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EDITORIAL

Chemicals: Perceptions Versus Facts

Recently some environmentalists have demanded that chlorine and compounds containing it be banned. Carol Browner, administrator of the Environmental Protection Agency (EPA), has indicated a willingness to be guided by environmentalists' urgings. The rhetoric about chlorine overlooks the role it plays in the economy and in our standard of living. Millions of lives have been saved by the use of chlorine for disinfection of water. The demand for banning implicitly accepts as valid the results of the questionable procedures on which EPA regulations are based.

With increasing frequency conventional risk assessments are being shown to produce fallacious results. A recent paper debunks the alleged hazards of chloroform,* a by-product of using chlorine to disinfect water. EPA has long taken the position that the carcinogenicity of chloroform is substantial. Its estimates are based on experiments in which chloroform was dissolved in corn oil and then administered to test animals by gavage. Five times each week for nearly a 2-year lifetime, a tube was inserted through a rodent's mouth and a bolus of lipid was shot into the stomach. The animals employed were B6C3F_1 mice, which have a variable and elevated natural rate of liver cancer. The mice responded to the gavage treatment with additional liver tumors. Other scientists later conducted experiments in which the chloroform was administered to B6C3F_1 mice in drinking water. The results showed that even with high levels of chloroform in the water, there were practically no tumors. However, it is the usual policy of EPA to disregard negative results, and so official concern about chloroform has been maintained.

The new research explored mechanisms leading to the differing results of the two modes of administration of chloroform. After treatment with various levels of chloroform, in one case for 4 days and in another for 3 weeks, detailed pathological studies were made. These included examination of liver sections and tests to quantitate cellular proliferation. Blood serum samples were analyzed for two liver enzymes, alanine aminotransferase (ALT) and sorbitol dehydrogenase. Excess amounts of these enzymes in serum indicates leakage from damaged cells. The new results showed a great contrast in the detailed pathological effects of administration of chloroform by gavage or in drinking water.

In the gavage experiments, extent of pathology increased with dosage. At the maximum tolerated dose of 477 mg/kg the mice displayed "severe centrilobular coagulative necrosis....The midzonal and periportal hepatocytes had severe vacuolar degeneration...." Elevated levels of hepatocyte proliferation and serum enzymes correlated well with histopathological evidence of hepatotoxicity. When high doses of chloroform were administered in drinking water, there was no increase in liver pathology or in serum levels of liver enzymes.

The conventional EPA analysis of results of the gavage experiment suggests that human risk of cancer would be increased by 1 in 100,000 by drinking water containing 4.3 parts per billion (ppb) of chloroform for a lifetime. In contrast, after administration of chloroform in drinking water, there was no induced cellular proliferation in rodent livers or increased levels of serum enzymes even when the concentration of chloroform was 1,800,000 ppb.

The close relationship observed between cytotoxic effects, cellular proliferation, and cancer lends weight to comments by Bruce Ames. He noted that a large number of nongenotoxic chemicals had been labeled carcinogens on the basis of results of experiments conducted employing huge toxic doses. He suggested that the tumors arose because DNA repair mechanisms could not match the high rate of toxicity-induced cellular proliferation.

Another consequence of the chloroform studies is to cast doubt on the validity of other risk assessment studies in which gavage was used. Questions had already been raised on a number of grounds, including the fact that a sudden bolus of lipid would interfere with normal metabolism. Nevertheless, in the official rodent risk assessment experiments reported on from 1980 to 1992 gavage was the method most frequently used.

Before acting further to ban chlorine and its compounds and issuing more stringent regulations of other chemicals, EPA should engage in a critical evaluation of its risk assessment policies and procedures. Ill-considered experiments leading to inflated perceptions of risk are no substitute for good science and facts.

Philip H. Abelson

* J. L. Larson, D. C. Wolf, B. E. Butterworth, *Fund. Appl. Toxicol.* **22**, 90 (1994).