UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

11/4/83

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Dr. W. Woodrow, Toxicologist
Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: William L. Burnam, Chief
Toxicology Branch/HED

11/10/83

THRU: Laurence D. Chitlik, Section Head
Toxicology Branch, HED

SUBJECT: Bladex Teratology Study in F344 Rats

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We are forwarding to you the following review to be incorporated in the Bladex Registration Standard. This review covers the following two items:

1. A new teratology study in the Sprague-Dawley rat strain (RTI #31T-2564, 5/16/83); Project #61230.

2. An addendum to the teratology study in the Fischer 344 rat strain (WRC RIR-311, by Lu, C.C.; Tang, B.C.; Chai, E. Y., 1981); Project #61230.

It should be noted that the teratology study in the Fischer 344 rat mentioned above was originally reviewed by Dr. W. Dykstra on 2/6/82 and an addendum which contained the registrant's comments was also reviewed by Dr. Dykstra on 1/26/83 (copies of these reviews are attached to this memo). However we noted on 11/2/83 in the draft of the Bladex Registration Standard that this study in the F344 rats was re-reviewed by MITRE Corporation (see MITRE's draft review dated 6/9/83).

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We also noted that, although the MITRE's draft review has addressed several issues relevant to the lower classification of the study and has a comprehensive assessment of some findings , i.e. maternal body weights, it did not adequately address the major fetal malformation issues i.e. diaphragmatic hernia, and anophthalmia/microphathalmia. These malformations were the subject of subsequent addenda by the registrant, and they were effectively addressed by Dykstra in his 1/26/83 review and in the attached review.

The registrant considers that the diaphragmatic hernia is an artifact and/or has attempted to define this finding as a developmental variation in the F344 rat. However, we note that this is a retroactive assumption and we have suggested in the attached memo to the registrant that the control and high dose group, 25 mg/kg/day, should be repeated in order to confirm the nature and incidence of this finding (i.e. artifact or terata),see the attached review, page 1 and 2.

The registrant also considers that the anophthalmia/microphthalmia incidences at the high dose are related to maternal toxicity. However, we note that the extent of maternal toxicity at this dose level is not biologically meaningful, i.e. approximately 6% reduction in body weight during days 10 to 15 of gestation; and does not justify the registrant's claims discussed above.

In conclusion, it seems that the nature and incidence of fetal malformations are the most relevant issues in a teratology study. In the Bladex study, these issues have been adequately addressed in Dykstra's reviews and in the attached review.

We suggest that Bladex should be regulated as a teratogen with 25 mg/kg/day as the lowest effect level and 10 mg/kg/day as the NOEL for anophthalmia/microphthalmia until adequate confirmation is available concerning the nature and incidence of diaphragmatic hernia; see the recommendation section in the attached review.

We also suggest that a tentative margin of safety (MOS) should be calculated based on a 10 mg/kg/day NOEL; this may need to be reconsidered once the requested study is submitted.

For the Registration Standard, a decision should be made to either use the in-house evaluations of the teratology study in F344 rat or to use the MITRE's draft review.

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