

In the first two litters there are slightly lower birth weights, considerably lower 21 day weights, (50% decrease—1st litter; 25%—2nd) and a very low 21 day survival of offspring of animals receiving the drug. The third litter study in which drug was stopped 10 days following 3rd pairing is claimed to support the contention that maternal hyperactivity on the drug is an important factor in poor survival and growth in the offspring in the previous two litters. However, it does not rule out the effect of the drug on the fetus and neonates during late pregnancy and lactation. Moreover, 6 of 12 pregnant females had been taken off the drug before they conceived in the third cycle. (IND 1134 Summary delivery data dated February 16, 1964. This table is not included in final report to NDA 11-613.) Fifty percent of females who eventually became pregnant failed to conceive during the ten day period of pairing on the drug as opposed to 23% of controls during this same period. Since only 1 female received the drug for more than 6 days after conception (as calculated from day of littering) this third litter is of little value as a teratology study. While no anomalies have been observed grossly, adequate examinations by clearing and staining or sectioning for skeletal and visceral changes were not carried out.

Study 3.—Rats dosed 5 days per week, 2 mg or 5 mg/kg/day (3.3 and 8.3 HTD) pretermine resin complex (day of pairing to 21 days post partum) showed no significant differences in % pregnancies, live or dead fetuses per litter, birth weights or 21 day survivals. Twenty-one day weights were significantly higher at 2 mg/kg than in other groups but this is probably not drug related since not dose dependent. No anomalies reported.

EVALUATION

Lack of teratogenicity at doses of 3.3 and 8.3 times HTD in the pregnant rat appears satisfactorily established but since this drug is specifically recommended for weight control in pregnancy, teratologic studies according to 1966 guidelines should be run in another species at higher doses, given only at time of organogenesis.

The six month subacute toxicity study was carried out on the phentermine HC1 powder (not on the resin) in spite of earlier recommendations and queries as to the possibility of accumulation of the drug suggested by the increased death rate (9 during 13th–27th week) in the chronic 3 litter reproduction studies on 40 mg/kg as opposed to no deaths in a shorter 5 week study at the same level.

L. L. PHILLIPS, Ph. D.

MEMORANDUM

FOOD AND DRUG ADMINISTRATION,
August 13, 1958.

To: New Drug Branch.
Attention: Dr. DeFelice.
From: Division of Pharmacology.
Subject: Ionamine Resin (R. J. Strassenburgh Co.)

The toxicity data submitted in support of this NDA are not sufficient to evaluate the safety of this preparation. We have advised the company by telephone that they should complete the toxicity study so that we could properly evaluate the safety of the preparation. They have several groups of rats on the drug for about 8 weeks and plan to carry them for 6 months. They plan to start dogs on the drug by the end of the month and carry these animals for 3 months.

E. I. GOLDENTHAL