



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

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

SUBJECT: Bladex Teratology Study in F344 Rats

Caswell 188C

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).

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/microphthalmia. 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.

JPC
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