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DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity with Range Finding in Rabbits
OPPTS Number: 870.3700 OPP Guideline Number: §83-3

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

TEST MATERIAL (PURITY): KBR 3023 technical (97.8% a.i.)

SYNONYMS: 2-(2-Hydroxyethyl)-1-piperidine-carboxylic acid 1-methylpropyl ester

CITATION(s): Holzum, B. (1996) Developmental Toxicity Study in Rabbits After Dermal Application. Bayer AG, Department of Toxicology, Wuppertal, Germany. Laboratory Study Number T0059079, March 15, 1996. MRID 44408721. Unpublished

Holzum, B. (1995) Range Finding Developmental Toxicity Study in Rabbits After Dermal Application. Bayer AG, Department of Toxicology, Wuppertal, Germany. Laboratory Study Number T6059075. MRID 44408720. Unpublished

SPONSOR: Bayer AG, Friedrich-Ebert-Strasse 217-333, D-42096 Wuppertal, Germany

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44408721) KBR 3023 (97.8% a.i.) was dermally applied to 24 female CHBB:HM rabbits per dose level at 0, 50, 100, or 200 mg/kg body weight/day from days 0-28 of gestation.

Local dermal reactions at the dose site appeared in all treated animals. All treated females showed squamous skin beginning on gestation day 4-12, which continued until necropsy. A dose-related increase in slight erythema at the dose site was observed in all treated animals (low-dose, 11/24; mid-dose, 20/24; high-dose, 23/24 vs 1/24 controls). Very slight to slight edema was observed in the high-dose group (13/24 vs 0/24 controls). In addition, dermal toxicity was characterized by cracked skin at the dose site acting in a dose-dependent manner (low-dose, 2/24; mid-dose, 4/24; high-dose, 18/24 vs 0/24 controls).

There were no treatment-related effects noted in mortality, clinical signs, gross pathologic findings, or cesarean section parameters at any dose level. There were no treatment-related

effects on body weights or food consumption at dose levels of ≤200 mg/kg/day.

The maternal LOAEL for dermal irritation is 50 mg/kg/day.
The maternal NOAEL for dermal irritation is <50 mg/kg/day.

The maternal LOAEL for systemic toxicity was not established.
The maternal NOAEL for systemic toxicity is >200 mg/kg body weight/day.

There were no treatment-related effects on developmental parameters (pre- and post-implantation losses, number of fetuses per litter), fetal deaths, resorptions, altered growth, or malformations.

The developmental LOAEL was not established.
The developmental NOAEL is >≥200 mg/kg/day.

Dosing was considered adequate based on the results of the submitted range finding study (MRID 44408720) in which 3 pregnant female rabbits/dose were dosed at 0, 50, 200, 400, 700, or 1000 mg/kg body weight/day on gestation days 0-28. Maternal toxicity was observed at 1000 mg/kg body weight/day and was characterized by clinical signs of toxicity, gross pathology, severely decreased body weight gains, and decreased food consumption. The applied dose did not spread beyond the shaved area at the 50 mg/kg dose level. The area of humid and yellow stains increased in a dose-dependent manner for the 200 and 400 mg/kg groups. Severe lesions formed at the dose site for the higher dose groups of 700 and 1000 mg/kg. All treated animals showed erythema and squamous cells at the dose site. Edema and cracked skin were observed in animals dosed at ≥400 mg/kg.

This developmental toxicity study is classified **acceptable (§83-3[b]) and does satisfy the guideline requirements for a developmental toxicity study in the rabbit.**

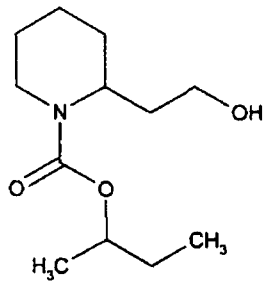
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: KBR 3023
   Description: Technical, clear, light yellow liquid
   Lot/Batch #: 030693
   Purity: 97.8% a.i.
   CAS #: 119515-38-7

   Structure:



2. Vehicle: None

3. Test animals: Species: rabbit
   Strain: CHBB:HM
   Age at mating: Not reported
   Weight at mating: 1892-2893 g
   Source: Dr. Karl Thomae GmbH, Biberach
   Housing: Individually in Macrolon cages with perforated cage sheets
   Diet: Ssniff® rabbit diet K-Z standard diet, Manufacturer (Ssniff Spezialdiäten GmbH,Soest), ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 22±2°C
   Humidity: 50-60%
   Air changes: At least 10/hr
   Photoperiod: 12 hrs dark/12 hrs light
   Acclimation period (P): At least 7 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - start: 8/21/95 end: 11/22/95.

2. Mating: Females were placed under observation (1 female:1 male) with stock males of the same strain. The day copulation was observed was designated day 0 of gestation.

3. Dose selection rationale: In a range finding study (MRID 4408720) included in the current submission, KBR 3023 (97.70% a.i.) was administered dermally (without occlusion) to 3 pregnant female rabbits/dose at dosages of 0, 50, 200, 400, 700, or 1000 mg/kg body weight/day on gestation days 0-28. Individual doses were based on the current body weights as determined daily before application.

Mortality, clinical observations, body weight, and food consumption were recorded. Dams were sacrificed on day 29 of gestation and gross necropsies were performed. The reproductive tract was removed and the number of corpora lutea in each ovary,. implantation sites (live and dead), individual weights and appearance of placentas, and gravid uterine weights were recorded. Fetuses were weighed and examined externally.

Maternal toxicity was observed at 1000 mg/kg body weight/day and was characterized by clinical signs of toxicity, gross pathology, severely decreased body weight gains, and decreased food consumption. Two 1000 mg/kg/day females showed severe weight loss and were killed for humane reasons on day 9 or 14 of gestation; these deaths left only one female in the high dose group. Clinical signs of toxicity noted in the high-dose group included lacrimation and reddish discoloration of the eyelid. Upon necropsy, one of the two sacrificed females of the high dose group displayed gastrointestinal changes consisting of whitish, granular stratifications in the gallbladder wall and hardened gastric contents.

The applied dose did not spread beyond the shaved area at the 50 mg/kg dose level. The area of humid and yellow stains increased in a dose-dependent manner for the 200 and 400 mg/kg groups, and spreading was evident after day 2 of gestation for the 200 mg/kg level and after day 1 of gestation for the 400 mg/kg level. Severe lesions formed at the dose site for the higher dose groups of 700 and 1000 mg/kg, and therefore, failed to indicate dose-dependent spreading since the compound was absorbed into the lesions. Movement beyond the dose site was apparent on day 0 of gestation for these higher dose levels. All treated animals showed erythema and squamous cells at the dose site. Edema and cracked skin were observed in animals dosed at $\geq$400 mg/kg.

The test compound had no affect on fertility rates at dose levels $\leq$700 mg/kg. The two high-dose females that were killed due to severe weight loss did not have implantations at necropsy, however, the one surviving female did have implantation sites. The numbers of corpora lutea and pre-implantation losses were unaffected by treatment at $\leq$1000 mg/kg/day. Post-implantation losses increased in the single high-dose female; this increase was due to an increased number of resorptions (2). The number of fetuses, fetal weight, external fetal findings, placental weights, and external placental findings were unaffected by treatment.

Based on the results of this range finding study, the doses summarized in Table 1 were selected for the full developmental toxicity study in rabbits.

Table 1. Animal assignment.[a]

Test Group	Dose level (mg/kg body weight/day)	Application volume (mL/kg body weight/day)	Number of Dams
Control[b]	0	0.20	24
Low	50	0.05	24
Mid	100	0.10	24
High	200	0.20	24

a Data extracted from study report, page 18.
b Control animals received only tap water.

4. Dosage preparation and analysis: Since analyses were performed on the same lot number, the following information was obtained from the KBR 3023 chronic oncogenicity study (MRID 44408728): undiluted technical grade KBR 3023 was stored frozen (-23°C) and approximately every two weeks, dosing aliquots were provided. From the information provided, it was inferred that the dosing aliquots were stored at room temperature. Prior to commencement of the study and approximately every 6 months, the stability of the test chemical stored at -23°C was assessed. In addition, stability analyses were performed on samples of KBR 3023 stored at room temperature (22°C) for 7, 14, 21, or 28 days.

   Results:
   Concentration/Stability Analysis: The chemical purity of KBR 3023 stored frozen was 96.7-98.5% throughout the study. It was stated that the compound is stable for 28 days when stored at room temperature.

   The information provided indicated that the test compound was stable for the duration of the study.

5. Dosage administration: An area representing approximately 10% of the body surface area of each female was shaved at the beginning of the study and as needed thereafter. All doses were applied once daily, dermally without occlusion on gestation days 0-28. The compound was applied undiluted and dispersed uniformly using a spatula. Dosing was based on daily body weights. Dose sites of the control animals were treated with tap water. To prevent oral ingestion of the test substance, the animals were fitted with collars from day 0 (after mating) until necropsy. The animals had also worn these collars for at least 7 days prior to mating for acclimatization.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked for mortality and clinical signs twice daily. Body weights were recorded daily and food consumption was

recorded on gestation days 6, 11, 16, 21, 24, and 29. Dams were sacrificed on day 29 of gestation. At sacrifice, evaluations consisted of a gross examination of the brain, skeletal system, abdominal, pelvic, and thoracic organs. The reproductive tract was removed, examined, and the following were recorded:

- gravid uterine weight
- number of corpora lutea and implantations in each ovary
- number of fetuses (live and dead)
- weight and sex of all live fetuses
- individual weights and appearance of placentas

2. Fetal Evaluations - Each fetus was weighed, sexed, and examined for external, visceral, and skeletal abnormalities. Visceral exams were performed on the fetuses according to the STAPLES technique. For skeletal examinations, the cartilage was stained using alcian blue, fetuses were cleared with diluted potassium hydroxide, and were stained with alizarin red S.

D. DATA ANALYSIS

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

2. Indices: The following indices were presented in the study report:

   Fertility rate = # females with implantations/ # females mated x 100%
   Gestation rate = # females with viable fetuses/ # females with implantations x 100%

3. Historical control data: Historical control data were provided to allow comparison with concurrent controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: There were no mortalities and no treatment-related effects noted in behavior or appearance. Following treatment, the number of females with soft feces increased (low-dose, 10/24; mid-dose, 9/24; high-dose, 18/24 vs 3/24 controls). These increases were not dose-dependent and therefore, not of toxicological significance and were considered to be related to the stress caused by local reactions at the dose site.

2. Body Weight: Absolute and corrected body weight gains in the dams were unaffected by treatment at levels ≤200 mg/kg body weight/day.

3. Food Consumption - Food consumption was unaffected by treatment up to and including 200 mg/kg body weight/day.

4. Gross Pathology - There were no treatment-related gross pathologic findings upon necropsy.

5. Dose Site Reactions - Local dermal reactions at the dose site were evident at all dose levels and acted in a dose-dependent manner. All treated females showed squamous skin beginning on gestation day 4-12 and continuing until necropsy. Slight erythema of the dose site, which appeared during the initial days of treatment and continued until necropsy, increased in a dose-dependent manner in all treated animals (low-dose, 11/24; mid-dose, 20/24; high-dose, 23/24 vs 1/24 controls). Very slight edema was observed in the high-dose group (10/24 vs 0/24 controls); slight edema also appeared at the dose site in the high-dose animals (3/24 vs 0/24 controls). Additionally, dermal toxicity was characterized by cracked skin at the dose site, increasing in a dose-related manner (low-dose, 2/24; mid-dose, 4/24; high-dose, 18/24 vs 0/24 controls). Table 3 summarizes findings at the dose site.

Table 3. Local reactions at the dose site.[a]

	Dose(mg/kg/day)			
Observation	0	50	100	200
Number Evaluated	24	24	24	24
Squamous skin	0	24	24	24
Erythema				
- very slight	10	13	4	0
- slight	1	11	20	23
- moderate	0	0	0	1
Edema				
- very slight	0	0	0	10
- slight	0	0	0	3
Cracked skin	0	2	4	18

a Data extracted from study report page 28.

6. Cesarean Section Data - Cesarean section observations are presented in Table 4. The fertility rates, numbers of corpora lutea, implantations, pre-implantation losses, and gestation rates were similar between control and treated groups. Two control females and one 200 mg/kg/day female aborted; one 200 mg/kg/day female resorbed all implantations. Although increases in individual fetal and placental weights were statistically significant in the 50 and 200 mg/kg/day groups, statistical significance was not achieved when calculated on a litter basis. In addition, all weights were within the range of historical

controls and changes in weight were not dose-dependent.

Table 4. Cesarean section observations [a]

Observation	Dose (mg/kg body weight/day)			
	0	50	100	200
# Animals Assigned (Mated)	24	24	24	24
# Animals Pregnant	24	22	22	24
Pregnancy Rate (%)	(100)	(92)	(92)	(100)
# Nonpregnant	0	2	2	0
# Total Dams Died	0	0	0	0
# Died Pregnant	0	0	0	0
# Died Nonpregnant	0	0	0	0
# Aborted [b]	2	0	0	1
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	189	177	192	176
Corpora Lutea/Dam	8.6±2.1	8.0±1.1	8.7±1.6	7.7±1.9
Total # Implantations	174	161	178	165
Implantations/Dam	7.9±2.2	7.3±1.2	8.1±1.6	7.2±2.0
Total # Litters	22	22	22	23
Total # Live Fetuses	155	146	167	140
Live Fetuses/Dam	7.0±2.5	6.6±1.4	7.6±1.8	6.1±2.3
Total # Dead Fetuses	0	0	0	0
Dead Fetuses/Dam	0	0	0	0
Total # Resorptions	19	15	11	25
Early	0	0	0	2
Late	19	15	11	23
Resorptions/Dam	0.9±1.2	0.7±0.8	0.5±0.8	1.1±0.9
Early	0	0	0	0.1±0.4
Late	0.9±1.2	0.7±0.8	0.5±0.8	1.0±1.0
Litters with Total Resorptions	0	0	0	1
Mean Weight (g)				
Individual basis	35.32±5.98	37.12±5.40**	36.55±4.83	38.41±4.79**
Litter basis	36.45±4.89	37.22±4.46	37.10±3.32	38.75±3.16
Males (litter basis)	36.79±5.31	37.78±5.13	37.50±3.16	38.39±3.03
Females (litter basis)	35.72±5.18	36.63±4.88	36.67±3.98	39.36±3.78
Mean Placental Weight (g)				
Individual basis	3.78±0.69	4.06±0.69**	3.88±0.67	4.01±0.77*
Litter basis	3.89±0.52	4.09±0.46	3.94±0.46	4.08±0.56
Sex Ratio (% Male)	51	48	45	51
Pre-implantation Loss (%) [c]	8	9	7	6
Post-implantation Loss (%) [c]	11	9	6	15

a Data extracted from the study report, pages 136-230.
* $p < 0.05$, ** $p < 0.01$

b Aborted litters excluded from mean.
c Pre- and post-implantation loss percentages calculated by reviewers.
Pre-implantation loss index:
100- the % corpora lutea that are represented as implantation sites.
Post-implantation loss index:
100- the % implantations that are viable at the time of intrauterine inspection.

B. DEVELOPMENTAL TOXICITY: Fetal examinations included external, visceral, and skeletal observations at necropsy. Statistically significant increases in external, visceral, and skeletal malformation rates on a fetal basis were found in the low- and mid-dose groups (low-dose, 6 malformed fetuses; mid-dose, 9 malformed fetuses vs 0 malformed controls, $p<0.05$).

1. External Examination - Increased incidence of gross external malformations in the dose groups was not considered treatment-related since the findings were not dose-dependent. During external examination, two malformed fetuses were found in the high-dose group, both with arthrogryposis, but this incidence was not statistically significant. Six mid-dose and four low-dose fetuses were found to have arthrogryposis. Arthrogryposis was found in the historical control data at incidence levels similar to or higher than levels found in this study, therefore, increased levels in this study were considered unrelated to treatment. Data are shown in Table 5a.

Table 5a. External examinations [a]

Observations	Dose (mg/kg body weight/day)				
	0	50	100	200	Historical controls[b]
#Fetuses (#litters) examined	155 (22)	146 (22)	167 (22)	140 (22)	4040 (656)
Arthrogryposis [c]					
fetal incidence (litter incidence)	0 (0)	4 (4)	6 (3)	2 (2)	
%fetal incidence (% litter incidence)	0 (0)	3 (18)	4 (14)	1 (9)	0.00-5.56
% affected fetuses/litter	0	18	27	9	(0.00-23.08)

a Data extracted from the study report, Table 7, page 35.
b Calculated by reviewers using data on pages 375-382.
c % Affected fetuses/litter were calculated by reviewers.
* Statistically significant from control at $p<0.05$.

2. Visceral Examination - There were no treatment-related visceral variations or malformations observed at levels ≤200 mg/kg body weight/day. Upon visceral examination, two malformed fetuses in the mid-dose group were found to have a cardiac septal defect. Findings are presented in Table 5b.

Table 5b. Visceral examinations [a]

Observations	Dose (mg/kg body weight/day)			
	0	50	100	200
#Fetuses(#litters) examined	155 (22)	146 (22)	167 (22)	140 (22)
Cardiac septal defect [b]				
fetal incidence (litter incidence)	0 (0)	0 (0)	2 (2)	0 (0)
% fetal incidence (% litter incidence)	0 (0)	0 (0)	1 (9)	0 (0)
% affected fetuses/litter	0	0	9	0
#Deviations(#litters)	0 (22)	1 (22)	1 (22)	0 (22)

a Data extracted from the study report, Table 7, page 35 and page 85.
b % Affected fetuses/litter were calculated by reviewers.
* Statistically significant from control at $p<0.05$.

3. Skeletal Examination - The most common skeletal findings are presented in Table 5c. There were no treatment-related skeletal retardations or variations observed at any dose level when skeletal retardations and variations were calculated on a litter basis. At skeletal examination, one low-dose fetus was found with an anomaly of vertebrae and ribs; another low-dose fetus was found with fusion of the ribs. A mid-dose fetus was found to have fusion of caudal vertebral bodies. Skeletal variations were noted in the treatment groups, when compared to the controls, that indicate a decrease in incomplete ossification of the medial phalanx digit(s), medial phalanx toe(s), frontal bone, and parietal bone; however, this progressive effect on fetal ossification is not an adverse effect. The report stated that "the statistical significances when calculation was done on an individual basis reflect more progressed ossification when compared to the control group in all cases. This higher stage of ossification correlated with the incidentally higher fetal weights in all dose groups which also achieved statistical significance in the 50 mg and 200 mg/kg groups when calculated on an individual basis". The findings of skeletal variations were not statistically significant on a litter basis, were not dose-dependent, and were inside the historical control ranges; therefore, they do not indicate an adverse effect on fetal development.

Table 5c. Skeletal examinations [a]

Observations	Dose (mg/kg body weight/day)			
	0	50	100	200
#Fetuses (#litters) examined	155 (22)	146 (22)	167 (22)	140 (22)
Sternebra(e)				
Incomplete oss.-5th				
fetal incidence (litter incidence)	121 (22)	109 (22)	129 (21)	108 (22)
% fetal incidence (% litter incidence)	78.1 (100.0)	74.7 (100.0)	77.2 (95.5)	77.1 (100.0)
Medial phalanx digit(s)				
Incomple oss.- 5th right				
fetal incidence (litter incidence)	33 (11)	13* (6)	20 (8)	5** (4)
% fetal incidence (% litter incidence)	21.3 (50.0)	8.9 (27.3)	12.0 (36.4)	3.6 (18.2)
Incomplete oss.- 5th left				
fetal incidence (litter incidence)	36 (12)	16* (7)	19* (7)	5** (4)
% fetal incidence (% litter incidence)	23.2 (54.5)	11.0 (31.8)	11.4 (31.8)	3.6 (18.2)
Medial phalanx toe(s)				
Incomplete oss.- 5th right				
fetal incidence (litter incidence)	29 (10)	5** (3)	18 (7)	5** (4)
% fetal incidence (% litter incidence)	18.7 (45.5)	3.4 (13.6)	10.8 (31.8)	3.6 (18.2)
Incomplete oss.- 5th left				
fetal incidence (litter incidence)	29 (11)	7** (4)	20 (8)	5** (4)
% fetal incidence (% litter incidence)	18.7 (50.0)	4.8 (18.2)	12.0 (36.4)	3.6 (18.2)
Frontal bone				
Incomplete oss.- bilateral				
fetal incidence (litter incidence)	32 (13)	17 (7)	15* (7)	5** (5)
% fetal incidence (% litter incidence)	20.6 (59.1)	11.6 (31.8)	9.0 (31.8)	3.6 (22.7)
Parietal bone				
Incomplete oss.- bilateral				
fetal incidence (litter incidence)	30 (10)	13* (9)	13** (6)	5** (5)
% fetal incidence (% litter incidence)	19.4 (45.5)	8.9 (40.9)	7.8 (27.3)	3.6 (22.7)
Anomaly of vertebrae and ribs [b]				
fetal incidence (litter incidence)	0 (0)	1 (1)	0 (0)	0 (0)
% fetal incidence (% litter incidence)	0 (0)	0.68 (5)	0 (0)	0 (0)
% affected fetuses/litter	**0**	**5**	**0**	**0**
Fusion of ribs (cartilaginous part) [b]				
fetal incidence (litter incidence)	0 (0)	1 (1)	0 (0)	0 (0)
% fetal incidence (% litter incidence)	0 (0)	0.68 (5)	0 (0)	0 (0)
% affected fetuses/litter	**0**	**5**	**0**	**0**

Table 5c. Skeletal examinations [a]

Observations	Dose (mg/kg body weight/day)			
	0	50	100	200
#Fetuses (#litters) examined	155 (22)	146 (22)	167 (22)	140 (22)
Fusion of caudal vertebral bodies [b]				
fetal incidence (litter incidence)	0 (0)	0 (0)	1 (1)	0 (0)
% fetal incidence (% litter incidence)	0 (0)	0 (0)	0.60 (5)	0 (0)
% affected fetuses/litter	**0**	**0**	**5**	**0**

a Data extracted from the study report, Table 7, page 35, and pages 62-83.
b **% Affected fetuses/litter** were calculated by reviewers.
* $p<0.05$, ** $p<0.01$ Fisher's Exact

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS: The study report concluded that dermal application of KBR 3023 (97.8% a.i.) at 0, 50, 100, or 200 mg/kg body weight/day to pregnant rabbits from gestation day 0-28 was associated with local reactions at the dose site at all dose levels. Slight erythema was evident at 200 mg/kg/day, squamous and cracked skin were apparent at the low-dose, and edema occurred at the high-dose level. Maternal behavior, mortality, food intakes, and body weight gains were unaffected by treatment. An increased incidence of females with soft feces at the high-dose level was attributed to stress caused by local reactions at the dose site. The maternal NOAEL is 100 mg/kg body weight/day. The maternal LOAEL is 200 mg/kg body weight/day.

Regarding intrauterine development, fertility rate, gestation rate, number of corpora lutea, pre-implantation loss, number of implantation sites, post-implantation loss, number of fetuses, fetal sex, fetal weight, and appearance and weight of placentas, all were unaffected by treatment at levels ≤200 mg/kg body weight/day. External, visceral, and skeletal examinations of the fetuses showed no effects of the test substance on fetal morphology at levels ≤200 mg/kg body weight/day. Teratogenic potential of KBR 3023 was not evident. The developmental NOAEL is 200 mg/kg body weight/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: Following dermal application of KBR 3023 (97.8% a.i.) at 0, 50, 100, or 200 mg/kg body weight/day to pregnant rabbits on days 0-28 of gestation, maternal toxicity was demonstrated by local reactions at the dose site. All treated females showed squamous skin beginning on gestation day 4-12 and continuing until necropsy. Slight erythema of the dose site, which appeared during the initial days of treatment and

treatment, the number of females with soft feces increased (low-dose, 10/24; mid-dose, 9/24; high-dose, 18/24 vs 3/24 controls). These increases were not dose-dependent and therefore, not of toxicological significance and were considered to be related to the stress caused by local reactions at the dose site.

There were no treatment-related effects noted in mortality, clinical signs, gross pathologic findings, or cesarean section parameters at any dose level. There were no treatment-related effects on body weights or food consumption at dose levels of ≤200 mg/kg/day.

The maternal LOAEL for dermal irritation is 50 mg/kg/day.
The maternal NOAEL for dermal irritation is <50 mg/kg/day.

The maternal LOAEL for systemic toxicity was not established.
The maternal NOAEL for systemic toxicity is ≥200 mg/kg body weight/day.

2. DEVELOPMENTAL TOXICITY: There were no treatment-related effects on developmental parameters (pre- and post-implantation losses, number of fetuses per litter), fetal deaths, resorptions, altered growth, or malformations. Skeletal retardations and variations noted in the treatment groups, when compared to the controls, indicate a decrease in incomplete ossification of the medial phalanx digit(s), medial phalanx toe(s), frontal bone, and parietal bone; however, this progressive effect on fetal ossification is not an adverse effect.

In the KBR 3023 rat developmental study (MRID 44408725), an increased incidence ($p \leq 0.05$) of incomplete ossification of the supraoccipital bone in the 400 mg/kg/day high-dose group was observed. This variation was considered to be treatment-related because (i) the fetal (43.6 % treated vs 30.3% controls) and litter (89% treated vs 75% controls) incidences were above the concurrent controls as well as the historical control ranges (fetal, 3.6-30.6, litter, 13.3-74.1) and (ii) supporting data were found in the submitted oral range finding study (MRID 44408722) in which an increased incidence of delayed bone ossification (70.8% treated fetuses vs 47.3% of controls, $p<0.01$) was observed in the 500 mg/kg/day group; litter incidences were not reported. While the increased incidence of incomplete ossification in rats is indeed an adverse effect, the decrease in incomplete ossification noted in rabbits is not an adverse effect.

No observations of developmental toxicity were noted in rabbits treated with KBR 3023:

a. Deaths/Resorptions: The numbers of resorptions/dam and viable fetuses/dam for the treatment groups were not significantly different from the concurrent controls.
b. Altered Growth: There were no treatment-related changes in fetal body weights at any dose level.
c. Developmental Variations: No significant, dose-related skeletal variations were noted which were outside the historical control range.
d. Malformations: There were no treatment-related developmental malformations noted at any dose level.

any dose level.

c. Developmental Variations: No significant, dose-related skeletal variations were noted which were outside the historical control range.
d. Malformations: There were no treatment-related developmental malformations noted at any dose level.

The developmental LOAEL was not established.
The developmental NOAEL is ≥200 mg/kg/day.

Dosing was considered adequate based on the results of the submitted range finding study (MRID 44408720) in which 3 pregnant female rabbits/dose were dosed at 0, 50, 200, 400, 700, or 1000 mg/kg body weight/day on gestation days 0-28. Maternal toxicity was observed at 1000 mg/kg body weight/day and was characterized by clinical signs of toxicity, gross pathology, severely decreased body weight gains, and decreased food consumption. The applied dose did not spread beyond the shaved area at the 50 mg/kg dose level. The area of humid and yellow stains increased in a dose-dependent manner for the 200 and 400 mg/kg groups. Severe lesions formed at the dose site for the higher dose groups of 700 and 1000 mg/kg. All treated animals showed erythema and squamous cells at the dose site. Edema and cracked skin were observed in animals dosed at ≥400 mg/kg.

This developmental toxicity study is classified **acceptable (§83-3[b]) and does satisfy the guideline requirements for a developmental toxicity study in the rabbit.**

C. STUDY DEFICIENCIES: None.