CASWELL FILE

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

JAN 14 1988

006550

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Gene Wilson, PM # 32
Herbicides/Fungicides Branch
Registration Division TS-767C

THRU: R. Bruce Jaeger, Section Head
Rev. Sec. #1/Toxicology Branch
Hazard Evaluation Division TS-769C

THRU: Dr. T. M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division TS-769C

FROM: D. Ritter, Adjuvants Toxicologist
Rev. Sec. #1/Toxicology Branch
Hazard Evaluation Division TS-769C

Subject: Dowicil 75 and Dowicil 150, review of teratology study submitted in support of Data Call In notice (3/4/87) for Antimicrobials.

Registrant: DOW Chemical Co., Midland, MI.

EPA #: 464-403, Dowicil 75 Preservative [1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride]; 464--327, Dowicil 150 Antimicrobial (Cis isomer of Dowicil 75).

Caswell #: 181
Potomac #: P430

The company submits this study in response to a DCI Notice for Antimicrobial active ingredients. Use of the cis isomer of Dowicil 75 as being representative is acceptable. Our review is attached.

Primary Reviewer: D. Ritter Caswell #: 181
Rev. Sec. # I
Secondary Reviewer: R. Bruce Jaeger, Section Head 006550
Rev. Sec. # I

DATA EVALUATION RECORD

Study: Dermal Teratology study, Rat. EPA Guideline #: 83-3

Laboratory: Health & Environmental Sciences, Midland, MI.

Study Director: J. A. John, et al.

Date of Study: 6/21/84.

Accession #: 403497-01.

Material Tested: Dowicil 200; cis isomer of [1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride].

Animals: Male & Female Fischer 344 rats.

METHODS:

Animals -

Young adult virgin female rats weighing 165- 220 gms were mated one to one with males. The day sperm were found in the vaginal smear was day 0. Females were then housed individually. Feed and water were available ad libitum. 25 mated females were randomized into three groups of 25 females each.

Husbandry - Acceptable GLP.

Compound Administration - Dowicil 200 was diluted to 50% in an aqueous solution and applied by clipping the dorsal surface and occluding this site with gauze and nonabsorbent cotton, then administering the proper dose via a syringe under the dressing each day of the exposure period. The doses applied were 0, 250 or 500 mg/kg/day.

Feed and water intake were measured at 3 day intervals starting on day 6 of gestation.

Body weights were recorded on days 3, 6, 9, 12, 16 and 21. Maternal livers were weighed at autopsy and were saved for subsequent histophathological examination, if necessary.

Fetal Observations:

Females were killed at day 21 of gestation and the uterine contents examined for: number of fetuses and their position in the uterine horn; number of live and dead fetuses; number and position of resorption sites; weight and length of all fetuses and any gross external

alteration. Uteri of non-pregnant animals were examined with 10% sodium sulfide solution to detect implantation sites.
Half the pups were examined for evidence of soft tissue malformations. The heads of these pups were placed in Bouin's solution and examined by serial section. All pups were eviscerated and then cleared and stained with alizarin red for skeletal examinations.

Data were analyzed statistically using Bartlett's test, Dunnett's test,
Wilcoxon's test and the Fisher's test.

RESULTS:

Maternal effects:

No maternal mortality was reported. Animals losing 15 or more grams between days 3 - 5 were discontinued, as were animals which were injured by wrapping or handling. 5 or 6 animals in each group were discontinued because of weight loss. One control and one 500 mg/kg animal were injured enough to discontinue. One 250 mg/kg rat, and one 500 mg/kg rat showed vaginal bleeding. The lower dose animal showed early implantation sites at term while the other animal cast a normal litter with no increase in resorptions reported.

Body weights, weight gains, and liver weights were not affected by dermal exposure to the TM; although the high dose group rats had increased weight gain in the 12 - 15 day period this is not considered to be of toxicological significance. Animals in both treated groups consumed more water than the controls, but the actual differences are small and are not considered to be of toxicological significance.

In Utero Fetal Effects:

No adverse effects were reported for pregnancy rate, numbers of corpora lutea or litter size. Sex ratios were approximately equal among the groups. Litter weights and crown-rump lengths were not affected by exposure to TM. The low dose group percent resorption rate was significantly increased when compared to that of the controls; however, the high dose group did not show this effect, and, though statistically significant, the percentage change in the low dose group is small and is thus not considered to be of toxicological significance.

Developmental Effects:

There were no significant dose-related effects on soft tissue or skeletal parameters in the treated groups.

CONCLUSIONS:

Dowicil 200 does not induce dermal irritation, mortality, or maternal and fetal developmental effects when applied dermally to mated female Fischer 344 rats during days 6 -15 of gestation at levels of 250 and 500 mg/kg/day, the highest level practicable in this assay.

The guideline requirement is for three dose groups and a control group. However, the relatively high levels used in this assay, 250 and 500 mg/kg/day, the lack of a demonstrable effect level at the high dose level, and the inability to administer higher levels than 500 mg/kg/day dermally, fulfills the intent of this requirement.

CORE RATING: Guideline.