EPA Reviewer: John E. Whalan
Registration Action Branch 2 (7509C)

John E Whalan 5-19-99

EPA Work Assignment Manager: Sanjivani Diwan, Ph.D.
Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - rat
OPPTS Number: 870.3700 OPP Guideline Number: §83-3a

DP BARCODEs:D241232, D241258, & D241261 SUBMISSION CODEs: S534142, S534200, & S534203

P.C. CODE: 070705 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): KBR 3023, Technical (97.4-97.7% a.i.)

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

CITATION: Astroff, A. B., (1996) A Developmental Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat. Bayer Corporation, Stilwell, Kansas. Laboratory Study Number 95-622-DI, September 11, 1996. MRID 44408725. Unpublished

Holzum, B., (1990) Range-Finding Study for Embryotoxic Effects on Rats After Oral Administration. Bayer AG, Wuppertal, Germany. Laboratory Study Number T5033216/19645, August 28, 1990. MRID 44408722. Unpublished

Astroff, A. B., (1995) A Dose Range-Finding Developmental Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat. Miles Inc., Stilwell, Kansas. Laboratory Study Number 94-612-ZK, March 10, 1995. MRID 44408723. Unpublished

Astroff, A. B., (1996) A Dose Range-Finding Developmental Toxicity Study with KBR 3023 Technical in the Sprague-Dawley Rat. Bayer Corporation, Stilwell, Kansas. Laboratory Study Number 95-622-DM, June 7, 1996. MRID 44408724. Unpublished

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

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44408725), undiluted KBR 3023 (97.4-97.7% a.i.) was dermally administered to 30 Sprague-Dawley female rats/dose at dose levels of 0, 50, 200, or 400 mg/kg/day from days 0 through 20 of gestation.

Dermal effects were observed at the dose site of all treated groups. These findings were considered to be due to the Elizabethan collars (nasal stain) or topical application of the drug (scab formation or scaling and/or sloughing of skin). Slight maternal toxicity was noted as increases in absolute (↑9%, $p \leq 0.01$) and relative (↑5%, $p \leq 0.05$) liver weights in the high-dose group at final necropsy compared to controls. Histopathological data were not submitted. The liver was not a target organ in a previously submitted dermal oncogenicity study (MRID 44408719). Therefore, in the absence of corroborating histopathological data, the differences in liver weights are considered to be an adaptive response. The numbers of corpora lutea, implantation, viable fetuses, and the extent of pre-implantation losses were unaffected by treatment.

The maternal LOAEL is >400 mg/kg/day. The maternal NOAEL is 400 mg/kg/day.

There were no treatment-related external, visceral, or skeletal malformations or external and visceral variations noted at any dose level. Findings in all groups of incomplete ossification in the supraoccipital bone and increased incidences of rib ossification centers is attributed to maternal stress caused by the dermal dosing regimen.

The developmental LOAEL is >400 mg/kg/day. The developmental NOAEL is 400 mg/kg/day.

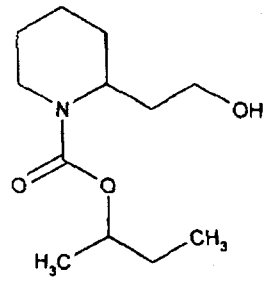
The developmental toxicity study in the rat is classified as **Acceptable/Guideline (870.3700)**.

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: 97.4-97.7% a.i.
   CAS #: 119515-38-7
   Structure:



2. Vehicle: None

3. Test animals: Species: Rat
   Strain: Sprague-Dawley
   Age at mating: 12-15 weeks
   Weight at mating: 207.3-285.5 g (Day 0 gestation)
   Source: Sasco, Inc., Omaha, Nebraska
   Housing: Individually in suspended stainless steel wire-mesh cages
   Diet: Purina Mills Rodent Lab chow 5001-4, ad libitum
   Water: 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): at least 6 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - start: June 26, 1995 end: August 10, 1995.
2. Mating: Rats were mated with a maximum of two females per male. Morning vaginal smears were taken and examined for the presence of sperm. The day on which sperm was identified in the vaginal smear was designated day 0 of gestation.

3. Animal Assignment: Animals were randomly assigned to dose groups as indicated in Table 1. Assignment was performed upon the identification of sperm in the vaginal smear.

Table 1. Animal assignment

Test Group	Dose (mg/kg/day)	Number of Females
1 - Control	0	30
2 - Low (LDT)	50	30
3 - Mid (MDT)	200	30
4 - High (HDT)	400	30

4. Dose selection rationale: Dose selection for this study was based on two previous range-finding studies. In the first range-finding study (MRID 44408723), gravid Sprague Dawley rats were dermally administered KBR 3023 at 0, 50, 100, or 200 mg/kg body weight over gestation days 0 through 19. On gestation day 20, gross necropsies were performed on all dams and fetuses were examined externally. No compound-related maternal, embryo, or fetal effects were observed in any treatment groups. In view of these results, it was decided to perform another range-finding study with higher doses of KBR 3023 before proceeding to the definitive study. In the second range-finding study (MRID 44408724), gravid Sprague Dawley rats were dermally administered KBR 3023 at 0, 250, 500, 750, or 1000 mg/kg body weight/day over gestation days 0 through 20. On gestation day 20, gross necropsies were performed on all dams and fetuses were examined externally. The only compound-related effects were dermal scaling and sloughing of the dams. There were no significant necropsy findings or any effects on the reproductive, embryologic, or fetal parameters evaluated. Excessive spreading of the compound beyond the application area was noted at doses greater than 250 mg/kg/day. These results suggest that the physical limit of applications is less than 250 mg/kg/day. However, given the relatively short duration of a developmental toxicity study, a dose greater than 250 mg kg was used even though the spreading would be substantial.

Based on the results of these studies, 400 mg/kg/day was selected as the high dose for the subsequent dermal developmental toxicity study in rats. Low- and mid-dose levels chosen were 50 and 200 mg/kg/day, respectively.

An additional oral range-finding study (MRID 44408722) was submitted for review, but was not used in dose selection. In this range-finding study, groups of 25 inseminated Wistar rats were given KBR 3023 by stomach tube at doses of 0 and 500 mg/kg body weight/day, daily from day 6 to 16 of gestation. On day 20 of gestation, caesarean sections were carried out. Dams in the 500 mg/kg/day group showed diminished food and water intake and diminished body weight gain. The fetuses in the 500 mg/kg/day group exhibited an increased incidence of delayed bone ossification (70.8% treated

fetuses vs 47.3% of control fetuses, $p<0.01$), primarily in the vertebrae, skul, and hyoid. Litter incidences were not reported. All other reproductive or fetal parameters were comparable between groups or differences were not treatment-related.

5. Dosage preparation and analysis: KBR 3023 was used undiluted and stored at room temperature. The concentration of the test substance was determined by the Sponsor prior to use. Because the test substance was used undiluted, further testing of the concentration was not done. Dose homogeneity and stability analyses were also not performed by the study lab. According to the information provided by the Sponsor (page 14 of study report), the test material is stable for ≥6 months apparently under frozen conditions. In an accompanying study (MRID 44408719) submitted to EPA for review, the sponsor also cited a study (Bayer Corporation unpublished report No. 107418) in which the stability of KBR 3023 was determined after 7, 14, 21, and 28 days of storage at ambient temperature (22 C). The Bayer Corporation study concluded that KBR 3023 is stable for up to 28 days of storage at room temperature. The data from the Bayer study were not presented in MRID 44408719, however, the study was submitted to the Agency and reviewed separately.

6. Dosage administration: An area representing approximately 10% of the total surface area of each female was clipped at the beginning of the study and as needed thereafter. With two exceptions, all females wore Elizabethan collars for the duration of the study, beginning at least seven days prior to the initiation of dosing. The test formulation was administered by applying 0.0, 0.05, 0.20, and 0.40 ml/kg bodyweight of the undiluted solution (approximately 1 g/ml KBR 3023) to the animal's back. All doses were administered once daily on gestation days 0 through 20. Dosing was based on the daily body weight determination.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked twice daily for clinical signs. Body weights were recorded daily. Food consumption was recorded on gestation days 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20. The dose site was evaluated weekly and any spreading of the applied dose beyond the shaved dose site was noted. All dams were sacrificed following observations on day 20 of gestation. Aborting females were also sacrificed and subjected to full macroscopic examination. Examinations at sacrifice consisted of gross evaluations of the thoracic, abdominal, and pelvic cavities. The liver and thyroid were excised and weighed. The reproductive tract was removed and the following data were recorded:
   - pregnancy status
   - number of corpora lutea in each ovary
   - gravid uterine weight
   - numbers of live and dead fetuses
   - number of implantation sites
   - numbers of resorptions (early and late)
   - placental weight

2. Fetal Evaluations - Each fetus was weighed, sexed, and examined for external abnormalities. Approximately half of the live fetuses were given a gross visceral exam, then placed in Bouin's solution. Cranial examinations were performed on these fetuses according to the methods of Wilson. The other half of the fetuses were fixed in 70% denatured alcohol, eviscerated, processed with aqueous KOH and Alizarin Red S, and evaluated for general skeletal development.

D. DATA ANALYSIS

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

2. Indices: The following indices were calculated by the investigator:

Fertility Index= # pregnant/# sperm-positive x 100
Gestation Index= # with viable progeny/# pregnant x 100
Mating Index= # sperm-positive/# co-housed 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 - All animals survived until the scheduled sacrifice. No treatment-related clinical signs of toxicity were noted. Clinical signs observed were considered to be due to the Elizabethan collars (nasal stain) or topical application of the drug (scab formation or scaling and/or sloughing of skin) observed in all dose groups. The investigators stated that these findings are "attributed to the adaptive response of the skin following the cumulative exposure to the test material".

2. Body Weight - Body weights and body weight gains were comparable between groups throughout the course of the study. Table 2 presents the results for body weight gain.

Table 2. Body Weight Gains (grams)[a]		
Group (mg/kg/day)	Entire Gestation Period[b]	Corrected Body Weight Gain[c]
Control	131.3 ± 5.63	59.5 ± 3.10
LDT	133.9 ± 3.67	60.3 ± 1.68
MDT	140.2 ± 3.20	55.8 ± 1.78
HDT	135.3 ± 4.80	57.2 ± 1.93

[a]Data extracted from (study number 95-622-DI and tables 3 and 8)
[b]The rats were dosed over the entire gestation period.
[c]Corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight.

3. Food Consumption - Food consumption was not affected by treatment.

4. Gross Pathology - There were no treatment-related gross pathologic findings noted in any of the dams.

5. Organ Weights - Minor, but statistically significant increases in the absolute (↑9% $p \leq 0.01$) and relative (↑5%, $p \leq 0.05$) liver weights were noted in the high-dose group (Table 3). Thyroid weights were similar in the controls and dose groups.

Table 3. Mean absolute and relative liver weights at final necropsy.[a]

	Dose (mg/kg/day)			
	0	50	200	400
# Animals	24	29	27	28
Final Body Weight (g)	369	376	385	384
Absolute Liver Weight (g)[b]	15.27	15.60	16.16	16.68**
Relative Liver Weight[b]	4.14	4.15	4.19	4.35*

a Data extracted from the study report, Tables 6 and 7, pages 43 and 45.
b Absolute and relative liver weights were rounded to the nearest hundredth by the reviewers.
* and ** = $p \leq 0.05$ and $p \leq 0.01$, respectively.

6. Cesarean Section Data - Cesarean section observations are presented in Table 4. The numbers of corpora lutea, implantations, viable fetuses, the extent of resorptions/implantations and mean fetal weights were similar between control and

treated groups. There were no treatment-related differences observed in the high-dose group compared to controls, however the following were increased (not statistically significant) in the high-dose group (not including the one litter that was totally resorbed): (i) total resorptions (37 treated vs 22 controls); (ii) resorption/implantation ratio (9.20% treated vs 7.28% controls); (iii) early resorptions/dam (1.1 treated vs 0.8 controls); and (iv) post-implantation loss (9.5% treated vs 7.7% controls). The viable fetus/implantation ratio was decreased in the high-dose group (87.2% treated vs 92.3% controls). These differences were judged not to be treatment-related because (i) the absolute numbers from many of these parameters were higher in the high-dose group because more of the high-dose dams were pregnant than controls (28 treated vs 24 controls), (ii) the early resorptions/dam ratio was within historical control ranges (0.5-1.5); and (iii) percent post implantation loss was also within historical control ranges (3-14.4%). The decreased number of male offspring observed in the high-dose group (47% treated vs 57% controls) was considered an incidental occurrence.

Table 4. Cesarean section observations[a]

Observation	Dose (mg/kg/day)			
	0	50	200	400
Animals Assigned (Mated)	30	30	30	30
Animals Pregnant	24	29	27	28
Pregnancy Rate (%)	(80)	(97)	(90)	(93)
Nonpregnant	6	1	3	2
Maternal Wastage				
Died	0	0	0	0
Died Pregnant	0	0	0	0
Died Nonpregnant	0	0	0	0
Aborted	0	0	0	0
Premature Delivery	0	0	0	0
Total Corpora Lutea(FTG)	345	428	423	418
Corpora Lutea/Dam	14.4±0.6[b]	14.8±0.5	15.7±0.4	15.5±0.3
Total Implantations(FTG)	302	379	395	402
Implantations/Dam	12.6±0.6	13.1±0.6	14.6±0.4	14.4±0.4
Total Litters	24	29	27	27
Total Live Fetuses	280	351	370	351
Live Fetuses/Dam	11.7±0.7	12.1±0.5	13.7±0.4	12.5±0.7
Total Dead Fetuses	0	1	0	0
Dead Fetuses/Dam	0	0.2±0.2	0	0
Total Resorptions	22	27	25	51 (37)[d]
Early	20	24	20	42 (31)[d]
Late	2	3	5	9
Resorptions/Dam	0.9±0.2	0.9±0.2	0.9±0.2	1.8±0.5 (1.3)[d]
Early	0.8±0.2	0.8±0.2	0.7±0.2	1.5±0.4 (1.1)[d]
Late	0.1±0.1	0.1±0.1	0.2±0.1	0.3±0.2
Litters with Total Resorptions	0	0	0	1
Mean Fetal Weight (g)	4.1±0.1	4.0±0.0	4.1±0.1	4.1±0.1
Males	4.2±0.1	4.1±0.0	4.2±0.1	4.2±0.1
Females	4.0±0.1	3.9±0.0	4.0±0.1	4.1±0.1
Sex Ratio (% Male)	57	51	49	47
Resorption/Implantation Ratio (%)	7.28[c]	7.12	6.33	12.69 (9.2)[d]
Viable Fetus/ Implantation Ratio (%)	92.3	93.4	93.7	87.2
Pre-implantation Loss (%)	11.8	11.7	6.2	7.2
Post-implantation Loss (%)	7.7	6.6	6.3	12.8 (9.5)[d]

[a]Data extracted from the study report, Tables 9 and 10; also Appendix IX, pages 160 through 163.
[b]Standard errors were rounded off to the nearest tenth by the reviewers.
FTG - Full term gestating females.
[c]Calculated by the reviewers.
[d] Number in parenthesis does not include litter totally resorbed.

B. DEVELOPMENTAL TOXICITY Fetal evaluations included external, visceral, and skeletal examinations. There were no treatment-related external, visceral, or skeletal malformations or external and visceral variations noted at any dose level. An increased incidence ($p \leq 0.05$) of incomplete ossification of the supraoccipital bone in the high-dose group was observed. This finding 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 above 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. Also observed at the high-dose were increased fetal incidences of thoracic centra (↑34%, $p \leq 0.05$) and sternebrae #5 (↑17%, $p \leq 0.05$) and an increase in the number of rib ossification centers (↑113%, $p \leq 0.01$). However, the thoracic centra and sternebrae #5 findings were found at litter incidence rates within the historical control ranges (57.9-96.6% and 96.3-100%, respectively) and the increased incidences of rib ossification centers are considered to be not an adverse effect.

External, visceral, and skeletal fetal findings are presented in Tables 5a, 5b, 5c, and 5d below.

Table 5a. Fetal external examinations[a]

Observations [b]	Dose (mg/kg/day)			
	0	50	200	400
#Fetuses(litters) Examined	280(24)	351(29)	370(27)	351(27)
#Fetuses(#litters) with Malformations	1(1)	1(1)	1(1)	1(1)
#Fetuses(#litters) with Variations	0(0)	11(1)	1(1)	0(0)
Edema	0(0)	3.1**(3.4)	0(0)	0(0)
Pale	0(0)	0(0)	0.3 (3.7)	0(0)
Domed Head	0(0)	0(0)	0(0)	0.3(3.7)
Protruding Tongue	0(0)	0(0)	0(0)	0.3(3.7)
Torso Anasarca	0(0)	0.3(3.4)	0(0)	0(0)
Anal Imperforate	0(0)	0(0)	0.3(3.7)	0(0)
Acaudate Tail	0(0)	0(0)	0.3(3.7)	0(0)
Shortened Tail	0.4(4.2)	0(0)	0(0)	0(0)

a Data extracted from the study report, Table 12, pages 56, 57, and 58.
b Values for individual observations are as follows: %fetal(%litter).
** = $p \leq 0.01$.

Table 5b. Fetal visceral examinations.[a]

Observations [b]	Dose (mg/kg/day)			
	0	50	200	400
#Fetuses(litters) examined	135(24)	169(29)	178(27)	169(27)
#Fetuses(#litters) with Malformations	4(4)	1(1)	3(3)	2(2)
#Fetuses(#litters) with Variations	11(9)	3*(2*)	9(7)	20(13)
Left-sided Umbilical Artery	0.7(4.2)	0(0)	1.1(7.4)	1.2(7.4)
Enlarged Auricles	1.5(8.3)	0(0)	1.1(3.7)	1.8(11.1)
Reduced Heart Size	2.2(12.5)	0.6(3.4)	1.7(11.1)	0.6(3.7)
Hydroureter	5.9(25.0)	1.8(6.9)	2.8(14.8)	8.9(37.0)
Dilated Renal Pelvis	0.7(4.2)	0(0)	0.6(3.7)	0.6(3.7)
Malpositioned Kidney	0.7(4.2)	0(0)	0(0)	0(0)
Anophthalmia	0.7(4.2)	0(0)	0(0)	0(0)
Dilated Brain Ventricles	0(0)	0(0)	0(0)	0.6(3.7)
Cleft Palate	0(0)	0(0)	0(0)	0.6(3.7)

a Data extracted from the study report, Tables 13 and 14, pages 60 through 64.
b Values for individual observations are as follows: %fetal (%litter).
* = $p \leq 0.05$.

Table 5c. Fetal skeletal variations.[a]

Observations [b]	Dose (mg/kg/day) 0	50	200	400	Historical controls
#Fetuses (#litters) examined	145(24)	182(29)	192(27)	181(27)	847(116)
#Fetuses (#litters) with Variations	145(24)	182(29)	192(27)	181(27)	--
Incomplete ossifications:					
Supraoccipital	30.3 (75)	42.9 (90)	42.2 (82)	43.6* (89)	3.6-30.6 (13.3-74.1)
Thoracic Centra	42.8 (92)	45.6 (93)	50.5 (96)	57.5* (96)	15.7-68.7 (57.9-96.6)
Sternebrae #5	78.6 (100)	78.6 (100)	80.2 (100)	92.3* (100)	60.2-78.4 (96.3-100.0)
Abnormal ossifications:					
Rib ossification centers	11.7 (46)	8.2 (38)	20.3 (48)	24.9** (67)	0.5-20.0 (3.7-61.5)

a Data extracted from the study report, Tables 15 and 16, pages 66 through 85.
b Values for individual observations are as follows: %fetal (%litter). % litter rounded to whole number by the reviewers.
* = $p \leq 0.05$ and 0.01, respectively. --=information not provided.

Table 5d. Fetal skeletal malformations.[a]

Observations [b]	Dose (mg/kg/day)			
	0	50	200	400
#Fetuses (#litters) examined	145(24)	182(29)	192(27)	181(27)
#Fetuses (#litters) with Malformations	1(1)	1(1)	1(1)	0(0)
Missing Lumbar Arch	0.7(4)	0.5(3)	0.5(4)	0(0)
Missing Lumbar Centra	0.7(4)	0.5(3)	0.5(4)	0(0)

a Data extracted from the study report, Table 16, page 76.
b Values for individual observations are as follow: %fetal, (%litter). %litter rounded to whole number by the reviewers.

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS The study author concluded that dermal administration of KBR 3023 at up to 400 mg/kg/day to pregnant rats during days 0-20 of gestation provoked no reproductive toxicity, embryo toxicity or teratogenic effects. The test article did cause cutaneous sloughing and scaling at the site of application. In addition, the high-dose group had significantly elevated absolute and relative liver weights. The maternal LOAEL is 400 mg/kg/day. A developmental LOAEL was not observed.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: Following dermal administration of KBR 3023 (97.4-97.7% a.i.) at 50, 200, and 400 mg/kg/day to pregnant rats during days 0-20 of gestation, all treated groups experienced dermal sloughing and scaling in the area of administration. This finding was considered an adaptive response to prolonged exposure to the test material.

   The high-dose group had a marginal increase in absolute (↑9%, $p \leq 0.01$) and relative (↑5%, $p \leq 0.05$) liver weights at final necropsy. Histopathological data were not submitted. The liver was not a target organ in a previously submitted dermal oncogenicity study (MRID 44408719). Therefore, in the absence of corroborating histopathological data, the differences in liver weights are considered to be an adaptive response. The numbers of corpora lutea, implantations, viable fetuses, and the extent of pre-implantation losses were unaffected by treatment.

Maternal LOAEL >400 mg/kg/day
Maternal NOAEL = 400 mg/kg/day

2. DEVELOPMENTAL TOXICITY: A treatment-related increase in a skeletal variation was observed.

   a. Deaths/Resorptions: No effects on fetal viability were observed.
   b. Altered Growth: No effects on fetal growth were observed.
   c. Developmental Variations: An increased incidence ($p \leq 0.05$) of incomplete ossification of the supraoccipital bone in the high-dose group was observed. This finding is not considered to be treatment-related because (i) fetal and litter incidences in the controls were at the maximum historical levels, and (ii) there was no evidence of a dose response (all dosed groups had similar incidences), and (iii) it is inappropriate to compare incidence in a dermal study against oral historical values. Dermal historical data would likely have higher ranges for ossification variations. Thus, incomplete ossification is most likely a manifestation of maternal stress caused by the unusual dermal dosing regimen.

      Abnormal rib ossification centers in the high-dose fetuses (24.9% v 11.7%) are also not considered to be adverse because (i) fetal and litter incidences were marginally greater than historical values, (ii) it is inappropriate to compare incidence in a dermal study against oral historical values, (iii) "rib" ossification centers are frequently connected via cartilage to the vertebra transverse process (this can only be confirmed via dual staining techniques not used in this study), and (iv) an increase in rib ossification centers is associated with maternal stress. These conclusions regarding skeletal variations are based upon discussions with Sue Makris (HED) and the study director at Bayer AG on May 19, 1999.

   d. Malformations: No treatment-related malformations were observed.

Developmental Toxicity LOAEL > 400 mg/kg/day
Developmental Toxicity NOAEL = 400 mg/kg/day

The developmental toxicity study in the rat is classified as **Acceptable/Guideline (870.3700)** and satisfies the guideline requirement for a developmental toxicity study in the rat.

C. STUDY DEFICIENCIES: None.