UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 6 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Transmissal of Technical Report Critiquing the Statistical Analysis of the Dimethoate Rabbit Teratology Study.

Tox Chem. # 358

FROM: Bertram Litt, Team Leader
Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: Karen Hamernik, Ph.D.
Section VII, Toxicology Branch/HED (TS-769)

The attached report indicates that the statistical methods used by Edwards, Leeming and Clark in their report to DTF tend to underestimate the probability of finding a statistically significant difference among treated and control groups of rabbits and more specifically between individual treatment groups and the controls. D. Gosh has indicated alternative procedures which take into account the study design features and which should provide more accurate estimates of the probabilities of detecting specific differences among or between study groups.

Attachment

cc: File
Coberly
Gosh
Litt (2)

OPP:HED:TOX:B.LITT:sb 5/6/85 X73715 #a

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: B. Litt

FROM: D. Ghosh

SUBJECT: Dimethoate, New Zealand White Rabbit Teratology Study: Statistical Comments

Variation in response is to be expected not only between fetuses in the same litter but also between litters receiving the same dosage. An analysis based on the response of individual foetuses, ignoring litters, underestimates the true standard errors of estimated dosage differences. The analysis of a summary variable like the mean foetus weight is inefficient because it ignores the differences in litter size. Healy (1972) has shown that a weighted analysis is appropriate for such cases.

A variable measured as a reading in such an experiment can be expressed as the sum of three parts:

$$y = \mu + \varepsilon_1 + \varepsilon_2$$

where μ is an overall mean value which depends upon the dosage (treatment) applied, ε_1 is a random term with mean zero and variance σ_1^2, which is common to all readings within a particular litter and ε_2 is an independent random term with mean zero and variance σ_2^2. The variance of the mean of a litter of n animals is this $\sigma_1^2 + \sigma_2^2/n$ and its appropriate weight is the reciprocal of this.

In this case the treatments have been applied at random, so the analysis suggested by Healy is straightforward. First a three-level analysis of variance could be constructed with rows for treatments, litters within treatments and within litters. The mean squares from this analysis are used to estimate σ_1^2 and σ_2^2 and finally weighted treatment means can calculated and compared. The first two steps form a standard type of hierarchical analysis of variance.

References

Healy, M. J. R. (1972) "Animal Litters as Experimental Units" Applied Statistics. Vol 21, (1975) 155-159.

Williams, D. A. "The analysis of binary responses from toxicological experiment involving reproduction and teratogenicity" Biometrics 31, 949-952.

Kupper L. L. and Haseman J. K. (1978) The use of correlated binomial model for the analysis of certain toxicological experiments. Biometrics 34, 69-76.

Altham P. M. E. (1978) Two generalizations of the binomial distribution. Applied Statistics 27, 162-167.

Gladen B. (1979) The use of Jackknife to estimate proportions from toxicological data in the presence of litter effects. Jour. Am. Stat Assoc. Vol 74, 278-83.