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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 2-Generation Reproduction Study - Kidney Effects

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

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 8/31/92
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 9/1/92
Section II Head, Toxicology Branch II
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and

Marcia van Gemert, Ph.D. Marcia van Gemert 9/2/92
Chief, Toxicology Branch II/HFAS/HED (H7509C)

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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: | D181575 |
| Submission: | S423486 |
| ID #: | 012301 |
| Case: | 818592 |

Action Requested: Review the registrant's response to review and determine if the information they have provided suffices to change the classification of the original submission.

Comment: In response to the Agency's review (TB II cover memo dated 7/26/91) of the two-generation reproduction study (MRID # 418046-01) in rats, which was classified Core Supplementary, pending the submission of additional information/data regarding the incidence of kidney hydronephrosis, the Registrant has submitted additional arguments as to why the hydronephrosis was judged not to be treatment-related.

BACKGROUND

The original TB II reviewer of the study raised a concern regarding

an apparent increase in the incidence of hydronephrosis in the F1 male kidneys. Since only those rats displaying gross kidney effects at necropsy were examined microscopically for kidney lesions in the original final report, the reviewer requested that the Registrant examine all kidneys microscopically.

DISCUSSION

It is stated in the current submission that it will not be possible to examine all rat kidneys (as requested) because the kidney was not a tissue listed in the protocol to be examined. Only kidneys with gross lesions at necropsy were examined histologically.

Arguments set forth by the Registrant to support the conclusion that the hydronephrosis observed in this study is not compound-related are: (1) the kidneys were examined microscopically only if hydronephrosis was observed grossly, so the true incidence of this lesion is not known for this study; (2) the hydronephrosis observed was unilateral (right kidney in 15 out of 18) in all but one rat in the 250 ppm group, which the Registrant suggests indicates a spontaneous occurrence; (3) hydronephrosis (also termed renal pelvic dilation) occurs spontaneously in the rat, with the frequency varying from 1 to 95%; (4) the incidence of hydronephrosis (also termed dilated renal pelvis) has a high spontaneous incidence in the CD-1® rat, with the incidences ranging from 0-27.8% in 3617 control Charles River rat fetuses; (5) the incidence of hydronephrosis (also termed renal pelvic dilatation) in 379 control F1 males from the testing facility where the 2-generation study was performed is reported as high as 5/30, with a range of 0-16.7%; and (6) Bromacil has been tested in two developmental toxicity studies (CD-1 rat and New Zealand white rabbit), in which no compound-related effects were observed in the kidneys, and in a 2-year rat study where no compound-related kidneys effects were noted.

Additionally, several published articles (or parts of) on hydronephrosis (heritable, spontaneous) were submitted and referred to in the discussion. One article on spontaneous hydronephrosis in rats states that (1) unilateral hydronephrosis occurs most frequently, (2) it usually affects the right kidney, and (3) it is more frequent in males than females.

With regard to the assertion that no kidney effects were observed in the 2-year rat study, TB II notes that males displayed kidney carcinomas at each dose level (one per group), and this tumor type is considered rare for the rat.

The incidence of hydronephrosis (confirmed microscopically/observed grossly) in the reproduction study was 1/1, 5/5, 4/5, and 8/8 in the control, low-, mid-, and high-dose F1 males, respectively, which equates to 3%, 17%, 13%, and 27% of the rats in each group, respectively. Although this incidence is within the spontaneous

incidence rate in CD-1 rats overall, it is greater than the highest observed (5/30) at the testing facility where the study was performed.

CONCLUSION

The Registrant has presented additional information/arguments to support the contention that the apparent increase in the incidence of hydronephrosis observed in the F1 males in the 2-generation reproduction study is not treatment-related. Facts supporting this determination include: (1) the lesions are not unusual, (2) they were unilateral, (3) the right kidney was affected almost exclusively, and (4) they occurred in males; these are all aspects of spontaneously-occurring hydronephrosis. However, although the initial diagnosis was from gross inspection and not all kidneys were examined microscopically so the real incidence is unknown in this study, the high-dose F1 males displayed a higher incidence than has been observed at the testing facility, even if no other high-dose F1 rats were found with this lesion (8 out of 30 vs 5 out of 30 in the historical control). TB II concludes that the increase in hydronephrosis in the F1 males may be related to treatment.

The NOEL for systemic effects can be set at 250 ppm, the LEL at 2500 ppm, based on body weight reductions in both sexes of the P and F1 rats during the pre-mating period and the possible treatment-related increase in hydronephrosis in the F1 males. This 2 generation reproduction study can be upgraded to Core minimum, and it satisfies the guideline requirement (83-4) for a 2-generation reproduction study in rats.