DATA EVALUATION RECORD

BAS 670H

Study Type: Non-guideline Study; Developmental Toxicity Study in Rabbits

Work Assignment No. 1-01-11 N (MRID 45902212)

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DATA EVALUATION RECORD

STUDY TYPE: Non-guideline Study; Prenatal Developmental Toxicity Study - Rabbit

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

TEST MATERIAL (PURITY): BAS 670H (95.2-95.8% a.i.)

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

CITATIONS: Schneider, S., K. Deckardt, and Ravenzwaay, B. (2003) BAS 670H - Prenatal developmental toxicity study in New Zealand white rabbits: oral administration (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen, Germany. Laboratory Project ID: Project No. 40R0124/98148, BASF Registration Document No. 2003/1006258, February 27, 2003. MRID 45902212. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, Research Triangle Park, NC.

EXECUTIVE SUMMARY: The purpose of this study was to compare the effects of two different batches (N17 and N26) of BAS 670H on embryonic and fetal development. In this developmental toxicity study (MRID 45902212), two batches of BAS 670H (Lot/Batch # N17, 95.2% a.i.; Lot/Batch # N26, 95.8% a.i.) in 0.5% (w/v) aqueous carboxymethylcellulose were administered daily by gavage at a dose volume of 10 mL/kg body weight to 25 female New Zealand White [Crl:KBL (NZW)] rabbits/group at dose levels of 0, 1.5, or 5.0 mg/kg on gestation days (GD) 6 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean and examined.

No effects of treatment were observed on maternal survival, clinical signs, body weights, body weight gains, food consumption, or gross pathology. Serum tyrosine levels were increased ($p \leq 0.01$) in both batches at 1.5 mg/kg (incr. 178-243%) and 5.0 mg/kg (incr. 504-563%). No differences were noted between Batches N17 and N26.

The maternal NOAEL was not observed. The maternal LOAEL is 1.5 mg/kg/day based on increased serum tyrosine level.

There were no treatment-related effects on the numbers of litters, fetuses (live or dead), resorptions (early, late or complete litter), or post-implantation loss. There were no treatment-related external, visceral, or skeletal malformations.

Increased incidences of absent kidney and ureter were observed in both batches at 1.5 mg/kg fetuses (0.6-1.6% fetuses; 5.0-8.7% litters) and 5.0 mg/kg fetuses (0.5-1.2% fetuses; 4.5-4.8% litters) compared to concurrent (0) and historical controls (0-0.5% fetuses; 0-4.2% litters). The Batch N26 findings were confined to single fetuses in each litter while the increased incidence in the Batch N17 fetuses was suggestive of a treatment-related finding. Similar findings were observed in another rabbit study (MRID 45902211, Lot/batch # WH 20089, 98.7%) at doses of 50 and 500 mg/kg/day. Therefore, the absent kidney and ureter may be treatment-related. Increased fetal and litter incidences of supernumerary thoracic vertebrae were observed in both batches of 1.5 mg/kg and 5.0 mg/kg fetuses compared to concurrent and historical controls. Increased incidences of supernumerary 13th rib (with cartilage present) were observed in both batches of the 1.5 mg/kg and 5.0 mg/kg fetuses compared to concurrent and historical controls.

Decreased mean fetal weight were observed in both batches at 1.5 and 5.0 mg/kg/day; however, statistical significance was achieved in the batch 26 only at 5.0 mg/kg/day. Increased incidences of incomplete ossification of the cervical centrum (with unchanged cartilage) was observed in the 5.0 mg/kg fetuses of both batches compared to concurrent and historical controls. Increased incidences of incomplete ossification of the hyoid bone (with cartilage present) were observed in the 5.0 mg/kg fetuses of both batches compared to concurrent and historical controls.

Under the condition of this study, no significant differences were noted between Batches N17 and N26 in maternal and developmental toxicities.

The developmental LOAEL is 1.5 mg/kg/day based on increased incidence of absent kidney and ureter and increased incidence of supernumerary thoracic vertebrae and supernumerary 13th rib. The developmental NOAEL was not established.

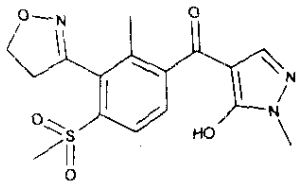
This study is classified as **acceptable/non-guideline**.

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
Lot/Batch #:	N17, N26
Purity:	95.2% a.i.; 95.8% a.i.
Compound Stability:	Batch N26: stable suspended in water for up to 7 days (room temperature or refrigerated)
CAS #of TGAI:	210631-68-8
Structure:	

2. Vehicle and/or positive control: 0.5% (w/v) aqueous carboxymethylcellulose

3. Test animals:

Species:	Rabbit	
Strain:	New Zealand White [Crl:KBL (NZW)]	
Age/body weight range on GD 1:	Approximately 18-19 weeks/2837-4500 g	
Source:	Elevage Scientifique des Dombes, Châtillon/Chalaronne, France	
Housing:	Individually in stainless steel wire mesh cages	
Diet:	Pelleted Kliba maintenance diet type 3418 for rabbits (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	Not provided
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	At least 5 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates: Start: 09/02/2001 End: 10/04/2001

2. Purpose: The purpose of this study was to compare the effects of 2 different batches of BAS 670H on embryonic and fetal development.

3. Mating: The females were naturally mated with breeder male rabbits of the same strain by the supplier prior to shipment. The day of insemination was designated as gestation day (GD) 0. Rabbits were shipped on GD 0 and arrived at the performing laboratory on GD 1.

4. Animal assignment: After arrival, does were randomly assigned to the treatment groups (stratified by body weight), as indicated in Table 1.

Table 1. Animal assignment [a]

Dose (mg/kg bw/day)	0	1.5		5.0	
Batch #	NA	N17	N26	N17	N26
# Females	25	25	25	25	25

a Data obtained from page 20 of the study report (MRID 45902212).
NA Not applicable

5. Dose selection rationale: It was stated that for comparison purposes, doses of 1.5 and 5.0 mg/kg/day were sufficient to compare the effects of 2 different batches of BAS 670H. No other information regarding dose selection was provided.

6. Dosage preparation and analysis: It was stated that dosing solutions were prepared at the beginning of the study and thereafter at a frequency depending on their stability; however, the precise frequency of preparation was not provided. For each dose group, an appropriate amount of test substance (N17 and N26) was suspended in (doubly-distilled) aqueous 0.5% (w/v) carboxymethylcellulose using a high-speed laboratory homogenizer and stirred during dosing. Homogeneity was confirmed by analyses of three samples (top, middle, and bottom) for all dose formulations prepared for use on the first day of treatment; concentration was confirmed by analysis of samples for all dose formulations prepared for use at the beginning and near the end of treatment. For stability analysis, the test substance (N26) was suspended at a concentration of 0.1 mg/L in water having different purities (referred to as tap, M4, OECD, and superpure) and stored for 0, 1, or 7 days at room temperature or refrigerated. Stability data in carboxymethylcellulose was not provided.

Results -

Homogeneity (range as % CV): 92.4-104.0% of nominal, C.V. =1.0-2.2%

Stability (range as % of nominal value):
0 days at room temperature: 96.2-102.2%
0 days refrigerated: 96.2-102.2%
1 day at room temperature: 98.8-100.4%
1 day refrigerated: 99.8-101.1%
7 days at room temperature: 100.3-103.1%
7 days refrigerated: 102.3-103.8%

Concentration (range as % nominal): 92.4-104.0%

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.

7. **Dosage administration:** All doses were administered once daily by oral gavage, on GDs 6-28, in a volume of 10 mL/kg of body weight. Dosing was based on the most recent individual body weight determined prior to gavage. Rabbits were dosed in an ascending dose order at approximately the same time each day.

C. OBSERVATIONS

1. **Maternal observations and evaluations:** All does were checked for mortality and morbidity twice daily (once daily on weekends or holidays), and for clinical signs of toxicity at least once per day. Body weights were measured on GD 1, 4, 6, 9, 11, 14, 16, 19, 21, 23, 25, 28, and at sacrifice. Body weight gains were calculated for each of the intervals between body weight measurements. Additionally, body weight gains corrected for gravid uterine weights were calculated for GD 6-29. Food consumption (g/rabbit/day) was measured daily on GD 2-29. Blood samples were collected from all surviving animals prior to sacrifice on GD 29 for analysis of BAS 670H and tyrosine levels in the serum. On GD 29, surviving does were killed by an intravenous injection of pentobarbital, the uteri excised and weighed, and all fetuses were removed by cesarean section. The numbers of corpora lutea, and the number and distribution of live and dead fetuses, resorptions (early and late), and implantation sites were recorded. Also, does that died or were sacrificed prematurely were examined according to the same procedures as those sacrificed on schedule, except that gravid uterine weights were not determined. All rabbits were necropsied and the condition of the placentae, umbilical cords, fetal membranes, and fluids were examined. Individual placental weights were recorded.

2. **Fetal evaluations:** On removal from the uterus, all fetuses were weighed and given a detailed external examination. Live fetuses were killed by a subcutaneous injection of pentobarbital, dissected for visceral examination, and sexed. The heads of approximately one half of the fetuses (and fetuses having severe external findings of the head) were removed, fixed in Bouin's solution, and assessed by Wilson's method. These heads were subsequently discarded. After skinning, all fetuses were fixed in ethyl alcohol, and a cross sectional cut was made in the heads of the intact fetuses. The brain was examined, then the carcasses were stained according to a modification of the method of Kimmel and Trammel, and a detailed examination of the skeletal bone and cartilage was performed.

D. DATA ANALYSIS

1. **Statistical analyses:** Data were subjected to the following statistical procedures:

Parameter	Statistical test
Body weight, body weight gains (uncorrected and corrected), food consumption, gravid uterus weight, numbers of corpora lutea, implantations, resorptions, and live fetuses, proportions of pre-implantation losses, post-implantation losses, resorptions, and live fetuses in each litter, litter mean fetal body weight, and litter mean placental weight	Dunnett's test (two-sided)
Mortality (does), # does pregnant at sacrifice, and number of litters with fetal findings	Fisher's exact test (one-sided)
Proportion of fetuses with malformations, variations, or unclassified observations	Wilcoxon's test (one-sided)
Serum tyrosine	Kruskal-Wallis test (two-sided), followed by Wilcoxon's test (two-sided) if significance achieved

Significance was denoted at $p \leq 0.05$ or $p \leq 0.01$ for each comparison.

2. **Indices**: The following indices were calculated from the cesarean data:

Conception rate (%) = # of pregnant females/# of fertilized animals x 100

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

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

3. **Historical control data**: Historical control data were provided for maternal body weight, cesarean parameters and external, visceral, and skeletal findings in the fetuses. Data were comprised of 3 studies on 29-77 does and 73 litters of the same strain.

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical observations**: Mortality observations are shown in Table 2. There were no treatment-related deaths or clinical signs of toxicity. One control doe, one 1.5 mg/kg Batch N17 doe, and two 1.5 mg/kg Batch N26 does were found dead, and one 1.5 mg/kg Batch N17 female died after a gavage error. Two control females, two 1.5 mg/kg Batch N26 females, and one 5.0 mg/kg female from each of Batches N17 and N26 were sacrificed after abortion. No clinical signs were observed in any of these animals prior to death, and the incidences of mortality and abortion were unrelated to dose; therefore, these deaths and abortions are considered spontaneous and not treatment-related. There were no other deaths.

Table 2. Maternal clinical observations[a]

Observation	Dose (mg/kg/day)				
	0	1.5		5.0	
Batch #	NA	N17	N26	N17	N26
Found dead	1	1	2	0	0
Died after gavage error	0	1	0	0	0
Sacrificed after abortion	2	0	2	1	1

a Data obtained from pages 34 and 57-58 of the study report (MRID 45902212).
NA Not applicable

2. **Body weight**: Body weight gain data are shown in Table 3. No treatment-related effects were observed on body weights, body weight gains, gravid uterus weights, or overall body weight gains from GD 6, either uncorrected or corrected for gravid uterus weights. Increases ($p \leq 0.05$) in body weight gains were observed in the 1.5 mg/kg Batch N26 and 5.0 mg/kg Batch N17 does on GD 21-23 (↑663%), but these increases were incidental and not dose-dependent.

Table 3. Mean (±SD) maternal body weight (BW) and body weight gain (BWG) (g)[a]

Interval	Dose in mg/kg bw/day (# of Does)				
	0	1.5		5.0	
Batch #	NA (n=21-24)	N17 (n=23-24)	N26 (n=23-24)	N17 (n=21-25)	N26 (n=22-23)
BW: GD 1	3389±321.8	3374±327.3	3444±311.6	3355±362.8	3521±351.4
BW: GD 6	3526±298.0	3572±333.3	3673±297.5	3578±350.1	3753±347.6
BW: GD 28	3924±230.1	3921±327.1	4030±246.4	3929±325.7	4045±357.4
BWG: GD 1-6	236.4±92.94	198.1±64.75	229.1±124.50	223.4±100.58	232.6±67.90
BWG: GD 6-28	290.5±214.14	356.5±157.99	376.2±189.18	357.4±247.72	318.3±245.46
BWG: GD 21-23	5.6±52.6	24.4±38.5	42.7±34.9*	42.7±54.4*	33.1±61.5
BWG Overall: GD 1-29	545.4±254.06	579.1±188.99	621.2±242.91	595.4±272.59	561.8±276.48
Gravid uterus (g)	427.0±101.56	454.2±124.14	413.7±130.02	399.7±110.58	444.0±135.51
Carcass[b](g)	3511.5±245.07	3489.8±276.12	3638.7±253.46	3547.7±338.42	3616.1±349.40
Net change: GD 6-29[c]	-122.3±203.90	-74.5±182.00	-14.9±218.47	-23.9±288.43	-114.5±249.59

a Data obtained from pages 67-68 of the study report (MRID 45902212).
b Carcass = terminal body weight - gravid uterine weight
c Net weight change = carcass - GD 6 body weight
NA Not applicable

3. **Food consumption**: No treatment-related effect was observed on food consumption. An increase ($p \leq 0.05$) was observed in the 5.0 mg/kg Batch N26 females during GD 19-20 (↑37%), but this increase was isolated and not considered treatment-related.

4. Serum BAS 670H and tyrosine levels: Serum samples were taken approximately 24 hours after the last dose. Serum levels of BAS 670H and tyrosine are shown in Table 4. Dose-dependent increases (not significant) in serum concentrations of the test substance were observed: however, no differences were noted between batches. Serum tyrosine levels were dose-dependently increased ($p \leq 0.01$) at 1.5 mg/kg (↑178-243%) and 5.0 mg/kg (↑504-563%); however, no differences were noted in serum tyrosine levels as a function of batch group.

Table 4. Maternal serum levels of BAS 670H and tyrosine[a]

Parameter	Dose (mg/kg/day)				
	0	1.5		5.0	
Batch #	NA	N17	N26	N17	N26
BAS 670H (µg/g)	0.0±0.0	0.0164±0.0088	0.0199±0.0113	0.0485±0.0220	0.0498±0.0436
Tyrosine (µmol/L)	52.60±4.38	146.04±29.29** (↑178)	180.60±47.06** (↑243)	348.85±164.55** (↑563)	317.91±120.49** (↑504)

a Data obtained from pages 109-110 and 333 of the study report (MRID 45902212). Percent differences from controls, calculated by reviewers, are included in parentheses.
** Significantly different from controls; $p \leq 0.01$
NA Not applicable

5. Gross pathology: No treatment-related macroscopic findings were observed in any group.

6. Cesarean section data: Cesarean section data are presented in Table 5. Decreases ($p \leq 0.05$) in mean fetal body weight were observed in the male (↓12%), female (↓8%; not significant), and in combined both sexes (↓10%) at 5.0 mg/kg (Batch N26) fetuses. Decreased fetal weight also was observed in the Batch 17 (Not statistically significant) at 5 mg/kg/day. One doe in the 1.5 mg/kg Batch N26 group and one doe in each of the 5.0 mg/kg groups had a complete litter resorption, but these findings were considered spontaneous. One 1.5 mg/kg Batch N26 doe had late resorptions and 4 dead fetuses, but this finding was incidental and not dose-dependent. No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early or late), placental weight, sex ratio, or post-implantation loss.

Table 5. Cesarean section observations[a]

Observation	Dose (mg/kg bw/day)				
	0	1.5		5.0	
Batch #	NA	N17	N26	N17	N26
# Animals Assigned (Mated)	25	25	25	25	25
# Animals Pregnant	24	25	25	24	23
Pregnancy Rate (%)	96	100	100	96	92
# Nonpregnant[b]	1	0	0	1	2
Maternal Wastage					
# Died	3	2	4	1	1
# Died Pregnant	1	2	2	0	0
# Died Nonpregnant	0	0	0	0	0
# Aborted	2	0	2	1	1
# Premature Delivery	0	0	0	0	0
Total # Corpora Lutea Corpora Lutea/Doe	200 9.5±1.44	211 9.2±1.67	204 9.7±1.82	194 8.4±2.33	209 9.5±2.30
Total # Implantations (Implantations/Doe)	183 8.7±1.76	203 8.8±1.83	183 8.7±2.15	185 8.0±2.33	198 9.0±2.37
Total # Litters	21	23	21	23	22
Total # Live Fetuses (Live Fetuses/Doe)	158 7.5±2.23	188 8.2±2.52	150 7.9±2.35	165 7.5±1.60	182 8.7±1.71
Total # Dead Fetuses (Dead Fetuses/Doe)	1 0.0±0.2	0 0.0±0.0	4 0.2±0.9	0 0.0±0.0	0 0.0±0.0
Total # Resorptions	24	15	29	20	16
Early	21	8	20	12	11
Late	3	7	9	8	5
Total Resorptions/Doe	1.1±2.20	0.7±1.37	1.4±2.18	0.9±1.22	0.7±0.98
Early	1.0±2.14	0.3±0.65	1.0±2.06	0.5±0.79	0.5±0.86
Late	0.1±0.48	0.3±1.26	0.4±1.16	0.3±0.65	0.2±0.61
Complete Litter Resorption	0	0	1	1	1
Mean Fetal Weight (g)/litter	40.4±5.72	39.2±4.08	39.0±6.47	38.3±3.79	36.4±4.14* (↓10)
Males	40.5±6.66	39.3±4.54	38.3±6.86	38.6±4.34	35.7±4.83* (↓12)
Females	39.9±5.61	39.0±4.40	39.3±6.97	38.1±4.03	36.9±4.36 (↓8)
Mean Placental Weight (g)/litter	5.4±0.98	5.3±0.68	5.2±0.87	5.1±0.68	5.1±0.67
Males	5.4±1.02	5.4±0.75	5.0±0.84	5.2±0.89	5.0±0.78
Females	5.3±1.03	5.2±0.73	5.3±0.96	5.1±0.61	5.2±0.75
Sex Ratio (Mean % Male)	55.1	46.3	48.7	50.3	53.8
Pre-implantation Loss (%)	8.7±10.99	4.0±8.11	10.2±17.11	4.9±10.01	6.1±11.95
Post-implantation Loss (%)	12.5±21.03	8.5±18.96	17.9±29.28	11.8±21.84	10.9±22.03

a Data obtained from pages 72-75 and 165-169 of the study report (MRID 45902212).
b Calculated by reviewers from data presented in this table
NA Not applicable

B. DEVELOPMENTAL TOXICITY

1. **External examination:** External abnormalities are presented in Table 6a. One fetus in the 5.0 mg/kg Batch N26 group showed ectrodactyly (0.5% fetuses; 4.8% litters), this fetus also showed additional skeletal malformations (absent phalanx). Other observations included macroglossia in the 1.5 mg/kg Batch N26 fetuses (1.3% fetuses; 5.0% litters) and 5.0 mg/kg Batch N26 fetuses (0.5% fetuses; 4.8% litters) compared to 0 concurrent and historical controls. Cleft palate was noted in the 1.5 mg/kg fetuses (0.5-0.6% fetuses; 4.3-5.0% litters), and the 5.0 mg/kg Batch N26 fetuses (0.5% fetuses; 4.8% litters) compared to 0 concurrent and historical controls. These findings occurred without a consistent pattern and dose-response relationship and were considered not treatment-related.

2. **Visceral examination:** Selected visceral abnormalities are presented in Table 6b. Increased incidences of absent kidney and ureter were observed in both batches at 1.5 mg/kg fetuses (0.6-1.6% fetuses; 5.0-8.7% litters) and 5.0 mg/kg fetuses (0.5-1.2% fetuses; 4.5-4.8% litters) compared to concurrent (0) and historical controls (0-0.5% fetuses; 0-4.2% litters). The Batch N26 findings were confined to single fetuses each and the increased incidence in the Batch N17 fetuses was suggestive of a treatment-related finding. Small spleen was observed in the 5.0 mg/kg Batch N17 fetuses (4.8% fetuses; 4.5% litters) compared to concurrent (0) and historical controls (0-0.9% fetuses; 0-4.2% litters); however, all of these fetuses came from a single litter. Therefore, this finding is not considered to be related to treatment. Muscular ventricular septum defect and malpositioned kidney, malformations, were each noted in one 5.0 mg/kg Batch N17 fetus (0.6% fetuses; 4.5% litters) compared to 0 concurrent and historical controls, but these findings were considered incidental. All other visceral malformations were unrelated to dose.

Pale kidney was observed in the 5.0 mg/kg Batch N17 fetuses (0.6% fetuses; 4.5% litters) compared to 0 concurrent controls; however this finding fell below the range of historical controls (1.3-1.7% fetuses; 9.5-14.3% litters). Cyst in the thoracic cavity was noted in a single 5.0 mg/kg Batch N26 fetus (0.5% fetuses; 4.8% litters); therefore, this finding was considered incidental. All other visceral findings were unrelated to dose.

3. **Skeletal examination:** Selected skeletal abnormalities are presented in Table 6c. Severely malformed vertebral column and/or ribs and short rib (with discontinuous cartilage) were each observed in single 5.0 mg/kg Batch N17 fetuses (0.6% fetuses; 4.5% litters) compared to 0 concurrent and historical controls. Absent phalanx, a malformation, was noted in one 5.0 mg/kg Batch N26 fetus (0.5% fetuses; 4.8% litters) compared to 0 concurrent and historical controls. All of these malformations were considered incidental. All other skeletal malformations were unrelated to dose.

Increased fetal (not significant) and litter ($p \leq 0.05$) incidences of the following treatment-related variations were observed in both batches: (i) supernumerary thoracic vertebrae in the 1.5 mg/kg (46.0-55.0% fetuses; 87.0-90.0% litters) and 5.0 mg/kg (64.0-81.0% fetuses; 90.0-100% litters) fetuses compared to concurrent (21.0% fetuses; 57.0% litters) and historical (21.4-30.4% fetuses; 57.1-92.9% litters) controls; (ii) supernumerary 13th rib (with cartilage present) in the 1.5 mg/kg Batch N26 (71.0% fetuses; 90.0% litters) and 5.0 mg/kg (87.0-94.0% fetuses; 100% litters)

fetuses compared to concurrent (45.0% fetuses; 81.0% litters) and historical (62.3-81.7% fetuses; 85.7-96.4% litters) controls; (iii) incomplete ossification of the cervical centrum (with unchanged cartilage) in the 5.0 mg/kg fetuses (16.0-21.0% fetuses; 52.0-77.0% litters) compared to concurrent (6.9% fetuses; 29.0% litters) and historical (2.1-12.6% fetuses; 12.5-64.3% litters) controls; and (iv) incomplete ossification of the hyoid bone (with cartilage present) in the 5.0 mg/kg fetuses (30.0-32.0% fetuses; 86.0-100% litters) compared to concurrent (23.0% fetuses; 62.0% litters) and historical (21.1-27.8% fetuses; 61.9-92.9% litters) controls.

Increased incidence of incomplete ossification of the supraoccipital bone (with unchanged cartilage) was observed in the 5.0 mg/kg Batch N26 fetuses (3.3% fetuses; 19.0% litters) compared to concurrent controls (1.3% fetuses; 9.5% litters). However, these values fell within the range of historical controls (0.5-9.1% fetuses; 4.2-57.1% litters), and were not considered treatment-related. Incomplete ossification of the interparietal bone (with unchanged cartilage) was noted in the 1.5 mg/kg Batch N26 fetuses (2.4% fetuses; 18.0% litters) and the 5.0 mg/kg fetuses (2.6-5.5% fetuses; 20.0-24.0% litters) compared to concurrent controls (1.3% fetuses; 9.5% litters). These findings fell within the range of the historical controls (0.9-4.6% fetuses; 7.1-29.2% litters), and were not considered treatment related. Incomplete ossification of the metacarpals was noted in the 5.0 mg/kg fetuses (0.6-1.6% fetuses; 4.5-4.8% litters) compared to 0 concurrent and historical controls; unossified talus was observed in the 1.5 mg/kg Batch N26 fetuses (0.6% fetuses; 5.0% litters) and the 5.0 mg/kg fetuses (0.6-1.6% fetuses; 4.5-4.8% litters) compared to concurrent (0) and historical (0-0.5% fetuses; 0-4.2% litters) controls. Both of these findings were considered incidental. All other skeletal variations were unrelated to dose.

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

Observations	Dose (mg/kg bw/day)					Historical controls[b]
	0	1.5		5.0		
Batch #	NA	N17	N26	N17	N26	
# Fetuses (# litters) examined	159 (21)	188 (23)	154 (20)	165 (22)	182 (21)	601 (73)
Malformations						
Ectrodactyly	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.8)	Not observed
Macroglossia	0 (0)	0 (0)	1.3 (5.0)	0 (0)	0.5 (4.8)	Not observed
Cleft palate	0 (0)	0.5 (4.3)	0.6 (5.0)	0 (0)	0.5 (4.8)	Not observed
Anasarca	0.6 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0-0.6 (0-4.8)
Open eye	0 (0)	0.6 (4.3)	0 (0)	0 (0)	0 (0)	0-0.5 (0-4.2)
Meningocele	0 (0)	0 (0)	0.6 (5.0)	0 (0)	0 (0)	Not observed
Spina bifida	0 (0)	1.1 (8.7)	0.6 (5.0)	0 (0)	0 (0)	0-0.5 (0-4.2)
Total malformations	0.6 (4.8)	2.1 (17.0)	2.6 (10.0)	0 (0)	1.6 (14.0)	0.6-1.3 (4.8-8.3)
Variations						
Paw hyperflexion	0.6 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0-0.6 (0-4.8)
Total variations	0.6 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0-0.6 (0-4.8)
Unclassified						
Polyhydramnios	0.6 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0-0.6 (0-4.8)
Umbilical cord interrupted	0.6 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0-0.6 (0-4.8)
Total unclassified	0.6 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0.6-2.8 (3.6-4.8)

a Data obtained from pages 77-81 in the study report (MRID 45902212).
b Historical control data obtained from page 341-343 in the study report.
NA Not applicable

Table 6b. Selected visceral abnormalities [% fetuses affected (% litters affected)][a]

Observations	Dose (mg/kg bw/day)					Historical controls[b]
	0	1.5		5.0		
Batch #	NA	N17	N26	N17	N26	
#Fetuses (# litters) examined	159 (21)	188 (23)	154 (20)	165 (22)	182 (21)	601 (73)
Malformations						
Absent kidney	0 (0)	1.6 (8.7)	0.6 (5.0)	1.2 (4.5)	0.5 (4.8)	0-0.5 (0-4.2)
Absent ureter	0 (0)	1.6 (8.7)	0.6 (5.0)	1.2 (4.5)	0.5 (4.8)	0-0.5 (0-4.2)
Small spleen	0 (0)	0 (0)	0 (0)	4.8 (4.5)	0 (0)	0-0.9 (0-4.2)
Muscular ventricular septum defect	0 (0)	0 (0)	0 (0)	0.6 (4.5)	0 (0)	Not observed
Malpositioned kidney	0 (0)	0 (0)	0 (0)	0.6 (4.5)	0 (0)	Not observed
Total malformations	1.3 (9.5)	1.6 (8.7)	1.3 (10.0)	7.3 (14.0)	1.1 (9.5)	1.3-2.4 (9.5-16.7)
Unclassified						
Pale kidney	0 (0)	0 (0)	0 (0)	0.6 (4.5)	0 (0)	1.3-1.7 (9.5-14.3)
Cyst in thoracic cavity	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.8)	Not observed
Total unclassified	6.3 (43.0)	3.7 (22.0)	3.9 (15.0)	4.2 (32.0)	3.3 (24.0)	1.7-6.3 (14.3-42.9)

a Data obtained from pages 83-90 in the study report (MRID 45902212).
b Historical control data obtained from page 344-346 in the study report.
NA Not applicable

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

Observations	Dose (mg/kg bw/day)					Historical controls[b]
	0	1.5		5.0		
Batch #	NA	N17	N26	N17	N26	
#Fetuses (# litters) examined	159 (21)	188 (23)	154 (20)	165 (22)	182 (21)	583 (73)
Malformations						
Severely malformed vertebral column and/or ribs	0 (0)	0 (0)	0 (0)	0.6 (4.5)	0 (0)	Not observed
Short rib (discontinuous cartilage)	0 (0)	0 (0)	0 (0)	0.6 (4.5)	0 (0)	Not observed
Absent phalanx	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.8)	Not observed
Total malformations	2.5 (14.0)	1.6 (13.0)	2.6 (20.0)	1.2 (9.1)	2.7 (24.0)	2.2-5.2 (14.3-33.3)
Variations						
Supernumerary thoracic vertebrae	21.0 (57.0)	46.0 (87.0)*	55.0 (90.0)*	81.0 (100)**	64.0 (90.0)*	21.4-30.4 (57.1-92.9)
Supernumerary 13th rib (cartilage present)	45.0 (81.0)	58.0 (100)*	71.0 (90.0)	94.0 (100)*	87.0 (100)	62.3-81.7 (85.7-96.4)
Incomplete ossification of cervical centrum (unchanged cartilage)	6.9 (29.0)	11.0 (48.0)	8.4 (40.0)	21.0 (77.0)**	16.0 (52.0)	2.1-12.6 (12.5-64.3)
Incomplete ossification of hyoid (cartilage present)	23.0 (62.0)	27.0 (78.0)	24.0 (70.0)	30.0 (86.0)	32.0 (100)**	21.1-27.8 (61.9-92.9)
Incomplete ossification of supraoccipital (unchanged cartilage)	1.3 (9.5)	0.5 (4.3)	0.6 (5.0)	0.6 (4.5)	3.3 (19.0)	0.5-9.1 (4.2-57.1)
Incomplete ossification of interparietal (unchanged cartilage)	1.3 (9.5)	0 (0)	2.6 (20.0)	2.4 (18.0)	5.5 (24.0)	0.9-4.6 (7.1-29.2)
Incomplete ossification of metacarpal (cartilage present)	0 (0)	0 (0)	0 (0)	0.6 (4.5)	1.6 (4.8)	Not observed
Unossified talus (cartilage present)	0 (0)	0 (0)	0.6 (5.0)	0.6 (4.5)	1.6 (4.8)	0-0.5 (0-4.2)
Total variations	88.0 (100)	93.0 (100)	97.0 (100)	99.0 (100)	99.0 (100)	88.1-95.7 (100)

a Data obtained from pages 91-107 in the study report (MRID 45902212).
b Historical control data obtained from pages 347-352 in the study report.
* Significantly different from controls, $p \leq 0.05$
** Significantly different from controls, $p \leq 0.01$
NA Not applicable

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: No significant difference was noted between batches N17 and N26 of BAS 670H in terms of maternal and prenatal developmental toxicity. Neither batch caused maternal toxicity at doses of 1.5 and 5 mg/kg body weight. Both batches at both doses slightly influenced ossification, particularly of the thoracic/lumbar vertebral column. No teratogenic potential was noted for batch N26. A slight elevation in the number of fetuses with unilaterally absent kidneys was observed in Batch N17 at both doses compared to Batch N26. Although this finding was not clearly dose-related, an effect of this batch cannot be excluded with certainty.

B. REVIEWER COMMENTS

1. **Maternal toxicity:** No effects of treatment were observed on maternal survival, clinical signs, body weights, body weight gains, food consumption, or gross pathology. Serum tyrosine levels were increased ($p \leq 0.01$) in both batches at 1.5 mg/kg (↑178-243%) and 5.0 mg/kg (↑504-563%), but were not considered adverse due to the lack of corroborating evidence. No differences were noted between Batches N17 and N26 regarding elevated tyrosine level.

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 NOAEL was not observed. The maternal LOAEL is 1.5 mg/kg/day based on increased serum tyrosine level.

2. **Developmental toxicity:**

a. Deaths/Resorptions: There were no treatment-related effects on the numbers of litters, fetuses (live or dead), resorptions (early, late or complete litter), or post-implantation loss.

b. Altered Growth: Decreased mean fetal weight were observed in both batches at 1.5 and 5.0 mg/kg/day; however, statistical significance was achieved in the batch 26 only at 5.0 mg/kg/day. Decreases ($p \leq 0.05$) in mean fetal weight were observed in the male (↓12%), female (↓8%; not significant), and combined sexes (↓10%) 5.0 mg/kg Batch N26 fetuses. Decreased fetal weights were also observed in the Batch N17 animals but did not show statistically significant. Incomplete ossification of the cervical centrum (with unchanged cartilage) was increased in the 5.0 mg/kg fetuses compared to concurrent and historical controls. Incomplete ossification of the hyoid bone (with cartilage present) was increased in the 5.0 mg/kg fetuses compared to concurrent and historical controls.

c. Developmental Variations: Increased incidences of absent kidney and absent ureter were observed in both batches in the 1.5 mg/kg fetuses (0.6-1.6% fetuses; 5.0-8.7% litters) and the 5.0 mg/kg fetuses (0.5-1.2% fetuses; 4.5-4.8% litters) compared to concurrent (0) and historical controls (0-0.5% fetuses; 0-4.2% litters). The Batch N26 findings were confined to single fetuses each while the increased incidence in the Batch N17 fetuses was suggestive of a treatment-related finding. Similar findings were observed in another rabbit study (MRID 45902211, Lot/batch # WH 20089, 98.7%) at doses of 50 and 500 mg/kg/day but not observed at 5 mg/kg/day. Therefore, the absent kidney and ureter may be treatment-related. Increased fetal and litter incidences of supernumerary thoracic vertebrae were observed in the 1.5 mg/kg and 5.0 mg/kg fetuses compared to concurrent and historical controls. Increased incidence of supernumerary 13th rib (with cartilage present) was observed in both batches at 1.5 mg/kg and 5.0 mg/kg fetuses compared to concurrent and historical controls. However, these variations were not observed at higher doses in the definitive study (MRID 45902210).

d. Malformations: There were no treatment-related external, visceral, or skeletal malformations.

The developmental LOAEL is 1.5 mg/kg/day based on increased incidence of absent kidney and ureter and supernumerary thoracic vertebrae and supernumerary 13th rib. The developmental NOAEL was not established. There was no evidence of teratogenicity.

Based on results of this study, no significant difference between Batch 17 and 26 of BAS 670H were observed regarding maternal and developmental toxicity.

This study is classified as **acceptable/non-guideline.**

C. **STUDY DEFICIENCIES:** The following minor deficiencies were noted but do not alter the conclusions of this DER:

- A dose selection rationale was not provided.
- Stability data were not provided for the test compound in the vehicle