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DATA EVALUATION RECORD

STUDY TYPE: Two Generation Reproduction Study - Rat
OPPTS Number: 870.3700 OPP Guideline Number: §83-4

DP BARCODE: D241232 SUBMISSION CODE: S534142
P.C. CODE: 070705 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): KBR 3023 Technical (96.7-97.7% a.i).

SYNONYMS: 2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester

CITATION: Astroff, A.B., (1996). A Two Generation Reproductive Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat. Bayer Corporation, Agricultural Division, Stilwell, Kansas. Laboratory Study Number 95-622-EH, December 18, 1996. MRID 44408727. Unpublished.

Astroff, A.B., (1995). A Pilot Reproductive Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat. Bayer Corporation, Agricultural Division, Stilwell, Kansas. Laboratory Study Number 94-972-DA, September 8, 1995. MRID 44408726. Unpublished

SPONSOR: Bayer AG, D-51368 Leverkusen, Bayerwerk, Bldg. 6210, Germany

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 44408727), KBR 3023 (96.7-97.7% a.i) was administered to the shaved skin of Sprague-Dawley rats (30/sex/dose) at dose levels of 0, 50, 100, or 200 mg/kg/day for 5 days/week. P male and female exposure to KBR 3023 began at 8-9 weeks of age and lasted for 10 weeks prior to mating to produce F_1 pups. At 21 days of age, F_1 pups (30/sex/dose) were selected to become the parents of the F_2 generation and were treated with the same levels of KBR 3023 as their dam for 10 weeks prior to mating. P and F_1 females were continuously dosed throughout gestation and lactation.

No treatment-related parental systemic toxicity was observed. No treatment-related clinical findings, increases in mortality, differences in body weight gains or food consumption, or changes in reproductive performance were noted in the P females or males at any dose level. Dermal findings at the treatment site (acanthosis and hyperkeratosis) were considered to be due to the treatment methodology and not compound-related.

The systemic NOAEL is >200 mg/kg/day; the NOEL = 200 mg/kg/day.

There was no treatment-related reproductive toxicity. There were no clinical signs of toxicity or changes in pup weight, viability, or litter sizes noted in the pups at any dose level for the F_1 or F_2 generations. No treatment-related macroscopic findings in the F_1 or F_2 pups were observed at any dose level.

The reproductive NOAEL is >200 mg/kg/day; the NOEL = 200 mg/kg/day.

Dosing was considered adequate based on the results of a previously reviewed range finding study (MRID 44408716) in which KBR 3023 (99.2% a.i.) was applied to the shaved skin of young adult Sprague-Dawley rats (10-20/sex/dose) at dose levels of 0, 80, 200, 500, or 1000 mg/kg/day for 5 days/week, 5 hours/day, for 90 days. KBR 3023 elicited diffuse liver hypertrophy in both sexes treated at 1000, 500, or 200 mg/kg/day. The LOAEL for systemic toxicity is 500 mg/kg/day, based on liver and kidney effects, and the NOAEL is 200 mg/kg/day.

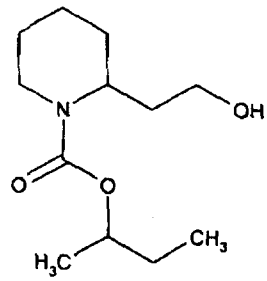
This reproductive toxicity study is classified **acceptable (§83-4[a]) and does satisfy the guideline requirement for a multi-generational reproductive toxicity (reproduction) study in rats.**

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: KBR 3023 Technical
   Description: Clear, colorless liquid
   Lot/Batch #: 030693
   Purity: 96.7-97.7%
   CAS #: 119515-38-7
   Structure:



2. Vehicle: None

3. Test animals: Species: rat
   Strain: Sprague-Dawley
   Age at start of dosing: P: 8-9 weeks. F_1: 21 days (weaning).
   Weight at start of dosing:
   (P) Males: 197.2-275.5 g Females: 130.4-198.7 g
   (F_1) Males: 84.0-206.3 g Females: 72.5-162.1 g
   Source: Sasco Inc. Omaha, NE
   Housing: Suspended stainless steel cages during the pre-mating (1/cage) and mating (2/cage) period, in plastic cages during gestation (1 dam/cage) and lactation (1 dam and litter/cage) and for up to approximately one week post-weaning (1 litter/cage).
   Diet: Purina Mills Rodent Lab Chow 5001-4, *ad libitum*
   Water: Municipal tap water, *ad libitum*
   Environmental conditions:
   Temperature: 18-26°C
   Humidity: 40-70%
   Air changes: Not reported
   Photoperiod: 12 hrs dark/12 hrs light
   Acclimation period (P): ≥6 days

B. PROCEDURES AND STUDY DESIGN

1. Study duration (in life dates): start - 5/2/95; end - 2/11/96.

2. Mating procedure: One male was caged with one female from the same test group until sperm (or a copulation plug) was observed in the vaginal tract. Cohabitation lasted no longer than 21 days. After successful mating, each pregnant female was individually placed into a cage with a solid bottom where it was kept throughout gestation and lactation.

3. Study schedule: Starting at approximately 8-9 weeks of age, P animals were administered the test compound dermally for 10 weeks before mating. After the mating period, P males were sacrificed and necropsied. P female dosing continued throughout gestation and lactation. Litters were culled to 8 pups/litter on day 4 of lactation and weaned at 21 days of age. P dams were sacrificed and necropsied after weaning. Upon weaning, F_1 animals were dosed dermally with the same dose of test compound as their dams for 10 weeks before they were mated to produce the F_2 generation. F_1 adults and F_2 litters were sacrificed and necropsied at weaning. Exposure of all animals to the test material was 5 days/week throughout the study.

4. Animal assignment: P animals were randomly assigned (stratified by weight) to test groups (Table 1).

Table 1. Animal assignment[a,b]

Test Group	Dose (mg/kg/day)	Animals/group	
		P Males	P Females
Control	0	30	30
Low-dose	50	30	30
Mid-dose	100	30	30
High-dose	200	30	30

a Test compound was administered 5 days/week from the beginning of the study until sacrifice.
b Data extracted from the study report page 20.

5. Dose selection rationale: Dose selection was based on the results of a previously reviewed 90-day dermal toxicity study (MRID 44408716) and a pilot reproductive toxicity study (MRID 44408726). In the 90-day dermal toxicity study, KBR 3023 (99.2% a.i.) was applied to the shaved skin of young adult Sprague-Dawley rats (10-20/sex/dose) at dose levels of 0, 80, 200, 500, or 1000 mg/kg/day for 5 days/week, 5 hours/day, for 90

days. Following the 90 days of treatment, 10 rats/sex/dose were sacrificed. The remaining 10 rats/sex in the 0 and 1000 mg/kg/day groups were maintained without treatment for an additional 4 weeks to assess recovery potential. Treatment-related lesions in rats from all treatment groups consisted of scabs, red foci, and exfoliation limited to the dose site. The incidence and frequency of scabs and red foci were concentration-dependent. Females in all treatment groups exhibited very slight erythema. KBR 3023 was hepatotoxic, as evidenced by diffuse liver hypertrophy in both sexes treated at 1000, 500, or 200 mg/kg/day. Individual liver cells were necrotic in the 1000 and 500 mg/kg/day group males (3-4/group), and in one 1000 mg/kg/day group female. Absolute and relative liver weights were increased in the 1000 (23-28%) and 500 mg/kg/day (8-14%) treatment groups. KBR 3023 was toxic to kidneys, causing minimal to slight hyaline degeneration in both sexes treated at 1000 or 500 mg/kg/day. The kidneys of the 1000 mg/kg/day group males exhibited an increased incidence of foci of tubular regeneration compared to the other test groups, chronic kidney inflammation (3/10 males), and increased absolute and relative weights (24-26%). The 500 mg/kg/day group males had increased relative kidney weights (14%). Urine pH and urobilinogen (males only) was decreased in the 1000 mg/kg/day group, and urine pH was decreased in the 500 mg/kg/day group compared to the controls. All compound-related changes returned to normal by the end of the 4-week recovery period. Other than dermal response on treated skin, no toxic response to KBR 3023 was noted in the 80 mg/kg/day treatment groups. No animals died during the study. There were no treatment-related differences in body weights or body weight gains, food consumption, ophthalmology, hematology parameters, clinical blood chemistry, or macroscopic organ morphology between rats in the treated and control groups. No neoplastic tissue was observed. The investigators determined that the LOEL for systemic toxicity was 200 mg/kg/day, based on diffuse liver hypertrophy in both sexes; and the NOEL was 80 mg/kg/day. The LOEL for dermal toxicity was determined to be 80 mg/kg/day based on the presence of scabs, red foci, and exfoliation at the dose site; a NOEL was not established.

In a pilot reproduction study (MRID 44408726), Sprague-Dawley rats were fitted with Elizabethan collars and dermally adminstered KBR 3023 at 0 or 200 mg/kg/day for 5 days/week throughout the study. Dosing started with a two-week pre-mating period and continued throughout mating, gestation and lactation. Litters were culled to 8 pups/litter on day 4 of lactation and weaned at 21 days of age. One pup/sex/litter from the F_1 generation was maintained beyond weaning and dermally treated with KBR 3023. There were no treatment-related clinical signs (including signs of dermal irritation) or effects on body weight or food consumption in the P generation and no treatment-related clinical signs or effects on body weight in the F_1 generation. There were no significant effects on any litter parameters or reproductive indices. No treatment-related necropsy findings were observed in either generation.

Based on the results of these studies, 200 mg/kg/day was chosen as the high-dose treatment level for the two-generation reproduction study. The low- and mid-dose levels chosen were 50 and 100 mg/kg/day, respectively.

6. Dosage preparation and analysis: KBR 3023 was applied neat to the animals' backs; therefore, no preparation and consequently, no analysis of homogeneity was required. The concentration of the batch of KBR 3023 used in this study was determined before, during, and after the study. Aliquots of the batch were maintained frozen prior to use. During use, an aliquot was thawed and maintained at room temperature. The compound has been reported to be stable at room temperature for up to four weeks. The test material was not adjusted for the percent of active ingredient.

   Results - Homogeneity Analysis: Not necessary.

   Stability Analysis: It was stated that neat KBR 3023 has been previously shown to be stable at room temperature for up to 4 weeks.

   Concentration Analysis: The percent active ingredient of KBR 3023 in batch # 030693 was 97.7% (prior to study start), 97.4% (during study), and 96.7% (after study termination).

   The information provided indicated that the test compound was stable for the duration of the study and that compound concentration was within acceptable limits.

7. Dosage administration: All P animals wore Elizabethan collars for the duration of the study, beginning at least seven days prior to the initiation of dosing. F_1 pups received their collars when placed into individual cages, approximately one week after weaning. Collars were removed during weighing. An area representing approximately 10% of the total surface area of each animal was clipped at the beginning of the study and as needed thereafter. The test formulation was administered by applying 0.0, 0.05, 0.10, and 0.20 ml/kg body weight of the undiluted solution (KBR 3023 density is approximately 1 g/ml) to the animal's back. All doses were administered once daily, 5 days/week (Monday-Friday). Dosing was based on the weekly body weight determination, except for F_1 pups, where body weight measurements were taken every three days from weaning until the start of the premating phase.

C. OBSERVATIONS

1. Parental animals: All parental animals were observed twice daily for clinical signs, morbidity and mortality, and once daily on weekends and holidays. In addition, a physical and clinical exam was performed once a week. Males were weighed pre-dose and weekly throughout the study. Females were weighed pre-dose, weekly throughout mating and pre-mating, on gestation days 0, 6, 13, and 20, and on lactation days 0, 4, 7, 14, and 21. Body weight gains, but not body weights, were compared statistically. Food consumption was measured daily for both sexes during the premating period. During gestation, maternal food consumption was recorded on days 0, 6, 13, and 20. During lactation, food consumption was recorded on days 0, 7, 14, and 21.

2. Litter observations: Litters were examined in detail once daily for clinical signs, morbidity, and mortality. Table 2 shows litter observations (X).

Table 2. F_1 and F_2 litter observations[a]

Observation	Time of observation (lactation day)					
	Day 0	Day4[b]	Day 4[c]	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X	X
Pup weight	X	X	X	X	X	X
External alterations	X	X	X	X	X	X
Number of dead pups	X	X	X	X	X	X
Sex of each pup	X	X	X	X	X	X

a Data extracted from the study report, page 22.
b Before standardization (culling).
c After standardization (culling).

On day 4 postpartum, litters were standardized to a maximum of 8 pups/litter with 4/sex/litter, as nearly as possible; excess pups were killed and necropsied.

3. Postmortem observations:

1) Parental animals: Sires were sacrificed after the mating period. Dams were sacrificed after the litters were weaned. These animals were subjected to postmortem examinations, including an examination of external surfaces and major organs. Uterine implant sites were also counted. In addition, the CHECKED (X) tissues were collected and examined histologically in all animals that died or were killed *in extremis* and those sacrificed on schedule. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT		NEUROLOGIC
	Tongue		Aortic arch		Brain
	Salivary glands		Heart		Peripheral nerve
	Esophagus		Bone marrow		Spinal cord (3 levels)
	Stomach		Lymph nodes	X	Pituitary
	Duodenum		Spleen		Eyes (optic n.)
	Jejunum		Thymus		GLANDULAR
	Ileum		UROGENITAL		Adrenal glands
	Cecum	XX	Kidneys		Harderian gland
	Colon		Urinary bladder		Mammary gland
	Rectum	XX	Testes		Parathyroids
XX	Liver	X	Epididymides		Thyroids
	Gall bladder	X	Prostate		OTHER
	Pancreas	X	Seminal vesicles		Bone
	RESPIRATORY	XX	Ovaries		Skeletal muscle
	Trachea	X	Uterus	X	Skin (shaved)
	Lungs	X	Vagina		Lacrimal gland
	Nasal cavity		Ureter		Zymbal gland
	Pharynx		Urethra	X	All gross lesions and
	Larynx	X	Cervix		masses

2) Offspring: Preweaning pups that died or were stillborn, day 4 culled pups, and weanling pups were examined macroscopically internally and externally. No tissues were collected from the pups.

D. DATA ANALYSIS

1. Statistical analyses: All collected data were subjected to routine, appropriate statistical procedures.

2. Indices:

Reproductive indices: The following reproductive indices as presented in the study report were calculated for the P and F_1 adults:

mating index = # of inseminated females/# of females paired x 100%
fertility index = # of females pregnant/# of inseminated females x 100%

Offspring viability indices: The following viability indices as presented in the study report were calculated for the F_1 and F_2 litters:

gestation index = # of females delivering a live litter/# of females pregnant x 100%
birth index = total # of pups/litter/ total # of implantation sites/litter x 100%
livebirth index = # of live pups at birth/litter/total # of pups born/litter x 100%
viability index = # of live pups/litter at day 4 (preculling)/# of live pups born/litter x 100%
lactation index = # of live pups/litter on day 21/# of live pups/litter at day 4 (postcull) x 100%
sex ratio = # of males/number of pups x 100%

3. Historical control data: No historical control data were provided.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: No treatment-related mortality or clinical findings were noted in the P or F_1 males or females during premating, gestation, or lactation. In the P generation, one mid-dose female was found dead during the premating phase. In the F_1 generation, one control male and one high-dose male were found dead during the premating/mating phase. One high-dose male was sacrificed after exhibiting labored breathing, urine stain, rough coat, unthrifty appearance, and being cold to the touch. Clinical signs observed were lacrimation, scab formation, and lacerations. These signs were believed to be due to the wearing of Elizabethan collars and were not considered of toxicological significance.

   Scaling/sloughing of the skin at the treatment site was observed in the P generation in two high-dose males, two mid-dose females, and five high-dose females. In the F_1 adults, these signs were observed in one high-dose male and one mid-dose female. These signs were not believed due to compound biochemical toxicity, but rather due to physical effects of the compound on the skin. Similar effects have been seen when skin has been exposed to water or petrolatum. Therefore, these effects were not considered compound-related, but rather an adaptive response of the skin to exposure.

2. Body weight and food consumption: Sporadic, statistically significant ($p \leq 0.05$ or 0.01) decreases and increases in body weight gains occurred in P and F_1 adults during premating. Due to the sporadic nature and the occurrence of both increases and decreases, these differences were not considered treatment-related. Absolute body weights were not compared. However, the differences in body weights between controls and treatment groups in the P and F_1 generations at the end of premating were <7% (calculated by reviewers). No significant differences in body weight gains were noted in

P or F_1 females during gestation or lactation.

Sporadic, statistically significant ($p \leq 0.05$ or 0.01) decreases and increases in food consumption occurred in the P adults and F_1 females during premating and in the P and F_1 females during gestation and/or lactation. F_1 males did not show any significant differences between treated and control groups. Due to their sporadic nature and the presence of increases and decreases, these differences were not considered to be of toxicological concern.

3. Reproductive function:

   a. Estrous cycle length and periodicity: There were no significant differences in estrous cycle length and periodicity in the P and F_1 dams in this study. Precoital intervals were comparable to the controls (Table 3).
   b. Sperm measures: No sperm parameter observations were made in this study; however, there were no indications of treatment-related fertility abnormalities in P or F_1 male rats during this study.
   c. Sexual maturation (F_1): No observations were made pertaining to the sexual maturation rates of the F_1 or F_2 litters.

4. Reproductive performance: Reproductive performance results are presented in Table 3. There were no treatment-related effects noted in the reproductive performance of the P adults.

Table 3. Reproductive performance.[a]

Observation	Dose Group (mg/kg/day)			
	0	50	100	200
P Generation - Litter F_1				
Day to Insemination	3.5	3.5	3.8	3.4
Estrous Cycle Length (days)	4.6	4.2	4.2	4.5
Mating Index	100	100	96.7	100
Fertility Index	100	96.7	89.7	100
Gestation Index	100	96.6	100	100
Mean Gestation Interval (days)	22.5	22.5	22.0	22.5
Mean Implantations	12.6	12.8	12.9	12.1
Number of Litters	30	28	26	30
F_1 Generation - Litter F_2				
Day to Insemination	3.4	3.4	4.2	4.3
Estrous Cycle Length (days)	5.4	6.5	5.5	5.3
Mating Index	100	100	96.7	100
Fertility Index	96.7	90.0	89.7	96.7
Gestation Index	96.6	100	100	100
Mean Gestation Interval (days)	22.5	22.6	22.4	22.5
Mean Implantations	12.0	12.3	12.3	11.4
Number of Litters	28	27	26	29

a Data extracted from the study report Tables 4 and 18, pages 47 and 86.

5. Parental postmortem results

a) Organ weights: Compared to controls, absolute kidney and liver weights were decreased ($p \leq 0.05$) in the low- (kidneys - ↓7%; liver - ↓9%) and mid-dose P males (kidneys - ↓7%; liver - ↓10%), but not in the high-dose males (Table 4). The relative organ weights were not affected. Liver weights were decreased ($p \leq 0.05$) in the mid-

dose F_1 males (absolute 113% and relative 19%). Because there was no dose-dependent response, these differences were not considered of toxicological concern. There were no significant differences in the absolute and relative organ weights of the P and F_1 females.

Table 4. Absolute and relative organ weights in P and F_1 males at necropsy.[a]

Organ	Dose Group (mg/kg/day)			
	0	50	100	200
P Generation Males				
Absolute Organ Weights				
Kidneys	3.681	3.409*	3.434*	3.448
Liver	18.156	16.455*	16.428*	17.450
Testes	3.778	3.690	3.719	3.648
Relative Organ Weights				
Kidneys	0.923	0.885	0.891	0.914
Liver	4.530	4.271	4.242	4.617
Testes	0.953	0.960	0.967	0.970
F_1 Generation Males				
Absolute Organ Weights				
Kidneys	3.458	3.358	3.281	3.237
Liver	19.151	17.474	16.609*	17.684
Testes	3.828	3.652	3.718	3.595
Relative Organ Weights				
Kidneys	0.877	0.892	0.877	0.875
Liver	4.856	4.625	4.430*	4.759
Testes	0.973	0.974	0.999	0.985

a Data extracted from the study report P generation and F_1 generation Tables OW1K-SUM, pages 444 and 785.

* Significantly different from controls at $p \leq 0.05$.

b) Pathology: There were no significant necropsy findings in the P or F_1 adults. Dermal effects noted have been discussed (see Mortality and clinical signs) and were considered a result of the treatment methodology and not a direct effect of the the test compound itself.

B. OFFSPRING

1. Viability and clinical signs: There were no treatment-related clinical signs or treatment-related changes in mean litter size or viability indices in the F_1 or F_2 generation pups. Mean litter size and viability results from F_1 and F_2 litters during lactation are summarized in Tables 5a and b, respectively.

Table 5a. F_1 generation mean litter size and viability.[a]

Observation	Dose Group (mg/kg/day)			
	0	50	100	200
Mean litter size				
Day 0	12	11	12	11
Day 4[b]	12	11	11	11
Day 4[c]	8	8	8	8
Day 21	8	8	8	8
Number live pups[d]				
Day 0	349	318	305	325
Day 4[b]	345	312	296	316
Day 4[c]	227	221	206	231
Day 7	225	220	206	229
Day 14	225	220	206	229
Day 21	225	218	206	228
Number deaths[d]				
Days 0-4	4	6	9	9
Days 5-21	2	3	0	3
% Males (day 0)	50.2	44.8	47.1	45.4
Survival indices (%)				
Birth	94.0	90.8	92.2	89.3
Livebirth	97.5	98.1	98.4	98.1
Viability	98.8	98.3	96.8	97.5
Lactation	99.0	98.7	100	98.9

a Data extracted from the study report Tables 14 and Appendix IV, pages 71, 72 and 154 through 161.
b Before standardization (culling).
c After standardization (culling).
d Calculated by the reviewers.

Table 5b. F_2 generation mean litter size and viability.[a]

Observation	Dose Group (mg/kg/day)			
	0	50	100	200
Mean litter size				
Day 0	11	11	11	10
Day 4[b]	10	10	11	9
Day 4[c]	8	8	8	7
Day 21	8	8	8	7
Number live pups[d]				
Day 0	301	296	285	279
Day 4[b]	292	280	273	260
Day 4[c]	220	204	203	204
Day 7	220	204	202	204
Day 14	219	203	202	204
Day 21	219	203	202	203
Number deaths[d]				
Days 0-4	9	16	12	19
Days 5-21	1	1	1	1
% Males (day 0)	52.1	56.0	54.9	51.9
Survival indices (%)				
Birth	90.6	91.8	92.8	87.5
Livebirth	99.1	96.6	95.9	94.4
Viability	97.1	93.1	96.0	91.7
Lactation	99.6	99.5	99.5	99.5

a Data extracted from the study report Table 28 and Appendix XIX, pages 110, 111 and 293 through 300.
b Before standardization (culling).
c After standardization (culling).
d Calculated by the reviewers.

2. Body weight: There were no significant differences in pup weight or pup body weight gain for the F_1 or F_2 litters (Table 6).

Table 6. Mean pup weights for the F_1 and F_2 litters (g).[a]

Day of lactation	Dose Group (mg/kg/day)			
	0	50	100	200
F_1 generation				
Day 0	6.7	6.7	6.7	6.8
Day 4[b]	10.3	10.2	10.0	10.5
Day 4[c]	10.3	10.3	10.0	10.5
Day 7	16.1	15.7	15.6	15.9
Day 14	29.9	29.7	29.3	29.1
Day 21	48.0	48.3	46.8	47.5
F_2 generation				
Day 0	6.8	6.7	6.5	6.8
Day 4[b]	10.6	10.1	10.0	10.3
Day 4[c]	10.6	10.1	10.0	10.2
Day 7	16.0	15.4	15.2	15.4
Day 14	29.5	29.0	28.7	28.7
Day 21	46.5	46.9	44.4	45.7

a Data extracted from the study report Tables 12 and 26, pages 63 through 65 and 102 through 104.
b Before standardization (culling).
c After standardization (culling).

3. Offspring postmortem results:

a) Organ weights: Organs were not weighed for any of the pups in this study.

b) Pathology

1) Macroscopic examination: There were no treatment-related findings at necropsy in the F_1 or F_2 pups.

2) Microscopic examination: Histopathology was not performed on any offspring in this study.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS: Dermal administration of KBR 3023 at 50, 100, or 200 mg/kg/day did not cause any treatment-related clinical signs or effects on body weight or food consumption in adults or offspring throughout the study. There were no treatment-

related effects on any reproductive or litter parameters. Dermal findings (acanthosis and hyperkeratosis) were observed in both generations, but were considered to be due to the dermal application methodology, although the relationship between these findings and KBR 3023 cannot be excluded. No treatment-related necropsy findings were observed in the adults or pups, other than the aforementioned dermal findings. No treatment-related histopathologic findings were observed in the reproductive organs of either males or females.
The NOEL for reproductive toxicity was 200 mg/kg/day.

B. REVIEWER'S DISCUSSION: In this two-generation reproduction study, KBR 3023 was administered dermally to Sprague-Dawley rats at dose levels of 0, 50, 100, or 200 mg/kg/day (5 days/week). P male and female animal exposure to KBR 3023 (30/sex/dose) began at 8-9 weeks of age and lasted for 10 weeks prior to mating to produce the F_1 litters. At 21 days of age, F_1 pups (30/sex/dose) were selected to become the F_1 parents of the F_2 generation. F_1 parents were given the same levels of KBR 3023 as their dam for 10 weeks prior to mating.

The analytical data indicated that the actual concentration of KBR 3023 was within required limits. Because the compound was administered neat, no homogeneity data were required and previous studies demonstrating stability were acceptable.

1. Systemic Toxicity: No treatment-related parental systemic toxicity was observed. No treatment-related clinical findings, increases in mortality, differences in body weight gains or food consumption, or changes in reproductive performance were noted in the P females or males at any dose level. Dermal findings at the treatment site (acanthosis and hyperkeratosis) were considered to be due to the treatment methodology and were not considered compound-related.

The NOAEL for systemic toxicity was not established. The systemic NOEL is $\geq$200 mg/kg/day.

2. Reproductive Toxicity. There were no treatment-related clinical signs of toxicity or changes in pup weight, viability, or litter sizes noted in the pups at any dose level for the F_1 or F_2 generations. No treatment-related macroscopic findings were observed in the F_1 or F_2 pups at any dose level.

The NOAEL for reproductive toxicity was not established. The reproductive NOEL is $\geq$200 mg/kg/day.

No toxicity was seen in a pilot reproductive toxicity study in which Sprague-Dawley rats were dosed at 200 mg/kg/day (MRID 44408726). Nevertheless, dosing was considered adequate based on the results of a 90-day dermal toxicity study (MRID 44408716) in which KBR 3023 (99.2% a.i.) was applied to the shaved skin of young adult Sprague-Dawley rats (10-20/sex/dose) at dose levels of 0, 80, 200, 500, or 1000 mg/kg/day for 5 days/week, 5

hours/day, for 90 days. KBR 3023 elicited diffuse liver hypertrophy in both sexes treated at 1000, 500, or 200 mg/kg/day. The LOAEL for systemic toxicity was determined to be 500 mg/kg/day, based on liver and kidney effects, including diffuse liver hypertrophy, individual necrotic liver cells, slight hyaline degeneration in the kidneys, an increased incidence of foci of tubular regeneration, and chronic kidney inflammation; the NOAEL is 200 mg/kg/day. The LOAEL for dermal toxicity is 80 mg/kg/day based on the presence of scabs, red foci, and exfoliation at the dose site; a dermal NOAEL was not established.

This reproductive toxicity study is classified **acceptable (§83-4[a]) and does satisfy the guideline requirement for a multi-generational reproductive toxicity (reproduction) study in rats.**

C. STUDY DEFICIENCIES: There were no deficiencies noted in this study.