Caswell file

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAR 15 1985

MEMORANDUM

Caswell #181

SUBJECT: Dowicil 150 Antimicrobial
EPA Registration No. 464-327

TO: Mr. Arturo E. Castillo, PM No. 32
Disinfectant Branch
Registration Division (TS-767C)

FROM: Carlos A. Rodriguez CAR 3/14/85
Review Section No. VI
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THRU: Jane E. Harris, Ph.D., Section Head JEH 3/14/85
Review Section No. VI
Toxicology Branch/HED (TS-769C)

3/15/85

Applicant: The Dow Chemical Company
P.O. Box 1706
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Action Type:

Review dermal teratology study for the subject file on Cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride, the active ingredient of Dowicil 150 Antimicrobial.

Recommendation:

1. The teratogenic evaluation of Dowicil 200 is adequate and designated Core Minimum Data.

2. The study will be part of the files for the above registered product EPA Registration No. 464-327.

A. Formulation of Dowicil 150 Antimicrobial

Active Ingredient:

Cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride	94.00%
Inert Ingredients:	6.00%
Total	100.00%

B. Use: For the control of bacteria and fungi in industrial applications.

C. Teratology Study Review:

Rat Dermal Teratology Study of Dowicil 200*, (Toxicology Research Lab., Dow Chemical Co., Report No. HETK-27342-59, June 21, 1984).

Sexually mature Fischer 344 virgin female rats, weighing between 165-220 g were mated 1:1 with adult males of the same strain. The day sperm were evident in a vaginal smear was considered as Day 0 of pregnancy. Groups of 25 pregnant rats were treated with 0, 250, and 500 mg/kg/day of Dowicil 200 applied dermally as a 50% solution in distilled water on days 6 through 15 of gestation (approximately 0.1 ml and 0.2 ml of test solution applied per rat per day, respectively). The control group (0) received applications of 0.2 ml of distilled water. The test solutions were applied to the dorsal surface of the thorax which was clipped free of hair.

The application site was occluded throughout the period of dosage by wrapping each animal with elastic gauze bandage secured with adhesive tape. A piece of gauze and then an impervious material was placed between the bandage and the skin to avoid loss of the test material.

Animals were observed daily for toxic signs and adverse effects to treatment. Body weights were recorded on Days 3, 6 through 16, and 21 of gestation. Food and water consumption were recorded for each rat at 3-day intervals starting on day 6 of gestation. Body weight and body weight gain were analyzed statistically using data recorded on days 3, 6, 9, 12, 16 and 21 of gestation. Maternal liver weight was recorded at the time of caesarean section and sections of the skin from the application site were preserved in 10% formalin for possible histologic examination.

On Day 21 of gestation all surviving animals were sacrificed by carbon dioxide inhalation. All fetuses were removed by caesarean section and the number and position of fetuses in utero, number and dead fetuses, number and position of resorption sites, weight and length of each fetus and any gross external alterations were determined. The uteri of apparently non-pregnant animals were examined for evidence of implantation sites. One-half of each litter were examined for soft tissue alterations, heads were removed, placed in Boulin's fixative and examined by the serial sectioning technique of Wilson (1965). All fetuses were preserved in alcohol, stained with Alizarin and examined for skeletal alterations.

Various parameters were analyzed statistically, including body weights and absolute and relative organ weights, food and water consumption, frequency of fetal alterations, pre-implantation loss and fetal population. *Dowicil 200 on which the study was run is a chemical formulated into products regulated by FDA and is identical to Dowicil 150.

Results

Mortality (Maternal)

No mortality was observed in the control and the experimental groups.

Maternal Body Weight

At dose 500 mg/kg/day - rats exhibited an increased body weight gain during the exposure period on days 12 and 15 of gestation. The 250 mg/kg/day dose did not alter the mean body weight of pregnant rats. Initial and final mean groups body weight are as follows:

Diet (mg/kg/day)	Day of Gestation					
	3	6	9	12	16	21
0	191±9	186±11	185±9	193±10	201±11	239±15
250	194±8	189±10	185±6	193±8	204±8	243±14
500	187±10	183±12	182±12	187±12	201±14	242±17

Maternal Liver Weight

There was no change in liver weights of control group and treated groups.

Maternal Food Consumption

The maternal daily food consumption for the control group and the treated groups was not affected.

Maternal Water Consumption

The experimental animals given 500 or 250 mg/kg/day of the test material consumed significantly more water than the control group on gestation days 15-17 or 18-20, respectively. Laboratory investigators suggest that these differences are considered to be random variations and not treatment related.

Cesarean Data (Table 3 - Page 20 of Report)

The percentage of pregnant females, implantation sites per dam, corpora lutea, pre-implanation loss of litter size were unaffected by treatment, except at 250 mg/kg/day when the incidence of resorptions was increased when compared to the control group. This incidence of resorptions was not statistically increased over the controls in the 500 mg/kg/day group.

The incidence of resorptions were as follows:

Dose (mg/kg/day)	% Implantation resorbed	% Litters with resorptions
0	5 (8/172)	30 (6/20)
250	11 (22/193)*	65 (13/20)*
500	7 (11/163)	50 (9/18)

* Significantly different from control value by a modified Wilcoxon test, $\alpha = 0.05$.

The number of fetuses examined and the incidence of fetal alterations were as follows:

	Doses (mg/kg/day)		
	0	250	500
	Number of Fetuses Examined (Number of Litters)		
External	164(20)	171(20)	152(18)
Soft tissue	88(20)	92(20)	82(18)
Skeletal	164(20)	171(20)	152(18)
Bones of the Skull	76(18)	81(19)	77(17)

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% Incidence (# Fetuses)
External Alterations
F=fetuses; L=litters

Anophthalmia				
	F	0.6(1)	0	0
	L	5(1)	0	0
Microphthalmia				
	F	0.6(1)	0.6(1)	0.7(1)
	L	5(1)	5(1)	6(1)
Soft tissue				
Right-sided aortic arch	F	1(1)	1(1)	0
	L	5(1)	5(1)	0
Patent ductus arteriosis	F	1(1)	0	0
	L	5(1)	0	0
Dilated ureter	F	0	1(1)	0
	L	0	5(1)	0
Dilated renal pelvis	F	0	1(1)	0
	L	0	5(1)	0

Skeletal Alterations
F=fetuses; L=litters

Skull-extra site of ossification	F	0.6(1)	0	0
	L	5(1)	0	0
Vertebrae -irregular ossification	F	0	0.6(1)	0
	L	0	5(1)	0
-fused (thoracic)	F	0	0.6(1)	0
	L	0	5(1)	0

		% Incidence (# of Fetuses)		
Ribs bilateral/forked	F	0.6(1)	0	0
	L	5(1)	0	0
Missing	F	0	0.6(1)	0
	L	0	5(1)	0

There were no compound-related effects on the incidence of external, soft tissue or skeletal variations of the treated groups when compared with the control group.

Conclusions:

No mortality was observed in the control and the treated groups given Dowicil 200 dermally during gestation days 6 through 15.

At dose 500 mg/kg pregnant rats exhibited an increase in body weight gain during the exposure period on days 12 and 15 of gestation. The 250 mg/kg dose did not alter the mean body weight of pregnant rats. Authors considered this single variation to be of no toxicological significance.

There were no differences in the mean number of implantation sites per dam, percent of pregnant females, pre-implantation loss or litter size between control group and treated groups.

The average number of resorptions was very slightly increased in the 250 mg/kg/day group, this incidence appears not to be compound related, since the number of resorptions in the 500 mg/kg/day group was not statistically increased over the control group.

There were no significant differences on the incidence of external, soft tissue or skeletal variations between control group and treated groups.

No adverse effects were noted on fetal weight, measurements or sex ratio among Dowicil 200 treated groups and control group.

Evaluation:

Dowicil 200 is not teratogenic to rats at 500 mg/kg/day (highest dose tested).

Fetotoxic NOEL = 500 mg/kg/day (highest dose tested).

Maternal NOEL = 500 mg/kg/day (highest dose tested).

Levels tested 250 and 500 mg/kg/day.

Classification: Core Minimum

It should be noted that the high dose, 500 mg/kg/day was presented as the maximum amount possible before causing skin irritation or test material run-off from the application site.

JOB-44598:Carletta:Kendrick:898-1270:liz:HED-19:3/5/85:del./3/13/85
REVISED:JOB-44598:Carletta:Kendrick:898-1270:tar:HED-19:3/13/85:del./3/20/85