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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study -Mouse; OPPTS 3700, OECD 414

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

TEST MATERIAL (PURITY): BAS 670H Technical (99.7% 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: Barnett, J.F. (2003) Oral (gavage) developmental toxicity study of BAS 670H in mice. Argus Research Laboratories, Inc., Horsham, PA. Laboratory Project No.: 36R0124/989172. March 11, 2003. MRID 45902208. Unpublished.

Barnett, J.F. (2003) Oral (gavage) dosage-range developmental toxicity study of BAS 670H in mice. Argus Research Laboratories, Inc., Horsham, PA. Laboratory Project No.: 28R0124/989171, March 5, 2003. MRID 45902209. Unpublished.

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

EXECUTIVE SUMMARY: In a developmental toxicity study (MRIDs 45902208), BAS 670H (99.7% a.i.; Lot # 30786/4/2) in 0.5% (w/v) aqueous carboxymethylcellulose was administered orally via gavage in a dosing volume of 10 mL/kg to 25 presumed pregnant Crl:CD-1®(ICR)BR mice/group at dose levels of 0, 30, 200, or 1000 mg/kg on gestation days (GD) 6 through 17. All dams were sacrificed on GD 18, and their fetuses were removed by cesarean section and examined. Clinical chemistry and organ weights were also evaluated.

No treatment-related effect was observed on mortality, clinical signs of toxicity, body weights, or gross pathology.

A decrease ($p \leq 0.01$) in body weight gain was observed at 1000 mg/kg/day during GD 6-9; all other measured body weight gains in the treated groups (including for the overall study, and overall treatment period) were similar to the controls. Clinical chemistry showed an elevated alanine aminotransferase level ($p \leq 0.01$) at 1000 mg/kg/day with a dose-dependent response. An

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increase ($p \leq 0.05$) of relative liver weights was also observed at 1000 mg/kg/day. Serum tyrosine was increased ($p \leq 0.05$) dose-dependently at 30 (↑2-3X) and ≥200 (↑6-10X) mg/kg/day.

The maternal LOAEL is 30 mg/kg/day, based on increased serum tyrosine level. The maternal NOAEL was not established.

There were no abortions or complete litter resorptions. Similarly, there were no effects of treatment on the number of premature deliveries, resorptions (early or late), number of fetuses (live or dead), fetal sex ratio, or post-implantation losses. There were no treatment-related effects on external, visceral, or skeletal malformations, variations, or retardations.

The developmental LOAEL was not observed. The developmental NOAEL is 1000 mg/kg/day.

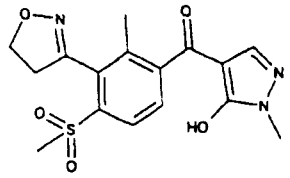
This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the requirements for a developmental toxicity study in the mouse.

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:	Brownish solid
Lot #:	30786/4/2
Purity:	99.7% a.i.
Compound Stability:	The compound was stable in the vehicle for 7 days at room temperature
CAS #:	210631-68-8
Structure:	

2. **Vehicle:** 0.5% aqueous carboxymethylcellulose

3. **Test animals**

Species:	Mouse	
Strain:	Crl:CD-1®(ICR)BR	
Apx. age at mating/ mean weight on GD 0:	79 days 32.4-32.6 g	
Source:	Charles River Laboratories, Inc. (Raleigh, North Carolina)	
Housing:	Individually, in stainless steel, wire bottomed cages	
Diet:	Certified Rodent Diet® #5002 (PMI Nutrition International, St. Louis, MO), *ad libitum*	
Water:	Chlorinated, reverse osmosis treated tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	18-26°C
	Humidity:	30-70%
	Air changes:	10/hour
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	6 days	

B. PROCEDURES AND STUDY DESIGN

1. **In life dates:** Start: 08/07/02 End: 08/23/02

2. **Mating:** After acclimation, sexually mature, virgin females were paired for a maximum of five days with males (1 male: 1 female). The females were checked daily for evidence of successful mating (the presence of a copulatory plug), and the day on which successful mating was observed was designated as gestation day (GD) 0.

3. **Animal assignment:** Dams were randomly assigned, stratified by weight, to dose groups as indicated in Table 1.

Table 1. Animal assignment [a]

Dose (mg/kg bw/day)	0	30	200	1000
# Females	25	25	25	25

a Data were obtained from MRID 45902208 on page 19.

4. **Dose-selection rationale:** Based upon the results of a range-finding developmental toxicity study (MRID 45902209) submitted with this developmental toxicity study, the doses summarized in Table 1 were selected. Details of the range-finding developmental study are in the Appendix of this DER.

5. **Dosage preparation and analysis:** Dose formulations were prepared at least once weekly by suspending the appropriate amount of test substance in 0.5% aqueous carboxymethylcellulose. The vehicle and formulations were stored at room temperature. The stability of the test substance was verified for up to 7 days at room temperature or refrigerated at a concentration of 0.1 mg/L superpure water prior to the study. Homogeneity (top, middle, bottom) and concentration analyses were determined from duplicate samples. Homogeneity was determined once in each formulation from the first preparation. Concentration analyses were also performed in all dosage preparations from the final preparation.

Results

Homogeneity (range as % nominal, CV): 96.7 - 106.0%; C.V.= 0.0-4.0%

Stability (% of initial concentration):
102.1% (in superpure water, daylight, room temp, 7 days)
102.8% (in superpure water, darkness, refrigerator, 7 days)
103.1% (in tap water, daylight, room temp, 7 days)
102.3% (in tap water, darkness, refrigerator, 7 days)

Concentration (range as % of nominal): 100-104%

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 17 at a dosing volume of 10 mL/kg. The administered dosage volume was adjusted daily on the basis of the most recent body weight.

C. **OBSERVATIONS**

1. **Maternal observations and evaluations:** Dams were examined for mortality at least twice daily during the study. Clinical signs of toxicity were evaluated in all dams weekly during

acclimation, twice daily during treatment, and on the day of scheduled sacrifice. Food consumption was not reported. Body weights were recorded prior to treatment, on GD 0, daily during treatment, and at sacrifice. Body weight gain was calculated for intervals, Days 0-6, 6-9, 9-12, 12-15, 15-18, 6-18, and 0-18. The corrected body weight gain was determined by subtracting the gravid uterine weight on GD 18 from the body weight gain (GD 6-18 and 0-18). On GD 18, all surviving dams were sacrificed, and blood was collected from the inferior vena cava. Whole blood samples from approximately half the mice of each group were analyzed for clinical chemistry (see the table below), and the remaining samples were analyzed for serum tyrosine concentration. Following blood collection, gross necropsy of the pelvic, abdominal, and thoracic viscera was performed. The gravid uterus, liver, kidneys, spleen, and adrenals of each mouse was excised and weighed. Gross lesions were retained in 10% formalin. Caesarean-sections were performed. The gravid uterus was removed from each dam and weighed. The number and distribution of corpora lutea were recorded. The uterus of each mouse was examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. Mice that died or were sacrificed because of premature delivery were examined similarly.

Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
X	Chloride	X	Creatinine
	Magnesium	X	Urea nitrogen
X	Phosphorus	X	Total Cholesterol
X	Potassium	X	Globulins
X	Sodium	X	Glucose
		X	Total bilirubin
	ENZYMES	X	Total protein
X	Alkaline phosphatase (ALK)	X	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophoresis
	Creatine phosphokinase	X	Albumin/globulin
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)		
X	Aspartate aminotransferase (AST/also SGOT)		
	Sorbitol dehydrogenase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

2. **Fetal evaluations:** Each fetus was weighed, sexed, and examined externally. Approximately half of the fetuses per dam were examined for visceral alterations using a variation of the microsection technique of Staples. The heads of these fetuses were fixed in Bouin's solution, free-hand sectioned (sections were retained in ethanol) and examined. The remaining fetuses were eviscerated, cleared, stained with alizarin red S, and examined for skeletal alterations. These fetuses were initially fixed in alcohol, but skeletal preparations were retained in glycerin with thymol. Delivered premature pups were examined in the same way.

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
Body weight, body weight gain (uncorrected and corrected) Litter averages for percent male fetuses, percent resorptions, fetal body weights, fetal anomaly data, and fetal ossification site data	Bartlett's test of homogeneity ($p \leq 0.001$) and (1) Analysis of Variance ($p \leq 0.05$) and Dunnett's test or (2) Kruskall-Wallis test ($p \leq 0.05$) and Dunn's method of multiple comparisons or (3) Fischer's exact test
Clinical observations Proportion data	Variance test for homogeneity of the binomial distribution
Count data obtained at the Caesarean-section	Kruskal-Wallis test and Dunn's test, as necessary

2. **Historical control data**: Historical control data were provided for maternal cesarean section parameters and gross findings; and fetal external, visceral, and skeletal findings. Data were comprised of 15-38 studies from 1997-2001 on mice of the same strain as the current study.

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical observations**: There were no treatment-related deaths or clinical signs. One 30 mg/kg/day mouse died as a result of an intubation accident on GD 7, and one 200 mg/kg/day mouse had localized alopecia. No other deaths or clinical signs were observed.

2. **Body weight**: No treatment-related effects were observed on body weights. The body weights of the treated groups were similar to the controls throughout the study. A significant decrease ($p \leq 0.01$) in body weight gain was observed at 1000 mg/kg/day during GD 6-9 (Table 2).

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

Interval		Dose in mg/kg bw/day (# of Dams)			
		0 (25)	30 (24)	200 (24)	1000 (24)
Pretreatment: GD 0-6		3.0±1.3	3.0±1.4	2.6±1.4	3.8±1.8
Treatment:	GD 6-9	2.0±1.1	2.4±1.0	1.9±1.3	1.0±1.3** (↓50)
	GD 9-12	5.0±1.2	5.6±1.3	6.0±1.4	5.7±1.7
	GD 15-18	8.6±2.6	9.1±2.8	10.3±2.8	9.3±3.2
Overall	GD 6-18	23.2±5.2	25.0±5.9	26.5±5.3	23.1±5.7
	GD 0-18	26.1±5.5	28.0±6.1	29.0±5.3	27.0±6.4
Body weight (GD 18)		58.6±4.6	60.4±7.1	61.8±5.4	59.3±6.4
Gravid uterus		20.0±4.4	20.8±6.0	22.9±4.3	20.0±5.6
Corrected BWG (GD 6-18)[b]		3.2±2.0	4.2±2.1	3.6±1.7	3.1±2.3

a Data (n=22-25) were obtained from pages 41-42 of MRID 45902208 and excluded values for mice that delivered or had an accidental death (0-3 mice).

b Corrected weight gain (GD 6-18) is equivalent to the terminal body weight minus gravid uterine weight minus Day 6 body weight.

3. **Clinical chemistry:** Serum alanine aminotransferase was increased dose-dependently at 30 (↑15%), 200 (↑26%), and 1000 (44%; $p \leq 0.01$) mg/kg/day (Table 3). Serum tyrosine was increased dose-dependently ($p \leq 0.05$) in all treated groups. No other significant adverse effects were observed since differences ($p \leq 0.05$) were minor and/or unrelated to dose.

Table 3. Selected clinical chemistry parameters (Mean ± SD)[a]

Clinical Chemistry	Dose in mg/kg bw/day (# of Dams)			
	0 (11)	30 (12)	200 (11)	1000 (12)
Alanine Aminotransferase (u/l)	34±8.0	39±10.8	43±6.6	49±15.1**
Tyrosine (µmol/l)	47.3±16.1	130.9±98.4**	261.3±93.4**	413.6±103.4**

a Data (n=11-12) were obtained from pages 192, 201-202 of MRID 45902208 and excluded values for mice that delivered or had an accidental death (0-3 mice).

4. **Organ weight:** A statistically significant increase of relative liver weight was observed at 1000 mg/kg/day (Table 4). There were no other significant treatment-related effects on organ weights since the differences ($p \leq 0.05$) were minor and/or unrelated to dose..

Table 4. Absolute and relative liver weight (Mean ± SD)[a]

	Dose in mg/kg bw/day (# of Dams)			
	0 (23)	30 (22)	200 (22)	1000 (23)
Absolute liver weight (g)	2.61±2.68	2.76±0.29	2.75±0.25	2.82±0.29
Relative liver weight (%)	4.46±0.47	4.59±0.45	4.45±0.29	4.78±0.47*

a Data (n=22-23) were obtained from page36 of MRID 45902208 and excluded values for mice that delivered or had an accidental death (0-3 mice).

5. **Gross pathology:** No treatment-related effect was observed during necropsy.

6. **Cesarean section data:** Cesarean section data are presented in Table 5. There were no complete litter resorptions and no effects of treatment on the number of litters, live fetuses, dead fetuses. resorptions (early or late), fetal weights, sex ratio, or post-implantation losses.

Table 5. Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	30	200	1000
# Animals Assigned (Mated)	25	25	25	25
# Animals Pregnant	25	24	24	24
Pregnancy Rate (%)	100	96	96	96
# Nonpregnant [b]	0	1	1	1
Maternal Wastage				
# Died	2	2	2	1
# Died Pregnant	2	2	2	1
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	0	0
# Premature Delivery	2	1	2	1
Total # Corpora Lutea [c]	317	300	322	326
(Corpora Lutea/Dam)	13.8±3.2	13.6±2.3	14.6±1.7	14.2±2.7
Total # Implantations [c]	303	282	310	299
(Implantations/Dam)	13.2±2.7	12.8±2.9	14.1±1.6	13.0±2.8
Total # Litters	25	24	24	24
Total # Live Fetuses	256	246	287	252
(Live Fetuses/Dam)	11.1±3.3	11.2±3.5	13.0±2.8*	11.0±3.7
Total # Dead Fetuses	2	3	2	2
(Dead Fetuses/Dam)	0.1±0.3	0.1±0.4	0.1±0.3	0.1±0.3
Total # Resorptions	45	33	21	45
Early	36	24	18	39
Late	9	9	3	6
Resorptions/Dam	2.0±2.1	1.5±1.8	1.0±2.1	2.0±1.9
Early	1.6±1.8	1.1±1.6	0.8±1.7	1.7±1.6
Late	0.4±0.7	0.4±0.6	0.1±0.5	0.3±0.5
Complete Litter Resorptions	0	0	0	0
Mean Fetal Weight (g), All	1.39±0.18	1.43±0.12	1.39±0.10	1.43±0.13
Males	1.41±0.18	1.46±0.12	1.40±0.11	1.45±0.13
Females	1.36±0.16	1.39±0.12	1.38±0.11	1.41±0.14
Sex Ratio (% Male)	55.4±14.6	53.9±21.0	52.4±16.1	44.9±17.1
Preimplantation Loss (%) [d]	4.4	6.0	3.7	8.3
Postimplantation Loss (%) [e]	15.5	12.8	7.4	15.7

a Data obtained from pages 25, 36, 43-44, and 72-75 of MRID 45902208. Percent difference from controls, calculated by the reviewers, is included in parentheses.
b Calculated by the reviewers by subtracting the animals pregnant from the animals assigned
c Calculated by the reviewers from individual data on pages 73-76 of MRID 45902207.
d Calculated by the reviewers as (total # corpora lutea - total # implantations)/total corpora lutea x 100
e Calculated by the reviewers as (total # implantations - total # live fetuses)/total # implantations x 100
* Significantly different from the controls at $p \leq 0.05$

B. DEVELOPMENTAL TOXICITY

1. **External examination:** External findings are presented in Table 6a. No treatment-related finding was observed during external examination. Although the incidence of fore and/or hindpaw rotated medially exceeded the concurrent controls (0.4% fetuses; 4.3% litters) and historical controls (0-0.7% fetuses; 0-8.3% litters) in all treated animals (0.8-1.7% fetuses; 9.1-18.2% litters). the effect was unrelated to dose.

2. **Visceral examination:** Visceral findings are presented in Table 6b. No treatment-related finding was observed during visceral examination.

3. **Skeletal examination:** Selected skeletal findings are presented in Table 6c. No treatment-related finding was observed during skeletal examination, and there was no treatment-related effect on ossification sites. Although the incidence of incompletely ossified skull frontals exceeded the concurrent controls (0.7% fetuses; 4.3% litters) and historical controls (0% fetuses; 0% litters) in all treated groups (2.3-3.3% fetuses; 9.1-13.6% litters), the effect was unrelated to dose.

Table 6a. External findings (% fetuses affected [% litters affected]) [a]

Observations	Dose (mg/kg/day)				Historical Controls
	0	30	200	1000	
# Fetuses (litters) examined	258 (23)	249 (22)	289 (22)	254 (23)	5975 (508)
Exencephaly	0 (0)	0.4 (4.5)	0 (0)	0 (0)	0-0.4 (0-5.3)
Eye lid open	0 (0)	0 (0)	0.3 (4.5)	0 (0)	0-0.4 (0-5.0)
Fore and/or hindpaw rotated medially	0.4 (4.3)	0.8 (9.1)	1.7 (18.2)	1.2 (13.0)	0-0.7 (0-8.3)

a Data were obtained from pages 46 and 208 of MRID 45902208.

Table 6b. Visceral findings (% fetuses affected [% litters affected]) [a]

Observations	Dose (mg/kg/day)				Historical Controls
	0	30	200	1000	
# Fetuses (litters) examined	120 (23)	118 (21)	137 (22)	123 (23)	1813 (327)
Folded retina	0 (0)	0.8 (4.8)	0.7 (4.5)	0 (0)	0 (0)
Umbilical artery descended to the left of the urinary bladder	1.7 (8.7)	0.8 (4.8)	0.7 (4.5)	2.4 (4.3)	0-11.8 (0-41.7)
Right kidney absent	0 (0)	0 (0)	0.7 (4.5)	0 (0)	0 (0)

a Data were obtained from pages 47 and 210 of MRID 45902208.

Table 6c. Selected skeletal findings (% fetuses affected [% litters affected]) [a]

Observations	Dose (mg/kg/day)				Historical Control Range
	0	30	200	1000	
# Fetuses (litters) examined	138 (23)	131 (22)	152 (22)	131 (23)	1991 (327)
Skull frontals incompletely ossified	0.7 (4.3)	3.1 (13.6)	3.3 (9.1)	2.3 (13.0)	0 (0)
contained an interfrontal	5.1 (17.4)	4.7 (18.2)	2.0 (9.1)	1.5 (8.7)	0-34.9 (0-79.2)
Sternal centra: assymetric	0.7 (4.3)	1.6 (9.1)	0 (0)	1.5 (8.7)	0-2.6 (0-15.4)

a Data were obtained from pages 48-51 and 211-212 of MRID 45902208.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that the maternal LOAEL was 200 mg/kg/day based on decreased body weight gain and relative to body liver weight, and increased serum tyrosine, alanine aminotransferase, and calcium. The maternal NOAEL was 30 mg/kg/day. No treatment-related effect was observed on embryo-fetal development. The developmental LOAEL was not observed, and the developmental NOAEL was 1000 mg/kg/day.

B. REVIEWER COMMENTS

1. Maternal toxicity: No treatment-related effect was observed on mortality, clinical signs, body weights, or gross pathology.

A decrease ($p \leq 0.01$) in body weight gain was observed at 1000 mg/kg/day during GD 6-9; all other measured body weight gains in the treated groups (including for the overall study, and overall treatment period) were similar to the controls. Clinical chemistry showed an increased alanine aminotransferase level at a dose-dependent response: 30 (↑15%), 200 (↑26%), and 1000 (↑44%; $p \leq 0.01$) mg/kg/day. An increase ($p \leq 0.05$) of relative liver weights was observed at 1000 mg/kg/day. Although the difference was minor (4.78% treated vs 4.46% controls), it is possible an indicative of hepatotoxicity considered with elevated liver enzyme activities. Serum tyrosine was increased ($p \leq 0.05$) dose-dependently at 30 (↑2-3X) and ≥200 (↑6-10X) mg/kg/day.

BAS 670H is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD); this results in elevated serum tyrosine levels. Currently, it is not known what level of inhibition of the 4-HPPD enzyme results in an adverse effect. Therefore, the observation of elevated serum tyrosine levels due to enzyme inhibition could be considered a biomarker of exposure, not an adverse effect.

The maternal LOAEL is 30 mg/kg/day, based on increased serum tyrosine level. The maternal NOAEL is not established.

2. Developmental toxicity

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

b. Altered Growth: There were no treatment-related effects on growth or development.

c. Developmental Variations: There were not treatment-related developmental variations.

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

The developmental LOAEL was not observed. The developmental NOAEL is 1000 mg/kg/day.

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

C. STUDY DEFICIENCIES: Stability analyses should have been performed on the dose formulation rather than just the test substance in water. This minor deficiency does not affect the conclusions of this study.

DATA FOR ENTRY INTO ISIS

Developmental Study - mouse (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	45902208	developmental	mouse	GD 6-18	oral	gavage	30-1000	0, 30, 200, 1000	Not established	30	Incr. tyrosine level	Maternal
123009	45902208	developmental	mouse	GD 6-18	oral	gavage	30-1000	0, 30, 200, 1000	1000	not observed		Developmental

APPENDIX

28-day Range-Finding Developmental Study in the Mouse

Since this range-finding study was performed to determine adequate dose levels for subsequent studies, only a summary is provided.

In this developmental toxicity study (MRID 45902209), BAS 670H (98.8% a.i., Lot #: N33) was administered daily via oral gavage in a dosing volume of 10 mL/kg to 9 Crl:CD-1®(ICR)BR mice/sex/group at dose levels of 0, 30, 100, 300, or 1000 mg/kg/day (limit dose) on gestation days (GD) 6 through 17. All dams were sacrificed on GD 18, and their fetuses were removed by cesarean section. Hematology and clinical chemistry evaluations were performed on dams, and organs were excised and weighed at necropsy. Blood samples were collected from the fetuses for the examination of serum tyrosine levels, but fetuses were not further examined. No treatment-related effect was observed on mortality, clinical signs, body weights, body weight gains, organ weights, hematology, or gross pathology.

At 1000 mg/kg/day, alanine and aspartate aminotransferase were increased by 102-197%.

The maternal LOAEL is 1000 mg/kg/day, based on increased alanine and aspartate aminotransferase. The maternal NOAEL is 300 mg/kg/day.

No Cesarean section data were reported. There was a treatment-related increase ($p \leq 0.01$) serum tyrosine in all dose groups. The biological significance of this finding is unclear. The fetuses were not evaluated further. Further examination of the fetuses should have been performed to allow the determining of a developmental LOAEL; however, the dams were tested at the limit dose.

A developmental LOAEL could not be determined because no Cesarean section data were provided and fetuses were not examined for external, visceral, or skeletal malformations, variations, or retardations.

The submitted study is classified as **acceptable/non-guideline**.

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