Monsanto

FROM (NAME LOCATION PHONE)

Dept. of Medicine & Environmental Health - P.E. Berteau, A2SC (4-2164)

DATE: July 19, 1979

SUBJECT: Review of Litton-Bionetics study on the effects of PCB's on non-human primates

REFERENCE: BIO-77-2
JRGO to PEB, et al, 7-3-79
FAP to PEB, 7-10-79

TO J.C. Weber, B2SK

cc: G.F. Cahill, B2SA
G.J. Levinskas, A2SA
J.R.G. Ortiz, E2ND
F.A. Provorny, B3NJ
R.A. Stohr, B3NJ
D. Wood, B2SD

JUL 19 1979

In preparation for our meeting on July 20, 1979, the following will provide a brief summary of the draft final report recently issued by Litton-Bionetics on the above referenced subject.

Groups consisting of four male and eight female rhesus monkeys were fed daily doses of PCB's (AROCHLOR 1254) of 0, 5, 25, and 100 µg/kg for 14 months (4-1-77 - 6-1-78) and then held for an additional six months (6-1-78 - 12-5-78) without administration of PCB's until terminal sacrifice. During the feeding period, the animals were bred over an eight month period commencing six months after feeding was started (10-1-77 - 6-1-78). The animals were wild-caught, were estimated to be at least six years old, and had an established record of average or better than average reproductive capacity. Due to the erratic behavior of the specie and the occurrence of some rather unexpected findings, frequent protocol changes were necessary. Litton has deligently documented these changes and the reason for them according to Good Laboratory Practice.

The reproductive function of the males was determined by semen evaluation which was conducted monthly for the first 14 months; the reproductive function of the females was evaluated by breeding, the essential parameters being induction of pregnancy and delivery of a viable infant. Periodic fat biopsies were taken for determination of PCB levels in tissue. Levels in the milk of nursing mothers, the placentas at birth, and the skin of infants were also submitted for analyses for PCB's. These analyses were conducted at Monsanto MICC analytical facilities or Monsanto Research Corporation, Dayton.

The following summarizes the essential findings in this study:

(1) Mortality

Incidences of mortality in the adults during the entire period of the study were:

0536189

IN-10M (REV. 2/78)

PCB-ARCH0744975

Dose (mg/kg)	Males	Females
0	0/4	1/8
5	0/4	0/8
25	0/4	1/8
100	1/4	4/8

Of these deaths, only the 1/4 incidence in the males and 4/8 in the females in the high dose group were considered to be related to PCB administration.

Because of the incidence of early fetal wastage, still-births and deaths during infancy, it is not possible to make a clear-cut comparison of dose-related mortality with the infants. One formerly viable infant in the high dose group and one in the medium dose group died of causes that appear to be related to administration of PCB's to the mother.

(2) Fertility

No effect on male fertility was evident in the males. Fertility in the females was markedly effected in the high dose group, but not at lower dosages. Numbers of viable infants born was: control (7), 5 μg/kg (5), 25 μg/kg (7), and 100 μg/kg (1).

(3) Toxic Signs

Various signs of PCB toxicity such as redness and/or edema and puffiness of the eyelids, swelling of the lips, etc. began to become evident after nine months of feeding PCB's and one or other of such symptoms occurred in all animals in both sexes in the high dose group and in one male in the medium dose group at the time of termination of PCB administration. These signs partially regressed during the six months withdrawal period, but some signs remained until terminal necroscopy. Blackening of the teeth and alopecia were also seen; these signs may or may not be related to PCB administration. Chloracne was not reported. Signs in the infants were more marked, being evident both in one infant born to a mother fed the high dose and in two from the medium dose group. Infants from the low dose group did not exhibit signs of PCB toxicity, except possibly in one case where an intraosseous cyst occurred in an infant from the low dose group.

(4) Biochemistry

The only biochemical parameters which were considered to be affected by PCB's were serum cholesterol, which was significantly reduced in the high dose females during feeding of PCB's, but which slowly increased

PCB-ARCH0744976

after withdrawal, and serum iron levels which were elevated in females in the high dose group. This finding was considered to be consistent with the hematological findings (see below). Based upon a hypothesis that the toxicity of PCB's may be related to an effect upon Vitamin A, analysis for this vitamin was made in serum, just prior to terminal necroscopy. No dose related changes were evident.

(5) Hematology

Depression of red cell values was evident at certain blood collection periods in animals in the high and medium dose groups, as well as platelet depletion. Four females in the high dose group and one male, died of symptoms which may have developed due to these effects. Statistical analysis of the overall hematological parameters in the high dose group compared to other groups is difficult because of death and removal of the lowest values from the groups, thus affecting the means and standard deviations. However, an effect on blood parameters almost certainly did occur in the high dose group. Based upon the findings at terminal necroscopy, the mechanism of action appears to be an effect upon bone marrow.

(6) Histopathology

Major findings include: Meibomian glands, loss of secretory epithelium; mucinous metaplasia in the ducts. Skin, follicular keratosis, squamous cysts. Mandible, intraosseous cysts. Pancreas, hyperplastic epithelial changes in the duct. Bone marrow, non specific alterations. Kidneys, areas of cortical retardation in the infants. Litton-Bionetics reports that these lesions are similar to those reported in the literature following PCB administration.

(7) Analysis of Tissues

Litton-Bionetics do not include these values in this draft report since some discrepancies in the data had not been resolved at the time that the report was written. A separate report is available from Monsanto Research Corporation. Considerable variation is evident. A dose related trend in tissue levels appears evident, although specific incidences of wide variation and confusion regarding measurement of PCB's on a lipid or wet weight basis as well as many missing samples will make a statistical analysis difficult or impossible. It is extremely unlikely that the extent of toxicity will be able to correlated with PCB accumulation in tissue in specific animals.

Conclusion

Relative to reproductive performance, the no-effect level for males is 100 µg/kg and 25 µg/kg for females.

0536191

PCB-ARCH0744977

Relative to hematological abnormalities, the no-effect level appears to be 25 µg/kg for both sexes.

Relative to toxic signs, the no-effect level is 25 µg/kg for males and 5 µg/kg for females.

These no-effect levels refer to adults only; relative to effects upon offspring, the no-effect level can tentatively be set at 5 µg/kg fed to the mother.

This information is based upon a preliminary review of Litton-Bionetics draft report which contains many areas of information which will need clarification before the report will be accepted by DMEH. Thus the information given in this review may change when the report and data have been more extensively examined.

Peter E. Berteau

alw

PCB-ARCH0744978