DATA EVALUATION RECORD

BAS 670H

Study Type: §83-3a; Developmental Toxicity Study in Rats

Work Assignment No. 1-01-11 J (MRID 45902207)

Prepared for
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U.S. Environmental Protection Agency
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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity- Rat OPPTS 870.3700, OECD 414

PC CODE: 123009 **DP BARCODE:** D292904

TEST MATERIAL (PURITY): BAS 670H (95.8% a.i.)

SYNONYMS: [3-(4,5-Dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methyl-phenyl}-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-methanone

CITATION: Schneider, S., J. Hellwig, B. van Ravenzwaay (2003) BAS 670 H - prenatal developmental toxicity study in Wistar rats: oral administration (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory Project ID.: 30R0124/98120, February 27, 2003. MRID 45902207. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45902207), BAS 670H (95.8% a.i.; Batch # N26) in 0.5% (w/v) aqueous carboxymethylcellulose was administered orally via gavage in a dosing volume of 10 mL/kg bw to 25 presumed pregnant female Wistar rats/group at dose levels of 0, 100, 300, or 1000 mg/kg on gestation days (GD) 6 through 19. All dams were sacrificed on GD 20, and their fetuses were removed by cesarean and examined.

For maternal toxicity, there were no treatment-related effects on mortality, clinical signs, food consumption, or gross pathology. There were statistically significant decreases of body weight gains in the 1000 mg/kg/day group at GD 6-8 (↓73%) and in all treated groups at GD 8-10 (↓28-36%) compared with the control. The overall (GD 0-20) body weight gains were dose-dependently decreased in treated animals; however, corrected (for gravid uterine weight) body weight gains did not show significant difference among treatment and control groups.

The maternal NOAEL was not established. The maternal LOAEL is 100 mg/kg/day based on decreased body weight gains.

For developmental toxicity, there were no abortions, premature deliveries, or complete litter resorption. Similarly, there were no effects of treatment on the number of resorption (early or late), number of fetuses (live or dead), post-implantation loss, or fetal sex ratio. There were no treatment-related external, visceral, or skeletal malformations. Decreased fetal body weights ($p \leq 0.01$) by 6-9% compared to controls were observed at doses ≥100 mg/kg/day. Increased incidences of the following skeletal variations that exceeded concurrent and historical controls were observed at doses ≥100 mg/kg/day: (i) supernumerary thoracic vertebrae; (ii) misshapen sacral vertebrae; (iii) supernumerary 14th rib with or without cartilage; and (iv) unossified sternebra. In addition, increased incidences of incomplete ossification of the thoracic centrum and basioccipital holes were observed at ≥300 mg/kg/day and increased incidences of the following skeletal variations were observed at 1000 mg/kg/day: (i) unossified hyoid and thoracic centrum; (ii) incomplete ossification of the cervical arch and pubis; and (iii) sacral arch cartilage, not connected.

The developmental LOAEL is 100 mg/kg/day based on decreased fetal body weights and increased incidences of skeletal variations. The developmental NOAEL was not established.

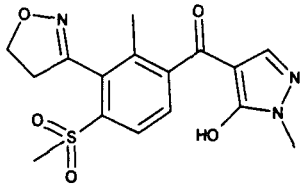
This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the requirements for a developmental toxicity study in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** BAS 670H

Description:	Beige crystalline solid
Batch #:	N26
Purity:	95.8% a.i.
Compound Stability:	The compound was stable in the vehicle for 96 hours at room temperature
CAS #:	210631-68-8
Structure:	

2. **Vehicle and/or positive control:** 0.5% aqueous carboxymethylcellulose

3. **Test animals**

Species:	Rat	
Strain:	Wistar (CrlGlxBrlHan:WI)	
Age and weight on GD 0:	77-95 days 159-241 g	
Source:	Charles River Laboratories (Germany)	
Housing:	Individually, in type DK III stainless steel wire mesh cages	
Diet:	Ground Kliba maintenance diet, rat/mouse/hamster meal (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Not reported
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	≥20 Days	

B. PROCEDURES AND STUDY DESIGN

1. **In life dates** - Start: 03/07/00 End: 03/29/00

2. **Mating:** After acclimation, sexually mature, virgin females were paired overnight (15.5 hours) with males (1 male: 1-3 females). The day on which successful mating was determined (presence of spermatozoa in a vaginal smear) was designated as gestation day (GD) 0.

3. **Animal assignment:** After mating, dams were randomly assigned to dose groups as indicated in Table 1.

Table 1. Animal assignment [a]

Dose (mg/kg bw/day)	0	100	300	1000
# Females	25	25	25	25

a Data were obtained from MRID 45902207 on page 19.

4. **Dose-selection rationale:** No dose-selection rationale was provided.

5. **Dosage preparation and analysis:** Dose formulations were prepared by suspending the appropriate amount of test substance in 0.5% aqueous carboxymethylcellulose at 3-4 day intervals. Storage conditions were not reported. The stability of the test substance for up to 96 hours at room temperature was verified in a 1000 mg/l formulation prior to the study. Homogeneity (top, middle, bottom) and concentration analyses were performed in all dosage preparations (10, 30, 100 mg/l) twice during the study. All analyses were performed on duplicate samples.

Results

Homogeneity (range as % of nominal, CV): 90.0-99.7%; C.V. = 1.0-4.9%

Stability (% of initial concentration): 96.2% at 4 and 96 hour.

Concentration (range as % of nominal): 90.0-109.7%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered in 0.5% aqueous carboxymethyl-cellulose daily via oral gavage on GD 6 through 19 in a dosing volume of 10 mL/kg bw, based on the most recent body weight.

C. **OBSERVATIONS**

1. **Maternal observations and evaluations:** Throughout the study, clinical signs of toxicity were evaluated in all dams at least once daily, and mortality was evaluated twice daily (once daily on weekends and holidays). Food consumption (g/animal/day) and body weight was measured on GD 0 (body weight only), 1, 3, 6, 8, 10, 13, 15, 17, 19, and 20. Body weight gain was calculated for these intervals, and for GD 0-6, 6-19 and 0-20. The corrected body weight gain was determined by subtracting the gravid uterine weight on GD 20 from the body weight gain (GD 6-20). On GD 20, all dams were sacrificed in randomized order and necropsied. The gravid uterus was removed from each dam and weighed. The ovaries were also removed. All fetuses were removed by cesarean section. The numbers of corpora lutea, implantations, live fetuses, dead fetuses, and early, late, and complete resorptions were recorded.

2. Fetal evaluations: Each fetus was weighed, sexed, and examined externally. The condition of the placentae, umbilical cords, fetal membranes, and fluids were also evaluated. The placentae were weighed. Approximately half of the fetuses per dam were fixed in ethanol, stained by the method of Kimmel and Trammell, and the skeletons were examined microscopically. The remaining fetuses were fixed in Bouin's solution, and visceral findings were evaluated according to the method of Barrow and Taylor.

D. DATA ANALYSIS

1. Statistical analyses: Data were subjected to the following statistical procedures ($p \leq 0.05$ and $p \leq 0.01$):

Parameter	Statistical test
Food consumption Body weight, body weight gain (uncorrected and corrected), and carcass weight Weight of gravid uterus Numbers of corpora lutea, implantations, resorptions, and live fetuses Proportions of preimplantation loss, postimplantation loss, resorptions, and live fetuses in each litter Litter mean fetal body weight and placental weight	Dunnett's test (two-sided)
Female mortality Females pregnant at terminal sacrifice Number of litters with fetal findings	Fisher's exact test (one-sided)
Proportions of fetuses with malformations, variations, and/or unclassified observations in each litter	Wilcoxon-test (one-sided)

2. Indices: The following indices were calculated:

Conception rate (%) = # pregnant rats/# fertilized rats x 100

Pre-implantation loss (%) = (# corpora lutea - # implantations)/# corpora lutea x 100

Post-implantation loss (%) = (# implantations - # live fetuses)/# implantations x 100

3. Historical control data: Historical control data were provided for maternal body weights cesarean section parameters; and fetal external, visceral, and skeletal findings. Data were comprised of 9 studies (8 gavage studies and 1 inhalation study) from 2000-2001 on rats of the same strain as the current study (225 females mated providing 211 litters with 2010 fetuses).

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical observations:** There were no deaths and no treatment-related clinical signs.

2. **Body weight:** There were no significant difference on body weight between treated and control groups (Table 2). However, after start dosing, statistically significant decreases of body weight gains were observed in the 1000 mg/kg/day group at GD 6-8 (↓73%) and in all treated groups at GD 8-10 (↓28-36%) compared with the control. The overall (GD 0-20) body weight gains were dose-dependently decreased in treated animals; however, corrected (for gravid uterine weight) body weight gains did not show significant difference among treatment and control groups.

Table 2. Mean (±SD) maternal body weight and body weight gain (g) [a]

Interval	Dose in mg/kg bw/day (# of Dams)			
	0 (24)	100 (25)	300 (24)	1000 (22)
Body Weight				
GD 0	190.5±14.2	191.0±12.2	189.9±9.7	193.7±16.3
GD 6	211.8±15.6	210.5±13.8	210.1±11.9	213.9±18.0
GD 8	215.4±16.2	212.5±14.0	211.8±12.3	215.0±17.9
GD 19	277.6±21.6	273.6±18.1	271.7±18.2	275.0±23.8
Body Weight Gain				
GD 0-6	21.3±4.18	19.5±3.65	20.3±5.24	20.2±4.96
GD 6-8	3.7±2.23	2.0±2.93	1.6±3.06	1.0±5.22*(↓73)
GD 8-10	8.3±2.97	6.0±3.17*(↓28)	6.0±2.27*(↓28)	5.3±2.96**(↓36)
GD 10-13	10.4±3.01	10.6±3.12	10.0±3.73	11.5±3.40
GD 6-19	65.8±10.81	63.1±1.78	61.6±10.68	61.1±10.94
Overall: GD 0-20	97.4±12.48	94.2±11.18	93.5±15.28	92.2±14.10
Corrected Body Weight Gain				
Gravid uterus	51.9±13.63	50.3±8.85	50.8±9.79	47.4±11.29
Carcass	235.9±18.6	234.8±15.8	232.6±14.7	238.5±19.1
Net Body Weight Gain (GD 6-20) [b]	24.2±7.62	24.3±5.81	22.5±7.18	24.5±6.88

a Data obtained from pages 51-52 of MRID 45902207.Percent differences from the control group included in the parentheses were calculated by the reviewer. * P≤0.05; ** P≤0.01.

b Corrected weight gains (Days 6-20) is equivalent to the terminal body weight minus uterine weight minus Day 6 body weight.

3. **Food consumption:** No treatment-related effect was observed on food consumption. Transient decreases in food consumption were observed in all dose groups; however, the grand

mean for the treated animals was similar to controls during pretreatment, treatment periods, and for the overall study.

4. **Gross pathology:** No abnormalities were observed in any animal at necropsy.

5. **Cesarean section data:** Cesarean section data are presented in Table 3. In all dose groups, fetal body weights were decreased ($p \leq 0.01$) by 6-9% compared to controls. There were no abortions, premature deliveries, dead fetuses, or complete litter resorptions, and there were no effects of treatment on the number of litters, live fetuses, resorptions (early or late), placental weights, sex ratio, or implantation loss.

Table 3. Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	100	300	1000
# Animals Assigned (Mated)	25	25	25	25
# Animals Pregnant	24	25	24	22
Pregnancy Rate (%)	96	100	96	88
# Nonpregnant	1	0	1	3
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	301	302	280	254
Corpora Lutea/Dam	12.5±1.56	12.1±1.71	11.7±1.46	11.5±1.82
Total # Implantations	257	278	265	230
(Implantations/Dam)	10.7±2.61	11.1±2.22	11.0±2.16	10.5±2.18
Total # Litters	24	25	24	22
Total # Live Fetuses	244	257	246	215
(Live Fetuses/Dam)	10.2±2.96	10.3±2.05	10.3±2.15	9.8±2.51
Total # Dead Fetuses [b]	0	0	0	0
(Dead Fetuses/Dam)	0	0	0	0
Total # Resorptions	13	21	19	15
Early	11	19	19	15
Late	2	2	0	0
Resorptions/Dam	0.5±1.14	0.8±1.07	0.8±0.72	0.7±1.04
Early	0.5±0.93	0.8±0.97	0.8±0.72	0.7±1.04
Late	0.1±0.28	0.1±0.28	0±0	0±0
Complete Litter Resorptions	0	0	0	0
Mean Fetal Weight (g), All	3.3±0.19	3.1±0.20** (↓6)	3.1±0.17** (↓6)	3.0±0.21** (↓9)
Males	3.4±0.21	3.1±0.20** (↓9)	3.2±0.19** (↓6)	3.1±0.25** (↓9)
Females	3.2±0.20	3.0±0.23** (↓6)	3.0±0.20** (↓6)	3.0±0.20** (↓6)
Mean Placental Weight (g), All	0.41±0.076	0.40±0.045	0.43±0.073	0.40±0.037
Males	0.42±0.062	0.42±0.048	0.42±0.045	0.41±0.039
Females	0.41±0.090	0.39±0.044	0.42±0.077	0.40±0.045
Sex Ratio (% Male)	43.0	45.5	50.8	49.3
Preimplantation Loss (%)	14.9±18.8	8.2±12.4	5.7±14.7	9.5±12.2
Postimplantation Loss (%)	5.5±13.3	7.1±8.89	7.8±8.06	7.1±13.0

a Data obtained from pages 31 and 54-57 of MRID 45902207. Percent difference from controls, calculated by the reviewers, is included in parentheses.

b It was determined that there were no dead fetuses, because the difference between the numbers of implantations and live fetuses is entirely accounted for by resorptions.

** Significantly different from the controls at $p \leq 0.01$

B. DEVELOPMENTAL TOXICITY

1. **External examination** - External findings are presented in Table 4a. No treatment-related finding was observed during external examination.

Table 4a. External findings (% fetuses affected [% litters affected]) [a]

Observations	Dose (mg/kg/day)				Historical Controls
	0	100	300	1000	
# Fetuses (litters) examined	244 (24)	257 (25)	246 (24)	215 (22)	2010 (211)
Malformations					
Umbilical hernia	0 (0)	0.4 (4)	0 (0)	0 (0)	0-0.4 (0-4)
Anasarca	0 (0)	x [b] (4)	0 (0)	0 (0)	0-0.5 (0-4)
Cleft palate	0 (0)	0 (0)	0.4 (4)	0 (0)	0 (0)
Anophthalmia	0 (0)	0.4 (4)	0 (0)	0 (0)	0 (0)
Short tail	0 (0)	0.4 (4)	0 (0)	0 (0)	0-0.4 (0-4)
Total external malformations	0 (0)	0.8 (4)	0.4 (4)	0 (0)	0-0.8 (0-8)
Variations					
Total external variations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unclassified					
Blood coagulum around placenta	0 (0)	0 (0)	0.8 (4)	0 (0)	0-1.0 (0-8)
Total external unclassified	0 (0)	0 (0)	0.8 (4)	0 (0)	0-1.0 (0-8)

a Data were obtained from pages 59-62 and 257-259 of MRID 45902207.
b Erroneous value in the summary table

2. Visceral examination - Visceral findings are presented in Table 4b. No treatment-related finding was observed during visceral examination.

Table 4b. Visceral findings (% fetuses affected [% litters affected]) [a]

Observations	Dose (mg/kg/day)				Historical Controls
	0	50	150	450	
# Fetuses (litters) examined	117 (24)	123 (25)	117 (24)	101 (22)	904 (197)
Malformations					
Small kidney	0 (0)	0.8 (4)	0 (0)	0 (0)	0 (0)
Total soft tissue malformations	0 (0)	0.8 (4)	0 (0)	0 (0)	0-1.0 (0-5)
Variations					
Dilated cerebral ventricle	0 (0)	0.8 (4)	0 (0)	1 (5)	0 (0)
Dilated ureter	x [b] (13)	4.1 (20)	0.9 (4)	2.0 (9)	0-3.3 (0-10)
Dilated renal pelvis	15 (38)	20 (56)	16 (46)	11 (3)	3.3-8.7 (4-33)
Total soft tissue variations	15 (38)	21 (60)	16 (46)	12 (32)	3.3-8.7 (4-33)
Unclassified					
Total soft tissue unclassified	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

a Data were obtained from pages 64-67 and 260-262 of MRID 45902207.
b Erroneous value in the summary table

3. Skeletal examination - Selected skeletal findings are presented in Table 4c. The incidence of all the following skeletal variations and unclassified findings exceeded the historical control range. At ≥100 mg/kg/day, there were increased ($p \leq 0.05$) incidences (% fetuses affected [% litters affected]) of the following skeletal variations/unclassified: (i) supernumerary thoracic vertebrae (11-12 [36-48] treated vs 1.6 [4] controls); (ii) misshapen sacral vertebrae (4.5-16 [24-41] treated vs 1.6 [8] controls); (iii) supernumerary 14th rib with cartilage (21-28 [59-76] treated vs 4.7 [21] controls) and without cartilage (59-68 [96-100] treated vs 41 [79] controls); and (iv) unossified sternebra (40-48 [80-83] treated vs 16 [46] controls); and (v) notched cartilage between basisphenoid and basioccipital (5.2-6.2 [14-25] treated vs 3.1 [17] controls). At ≥300 mg/kg/day, increased incidences of incomplete ossification of the thoracic centrum and basioccipital holes were observed. At 1000 mg/kg/day, there were increased incidences of the following skeletal variations/unclassified: (i) unossified hyoid and thoracic centrum; (ii) incomplete ossification of the cervical arch and pubis; and (iii) sacral arch cartilage, not connected.

Table 4c. Selected skeletal findings (% fetuses affected [% litters affected]) [a]

Observations	Dose (mg/kg/day)				Historical Controls
	0	100	300	1000	
# Fetuses (litters) examined	127 (24)	134 (25)	129 (24)	114 (22)	984 (195)
Malformations					
Severe delays in skeletal ossification	0 (0)	x [b] (4)	0.8 (4)	0 (0)	0 (0)
Total skeletal malformations	0 (0)	0.7 (4)	2.3 (13)	0 (0)	0-4.9 (0-25)
Variations					
Supernumerary thoracic vertebrae	1.6 (4)	12 (48)**	12 (42)**	11 (36)**	0.7-5.5 (4-22)
Misshapen sacral vertebrae	1.6 (8)	4.5 (24)	16 (38)*	11 (41)*	0-2.7 (0-12) [d]
Supernumerary rib (14th) cartilage present	4.7 (21)	26 (76)**	28 (71)**	21 (59)**	44.1-63.6 (79-95) [c]
Cartilage not present)	41 (79)	68 (100)*	59 (96)	66 (100)*	
Unossified, Hyoid (cartilage present)	1.6 (8)	3.0 (12)	1.6 (8)	5.3 (23)	0-4.5 (0-20)
Thoracic centrum (unchanged cartilage)	0 (0)	0.7 (4)	0.8 (4)	1.8 (9.1)	0-0.7 (0-4)
Sternebra (unchanged cartilage)	16 (46)	46 (80)*	40 (83)**	48 (82)*	4.7-29.1 (17-50)
Incomplete ossification, Cervical arch	0.8 (4)	1.5 (4)	0 (0)	3.5 (14)	0 (0)
Pubis	1.6 (8)	3.7 (8)	1.6 (8)	5.3 (18)	0-1.5 (0-8)
Thoracic centrum	2.4 (8)	x [b] (20)	9.3 (33)*	11 (36)*	0-6.9 (0-28)
Sternebra (unchanged cartilage)	50 (79)	52 (96)	64 (100)*	68 (100)*	32.1-75.7 (79-100)
Basioccipital holes	0 (0)	0 (0)	2.3 (13)	1.8 (9)	0-0.7 (0-4)
Total skeletal variations	87 (6)	98 (100)	99 (100)	98 (100)	77.7-100 (100)
Unclassified					
Notched cartilage between basisphenoid and basioccipital	3.1 (17)	5.2 (24)	6.2 (25)	6.1 (14)	0-2.4 (0-12)
Sacral arch, cartilage not connected	3.1 (13)	3.0 (16)	3.1 (17)	5.4 (27)	0-3.6 (0-20)
Total skeletal unclassified	31 (83)	29 (84)	23 (67)	32 (73)	0-63.4 (0-100)

a Data were obtained from pages 69-86 and 263-268 of MRID 45902207.
b Tabulated by the reviewers from individual data listed on pages 139-160 and 188-212 of MRID 45902207.
c Dumbbell ossification, thoracic centrum was listed in the historical controls without distinction in regards to cartilage.
d Classified as a malformation in the historical controls

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The study authors stated that there were minor signs of systemic maternal toxicity, i.e., slightly and temporarily reduced body weight gain during early treatment in all treated groups. No substance-induced dose-related influences on the gestational parameters and no test substance-induced indications of teratogenicity were observed. A slight retardation of ossification of axial skeleton and slight embryo/fetal toxicity were presumably caused by the test substance at all dose levels along with a decrease of the mean weight of the fetuses. Based on these results, the authors determined that the NOAEL for maternal and developmental toxicity is below 100 mg/kg/day.

B. REVIEWER COMMENTS

1. **Maternal toxicity:** No treatment-related effect was observed on mortality, clinical signs, food consumption, or gross pathology. There were no significant difference on body weight between treated and control groups. However, after start dosing, statistically significant decreases of body weight gains were observed in the 1000 mg/kg/day group at GD 6-8 (↓73%) and in all treated groups at GD 8-10 (↓28-36%) compared with the control. The overall (GD 0-20) body weight gains were dose-dependently decreased in treated animals; however, corrected (for gravid uterine weight) body weight gains did not show significant difference among treatment and control groups.

The maternal LOAEL is 100 mg/kg/day based on decreased body weight gains. The maternal NOAEL was not established.

2. **Developmental toxicity**

a. Deaths/Resorptions: There were no abortions, premature deliveries, or complete litter resorptions. Similarly, there were no effects of treatment on the number of resorptions (early or late), number of fetuses (live or dead), post-implantation loss, or fetal sex ratio.

b. Altered Growth: In all dose groups, fetal body weights were decreased ($p \leq 0.01$) by 6-9% compared to controls. The incidence of all the following skeletal variations exceeded the concurrent and historical controls. At ≥100 mg/kg/day, there was an increased ($p \leq 0.05$) incidence unossified sternebra. At ≥300 mg/kg/day, an increased ($p \leq 0.05$) incidence of incomplete ossification of the thoracic centrum was observed. At 1000 mg/kg/day, there were increased incidences of unossified hyoid and thoracic centrum; and incomplete ossification of the cervical arch and pubis.

c. Developmental Variations: The incidence of all the following skeletal variations and unclassified findings exceeded the concurrent and historical controls. At≥100 mg/kg/day, there were increased incidences of the following skeletal variations/unclassified: (i) supernumerary thoracic vertebrae; (ii) misshapen sacral vertebrae; (iii) supernumerary (14^{th}) rib with or without cartilage; and (iv) notched cartilage between basisphenoid and basioccipital (skeletal unclassified). At ≥300 mg/kg/day, increased incidences of basioccipital holes was observed. Sacral arch cartilage, not connected (skeletal unclassified), was observed at 1000 mg/kg/day.

d. Malformations: There were no treatment-related malformations.

The developmental LOAEL is 100 mg/kg/day based on decreased fetal body weights and increased incidences of skeletal variations. The developmental NOAEL was not established.

This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the guideline requirements for a developmental toxicity study in the rat.

C. **STUDY DEFICIENCIES:** Maternal and fetal toxicity occurred at 100 mg/kg/day (the lowest dose tested); thus, the Sponsor should have tested at lower doses to determine a developmental NOAEL. A dose-rationale was not provided.

DATA FOR ENTRY INTO ISIS

Developmental Study - rats (870.3700a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
123009	45902207	developmental	rats	GD 6-19	oral	gavage	100-1000	0, 100, 300, 1000	not observed	100	decr. BWG	Maternal
123009	45902207	developmental	rats	GD 6-19	oral	gavage	100-1000	0, 100, 300, 1000	not observed	100	decr BW; incr skeletal variations	Developmental