The Chloroform Story: How Science Can Improve Regulatory Decision Making

“The research by the CIIT Centers for Health Research shows that chloroform-induced cancer in mice and rats is associated with killing of cells in the liver and kidney. This cell killing mechanism does not operate in people at the concentrations of chloroform that occur in the environment. The carcinogenicity of chloroform in laboratory animals is thus not predictive of expected human effects.”

—Dr. Rory B. Conolly, CIIT Centers for Health Research

The chloroform story is a triumph of the application of sound science in regulatory decision making. When science is brought to bear in this manner, the dual goals of protecting the public health and avoiding an unnecessary regulatory burden are achieved. The body of scientific knowledge about chloroform and the associated regulatory outcome both have far-reaching implications for regulatory decisions and the cancer risk assessments upon which many regulations are based.

A research effort during the 1990s to improve the scientific basis for estimating the cancer risk from exposure to chloroform provided a better understanding of chloroform toxicology and new insights into how to test appropriately for suspected carcinogens. The findings on chloroform prompted the U.S. Environmental Protection Agency (EPA) to accept that the dose-response for the carcinogenic effects of chloroform in rodents has a threshold. This is a key issue in cancer risk assessment as exposure below the threshold level does not cause an additional cancer risk.

In the late 1960s, increasing concern about carcinogens in the environment led to laboratory testing of many substances to determine whether they caused cancer in laboratory animals. The studies typically were performed by treating animals with repeated large doses of a compound, often at levels so high that frankly toxic effects were caused in tissues, such as the liver and kidney. Although not appreciated at the time, this approach produced many cancers that were secondary to the frankly toxic effects. The doses used to produce these toxicities and associated cancers were typically much higher than are encountered by people on a day-to-day basis. These laboratory animal-based tests for cancer were thus detecting cancer under special circumstances that are not relevant to actual human exposures.

Chloroform, a compound that can be formed as a byproduct when drinking water is disinfected with chlorine, was one of the chemicals tested in this way. EPA labeled chloroform as a probable human carcinogen based in part on studies in which a large dose of the chemical (roughly equivalent to that of a person drinking a glass of chloroform each day of his or her life) was given directly to the animal’s stomach via a tube—a method called “gavage”—once a day over most of the lifetime of the animal. These exposures were found to cause tumors in the livers of mice. Other studies, also at doses much higher than are encountered by people, found that exposure to chloroform in drinking water can cause tumors in rat kidneys.

EPA has regulated the allowable levels of chloroform and certain other disinfection byproducts in drinking water since 1979. However, the Safe Drinking Water Act of 1986 led EPA to reconsider these standards. In 1994, based on evidence of carcinogenicity from the early gavage studies and the lack of data to indicate how carcinogens cause cancer

How Carcinogens Cause Cancer

A carcinogen may lead to cancer through one of several mechanisms and processes, known as its “mode of action.” Understanding the mode of action is important for determining potential effects at low doses, which in turn is necessary for determining safe levels of exposure. There are two categories of carcinogens based on their modes of action:

Genotoxic carcinogens cause cancer by interacting directly with the DNA of a cell, altering or mutating the structure and function of DNA.

Non-genotoxic carcinogens cause cancer by other mechanisms. For example, a substance may be toxic or irritating to certain tissues, leading the cells in the tissue to grow and divide in a healing response. With this proliferation of cells, an altered or cancerous cell can arise due to genetic mistakes that can occur with frequent cell division.
any threshold in the dose-responses for cancer, EPA proposed a maximum contaminant level goal (MCLG) of zero for chloroform in drinking water. The MCLG is defined as a concentration of the compound in water at which no adverse human health effects are expected. EPA then sets an enforceable drinking water standard—called a maximum contaminant level (MCL)—as close to the MCLG as possible, taking into account technical feasibility and compliance costs.

The Chlorine Chemistry Council (CCC), the American Chemistry Council (ACC), then known as the Chemical Manufacturers Association, and other industry groups recognized that EPA’s proposed goal could lead to an extremely stringent MCL of uncertain public health value. This would pose significant costs to the chemical industry, water utilities, and society as a whole, and could dramatically impact the continued use of chlorine as a drinking water disinfectant, perhaps leading to a health risk from microbial infections. Facing such implications, industry wanted to ensure that EPA’s decisions were supported by a risk assessment that was based on sound science.

Many organizations participated in the research effort, conducting more than 30 studies of chloroform in laboratory animals. CIIT Centers for Health Research (CIIT) led the way on characterizing mechanisms of action of chloroform. One key approach was to compare the results of exposing mice to chloroform by gavage (one large dose per day) vs. their drinking water (same total dose per day, but administered slowly). In addition, changes in the liver caused by the different means of administration were evaluated. Another study at CIIT examined the role of chloroform-induced tissue damage in the kidney tumor response seen in rats.

CIIT found that very large doses of chloroform, when given to mice daily by gavage, produced liver damage. However, when mice were given the same daily dose in the animals’ drinking water, no liver damage was found. Follow-up research showed that the daily gavage doses overwhelmed the liver’s capacity to detoxify the chloroform, thereby resulting in a process of liver damage and proliferation of surviving cells that eventually led to cancer. When chloroform was given to the animals through drinking water, the liver was able to continually detoxify the chloroform as the mice sipped the water throughout the day. This research showed how the method used to administer chloroform to the animals was an important determinant of the carcinogenic effect in the liver. The research revealed that chloroform does not cause cancer by interacting directly with and damaging cellular DNA. Rather, the carcinogenic effects observed were due to the use of very large doses of chloroform—levels a thousand times greater than those found in drinking water. These large doses act through a different “non-genotoxic” mechanism that does not occur as a result of the levels of chloroform found in the environment. The kidney tumor response seen in rats was also found to be secondary to acute tissue damage that also does not occur at environmentally-relevant levels of exposure.

Historically, EPA had assumed that all chemicals identified as carcinogens or probable carcinogens could cause cancer at any exposure level or dose (i.e., there was no threshold or safe level). However, the research described shows that, for chemicals like chloroform that do not directly react with DNA, no increased risk of cancer is expected at doses that do not cause other toxic effects.

The new findings prompted EPA to revise its drinking water risk assessment for chloroform. In March 1998, EPA indicated that it was considering changing the proposed MCLG for chloroform from zero to 300 parts per billion—the first time the EPA recognized a safe level above zero for a compound identified as a known or probable carcinogen. Nevertheless, in December 1998, the EPA set a final MCLG of zero for chloroform, stating that it could not complete its analysis in time to meet the deadline for promulgating the final rule.

In December 1998, CCC and other industry groups filed suit against EPA for violating the Safe Drinking Water Act’s mandate to “use the best available, peer-reviewed science” when it finalized the MCLG for chloroform. The court agreed unanimously with the plaintiffs, and EPA subsequently withdrew the MCLG for chloroform. The EPA expects to finalize a new, non-zero, MCLG in 2004. Although this research had a profound effect on drinking water regulations for chloroform, its impact extends to other chemicals with non-genotoxic modes of action and the regulations that govern them. Their risk assessments will be more accurate, and the science will not be ignored.