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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: **BROMACIL** - Registrant's Response to Review of One-Year Feeding Study in Dogs - Testicular Effects

TO: Mario F. Fiol
PM Team Reviewer (73)
Reregistration Branch, SRRD (H7508C)

FROM: Linda L. Taylor, Ph.D. 9/3/92
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Health Effects Division (H7509C)

THRU: K. Clark Swentzel 9/3/92
Section II Head, Toxicology Branch II
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and

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Registrant: DuPont
Chemical: 5-Bromo-3-sec-butyl-6-methyluracil
Synonyms: Bromacil; INN-976
Caswell No.: 111
Shaughnessy No. 012301
DP Barcode: D181060
Submission: S422621
ID #: 012301
Case: 818592

Action Requested: Review the attached E.I.DuPont's response to the One Year Dog Study deficiencies.

Comment: In response to the Agency's review (TB II cover memo dated 12/13/91) of the one-year feeding study in dogs (MRID # 418697-01), which was classified Core Supplementary, the Registrant has submitted additional data/information on the incidence of testicular atrophy/degeneration, which they believe support the conclusion that the findings are not toxicologically significant.

BACKGROUND

The original TB II reviewer of the study raised a concern regarding an apparent effect on the testes (EPA memorandum, Levy to

Rossi/Fiol, 12/13/91; copy appended). Three of the five male dogs at each of the dose levels of Bromacil displayed testicular atrophy/ degeneration; none of the 5 control dogs displayed this lesion. In the historical control data submitted with the final report, the highest incidence was 2 of 5 dogs, which was observed in 3 of 6 studies.

DISCUSSION

The Registrant stated that the lesion occurs spontaneously in laboratory beagles and has submitted 2 published papers cited in the pathology report in which the incidence of focal atrophy/ atrophy of seminiferous tubule ranges from 3-10%.

The Registrant argues that neither the incidence nor the severity of the lesion increased with dose, and there were no accompanying systemic effects observed. Additionally, the Registrant cited a previous 2-year study in dogs at higher dose levels that had not demonstrated any testicular effects; i.e., there was no increase in focal testicular atrophy compared to the control value (1/3 controls, 0/2 at 50 ppm, 1/3 at both 250 and 1250 ppm).

CONCLUSION

TB II agrees with the Registrant that the testicular effects observed in the treated groups appear to be unrelated to treatment, based on (1) the lack of a dose response for the unilateral, the bilateral, and the combined unilateral/bilateral lesions and (2) the lack of an increase in the incidence or severity with a 25-fold increase in dose. This study is upgraded to Core Minimum, and it satisfies the guideline requirement (83-1) for a chronic oral toxicity study in nonrodents.

NOTE: The published papers on the spontaneous occurrence of this lesion do not detract from the Registrant's arguments, but as presented, do not rigorously support their arguments in that (1) it is not possible from these papers to determine what the incidence was in each of the studies where the lesion was observed; (2) the ages of the dogs from the studies that comprise the historical control data varied from 7-20 months. The age of the dogs in the Bromacil study were 18-19 months. A more appropriate comparison would be to those studies involving dogs of a comparable age (≈ 18-19 months) and to those where the lesion was observed.