SCIENCE

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EDITORIAL

Flaws in Risk Assessments

Chemical risk assessment studies conducted with rodents have helped to justify expenditures of more than a trillion dollars over the past 20 years. Large additional outlays are planned, although it has not been shown that such studies have substantially benefited human health. In fact, it has become increasingly clear that the main causes of untimely human death are smoking and diet. For example, a recent article in the *New England Journal of Medicine** indicates that excess weight has a wide range of deleterious effects on health.

The risk assessment procedures used by the Environmental Protection Agency (EPA) have been criticized for many years and for many reasons. Their quality has recently come under intensified criticism, as is evident in the proceedings of a July 1995 meeting sponsored by Toxicology Forum of Washington, D.C., and in a recently published book, *Dietary Restriction.*† The critics point out that rodent risk assessment studies lack reproducibility because of genetic drift in the test animals and because of a failure to control their consumption of food.

Most standard risk assessment experiments expose rodents to large doses of a test chemical for about 2 years, which is approximately their natural life-span. For most tests, one or more of three strains of rodents are used: Sprague-Dawley (SD) rats, Fischer (F-344) rats, and B6C3F1 mice. These animals have a higher natural incidence of tumors than do humans, and some of the tumors are not common to humans. These rodent strains were adopted in the belief that they would exhibit less variability than wild-type animals do. On the basis of this assumption, enormous effort has been expended in studies of about 500 different chemicals. Each experiment has involved comparison between dosed and nondosed animals (controls). Thus a large database is available concerning the weight, longevity, and pathology of control animals. Data cited in the Toxicology Forum proceedings and in *Dietary Restriction* indicate that, during the past 25 to 30 years, the adult body weight of rodents from most of the strains used in toxicity testing has increased 20 to 30%. Degenerative diseases and tumor incidence also have increased. Rodent survival has decreased. At the Merck Research Laboratory in the 1970s, the survival rate at age 2 of SD rats used as controls was 58%. In the 1980s it was 44%, and in the 1990s it had dropped to 24%. A different laboratory compiled data on F-344 rats. In 1970, 80% of males survived for 2 years. In 1981, 60% survived. Their current survival rate is 36%. The incidence of tumors in control rodents has also changed with time. For example, the number of liver tumors in control B6C3F1 mice increased from an average of 32% in 1980 to about 50% in 1984. In tests at various laboratories, liver tumor incidence in male B6C3F1 mice has varied between 10 and 76%.

A partial explanation for this variability in longevity and health lies in practices at the breeder companies. Apparently, they have unwittingly caused genetic drift by their methods of selecting breeding stock. The standardized procedure at risk assessment laboratories has also been a factor. In general, animals are fed ad libitum (ad lib); that is, they are given as much food as they want to eat. As a result of overeating, the health of ad lib animals is impaired. This is clearly shown by the fact that if the food intake of littermates of ad lib animals is reduced to 70% or less of ad lib amounts, rodent health and longevity are much improved. A recent experiment using SD rats compared the longevity of control rats fed ad lib with that of rats fed 65% of the ad lib amounts. At maturity, the ad lib males weighed 60% more than did the diet-restricted males. Only 7% of the ad lib males lived as long as 2 years. In contrast, 72% of the diet-restricted rats survived for more than 2 years. They were sleek and healthy. Although this phenomenon has been widely observed and well known for many years, the standard protocol still calls for ad lib feeding, so that in effect, when animals are exposed to chemicals in risk assessments, they simultaneously receive one potential carcinogen and one known carcinogen—their food.

When scientists plan experiments, they seek to control the important variables and to achieve time-invariant reproducible results. Those at EPA with the responsibility for establishing protocols for risk assessment experiments have acted as if they did not share these goals.

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*J. E. Manson *et al.*, *N. Engl. J. Med.* **333**, 677 (1995). †R. W. Hart, D. A. Neumann, R. T. Robertson, Eds., *Dietary Restriction: Implications for the Design and Interpretation of Toxicity and Carcinogenicity Studies* (ILSI Press, Washington, DC, 1995).