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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: ACEPHATE - Statistical Review of Cholinesterase Activity in Humans, Monkey and Rat Caswell #2A

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SUMMARY:

This memo addresses the question: Did the sponsor do an adequate statistical analyses to say there is a statistical difference between species?.

The statistical analysis that was done gives estimates of the I_{50} (estimated dose that would cause 50% inhibition of cholinesterase) but no statistical test of the difference between species is made. An analysis of variance is recommended for testing for species differences in the comments section of this memo.

BACKGROUND:

This is a study of the comparative in vitro activity of Acephate Technical SX-1102 (98.7% purity) on brain, erythrocyte, and plasma cholinesterase from the human, monkey, and rat. Most of the rat data comes from 3 Charles River CD rats, the monkey data is from 3 wild-caught cynomolgus monkeys from Charles River, the human blood data comes from 4 volunteers, and the human brain

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tissue is from three accident victims. The study was conducted by the Melvin Calvin Laboratory for Chevron Chemical Company. The study number is S-2150, EPA accession number 249639, EPA Record Number 92537. The study date was November 30, 1982.

COMMENTS:

Basically the experimental design is a 2-factor factorial design with doses, anywhere from 4 to seven, as one factor and subjects as the other factor for each species. All subjects were measured at all doses. For monkeys, the plasma, erythrocyte, and brain data came from the same monkeys. For humans, brain data was from one set of subjects and the plasma and erythrocyte data from another set of subjects. In the rats most of the data comes from rats 8, 9, and 10 but there is some data from 11, 12, 13, 15, and 16. The sample size is very small in all groups, 3 or 4 subjects. This will affect the size of the type I error (probability of a false positive) as well as the type II error (probability of a false negative).

There appears to be a correlation between the time of the analysis and the magnitude of the response, e.g. the human data in the company's report, reference 3, table 6.

The statistical analyses makes no test of the hypothesis of no differences between species. They simply do a regression analyses for each species and then say that they are obviously different. An alternative technique would be to do a factorial analysis on the data, with species as one factor, dose as the second factor, and subjects nested within species. This would allow for a test of the hypothesis of a statistical difference between species mean cholinesterase level.

The data is converted from cholinesterase activity to percent of the control activity, then subtracted from one to get percent inhibition, and then the arc-sine transformation is applied to normalize the data. It would appear that by merely taking the difference of the dosed activity from the control activity and doing the analysis on the deviations from the control value would be simpler. This assumes that cholinesterase activity is normally distributed. The reason that all the transformations bother me is that the single degree-of-freedom test made in the regression analyses removes 90% to 99% of the variability in the data. This is not even considering that all of the measure that the regression is done on are not independent.

The statement made in the statistical report as to the order of the three species is undoubtedly correct. Since no statistical test of significance was made I can not agree with the statement "Comparison of the 95% confidence intervals

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clearly indicates that rat brain AChE is significantly more sensitive to inhibition by acephate than monkey brain which is more sensitive than human brain." I am not saying that the statement is wrong but that I would not make the statement without a statistical test.

The ratios of the percent inhibitions that are calculated in the company's report, reference 3,table 1 (attached), indicate that the monkey is consistently closer to the human values but the rat values differ by at most a factor of 3.4.

The study appears to be very well conducted and many possible sources of variation were explored. There are many other parameters that could be estimated from this study.

ACEPHATE

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