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CC/07/19

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

Draft Working Paper on Chlorinated Drinking Water and Cancer

At the July meeting, the committee discussed new epidemiological studies on chlorinated drinking water and cancer (CC/07/11). A draft working paper (update statement) on this topic is attached, for members' comments.

Copies of the papers discussed at the last meeting are also attached for information, as Members have not previously seen the full papers.

Secretariat
September 2007

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Draft Working Paper – Not for Publication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. 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 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. 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 was 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 COC considered further epidemiological studies in 1992 and 1999 and reviewed the animal carcinogenicity

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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.

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

New epidemiological studies

4. 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
Pancreatic cancer	4

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

5. Of the original studies, most were either hospital-based or population-based case-control studies. One was a cohort study (9) and one a retrospective mortality study of ecological design (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.

6. As we 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. Consequently, 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 this studies.

7. 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 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.

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Bladder cancer

8. 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 significantly elevated combined odds ratios (ORs) for men but not for women (10). In the first pooled analysis of 6 case-control studies (3 of which were included in the meta-analysis), there was a weakly positive association in men between cumulative exposure to THMs and risk of bladder cancer and estimated RRs increased with increasing exposure (11). No association was found among women. Additional results from the pooled analysis using a different measure of exposure to THMs again found a positive association with bladder cancer in men, but not in women (12); numbers of cases for women were much fewer than for men.

9. 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 association of bladder cancer with various measures of THM exposure (3). When adjusted for duration of exposure to ozonated water, an association was found at the highest average levels of THM concentration and with cumulative exposure to THM but there was no significant trend with exposure levels. A large case-control study reported an increased risk of bladder cancer association with estimates of DBP exposure from ingestion of drinking water, dermal absorption, and inhalation while showering, bathing and swimming in pools (13). In both the above studies, analyses by gender showed statistically significantly raised ORs in men but not in women.

10. 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.

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11. We consider that the additional studies provide limited evidence for an association between bladder cancer and exposure to CBPs but it is difficult to be certain because of the small relative risks recorded, the possibility of residual confounding and the problems with exposure assessment described above.

Colon and rectal cancers

12. A number of studies have examined the association between cancer of the colon or rectum and exposure to chlorinated drinking water. One new, good quality case-control study has been published on these endpoints (8). It found an increased risk of colon cancer among males with a number of measures of exposure to THMs. No increased risk was found for colon cancer in females nor for rectal cancer.

Other sites

12. A study of exposure to drinking water contaminants and childhood ALL found no 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 between pre- and post-natal exposure to THMs and polymorphisms in the *GSTT1* and *CYP2E1* genes (6). The finding is interesting but it is not possible to draw conclusions from these preliminary results. 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).

13. In a well-conducted, case-control study, a positive, dose-related association was found in men between measures of exposure to CBPs and brain cancer (glioma) (2). In contrast, no association was found in women. The reason why such an association should be sex-specific is not clear. There remains a possibility of residual confounding and it is questionable whether the association is biologically plausible given the low exposures.

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14. No increased risk of pancreatic cancer with increasing measures CBP levels was found in a population-based case-control study (4).

Conclusion

15. We have reviewed the new epidemiological studies on chlorinated drinking water and cancer published since 1999 and consider that they still fail to provide persuasive evidence of a consistent relationship. The additional studies provide limited evidence for an association between bladder cancer and exposure to CBPs but it is difficult to be certain because of the small relative risks recorded, the possibility of residual confounding and the problems with exposure assessment. No convincing evidence is provided for an association with other types of cancer.

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

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Appendix 1 to CC/07/19

Copies of papers reviewed in CC/07/11.

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