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# This Week's Citation Classic®

**Kastenbaum M A & Bowman K O.** Tables for determining the statistical significance of mutation frequencies. *Mutat. Res.* 9:527-49, 1970.
[Oak Ridge National Laboratory, and Computing Technology Center, Oak Ridge, TN]

Low frequency events such as mutation, chromosome breakage, and nondisjunction are Poisson events that require special statistical treatment. For the geneticist who has counted a total of *n* mutations in two experimental groups, this paper provides answers to the question, "What is the number of mutations, *c*, in group 1, that will allow me to conclude that the mutation frequency in group 1 is significantly greater than that of group 2?" [The *SCI*® indicates that this paper has been cited in over 265 publications.]

## Eight Billion Mice Is the Answer—What Is the Question?

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For over two decades after World War II, the Biology Division of the Oak Ridge National Laboratory was a major center for basic research on the effects of ionizing radiation on biological systems. Its director, Alexander Hollaender, was a brilliant visionary and a superb scientific administrator whose talents attracted some of the best biologists from around the world to his laboratory in the remote foothills of East Tennessee. Under his direction, their research contributed vastly to our current understanding of the mechanisms associated with the somatic and genetic effects of ionizing radiation.

Sometime during the early, formative years of his laboratory, Hollaender recognized the need for mathematical and statistical support in the modeling and fitting of the rapidly accumulating data on dose-response relationships. Among those in Oak Ridge who could readily appreciate this need were Alvin Weinberg, director of the National Laboratory, and Alston Householder, director of the Mathematics Panel. Both Weinberg and Householder had come to Oak Ridge from the University of Chicago, where they were, just a few years earlier, students and associates of Nathan Rashevsky, the leading proponent of mathematical biology in the US.

Formal statistical consultation began with the appointment, in 1950, of Allyn Kimball to the staff of the Mathematics Panel. Soon after his arrival, Kimball set up shop in offices adjacent to the Biology Division. He thus established a precedent that survives to this day in Oak Ridge of "lodging" mathematical and statistical support in close proximity to the laboratories of biological scientists.

In one of Kimball's many publications during his 10-year residency in Oak Ridge, he showed how certain general statistical concepts could be applied to the calculation of confidence intervals for recombination experiments with microorganisms. Our 1970 paper in *Mutation Research* represents a further elaboration and extension of these concepts. It was stimulated by the research of Heinrich Malling, a biochemical geneticist who had arrived in Oak Ridge from Denmark in the early 1960s. Malling had been recruited to collaborate with a group of geneticists led by Frederick de Serres. The specific microorganism they worked with was *Neurospora crassa*.

The question raised by Malling and de Serres was not unique to their area of research. Indeed, it is a problem that many scientists, biologists and others, face when they set out to plan an experiment. They need to know the optimal number of sample observations that must be made to detect a *real effect*, if such an effect truly exists. We and our collaborators have addressed this problem in a number of publications.[1-9]

One particularly fascinating application has even been characterized as *trans-scientific*.[10] Our own characterization of this example is expressed by the title, "Eight billion mice is the answer—what is the question?" It arises as follows: If the genetic response to X-radiation is linear, then a dose of 150 millirems would be expected to increase the spontaneous mutation rate in mice by 0.5 percent. To determine, with 95 percent confidence by direct experiment, whether 150 millirems will increase the mutation rate by 0.5 percent requires about 8,000,000,000 mice! This number is so large that the question is unanswerable by direct scientific investigation.

The methodology used to achieve this result is similar to the one discussed in our 1970 paper in *Mutation Research*. We are indeed pleased that this paper has proved to be so valuable a guideline to the many scientists who have used it in planning their mutation experiments.

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10. **Weinberg A M.** Science and trans-science. *Minerva* 10:209-22, 1972. (Cited 65 times.)




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