DATA EVALUATION RECORD

BAS 670H

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

Work Assignment No. 1-01-11 R (MRID 46020303)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700b [§83-3b]; OECD 414.

PC CODE: 123009 **DP BARCODE:** D292904
SUBMISSION NO.: Not provided

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: Foulon, O. (2003) Prenatal developmental toxicity study in New Zealand white rabbits: oral administration (gavage). CIT, BP 563-27005 Evreux, France. Laboratory Project ID: Project No. 40R0124/989170, BASF Registration Document No. 2003/1009308, March 21, 2003. MRID 46020303. Unpublished.

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

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46020303), BAS 670H (95.8% a.i.; Lot/Batch # N26) in 0.5% (w/v) aqueous carboxymethylcellulose was administered daily by oral gavage at a dose volume of 10 mL/kg body weight to 25 female New Zealand White (INRA A9077) rabbits/group at dose levels of 0, 0.5, 5, 50, or 450 mg/kg on gestation days (GD) 6 through 28. All does were sacrificed on GD 29; their fetuses were removed by cesarean section and examined.

No effects of treatment were observed on maternal survival, clinical signs, body weights, body weight gains, food consumption, or gross pathology.

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

There were no treatment-related effects on the numbers of dead fetuses or resorptions (early, late or complete litter). Slightly lower fetal weight were observed in the 5, 50 and 450 mg/kg/day

groups; however, no statistical significance was achieved. There were no treatment-related external, visceral, or skeletal malformations.

Increased presence of 27 pre-sacral vertebrae, a variation, was observed in the 5 (not significant), 50 ($p \leq 0.001$), and 450 ($p \leq 0.001$) mg/kg groups compared to concurrent and historical controls. Increased ($p \leq 0.001$) incidence of full supernumerary 13th rib, a variation, was noted in the 5, 50, and 450 mg/kg groups compared to concurrent and historical controls. Unossified 1st to 4th sternebrae, a variation, was observed in the 50 and 450 mg/kg groups compared to concurrent controls. Cartilage present in the ribs was observed in the 50 and 450 mg/kg groups compared to concurrent controls, and increased ($p \leq 0.01$) incidence of fused cartilage in the ribs was noted in the 50 and 450 mg/kg groups compared to concurrent controls. Additionally, increased ($p \leq 0.05$) incidence of incomplete ossification of the ribs was observed in the 450 mg/kg group compared to concurrent and historical controls.

The developmental LOAEL is 5 mg/kg/day based on increased presence of 27 pre-sacral vertebrae and increased incidence of full supernumerary 13th rib. The developmental NOAEL is 0.5 mg/kg/day.

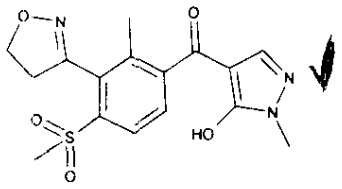
This study is classified **acceptable/guideline (OPPTS 870.3700b)** and satisfies the requirements for a developmental study in the rabbit.

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:	Golden-yellow 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 (INRA A9077)	
Age/body weight range at treatment initiation:	18-20 weeks/2795-4035 g	
Source:	Charles River Laboratories (Elevage Scientifique des Dombes, Châtillon sur Chalaronne, France)	
Housing:	Individually in suspended stainless steel cages	
Diet:	Pelleted Rabbit Breeding Diet, Type 110 (UAR, Villemoisson, Epinay-sur-Orge, France), *ad libitum*	
Water:	Filtered tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	18±3°C
	Humidity:	50±20%
	Air changes:	Approximately 12/hour
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	5 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates: Start: March 13, 2001 End: April 19, 2001

2. Mating: The females were naturally mated with breeder male rabbits of the same strain by the supplier prior to shipment. The day of insemination (assessed visually) was designated as gestation day (GD) 0. Rabbits were shipped on GD 1.

3. Animal assignment: After arrival, does were randomly assigned 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 15 of the study report (MRID 46020303).

4. **Dose selection rationale:** The study stated that the dose-levels were specified by the sponsor. In a developmental toxicity study (MRID 46020301) submitted concurrently with this study, 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.

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

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.

Based on these findings, an additional dose of 0.5 mg/kg was included as the expected NOAEL dose.

5. **Dosage preparation and analysis:** It was stated that dosing solutions were prepared at a frequency depending on their stability, but the frequency of preparation was not provided. A weighed amount of test substance was suspended in (reverse osmosis deionized) aqueous 0.5% (w/v) carboxymethylcellulose with a laboratory mixer and stirred during dosing. Concentration and homogeneity were confirmed by analyses of three samples taken from the top, middle, and bottom of the mixing containers for all dose formulations prepared for use on the first and last days of treatment. It was stated that stability of the test substance in the vehicle was determined by the Sponsor, and that dose formulations were stable for at least 96 hours at room temperature. No further stability data were provided.

Results -

Homogeneity (range as % CV): 0.2-3.1%

Concentration (range as % nominal): 94.7-102.0%

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 and morbidity at least twice daily during treatment (once daily on other days), and for clinical signs of toxicity at least once per day. Body weights were measured daily throughout the study, beginning on GD 1, and at sacrifice. Food consumption (g/rabbit/day) was measured daily beginning on GD 1. Blood samples were collected from all surviving animals prior to sacrifice on GD 29 and centrifuged; the serum was stored at -80°C for possible future analysis. On GD 29, surviving does were killed by an intravenous injection of thiopental sodium. The uteri were 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 or scars were recorded. Also, the number of corpora lutea and implantation sites were recorded, wherever possible, in does that died or were sacrificed prematurely. All rabbits were necropsied, and a gross evaluation of the placentae was performed.

2. Fetal evaluations: On removal from the uterus, all fetuses were weighed and given a detailed external examination. Dead fetuses were sexed and discarded, and live fetuses were killed by a subcutaneous injection of thiopental sodium, dissected for visceral examination, and sexed. The heads were removed from one half of the fetuses, fixed in Harrisson's fluid, and processed for evaluation of the brain, eyes, nasal passages, and tongue. The brain was removed from the remaining fetuses, fixed in Bouin's fluid, horizontally sectioned, and examined. The carcasses of all fetuses were then fixed in ethyl alcohol, stained with alizarin red S and alcian blue, and a detailed examination of the skeletal bone and cartilage was performed.

D. DATA ANALYSIS

1. Statistical analyses: Data were expressed as group mean values ± standard deviations or proportions, and were subjected to the following statistical procedures:

Parameter	Statistical test
Body weight, body weight gain, food consumption, fetal weight, numbers of corpora lutea, implantations, fetuses, and resorptions	One-way ANOVA and Dunnett's Test (mean values were considered normally distributed and variances homogeneous)
Percentage values for pre-implantation loss and post-implantation loss and fetal findings	Fisher exact probability test

Significance was denoted at $p \leq 0.05$ or $p \leq 0.01$ for each comparison. For data analyzed by ANOVA and Dunnett's test, it was stated that mean values were considered normally distributed

and variances homogeneous. However, these assumptions should have been verified statistically prior to parametric analysis.

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

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

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

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

3. **Historical control data:** Historical control data were provided for cesarean parameters and external, visceral, and skeletal findings in the fetuses. Data were comprised of an unspecified number of studies on 172 does and 74-137 litters of the same strain.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical observations: There were no treatment-related deaths or clinical signs of toxicity. One 5 mg/kg female (X30577) was found dead following treatment on GD 27. No clinical signs were observed prior to death, and both body weight gain and food consumption were normal. Necropsy revealed reddish contents in the trachea and lungs, suggesting regurgitation and aspiration of the test substance or a gavage error. One 450 mg/kg female (X30621) was found dead following treatment on GD 12. No clinical signs were observed prior to death, and both body weight gain and food consumption were normal. Necropsy revealed reddish areas on one lung, but a definitive cause of death was not determined. One control female (X30520) aborted her litter on GD 28 and was killed. There were no other deaths.

2. Body weight: Body weight gain data are shown in Table 2. No treatment-related effects were observed on body weights, body weight gains, gravid uterus weights, or overall (GD 6-29) body weight gains either uncorrected or corrected for gravid uterus weights.

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

Interval	Dose in mg/kg bw/day (# of Does)				
	0 (22-23)[b]	0.5 (23)[c]	5 (20-21)[d]	50 (25)	450 (22-23)[e]
Pretreatment: GD 1-6[f]	29	54	68	68	27
Treatment GD 6-7	2±35	7±26	22±26	16±33	-3±35
Treatment GD 7-8	8±31	29±28	19±39	9±25	21±42
Treatment GD 15-16	11±34	20±35	36±65	19±56	18±35
Treatment GD 28-29	-8±30	-13±33	-9±54	-5±48	-18±37
Overall: GD 6-29	314±167	333±126	352±124	372±125	335±116
Gravid uterus weight	511.4±83.6	520.0±100.7	553.5±109.6	557.6±81.1	526.8±92.7
Carcass[g]	3315.4±189.9	3345.9±184.2	3418.0±237.7	3324.4±209.3	3360.0±253.4
Net weight change: GD 6-29[h]	-197.6±193.3	-186.8±147.7	-202.0±124.4	-185.2±138.5	-191.4±100.0

a Data obtained from pages 24 and 39-46 of the study report (MRID 46020303).
b Excludes values for 2 females that were not pregnant and 1 female that aborted.
c Excludes values for 2 females that were not pregnant.
d Excludes values for 4 females that were not pregnant and 1 female that was found dead.
e Excludes values for 1 female that was not pregnant and 1 female that was found dead.
f Calculated by reviewers from data found on pages 39-41 of the study report (MRID 46020303).
g Carcass = terminal body weight - gravid uterine weight
h Net weight change = carcass - GD 6 body weight

3. Food consumption: No treatment-related effect was observed on food consumption. Increases ($p \leq 0.01$) were observed in the 5 mg/kg females during GD 15-17 (↑28-40%), but these increases were sporadic and not dose-dependent.

4. Gross pathology: There were no treatment-related macroscopic findings.

5. Cesarean section data: Cesarean section data are presented in Table 3. There were no premature deliveries or complete litter resorptions. Late resorptions were increased ($p \leq 0.05$) in the 50 mg/kg group (22 treated vs 7 controls); however, this increase was largely attributed to a single doe (X30606) that had a large litter (7 fetuses) and a high number of late resorptions (10 late resorptions). Slightly lower fetal weight were observed in the 5, 50 and 450 mg/kg/day groups; however, no statistical significance was achieved. No effects of treatment were noted on numbers of litters, live fetuses, dead fetuses, resorptions (early or late), sex ratio, or postimplantation loss.

Table 3. 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	22	23	20	25	22
Pregnancy Rate (%)[b]	88	92	80	100	88
# Nonpregnant	2	2	4	0	2
Maternal Wastage					
# Died	0	0	1	0	1
# Died Pregnant	0	0	1	0	1
# Died Nonpregnant	0	0	0	0	0
# Aborted	1	0	0	0	0
# Premature Delivery	0	0	0	0	0
Total # Corpora Lutea	211	227	216	264	225
Corpora Lutea/Doe	9.6±2.0	9.9±1.6	10.8±2.0	10.6±2.6	10.2±1.7
Total # Implantations	197	206	201	252	202
(Implantations/Doe)	9.0±1.6	9.0±2.2	10.1±2.2	10.1±2.8	9.2±1.6
Total # Litters	22	23	20	25	22
Total # Live Fetuses	185	201	190	229	196
(Live Fetuses/Doe)	8.4±1.7	8.7±2.2	9.5±2.1	9.2±2.0	8.9±1.7
Total # Dead Fetuses	0	1	2	0	0
(Dead Fetuses/Doe)	0.0±0.0	0.0±0.2	0.1±0.4	0.0±0.0	0.0±0.0
Total # Resorptions	12	4*	9	23	6
Early	5	0*	3	1	3
Late	7	4	6	22*	3
Total Resorptions/Doe	0.5±1.0	0.2±0.4	0.4±0.7	0.9±2.2	0.3±0.6
Early	0.2±0.7	0.0±0.0	0.2±0.5	0.0±0.2	0.1±0.5
Late	0.3±0.8	0.2±0.4	0.3±0.6	0.9±2.2	0.1±0.4
Complete Litter Resorption	0	0	0	0	0
Mean Fetal Weight (g)/litter	42.2±4.4	41.0±5.3	39.7±4.6	39.9±3.9	39.6±2.5
Males	42.3±5.0	41.5±6.1	39.9±4.1	40.2±4.1	39.9±3.6
Females	42.9±5.3	40.1±5.4	39.7±5.5	39.5±4.6	39.0±3.1
Sex Ratio (Mean % Male)	58.4	59.9	58.3	55.0	49.0
Pre-implantation Loss (%)	6.6	9.3	6.9	4.5	10.2
Post-implantation Loss (%)	6.1	2.4	5.5	9.1	3.0

a Data obtained from pages 24 and 50-51 of the study report (MRID 46020303).
b Calculated by reviewers from data presented in this table
* Significantly different from controls; $p \leq 0.05$

B. DEVELOPMENTAL TOXICITY

1. External examination: External abnormalities are presented in Table 4a. No treatment-related external abnormalities were observed. The following external malformations were noted in single fetuses in their respective groups compared to 0 concurrent controls: (i) short digits at 0.5 mg/kg (0.5% fetuses; 4.3% litters); (ii) acephaly at 0.5 mg/kg (0.5% fetuses; 4.3% litters); (iii) umbilical hernia at 5 mg/kg (0.5% fetuses; 5.0% litters); and (iv) lordosis at 450 mg/kg (0.5% fetuses; 4.5% litters). These malformations were considered incidental because no dose

response was observed. Spina bifida (aperta) was observed in single fetuses in the 5 (0.5% fetuses; 5.0% litters) and 450 (0.5% fetuses; 4.5% litters) mg/kg groups compared to 0 concurrent controls; however, these observations fell within the range of historical controls (0.0-0.7% fetuses; 0.7-6.3% litters). Malrotated paw, a variation, was observed in one 0.5 mg/kg fetus (0.5% fetuses; 4.3% litters) and three 5 mg/kg fetuses (1.6% fetuses; 10.0% litters) compared to one concurrent control fetus (0.5% fetuses; 4.5% litters). However, dose-dependency was not observed; therefore, this finding was considered unrelated to treatment. No other external abnormalities were observed.

2. **Visceral examination:** Selected visceral abnormalities are presented in Table 4b. There were no treatment-related visceral findings. Gall bladder absent, a malformation, was observed in the 0.5 (0.5% fetuses; 4.3% litters), 50 (0.4% fetuses; 4.0% litters), and 450 (0.5% fetuses; 4.5% litters) mg/kg groups compared to 0 concurrent controls. However, dose-dependency was not observed; therefore, this finding was considered unrelated to treatment. Malpositioned kidney, marked dilated ureter, and short ureter, all malformations, and small kidney, serous ovarian cyst, and distended bladder, all variations, were all observed in one 450 mg/kg fetus (0.5% fetuses; 4.5% litters) compared to 0 concurrent controls. These findings were considered incidental. Hemorrhagic eye, a variation, was noted in the 50 (0.4% fetuses; 4.0% litters) and 450 (0.5% fetuses; 4.5% litters) mg/kg groups compared to 0 concurrent controls. This variation was considered incidental. All other visceral findings were unrelated to dose.

3. **Skeletal examination:** Selected skeletal abnormalities are presented in Table 4c. There were no treatment-related skeletal malformations. Open arches of the lumbar, sacral, and caudal vertebrae (spina bifida aperta), all malformations, were observed in one 450 mg/kg fetus (0.5% fetuses; 4.5% litters) compared to 0 concurrent controls. However, this finding fell within the range of historical controls (0.0-0.7% fetuses; 0.0-6.3% litters). All other skeletal malformations were unrelated to dose.

Increased ($p \leq 0.001$) presence of 27 pre-sacral vertebrae, a variation, was observed in the 5 (0.5% fetuses; 5.0% litters; not significant), 50 (10.5% fetuses; 28.0% litters), and 450 (15.3% fetuses; 31.8% litters) mg/kg groups compared to 0 concurrent or historical controls. Increased ($p \leq 0.001$) incidence of full supernumerary 13th rib, a variation, was noted in the ≥5 mg/kg groups (91.6-97.8% fetuses; 100% litters) vs concurrent (67.0% fetuses; 100% litters) or historical (54.0-80.4% fetuses; 93.8-100% litters) controls. Unossified 1st to 4th sternebrae, a variation, was observed in the 50 (1.3% fetuses; 12.0% litters) and 450 (1.5% fetuses; 13.6% litters) mg/kg groups compared to 0 concurrent and historical (0-0.6% fetuses; 0-5.0% litters) controls. Additionally, increased ($p \leq 0.05$) incidence of incomplete ossification of the ribs was observed in the 450 mg/kg group (3.6% fetuses; 22.7% controls) compared to 0 concurrent controls. This finding was also above the range of historical controls (0.0-0.7% fetuses; 0.0-6.3% litters). All of these variations were considered to be treatment-related. Incomplete ossification of the cervical vertebrae was observed in the 450 mg/kg group (0.5% fetuses; 4.5% litters); short supernumerary 14th rib was noted in the 50 (0.4% fetuses; 4.0% litters) and 450 (0.5% fetuses; 4.5% litters) mg/kg groups; and supernumerary ribs were observed in the 5 (0.5% fetuses; 5.0% litters) and 450 (1.5% fetuses; 9.1% litters) mg/kg groups, all compared to 0 concurrent or

historical controls. These findings were minor and incidental, and were not considered treatment related. All other skeletal variations were unrelated to dose.

Selected skeletal retardations are presented in Table 4d. Cartilage present in the ribs was observed in the 50 (1.3% fetuses; 12.0% litters) and 450 (3.6% fetuses; 22.7% litters) mg/kg groups compared to concurrent controls (0.5% fetuses; 4.5% litters), and increased ($p \leq 0.01$) incidence of fused cartilage in the ribs was noted in the 50 (3.5% fetuses; 20.0% litters) and 450 (4.1% fetuses; 22.7% litters) compared to 0 concurrent or historical controls. Both of these retardations were considered related to treatment. Cartilage was present in the cervical, sacral, and caudal vertebrae in the 450 mg/kg group (0.5% fetuses; 4.5% litters) compared to 0 concurrent or historical controls. These findings were considered incidental. All other skeletal retardations were unrelated to dose.

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

Observations	Dose (mg/kg bw/day)					
	0	0.5	5	50	450	Historical controls[b]
# Fetuses (# litters) examined	185 (22)	202 (23)	192 (20)	229 (25)	196 (22)	1220 (137)
Malformations						
Short digits	0 (0)	0.5 (4.3)	0 (0)	0 (0)	0 (0)	Not observed
Acephaly	0 (0)	0.5 (4.3)	0 (0)	0 (0)	0 (0)	Not observed
Umbilical hernia	0 (0)	0 (0)	0.5 (5.0)	0 (0)	0 (0)	Not observed
Lordosis	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)	Not observed
Spina bifida (aperta)	0 (0)	0 (0)	0.5 (5.0)	0 (0)	0.5 (4.5)	0-0.7 (0.7-6.3)
Total malformations	0 (0)	1.0 (8.7)	1.0 (10.0)	0 (0)	0.5 (4.5)	NA
Variations						
Malrotated paw	0.5 (4.5)	0.5 (4.3)	1.6 (10.0)	0 (0)	0 (0)	Not observed
Total variations	0.5 (4.5)	0.5 (4.3)	1.6 (10.0)	0 (0)	0 (0)	NA

a Data obtained from pages 53-56 in the study report (MRID 46020303).
b Historical control data obtained from page 361 in the study report.
NA Not applicable

Table 4b. Selected visceral abnormalities [% fetuses affected (% litters affected)][a]

Observations	Dose (mg/kg bw/day)					
	0	0.5	5	50	450	Historical controls[b]
#Fetuses (# litters) examined	185 (22)	201 (23)	190 (20)	229 (25)	196 (22)	914 (103)
Malformations						
Gall bladder						
absent	0 (0)	0.5 (4.3)	0 (0)	0.4 (4.0)	0.5 (4.5)	Not observed
Kidney						
malpositioned	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	Not observed
Ureter						
marked dilated	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	Not observed
short	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	Not observed
Total malformations	0.5 (4.5)	1.0 (8.7)	0 (0)	1.3 (12.0)	1.0 (9.1)	NA
Variations						
Eye						
hemorrhagic	0 (0)	0 (0)	0 (0)	0.4 (4.0)	0.5 (4.5)	Not observed
Kidney						
small	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	Not observed
Gonads						
serous cyst, ovary	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	Not observed
Bladder						
distended	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	Not observed
Total variations	2.2 (18.2)	2.0 (8.7)	1.6 (15.0)	2.2 (20.0)	1.0 (9.1)	NA

a Data obtained from pages 57-66 in the study report (MRID 46020303).
b Historical control data obtained from page 362 in the study report.
c Findings were observed in the same fetus (X30618) on pages 322-323.
NA Not applicable

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

Observations	Dose (mg/kg bw/day)					
	0	0.5	5	50	450	Historical controls[b]
#Fetuses (# litters) examined	185 (22)	201 (23)	190 (20)	229 (25)	196 (22)	643 (74)
Malformations						
Vertebrae						
lumbar, open arch	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	0-0.7 (0-6.3)
sacral, open arch	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	0-0.7 (0-6.3)
caudal, open arch	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)[c]	0-0.7 (0-6.3)
Total malformations	3.2 (27.3)	2.0 (17.4)	0 (0)	1.7 (16.0)	1.5 (13.6)	NA
Variations						
Vertebrae						
cervical, incomplete ossification	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)	Not observed
lumbar, presence of 27 pre-sacral	0 (0)	0 (0)	0.5 (5.0)	10.5*** (28.0)*	15.3*** (31.8)**	Not observed
Sternebrae						
unossified 1st to 4th	0 (0)	0.5 (4.3)	0 (0)	1.3 (12.0)	1.5 (13.6)	0-0.6 (0-5.0)
Ribs						
full supernumerary 13th	67.0 (100)	70.6 (95.7)	91.6*** (100)	97.8*** (100)	95.9*** (100)	54.0-80.4 (93.8-100)
incomplete ossification	0 (0)	0 (0)	0 (0)	0.9 (8.0)	3.6* (22.7)*	0-0.7 (0-6.3)
short supernumerary 14th	0 (0)	0 (0)	0 (0)	0.4 (4.0)	0.5 (4.5)	Not observed
supernumerary	0 (0)	0 (0)	0.5 (5.0)	0 (0)	1.5 (9.1)	Not observed
Total variations	88.6 (100)	94.0 (100)	98.4*** (100)	99.6*** (100)	99.5*** (100)	NA

a Data obtained from pages 67-79 in the study report (MRID 46020303).
b Historical control data obtained from pages 363-364 in the study report.
c Findings were found in one fetus (X30620) on page 327.
* Significantly different from controls, $p \leq 0.05$
** Significantly different from controls, $p \leq 0.01$
*** Significantly different from controls, $p \leq 0.001$
NA Not applicable

Table 4d. Skeletal retardations [% fetuses affected (% litters affected)][a]

Observations	Dose (mg/kg bw/day)					
	0	0.5	5	50	450	Historical controls[b]
#Fetuses (# litters) examined	185 (22)	201 (23)	190 (20)	229 (25)	196 (22)	643 (74)
Vertebrae						
cervical, cartilage present	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)	Not observed
sacral, cartilage present	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)	Not observed
caudal, cartilage present	0 (0)	0 (0)	0 (0)	0 (0)	0.5 (4.5)	Not observed
Ribs						
cartilage present	0.5 (4.5)	0 (0)	0.5 (5.0)	1.3 (12.0)	3.6 (22.7)	Not observed
cartilage fused	0 (0)	0 (0)	0 (0)	3.5** (20.0)	4.1** (22.7)*	Not observed
Total retardations	54.6 (95.5)	68.7** (100)	65.8* (100)	57.2 (96.0)	58.7 (86.4)	NA

a Data obtained from pages 80-87 in the study report (MRID 46020303).
b Historical control data obtained from pages 363-364 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: The oral administration of BAS 670H to pregnant New Zealand rabbits from implantation to 1 day prior to the day of hysterectomy (GD 6-28 inclusive) produced no signs of maternal toxicity at any dose level. The NOAEL for maternal toxicity was found to be 450 mg/kg/day; the NOAEL for developmental toxicity was found to be 0.5 mg/kg/day.

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.

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

2. **Developmental toxicity:**
   a. Deaths/Resorptions: There were no treatment-related effects on the number of dead fetuses, resorptions (early, late or complete litter), or on post-implantation losses.
   b. Altered Growth: Slightly lower fetal weight were observed in the 5, 50 and 450 mg/kg/day groups; however, no statistical significance was achieved. Increased incidence of unossified 1st to 4th sternebrae was observed in the 50 and 450 mg/kg groups compared to concurrent and historical controls. Additionally, increased ($p \leq 0.05$) incidence of incomplete ossification of the ribs was observed in the 450 mg/kg group compared to concurrent and historical controls. Cartilage present in the ribs was observed in the 50 and 450 mg/kg groups compared to concurrent controls, and increased ($p \leq 0.01$) incidence of fused cartilage in the ribs was noted in the 50 and 450 mg/kg groups compared to concurrent controls.
   c. Developmental Variations: At ≥5 mg/kg, increased ($p \leq 0.001$) incidences of the presence of 27 pre-sacral vertebrae and full supernumerary 13th rib compared to concurrent and historical controls were observed.

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

The developmental LOAEL is 5 mg/kg/day based on increased presence of 27 pre-sacral vertebrae and increased incidence of full supernumerary 13th rib. The developmental NOAEL is 0.5 mg/kg/day. There was no evidence of teratogenicity.

This study is classified as **acceptable/guideline (OPPTS 870.3700b)** in conjunction with MRID 45902210 and satisfies the requirements for a developmental study in the rabbit.

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

- Stability data for the test compound in vehicle was not provided
- No maternal LOAEL was observed; however, in the definitive study (MRID 45902210), a maternal LOAEL was observed at 450 mg/kg/day. Therefore, this study is acceptable in conjunction with the definitive study.

DATA FOR ENTRY INTO ISIS

Developmental Study - rabbits (870.3700b)

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	46020303	developmental	rabbit	GD 6-28	oral	gavage	0.5-450	0, 0.5, 5, 50, 450	450	Not observed		Maternal
123009	46020303	developmental	rabbit	GD 6-28	oral	gavage	0.5-450	0, 0.5, 5, 50, 450	0.5	5	Skeletal variations	Developmental

Deleted