

## Statistical Issues in the Analysis of Rodent Carcinogenicity Studies

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The carcinogenic risk of a compound is routinely evaluated by giving it to rodents over a two-year period. If the incidence of cancer increases with increasing dose of compound, the study is “positive”. We will give an overview of statistical issues important to assessment of carcinogenicity studies, including sample size, use and misuse of dual control groups, maximum tolerated dose, need to account for survival differences, tumor lethality, time-to-tumor, interim sacrifice, use of *a priori* information, and the impact of housing and feeding protocol on statistical analysis. We will assess multiplicity in detail. Multiplicity arises because each type of cancer observed is analyzed separately for males and females, resulting in several dozen statistical tests. With so many tests there is need to control for the risk of “false-positive” findings arising purely by chance. Rodent carcinogenicity studies offer a good context to study multiplicity because similar designs have been used many times so rich historical data are available. We begin by using historical control data from dual control groups to illustrate the risk of false-positive findings. Methods to control the false-positive rate are discussed including that currently used by the U.S. FDA. The FDA method maintains power at the cost of variable false-positive rate depending on sample size, survival, rodent species, and even strain of rodent. The method routinely used at Merck will be described. Methods will be compared and issues illustrated using a “true negative” study and historical data. Transgenic animal models offer a powerful means to assess carcinogenic risk while avoiding many of the issues in conventional two-year studies, while raising new issues.

**KEYWORDS:** multiplicity, safety assessment, risk, tumorigenicity