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

AUG 16 1984

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Larvadex® (cyromazine). Re-evaluation of Mouse Oncogenicity Study.
Tox Chem. No. 167B

TO: Herb Harrison, Branch Chief
Insecticide and Rodenticide Branch
Registration Division (TS-767)

FROM: Edwin R. Budd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 8/16/84

THRU: William Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

WJB 8.16.84

Background:

In response to recent concerns regarding the mouse oncogenicity study on Larvadex®, this study was re-evaluated. The results of this re-evaluation are presented below.

Summary:

This oncogenic study is classified as Core Supplementary pending submission by the registrant (Ciba-Geigy) of the information described below under "Outstanding Requirements." When this information is received by the Agency and found to be satisfactory, this study will be upgraded to Core Guidelines. As such, it will be acceptable in fulfillment of the requirement for an oncogenicity study. With the possible exception of "malignant lymphomas" (for which the additional information is being requested in order to further evaluate this possible effect), no oncogenic potential was observed in male or female mice at dosage levels up to and including 3000 ppm of Larvadex® in the diet for 2 years.

Outstanding Requirements:

1. Historical control data (on an animal by animal basis) for malignant lymphomas in male and female mice from the same strain and testing laboratory (i.e. IRDC) as this Larvadex® study. This data should, if possible, include a separate listing for "lymphocytic lymphoma" and "histiocytic lymphoma" as was done in this Larvadex® study. See also below for distinguishing between type A and type B "histiocytic lymphoma" (if the data permits). This data should be presented in a

format listing individual study results--including date of study, duration of study, results by sex, incidence of lesion and number of animals examined for the lesion in question. As much recent data (since 1978) should be included as is possible.

2. A re-reading of microscopic slides should be made for those male and female mice in this study with "histiocytic lymphoma" in order to distinguish between type A (uniform type cells) and type B (polymorphic type cells). This re-reading of slides is necessitated by the fact that type B is properly included with "malignant lymphomas", but type A is not.

Study Identification:

"Oncogenicity Study with CGA-72662 in Albino Mice", International Research and Development Corporation (IRDC), Study No. 382-082, June 30, 1982 (submitted by Ciba-Geigy).

Test Material:

CGA-72662 Technical
95.3% to 95.5% active ingredient

Protocol:

See the attached 6 pages which were copied directly from the study report (pp 4-10). This protocol is judged to be fully adequate to assess the oncogenic potential of the test material in mice. It is noted that no urinalyses or clinical chemistries were performed on the mice in this study, but these tests are not required for an oncogenic study. Also, organ weights at necropsy were not determined for lungs, spleen and ovaries. These determinations are not essential to the assessment of oncogenic potential since detailed gross and histopathological examinations were made on these organs. It should also be noted that the entire in-life phase including gross necropsies were performed and reported by IRDC whereas all the histopathological procedures and the entire histopathology report were performed and reported by Experimental Pathology Laboratories, Inc. The histopathology report, dated May 31, 1982, was signed by Jerry F. Hardisty, D.V.M., pathologist.