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July 27, 1987

Dr. Harold L. Kaplan
Southwest Research Institute
P.O. Drawer 28510
6220 Culebra Rd.
San Antonio, TX 78284

Dear Hal:

As you may recall we decided to ask Dr. Sara Debanne to review the statistical analyses that we have used. Her comments are enclosed; please review these so that we can discuss them.

Sincerely,

Bob Hinderer

Robert K. Hinderer, Ph.D.
Manager, Toxicology

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CASE WESTERN RESERVE UNIVERSITY • CLEVELAND, OHIO 44106

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July 22nd, 1987

Dear Bob,

Here, finally, is the critical review of the statistical portions of your paper; I had hoped to have it completed sooner but the study is just too intricate.

While I am essentially suggesting that you reanalyze the data, it should also be said that this is related to just two issues. A more proper handling of these would require the use of different models of the ANOVA family than the ones you used, but the approach and the interpretation of findings would be the same.

The review took more time than I expected. I estimate that, over and above what I originally perceived this would require, I spent one half day on it. Please let me know if I may send you an invoice for this amount of time. Thank you. Cordially,

Sara

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Statistical Review of "Effects of HCl on Respiratory Response and Pulmonary Function of the Baboon."

The main statistical comments are summarized in detail in the attached TABLE. The several comments of mine in the critique of the TABLE are based on a few issues appearing in various combinations. Here, they will be addressed in a general sense.

1. Transformations of Data

Some dependent variables used in the statistical analyses were derived by mathematical transformation of more original outcome data. The variables, respiratory rate, tidal volume and minute volume, underwent transformation in the analyses of respiratory response (ratio during exposure to baseline), and CO_2 challenge response (slope during ramping period and ratio of maximum value during exposure to baseline average).

It could be suggested that the resultant transformed variables have distributions further from the Normal than do the original data and for the respiratory response tests the use of baseline value as a covariate might be more appropriate.

The danger here is that the p-value of a test may be understated (i.e., more likely to result in rejection of a true null hypothesis than presumed) through the use of such transformed data.

2. Statistical Tests

The critique of statistical test utilized involves some subtle modeling points. First, is the general notion that the potential interdependence of outcome variables suggests that the multivariate ANOVA (MANOVA) model structure is more appropriate for analyzing the data than are the separate ANOVA's of the paper. Second, is the comment that 1-way tests (MANOVA's) with repeated measures are preferable to the 2-way ANOVA's presented in much of the paper. Indeed, it is inappropriate to model time as a main effect in a 2-way ANOVA when parallel values over time correspond to values from the same animal (repeated measures).

Along with the TABLE are further ADDITIONAL COMMENTS addressing various items.

Summary Table of Statistical Tests and Comments

Issue	Variables	Transformations (if any)	Analysis Technique	Critique
Respiratory response	Respiratory rate, tidal volume, minute volume	Ratio (exposure to baseline)	1-way ANOVA's, Duncan groupings	Is transformation necessary? If so, 1-way MANOVA might be preferable. If not, multivariate CANOVA or 1-way MANOVA with repeated measures might be preferable.
	Arterial blood gas sample averages		2-way ANOVA's (exposure and time as main effects)	The 1-way MANOVA with repeated measures is a preferable test.
Pulmonary function tests	PFT variables and arterial blood gas sample averages		2-way ANOVA's	The 1-way ANOVA with repeated measures is a preferable test.
CO_2 challenge responses	Respiratory rate, tidal volume, minute volume	Slope (during ramping period)	2-way ANOVA's with repeated measures. Multiple comparisons	Is transformation (use of slope) appropriate? It may understate p-values. Even so, model should be 1-way MANOVA with repeated measures. Otherwise, a complex MANOVA model might be fitting.
		Ratio (of maximum exposure value to baseline average)	2-way ANOVA's with repeated measures. Multiple comparisons	This transformation may also understate p-values. Possibly a MANOVA with repeated measures would be preferable.

Additional Comments

1. On pages 4 & 5 there is discussion of a change in the control of exposure. Possibly, it would be appropriate to conduct a test of homoscedasticity (e.g., Bartlett's, Cochran's tests) for data generated under each method of control.

   Heteroscedasticity could lead to understating p-values.

2. On page 14 it appears to indicate that raw response rate data was analyzed by a statistical test, the result of which was non-rejection of the null hypothesis of equality of exposure groups.

   It is then stated that an ANOVA of slopes during ramping time was conducted whereby some significant differences were detected.

   Only the second of these statements seems to described on page 10.

3. A textual comment referring to page 10, second paragraph:

   LINE 2 of that paragraph replace "with" by "against."
   LINE 3 of that paragraph replace "between" by "to each other across."