Monsanto

FROM (NAME & LOCATION) Dept. of Medicine & Environmental Health - P.L. Wright, A2SC

DATE: March 24, 1976 CC:

SUBJECT: Toxicity Studies with PCB in Primates

REFERENCE:

TO George Roush, Jr., M.D.
A2SA

Studies conducted under the direction of Dr. J. R. Allen, University of Wisconsin, have resulted in reports of specific toxicity manifestations following prolonged PCB administration to Rhesus monkeys. These reports have been used to support the conclusion that the subhuman primate is much more sensitive to PCB than is the rat. The greater sensitivity of man is implied. One toxic manifestation reported was impaired reproduction performance in the treated females. One of 8 females fed 5 ppm AROCLOR 1248 for 6 months conceived. Three of 8 females fed 2.5 ppm conceived. These conception rates were compared with a 90% conception rate in control females in the same facility. Although other signs of PCB toxicity were reported, the major emphasis was placed upon the impaired reproduction performance. Allen concluded that significant toxic effects were produced at the lowest level (2.5 ppm, 100 µg/kg/day) tested. A no-effect level was not determined in the subhuman primate. This defiency may have future critical implications for Monsanto.

In an effort to develop data that would define a no-effect level for PCB in subhuman primates, protocols and cost estimates were obtained from the following sources:

Source	Quotation
The Albany Medical College	$ 147,000
Hazleton Laboratories	128,000
Litton-Bionetics	138,500
Oregon Regional Primate Center	219,700
Southwest Foundation for Research and Education	547,100

Each of these sources has had previous experience with subhuman primate reproduction studies. LEMSIP (New York University Medical Center) declined to submit a proposal, citing their inability to obtain monkeys until late Fall, 1976.

A critical review of the submitted proposals indicated that the Oregon and Southwest protocols were not responsive to our needs. The Southwest proposal would utilize baboons and is far more elaborate in scope than the current ability to interpret the possible results. The Oregon proposal objective is to conduct

subacute toxicity studies with 10 pure homologs. Tissue residue and metabolite identification studies will be conducted. The Oregon proposal does not involve any reproduction parameters.

The Litton-Bionetics proposal incorporates the most evidence of previous experience with primate studies. This protocol is also most directly related to our need to demonstrate a no-effect level. Doses equivalent to 0, 5, 25 or 100 µg/kg/day would be administered for 6 months. Mating would be initiated after 6 months and continued until pregnancy or for up to 12 months after treatment was initiated. Treated males would be mated with control females from the existing breeding colony. In addition, conventional clinical parameters and gross and histopathological evaluations would be conducted.

Litton-Bionetics has an adequate number of breeding animals available to conduct this study. Every other laboratory, except Southwest, would have to acquire animals prior to the initiation of the study. Initiation of treatment in April or May will allow completion of the 4 to 6 month period required to reach steady state tissue concentrations prior to the normal fall mating period.

The business group Product Acceptability Manager, J.C. Weber, has agreed to arrange for the proper persons to attend a meeting when we have our recomendations finalized. I will review this with you at your convenience.

PLW

Paul L. Wright

/bkp