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

JUL 26 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of A Reproductive and Fertility Effects with Bromacil Multigeneration Reproduction Study in Rats

TO: Lois Rossi, PM-79
Registration Division (H-7508C)

FROM: David S. Liem, Ph.D. David Liem 7/16/91

THROUGH: K. Clark Swentzel, Section Head K. Clark Swentzel 7/17/91
Toxicology Branch/Sect. II (H-7509C)
and
Marcia van Gemert, Ph.D., Branch Chief Marcia van Gemert 7/23/91
Toxicology Branch/HED (H-7509C)

MRID No.: 418046-01 ID No.: 012301 DP BARCODE No.: D163116
CASWELL No.: 111 HED Project No.: 1-1003

ACTION REQUESTED

To review a study entitled "Reproductive and Fertility Effects with Bromacil, Multigeneration Reproduction Study in Rats" submitted by E.I. Du Pont de Nemours and Company, Inc.

CONCLUSIONS

Four groups of 60 (30 males and 30 females) Crl:CD®BR rats (P generation) were fed technical Bromacil in the diet at 0, ~~100~~ 50, ~~500~~ 250, and 2500 ppm for a 75-day pre-mating period, and continued during the mating, gestation and lactation periods to breed the F1 rats. Four groups of 60 (30 males and 30 females) F1 rats were selected and continued on the same diet at the same dose levels to breed F2 offspring.

Based on the data presented in the study report, the systemic parental toxicity NOEL and LOEL cannot be determined at this time, because of a possible dose-related effect observed in the F1 male rat kidneys (increased incidence of kidney hydronephrosis) which could not be adequately evaluated from data presented in the study report, because only rats observed with gross renal pelvis dilatation were microscopically evaluated. The reproduction NOEL is determined to be ~~500~~ 250 ppm, based on the slight body weight decrease in the 2500 ppm F2 pups. The reproduction LOEL is 2500 ppm

1 CFU

Based on data presented in the study report, the following treatment-related effects were observed:

- Body weight reductions in both sexes of the P and F1 2500 ppm dose groups during the pre-mating period.
- Food consumption and food consumption efficiency reduction in the F1 males of the 2500 ppm dose group.
- Increased renal pelvis dilatation in the F1 males of the 2500 ppm dose group.
- Body weight reduction in the 2500 ppm F2 pups

There was possible evidence of a dose-related increase in kidney hydronephrosis in the treated F1 males as compared to the control as determined microscopically, [1/1 in control, 5/5 in low-, 4/5 in mid-, and 8 (incidence) /8 (total evaluated) in high-dose groups]. Since only those kidneys with observed gross lesions (noted as renal pelvis dilatation), were histopathologically evaluated, it is not apparent whether additional cases of developing kidney hydronephrosis may have been present. The registrant is requested to microscopically evaluate all rat kidneys from all dose levels to determine if additional cases of developing kidney hydronephrosis may have been present. The classification of this study is upgradable, upon satisfactory review of the requested information.

CLASSIFICATION: Core-supplementary. This study does not satisfy the guideline requirements (83-4) for a two-generation reproduction toxicity study in rats. This study is upgradable upon satisfactory review of the requested information.

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Primary Reviewer: David S. Liem, Ph.D. David S. Liem 7/16/91
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Tertiary Reviewer: K. Clark Swentzel, Section Head K. Clark Swentzel 7/17/91
Section II, Toxicology Branch II/HED

DATA EVALUATION RECORD

Study Type: Two-Generation Reproduction Study

Test Animal: Crl:CD®BR Rat Guideline: 83-4

EPA ID Nos.: MRID No.: 418046-01 ID No.: 012301
Caswell No.: 111 HED Project No.: 1-1003

Test Material: Bromacil with a purity of 95%

Synonym: 5 Bromo-3-sec-butyl-6-methyluracil

Dosages: 0, 50, 250, and 2500 ppm

Sponsor: Agricultural Products, E.I. du Pont de Nemours and Co., Wilmington, DE 19805

Study Number: HLR-724-90; Med. Res. Project no.: 8767-001

Testing Facility: Haskell Laboratory for Toxicology and Industrial Medicine, Elkton Rd., Box 50, Newark, DE 19714

Title of Report: Reproductive and Fertility Effects with Bromacil Multigeneration Reproduction Study in Rats

Author: Linda Miller, M.A. Report Issued: February 20, 1991

CONCLUSIONS

Four groups of 60 (30 males and 30 females) Crl:CD®BR rats (P generation) were fed technical Bromacil in the diet at 0, ~~100~~ 250, ~~500~~ 2500, and 2500 ppm for a 75-day pre-mating period, and continued during the mating, gestation and lactation periods to breed the F1 rats. Four groups of 60 (30 males and 30 females) F1 rats were selected and continued on the same diet at the same dose levels to breed F2 offspring.

Based on the data presented in the study report, the systemic parental toxicity NOEL and LOEL cannot be determined at this time, because of a possible dose-related effect observed in the F1 male rat kidneys (increased incidence of kidney hydronephrosis) which could not be adequately evaluated from data presented in the study report, because only rats observed with gross renal pelvis dilatation were microscopically evaluated. The reproduction NOEL is determined to be ~~500~~ 250 ppm, based on the slight body weight decrease in the 2500 ppm F2 pups. The reproduction LOEL is 2500 ppm

Based on data presented in the study report, the following treatment-related effects were observed:

- Body weight reductions in both sexes of the P and F1 2500 ppm dose groups during the pre-mating period.
- Food consumption and food consumption efficiency reduction in the F1 males of the 2500 ppm dose group.
- Increased renal pelvis dilatation in the F1 males of the 2500 ppm dose group.
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There was possible evidence of a dose-related increase in kidney hydronephrosis in the treated F1 males as compared to the control as determined microscopically, [1/1 in control, 5/5 in low-, 4/5 in mid-, and 8 (incidence) /8 (total evaluated) in high-dose groups]. Since only those kidneys with observed gross lesions (noted as renal pelvis dilatation), were histopathologically evaluated, it is not apparent whether additional cases of developing kidney hydronephrosis may have been present. The registrant is requested to microscopically evaluate all rat kidneys from all dose levels to determine if additional cases of developing kidney hydronephrosis may have been present. The classification of this study is upgradable, upon satisfactory review of the requested information.

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Author: Linda Miller, M.A.

Report Date: February 20, 1991

Study No.: HLR-724-90; Med. Res. Project no.: 8767-001

Study Period: August 21, 1989 to June 14, 1990 (In-life phase)

Test Material: Bromacil with a purity of 95% (5 Bromo-3-sec-butyl-6-methyluracil)

Test Animal: Crl:CD®BR Rat

A. OBJECTIVE

The objective of this study was to assess the reproductive and fertility effects of the parents and the growth and development of the offspring following oral administration of bromacil technical to rats for two generations.

B. MATERIALS AND METHODS

Test Compound: Physical properties not noted; purity = 95%
Lot no.: 180-806 3T Batch 31
Storage: Under refrigeration in the dark

Test Animals: Species: Crl:CD®BR Rat
Source: Charles River Laboratories Inc., Raleigh, NC
Acclimation Period: Twenty days
Age: Rats were 5 weeks old on arrival
Body Weight: Females = 99 - 141 g on arrival (N=139)
Males = 108 - 171 g on arrival (N=139)
Caging: Individual stainless steel, wire-mesh cages; polycarbonate pans for females during gestation and lactation periods; during the mating period, males and females (1:1) were housed in one cage; after mating the males were removed and on the day of weaning, the dams were removed and placed in another cage
Basal Feed: Purina Certified Rodent Chow #5002 meal and water ad libitum

Environmental Parameter: Air temperature = 23 ± 2°C; Relative Humidity = 50 ± 10%; Photoperiod: 12 hrs dark/light cycle; Air exchanges in test rooms were not specified.

Dose Selection:

Dose levels for this study were based on the results of a 2-year feeding study (0, 50, 250, and 2500 ppm), and a 3-generation reproduction feeding study (0 and 250 ppm) conducted in rats. In the 2-year feeding study body weight reduction was noted at 2500 ppm dose level in the first year and at the 250 ppm level in the second year. No compound-related effects were noted in the 3-generation reproduction study. Based on the results of these studies, dose levels of 0, 50, 250, and 2500 ppm were selected for this study.

Group Arrangement:

The parent (P) and F1 rats were randomly grouped, as follows:

Parental (P) Animal Groupings

Dose Groups	Dose Level (ppm)	Mean Body Weights (g) At start of Treatment		Number Assigned	
		Males(M)	Females(F)	M	F
Control	0	300	205	30	30
Low Dose	50	300	204	30	30
Mid Dose	250	302	206	30	30
High Dose	2500	302	204	30	30

F1 Animal Groupings

Dose Groups	Dose Level (ppm)	Mean Body Weights (g) At Start of Treatment		Number Assigned	
		Males(M)	Females(F)	M	F
Control	0	58	54	30	30
Low Dose	50	58	54	30	30
Mid Dose	250	60	57	30	30
High Dose	2500	54	51	30	30

Duration of Dose Administration

For the parent (P) animals, the test art cle was administered during the 75-day pre-mating period, and subsequent mating, gestation and lactation periods. For the F1 animals, the test article was administered following the weaning of the F1 litters on day 21 post partum for a total of the 105-day pre-mating period, and during the mating, gestation and lactation periods.

Diet Preparation and Test Article Analyses

The test article was mixed with Purina Certified Rodent Chow in a mixer. All diets were prepared weekly and refrigerated until use. Prepared diets were analyzed to verify concentration, homogeneity, and stability of bromacil. Stability samples collected from feed jars were stored for 7 and 14 days at room temperature, and stability samples from the diet mixer were refrigerated for 14 days before analysis. Five times during the study, samples were collected at the cage site to verify concentration of bromacil at each dose level.

Mating and Breeding Procedures for Parent (P) and F1 Generations

Seventy-five days after the start of dosing, the P female rats were mated with males (1:1) for a maximum of 21 days. After 105 days of dietary exposure the F1 parental rats were mated for a maximum of 15 days to produce F2 offspring.

- P Generation
  Animals of the P generation were approximately 8 weeks old at the start of treatment, and were maintained on diet for 75 days prior to mating. Pups in each litter were counted and weighed collectively by sex. On day 4 post partum, pups were culled randomly to 8 (four/sex when possible) and reared until weaning. Litter counts and weights were conducted on day 4, 7, and 14 post partum, and individual pup weights were taken on day 21 post partum. Clinical observations of pups were conducted on day 0, 4, 7, 14 and 21 post partum. On day 21 post partum, 30 pups/sex/group were randomly selected for the F1 generation study. Twenty additional F1 weanlings/sex/dose were randomly selected for gross pathological evaluation. The remaining pups were sacrificed and discarded. All P generation rats were subjected to gross pathological examination, including those that died, were sacrificed in extremis, and nonpregnant dams. At necropsy, organs and tissues from all P animals were fixed in formalin.

- F1 Generation
  The selected F1 animals were reared on their respective diets for 105 days prior to mating. Selection and culling of the F2 pups were essentially the same as described above for the F1 pups. Twenty F2 weanlings/sex/dose were randomly selected for gross pathological evaluation. The remaining pups were sacrificed and discarded. All gross lesions were preserved. All F1 parental generation rats were subjected to gross pathological examination, including those that died, were sacrificed in extremis, and nonpregnant dams. At necropsy, organs and tissues from all adult F1 animals were fixed in formalin.

Clinical Observations

The animals were checked at least once daily for mortality, moribundity, and signs of toxicity. At least once a week throughout the pre-mating, gestation, and lactation periods, each P and F1 rat was individually examined for abnormal behavior and/or appearance. Moribund rats were sacrificed, and along with rats found dead, were subjected to gross pathological examination.

Parental Body Weights

Individual body weights (BW) were recorded weekly (except during the mating periods). After mating, females were weighed on days 0, 7, 14 and 21 of gestation. Dams which littered were weighed on days 1, 4, 7, 14, and 21 post partum. Weekly body weights were recorded for females without known start date of gestation, mated females that did not deliver a litter, and for all males.

Parental Food Consumption Data

Individual food consumption (FC) was recorded weekly (except during the mating period). Food consumption was also recorded on days 0, 7, and 14 of gestation. Relative food consumption ratios and test material intake expressed as mg/kg/day were computed.

Gestation and Parturition Data

After mating females were observed twice daily for signs of parturition. Dams without fetuses or which lost their fetuses were sacrificed together with the other dams which had weaned their pups. All dams were necropsied and all organs were eamined.

Lactation and Litter Data

Day 0 of lactation is the day on which a female delivered all pups. After delivery, litter size, live birth, stillbirth and gross anomalies of fetuses were recorded. Sex ratio of pups was recorded on days 0, 4, and 21 of lactation. Individual pup weights were taken on days 0 and/or 1, 4, 7, 14, and 21 of lactation. Litters were caged with dam and observed daily for survival and behavioral abnormalities, until weaning on day 21 of lactation. On day 4 post partum, 4 male and 4 female pups per litter were randomly selected for further evaluation and use. Extra offspring were sacrificed and discarded without gross pathology exams. Dead pups were necropsied and preserved in fixative for possible further evaluations.

Postmortem Examination and Data

After the necessary evaluations were conducted on all P and F1 animals used for breeding, they were sacrificed on day 21 post partum and subjected to macroscopic and histopathological evaluations. F1 pups not selected for breeding were sacrificed, examined macroscopically and discarded. All F2 pups were sacrificed and examined for abnormalities after weaning, and those not selected for organ weight recording and histopathology were discarded after gross necropsy evaluations. Tissues from all P and F1 animals selected for breeding and from those that died, or were sacrificed in extremis were harvested at necropsy and fixed in formalin, as follows:

- o gross lesions
- o testes (weighed)
- o prostate, epididymides, seminal vesicles, and coagulating gland
- o pituitary gland
- o ovaries
- o uterus (cervix, uterine horns and uterine body)
- o vagina

Histopathological Evaluations

Harvested tissues of the control and high-dose groups of both generations listed above were stained with hematoxylin and eosin and were subjected to histopathological evaluations.

Statistical analysis

The statistical methods are appended as Appendix A.

Compliance

- o A signed Statement of Confidentiality Claim was provided.
- o A signed Statement of compliance with EPA GLP's was provided
- o A signed Quality Assurance Statement was provided.

C. RESULTS AND DISCUSSIONS

a. Test Article Analysis in Feed Pellets

The stated purity of bromacil supplied by the sponsor was approximately 95%. The purity of bromacil analyzed by the testing facility was 94% (range 93%-96%), 93% (range 91%-94%), and 92% (range 91%-94%) at the beginning, the middle, and at the end of the study period.

The nominal concentrations of the test material were between 71 to 106% of nominal. The range of bromacil concentrations in the feeder samples were 72%-106%, 71%-99%, and 86%-104% of nominal for the low-, mid- and high-dose groups, respectively. The homogeneity of bromacil in the diet varied from 91% to 102% of nominal.

Bromacil remained stable in the feed when refrigerated for up to 14 days. However, the 50 ppm samples stored for 7 and 14 days and 250 ppm samples stored for 14 days at room temperature showed a slight decline in concentration.

b. P and F1 Parental Animal Data

1. Parental Mortality

No parental P animals died prior to scheduled sacrifice. A total of five F1 rats died within the first week after weaning, including two control males, one control female, one mid-dose female, and one high-dose female. One control F1 female was sacrificed in extremis due to weight loss and irregular breathing. One F1 male rat was sacrificed because it was erroneously assigned to the F1 low-dose female group. None of the deaths was considered to be related to treatment.

2. Parental Clinical Observations

No treatment-related clinical signs were observed in any P or F1 parental groups. Fewer hyperactive high-dose P and F1 male, P and F1 female rats were observed as compared to their respective controls. Fewer high-dose F1 females showed alopecia as compared to the controls. It is not clear whether these findings have any biological significance.

c. P and F1 Parental Body Weights and Body Weight Gain Data

The summary mean P and F1 male body weights and body weight gains data are presented in Appendices B1 and B2. High-dose F1 male body weights were significantly ($P < 0.05$) reduced starting from day 7 after the start of the study, as compared to the control. The high-dose P male body weights were slightly reduced but not statistically significant. Overall body weight gains were slightly (4.8%) reduced in high-dose P males and were significantly reduced (8.4%) in F1 high-dose males, as compared to their respective controls. The reductions of body weights and body weight gains in high-dose P and F1 males are considered to be biologically significant and thus related to treatment.

The summary mean P and F1 female body weights and body weight gains data during pre-mating, gestation and lactation periods are presented in Appendices C1 to C4, respectively. As seen from Appendices C1 and C2, during the pre-mating period, the high-dose P and F1 female body weights were lower with scattered statistically significant values, as compared to their respective controls. Although not statistically significant, the overall body weight gain reductions were 10.2% and 7.6% in the P and F1 females, respectively, as compared to the control. These reductions are judged to be treatment-related.

As seen from Appendix C3, on day 14 of gestation, the high-dose F1 female body weight was lower (statistically significant at $P<0.05$) compared to the controls. However, higher body weight gain was observed in the F1 female high-dose group as compared to the control during the last week of gestation. Overall body weight gains (days 0-21 of gestation) of both the P and F1 females were comparable among all groups, with no significant differences.

As seen from Appendix C4, during the lactation period, the body weights of the P and F1 high-dose females were not significantly different from the controls. The P high-dose group had an overall net body weight gain during lactation, while the other P females had a net body weight gain loss. A similar pattern was observed for the F1 females, where the control, low- and mid-dose groups had weight losses at some intervals during the lactation period, while the P high-dose group had weight gains throughout lactation. The overall body weight gain in the F1 female high-dose group was statistically significant, as compared to the control. Since the F1 female high-dose group started at a lower body weight, the observed net body gain during the lactation period may indicate that these rats' growth curve had not plateaued.

d. Food Consumption Values

The summary mean food consumption values of P and F1 males during the pre-mating period are presented in Appendix D1. No significant differences were observed for any group of the P males as compared to the control. Statistically significant reduced food consumption values were observed in the high-dose F1 males at various intervals between days 7 and 91 of the pre-mating periods, as compared to the control. This difference is considered to be a compound related effect.

The food efficiency of the P and F1 males is presented in Appendix D2. No treatment-related effects were observed. The observed scattered statistically significant differences in reduced food intake efficiency values were considered to be unrelated to treatment.

The summary mean food consumption and food efficiency values of the P and F1 females during the pre-mating period are presented in Appendices D3 and D4, respectively. The high-dose P and F1 females food consumption values were significantly reduced at various intervals, as well as for the overall food intake during the pre-mating period, relative to their controls. Overall food consumption efficiencies were similar despite occasional weekly fluctuations.

Summary mean food consumption and food efficiency values of the P and F1 females during the gestation period are presented in Appendix D5. Food consumption values of the high-dose P females were significantly reduced during the first week and overall during the gestation period as compared to controls. Although the food consumption values of the F1 high-dose rats were somewhat lower than the controls, they were not statistically significant. The food consumption efficiency of the high-dose P rats was significantly greater during the second week of gestation, but lower during the first week as compared to the control.

e. Test Article Intake

The calculated mean test article intakes, based on the food consumption and body weight determinations for the P and F1 rats during the pre-mating and gestation periods are presented in Appendices E1, E2, and E3. The mean daily compound intake was greater for females than the males and greater for the F1 than the P generation. In the females, there was a slight increase in test article intake during the gestation as compared to the end of the pre-mating period. Variability of values over time and between sexes and generation may be related to normal differences in body weight and food consumption relative to age, sex, and pregnancy status.

f. Reproductive Indices of the P and F1 Animals

The results of the mating, fertility, and gestation length of the P and F1 animals are presented in Appendix F. As seen from this Appendix, there was no indication of any treatment-related effects.

g. Summary Data of F1 Litter Size and Pup Survival

The summary data of F1 and F2 litter size and pup survival are presented in Appendices G1 and G2, respectively. As seen from Appendix G1, there were no significant differences in litter size and pup survival between the F1 treated groups and the control. As seen from Appendix G2, mean litter size for high-dose live pups from post-culling until weaning was significantly greater than the controls. This litter size difference is not considered related to treatment.

i. F1 and F2 Pups External Observation

No treatment-related external observation findings were observed in the F1 and F2 pups (p. 109-110 of the study report).

j. Body Weights of the F1 and F2 Pups

The summary mean body weights of the F1 and F2 pups are presented in Appendix G3. The mean body weights of the high-dose F1 pups were less (males: 8.5% less; females: 5.3% less) than the controls toward the end of the lactation period. The difference was significant ($P < 0.05$) for female pups on postnatal days 4 (post-culling), 7, and 21. For the F2 pups, mean body weights of the high-dose group were not significantly different than the controls. The mean body weights of the low- and mid-dose group pups were greater (some intervals were statistically significant) than the controls. The increased body weights in these groups are not considered to be related to treatment. A slight decrease in body weights in the F1 high-dose group is considered to be related to treatment.

l. Testes Weights and Testes/Body Weight Ratios

The testes weights of the P and F1 generation rats are presented in Appendices H, and I, respectively. Mean testes and final body weights of the P high-dose males were not significantly different from the controls. The mean final body weights of the F1 male high-dose group was significantly lower (8.0%) as compared to controls. The body weight effects in the high-dose groups were consistent with the effect observed in the in-life portion of the study. The high-dose F1 male mean absolute testes weight was slightly (not statistically significant) increased (0.95%) and the testes/body weight ratio was significantly ($P < 0.05$) increased as compared to controls. The significant increase of testes/body weight ratio in the high-dose F1 males is not considered to be a treatment-related effect, because this increase was due to reduced body weight and the presence of testes weight outliers in this dose group. No difference of testes weight was seen among the P dose groups.

m. Macroscopic Findings

The only pertinent macroscopic finding is the increased of renal pelvis dilation in the F1 treated males (1/30, 5/30, 4/30, and 8/30, in the control, low-, mid-, and high-dose groups). Since the renal pelvis dilatation incidence showed a dose-related trend, it appears to be a treatment-related effect. This is contrary to the investigators' conclusions noted on p. 40 of study report.

n. Microscopic Findings

The summary microscopic findings were presented in Tables 52-55 and the microscopic findings for individual rats were presented in Appendices Z and AA on p. 121-128 and p. 589-1071 of the study report, respectively. The investigators concluded that no microscopic findings in the adult rats were considered compound

microscopic data presented in the report (p. 121-128 and p. 589-1071 of the study report), this reviewer arrived at a different conclusion. Since the total number of rats evaluated for tissues classified as "other organ" (indicated as underlined total number in Summary Tables 52-55 on p. 121-128 of the study report) were lumped together, it is impossible to determine the total number of animals evaluated for a specific "other" tissue/organ, for example, the kidney. For this one must consult the individual incidence data. This reviewer tabulated pertinent summary microscopic findings derived from the study report (p. 121-128 and p. 923-952 of the study report) and it is presented in Appendix J. As seen from this Table, there is an evidence that kidney hydronephrosis observed in the treated group was related to treatment, because the data showed a dose-related trend. Increased renal pelvis dilatation during gross necropsy evaluation was observed in the treated groups (5/30 in low-dose, 4/30 in mid-dose, and 8/30 in high-dose groups), as compared to the control (1/30 of control). After histopathological evaluation, most of these lesions were determined to be kidney hydronephrosis, 1/1 of the control, 5/5 in low-dose, 4/5 in mid-dose, and 8/8 in high-dose groups. However, the microscopic data of kidney incidences presented in the study report only included those that showed gross lesions during necropsy. Since kidney hydronephrosis can only be determined microscopically, therefore, it is difficult to make conclusions from data that were derived only from kidney with gross lesions. It requested that kidneys of all other adult rats (including those without gross lesions) of all dose levels be histopathologically evaluated in order to obtain the actual distribution of kidney hydronephrosis in this study (see Subdivision F Guideline 83-4 for a multigeneration study).

CONCLUSIONS

Four groups of 60 (30 males and 30 females) Crl:CD®BR rats (P generation) were fed technical Bromacil in the diet at 0, ~~100~~, 250 ~~500~~, and 2500 ppm for a 75-day pre-mating period, and continued during the mating, gestation and lactation periods to breed the F1 rats. Four groups of 60 (30 males and 30 females) F1 rats were selected and continued on the same diet at the same dose levels to breed F2 offspring.

Based on the data presented in the study report, the systemic parental toxicity NOEL and LOEL cannot be determined at this time, because of a possible dose-related effect observed in the F1 male rat kidneys (increased incidence of kidney hydronephrosis) which could not be adequately evaluated from data presented in the study report, because only rats observed with gross renal pelvis dilatation were microscopically evaluated. The reproduction NOEL is determined to be ~~500~~ 250 ppm, based on the slight body weight decrease in the 2500 ppm F2 pups. The reproduction LOEL is 2500 ppm

Based on data presented in the study report, the following treatment-related effects were observed:

- Body weight reductions in both sexes of the P and F1 2500 ppm dose groups during the pre-mating period.
- Food consumption and food consumption efficiency reduction in the F1 males of the 2500 ppm dose group.
- Increased renal pelvis dilatation in the F1 males of the 2500 ppm dose group.
- Body weight reduction in the 2500 ppm F2 pups

There was possible evidence of a dose-related increase in kidney hydronephrosis in the treated F1 males as compared to the control as determined microscopically, [1/1 in control, 5/5 in low-, 4/5 in mid-, and 8 (incidence) /8 (total evaluated) in high-dose groups]. Since only those kidneys with observed gross lesions (noted as renal pelvis dilatation), were histopathologically evaluated, it is not apparent whether additional cases of developing kidney hydronephrosis may have been present. The registrant is requested to microscopically evaluate all rat kidneys from all dose levels to determine if additional cases of developing kidney hydronephrosis may have been present. The classification of this study is upgradable, upon satisfactory review of the requested information.

CLASSIFICATION: Core-supplementary. This study does not satisfy the guideline requirements (83-4) for a two-generation reproduction toxicity study in rats. This study is upgradable upon satisfactory review of the requested information.

LIST OF APPENDICES

APPENDIX D5: Summary Mean Daily Food Consumptions (g/rat) and Mean Food Consumption Efficiency (g BW Gain/g FC) of P and F1 Females During the Gestation Period (Copied from p. 87-88 of the study report)

APPENDIX E1: Summary Mean Daily Bromacil Intake (mg/kg/day) by P and F1 Males During the Pre-mating Period (copied from p. 89-90 of the study report)

APPENDIX E2: Summary Mean Daily Bromacil Intake (mg/kg/day) by P and F1 Females During the Pre-mating Period (copied from p. 91-92 of the study report)

APPENDIX E3: Summary Mean Daily Bromacil Intake (mg/kg/day) by P and F1 Females During the Gestation Period (copied from p. 93 of the study report)

APPENDIX F: Summary of the Reproductive Indices of the P and F1 Females (copied from p. 102 of the study report)

APPENDIX G1: Summary Mean Pup Numbers and Survival of the F1 Generation (copied from p. 103 & 104 of study report).

APPENDIX G2: Summary Mean Pup Numbers and Survival of the F2 Generation (copied from p. 105 & 106 of study report).

APPENDIX G3: Summary Mean Pup Weights (g) of the F1 and F2 Generations (copied from p. 107 & 108 of study report)

APPENDIX H: Summary Mean Final Body and Organ Weights (g) of Male and Female P and F1 Adult Rats (copied from p. 111 and 112 of the study report).

APPENDIX I: Summary Mean Body and Organ Weights (g), the Male and Female F1 Adult Rats (copied from p. 113 and 114 of the study report).

APPENDIX J: Summary of Pertinent Microscopic Findings (derived from p. 121-128 and p. 923-952 of the study report)

Bromacil RIN: 1607-93

Page_____ is not included in this copy.

Pages 18 through 40 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

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