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

Second draft working paper on Chlorinated Drinking Water and Cancer

The second draft working paper on chlorinated drinking water and cancer has been revised following comments at the last meeting. Members are asked if they can agree the working paper for publication as a statement.

Secretariat
March 2008

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Second Draft Working Paper – Not for Publication

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

Chlorinated drinking water and cancer

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. Disinfection of drinking water is fundamental to preventing the spread of waterborne disease, such as cholera.

2. 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. Each of these chlorination byproducts (CBPs) is typically present in drinking water at a concentration below 1 µg/l. Some, however, such as the trihalomethanes (THMs, ie chloroform, bromodichloromethane, chlorodibromomethane and bromoform) may be present at concentrations up to 100 µg/l. Numerous CBPs have been identified, but many have yet to be detected or characterised in drinking water.

3. Some CBPs, including some of the THMs, are known to be carcinogenic in laboratory mammals and some 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 experimental studies of the mutagenicity and carcinogenicity of CBPs. In 1986, the Department of Health Committee on Medical Aspects of Contamination of Air, Soil and Water (CASW) reviewed the data which were then available and concluded 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

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COC considered further epidemiological studies in 1992 and 1999 and reviewed the animal carcinogenicity data in 1996. In 1996 it concluded 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.” In 1999, it concluded that the new epidemiological studies failed to provide persuasive evidence of a consistent relationship between chlorinated drinking water and cancer. The committee stated: “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” (1). The COC considered that efforts to minimise exposure to CBPs remain appropriate, providing that they do not compromise the efficiency of disinfection of drinking water.

4. Thirteen further relevant epidemiological papers have been published since the 1999 review. At our July 2007 meeting, we were asked to review these and to advise whether revision of the 1999 statement was required.

New epidemiological studies

5. The 13 new studies were on a range of cancers:

Type of cancer	Reference
Bladder cancer	3, 9, 10, 11, 12, 13
Colorectal cancer	8
Childhood acute lymphoblastic leukaemia (ALL)	5, 6
Adult leukaemia	7
Brain cancer	2

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One study (14) examined mortality from a wide range of cancers.

6. Of the original studies, most were either hospital-based or population-based case-control studies. One was a prospective cohort study (9) and one a retrospective cohort study (14). There was one meta-analysis and two pooled analyses of overlapping sets of papers on bladder cancer. Four of the 13 studies were from Canada, with others from the US, France, Italy, Spain and Australia. None was from the UK. We recognise that the levels of and, therefore, exposure to, CBPs may not be the same in other countries as in the UK. Nevertheless, it is important to review these studies to determine whether there is a carcinogenic hazard from CBPs in drinking water.

7. As the Committee noted in 1999, those animal 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. A number of different surrogates of exposure have been employed in epidemiological studies. In the recent studies, they include:

- Duration of time exposed to chlorinated water
- THM levels (usually total THMs)
- Chlorinated vs. non-chlorinated water source
- Source of water

In some papers, several exposure measures were used, resulting in multiple comparisons, which can influence the number of positive associations reported. Frequently, no historical measurements of THMs were available and estimates had to be made, for example, from information on water sources and history of chlorination treatment. There is also uncertainty about the lifetime estimates of water consumption made in some studies. Different exposure ranges were used, rendering comparisons between studies difficult. Overall, adequate exposure assessment continues to be a major problem with these studies.

8. Most of the new studies have attempted to control for known or suspected risk factors although the extent of control varied from study to study and was in part dependent

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on the degree to which there are known or suspected risk factors for the cancer under study. Nevertheless, as noted in 1999, where there are positive associations between cancer risk and measures of exposure, they are usually weak and the elevated risks may be within the range of uncertainty arising from possible confounding factors.

Bladder cancer

9. Previous epidemiological studies have suggested associations between bladder cancer and CBPs although the studies reviewed in 1999 were not considered to show any consistent dose-response relationship with estimated exposures to CBPs or THMs. Of the 6 new papers concerning bladder cancer, 3 were pooled analyses or meta-analyses of overlapping sets of papers, most of which we have already considered. The meta-analysis compared individual consumption of chlorinated drinking water and bladder cancer and reported small but statistically significantly elevated combined odds ratios (ORs) for men but not for women (10) [combined OR for ever consumption in men = 1.4, 95% confidence interval (CI) 1.1-1.9; OR for women = 1.2, 95% CI 0.7-1.8]. In the first pooled analysis of 6 case-control studies (3 of which were included in the meta-analysis), the adjusted OR for bladder cancer in men exposed to an average of more than 1 µg THM/l compared to those who had lower or no exposure was 1.24 (95% CI 1.09-1.41). Estimated ORs in men increased with increasing exposure up to 1.50 (95% CI 1.22-1.85) (11). No association was found among women. Additional results from the pooled analysis using different measures of exposure to THMs (total fluid consumption and intake of tap water) found that total fluid consumption was associated with an increased risk of bladder cancer [adjusted OR = 1.08, 95% CI 1.03-1.13 overall for men and women] (12). Tap water consumption was also associated with an increased risk of bladder cancer [adjusted OR /l/day increase overall = 1.10, 95% CI 1.04-1.17], with higher ORs reported in men than women.

10. Using data from a case-control study whose main objective was to investigate whether ozonation of drinking water reduces the risk of bladder cancer, no statistically significant association of bladder cancer was found with various measures of THM exposure (3). When adjusted for duration of exposure to ozonated water, a statistically significant association was found at the highest average levels of THM concentration [OR

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= 2.00, 95% CI 1.11-8.5] and with cumulative exposure to THM [OR = 3.39, 95% CI 1.2-9.6] but there was no statistically significant trend with exposure levels. A large case-control study reported a statistically significantly increased risk of bladder cancer in men associated with various estimates of DBP exposure including average residential THM level [adjusted OR up to 2.53, 95% CI 1.23-5.20], ingestion of THMs [adjusted OR up to 1.61, 95% CI 1.06-2.44], exposure from showering and bathing [adjusted OR up to 2.01, 95% CI 1.23-3.28] and swimming in pools [never swimming vs. ever swimming: OR = 1.62, 95% CI 1.20-2.19] (13). In women, there were statistically significantly raised risks only at the highest estimated exposure levels from showering and bathing [1.83, 95% CI 1.17-2.87] and swimming in pools [never swimming vs. ever swimming: OR=1.57, 95% CI 1.18-2.09].

11. Conflicting results were found in two studies which examined the association between frequency of micronuclei in either urinary bladder epithelial cells (9) or “exfoliated urine cells” (13) and measures of THM exposure.

12. We consider that the additional studies provide limited evidence for an association between bladder cancer and exposure to CBPs.

Colon and rectal cancers

13. A number of studies have examined the association between cancer of the colon or rectum and exposure to chlorinated drinking water. A new, well conducted case-control study has been published on these endpoints (8). It found increased risks of colon cancer among males with a number of measures of exposure to THMs. The highest adjusted OR was 2.10 (95% CI 1.21-3.66) for ≥ 35 years exposure to ≥ 75 μg THM/l compared to < 10 years. No increased risks were found for colon cancer in females nor for rectal cancer.

Other sites

14. A study of exposure to drinking water contaminants and childhood ALL found no statistically significant increases in risk with a number of measures of exposure to THMs (5). However, an additional study of a subset of cases found significant interactions

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between pre- and post-natal exposure to THMs and polymorphisms in the *GSTT1* and *CYP2E1* genes (6). The OR for children with the *GSTT1* null genotype exposed to an average total THM level in the postnatal period above 95th percentile was 9.13 (95% CI 1.44-57.82), and that for children with one or more *CYP2E*1* alleles and average total THM level in the prenatal period at or above the 75th percentile was 9.75 (95% CI 1.10-86.01). We note that there were only 12 children with one or more *CYP2E*1* alleles, most of which would probably have been heterozygotes, and question the plausibility of such a large association being causal. Nevertheless, the finding is of potential interest. A large case-control study of adult leukaemia cases found an increased risk of chronic myelocytic leukaemia with increasing years of exposure to several CBP indices but the risk of other leukaemia subtypes was found to decrease with increasing years of exposure to CBP (7).

15. A well-conducted case-control study found a positive, dose-related association in men between measures of exposure to CBPs and brain cancer (glioma) [OR for exposure to chlorinated surface water of ≥ 40 years = 2.1 (95% CI 1.2-5.0)] (2). In contrast, no association was found in women [OR for exposure to chlorinated surface water of ≥ 40 years = 0.7 (95% CI 0.3-1.6)].

16. No association was found between pancreatic cancer and increasing CBP levels in a population-based case-control study [OR for the highest exposure level = 0.9 for men and women combined, 95% CI 0.62-1.33] (4).

17. In a retrospective cohort study which compared the mortality from a wide range of cancers in an area supplied with tap water with high THM levels with rates in an area with low THM levels, overall cancer mortality rates were slightly raised in the high THM area [men: SMR¹ = 1.2, 95% CI 1.1-1.4; women: SMR = 1.1, 95% CI 1.0-1.3] (14). In men, there were raised SMRs for cancers of the stomach [1.7 (1.2-2.5)], lung [1.3 (1.0-1.6)], melanoma [3.8 (1.0-10.5)] and breast [18.4 (1.0- 98.6)]. No individual cancer showed a raised rate in women.

Conclusion

¹ Standardised Mortality Rate

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18. We have reviewed the new epidemiological studies on chlorinated drinking water and cancer published since 1999. In 1999, the COC concluded that the studies which were reviewed on bladder cancer did not show any consistent dose-response relationship with estimated exposures to CBPs or THMs. We consider that the new studies on bladder cancer, which include a meta-analysis and two pooled analyses by the same group, provide limited evidence for an association between bladder cancer and exposure to CBPs in men. The evidence for an association in women is conflicting.

19. In the 1999 review, the COC commented that the studies of colorectal cancer gave inconsistent findings. In the current review, one well-conducted study provides some for an association with colon cancer, but not rectal cancer, in men only. In 1999, the COC did not consider the studies of other sites to be of good quality or to produce consistent associations. One new, well-conducted study has indicated an association with brain cancer in men but not in women.

20. Problems remain in the interpretation of published studies on CBPs. These include the small relative risks recorded, the possibility of residual confounding, and the problems with exposure assessment described above. There is no obvious reason why positive associations should be seen so frequently in men but not in women. An association between brain cancer and THM exposure is unlikely to be biologically plausible. There is always concern that publication may be biased in favour of positive results, as it may in any field of science. Moreover, as previously stated, none of the studies we have reviewed were carried out in the UK and it is possible that disinfection practices and constituents of the raw water may be different in other countries, in which case the study results may not be directly applicable to the UK.

21. We conclude that any association between cancer and exposure to CBPs is unlikely to be large. Efforts to minimise CBPs in drinking water should continue, providing that they do not compromise the efficiency of disinfection of drinking-water.

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