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

AUG 16 1984

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MEMORANDUM

SUBJECT: Larvadex® (cyromazine). Re-evaluation of Mouse Oncogenicity Study.

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

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)

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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

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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.

Page _____ is not included in this copy.

Pages 3 through 9 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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_____ Internal deliberative information.

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_____ Claimed Confidential by submitter upon submission to the Agency.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Results:

Diet Analyses and Diet Stability Tests

Mean values in percentage of target level and their standard deviations are presented below for each treatment group for the entire duration of the study. The respective ranges are also shown.

Nominal Dosage Level (ppm)	Percentage of Nominal Level Mean	S.D.	Range
0	-	-	-
50	97	21.4	58-162
1000	102	13.5	77-133
3000	99	8.6	77-117

The test material was found to be stable in the prepared diets for at least 35 days.

Appearance and Behavior

No changes in appearance, behavior, signs of toxicity or moribundity were observed which were considered to be biologically meaningful or attributable to the test material. Palpable masses were observed with about equal frequency in male and female control and test groups respectively.

Survival

Percent survivals for males were 62%, 63%, 55% and 55% and for females were 52%, 47%, 57% and 40% (out of the 60 animals in each group continued on the study for 24 months) for the control, low, mid and high dosage level groups respectively. The actual numbers of males surviving to termination of the study were 37, 38, 33 and 33 and of females were 31, 28, 34 and 24 for the control, low, mid and high dosage level groups respectively. Mortalities during the study at various intervals were about the same for control and test animals (by sex). There is a suggestion of a possible slightly increased mortality in the high dosage level female mice.

Body Weights

Statistically significant decreased body weights and decreased body weight gains were observed in male high dose mice after 8 weeks and in male mid dose mice after 19 weeks. These decreased body weights and body weight gains continued to termination of the study. No meaningful differences in body weights or body weight gains were observed in female mice between control and test groups throughout the study.

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Food Consumption -

For both male and female treated groups, food consumption was consistently less than for their respective controls throughout the study. Statistical significance, however, was irregular. There was no apparent dose relationship for males. For females, there was a suggestion of a possible dose relationship.

Mean Intake of Test Material

Based on body weights and food consumption, the mean intake of test material was calculated for weeks 0 to 104 for each sex and group. The mean intake of test material for males were 6.50, 126 and 384 mg/kg/day and for females were 8.24, 164 and 476 mg/kg/day for the low, mid and high dosage level groups respectively.

Hematology

Hematological parameters for both males and females showed no changes considered to be related to the test material. An increase in leucocyte counts for high dose females was observed at 24 months, but this was due primarily to highly elevated counts in a few animals only and was considered to be not related to the test material.

Gross Necropsy

The incidences of liver masses in male and female mice are presented below. No liver masses were observed in any animals prior to or at the 12 month interim sacrifice.

Dosage Level (ppm)	Male Mice(1)			Female Mice (2)		
	12-24 Mo.	Terminal	Total	12-24 Mo.	Terminal	Total
0	6	6	12	2	2	4
50	1	12	13	2	1	3
1000	4	9	13	1	0	1
3000	3	12	15	2	1	3

(1) First liver mass observed at 64 weeks.

(2) First liver mass observed at 64 weeks.

A slightly increased incidence of liver masses was observed in treated male mice at the terminal sacrifice. Masses were not observed earlier in treated male or female mice than in their respective control groups.

Other changes observed at gross necropsy were sporadic, not dose related and of a type often observed in mice of similar ages.

Organ Weights

At the 12-month interim sacrifice, significantly decreased absolute liver weights and/or liver/body weight ratios were observed in male mice at the low, mid and high dosage levels and in female mice at the mid dosage level. At the terminal sacrifice, a significantly increased liver/body weight ratio was observed in the high dosage level male mice. This latter observation may have been related, to some degree, to the significantly decreased body weights of these male mice. It should also be noted, however, that 1,2,1 and 4 male mice with extraordinarily high liver weights (described as "questionable weight"--see Appendix F) for the control, low, mid and high dosage level groups respectively were not included in the statistical analysis of this data. With the exception of the control animal, which had a liver cyst, each of these male mice had a mass in its liver--see Appendix G. A few other changes in organ weights were not considered to be biologically meaningful.

Histopathology - Neoplastic Lesions

Malignant Lymphomas - There were numerous instances of malignant lymphoma (lymphocytic lymphoma and/or histiocytic lymphoma) reported for both male and female mice in control and all treatment groups. The incidences were reported in the summary tables on a tissue by tissue basis only. In as much as these malignant neoplasms occur in numerous tissues for a single affected animal, it was not possible to determine from the summary tables how many individual animals in each group were effected with this lesion. This information, however, was extracted from the individual animal histopathology data in the report and is presented below.

" The following table shows the indivual animal examination summary for malignant lymphoma: (1) -

Malignant Lymphoma In Charles River CD-1 Mice Fed LARVADEX

DOSE (ppm)	0	50	1000	3000
MALES				
Lymphocytic Lymphoma				
- 12-Month Sacrifice	0/8	0/8	0/8	0/8
- Early Deaths	3/23	4/22	6/27	7/27
- Final Sacrifice	0/37	1/38	0/33	0/33
TOTAL	3/68	5/68	6/68	7/68
Histiocytic Lymphoma				
- 12-Month Sacrifice	0/8	0/8	0/8	0/8
- Early Deaths	1/23	1/22	1/27	2/27
- Final Sacrifice	1/37	1/38	1/33	3/33
TOTAL	2/68	2/68	2/68	5/68
FEMALES				
Lymphocytic Lymphoma				
- 12-Mounth Sacrifice	0/8	0/8	1/8	0/8
- Early Deaths	3/29	7/32	2/25	7/30
- Final Sacrifice	0/31	6/28	4/34	3/23
TOTAL	3/68	13/68*	7/67	10/61*
Histiocytic Lymphoma				
- 12-Mounth Sacrifice	0/8	0/8	0/8	0/8
- Early Deaths	4/29	2/32	2/25	1/30
- Final Sacrifice	7/31	2/28	2/34	0/23
TOTAL	11/68	4/68	4/67	1/61

* P= 0.05 (Chi-square)"

(1) Copied from a memorandum from Carolyn Gregario to William Butler, dated June 28, 1984, which presented a "preliminary review" of this mouse oncogenicity study on Larvadex®.

Increased incidences of lymphocytic lymphoma were observed in male and female mice at all treatment levels when compared to their respective control incidences. An increased incidence of histiocytic lymphomas was also observed in male mice at the high dosage level. The incidence of histiocytic lymphoma was decreased, however, in all female treatment groups.

To assist in the interpretation of this data, Ciba-Geigy should be requested to provide to EPA historical control data and the results of a re-reading of pertinent microscopic slides as described below.

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.

Liver Neoplasms - The incidences of primary liver neoplasms in male and female mice (excluding malignant lymphomas) are presented below for those animals which died or were sacrificed after 1 year. No primary liver tumors were noted prior to or at the 1 year sacrifice.

	Dosage Level (ppm)			
	0	50	1000	3000
MALES				
Hepatocellular carcinoma	6/60[1]	8/59	6/53	10/57[2]
Hepatocellular adenoma	5/60	9/59	11/53	5/57
Hemangiosarcoma	2/60	0/59	0/53	0/57
Hemangioma	1/60	0/59	0/53	0/57
FEMALES				
Hepatocellular carcinoma	0/56	0/57	0/57	0/57
Hepatocellular adenoma	0/56	2/57	1/57	3/57
Hemangiosarcoma	1/56	0/57	1/57	0/57
Hemangioma	0/56	0/57	0/57	0/57

(1) Number of animals with lesion/number of animals examined.

(2) One mouse had a carcinoma and an adenoma. It was counted once under carcinoma.

In male mice, a slightly increased incidence of hepatocellular adenomas and carcinomas was observed in each of the treated groups as compared to the control group. In female mice, a similarly increased incidence of hepatocellular adenomas was also observed in each of the treated groups as compared to the control group. Since there was no apparent dose response relationship, no evidence of a dose related incidence of preneoplastic lesions in the liver, no increase in degree of malignancy, no evidence of a decreased latency period with respect to formation of these tumors and the incidences were similar to those observed in historical control animals, the slightly increased incidences of liver neoplasms in the treated male and female mice were considered to be not biologically meaningful.

Hemangiosarcoma of the Spleen - In female mice, a slightly higher incidence of hemangiosarcomas of the spleen was observed in treated mice as compared to control mice.

	Dosage Level (ppm)			
	0	50	1000	3000
MALES				
Hemangiosarcoma	0/60	0/59	1/53	0/57
Hemangioma	0/60	1/59	0/53	0/57
FEMALES				
Hemangiosarcoma	0/56	2/57	3/57	3/57
Hemangioma	0/56	0/57	0/57	0/57

In as much as this is a frequently observed tumor type in the spleen of mice and there is no strong dose response relationship, a relationship between this tumor type in female mice and the test material can not be established.

Mammary Gland Neoplasms - In female mice, a slightly higher incidence of adenocarcinomas of the mammary gland was observed in treated mice as compared to control mice.

	Dosage Level (ppm)			
	0	50	1000	3000
FEMALES				
Adenocarcinoma	2/56	4/57	3/57	8/57
Adenoacanthoma	3/56	1/57	0/57	1/57
Total	5/56	5/57	3/57	9/57

Adenoacanthomas of the mammary gland were also reported in these same mice. Since adenocarcinomas and adenoacanthomas refer to the same disease process, their incidences were combined as shown above. The total incidences indicate that a relationship between this tumor type and the test material can not be established.

Other Neoplasms - Other neoplasms observed in control and treated mice were types oftentimes observed in this strain of mice and were not increased in treated mice to a level warranting concern.

Histopathology - Nonneoplastic Lesions

Incidences of numerous nonneoplastic lesions in control and treated animals were similar. In no instance did there appear to be a biologically meaningful difference between control and test animals. Commonly occurring lesions in both control and treated animals included the following:

- Chronic lung inflammation
- Chronic nephritis and tubular cysts in the kidneys
- Involution of the thymus
- Generalized amyloidosis
- Chronic adenitis of the Harderian gland
- Extramedullary hematopoiesis and brown granular pigment in the spleen
- In females, cystic endometrial hyperplasia, parovarian cysts, cystic follicles in the ovaries, cystic hyperplasia of the mammary gland.

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PC Code:	**121301**
HED File Code	**13000 Tox Reviews**
Memo Date:	**12/20/1984**
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Accession Number:	**412-01-0166**

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