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

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MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC S

TO: R. Mountfort (PM#23)
Registration Division (TS-767C)
and
J. McCann, Chief
Lab Audit Program, BFSD (TS-768)

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

SUBJECT: Review of Chronic Rat Study of Metolachlor
Accession Nos.: 250369-250375 CASWELL#188DD

Registrant: Ciba-Geigy Corp.
Agricultural Division
Greensboro, N.C.

Recommendation: It is recommended that this study be core classified as Supplementary Data. The NOEL is 30 ppm, based on atrophy of the testes with degeneration of the tubular epitheliu in the mid and high dose groups. An increase in primary liver tumors is observed in the male and female high dose groups. A risk assessment may eventually be required based on this study; however, it is first recommended that a laboratory audit be conducted on this study. This is triggered by conflicting reports of the incidence of liver tumors emanating from a preliminary report and the Final Report of the study. Depending upon the results of the audit, this study may be upgraded to Core Minimum Data.

Review of Data:

Chronic Feeding, Rats. Conducted by Hazelton Raltech, Inc Madison, WI, Study No. 80030 and submitted by Ciba-Geigy, May 2, 1983.

CD-Crl:CD(SD)BR rats were obtained from Charles River Bree Laboratories and were acclimated for two weeks prior to testing Seventy rats per sex were assigned to groups which were to rece either 0 or 3000 ppm. Sixty rats per sex were assigned to grou which would receive either 30 or 300 ppm. Test diet was offere ad libitum for 104 weeks of testing and was formulated with metolachlor technical. Water was available ad libitum.

All animals were individually housed in a room with a temperature of 72° ± 3 and 30 to 70% relative humidity.

Animals were examined twice daily within their cages. Once per week animals were removed and carefully examined. Starting at week 14, animals were palpated weekly for tissue masses.

Body weights were recorded weekly from weeks 0-13 and biweekly after week 16. Food consumption was recorded weekly for weeks 0-13 and biweekly after week 16 for 10 animals per group. In addition, food consumption was recorded for all animals in all groups at weeks 40, 52, 66, 78, 92 and 104.

Clinical studies were conducted on eight animals per group after 3, 6, 12, 18 and 24 months on test. At the 18th month of testing, an additional 10 animals per group were selected. Hematology consisted of RBC, WBC and leucocyte counts, hematocrit, hemoglobin and platelet counts. Clinical chemistry consisted of LDH, AST, ALT, AP, BUN, glucose, total protein, total cholesterol, direct and total bilirubin, Ca and K. Urinalysis consisted of "Ames multistix", specific gravity and microscopic examination.

All animals on test were necropsied. A total of 31 organs had tissues taken and all gross lesions and tissue masses were preserved. The following tissues were examined as reported by the registrant:

Adrenal glands
Bone marrow section (fumur)
Brain (cerebrum, cerebellum, and pons)
Cecum
Colon
Esophagus
Eyes
Gonads
Heart
Kidneys
Liver (at least two lobes)
Lungs (two coronal sections including all lobes and mainstem bronchii)
Lymph nodes (cervical and mesenteric)
Mammary gland
Muscle (skeletal)
Urinary bladders
Uterus
Optic nerve
Pancreas
Parathyroid glands
Pituitary gland (fixed *in situ*)
Prostate
Salivary glands (submaxillary)
Sciatic nerve
Skin
Small intestine (duodenum, jejunum, and ileum)
Spinal cord (two levels)
Spleen
Stomach (cardiac, fundus, pylorus)
Thymus
Thyroid glands

All animals on test had tissues microscopically examined. The following organs were weighed prior to fixation: heart, liver, spleen, kidney, gonads and brain.

Ten males and 10 females from the control and high dose groups were randomly selected after 12 months for a recovery study. Five of these animals were sacrificed immediately and 5 were placed on control diet (absent test compound) for 4 weeks. Clinical studies, organ weight determinations, gross and histopathology determinations for recovery animals were identical to those that continued on test. Statistical comparisons were conducted by the registrant on all parameters (this reviewer independently conducted statistical analysis for the liver tumor incidences using the Fisher's Exact Test).

Results:

Diet analyses were conducted for all dose levels at weeks 1-4 and for randomly selected test diets on a weekly basis for the remainder of the test period. No metolachlor (< 5.0 ppm) was found in control diets, time-weighted averages of 29.1, 273, and 2851 ppm were found in the diet.

Survival over the course of the study was adequate with 54, 57, 42 and 57% of the control, 30, 300 and 3000 ppm dose groups surviving until study termination at 24 months. It did not appear that the survival rate was influenced by test compound administration.

At week 9, animals in all groups began to show clinical symptoms indicative of sialodacryoadenitis virus. These symptoms included "palpable enlargement of the submaxillary salivary glands, a generalized edema in the cervical and mandibular areas, and red-tinged (porphyrin) discharges in the nasal and ocular areas."

The symptoms persisted for only 2-3 days and animals showed no further indication of disease. In addition to the above described clinical signs, animals lost weight (approximately 5 grams) during the time of infection. No animals died during this period. The disease outbreak is considered by this reviewer to be of little consequence to the interpretation of the study.

Mean body weights of females in the high dose group were consistently less than controls from week 2 until study termination. For 26 of the 59 intervals at which animals were weighed, this difference was significant at the $p < .01$ level. Neither male body weights nor low or mid dose female dose groups were affected by treatment. Food consumption in high dose females was slightly less than controls and the difference was statistically significant ($p < .05$) at 10 of 59 intervals with seven of these intervals between weeks 5 and 18. Male food consumption appeared unaffected by treatment.

Organ weights and organ to body weight ratios were similar among all dose groups.

A variety of differences in the clinical pathology measurements were found between control and dosed groups at various intervals but no consistent dose-related effects were apparent with one exception. Aspartate aminotransferase activity was less than controls in both sexes at 3000 ppm at 12 months and the decrease was significant ($p < .01$) in males. Nonstatistically significant decreases in AST activity were noted at 3000 ppm; at other intervals for both sexes and in females at the 300 ppm dose level at 18 and 24 months. It should be noted that the recovery study found that AST values in high group, which were depressed at 12 months, increased after one month recovery period to a level that was not statistically significant. The recovery study also suggests that body weight depression in the 3000 ppm dose level also is reversible with most of the difference between control and high dose body weights disappearing through the one month recovery period.

Gross pathology findings of the scheduled sacrifice, moribund sacrifice and "died on test" animals were unremarkable.

The incidence of neoplastic nodules and hepatocellular carcinomas reported in the Final Report was as follows:

Males

	Dose			
	0 ppm	30 ppm	300 ppm	3000 ppm
Neoplastic nodules	0	0	0	4
Hepatocellular Carcinomas	2	1	3	2
Total Examined	59	59	60	60

Females

	Dose			
	0 ppm	30 ppm	300 ppm	3000 ppm
Neoplastic Nodules	0	0	1	4
Hepatocellular Carcinomas	0	0	0	2
Total Examined	60	60	60	60
Total Examined After the Observation of the First Animal with Tumor	45	43	42	50

The numbers of animals examined after the observation of the first of females dying with tumors (a high dose animal observed at week 90) were 45, 43, 42 and 50 for the control, 30, 300 and 3000 ppm dose level females, respectively. Although the registrant asserts that the incidence of these tumors in high dose females is not statistically significant compared to the control group, this reviewer found statistical significance with p = .0183 (Fisher's Exact test, 0/45 vs. 6/50 for the control vs. high dose groups).

The incidence of these tumors in female rats at this laboratory can only be assessed from a single other study as indicated on p. 36 of Vol. 1 of the registrants submission. Apparently two control groups were used in the historical study and the incidence of these tumors were 0/47 and 1/46 for females of the two groups.

The incidence of other tumor types was unremarkable and did not appear to be related to treatment.

It should be noted that the increased incidence of these tumors is consistent with IBT Study No. 622-07926, conducted with the same doses and classified as "Supplementary Data". It should also be noted that a letter from the registrants dated December 9, 1983 (Attachment A) reported a different incidence of liver tumors in this study than was subsequently reported by the registrants in the Final Report. The incidence of liver tumors originally reported as 2, 2, 2 and 9 for control, low, mid and high dose males and 0, 1, 2, and 7 for control, low, mid and high dose females. This reviewer has requested an explanation for the differing incidences of primary liver tumors in the two reports of the the same study and the response from the registrant was received on November 2, 1983 (Attachment B). The response states that "Subsequently, liver sections were reviewed during the examination of all other protocol tissues and it became apparent that some of the "original diagnoses" would have to be changed. Primarily this was because the presence or absence of "compression of surrounding parenchyma" had not been given uniform consideration during the original examination...The primary difference in the two sets of data was that some of the lesions originally classified as proliferative foci (neoplastic nodules) were ultimately classified as foci of cellular change due to a lack of compression of surrounding parenchyma."

Microscopically, atrophy of the testes with degeneration of the tubular epithelium was found to a greater extent in mid and high dose animals than in the control group, with 6/60, 6/60, 10/60 and 12/60 animals affected in the control, low, mid, and high dose groups, respectively. Although the severity of this finding appeared similar in all groups the time of observation of the atrophy was sooner in the treated groups, with 0/27, 5/26, 7/35 and 10/26 of those animals that died-on-test animals having this finding. An increasd incidence of eosinophilic foci were observed in the livers of high dose males and females with 10/59, 15/59, 14/60, 21/60 (males) and 4/60, 7/60, 5/60 and 23/60 (females) affected in the control, low, mid and high dose groups, respectively. Other pathological findings are considered by this reviewer to be incidental to test compound administration.

Classification: Supplementary Data.

The NOEL for non-neoplastic effects is 30 ppm based on testicular atrophy with degeneration of the tubular epithelium. An increased incidence of neoplastic nodules/hepatocellular carcinomas were observed in this study. Due to a difference in the incidence of liver tumor reported in a preliminary report and the Final Report of the study, the conduct of a laboratory audit is recommended.

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12/14/83

Attachments A & B