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

MEMORANDUM

002617

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Adam Heyward
Registration Division (TS-767)
and
Franklin Gee
Registration Division (TS-767)

THRU: William Butler, Section Head #3
Toxicology Branch
Hazard Evaluation Division (TS-769) William J. Butler 3-21-83

SUBJECT: PP#2F2707; Larvadex (Cyromazine) on poultry and eggs, Conditional New Chemical Registration, Accession No. 071185-071193, Study No. 382-081; 382-082. June 30, 1982 and May 26 and 31, 1982 CASWELL#167B

Action Requested:

Review final report on 2-year chronic and oncogenicity study in albino rats and oncogenicity study in albino mice with technical larvadex for conditional registration.

Review of New Studies from Submission:

A. CGA-72662 Technical, Two-Year Chronic and Oncogenicity Study in Albino Rat, IRDC, Mattawan, Michigan, No. 382-081, Accession No. 071186-071188, June 30, 1982.

Material Tested:

CGA-72662 Technical, cream-colored powder, 96.3% pure, FL-790733 (SL-116) and 95.5% pure, FL-810262.

Methods:

Sixty individually housed Charles River CD rats per sex per group were fed control or treated diet plus water ad libitum at dosage levels of 0, 30, 300 and 3000 ppm after a seven day conditioning period. Ten extra animals per sex for interim sacrifice were added to the control and high dose group.

187

The animals were maintained on a 12 hour on/off lighting cycle and a constant room temperature (70-75°F) and monitored relative humidity from 32 to 90%. After one year of the study elapsed five animals per sex per satellite group were sacrificed the other five animals per sex per satellite group were put into a 4 week recovery period prior to sacrifice.

The appearance, behavior, signs of toxicity and moribundity were observed twice daily and individual detailed observations were recorded weekly. Individual body weights were recorded weekly for 13 weeks, and during the recovery period. Otherwise this was recorded every two weeks. The same schedule was followed for 10 randomly selected rats per sex per group for individual food consumption.

The hematological and biochemical testing was performed on 8 randomly selected rats per sex per group at 0, 6, 12, 18 and 24 months of the study. The blood was obtained by venipunction of the orbital sinus plexus after overnight fast of 16 hours during which time urine was collected.

The hematology study included hemoglobin, hematocrit, erythrocyte count, total and differential leucocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and MCHC, reticulocyte count and Heinz body examination. The latter two parameters were tested only at time 0 unless signs of anemia were exhibited.

Determination of Na^+, K^+, Ca^{++}, BUN, alkaline phosphatase, total bilirubin, AST, ALT, LDH, total protein, cholesterol, glucose, T_3 and T_4 were made.

Urinanlysis was used to determine color, appearance, microexamination of sediment, sp. gr., volume, pH, protein, glucose, occult blood, nitrites, libirubin, ketones and urobilinogen.

The macroscopic pathology and histopathology were evaluated in one-half of the satellite group at 12 month interim sacrifice. The animals were examined thoroughly externally and a gross examination of abdominal contents, thoracic and cranial cavities. The following tissues were trimmed and fixed: liver, kidneys, testes, heart, brain, subcutaneous tumors, adrenals, aorta, bone marrow, brain, cecum, cervix, colon, spleen, stomach, thymus, lung, epididymus, esophagus eyes and Harderian glands, optic nerves, ovaries, lymph nodes, mammary gland, muscle, rectum, thyroid, pancreas, peripheral nerve, pituitary prostate, salivary gland, sciatic nerve, skin, small intestine, trachea, urinary bladder, uterus, vagina, gross lesions.

2

EPL performed the histopathology.

The diet was sampled and tested for homogeneity and stability.

Results:

Appearance and Behavior:

There were no significant difference between the control animals and the treated animals. The signs frequently observed in all groups were palpable masses, corneal opacity, red area around eye, and red material in eye, decubital ulcer and hair loss. Some treated animals were noted to have excessive salivation, changes in eye size, emaciation and distention.

Morbidity:

There was no difference in the survival time among the control or treated groups at 104 weeks. The lowest number of animals surviving was in the female control group, 32/60.

Body Weights:

There was a dose-related decrease in mean body weight at terminal sacrifice, 104 weeks, in both sexes. This decrease was found to be significant during the study only in the 300 and 3000 ppm groups.

Food Consumption:

The decrease mean food consumption, g/rat/day was statistically significant in the male and female groups fed diets containing 300 and 3000 ppm test material in a dose related progression. Although Group 2 receiving 30 ppm had a decrease mean food consumption it was not statistically significant. The high dose interim sacrifice groups of both sexes immediately and continuely through the four weeks withdrawal period had mean food consumption equal to or greater than those control animals sacrificed at 12 month interim during the withdrawal period.

Clinical Laboratory Tests:

The results of the haematology, biochemistry and urinalysis did not indicate any test compound dose relationship. Only a few spurious values were statistically significantly different from the other values or from the range of normal values for the CRCD albino rat.

3

Macroscopic Observations:

In the group of animals that were deaths and unscheduled sacrifices from 0-12 months consisting of 5 treated males and 5 control and 4 treated males there no significant or dose related abnormalities and only 1 subcutaneous mass in a control female.

In the 12 month interim sacrifice group there were no tumors and no significant difference between the male or female control groups or 3000 ppm groups macroscopically.

There was a significant lowering of mean organ weights in only the 3000 ppm group (specifically liver, kidney, heart and testes).

The pilot investigation using 5 male 0 ppm and 5 male 3000 ppm rats for measurement of T_3 ug/dl and T_4 ug/dl and testosterone, pg/ml at 18 months and 24 months yielded results with no statistical significant difference of any value from control.

Organ Weights:

The mean organ weight decreases found only at 3000 ppm in liver, kidney, testes, heart and brain were associated with animal body weight loss and not compound related.

Oncogenicity:

In most tissues the histopathology evaluation by EPL indicated approximately equal tumor incidence in both test and control groups. There was no indication that these tumor were compound related.

In spite of the fact that, the total number of mammary tumors in the female, interstitial cell tumors of the testes in the male and pancreatic islet cell adenoma in the male rats show some dose and compound relationship, a statistical evaluation did not establish significances.

Based on the histopathology results and the statistical evaluation CGA-72662 could not be considered an oncogenic compounds in the CR-CD1 albino rats. Mr. Litt and Dr. Kasza agree with this conclusion.

4

The toxicity NOEL was 30 ppm and the oncogenicity NOEL was > 3000 ppm.

The historical data submitted by IRDC is not useful to Toxicology Branch for statistical evaluation in the form submitted. The data should be broken down into an experiment by experiment groupings with the individual protocols for each group.

Classification: Core-Minimum.

B. Oncogenicity Study with CGA-72662 in Albino Mice, IRDC, Mattawan, Michigan, No. 382-082, Accession No. 071189-071193, June 30, 1982.

Material Tested:

CGA-72662 Technical, coarse cream-colored powder, 95.3-95.5% pure, FL-790733-810262.

Methods:

Two hundred seventy-two male and 272 female 24 week old Charles River CD-1 (ICR derived) mice were housed individually conditioned for one week on control food and water. Then they were fed water and control or treated certified Rodent Chow (Purina) #5002 ad libitum after computerized randomized group selection. The groups I to IV each consisted of 68 males and 68 females receiving 0, 50, 1000 and 3000 ppm CGA-72562 respectively. The animals were maintained at consistent 12 hour on/off cycle, at room temperature from 70-77°F and relative humidity from 32 to 78%.

The appearance, behavior, overt toxicity and moribundity was observed 3 times a day on weekdays and twice day on weekends and holidays. And detailed records were made once a week. The mortality was observed at the same schedule and deaths recorded daily. For 13 weeks the body weights were recorded weekly and thereafter biweekly. The food consumption measurements were recorded for groups of ten animals according to the latter schedule.

Eight mice/sex/group were randomly selected for hematological testing of blood obtained from the orbital sinus plexus. The following determinations were made from these blood samples: hemoglobin, hematocrit, erythrocyte count, total leucocyte count, platelet count, mean corpuscular, volume, mean corpuscular hemoglobin (MCH) and MCH conc., differential leucocyte count and reticulocyte count.

The macroscopic postmortem examination were done on 8 animals/sex/group at twelve months. The mice that died on test or were moribund and sacrificed were also examined as well as the remainder of the surviving animals at 24 months. Organ weights of the liver, kidney, heart, testis and brain were measured in all animals. Several organs were preserved in formalin and sent to EPL for microscopic examination.

Results:

Appearance and Behavior:

The appearance and behavior of the animals in this study indicated a large number of abnormal signs but these were not dose related and were present in the controls as well as in treated groups.

Morbidity:

The survival time of the mice used in this 24 month study did not indicate CGA-72662 related mortality.

The test compound groups (in the males) at 1000 and 3000 ppm had lower survival time than control but the difference was not significant. In the female the lowest survival time group was high dose test compound but there was no dose relationship or any survival time outside the expected range.

Body Weight:

There were significant mean body weight difference from the control group in the 1000 and 3000 ppm males. Occasionally, individual animals in the low dose groups (50 ppm) males and females and in the mid and high dose groups were statistically significant different in body weight from the control groups but there was no consistent trend.

Food Consumption:

Although there was consistently lower mean food consumption in all test groups throughout the study this difference was not significant.

4

002617

Hematology:

In this experiment there was no significant difference from control values in any of the treated groups at either 12 or 24 month intervals. Some abberrant results were found in a few (3) high dose females with elevated leucocytes at 24 months apparently related to inflammatory processes.

Macroscopic Pathology:

At 12 month interim sacrifice no unexpected changes for this particular age and strain were found.

Upon reviewing the 24 month incidence of macroscopic changes and correlating this with some individual data the only finding was possibly the liver masses in the treated mice occurring at a slightly greater frequency than were found in the control mice. All other tissues were not significantly different grossly from control groups. No definitive conclusion can be reached prior to histopathological evaluation.

Organ Weights:

The organ weights with the exception of the statistically significant decrease in absolute and relative mean liver weights. All other statistically significant changes are random or considered spontaneous changes.

Histopathology and Oncogenicity:

The histopathology data revealed no treatment related effects except a possible slight increase in hepatocellular neoplasms in the male CD-1 mice with CGA-72662. In checking the individual and summary incidence there was no significant change in time for tumor development nor was there a dose relationship. The number of benign versus malignant neoplasms were comparable in control and test groups, and the slight increase in hepatocellular neoplasms in the treated male was not seen in the female. The number of hepatocellular neoplasms was within the expected range for CD-1 mice of that age.

Conclusion:

The toxicity NOEL was 50 ppm and the oncogenicity NOEL was > 3000 ppm. There is no indication of an oncogenic potential of CGA-72662 in mice in this study.

Classification: Core-Minimum.

Stephanie P. April 3-22-83

Stephanie P. April, Ph.D.
Toxicology Branch/HED (TS-769)

TS-769:th:TOX/HED:SApril:3-14-83:card misc. #3

3/28/83