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

007091

MEMORANDUM

DATE: SEP 14 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Terbacil Teratology Study
CASWELL NO. 821A

FROM: Carlos A. Rodriquez Carlos A. Rodriquez 9/11/81
Review Section #1
Toxicology Branch/HED (TS-769)

TO: Robert J. Taylor, PM #25
Fungicide - Herbicide Branch
Registration Division (TS-769)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769) 9/14/81
for WB

Registrant: E.I. duPont de Nemours & Co.
Legal Department
Wilmington, DE 19898

PP#8F2039 with EPA Reg. No. 352-317

Action:

Establish tolerance of 0.1 ppm in or on pecans for terbacil (3-tert-butyl-5-chloro-6-methyluracil) and its metabolites 3-tert-butyl-5-chloro-6-hydroxymethyl uracil, 6-chloro-2, 3-dihydro-7-hydroxymethyl-3, 3-dimethyl-5H-oxazolo (3,2-a) pyrimidin-5-one, and 6-chloro-2,3-dihydro-3,3,7-trimethyl-5H-oxazolo-(3,2-a) pyrimidin-5-one (calculated as terbacil).

Recommendations and Conclusions:

1. The teratogic evaluation of Terbacil (IND-732) is adequate and designated Core-Minimum Data.

2. Additional data desired, but lacking:

   a) oncogenicity study in a second species

   b) teratogenicity study in a second species (rabbit)

   c) additional mutagenicity study at such time the Agency determines a suitable protocol.

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Review:

Rat Oral Teratology with Terbacil (3-Tert-Butyl-5-Chloro-6-Methyluracil (IND732) (Haskell Labs; Report No. 481-79, Project No. 3143, February 20, 1980).

The test material was administered orally by gavage from days 6 through 15 of gestation to three groups of 27 female rats at levels of 250, 1250, and 5,000 ppm in the diet. Ground purina laboratory chow was provided without the test material through day 5 of gestation and for days 16 through 21. A control group received ground purina laboratory chow throughout the test period. Initial body weights ranged from 236 to 254 grams. Animals were individually housed. All animals were observed daily for clinical signs and changes in behavior. Body weights were recorded on Days 0,6,10,16, and 21. Food consumption for each rat was determined at each weighing period. On Day 21 all rats were sacrificed by chloroform inhalation. The uterus and ovaries were removed and inspected for gross changes. The uterus was then opened and the fetuses removed and examined.

The following observations and measurements were recorded: the number of corpora lutea in each ovary, number of implantation sites in each horn, number and location of all live and dead fetuses, number and location of resorptions, weight of each live fetus, crown-rump length of each live fetus, gross anomalies.

The report states that one half of the fetuses of each litter were cleared and stained, and then examined for skeletal abnormalities. The remaining fetuses were fixed and sectioned by Wilson's free hand razor technique and examined for visceral and neural anomalies. The uterus and ovaries of all animals in all groups were examined for gross changes and those of pregnant rats were preserved in Bouin's fluid for possible histologic examination.

Statistical Evaluation

The litter was considered the experimental unit of treatment and observation in this study. Maternal fetal weights and crown-rump measurements were compared to controls by analysis of variance and least significant difference tests. The Fisher exact probability test was used to evaluate the incidence of resorptions and abnormalities among litters. The number of corpora lutea, implantations and live fetuses per litter were subjected to analysis by the Wilcoxon rank sum test.

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Results

Maternal body weight and food consumption

At dosages of 1,250 and 5,000 ppm - rats exhibited a dose related reduction in mean body weight during the exposure period on days 10 and 16 of gestation and 5 days following diet removal on day 21 of gestation. The 250 ppm diet did not significantly alter the mean body weight of pregnant rats. Initial and final mean group body weight are as follows:

Diet (ppm)	Day of Gestation			
	6	10	16	21
0	213 ± 12	247 ± 13	302 ± 14	374 ± 24
250	216 ± 15	247 ± 16	294 ± 18	363 ± 23
1,250	215 ± 12	236 ± 11*	279 ± 16*	351 ± 28*
5,000	214 ± 15	225 ± 12*	271 ± 13*	345 ± 19*

*$p \leq 0.05$ level of significance from control.

Average Weight Gain (gms)

Diet (ppm)	Day of Gestation		
	6 - 10	10 - 16	16 - 21
0	34 ± 4	55 ± 7	72 ± 13
250	31 ± 5	47 ± 7*	69 ± 14
1,250	21 ± 7*	43 ± 9*	72 ± 16
5,000	11 ± 7*	45 ± 8*	74 ± 14

*$p \leq 0.05$ level of significant from control.

Gross Pathology - Maternal

No gross pathological changes were observed in the ovaries, uterus, and major organs and tissues of treated females.

Pregnancy and Fetal Development

In the groups that received 1,250 and 5,000 ppm, the mean numbers of live fetuses per litter and mean final maternal body weight were signicicantly lower than those in the control group.

At 5,000 ppm the mean number of implantation per litter was also significantly lower than the mean in tne control group.

	Control	250(ppm)	1250(ppm)	5,000(ppm)
Live fetuses/litter	10.9 ± 2.0	9.7 ± 3.3	9.1 ± 3.1*	8.6 ± 2.9*
Implantations/litter	11.4 ± 2.3	10.4 ± 3.3	10.0 ± 3.3	9.3 ± 3.1*

*Significantly ($p < 0.05$) lower than the control.

The decrease in the number of implantations and live fetuses per litter and final maternal body weights were dose related. The mean fetal body weight and crown-rump length were not affected by any of the dosages administered.

Fetal Anomalies and Malformations

All groups including the control group exhibited small subcutaneous and petechial hemorrhages on various part of the body. Undersized fetuses were found in all groups. An umbilical hernia was found in one undersized fetus from the control group and in one fetus from the lower group (250 ppm). Visceral anomalies occurred at a very low incidence in all groups. Dilation of the renal pelvis and ureter were found in all test groups but not in control.

Retarded ossification of pubic bones and centra, wavy ribs, and one pair of full fourteenth ribs were found only in the control group. Unossified sternebrae and rudimentary fourteenth ribs were found in all groups.

Conclusions

Terbacil is not teratogenic to rats at 5,000 ppm (highest dose tested).

Embryotoxic effects at 1250 and 5,000 ppm.

Systemic Maternal NOEL = 250 ppm

Classification: Core Minimum

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END