CASWELL FILE

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

JUN 27 1990

008009

MEMORANDUM

SUBJECT: CYPROCONAZOLE - MOUSE CARCINOGENICITY STUDY

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: SUSAN LEWIS/GRABLE
PRODUCT MANAGER (21)
REGISTRATION DIVISION (H7505C)

FROM: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 6/20/90
TOXICOLOGY BRANCH II, SECTION II
HEALTH EFFECTS DIVISION (H7509C)

THRU: K. CLARK SWENTZEL K. Clark Swentzel 6/21/90
SECTION II HEAD, TOXICOLOGY BRANCH II
HEALTH EFFECTS DIVISION (H7509C)

AND

MARCIA VAN GEMERT, PH.D. Marcia Gemert 6/21/90
CHIEF, TOXICOLOGY BRANCH/HFAS/HED (H7509C)

REGISTRANT: SANDOZ CROP PROTECTION CORPORATION
CHEMICAL: CYPROCONAZOLE
SYNONYMS: SAN 619 F
PROJECT: 9-1768
CASWELL No.: 272E
MRID No.: 411472-01
RECORD No.: 247640
IDENTIFYING No.: 55947-RGG
ACTION REQUESTED: PLEASE REVIEW MOUSE ONCOGENICITY STUDIES.

COMMENT: IN A COVER LETTER SUBMITTED WITH THE MOUSE ONCOGENICITY STUDY, THE REGISTRANT STATED THAT THE STUDY WAS BEING SUBMITTED VOLUNTARILY, SINCE SAN 619F IS NOT A REGISTERED PESTICIDE AND, THEREFORE, DOES NOT MEET THE CRITERIA FOR SUBMITTING UNDER FIFRA SECTION 6(A)(2).

THE MOUSE CARCINOGENICITY STUDY WAS REVIEWED BY THE CONTRACTOR, DYNAMAC CORPORATION, AND THEIR DER IS ATTACHED.

CYPROCONAZOLE WAS FED TO CHARLES RIVER CD-1 MICE AT CONCENTRATIONS OF 5, 15, 100, AND 200 PPM FOR 81 (MALES) AND 88 (FEMALES) WEEKS. THERE WERE NO EFFECTS OF TEST MATERIAL ADMINISTRATION ON MORTALITY, FOOD CONSUMPTION, OR HEMATOLOGY PARAMETERS. BODY-WEIGHT GAINS WERE DECREASED BY MORE THAN 10% IN BOTH SEXES AT THE TWO HIGHEST DOSE LEVELS OVER THE FIRST 26 WEEKS. THERE WERE INCREASED INCIDENCES OF FOCAL HEPATOCYTIC INFLAMMATION, SINGLE-CELL NECROSIS, AND DIFFUSE HEPATOCYTIC HYPERTROPHY IN THE 100 AND 200 PPM DOSE GROUPS, WITH MALES DISPLAYING A MORE SEVERE EFFECT THAN FEMALES. THERE WAS A DECREASE IN THE AMOUNT OF TESTICULAR GERMINAL EPITHELIUM IN THE 200 PPM MALES, WHICH CORRESPONDED TO THE INCREASED INCIDENCE OF FLACCID TESTES IN THIS GROUP. THERE WAS AN INCREASE IN LIVER WEIGHT IN BOTH SEXES AT THE HIGHEST DOSE AT 13 WEEKS. THERE WERE INCREASED INCIDENCES OF ADENOMAS, CARCINOMAS, AND ADENOMAS AND CARCINOMAS COMBINED (SEE TABLE BELOW).

	PPM				
MALES†	0	5	15	100	200
ADENOMAS	6	4	5	12**	12**
CARCINOMAS	0	0	3*	3*	1
ADENOMAS AND CARCINOMAS COMBINED	6°	4	8*	15***	13***

	PPM				
FEMALES†	0	5	15	100	200
ADENOMAS	0	0	0	2	6**
CARCINOMAS	0	0	0	0	7**
ADENOMAS AND CARCINOMAS	0	0	0	2	13***

† N = 50 FOR EACH GROUP EXCEPT CONTROL, WHICH = 100 (# EXAMINED)
* $P<0.05$; ** $P<0.01$; *** $P<0.001$
° SIGNIFICANT TREND BY COCHRAN-ARMITAGE TEST ($P<0.001$)

BASED ON A SIGNIFICANTLY INCREASED INCIDENCE OF HEPATOCYTIC SINGLE CELL NECROSIS AND DIFFUSE HEPATOCYTIC HYPERTROPHY IN MALE AND FEMALE MICE RECEIVING 100 AND 200 PPM CYPROCONAZOLE IN THE DIET, THE NOEL FOR SYSTEMIC TOXICITY CAN BE SET AT 15 PPM (1.8 MG/KG FOR MALES AND 2.6 MG/KG FOR FEMALES); THE LEL CAN BE SET AT 100 PPM (13.2 MG/KG FOR MALES AND 17.7 MG/KG FOR FEMALES).

TB II AGREES WITH THE CONTRACTOR'S ASSESSMENT OF THE NOEL.

THIS STUDY IS CLASSIFIED CORE GUIDELINE, AND IT SATISFIES THE GUIDELINE REQUIREMENTS (83-2) FOR A MOUSE ONCOGENICITY STUDY.

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