SCIENCE

EDITORIAL

Exaggerated Carcinogenicity of Chemicals

Results of tests using the cancer-prone $B_6C_3F_1$ mouse have had a major role in risk assessment of many chemicals. However, studies that reveal differences in metabolism of mice, rats, monkeys, and humans raise doubts about the relevance of the mouse experiments. In addition, epidemiologic studies of the morbidity and mortality of longtime chemical plant workers are providing a basis for evaluating cancer risks of some chemicals.

An example involves butadiene, an important monomer in the production of synthetic rubber. Butadiene, C_4H_6, is highly volatile. When inhaled, most of it is exhaled. The compound as such is benign, but once absorbed, some is oxidized to a monoepoxide, C_4H_6O, that is mutagenic. Retention of inhaled butadiene by mice is much greater than by rats or monkeys. After exposures to 10 parts per million (ppm) of butadiene, retention by $B_6C_3F_1$ mice was 10 times that of rats and 33 times that of monkeys. After exposures to 10 ppm, blood levels in mice of epoxide were 590-fold greater than in monkeys exposed to 10 ppm. A further species difference is in the hydrolase enzyme activity that supports harmless metabolism of the monoepoxide to $C_4H_8O_2$. The mouse has lower levels of the epoxide hydrolase activity than either rats or humans.

Contrasts in the retention and metabolism of butadiene by Sprague-Dawley rats and $B_6C_3F_1$ mice are accompanied by differences in carcinogenic responses to inhalation of butadiene. When the rats were exposed to 8000 ppm over 2 years, a weak pathological response was elicited.* Most of the tumors observed were nonmalignant. When the mice were exposed to 625 and 1250 ppm, the study was stopped at 60 and 61 weeks because tumors in the exposed mice were causing excessive mortality. The tumors were in many tissues and included alveolar (lung) and hepatocellular (liver) carcinomas.

The $B_6C_3F_1$ mice differ from some other mice and from humans and rats in possessing an endogenous murine leukemia virus (MuLV). This virus has been shown to have a substantial role in enhancing the incidence of malignant (thymus) lymphomas when the mice are exposed to butadiene.† The presence of the endogenous MuLV virus and its activation by butadiene exposure could also affect the incidence of other tumor types in exposed $B_6C_3F_1$ mice.

The $B_6C_3F_1$ mice differ from rats, monkeys, and humans in a propensity to oxidize the monoepoxide to a diepoxide $C_4H_6O_2$. This latter compound has been shown to participate in the formation of DNA-DNA and DNA-protein cross-links in the mouse. The final fate of much of the metabolites of butadiene is excretion in the urine as mercapturic acids formed by conjugation with glutathione. In the mouse urine a major part of the mercapturic acid conjugates involves the monoepoxide. In the monkey only trace levels of the monopoxide conjugate were found. The conjugate with the harmless hydrolysis product $C_4H_8O_2$ predominated. In vitro studies with liver and lung microsomes have shown that metabolism of the butadiene monoepoxide in humans also proceeds through the pathway to the non–DNA-reactive product.

The National Institute of Occupational Safety and Health (NIOSH) has based its "best estimate" of the carcinogenicity of butadiene solely on experiments on the $B_6C_3F_1$ mouse. The results of rat, monkey, and human tests showing major differences in uptake, retention, and metabolism, and far less risk of cancer, have been disregarded.

As is customary, extrapolations from doses in mice to low doses in humans are made with the use of arbitrary models. One model gives the result that 45 years of exposure to 2 ppm of butadiene in the workplace should lead to 10,000 deaths of 10,000 workers. The estimate made by NIOSH was 597 excess cancers per 10,000 workers having that same exposure.

A Texaco sub-cohort of 1066 butadiene monomer workers employed at or soon after industry start-up during World War II experienced the high exposures of those times (the mandated threshold limit value was 1000 ppm).‡ These workers have been followed from first employment in 1943 to 1945 through the end of 1985. Their overall mortality from cancer was only 75% of that of the rate for the ordinary public. Instead of the extra cancers predicted by NIOSH, workers had fewer cancers than expected.

With trillions of dollars, loss of competitiveness, and jobs at stake, a searching review of the risk assessment methodology of the regulatory agencies is overdue.

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*A. R. Dahl *et al.*, *Environ. Health Perspect.* **86**, 65 (1990). †R. D. Irons, W. S. Stillman, M. W. Cloyd, *Virology* **161**, 457 (1987). ‡B. J. Divine, *Environ. Health Perspect.* **86**, 119 (1990).