UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HEALTH EFFECTS RESEARCH LABORATORY
RESEARCH TRIANGLE PARK
NORTH CAROLINA 27711

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Date: June 28, 1984

Subj: Review of Teratology Studies on CGA-72662 Technical

From: Neil Chernoff, Director
Developmental Biology Division MD-67

To: Larry Chitlik, Section Head
Toxicology Branch TS-769C

I have reviewed two studies submitted by the IRDC to Ciba Geigy on the teratogenic potential of CGA-72662 Technical. The first study was the "Pilot Teratology Study in Rabbits" submitted 11-14-79 and the second was the "Teratology Study in Rabbits" submitted 5-7-81.

In general I am unable to draw any definite conclusions from these studies because of what I feel is the compromised health status of the dams. It is a basic principle of teratology testing that the maternal animals must be free of disease prior to, and during the studies. Animals in all groups including the control used in these studies suffered hair loss, nasal discharge, diarrhea, congested lungs, pitted kidneys, and hydroceles on the oviducts. While the statement is made that these are "common findings in Dutch Belted rabbits of this age" (7-9 months old) I would think that this is debatable. Many of these effects are characteristic of pasturellosis and/or Nosema infections. The utilizatin of such animals results in great difficulties when one attempts to interpret the data. What appears to be obvious from the reports is that the responses of both controls and treated animals in experiments one and two differ markedly. Maternal weight gain of the controls in these two experiments are not comparable nor are the incidences of malformations. It is my opinion that detailed analysis of such data may not be worth the effort involved given the uncertainties surrounding the dams. One or two general points should be made however. While historical controls are a valuable asset in any study, they cannot be used to discount differences seen in treated vs. experimental animals. All data has to be compared with concurrent controls and cannot be dismissed because the experimental group data "fell within the range of the historical control." Another point concerns the various reasons given for discounting the significant effects noted in experiment II. Presence of anomalies similar to those seen in historical controls cannot be considered a reason for discounting such effects. There has been, to my knowledge, no fetal effect which has only been found with a specific agent. All defects will arise spontaneously at some incidence in controls. Further, although a low frequency of occurrence (1-5%) is not typical of teratogenic induction" (pg. 22) such an event (a teratogenic producing anomalies at a low frequency) cannot be ruled out, and in fact, has occurred in my laboratory.

The central point, however, still remains the difficulty in comparing experiment I with experiment II, and in using either of these studies given the health status of the dams in all groups.

7-8-84