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

003882

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 6-15-83 JUN 17 1983

SUBJECT: Registration No. ~~352-325~~
Bromacil, Caswell #111
Acc. #249676, Reponse to
Bromacil Registration Standard

TO: Taylor/Remmers PM 21, (TS-767)

FROM: Alex Arce
Tox Branch (TS-769)

THRU: W. Butler,
W. Burnam,
R. Coberly, Tox Branch (TS-769) 6/17/83

Registrant: E.I. duPont de Nemours & Co. of Delaware

Request: Review three studies submitted to satisfy data gaps in the Bromacil Registration Standard.

1. Chronic feeding dog- Data on histopathology - thyroid tissue.

2. Oncogenicity - 18 months feeding mice.

3. Teratogenicity - rat inhalation.

Background Information

This reviewer was in charge of the toxicology phase of the Bromacil Registration Standard published on November 25, 1981 (Copy can be obtained from files at the Tox Branch).

The data gaps encountered were as follows:

1. Chronic feeding dog- Data on histopathology - thyroid tissue.

2. Oncogenicity - 18 months feeding mice.

3. Teratogenicity - rat inhalation.

Chronic Data

a. Repeat a chronic oral toxicity with dogs, emphasis on thyroid changes, or submit data in thyroid histopathology.

b. Oncogenicity/specie.

Teratogencity

A second study using another specie.

Recommendation

The duPont response to the data gaps is as follows and the submitted studies has been graded as:.

Chronic Data.

a. The histopathology part of the Chronic Oral Toxicity with dogs has been submitted. The study is acceptable and should be upgraded to core minimum data. Review attached.

b. Oncogenicity

An 18-month mice feeding study has been submitted to EPA but it has not reached this reviewer. Thus, at the time that Acc # 244069-70-71 reaches the Tox Branch it will be reviewed and properly graded.

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Teratogenicity

The registrant has submitted a second study in teratology, Report EPA-600l/1-78-003, "Teratology and Acute Toxicology of Selected Chemical Pesticides Administered by Inhalation."

Gordon, W. Newell & James Y. Dilly - January 1978. Stanford Research Institute. Sponsored by EPA Health Effects Research Laboratory.

This study was conducted in conjunction with other pesticidal products.

The study has been reviewed and found to be acceptable and graded core minimum.

Review of Submitted Data.

a. Chronic Feeding Dog.

The study was previously reviewed and classified as Supplementary data due to the lack of information on the histopathology of the thyroid.

I requested such information because in another chronic study, with rats, thyroid effects were reported.

Results

The major changes observed were:

Thyroid

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(a) Chronic inflammation with lymphoid and R.E. cell infiltration of interstitial tissue; hyperplasia of R.E. cells.

(b) Focal light cell hyperplasia. 17

follicular cell hyp. 20 +4.

fibrosis 2)

Number of occurrences

a. 2 males - control

1 male - at 50 ppm

LLT 2 X male - at 250 ppm

0 at - 1,250 ppm (high dose level)

b. 2 females - control

3 females - at 50 ppm

3 females - at 250 ppm

3 females - at 1,250 ppm

The severity of the changes was similar at all dose levels and the incidence is comparable for controls and dosed groups.

Thus, I concluded that the product does not induce thyroid changes IN DOGS and the study can be upgraded to core minimum data. NOEL = 1,250 ppm.

Teratogenicity

Report # EPA-600/1-78-003. This review includes only the part related to Bromacil. The other products assayed are not

pertinent to the purpose of this Registration Standard of Bromacil.

Product: Bromacil

Animals: Adult male and female Sprague-Dawley rats - 200 to 250 g; healthy. 10 animal per group.

Product Tested: Bromacil

Administration of the Material:

Daily, from the 7 through the 14 day of gestation in an inhalation chamber.

Dose levels:

165 $\pm$ 6 mg/m^3, 78 $\pm$ 6 mg/m^3 and 38 $\pm$ 2 mg/m^3.

Animals exposed for 2 hours daily from day 7 to 13.

Controls (solvent)

Restricted food, air and DMSO. 10 animals/per group for all the above-mentioned levels. 0 controls, 20 animals per group.

Application of the Aerosol

Instrument: ultrasonic or pneumatic generator that regulates the particle size and the concentration of the material. DeVelbiss nebulizer.

Solvent: DMSO

Analysis: By G.C.

Particle size: Analyzed "using a seven-stage cascade impactor." Aerodynamic - 0.44 u

The pesticides were analyzed. The tissue was also analyzed after performing a gross pathological exam. Exam includes weight of liver and gravid uterus.

The live fetuses were weighed and examined.

Uteruses were examined and number of resorptions recorded.

Fetuses were prepared in Bouin's solution for necropsy or fixed for skeletal analysis.

Pathology was performed in the selected tissue.

Results

Particle size: average of 0.5 to 0.65 um diameter.

Weight: comparable to controls

Food consumption: comparable to controls

Signs of Toxicity: none were observed

Litter size: comparable

Resorptions: Higher at the 165 mg/m^3 dose level, than the other treated groups. However, lower than control.

Fetal Weight: Significant dose-related weight reduction in the treated groups as compared to the controls.

Conclusions: The results indicate that the administration of the material to pregnant rats did not produce a teratogenic or pathological response. The mothers did not exhibit significant changes.

NOEL for terata 165 mg/m^3 = 7.92 mg/kg.