DATA EVALUATION RECORD

BAS 670H

Study Type: §83-3b; Developmental Toxicity Study in Rabbits

Work Assignment No. 1-01-11 L (MRID 45902210)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Michael E. Viana, Ph.D.

Signature: Michael E Viana
Date: 1/29/04

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W. Allran
Date: 01-29-04

Project Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 1/29/04

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 1/29/04

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Yung G. Yang, Ph.D. **Signature:**
Toxicology Branch, Health Effects Division (7509C) **Date** 7/26/05
EPA Work Assignment Manager: P. V. Shah, Ph.D. **Signature:**
Registration Action Branch 1, Health Effects Division (7509C) **Date** 7/27/05
PMRA Reviewer: Michael Honeyman **Signature:**
Fungicide and Herbicide Toxicological Evaluation Section, Health Evaluation Division **Date** 8/30/05

Template version 11/01

TXR#: 0052097

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity - Rabbit; OPPTS 870.3700b; 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

CITATIONS: Barnett, J. F. (2003) A definitive oral developmental toxicity (embryo-fetal toxicity/teratogenicity) study with BAS 670H in rabbits. Argus Research Laboratories, Inc., Horsham, PA. Laboratory Project ID: Project No. 40R0124/989167, BASF Registration Document No. 2003/1006256, March 13, 2003. MRID 45902210. Unpublished.

SPONSOR: BASF Aktiengesellschaft, Carl-Bosch-Strasse 38, D-67056 Ludwigshafen, Germany

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45902210), BAS 670H (95.8% a.i.; Lot/Batch # N26) in 0.5% (w/v) aqueous carboxymethylcellulose was administered by gavage at a dose volume of 10 mL/kg body weight to female New Zealand White [Hra:(NZW)SPF] rabbits (25/dose) at dose levels of 0, 0.5, 5, 50, or 450 mg/kg/day on gestation days (GD) 6 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean and examined.

There were no treatment-related effects on maternal survival, body weight, or gross pathology. Increased incidence and frequency of scant and tan feces were observed at 450 mg/kg/day. Decreased body weight gains (58%, $p \leq 0.01$) were observed on GD 20-24; the decrease was attributed to decreased gravid uterine weights (22%, $p \leq 0.01$). Decreased absolute food consumption was observed on GD 6-10 (5%, $p \leq 0.01$) and GD 10-29 (4-17%, not significant, NS) and throughout treatment (GD 6-29). Relative food consumption was decreased (NS) 4-15% on GD 6-29 and 8% throughout treatment. Increased serum tyrosine levels (≥127-570%) were observed in all treated groups (≥0.5 mg/kg/day).

For maternal toxicity, the LOAEL is 0.5 mg/kg/day based on increased serum tyrosine level The maternal NOAEL was not established.

For developmental toxicity, decreased litter weights (9-13%. $p \leq 0.05$) were observed at ≥50 mg/kg; fetal body weights were decreased in both sexes at 50 mg/kg (↓7-8%; NS) and 450 mg/kg (↓12%; $p \leq 0.05$). There were no treatment-related external, visceral, skeletal variations or malformations. Increased ($p \leq 0.01$) mean thoracic vertebrae ossification sites were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. Decreased ($p \leq 0.01$) mean lumbar vertebrae ossification sites were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. Increased ($p \leq 0.01$) mean caudal vertebrae ossification sites were observed in the 5 (NS), 50, and 450 mg/kg groups compared to concurrent controls. Increased ($p \leq 0.05$) mean number of pairs of ribs were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. All of these observations fell outside the range of historical controls and were considered treatment-related.

The developmental LOAEL is 5 mg/kg/day based on alterations in skeletal ossification sites and increased number of pairs of ribs. The developmental NOAEL is 0.5 mg/kg/day.

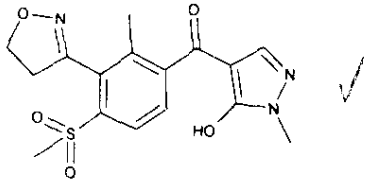
This study is classified **acceptable/guideline (OPPTS 870.3700b)** and satisfies the requirements for a developmental study in the rabbit.

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:	Brown powder
Lot/Batch #:	N26
Purity:	95.8% a.i.
Compound Stability:	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 [Hra:(NZW)SPF]	
Age/body weight range on GD 0:	Approximately 7 months/2.8-4.4 kg	
Source:	Covance Research Products, Inc. (Denver, PA)	
Housing:	Individually in stainless steel cages	
Diet:	Certified Rabbit Chow® #5322 (PMI Nutrition International, St. Louis, MO), 150 g daily until GD 6, then 180-185 g daily	
Water:	Reverse osmosis deionized tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	16-22°C
	Humidity:	30-70%
	Air changes:	Minimum of 10/hour
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	1-5 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates: Start: November 11, 2000 End: December 8, 2000

2. Mating: The females were naturally mated with breeder male rabbits of the same strain by the supplier prior to shipment. Rabbits were mated on 5 consecutive days and shipped on gestation day (GD) 1, 2, 3, 4, or 5. The day of insemination was designated as GD 0.

3. Animal assignment: After arrival, does were randomly assigned (stratified by GD 0 body weight) to the treatment groups, as indicated in Table 1.

Table 1. Animal assignment [a]

Dose (mg/kg bw/day)	0	0.5	5	50	450
# Females	25	25	25	25	25

a Data obtained from page 18 of the study report (MRID 45902210).

4. Dose selection rationale: No dose selection rationale was provided. However, in a developmental toxicity study (MRID 46020301) submitted concurrently with this MRID, BAS 670H in 0.5% (w/v) aqueous carboxymethylcellulose was administered daily by oral gavage at a dose volume of 10 mL/kg body weight to 30 female New Zealand White rabbits/group at dose levels of 0, 5, 50, or 450 mg/kg on gestation days (GD) 7 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean and examined.

There were no effects of treatment on maternal survival, clinical signs of toxicity, body weights, body weight gains, food consumption, or gross pathology. No effects of treatment were noted on numbers of litters, number of live fetuses per doe, resorptions (early or late), fetal weight, placental weight, sex ratio, or postimplantation loss.

The maternal LOAEL was not observed. The maternal NOAEL was 450 mg/kg/day.

There were no dead fetuses and no treatment-related effects on early, late, or complete litter resorptions.

For developmental toxicity, the following findings were increased over concurrent and historical controls at 5, 50, and 450 mg/kg: (i) fluid-filled abdomen; (ii) pale liver; (iii) dark content of the stomach and intestines; (iv) unilateral ossification or incomplete ossification (with unchanged cartilage) of the centrum of the cervical vertebrae; (v) incomplete ossification of the thoracic centrum (with unchanged cartilage); (vi) supernumerary thoracic vertebrae; (vii) supernumerary 13th rib (with cartilage present); and (viii) incomplete ossification (with cartilage present) of the talus.

Additionally, the following findings were increased over concurrent and historical controls at 50 and 450 mg/kg: (i) increased incidences of infarct of the liver; (ii) unossified cervical centra (with unchanged cartilage); (iii) extra ossification site (with unchanged cartilage) of the sternebrae; (iv) unossified talus (with cartilage present); and (v) short 1st rib with cartilage not present. At 450 mg/kg, the following were increased over concurrent and historical controls: (i) incidences of small thymus; (ii) severely malformed bones of the skull; (iii) increased incidences of absent and misshapen caudal vertebrae; (iv) fused ribs with unchanged cartilage; (v) absent 1st rib; (vi) pale kidney; (vii) incidence of incomplete ossification of the interparietal bone; (viii) unilateral ossification (with dumbbell-shaped cartilage) of the centrum of the cervical vertebrae; (ix) incomplete ossification of the forepaw phalanx; and (x) incomplete ossification (with cartilage present) of the hindpaw phalanx.

The developmental LOAEL was 5 mg/kg/day, based on visceral findings (fluid-filled abdomen, pale liver, and dark content of the stomach and intestines) and alterations in skeletal development (i.e., incomplete ossification of the vertebrae and talus, and supernumerary thoracic vertebrae and 13th rib). The developmental NOAEL was not established. There was no evidence of teratogenicity.

5. **Dosage preparation and analysis:** Stock dosing solutions were prepared at least once weekly and refrigerated until use. A weighed amount of test substance was ground with a mortar and pestle (if necessary) and suspended in (reverse osmosis deionized) aqueous 0.5% (w/v) carboxymethylcellulose. Homogeneity was confirmed by analyses of three samples of the low and high dose formulations taken from the top, middle, and bottom of the mixing container at Week 0. Samples of the dosing mixtures at each dose level were taken every 4 days starting at Week 0, and concentrations of the test substance were determined. It was stated that stability of the test substance in the vehicle was determined previously (BASF Study PCP 05767, on pages 358-360 of MRID 46020301). The test substance was suspended in water having different purities (tap, M4, OECD, and superpure) at a concentration of 0.1 mL/L and stored for 0, 1, or 7 days at room temperature or refrigerated.

Results -

Homogeneity (range as % CV): 3.3-4.2%

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): 93.2-111.0% (except for the 0.5 mg/mL formulation: 136.4% at Week 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.

6. **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 adjusted daily on the individual body weights determined prior to gavage. Rabbits were dosed at approximately the same time each day.

C. OBSERVATIONS

1. **Maternal observations and evaluations:** All does were checked for mortality, morbidity, clinical signs of toxicity, abortions, and premature deliveries prior to and approximately 1 hour

after dosing throughout the study and on the day of sacrifice. Body weights were determined by the supplier on GD 0, and then daily throughout the study beginning on GD 6 and at sacrifice. Food consumption (g/rabbit/day) was measured daily beginning on GD 6. Blood samples were collected from all animals prior to sacrifice on GD 29, and serum tyrosine levels were determined for 5 does/group. Rabbits sacrificed because of abortion were examined for gross lesions and pregnancy status, and their uterine contents were recorded. On GD 29, all surviving does were sacrificed and subjected to necropsy, the uteri excised, and gravid uterus weights determined. The uteri of apparently nonpregnant does were examined while being pressed between glass plates to confirm the presence or absence of implantation sites, and were preserved in neutral buffered 10% formalin. All fetuses were removed by cesarean section. The numbers of corpora lutea, implantations, live fetuses, dead fetuses, and resorptions (early and late) were recorded.

2. Fetal evaluations: All fetuses delivered by cesarean were sexed, weighed, and examined for external abnormalities. Any intact fetuses from does sacrificed due to abortion were examined for external and visceral abnormalities and preserved in neutral buffered 10% formalin. One 0.5 mg/kg fetus noted with kidney alterations and 2 control fetuses were fixed for approximately 20 minutes in Bouin's solution with 0.1% gluteraldehyde, washed for 2 hours in Bouin's solution followed by phosphate buffer until yellow coloration was no longer visible, then preserved by step-wise immersion in sugar solutions (final concentration 30%). All fetuses were dissected to look for visceral alterations, and any abnormalities were recorded and fixed in neutral buffered 10% formalin. The heads of one-half of the fetuses in each litter were removed and processed for visceral alterations using standard serial sectioning methods. The heads of the remaining fetuses were sectioned with a single mid-coronal incision for evaluation of internal brain structures. All fetuses (except the 3 mentioned above) were then skinned, fixed in 99% isopropyl alcohol, macerated in potassium hydroxide, and stained for skeletal examination with Alizarin Red S according to the method of Staples and Schnell.

D. DATA ANALYSIS

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

Parameter	Statistical test
Body weight, body weight gain, food consumption, percent male fetuses, percent resorptions, fetal weight, fetal anomaly data, and fetal ossification site data	Bartlett's Test of homogeneity of variances; if not significant, ANOVA followed by Dunnett's Test when ANOVA significant; if significant, Kruskal-Wallis Test when ≤75% of ties were present, followed by Dunn's method of multiple comparisons if Kruskal-Wallis Test significant. When >75% of ties were present, Fisher's Exact Test was used.
Count data at cesarean-section	Kruskal-Wallis Test
Clinical observations and other proportion data	Variance Test for the homogeneity of the binomial distribution

Note: Two control does and one doe in each of the 5 and 450 mg/kg dose groups had a single conceptus litter, while 2 does in the 5 mg/kg dose group had abnormal uteri. These animals and their litter observations were not included in the statistical analyses.

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

2. **Indices:** No indices were calculated.

3. **Historical control data:** Historical control data were provided for maternal necropsy and cesarean parameters, and external, visceral, and skeletal findings in the fetuses. Data were comprised of 72-73 studies on 933-955 does and 36-69 studies on 682-850 litters of the same strain performed from January 1998 through January 2000.

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical observations:** There were no treatment-related mortalities. Two 50 mg/kg does were sacrificed following abortion (on GD 20 or 26). The incidence was not dose dependent and was not considered treatment-related. Increased incidence ($p \leq 0.01$) and frequency of scant feces (9/25 treated vs 0/25 controls) and tan feces (2/25 treated vs 0/25 controls) were observed in the 450 mg/kg does (Table 2). No other clinical signs of toxicity were noted.

Table 2. Clinical signs observed from commencement of treatment [# of does (% frequency)][a]

Clinical sign	Dose in mg/kg bw/day (# of Dams)				
	0 (25)	0.5 (25)	5 (25)	50 (25)	450 (25)
Scant feces	0 (0)	2 (0.7)	1 (0.3)	2 (0.7)	9** (6.3)
Tan feces	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5)

a Data obtained from page 34 of the study report (MRID 45902210). Frequency is expressed as percentage of total animal days.

** Significantly different from controls, $p \leq 0.01$

2. Body weight: Body weight gain data are shown in Table 3. At 450 mg/kg, body weight gains were decreased ($p \leq 0.05$) on GDs 20-24 (↓58%) as well as throughout treatment (GD 6-29) by 38%. However, these decreased body weight gains were attributed to decreased gravid uterine weights (↓22%; $p \leq 0.01$), as both GD 6-29 and GD 0-29 body weight gains, corrected for gravid uterine weights, were comparable to controls. No other treatment-related effects on body weight or body weight gains were observed.

Table 3. Mean (±SD) maternal body weight gain (kg)[a], gravid uterus weight (kg) and corrected body weight (kg)

Interval		Dose in mg/kg bw/day (# of Does)				
		0 (20-23)	0.5 (23-24)	5 (24-25)	50 (21-23)	450 (22-23)
Pretreatment:	GD 0-6	0.06±0.09	0.07±0.10	0.10±0.12	0.05±0.10	0.09±0.10
Treatment:	GD 6-10	0.06±0.06	0.06±0.12	0.04±0.08	0.02±0.07	0.05±0.06
	GD 10-14	0.09±0.08	0.09±0.10	0.12±0.11	0.11±0.06	0.08±0.06
	GD 14-20	0.11±0.06	0.08±0.07	0.06±0.11	0.10±0.05	0.07±0.12 (↓36)
	GD 20-24	0.12±0.05	0.12±0.08	0.11±0.06	0.11±0.06[d]	0.05±0.09** (↓58)
	GD 24-29	0.03±0.13	0.06±0.12	0.07±0.11	0.07±0.16[e]	-0.02±0.22
Treatment	GD 6-29	0.40±0.14	0.41±0.20	0.40±0.16	0.42±0.21[e]	0.25±0.29* (↓38)
	Corrected	-0.16±0.18[f]	-0.15±0.20[c]	-0.09±0.17[b]	-0.13±0.17[e]	-0.20±0.25[d]
Overall	GD 0-29	0.46±0.14	0.48±0.23	0.50±0.18	0.48±0.17[e]	0.33±0.30
	Corrected	-0.11±0.16[f]	-0.08±0.21[c]	-0.01±0.21[b]	-0.07±0.14[e]	-0.10±0.27[d]
Body weight (GD 29, kg)		4.18±0.30	4.11±0.41	4.19±0.32	4.13±0.46	4.00±0.42
Gravid uterus weight (kg)		0.572±0.109	0.560±0.111	0.513±0.100	0.550±0.89	0.446±0.113** (↓22)
Corrected body weight (kg)		3.64±0.32	3.57±0.39	3.68±0.34	3.58±0.41	3.52±0.36

a Data obtained from pages 38-39 of the study report (MRID 45902210). Percent difference from controls (calculated by reviewers) is included in parentheses.
b n=24; excludes values for doe that had only one conceptus *in utero* on GD 29
c n=23; excludes values that were not recorded
d n=22; excludes values for doe that aborted (50 mg/kg group) or that had only one conceptus *in utero* on GD 29 (450 mg/kg group)
e n=21; excludes values for does that aborted
f n=20; excludes values for does that had only one conceptus *in utero* on GD 29, and excludes values that were not recorded
* Significantly different from controls, $p \leq 0.05$
** Significantly different from controls, $p \leq 0.01$

3. Food consumption: In the 450 mg/kg does, absolute food consumption (g/animal/day) was decreased (↓5%; $p \leq 0.01$) on GD 6-10 (Table 4). Additionally, decreases (NS) were observed in absolute food consumption on GD 10-29 (↓4-17%), and throughout treatment (↓10%); and in relative food consumption (g/kg body weight/day) on GD 6-29 (↓4-15%) as well as throughout treatment (↓8%). There were no other effects of treatment on food consumption.

Table 4. Mean (±SD) food consumption[a]

Interval	Dose in mg/kg bw/day (# of Does)				
	0 (22-23)	0.5 (23-24)	5 (24-25)	50 (20-23)	450 (23)
Absolute feed consumption (g/animal/day)					
GD 6-10	182.5±3.3	176.9±20.6	179.4±10.8	169.0±26.0	173.8±13.9** (↓5)
GD 10-14	168.2±26.3	170.5±32.6	170.2±27.4	170.8±21.1	161.1±35.6 (↓4)
GD 20-24	169.9±22.9[d]	171.7±15.9	169.6±22.0	167.4±23.6[d]	141.4±54.1 (↓17)
Treatment (GD 6-29)	164.3±16.2[d]	162.8±19.2[c]	166.0±17.9[b]	163.6±23.3[e]	148.5±31.6 (↓10)
Relative feed consumption (g/kg body weight/day)					
GD 6-10	48.1±3.3	47.7±6.6	47.4±4.0	45.4±6.2	46.0±3.4 (↓4)
GD 20-24	41.8±5.8[d]	43.4±5.8	41.8±5.6	42.0±5.1[d]	35.7±13.6 (↓15)
Treatment (GD 6-29)	41.3±4.6[d]	42.0±5.3[c]	41.6±4.4[b]	41.7±4.6[e]	38.0±7.8 (↓8)

a Data obtained from pages 40-41 of the study report (MRID 45902210). Percent difference from controls (calculated by reviewers) is included in parentheses.
b n=24; excludes values that were not recorded, as well as those associated with spillage
c n=23; excludes values that were not recorded, as well as those associated with spillage
d n=22; excludes values that were not recorded, as well as those associated with spillage
e n=20; excludes values that were not recorded, as well as those associated with spillage, and excludes values for does that aborted
** Significantly different from controls, $p \leq 0.01$

4. Serum tyrosine levels: Serum tyrosine levels are shown in Table 5. Substantial increases of circulating serum tyrosine level were observed (↑127-659%; no statistics performed) at dose groups ≥0.5 mg/kg compared to controls. The Sponsor stated that one mode of action of the test material was inhibition of the enzyme p-hydroxyphenylpyruvate-dioxygenase, an enzyme involved in tyrosine catabolism in animals. The inhibition of this enzyme resulted in increased tyrosine levels in the blood and urine of treated animals.

Table 5. Mean (±SD) serum tyrosine levels (µmol/L)[a]

Dose (mg/kg bw/day)	0	0.5	5	50	450
Serum tyrosine levels	43.30±8.45	98.1±35.23 (↑127)	244.75±122.77 (↑465)	328.78±143.31 (↑659)	290.46±150.05 (↑570)

a Data obtained from page 294 of the study report (MRID 45902210). Percent difference from controls (calculated by reviewers) is included in parentheses.

5. Gross pathology: There were no treatment-related macroscopic findings in any group. Abnormalities of the lungs (intermediate lobe absent, intermediate lobe fused to right diaphragmatic lobe) and uterus (uterine horn reduced to a ligament, uterine horn and cervix absent) were noted, but were minimal in incidence and not dose-dependent.

6. Cesarean section data: Cesarean section data are presented in Table 6. At 50 mg/kg, two does aborted: rabbit 4588 aborted after dosing on GD 20; rabbit 4579 aborted prior to dosing on GD 26. Also, one 5 mg/kg doe (rabbit 4569) had a litter of 8 dead fetuses. These findings were considered to be incidental, as they were not related to dose. At ≥50 mg/kg, litter weights were decreased ($p \leq 0.05$) 9-13%; fetal body weights were decreased for both sexes at 50 mg/kg (7-8%; NS) and 450 mg/kg (↓12%; $p \leq 0.05$). No effects of treatment were noted on numbers of litters, live fetuses, resorptions (early or late), placental appearance, sex ratio, or postimplantation loss.

Table 6. Cesarean section observations[a]

Observation	Dose (mg/kg bw/day)				
	0	0.5	5	50	450
# Animals Assigned (Mated)	25	25	25	25	25
# Animals Pregnant	23	24	25	23	23
Pregnancy Rate (%)	92	96	100	92	92
# Nonpregnant[b]	2	1	0	2	2
Maternal Wastage					
# Died	0	0	0	0	0
# Died Pregnant	0	0	0	0	0
# Died Nonpregnant	0	0	0	0	0
# Aborted	0	0	0	2	0
# Premature Delivery	0	0	0	0	0
Total # Corpora Lutea[c]	229	253	232	213	215
Corpora Lutea/Doe	10.0±2.2	10.5±2.4	9.3±2.1	10.1±2.3	9.3±2.5
Total # Implantations[c]	197	214	200	198	181
(Implantations/Doe)	8.6±3.3	8.9±2.0	8.0±2.6	9.4±1.7	7.9±2.7
Total # Litters	23	24	24	21	23
Total # Live Fetuses[c]	193	208	182	191	173
(Live Fetuses/Doe)	8.4±3.0	8.7±1.9	7.3±2.8	9.1±1.5	7.5±2.6
Total # Dead Fetuses[c]	0	0	8	0	4
(Dead Fetuses/Doe)[c]	0.0±0.0	0.0±0.0	0.3±1.6	0.0±0.0	0.2±0.7
Total # Resorptions[b]	4	6	10	7	4
Early	0	2	3	1	1
Late	4	4	7	6	3
Total Resorptions/Doe	0.2±0.6	0.2±0.4	0.4±0.6	0.3±0.6	0.2±0.5
Early	0.0±0.0	0.1±0.3	0.1±0.3	0.0±0.2	0.0±0.2
Late	0.2±0.6	0.2±0.4	0.3±0.6	0.3±0.6	0.1±0.4
Complete Litter Resorption[c]	0	0	0	0	0
Mean Fetal Weight (g)/litter	45.9±6.8	44.7±4.3	46.5±6.5	41.6±3.9* (↓9)	40.1±8.6** (↓13)
Males fetuses	45.7±6.0	45.5±4.4	47.0±6.5	42.3±3.8 (↓8)	40.1±8.5** (↓12)
Females fetuses	44.1±6.6	44.3±4.7	44.6±5.7	41.1±4.1 (↓7)	39.0±8.8* (↓12)
Placentae appearance normal	100	100	100	100	100
Sex Ratio (Mean % Male)	51.3±22.4	46.6±19.4	51.0±26.1	52.3±21.5	53.3±22.1
Preimplantation Loss (%)[d]	14.0	15.4	13.8	7.0	15.8
Postimplantation Loss (%)[e]	2.0	2.8	9.0	3.5	4.4

a Data obtained from pages 23 and 42-43 of the study report (MRID 45902210).
b Calculated by reviewers from data presented in this table
c Tabulated by reviewers from individual data presented in Table 15 on pages 88-92 of the study report (MRID 45902210)
d Calculated by reviewers as preimplantation loss (%)=(total # corpora lutea - total # resorptions)/total # resorptions
e Calculated by reviewers as postimplantation loss (%)=total # implantations - total # live fetuses)/total # implantations
* Significantly different from controls, $p \leq 0.05$
** Significantly different from controls, $p \leq 0.01$

B. DEVELOPMENTAL TOXICITY

1. **External examination**: There were no external abnormalities observed at necropsy.

2. **Visceral examination**: Visceral abnormalities are presented in Table 7a. There were no treatment-related visceral findings. Folded retina, a variation, was observed in a single 450 mg/kg fetus (0.6% fetuses; 4.3% litters), compared to 0 concurrent controls, but this finding fell within the range of historical controls (0-12.8% fetuses; 0-32.0% litters). All other visceral findings were unrelated to dose.

3. **Skeletal examination**: Selected skeletal findings are presented in Table 7b. Misaligned caudal vertebrae was noted in single fetuses of the 0.5 (0.5% fetuses; 4.2% litters), 5 (0.5% fetuses; 4.0% litters), 50 (0.5% fetuses; 4.8% litters), and 450 (0.6% fetuses; 4.3% litters) mg/kg groups. However, this finding occurred in the concurrent controls (0.5% fetuses; 4.3% litters) and fell within the range of historical controls (0-7.7% fetuses; 0-42.8% litters). Presence of intranasal bones in nasal bones was observed in the 0.5 (0.5% fetuses; 4.2% litters), 5 (0.5% fetuses; 4.0% litters), 50 (1.0% fetuses; 4.8% litters), and 450 (1.2% fetuses; 8.7% litters) mg/kg groups compared to concurrent controls (0.5% fetuses; 4.3% litters), but this finding fell within the range of historical controls (0-3.1% fetuses; 0-18.8% litters). Unossifed pubes of the pelvis were noted in a single 450 mg/kg fetus (0.6% fetuses; 4.3% litters) compared to 0 controls, but this finding also fell within the range of historical controls (0-0.8% fetuses; 0-6.7% controls). All other skeletal findings were unrelated to dose.

Several statistically significant ($p \leq 0.05$) alterations in skeletal ossification sites were observed (Table 7c). Increased ($p \leq 0.01$) mean thoracic vertebrae ossification sites were noted in the 5 (12.87), 50 (12.94) and 450 (12.98) mg/kg groups compared to concurrent controls (12.59). Decreased ($p \leq 0.01$) mean lumbar vertebrae ossification sites were noted in the 5 (6.13), 50 (6.06), and 450 (6.01) mg/kg groups compared to concurrent controls (6.40). Increased ($p \leq 0.01$) mean caudal vertebrae ossification sites were observed in the 5 (17.28; NS), 50 (17.57), and 450 (17.60) mg/kg groups compared to concurrent controls (17.06). Increased ($p \leq 0.05$) mean number of pairs of ribs were noted in the 5 (12.82), 50 (12.92), and 450 (12.95) mg/kg groups compared to concurrent controls (12.53). All of these observations fell outside the range of historical controls and were considered treatment-related. Mean hindlimb tarsal ossification sites were decreased (NS) in the 450 mg/kg group (1.98) compared to concurrent controls (2.00); however this finding was only slightly below the range of historical controls (1.99-2.00). All other skeletal ossification site data fell within the range of historical controls.

Table 7a. Visceral abnormalities [% fetuses affected (% litters affected)][a]

Observations		Dose (mg/kg bw/day)					
		0	0.5	5	50	450	Historical controls[b]
Malformation							
# Fetuses (# litters) examined		193 (23)	208 (24)	190 (25)	191 (21)	177 (23)	5692 (682)
Kidneys:	absent	0 (0)	0.5 (4.2)	0 (0)	0 (0)	0 (0)	0-1.1 (0-7.1)
Variations							
Eyes:	retina folded	0 (0)	0 (0)	0 (0)	0 (0)	0.6 (4.3)	0-12.8 (0-32.0)
	circumcorneal hemorrhage	0 (0)	0.5 (4.2)	1.1 (8.0)	1.0 (9.5)	0 (0)	0-1.3 (0-8.0)
Lung:	intermediate lobe absent	0.5 (4.3)	0 (0)	1.1 (8.0)	3.7** (14.3)	0.6 (4.3)	0-8.1 (0-40.0)
Brain:	dilation of the 3rd and lateral ventricles	0 (0)	0.5 (4.2)	0 (0)	0 (0)	0 (0)	0-0.6 (0-5.0)
Kidneys:	dilated pelvis	0 (0)	0.5 (4.2)	1.1 (4.0)	0 (0)	0 (0)	0-0.6 (0-5.0)

a Data obtained from page 46 in the study report (MRID 45902210).
b Historical control data obtained from page 303 in the study report.
** Significantly different from controls, $p \leq 0.01$

Table 7b. Skeletal findings [% fetuses affected (% litters affected)][a]

Observations	Dose (mg/kg bw/day)					
	0	0.5	5	50	450	Historical controls[b]
Malformations						
#Fetuses (# litters) examined	191 (23)	207 (24)	182 (25)	191 (21)	172 (23)	5692 (682)
Vertebrae						
thoracic, hemiveterbrae	0 (0)	0 (0)	0 (0)	0.5 (4.8)	0 (0)	0-2.2 (0-14.3)
caudal, misaligned	0.5 (4.3)	0.5 (4.2)	0.5 (4.0)	0.5 (4.8)	0.6 (4.3)	0-7.7 (0-42.8)
Variations						
Skull						
nasal bone contained an intranasal	0.5 (4.3)	0.5 (4.2)	0.5 (4.0)	1.0 (4.8)	1.2 (8.7)	0-3.1 (0-18.8)
Pelvis						
pubes unossified	0 (0)	0 (0)	0 (0)	0 (0)	0.6 (4.3)	0-0.8 (0-6.7)

a Data obtained from pages 47-50 in the study report (MRID 45902210).
b Historical control data obtained from pages 306-307 and 310 in the study report.

Table 7c. Skeletal ossification sites (mean ±SD)[a]

Observations	Dose (mg/kg bw/day)					
	0	0.5	5	50	450	Historical controls[b]
#Fetuses (# litters) examined	191 (23)	207 (24)	182 (25)	191 (21)	172 (23)	5691 (681)
Vertebrae						
thoracic	12.59±0.34	12.66±0.30	12.87±0.21**	12.94±0.13**	12.98±0.06**	12.47-12.82
lumbar	6.40±0.34	6.33±0.30	6.13±0.21**	6.06±0.13**	6.01±0.05**	6.18-6.53
caudal	17.06±0.35	16.96±0.32	17.28±0.36	17.57±0.40**	17.60±0.40**	16.77-17.14
Ribs						
pairs	12.53±0.33	12.60±0.32	12.82±0.24*	12.92±0.15**	12.95±0.12**	12.39-12.71

a Data obtained from page 51 in the study report (MRID 45902210).
b Historical control data obtained from page 312 in the study report.
* Significantly different from controls, $p \leq 0.05$
** Significantly different from controls, $p \leq 0.01$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The maternal LOAEL is 450 mg/kg based on: significant increase in the number of rabbits with scant feces and tan discoloration of the feces; reduced maternal body weight gains and absolute and relative feed consumption for the entire dosing period; and reduced gravid uterine weights. Fetal body weights were significantly reduced in the 450 mg/kg group. The 5, 50, and 450 mg/kg groups had significantly increased numbers of fetuses with 13 pairs of ribs, and significant increases in the litter average for number of ossified caudal vertebrae. However, the mean pre-sacral vertebrae count of 26 was unchanged. Therefore, the investigator estimated that the developmental NOAEL is 50 mg/kg body weight/day.

B. REVIEWER COMMENTS

1. Maternal toxicity: There were no treatment-related effects on maternal survival, body weight, or gross pathology. Increased incidence and frequency of scant and tan feces were observed at 450 mg/kg/day. Decreased body weight gains were observed on GD 20-24, the decrease was attributed to decreased gravid uterine weights (22%, $p \leq 0.01$). Decreased absolute food consumption was observed on GD 6-10 (5%, $p \leq 0.01$) and GD 10-29 (4-17%, NS) and throughout treatment (GD 6-29). Relative food consumption was decreased (NS) 4-15% on GD 6-29 and 8% throughout treatment. Increased serum tyrosine levels (≥127-570%) were observed in all treated groups (≥0.5 mg/kg/day) compared to controls.

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.

For maternal toxicity, the LOAEL is 0.5 mg/kg/day based on increased serum tyrosine level The maternal NOAEL was not established.

2. Developmental toxicity:

a. Deaths/Resorptions: At 50 mg/kg, two does aborted: rabbit 4588 aborted after dosing on GD 20; rabbit 4579 aborted prior to dosing on GD 26. Also, one 5 mg/kg doe (rabbit 4569) had a litter of 8 dead fetuses. These findings were considered to be incidental, as they were not related to dose.

b. Altered Growth: At ≥50 mg/kg, litter weights were decreased ($p \leq 0.05$) 9-13%; fetal body weights were decreased in both sexes at 50 mg/kg (↓7-8%; NS) and 450 mg/kg (↓12%; $p \leq 0.05$). Increased ($p \leq 0.01$) mean thoracic vertebrae ossification sites were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. Decreased ($p \leq 0.01$) mean lumbar vertebrae ossification sites were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. Increased ($p \leq 0.01$) mean caudal vertebrae ossification sites were observed in the 5 (NS), 50, and 450 mg/kg groups compared to concurrent controls. Increased ($p \leq 0.05$) mean number of pairs of ribs were noted in the 5, 50, and 450 mg/kg groups compared to concurrent controls. All of these observations fell outside the range of historical controls and were considered treatment-related.

c. Developmental Variations: There were no treatment-related external, visceral, or skeletal variations.

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

The developmental LOAEL is 5 mg/kg/day based on alterations in skeletal ossification sites and increased number of pairs of ribs. The developmental NOAEL is 0.5 mg/kg/day.

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

C. STUDY DEFICIENCIES: No deficiencies were noted.

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	45902210	developmental	rabbit	GD 6-28	oral	gavage	0.5-450	0.5, 5, 50, 450	50	450	Clinical signs, gravid uterine weights, FC	Maternal
123009	45902210	developmental	rabbit	GD 6-28	oral	gavage	0.5-450	0.5, 5, 50, 450	5	50	Decreased fetal body weights	Developmental

Deleted