines mortality from a wide range of cancers, including bladder, colon, rectum, brain, pancreas, and lymphatic leukaemia. Two studies investigated micronuclei in urinary bladder cells.

5. The eight original cancer epidemiology studies are summarised in detail in a table attached at Annex B, and all papers are briefly summarised below.

Bladder cancer

6. In its 1999 statement, COC commented that:

“Previous epidemiological studies have suggested associations between bladder cancer and CBPs, and eleven of the twenty recent studies have investigated this hypothesis.....These recent studies of bladder cancer do not show any consistent dose-response relationship with estimated exposures to CBPs or THMs.”

7. *Ranmuthugala et al (2003)*⁹ undertook a cohort study in 1997 of men in three Australian communities with varying levels of CBPs in the water supply. Exposure was assessed using both available dose (total THM concentration in the water supply) and intake dose (calculated by adjusting for individual variations in ingestion, inhalation, and dermal absorption). Micronuclei in urinary bladder epithelial cells were used as a preclinical biomarker of genotoxicity. Cells were scored for micronuclei for 228 participants, of whom 63% were exposed to CBPs and 37% were unexposed. The available dose of total THM for the exposed group ranged from 38 to 157 µg/L, whereas intake dose ranged from 3 to 469 µg/kg per day. This study provided no evidence that THM concentrations, at the levels investigated, were associated with DNA damage to bladder cells.

8. In contrast, in a study of 72 female control subjects from a case-control study in Spain, *Villanueva et al (2007)*¹¹ reported that the frequency of micronuclei in “exfoliated urine cells” was associated with THM exposure among the study controls, although, in most analyses, these results were not statistically significant. Women exposed to residential THM levels above the median (26 µg/L) had a 70 percent increased probability of a frequency of micronuclei above the median (9/1,000) compared with those exposed to lower THM levels. Higher associations were

reported for THM exposure through showering and bathing. The odds ratio (OR) adjusted for age and smoking status was 3.34 (95 percent confidence interval [CI] 0.90-2.39) for exposure above 200 [($\mu\text{g/L THMs}$) \times (minutes/day)], relative to below 200, during showering or bathing. Additional adjustment for geographic study area led to an OR of 13.7 (95 % CI 1.39-135).

9. In the parent 1998-2001 case-control study in Spain, lifetime personal information on water consumption and water-related habits was collected for 1,219 cases and 1,271 controls and was linked with THM levels in geographic study areas. Long-term THM exposure was associated with a twofold bladder cancer risk, with an OR of 2.10 (95% CI 1.09-4.02) for average household THM levels of more than 49 versus up to 8 $\mu\text{g/L}$. Compared with subjects not drinking chlorinated water, subjects with THM exposure of more than 35 $\mu\text{g/day}$ through ingestion had an OR of 1.35 (95% CI 0.92-1.99). The OR for duration of shower or bath weighted by residential THM level was 1.83 (95% CI 1.17-2.87) for the highest compared with the lowest quartile. In analyses by gender, statistically significantly raised ORs were reported for men but not for women.

10. Using data from a case-control study of bladder cancer conducted between 1985 and 1987 in seven French hospitals, *Chevrier et al*² compared 281 cases and 272 controls for whom they could reconstruct at least 70% of the residential exposure to drinking-water contaminants over a 30-year period. The authors' primary aim was to investigate the hypothesis that ozonation of drinking-water reduces the risk of bladder cancer. Only when duration of exposure to ozonated water was taken into account did statistically significantly raised ORs emerge for indices of exposure to CBPs (for example, OR 3.39 (95% CI 1.2-9.6) for cumulative exposure to THM (more than 1500 $\mu\text{g/L-years}$ versus 0), although the trends were not statistically significant. In analyses by gender, statistically significantly raised ORs were reported for men but not for women (female cases were outnumbered six-to-one by male cases).

11. *Villanueva et al (2003)*¹³ conducted a meta-analysis of published studies (six case-control and two cohort) evaluating individual consumption of chlorinated drinking-water and bladder cancer. The paper is attached at Annex C. Statistically significant elevated combined ORs were reported for men but not for women. Ever consumption of chlorinated drinking water was associated with an increased risk of bladder cancer in men (combined OR 1.4, 95% CI 1.1-1.9) (combined OR in women 1.2, 95% CI 0.7-1.8). The combined OR for long term exposure in men was 1.6 (95% CI 1.2-2.2) (combined OR in women 1.4, 95% CI 0.6-3.6). The combined estimate of the slope for a linear increase in risk was 1.13 (95% CI 1.08-1.20) for 20 years and 1.27 (95% CI 1.17-1.43) for 40 years of exposure (both sexes combined).

12. *Villanueva et al (2004)*¹⁰ published a pooled analysis of six case-control studies (three of which were included in the 2003 meta-analysis summarised in the preceding paragraph). The analysis included 2806 cases and 5254 controls, all of whom had measures of known exposure for at least 70% of the exposure window of 40 years before the interview. Cumulative exposure to THMs was estimated by combining individual year-by-year average THM level and daily tap water consumption. There was an adjusted OR of 1.24 in men exposed to an average of more than 1 $\mu\text{g/L}$ THM compared with those who had lower or no exposure (95% CI 1.09-1.41). Estimated relative risks increased with increasing exposure in men, with

an OR of 1.44 (1.20-1.73) for exposure higher than 50 µg/L. Similar results were found with other indices of THM exposure. Among women, THM exposure was not associated with bladder cancer risk.

13. Villanueva et al (2006)¹² reported additional results from the pooled analysis summarised in the preceding paragraph. There was an adjusted OR of 2.2 (95% CI 1.58-3.08) in men consuming more than 2.22 L tapwater daily at an average residential THM level of more than 35 µg/L, compared to no more than 0.8 L tapwater daily at an average residential THM level of no more than 0.5 µg/L; in women, the OR was not elevated.

14. Vinceti et al (2004)¹⁴ investigated the mortality of a cohort of 5144 residents in a municipality in northern Italy who were supplied tap water with high chloroform and THM content between 1965 and 1987. Using death rates of a nearby community as reference rates, the standardized mortality ratios (SMRs) for bladder cancer between 1987 and 1999 were 1.4 (95% CI 0.8-2.2) for men and 0.4 (95% CI 0.0-2.0) for women.

Colon and rectal cancers

15. In its 1999 statement, COC commented that:

“Since the 1992 evaluation there have been 7 epidemiological studies which have examined an association with cancer of the colon and 8 studies investigating rectal cancer. Of these only two studies were considered to be particularly well conducted, a case-control study of colon and rectal cancers and a prospective cohort study in postmenopausal women. Findings from these two studies were inconsistent; for cancer of the colon, a moderately strong association with increasing duration of exposure was found in the case-control study but no significant association was found in the cohort study; conversely, for rectal cancer, a moderately strong association was found in the cohort study but not in the case-control study. Inconsistent findings were also evident in the other reviewed studies of these sites.”

Colon cancer

16. King et al (2000)⁸ conducted a population-based case-control study in southern Ontario, Canada from 1992 to 1994. Interviews providing residence and water source histories were completed by 76% of eligible cancer cases and 72% of eligible controls. Supplemental data from municipal water supplies were used to estimate individual exposure to water source, chlorination status, and CBP levels as represented by THMs during the 40-year period before the interview. The analyses included 767 colon cancer cases, 661 rectal cancer cases, and 1545 controls with exposure information for at least 30 of these years (75% of subjects with completed interviews). Among males, colon cancer risk was associated with cumulative exposure to THMs, duration of exposure to chlorinated surface water, and duration of exposure to THM levels of at least 50 µg/L and of at least 75 µg/L. Males exposed to chlorinated surface water for 35–40 years had an increased risk of colon cancer compared with those exposed for less than 10 years (OR 1.53; 95% CI 1.13-2.09). Males exposed to an estimated THM level of 75 µg/L or more for at least 35 years had double the risk of those exposed for less than 10 years (OR 2.10; 95% CI 1.21-

3.66). The largest colon cancer risk among males was observed for those consuming high amounts of tap water with high cumulative THM exposure (OR 2.42; 95% CI 1.28-4.56). In contrast, these relationships were not observed in females.

17. In the retrospective cohort study by Vinceti *et al* (2004)¹⁴ the SMRs for colon cancer were not elevated.

Rectal cancer

18. The case-control study by King *et al* (2000)⁸ (described above) found no relationship between rectal cancer risk and any of the measures of exposure to CBPs.

19. In the retrospective cohort study by Vinceti *et al* (2004)¹⁴ the SMR for rectal cancer was statistically significantly low in men (0.2; 95% CI 0.1-0.8).

Cancers other than bladder, colon and rectal

20. In its 1999 statement, COC commented that:

“Studies of the other sites were not considered to be of good quality and, although some elevated risks were identified, these studies overall also failed to demonstrate any consistent association.”

Childhood acute lymphoblastic leukaemia

21. Infante-Rivard *et al* (2001)⁶ conducted a population-based case-control study to evaluate the relation between exposure to drinking water contaminants (including total and specific THMs) and childhood acute lymphoblastic leukaemia (ALL), comparing 491 cases 0–9 years of age with 491 controls. A municipality-exposure matrix was developed based on municipal and provincial historical data on THM levels, tapwater analyses in 227 homes, and information about residential history. The average level of exposure and cumulative average over the period were used as exposure indices. Risks were generally not increased for exposure during the prenatal period nor with average levels of exposure. Postnatal cumulative exposure for total THMs at above the 95th percentile of the distribution for cases and controls was associated with an elevated (but not statistically significant) OR of 1.54 (95% CI 0.78-3.03); for that same period, the OR associated with exposure to chloroform was increased (but not statistically significant: OR 1.63; 95% CI 0.84-3.19). The only statistically significant result was a decreased OR of 0.42 (95% CI 0.2-0.9) for cumulative exposure in the prenatal period to a THM (chlorodibromomethane) at greater than the 95th percentile of the distribution for cases and controls.

22. Infante-Rivard *et al* (2002)⁵ included a subset of cases from the population-based case-control study in a case-only study to estimate the interaction odds ratios (IORs) between prenatal and postnatal exposure to THMs and polymorphisms in the *GSTT1* and *CYP2E1* genes. These genes encode enzymes involved in the metabolism of THMs (the former, in particular, in the metabolism of brominated THMs). Cases with and without a given variant were compared regarding their exposure to THMs, using unconditional logistic regression. Few of the IORs differed statistically significantly from unity. The IOR for a postnatal average exposure to total THM

above the 95th percentile with *GSTT1* null genotype was 9.1 (95% CI 1.4-57.8). With *CYP2E1* (variant G-1259C, known as the allele *CYP2E1*5*), the IOR during the prenatal period for an average exposure to total THM at or above the 75th percentile was 9.7 (95% CI 1.1-86.0), and for an average exposure to chloroform at or above the 75th percentile was 10.2 (95% CI 1.1-89.9). The authors considered that these results contrasted strongly with those from the case-control analysis and showed “suggestive but imprecise” results, and noted that they had found no similar results in the literature.

Leukaemia in adults

23. *Kasim et al (2006)*⁷ conducted a population-based case-control study of 1,068 incident leukemia cases and 5,039 controls aged 20-74 years during 1994-1997 in Canada. Residence and drinking water source histories and data from municipal water supplies were used to estimate individual CBP exposure according to water source, chlorination status, and CBP levels during the 40-year period before the interview. The analysis included 686 cases and 3,420 controls for whom water quality information was available for at least 30 of these years. Increased risk of chronic myelocytic leukemia was associated with increasing years of exposure to several CBP indices, with an adjusted OR of 1.72 (95% CI 1.01-3.08) for the highest exposure duration to total THMs of more than 40 µg/L. In contrast, the risk of the other studied leukemia subtypes was found to decrease with increasing years of exposure to CBPs. Statistically significantly low ORs were noted for chronic lymphocytic leukaemia (OR 0.60; 95% CI 0.41-0.87) associated with the highest exposure duration to total THMs of more than 40 µg/L, and for hairy cell leukaemia (OR 0.31; 95% CI 0.1-0.8) in subjects in that exposure category in a sub-analysis of subjects exposed only to chlorinated water sources during the 40-year exposure period. The authors stated that “stratified analysis by gender showed no significant risk difference between men and women, particularly for chronic myelocytic leukaemia” but did not present the data.

24. In the retrospective cohort study by *Vinceti et al (2004)*¹⁴ the SMRs for lymphatic leukaemia were not statistically significantly different from unity.

Brain cancer

25. *Cantor et al (1999)*¹ conducted a population-based case-control study in Iowa of 375 brain cancer patients and 2,434 controls. Eligible cases were residents of Iowa, aged 40-85 years, newly diagnosed with histologically confirmed glioma in the period January 1984 to December 1987, and without previous diagnosis of a malignant neoplasm. Cases were registry-based, supplemented by a rapid reporting system during 1987. Controls under 65 were selected randomly from computerized state driver’s license records; those 65 and older from US Health Care Financing Administration listings. Anyone with a previous cancer diagnosis was excluded. Controls were matched by sex and 5-year aged group to all cases.

A postal questionnaire was used to gather information on lifetime residential history, primary source of drinking water, beverage intake, and other potential risk factors with follow-up by telephone to retrieve missing information. Of 412 eligible brain

cancer cases, 375 (91%) completed mail questionnaires or abbreviated telephone interviews. 74.4% of these respondents were proxies (mainly spouses or offspring).

Exposure to CBPs in drinking water was estimated by combining questionnaire data with historical information from water utilities and THM levels in recent samples. The analysis included 291 cases and 1,983 controls, for whom water quality information was available for at least 70% of lifetime years. Proxies represented 74.4% of cases. After multivariate adjustment, ORs for brain cancer (glioma) in men were 1.0, 1.3 (95% CI 0.8-2.1), 1.7 (95% CI 0.9-3.3), and 2.5 (95% CI 1.2-5) (p trend = 0.04) for exposure to chlorinated surface water of 0, 1-19, 20-39, and for at least 40 years. The association was stronger among men with above-median tap water consumption, for whom the corresponding ORs were 1.0, 1.3 (95% CI 0.7-2.7), 1.8 (95% CI 0.6-5.1) and 4 (95% CI 1.5-10.8), and was not statistically significant for men with below-median tap water consumption. In contrast, these relationships were not observed in women.

26. In the retrospective cohort study by *Vinceti et al (2004)*¹⁴ the SMRs for brain cancer were not elevated.

Pancreatic cancer

27. *Do et al (2005)*⁴ reported results from a population-based case-control study of 486 incident cases of pancreatic cancer and 3,596 age- and sex-matched controls. Exposure to CBPs was estimated by linking lifetime residential histories to two different databases containing information on CBP levels in municipal water supplies. Logistic regression analysis found no evidence of increased pancreatic cancer risk at higher CBP concentrations. Null findings were also obtained assuming a latency period for pancreatic cancer induction of 3, 8, or 13 years.

28. In the retrospective cohort study by *Vinceti et al (2004)*¹⁴ the SMRs for pancreatic cancer were not statistically significantly elevated.

Other cancers

29. In the retrospective cohort study by *Vinceti et al (2004)*¹⁴ the SMRs for “all cancers” were statistically significantly elevated in both sexes (men 1.2, 95% CI 1.1-1.4; women 1.1, 95% CI 1.0-1.3), and the SMRs for the following cancers were statistically significantly elevated in men only:

stomach (men 1.7; 95% CI 1.2-1.5; women 1.2; 95% CI 0.7-1.9)
lung (men 1.3; 95% CI 1.0-1.6; women 1.0; 95% CI 0.6-1.7)
melanoma (men 3.8; 95% CI 1.0-10.5; women 2.6; 95% CI 0.4-8.7)
breast (men 18.4; 95% CI 1.0-98.6; women 1.3; 95% CI 0.9-1.8)

Summary of results in the thirteen studies

30. The only statistically significant findings reported for females were the elevated SMR for “all cancers” in the retrospective cohort study by *Vinceti et al (2004)*¹⁴, and the association reported by *Villanueva et al (2007)*¹¹ between the

frequency of micronuclei in “exfoliated urine cells” in study controls and THM exposure.

31. *Kasim et al (2006)*⁷ stated that “stratified analysis by gender showed no significant risk difference between men and women, particularly for chronic myelocytic leukaemia” but did not present the data – thus, this study may have found statistically significant ORs for females and for males for chronic myelocytic leukaemia (elevated), for chronic lymphocytic leukaemia (reduced) and for hairy cell leukaemia (reduced). *Infante-Rivard et al (2002)*⁵ did not distinguish between genders in reporting statistically significantly raised interaction ORs between prenatal and postnatal exposure to THMs and polymorphisms in the *GSTT1* and *CYP2E1* genes, for childhood acute lymphoblastic leukaemia.

32. For males, statistically significantly raised ORs were reported for bladder cancer in the studies by *Villanueva et al (2007)*¹¹ and *Chevrier et al*², and in the overlapping meta-analyses and pooled analyses presented in *Villanueva et al (2003)*¹³, *Villanueva et al (2004)*¹⁰ and *Villanueva et al (2006)*¹². *King et al (2000)*⁸ reported statistically significantly raised ORs for colon cancer in men, and *Cantor et al (1999)*¹ reported statistically significantly raised ORs for brain cancer (glioma) in men. The retrospective cohort study by *Vinceti et al (2004)*¹⁴ found statistically significantly raised SMRs in men for malignant melanoma, “all cancers”, and for cancers of stomach, lung and breast, but a statistically significantly reduced SMR for rectal cancer in men.

Advice requested from COC

33. COC is asked to advise whether revision of the May 1999 COC statement on chlorinated water and cancer is required in the light of these recent published epidemiological studies.

Secretariat
June 2007

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**COMMITTEE ON CARCINOGENICITY OF CHEMICALS
IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

Chlorinated drinking water and cancer: COC statement COC/99/S2

1999 COC Statement on epidemiological studies of chlorinated drinking water and cancer.

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

CHLORINATED DRINKING WATER AND CANCER

COC Statement COC/99/S2 – May 1999

Introduction

1. In the United Kingdom, North America, and many other countries, chlorination has long been an important part of water treatment, intended to ensure that drinking-water contains no microbes hazardous to human health. In the mid-1970s, refinements in techniques of chemical analysis resulted in the detection in drinking-water of traces of chemicals formed when organic chemicals (such as those which may occur naturally in rivers, lakes, reservoirs and other water sources) are subjected to chlorination. In drinking-water, each of these chlorination byproducts (CBPs) is typically present at a concentration below 1 part per billion (1 µg/l). Some however, such as the trihalomethanes (THMs, ie chloroform, bromodichloromethane, chlorodibromomethane and bromoform), are often present at concentrations between 10 and 100 µg/l. Numerous CBPs have been identified, but many have yet to be detected or characterised.

2. Some CBPs, including some of the THMs, are known to be carcinogenic in laboratory mammals given doses far greater than human intakes from drinking-water. Some CBPs are genotoxic in test systems, including the bacterial "Mutagen X" (MX; 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone). There have been many epidemiological investigations into the possible association between chlorination of drinking-water and cancer in humans and also many experimental studies regarding the mutagenicity and carcinogenicity of CBPs which have been considered in this statement.

Previous evaluations

3. In 1986, the Department of Health (DH) Committee on Medical Aspects of the Contamination of Air, Soil and Water (CASW) reviewed the relevant data on carcinogenicity, mutagenicity and epidemiology, and advised that there was

no sound reason to conclude that the consumption of the byproducts of chlorination, in drinking-water which has been treated and chlorinated according to current practices, increases the risk of cancer in humans.

The effective disinfection of water supplies is clearly of great importance in maintaining public health. In our opinion, modification of chlorination processes which have proved effective over many years, or the replacement of chlorination by other disinfectants, is not required by the available data on cancer epidemiology, animal carcinogenicity and mutagenicity in relation to chlorination byproducts in drinking-water.

4. In 1991, the DH Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) considered research on methods for concentrating extracts of chlorinated drinking-water, and the mutagenicity of these extracts, and of MX. The COM concluded that treated drinking-water itself presents little risk in this regard, and that no further studies on the mutagenic potential of these compounds were warranted.

5. In 1992, the DH Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluated further epidemiological studies, and advised that

The conclusions of the 1986 CASW meeting were soundly based on the data available at the time. Many of the studies considered were correlation surveys which would have been difficult to interpret because of confounding factors such as other chemicals in the water supply, and there was also the problem of accurately determining the exposure of the population.

There was nothing in the more recent publications which would lead to alteration of the 1986 conclusions. The work by Cantor (1) and Lynch (17) was well conducted. The Cantor study was a case control study which took account of confounding factors, and showed a weak association between consumption of chlorinated drinking-water and an increase in bladder cancer once smoking had been taken into account, but this was insufficient to alter CASW's 1986 conclusions.

The Committee concluded that the 1986 conclusions of CASW were adequately founded and that information from subsequent investigations did not alter those conclusions. With regard to further epidemiological investigations within the UK the Committee pointed out that it would be very difficult to take account of consumption of chlorinated water in food, bottled water and other beverages. The Committee could not recommend that further epidemiological studies should be undertaken in the UK at the present time.

6. COC also reviewed a meta-analysis (20) published in July 1992. The authors estimated an overall relative risk (RR) of 1.15 (1.09-1.20) {95% confidence interval, used throughout this statement} for all cancer sites together, with statistically-significant elevated RRs for bladder cancer (1.21 [1.09-1.34]) and rectal cancer (1.38 [1.01-1.87]) but not for the other ten categories of cancer which were evaluated. COC considered that the meta-analysis gave insufficient evidence for increased concern over the carcinogenic effects of chlorinated drinking-water. It was noted that no account had been taken of consumption of water other than tap water, but that in fact bottled water and water used in food was often chlorinated in the manufacturing plant. COC concluded that the meta-analysis did not change its conclusions, but added a proviso that

*the Committee could not recommend that further epidemiological studies should be undertaken in the UK at the present time, **unless a population can be found with a distinctive exposure to chlorinated drinking-water.***

7. In 1996, COC and COM considered the carcinogenicity and mutagenicity data on the THMs, and COC advised that

The ratio between the lowest dose level giving rise to a carcinogenic effect in animals and the likely human exposure level from drinking-water for each of the four THMs considered by the Committee was in excess of 10,000. Thus the levels of these THMs in drinking-water in the UK are unlikely to provide a carcinogenic risk to humans.

New epidemiological studies

8. Twenty further relevant epidemiological studies (2-16, 18, 19, 21-23) have been published since COC's 1992 evaluation. They include studies on a wide range of cancers:

Type of Cancer	Reference Number
All Cancers combined	4,23
Brain and Nervous System	3,14,23
Oesophagus	14,23
Stomach	4,13,14,22,23
Liver	14,15,23
Gallbladder and Bile Ducts	14
Pancreas	9, 14-16, 23
Colon	4,7,8,13,14,23
Rectum/ Anus	4,7,8,10,13,14,21,23
Kidney	4,12-14,23
Bladder	2,4,6,10-14,19,21-23
Prostate	14,23
Testis	14
Ovary	4,14,23
Uterus	4,14,23
Breast	4,14,18,23
Lung	4,14,23
Skin	4,14
Soft Tissue	14,15
Thyroid	14
Leukaemia	5,14,15
Hodgkin's Lymphoma	14,15
Non-Hodgkin's Lymphoma	4,14,15

9. A mixture of case-control, cohort and ecological studies has been employed to investigate the association between chlorinated drinking water and various cancers. Most of the recent epidemiological studies were carried out in North America. None were from the United Kingdom. The focus for case control studies has been cancers at sites implicated in earlier epidemiological studies, and for which there may be, theoretically, a higher exposure to agents in drinking water.

10. Those carcinogenicity studies which have been performed on CBPs do not identify any CBP, or group of CBPs, which appears likely to cause cancer at these sites at the concentrations found in drinking-water. The Committee reaffirmed its view that since bottled water products may contain chlorinated water, it was not possible to identify an unexposed control group. In the absence of an identified aetiological agent, or a precise means of measurement, a number of different surrogates of exposure have been employed in these studies including the following comparisons :

- : chlorinated vs non-chlorinated water sources
- : duration of time exposed to chlorinated water
- : surface vs groundwater sources
- : trihalomethane levels (total and individual substances)
- : high organic content vs low organic content
- : high level of estimated water mutagenicity vs low level

This consequently introduces uncertainty in exposure classification and makes comparison between studies, and interpretation of individual studies, more difficult.

11. In addition to these uncertainties, lifetime estimates of actual water consumption cannot be ascertained with any certainty, and exposure to substances occurring in drinking water via other routes (ie inhalation, dermal) or from other sources (eg food) may also not be properly considered. Consequently cancer epidemiological studies of chlorinated water suffer to a lesser or greater degree from deficiencies of study design.

12. It is also not uncommon, in those studies where statistically significant relative risks are observed, for these to be typically in the region of 2 or lower. Consequently, the strength of association between health outcomes and measures of exposure is considered to be weak, and the elevated risks may be within the range of uncertainty arising from possible confounding factors.

13. Of the 20 recent studies, only 4 were particularly well conducted. These comprised two case control studies dealing solely with bladder cancer, (2, 6) one case control study considering colon and rectal cancers (7) and a prospective cohort study of postmenopausal women (4) which looked at many different cancer sites including the bladder, colon and rectum. The remaining studies were either ecological in nature or had other serious limitations in design. Overall, however, all studies suffered to some extent from the difficulty of assessing long term exposure to potential aetiological agents in chlorinated drinking water. Additionally there was a lack of consistency of effect across studies dealing with different cancer end points. Many studies were also not directly comparable as they contained different measures of assessing exposure to chlorinated drinking water.

Bladder cancer

14. Previous epidemiological studies have suggested associations between bladder cancer and CBPs, and eleven of the twenty recent studies have investigated this

hypothesis. Five were case-control studies,(2, 6, 10-12, 19) two were cohort studies, (4 14) and four were ecological.(13, 21-23) Most report some statistically significant elevated relative risks for groups with the highest estimated duration or level of exposure, but the associations are generally weak, with relative risks below 2. Exceptions are found in subgroups in four of the case-control studies, but are not consistent between studies. Thus, in two studies (2, 6) the relative risk was confined to male smokers (respectively, odds ratios [ORs] of 2.3 for more than 60 years of use of chlorinated water, and 3.2 for more than 40 years use of municipal water). This contrasts with another case-control study (12) which found an elevated OR only in male non-smokers (OR 2.59 for 30 years exposure to drinking-water estimated as "substantially mutagenic"), and with an earlier large case-control study (1) which found associations primarily in non-smokers of both sexes. Members noted that a new ecological study (23) of chlorination of drinking water and cancer mortality in Taiwan had recently been published but agreed that such studies were only useful in the generation of hypotheses and not in respect of the evaluation of risk. A retrospective cohort study in Finland (14) found an elevated relative risk for women only (1.48 [1.01-2.18]) but, as noted above, the same group's case-control study (12) found an elevated OR in male smokers only. In another case-control study (10, 11) the highest ORs (2.28-2.58) were seen in groups with 35 or more years of unusually high consumption of water with estimated THM levels greater than 50 µg/l.

15. These recent studies of bladder cancer do not show any consistent dose-response relationship with estimated exposures to CBPs or THMs.

Colon and rectal cancers

16. Since the 1992 evaluation there have been 7 epidemiological studies which have examined an association with cancer of the colon and 8 studies investigating rectal cancer. Of these only two studies were considered to be particularly well conducted, a case-control study of colon and rectal cancers (7) and a prospective cohort study in postmenopausal women. (4) Findings from these two studies were inconsistent; for cancer of the colon, a moderately strong association with increasing duration of exposure was found in the case-control study but no significant association was found in the cohort study; conversely, for rectal cancer, a moderately strong association was found in the cohort study but not in the case-control study. Inconsistent findings were also evident in the other reviewed studies of these sites.

Other sites

17. Studies of the other sites were not considered to be of good quality and, although some elevated risks were identified, these studies overall also failed to demonstrate any consistent association.

Conclusion

18. Overall, the further epidemiological studies fail to provide persuasive evidence of a consistent relationship between chlorinated drinking-water and cancer. It remains possible that there may be an association between chlorinated drinking water and

cancer which is obscured by problems such as the difficulty of obtaining an adequate estimate of exposure to chlorination by-products, misclassification of source of drinking water (including the use of bottled water), failure to take adequate account of confounding factors (such as smoking status), and errors arising from non-participation of subjects.

We therefore consider that efforts to minimise exposure to chlorination by-products remain appropriate, providing that they do not compromise the efficiency of disinfection of drinking-water.

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Summary of original cancer epidemiology studies

Ref/Country/ Aim/ Comments	Study design	Exposure assessment	Participants/Dates	Other data	Response rate	Analysis	Results
Cantor et al (1999) Iowa Risk of brain cancer vs. consumption of chlorinated drinking water	Population – based case- control study. 375 cases, 2,434 controls	Information on primary source of drinking water by postal questionnaire combined with historical information from water utilities and data from analyses of THM in recent samples	Cases: residents of Iowa, aged 40-85, registry- based, newly diagnosed with histologically confirmed glioma 1984- 1987 inc. Controls: matched by sex and 5-year age groups; randomly selected; under 65- from computerized driver's license records, over 65- from US Health Care Financing Admin listings. Previous cancer diagnosis excluded.	Postal questionnaire for lifetime residential history, primary source of drinking water, beverage intake, and other potential risk factors, with follow-up by telephone to retrieve missing information. Cases: 72% questionnaires completed by proxies; controls: only 1 completed by a proxy.	91% eligible cases completed questionnaires or abbreviated telephone interviews.	Maximum likelihood estimate of the OR. Adjustment by unconditional logistic regression analysis for age, sex, ever employed as a farmer, population size of places of residence.	For exposure to chlorinated surface water of 0, 1-19, 20-39 and ≥40 years. OR (95% CI) Men: 1.0, 1.3 (0.8-2.1), 1.7 (0.9-3.3), 2.5 (1.2-5.0), p trend 0.04. Women: 1.0, 1.0 (0.6-1.6), 1.6 (0.8-3.0), 0.7 (0.3-1.6), p trend 0.4
Chevrier et al (2004) France To investigate whether ozonation of drinking water reduces risk of bladder cancer	Hospital based case- control study 765 cases and 765 controls.	Residential history from 1948 until 5 years before diagnosis by interview. Modelling and expert advise to assign THM concentrations to each water utility. Then averaged levels of each utility supplying municipality, weighted by % of water supplied by each during the year	Cases recruited from newly diagnosed cases in 7 hospitals 1985-87 inc. and those seen for treatment of bladder cancer diagnosed 1982-4 inc. All cancers histologically confirmed. Controls randomly selected from various hospital departments.	Participants interviewed by investigator for social and demographic info., other potential risk factors, fluid intake from 18 years of age.	Analysis restricted to 281 cases and 272 controls for whom water treatment could be characterised for at least 70% exposure period.	Logistic regression analysis adjusted for sex, age (<60/≥60), hospital, SE status, coffee consumption and tap water consumption.	No stat sig association between bladder cancer and either duration of exposure to chlorinated surface water (yrs), average THM level or cumulative exposure to THM. Adjusted for duration of exposure to ozonated water: stat sig assn. at highest average levels of THM conc. [2.99 (1.11-8.5)] and cumulative exposure to THM [3.39 (1.2-9.6)]. No stat sig trends.

Ref/Country/Aim/Comments	Study design	Exposure assessment	Participants/Dates	Other data	Response rate	Analysis	Results
<p>Infante-Rivard et al, 2001 Canada</p> <p>To investigate exposure to various drinking water contaminants and childhood ALL</p>	<p>Population-based case-control study</p> <p>491 cases and 491 controls</p>	<p>Exposure indices for total and individual THMs derived from data on residential history (obtained by telephone interview), data on levels of THMs obtained from municipalities, Government and/or tapwater analyses.</p> <p>Two exposure indices used: average level of exposure, and cumulative exposure over the period.</p>	<p>Cases between 0 and 9 years of age diagnosed 1980-1983 recruited from tertiary care centres (“equivalent to population-based ascertainment”). Diagnosis by oncologist on basis of standard criteria.</p> <p>Population-based controls selected from family allowance files matched on age, sex, region of residence at diagnosis.</p>	<p>Method of collecting social and demographic info. not stated but assumed to be by telephone interview of parent.</p>	<p>Of eligible cases/controls, 96.3%/83.8% participated. Two controls subsequently rejected due to lack of cases for matching .</p> <p>Not clear that all participants had exposure data.</p>	<p>Conditional logistic regression. ORs adjusted for maternal age and level of schooling.</p>	<p>For total THMs: OR for period from pregnancy to diagnosis for those at average level values above the 95th percentile was 1.22 (0.53-2.81).</p> <p>For individual THMs, comparing > 95th percentile vs. ≤ 95th percentile: no significantly increased OR found for either average level of exposure or cumulative exposure.</p> <p>Exposure assessment limited in this study.</p>
<p>Infante-Rivard et al, 2002 Canada</p> <p>To determine whether the risk of ALL associated with DBP was modified by presence of variants of genes involved in metabolism of THMs.</p>	<p>Used subset of cases from the above study to estimate the interaction ORs between prenatal and postnatal exposure to THMs and polymorphisms in the GSTT1 and CYP2E1 genes.</p>	<p>As above</p>	<p>As above.</p> <p>170 cases were selected for present study: all from one centre where genotyping of all ALL cases had been systematically initiated and all French-Canadian.</p>	<p>As above</p>	<p>Only 161 subjects also had exposure data, therefore, only 161 entered analysis.</p>	<p>Cases with and without a given variant were compared with regard to their exposure to THMs using unconditional logistic regression to give IORs and 95%CI</p>	<p>GSTT1 null genotype: Increased risk associated with average total THM level in postnatal period of >95th percentile (9.13[1.44-57.82]) only.</p> <p>CYP2E*1 genotype: Increased risk associated with average total THM level in prenatal period of ≥ 75th percentile (9.75[1.10-86.01]) and average chloroform level in prenatal period of ≥ 75th percentile (10.17[1.15-89.89]) only.</p>

Ref/Country/ Aim/ Comments	Study design	Exposure assessment	Participants/Dates	Other data	Response rate	Analysis	Results
<p>Kasim et al, 2005 Canada</p> <p>To examine association between exposure to DBP and adult leukaemia risk.</p> <p>Seems to be a good quality study</p>	<p>Population-based case-control study</p> <p>1068 cases (307 AML, 51 ALL, 169 CML, 410 CLL, 64 hairy cell leukaemia, 67 leukaemia n.s.) 5039 controls.</p>	<p>Information on residential history, main sources of drinking water from questionnaire.</p> <p>THM monitoring data from multiple sources including surveys. Data from changes in water treatment practices. Used to estimate individual exposures over 40 years preceding interview.</p> <p>Individual water intake estimates. Analysis restricted to subjects with ≥ 30 years known water history. Subjects reporting no exposure to chlorinated surface water used as referent group.</p> <p>Examined risk by total years of exposure to a). chlorinated surface water; b). water with estimated total THM level of >20 and > 40 ug/l and water with estimated BDCM level of >5 ug/l.</p>	<p>Case and control data sourced from the Canadian National Enhanced Cancer Surveillance System (NECSS) which collected data from 8 Canadian provinces on individual risk factors between 1994-1997 from 20,755 Canadians recently diagnosed with one of 10 cancer types. 5039 population controls with similar age and sex distributions..</p>	<p>Mailed questionnaire for extensive info. on other risk factors. Telephone follow-up when necessary.</p>	<p>In the NECSS: Cases: 53.5% of those ascertained, 70% of those contacted. Controls: 63% of those ascertained, 67% of those contacted.</p>	<p>Analysis adjusted for age, gender, ethnicity, family income, residence, BMI, smoking, occupational exp to benzene and ionizing radiation.</p> <p>Unconditional logistic regression for OR and 95% CI.</p> <p>Tests for trend based on a likelihood-ratio test.</p>	<p>Risk of CML increased with increasing years of duration of residence with a chlorinated water source but not significantly so (OR for ≥ 36 years exposure = 2.20(0.93-5.23) $p_{\text{trend}}=0.09$. Risk of CML also increased with total TTHM >20 ug/l ($p_{\text{trend}}=0.11$), >40 ug/l ($p_{\text{trend}}=0.05$) and BDCM >5ug/l ($p_{\text{trend}}=0.12$).</p> <p>No association with duration of exposure for all leukaemias combined or other subtypes. In fact, some subtypes had lower risk with increasing exposure.</p> <p>Some differences between case and control populations e.g. cases had higher proportion of males and of occupational exp to benzene.</p>

Ref/Country/ Aim/ Comments	Study design	Exposure assessment	Participants/Dates	Other data	Response rate	Analysis	Results
<p>King et al, 2000. Ontario, Canada</p> <p>To assess the relationship between CBPs in public water supplies and cancers of the colon and rectum.</p> <p>Seems to be a good quality study</p>	<p>Population-based case-control study.</p> <p>767 colon cancer cases, 661 rectal cancer cases. 1545 controls included in final analysis.</p>	<p>Information on residence, water source history and water consumption collected by mailed questionnaire.</p> <p>Exposure estimated from residence, water source information, tap water consumption, survey of treatment plants for water source and treatment practices from 1950-1990 and modelled prediction of THM values.</p>	<p>Cases: 30-74 year old, with primary cancer of colon or rectum diagnosed between September 1992 and April 1994 inc., sourced from Ontario Cancer Registry.</p> <p>Controls randomly selected from database of residential telephone listings, frequency matched to age-gender distribution of combined case series (bladder, colon and rectal cancer cases).</p>	<p>Demographic and risk factor information collected by mailed questionnaire.</p>	<p>Cases: 3302 cases identified from registry, : overall response rate 77% colon and 75% rectal cancer cases.</p> <p>Controls: from 10,219 households, contacted, 72% overall response rate.</p> <p>Final analysis included only individuals for whom water information was available for ≥ 30 years</p>	<p>Unconditional logistic regression used to obtain ORs and 95% CIs. Tests for trend based on likelihood-ratio test.</p> <p>Adjustment for age, sex, and energy intake in all analyses. Also in parsimonious model for cancer risk: BMI, education, coffee consumption, cholesterol, calcium, alcohol consumption (colon only), previous medical conditions (rectal only).</p>	<p>Colon cancer:</p> <p>In males only, sig. increased risks cf. 0-9 years exposure for males with 10-19 and ≥ 35 years exp. to chlorinated drinking water but not 20-34 years.</p> <p>Sig. increased risk at ≥ 50 ug THM/l (1.69[1.02-2.76]) and ≥ 75 years THM/l (2.10[1.21-3.66]) for ≥ 35 years. Also, sig increased risk in highest quartile of THM-years (ug/l-yr): 1.17[1.25-2.43].</p> <p>Risk in males of consuming chlorinated surface water cf. ground water for ≥ 30 years: 1.49 (1.10-2.00). Sig trend with rising THM level $p_{\text{trend}}=0.005$</p> <p>No sig. increased associations for colon cancer in females or rectal cancer in either males or females.</p>

Ref/Country/ Aim/ Comments	Study design	Exposure assessment	Participants/Dates	Other data	Analysis	Results
<p>Vinceti M et al (2004). N. Italy</p> <p>To examine relationship between cancer mortality and supply of tap water with high THM levels</p> <p>No dose-response investigated. No adjustment for SE status or other risk factors.</p>	Retrospective cohort study	<p>Water in study area (Guastalla) between 1965 and 1987 provided by 3 wells where water chlorinated. 1984 survey found high THM levels: c.40-70 ug/l.</p> <p>Water in control area generally had low THM levels averaging 0.2 ug/l. However, it did contain a higher concentration of 1,1,1,TCE.</p>	<p>Examined mortality from 1987 to 1999 inc. or date of death or emigration outside region, whichever occurred first.</p> <p>Exposed: cohort of 5144 subjects (2446 males and 2698 females) residing in Guastalla, Reggion Emilia Province, N. Italy since 31/12/66 identified from electronic database of residents.</p> <p>A check of a sample of 50 showed 90% resident in "area where the municipal tap water had been distributed".</p> <p>Cause of death retrieved from death certificates held at Public Health Dept or other PHDepts if subjects had moved outside region (1.6%).</p> <p>Reference rates from municipal population of the town of Reggio Emilia (pop. C.140,000) because of similar ethnicity and lifestyle factors.</p>	Data on occupational status and education extracted from registry.	<p>SMRs with 95% exact mid-<i>P</i> CI (Rothman and Greenland, 1998). Person-years of follow-up and SMRs using <i>stset</i>, <i>stsplot</i> and <i>strate</i> routines of STATA-7 stat. software.</p>	<p>Overall cancer mortality higher in cohort than expected in both sexes: Males: SMR 1.2(1.1-1.4) Females: SMR 1.1 (1.0-1.3)</p> <p>Sig results for individual cancers: SMR (95%CI) O/E:</p> <p><u>Males</u> Stomach 1.7 (1.2-2.5) 30/17.3 Lung 1.3 (1.0-1.6) 66/51.5 Melanoma 3.8 (1.0-10.5) 3/0.8 Breast 18.4 (1.0-98.6) 1/0.1</p> <p><u>Females</u> None.</p> <p>More in exposed cohort had lower degree of educational attainment and were employed in industry</p>

Ref/Country/Aim Comments	Study design	Exposure assessment	Participants/Dates	Other data	Response rate	Analysis	Results
<p>Villanueva et al (2006) Spain</p> <p>To examine whether bladder cancer risk was associated with exposure to THMs through ingestion and through inhalation and dermal absorption during showering, bathing and swimming in pools.</p> <p>Big assumptions about historical THM exposure levels.</p>	<p>Multi-centre, hospital based, case-control study.</p>	<p>Information obtained by questionnaire on residential history from birth, drinking water source at teach residence, fluid consumption, average frequency and duration of showering and bathing, and lifetime swimming in pools, with checks for the latter parameters.</p> <p>Survey of water suppliers for historical data on waater parameters and analyses of 113 tap water samples from 1999.</p> <p>Average THM levels in recent years exptrapolated back to 1920 on assumption levels remained unchanged for a constant water source.</p> <p>Several exposure indices derived for from age 15 to time of interview.</p>	<p>Cases: identified between June 1998 and June 2001 in 18 hospitals from 5 areas of Spain. Histologically confirmed diagnosis of primary bladder cancer, aged 20-80 years, living in catchment area of participating hospitals. Extra checks to ensure complete case ascertainment.</p> <p>Controls: patients admitted to participating hospitals with diagnoses thought to be unrelated to the main risk factors for bladder cancer. Matched 1:1 by gender, age group and geographic area of residence.</p>	<p>Sociodemogra phic data, smoking habits,occupat ional and medical histories obtained by computer-assisted personal interview. Food frequency questionnaire self-administered.</p>	<p>84% of eligible cases and 87% eligible controls responded to questionnaire, but 21% of cases and 19% of controls were administered a reduced interview of critical items only.</p> <p>Due to further exclusions, numbers for individual analyses ranged from 546-787 cases and 570-963 controls.</p>	<p>Unconditional logistic regression for ORs and 95% CIs. Adjusted for age, gender, smoking status, sixe of the municipality of longest residece until age 18 years, education, geographic area, overall quality of interview.</p> <p>Further restrictions according to extent of exposure information and quality of interview.</p>	<p>Median age at interview 67 years. 87.5% study subjects male.</p> <p>Excess risks found for former and current smokers.</p> <p>Lower risk in those with longest residence in village cf. metropolitan area.</p> <p>Sig raised risk with increasing average residential THM level in men (highest level 2.53[1.23-5.20], $p_{trend} < 0.01$) and men and women combined (2.10[1.09-4.02] $p_{trend} < 0.01$). Women: OR = 1.50 (0.26-8.61).</p> <p>Sig raised risk in men only for average ingestion THM >35 ug/day (1.61[1.06-2.44] $p_{trend} = 0.02$) cf. no THM exposure. Women: 0.47 (0.15-1.51).</p> <p>Significant trend for men ($p_{trend} = 0.01$) and men and women combined ($p_{trend} < 0.01$) for duration of shower and bath weighted by average residential THM level</p> <p>Trend for increased swimming</p>

						<p>in pools: men $p_{\text{trend}} < 0.01$, women $p_{\text{trend}} = 0.97$, both $p_{\text{trend}} = 0.02$).</p> <p>Significantly raised risk in men and men and women combined for ever swimming vs. never swimming (1.62[1.20-2.19]; 1.57 [1.18-2.09]). Women: 1.53 (0.58-4.06).</p> <p>Limited evidence of multiplicative interaction between THM exposure and smoking.</p>
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**Villaneuva CM, Fernandez F, Malats N, Grimalt JO and Kogevinas M (2003).
Meta-analysis of studies on individual consumption of chlorinated drinking
water and bladder cancer. J Epidemiol Community Health 57: 166-173**

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