DATE: 4/17/80 4/17/80

SUBJECT: Exemption from tolerance for Dowacil(R) 75 Preservative under §180.1001(d).
EPA Reg. #464-403. CASWELL#181

FROM Gary Burin GB KHB
Toxicology Branch, HED (TS-769)

TO: A.E. Castillo
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Registration Division (TS-767)

THRU: William Burnam, Acting Chief William M Butler for William Burnam 4/23/80
Toxicology Branch, HED (TS-769)

Action Requested & Background Information

Dowacil(R) 75, [redacted] of the cis/trans isomer of 1-(3-chloroallyl)-3, 5,7-triaza-1-azoniaadamantance chloride, is proposed for use as an inert ingredient in pesticide formulations at a level of not more than 1%.

Dowacil(R) 75 will be added to pesticide such as herbicides, fungicides and insecticides which will be applied to growing crops only. The maximum amount of Dowacil(R) 75 that could be applied per acre is expected to be 82 grams with this use. Registrant states that no residues on food are likely to result from this use and has submitted data to support this contention (We defer to RCB for evaluation of residue data).

Recommendations

To insure consistency with past and current Toxicology Branch policy regarding registration of inert ingredients, I defer to Ken Bailey of Toxicology Branch for recommendation of any additional test requirements which may be necessary for registration of this compound.

Review:

1) The following studies were submitted with this action using Dowacil(R) 200 (the cis isomer only);

   A. 30-Day Dermal Exposure, Rabbits
   Systemic NOEL = 25 gm/kg/day

   B. Mutagenicity Evaluation of reversion in Salmonella typhimurium
   Not mutagenic

2a) Previously submitted studies using Dowacil(R) Q or Dowacil(R) 100 [redacted] of cis and trans isomers);

From review of 10-19-67 by P.D. Barron;

Acute Rabbit Oral	LD_{50} = 50 mg/kg
Acute Rat Oral	Male = LD_{50} = 550 mg/kg (280-1060) Female = LD_{50} = 940 mg/kg (640-1330)
Acute Cavy Oral	LD_{50} = 470 mg/kg (330-660)
Acute Dog Oral	LD_{50} = 500 mg/kg
Acute Rabbit Eye Irritation	Slight conjunctival redness persisting from 2-7 days in both unwashed and washed eyes.
Subacute Skin Irritation (unabraded skin, 10 applications abraded skin, 3 applications) (Rabbits)	No irritation on unabraded skin. Redness persisting for 4-7 days and subsiding, necrosis following 2-3 applications. Scar formation in three weeks.
Skin Intact Absorption	No untoward effects in animals with intact skin. 1/3 animals in abraded application sites.
Subacute Rabbit Dermal	1% and 5% solutions produced no systemic effects. Scar formation was noted under application sites.
Human Skin Irritation and Sensitization	0.5% solutions, in oil and water produced no irritation, or sensitization.

From memo of 3-10-78 by K.L. Bailey;

Dog 90-Day Oral Study	NOEL = 7.5 mg/kg/day
Acute Dermal LD_{50}, Rabbits	LD_{50} > 2 gm/kg

b) The following data is pertinent to Dowacil(R) 75 (the cis isomer);

From memo of 3-10-78 by K.L. Bailey;

Acute Rabbit Dermal LD_{50}	LD_{50} = 400 mg/kg
21-Day Rabbit Dermal Stduy	NOEL = 25 mg/kg

3) Toxicology Review of SUbmitted Studies:

a. 30-Day Dermal Study, Rabbits. COnducted and SUbmitted by Dow Chemical USA. Submitted August 28, 1978.

Test Material: Dowacil(R) 200

7 male rabbits per dose level were treated with a 20% aqueous solution, 5 days per week, seven hours a day. Skin was clipped and abraded once per week. Dose levels used were 25, 50 and 100 mg/kg/day, as well as controls which was treated with distilled water.

Animals were observed daily. Body weights and food consumption data was collected on all animals and gross and microscopic pathology was performed.

Results

Dose related erythema and eschar formation were reported. Local irritation was minimal with the 25 mg/kg/day exposure group.

Body weights were significantly depressed for animals exposed to 100 mg/kg/day from day 11 to the end of the test. Food consumption and liver weights were also significantly depressed for the highest exposure group. Food consumption at 50 mg/kg/day was slightly, but not significantly, depressed and liver weights were depressed ($p < .05$) at that dose level.

Hematologic findings were unremarkable. One animal at the highest dose level was diagnosed as having lymphosarcoma, a relatively uncommon tumor in rabbits. Other pathologic findings included nematodiasis, hypoplasia of the seminiferous tubules, kidney stones and stomach ulcertain. These findings were reported in a number of control and treated animals and did not appear to be dose related (hypoplasia of the seminiferous tubules is a genetic trait among rabbits and is common in some strains). Unlike an earlier study done by Industrial Biotest Laboratories, no effect on testicular weight or spermatogenesis was noted.

The NOEL for systemic was 25 mg/kg/day in this study. Local irritation was observed at all dose levels.

b. Mutagenicity Evaluation of Reversion in Salmonella typhimurium. Conducted by Raltech Scientific Services. Submitted by the Dow Chemical Co., September 23, 1979.

Test Material: Dowacil(R) 200

Strains TA-98, TA-100, TA-1537 and TA-1538 were treated with 25, 50, 100, 250 and 500 microliters per plate either in the presence or absence of S-9 mix (from an unspecified species). Nitroquinoline-N-oxide, Benzo (a) pyrene, methyl-N-nitro-N-nitrosoguanidine, amino-acridine and aminofluorene were used as positive controls. Spontaneous revertants per plate were also quantified.

Results

Number of revertants did not exceed twice the number of spontaneous reversions and therefore the compound can be considered to be negative with regard to mutagenicity, as tested by the method of Ames et al (Mutation Research, 31, 347-364, 1975).

TOX/HED:th:CFRICK:4-16-80

C. Frick
4/17/80