United States
Environmental Protection
Agency

Office of Health and
Environmental Assessment
Washington DC 20460

Research and Development

EPA/600/S8-89/068 Feb. 1990

EPA

Project Summary

Application of an Exact NOAEL—Procedure for Dichotomous Data from Animal Experiments

A statistical method has been developed that utilizes a step-wise hypothesis testing procedure to estimate the distribution of the no-observed-adverse-effect level (NOAEL), and thereby to estimate the expected value of the NOAEL and its variability. The methodology is dependent upon the sum of the dose group sizes, the expected response rates, experimental dose levels, and the type I error rates. The technique may be employed to evaluate the reliability of the NOAEL and to provide a measure of its variability.

This Project Summary was developed by EPA's Environmental Criteria and Assessment Office, Cincinnati, OH, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

In the risk assessment of systemic toxicity, the no-observed-adverse-effect level (NOAEL) is the highest experimental dose level at which one does not reject the hypothesis that the expected response rate is the same as in the control group. The NOAEL is then scaled downward, usually by a factor of 10, 100 or 1000, to obtain the reference dose (RfD). The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

There is a need to estimate the variability of the NOAEL (and consequently of the RfD) and to estimate the false negative rate, which is indicative of unacceptable increases in added risk over a specified background rate. A statistical method has been developed that addresses these issues (Brown et al., 1986). This project illustrates with real data sets how this method can be used in evaluating noncarcinogenic risks, and in measuring uncertainties in the process. The expected value of the NOAEL, its variability, and the relationship between Type I errors (false positive rates) and type II errors (false negative rates), are all interrelated and are dependent upon sample sizes, the expected (but unknown) response rates, dose values and the statistical analysis employed.

Results and Conclusions

The statistical procedure is applicable to experiments that produce dichotomous response data (presence/absence of a response of interest). The responses for each dose group are assumed to be independently distributed from binomial distributions. For example, the response rates for an experiment with control, low, and high dose groups are represented by the binomial population parameters p_0, p_1 and p_2, respectively. The approach utilizes methods of isotonic inference to incorporate *a priori* knowledge that $p_0 \leq p_1 \leq p_2$. (The inequalities could also be reversed.) The long-term relative frequency (probability) with which the NOAEL would take each dose value in repeated sampling is derived. From this distribution an estimate of the expected

value (long-term average) of the NOAEL and its standard deviation are obtained.

The power for detecting a treatment effect at any dose can be calculated for any background rate and value of added risk. This is particularly useful for determining the added risk that can be detected with a specified power, and to specify an upper limit of added risk that is consistent with the data even when no treatment effect has been detected.

Recommendations

The step-wise hypothesis procedure produces conditional probabilities for the second hypothesis test, which depend on the results of the first hypothesis test. Therefore, the testing of the second hypothesis and the determination of its corresponding type II error rate are accomplished using only part of the available data. Also, the entire procedure is dependent on the choice of values for the type I error rates. These observations lead to the recommendation that an in-depth analysis of this method be made.

It is apparent that the method will require extensive amounts of computer time when the dose group sizes are large or when there are more than three to four dose groups to analyze. The limits of this procedure because of data processing requirements should also be investigated.

References

Brown, K. G., L. M. LaVange, T. S. Farrell, and S. C. Wheeles. 1986. An Exact NOAEL—Procedure for Dichotomous (Incidence) Data, and Its Statistical Properties. Research Triangle Institute Report, RTI/3510,3516, Contract No. 68-01-6826, Statistical Policy Branch, U.S.EPA, 401 M Street, S.W., Washington, DC 20460.

This Project Summary was prepared by staff of the Environmental Criteria and Assessment Office, Cincinnati, OH 45268.
***Jeff Swartout** is the EPA Project Officer (see below).*
The complete report, entitled "Application of an Exact NOAEL—Procedure for Dichotomous Data from Animal Experiments," (Order No. PB 90-145 780/AS; Cost: $15.00, subject to change) will be available only from:
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Telephone: 703-487-4650
For information contact:
Environmental Criteria and Assessment Office
U.S. Environmental Protection Agency
Cincinnati, OH 45268

United States
Environmental Protection
Agency

Center for Environmental Research
Information
Cincinnati OH 45268

Official Business
Penalty for Private Use $300

EPA/600/S8-89/068