Monsanto

Dept. of Medicine & Environmental Health — P.E. Berteau, A2SC

DATE December 12, 1978

SUBJECT Current status of the toxicity study entitled "Effects of PCB on the Reproductive Performance of the Rhesus Monkey" conducted at Litton Bionetics

REFERENCE Memo: JCW to PEB, et al, 12-11-78

TO

cc J.P. Mieure, T3B
F.A. Provorny, B2SC
W.E. Ribelin, EHL
D. Wood, B2SD

J.C. Weber, B2SK

In connection with above referenced memorandum confirming the meeting on December 14, 1978 (B203C, 8:30-9:30 a.m.), the following will provide a status report on the study conducted for Monsanto by Litton Bionetics in which monkeys were fed varying levels of PCB's.

As indicated in the distributed trip report, W.E. Ribelin (Pathologist, Monsanto Environmental Health Laboratory) and myself visited Litton, December 4-5, 1978, just prior to terminal sacrifice. That sacrifice commenced December 5, 1978, according to protocol. As of that date, no animals had died since September 9, 1978, and none that can be attributed to feeding PCB's since August 21, 1978. Levels fed have been 0 (control), 5 µg/kg, 25 µg/kg, and 100 µg/kg to 4 males and 8 females. The PCB was fed for 14 months (April 1, 1977 to June 1, 1978). Breeding was conducted from October 1, 1977 to June 1, 1978. Feeding was discontinued after June 1, 1978, and terminal sacrifice was commenced approximately 6 months later (December 5-11, 1978).

Prior to sacrifice, 4/8 females in the 100 µg/kg group have died and 1/4 males in that group. These deaths appear to be related to complications arising from depression of hematological parameters (pancytopenia) and can tentatively be attributed to PCB administration. Except for 1 female which developed this syndrome and survived until terminal sacrifice (4-6 weeks), this lesion was fatal. No deaths have occurred below the 100 µg/kg dose that can be attributed to PCB's. Visible signs of PCB toxicity (eyelid puffiness, chloracne, etc.) were evident in most animals surviving 100 µg/kg. Signs of toxicity in adult animals fed 25 µg/kg are not clearly apparent. Reproductive function was markedly reduced in females fed 100 µg/kg, but not at lower doses. Male fertility (semen evaluation) was unaffected at any dose. Infant monkeys have done less well, and evidence of PCB toxicity may be apparent in those born to mothers fed 25 µg/kg and possibly at 5 µg/kg. However, because of the protocol, infants received varying amounts of PCB's from their respective mothers because of the June 1 cessation of feeding PCB's when many animals were nursing. Thus, little in utero information can be expected from this study.

IN 10M (REV. 2/78)

Upon our arrival December 4, 1978, Dr. Siebold (Pathologist, Litton) gave a slide presentation on some of the observations found in tissues of animals fed PCB's which had died or been sacrificed during the study. Among these findings were: Meibomian gland, squamous metaplasia, atrophy and impaction of duct. Skin changes, squamous impaction of hair follicles, loss of sebaceous glands. Thymus, cystic changes in the medulla, reactive involution. Stomach, metaplasia of the gastric gland. Liver, necrosis. Bile duct, hyperplasia. Pancreatic duct, hyperplasia, acina atrophy. Kidney, cortical dysplasia in the infants. Bone marrow, diminished cellularity. Heart, squamous metaplasia of the epicardium.

In the light of these observations, which must be recorded in the final report, it was agreed that the following additional tissues should be harvested at sacrifice and fixed in formalin: parathyroid, pyloric stomach, prostate gland, extrahepatic bile duct, cecum, bone marrow (smear from femur), left nipple, foreskin, labium, spleen, skeletal muscle, sciatic nerve, tibial nerve, spinal cord, skin from left hip, skin from left thigh. The cost of harvesting these tissues was estimated at $1450. In view of the urgency and to avoid the risk of compromising the study, I gave verbal approval for this expenditure at the meeting. However, the cost of preparing slides of these tissues and pathological examination would incur an additional $11,300. Bill Ribelin also observed lesions (he was present at the first day of necroscopy) which may be suggestive of inactivation of vitamin A and thus may provide some explanation of the lesions encountered in animals which received PCB's. It was suggested by both of us that levels of this vitamin be determined in blood and liver samples at the final necroscopy. This extra cost should be minimal.

I concur support

In view of the findings, we need to decide whether we are likely to be obligated to inform EPA or other government agencies of them under TOSCA regulations. In any case, we recommend that the additional tissues be examined and that the costs be funded. These 2 matters should comprise the areas of emphasis at the December 14, 1978, meeting. In addition, the difficulty in obtaining analyses from MRC Dayton should also be addressed. The final report cannot be issued until these analytical data have been obtained. Litton estimates a June 1, 1979, final report date; it would be regrettable and embarrassing to me if this report were delayed because of delay in generation of the analytical data by Monsanto.

Subject to decision. However, EPA has Jim Allen's data (Wisconsin) which casts suspicion on PCBs below existing levels approved by FDA. I doubt we have an obligation to report anything from this study.

P.E.B.

Peter E. Berteau

alw

if I'm free, I would like to attend.

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