

CHLOROFORM (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Two studies of trihalomethane levels in drinking-water supplies and community-based rates of cancer mortality have been reported. Correlations were found between these levels and various site-specific cancer mortality rates, especially those for bladder cancer, but also those for cancers of the rectum/large intestine, brain and kidney and lymphoma^{1,2}. In one study in which trihalomethane levels in drinking-water at place of residence were compared directly for 395 matched pairs of female teachers with regard to colorectal cancer, no association with trihalomethane exposure was observed³. A mortality study of anaesthesiologists who worked at the time chloroform was used provided no significant information⁴.

Several investigations have attempted to assess the effects of trihalomethanes in drinking-water indirectly by comparing risks of cancers at various sites with extent of chlorination. Although excesses of some cancers have been found, it is not possible to evaluate any effect of chloroform from such studies⁵⁻¹⁶.

B. Evidence for carcinogenicity to animals (*sufficient*)

Chloroform produced benign and malignant tumours of the liver and kidney in mice following oral gavage^{17,18}. Administration in drinking-water to female mice did not increase the incidence of liver tumours¹⁹. Administration of chloroform to rats by gavage or in drinking-water increased the incidences of kidney^{17,19} and thyroid tumours¹⁷ and of neoplastic nodules of the liver²⁰. Chloroform was tested inadequately by subcutaneous and intraperitoneal injection in mice¹⁷. A study by oral administration in dogs gave negative results²¹. Oral administration of chloroform did not enhance the incidences of liver and lung tumours induced in mice by intraperitoneal injection of *N*-ethyl-*N*-nitrosourea²², but it enhanced the incidence of liver preneoplastic foci induced in rats treated by gavage with a single dose of *N*-nitrosodiethylamine²³.

C. Other relevant data

No adequate data were available on the genetic and related effects of chloroform in humans.

Chloroform did not induce micronuclei in bone-marrow cells of mice or DNA damage in liver or kidney cells of rats treated *in vivo*. It did not induce chromosomal aberrations, sister chromatid exchanges or unscheduled DNA synthesis in human lymphocytes *in vitro*. Chloroform enhanced virus-induced cell transformation of Syrian hamster embryo cells. It did not induce sister chromatid exchanges or mutation in Chinese hamster cells or DNA damage in rat hepatocytes *in vitro*. Chloroform did not induce sex-linked recessive lethal mutations in *Drosophila* or aneuploidy, mutation or somatic segregation in *Aspergillus*. Chloroform induced DNA damage but not mutation, aneuploidy, mitotic recombination or gene conversion in *Saccharomyces cerevisiae*, whereas mutation, mitotic recombination and gene conversion were induced in *S. cerevisiae* under conditions in which endogenous levels of cytochrome P450 were enhanced. Chloroform did not induce mutation or DNA damage in bacteria²⁴.

References

- ¹Hogan, M.D., Chi, P.-Y., Hoel, D.G. & Mitchell, T.J. (1979) Association between chloroform levels in finished drinking water supplies and various site-specific cancer mortality rates. *J. environ. Pathol. Toxicol.*, 2, 873-887
- ²Cantor, K.P., Hoover, R., Mason, T.J., McCabe, L.J. (1978) Associations of cancer mortality with halomethanes in drinking water. *J. natl Cancer Inst.*, 61, 979-985
- ³Lawrence, C.E., Taylor, P.R., Trock, B.J. & Reilly, A.A. (1984) Trihalomethanes in drinking water and human colorectal cancer. *J. natl Cancer Inst.*, 72, 563-568
- ⁴Linde, H.W. & Mesnick, P.S. (1980) *Causes of Death of Anesthesiologists from the Chloroform Era* (PB 80-125172 (EPA/600/1-79-043)), Springfield VA, National Technical Information Service
- ⁵Cantor, K.P. (1982) Epidemiological evidence of carcinogenicity of chlorinated organics in drinking water. *Environ. Health Perspect.*, 46, 187-195
- ⁶Carlo, G.L. & Mettlin, C.J. (1980) Cancer incidence and trihalomethane concentrations in a public drinking water system. *Am. J. public Health*, 70, 523-525
- ⁷Craun, G.F. (1985) Epidemiologic studies of organic micropollutants in drinking water. *Sci. total Environ.*, 47, 461-472
- ⁸DeRouen, T.A. & Diem, J.E. (1977) *Relationships between cancer mortality in Louisiana drinking-water source and other possible causative agents*. In: Hiatt, H.H., Watson, J.D. & Winsten, J.A., eds, *Origins of Human Cancer, Book A, Incidence of Cancer in Humans*, Cold Spring Harbor, NY, CSH Press, pp. 331-345
- ⁹Gottlieb, M.S., Carr, J.K. & Morris, D.T. (1981) Cancer and drinking water in Louisiana: colon and rectum. *Int. J. Epidemiol.*, 10, 117-125
- ¹⁰Alavanja, M., Goldstein, I. & Susser, M. (1978) *A case control study of gastrointestinal and urinary tract cancer mortality and drinking water chlorination*. In: Jolley, R.L., Gorchev, H. & Hamilton, D.H., Jr, eds, *Water Chlorination, Environmental Impact and Health Effects*, Vol. 2, Ann Arbor, MI, Ann Arbor Science, pp. 395-409

- ¹¹Brenniman, G.R., Vasilomanolakis-Lagos, J., Amsel, J., Namekata, T. & Wolff, A.H. (1980) *Case-control study of cancer deaths in Illinois communities served by chlorinated or nonchlorinated water*. In: Jolly, R.J., Brungs, W.A., Cumming, R.B. & Jacobs, V.A., eds, *Water Chlorination, Environmental Impact and Health Effects*, Vol. 3, Ann Arbor, MI, Ann Arbor Science, pp. 1043-1057
- ¹²Crump, K.S. & Guess, H.A. (1982) Drinking water and cancer: review of recent epidemiological findings and assessment of risks. *Ann. Rev. public Health*, 3, 339-357
- ¹³Gottlieb, M.S., Carr, J.K. & Clarkson, J.R. (1982) Drinking water and cancer in Louisiana. A retrospective mortality study. *Am. J. Epidemiol.*, 116, 652-667
- ¹⁴Young, T.B., Kanarek, M.S. & Tsiatis, A.A. (1981) Epidemiologic study of drinking water chlorination and Wisconsin female cancer mortality. *J. natl Cancer Inst.*, 67, 1191-1198
- ¹⁵Kanarek, M.S. & Young, T.B. (1982) Drinking water treatment and risk of cancer death in Wisconsin. *Environ. Health Perspect.*, 46, 179-186
- ¹⁶Wilkins, J.R., III & Comstock, G.W. (1981) Source of drinking water at home and site-specific cancer incidence in Washington county, Maryland. *Am. J. Epidemiol.*, 114, 178-190
- ¹⁷*IARC Monographs*, 20, 401-427, 1979
- ¹⁸Roe, F.J.C., Palmer, A.K., Worden, A.N. & Van Abbé, N.J. (1979) Safety evaluation of toothpaste containing chloroform. I. Long-term studies in mice. *J. environ. Pathol. Toxicol.*, 2, 799-819
- ¹⁹Jorgenson, T.A., Meierhenry, E.F., Rushbrook, C.J., Bull, R.J. & Robinson, M. (1985) Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3F₁ mice. *Fundam. appl. Toxicol.*, 5, 760-769
- ²⁰Tumasonis, C.F., McMartin, D.N. & Bush, B. (1985) Lifetime toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. *Ecotoxicol. environ. Saf.*, 9, 233-240
- ²¹Heywood, R., Sortwell, R.J., Noel, P.R.B., Street, A.E., Prentice, D.E., Roe, F.J.C., Wadsworth, P.F., Worden, A.N. & Van Abbé, N.J. (1979) Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. *J. environ. Pathol. Toxicol.*, 2, 835-851
- ²²Pereira, M.A., Knutsen, G.L. & Herren-Freund, S.L. (1985) Effect of subsequent treatment of chloroform or phenobarbital on the incidence of liver and lung tumors initiated by ethylnitrosourea in 15 day old mice. *Carcinogenesis*, 6, 203-207
- ²³Deml, E. & Oesterle, D. (1985) Dose-dependent promoting activity of chloroform in rat liver foci bioassay. *Cancer Lett.*, 29, 59-63
- ²⁴*IARC Monographs, Suppl. 6*, 155-158, 1987