DATA EVALUATION RECORD

BAS 670H

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

Work Assignment No. 1-01-11 S (MRID 46020304)

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

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

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

CITATION: Richard, J. (2003) Prenatal developmental toxicity study in Himalayan rabbits: oral administration (gavage). CIT, Evreux, France. Laboratory Project Id.: 40R0124/989169, March 21, 2003. MRID 46020304. Unpublished.

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

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 46020304), BAS 670H (Batch # N26; 95.8% a.i.) was administered in 0.5% aqueous caroxymethylcellulose orally via gavage, in a dosing volume of 10 mL/kg, to 25 female Himalayan Chbb:HM rabbits/group, at dose levels of 0, 50, 150, or 450 mg/kg/day, on gestation days (GD) 6 through 28. All surviving does were sacrificed on GD 29, and their fetuses were removed by cesarean and examined.

There were no treatment-related adverse effects observed on maternal mortality, clinical signs, body weight, food consumption, or gross pathology. There were no abortions, premature deliveries, or dead fetuses; and no effects of treatment on the number of litters, fetal body weight, or sex ratio. There were no other effects observed from the Cesarean section data to indicate treatment-related toxicity.

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

At ≥50 mg/kg/day, the incidence of extra sternebral ossification sites (skeletal malformation) increased dose-dependently. Full supernumerary (13th) ribs (skeletal variation) increased dose-dependently ($p \leq 0.001$) in all groups. Additionally short supernumerary 13th rib (skeletal

variation) was observed ($p \leq 0.05$) more frequently; however, this effect was not clearly dose-dependent.

At ≥150 mg/kg, unossified rib(s) were observed, and cartilage was present in the cervical vertebra(e). At 450 mg/kg/day, the following variations/cartilage effects were increased compared to the controls: incomplete ossification of the frontal, parietal, cervical vertebra(e), and rib(s); unossified interparietal, 1st metacarpal, and talus; cartilage present in the interparietal and metacarpal bone(s). Incomplete ossification of the 1st to 4th sternebra(e) was also observed at 450 mg/kg/day.

The developmental toxicity LOAEL is 50 mg/kg/day based on an increased incidence of extra sternebral ossification sites and supernumerary 13th rib. The developmental toxicity NOAEL was not observed.

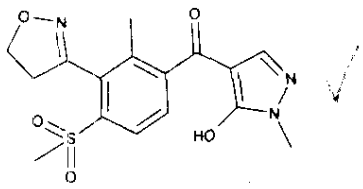
This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental toxicity study in the rabbit.

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

I. MATERIALS AND METHODS

A. MATERIALS

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

Description:	gold-yellow powder
Batch #:	N26
Purity:	95.8% a.i.
Compound Stability:	The compound was stable in the vehicle for 4 days at room temperature
CAS #:	210631-68-8
Structure:	

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

3. **Test animals**

Species:	Rabbit	
Strain:	Himalayan (Chbb:HM)	
Age at mating/ mean weight on GD 0:	22-25 weeks 2325-3025 g	
Source:	Boehringer Ingelheim Pharma KG (Biberach an der Riss, Germany)	
Housing:	Individually, in suspended stainless steel wire cages	
Diet:	Pelleted diet, Type 110 (UAR, Villemoisson, Epinay-sur-Orge, France), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	18±3°C
	Humidity:	50±20%
	Air changes:	about 12 cycles/hr
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	≥ 12 Days	

B. PROCEDURES AND STUDY DESIGN

1. **In life dates** - Start: 1/29/01 End: 3/13/01

2. **Mating:** Rabbits were artificially inseminated using the pooled ejaculate of males from the same strain (Charles River Laboratories, Sulzfeld, Germany). The day of insemination was designated as gestation day (GD) 0.

3. **Animal assignment:** The does were randomly assigned to dose groups as indicated in Table 1.

Table 1. Animal assignment [a]

Dose (mg/kg bw/day)	0	50 (LDT)	150 (MDT)	450 (HDT)
# Females	25	25	25	25

a Data were obtained from page 16 of MRID 46020304.

4. **Dose-selection rationale:** A dose-selection rationale was not provided.

5. **Dosage preparation and analysis:** Dose formulations were prepared by suspending the appropriate amount of test substance in 0.5% aqueous carboxymethylcellulose. The frequency of preparation and the storage conditions were not reported; however, the Sponsor stated that the compound stability was considered. The stability of the test substance for up to 96 hours at room temperature was verified in 10 mg/kg/day formulation prior to the study (results reported in MRID 46020302). Homogeneity (top, middle, bottom) and concentration analyses were determined in all dose formulations in duplicate, in the first and last weeks of the study.

Results -

Homogeneity (range as % CV): 0.9-4.9%

Stability (% of initial concentration): 96.2%

Concentration (range as % of nominal): 97.9-101.0%

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 in 0.5% aqueous carboxymethyl-cellulose orally via gavage on GD 6 through 28 in a dosing volume of 10 mL/kg bw, based on the most recent body weight.

C. OBSERVATIONS

1. **Maternal observations and evaluations:** All does were checked for clinical signs of toxicity at least once a day and for mortality twice daily during treatment and once daily otherwise. Food consumption (g/animal/day) and body weight was measured daily. Body weight gain was calculated for 2-3 day intervals throughout the study, Days 6-18 and 6-29. The corrected body weight gain was determined by subtracting the gravid uterine weight on GD 29 from the body weight gain (GD 6-29). On GD 29, all does were sacrificed and subjected to gross necropsy in which the thoracic and abdominal organs and the placentas were examined. The gravid uterus was removed from each doe and weighed. All fetuses were removed by cesarean section. The numbers of corpora lutea, and number and distribution of implantations, implant scars, live fetuses, dead fetuses, and early, late, and complete resorptions were recorded.

2. **Fetal evaluations:** Each fetus was weighed, sexed, and examined externally. Each fetus was then examined for visceral abnormalities. The heads of one half of the fetuses were removed,

fixed in Harrisson's fluid, and examined. The brain alone was examined in the remaining fetuses, after fixation in Bouin's fluid. The carcasses of the fetuses were fixed in ethanol, and the skeleton was stained with alizarin red S and alcian blue, and examined.

D. DATA ANALYSIS

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

Parameter	Statistical test
Food consumption Body weight, body weight gain (uncorrected and corrected), and carcass weight Weight of unopened uterus Number of corpora lutea, implantations, resorptions, and live fetuses Litter mean fetal body weight	ANOVA followed by Dunnett's test
Proportions of preimplantation loss, postimplantation loss, and fetal findings reported as percentage values Gross pathology	Fisher's exact test

2. Indices: The following indices were calculated:

Conception rate (%) = # pregnant animals/# inseminated animals x 100

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

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

3. Historical control data: Historical control data were not provided.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical observations: No treatment-related effects were observed on mortality or clinical signs. One 50 mg/kg/day female died intercurrently on GD 26. This female had soft feces from GD 14 until death; and at necropsy, dilatation of the lung and several brownish or reddish foci on the lung suggested that the death may have been due to an accident during gavage administration.

2. Body weight: No treatment-related effect was observed on body weight or body weight gain (Table 2). A statistical difference in body weights and body weight gain was not detected in any treatment group relative to the control. Although body weight gain in the treated groups was decreased by 12-32% for the treatment interval (GD 6-29), corrected for gravid uterine weights,

were similar to controls. Gravid uterine weights were decreased ($p \leq 0.05$) in the 50 and 450 mg/kg/day animals (↓22-23%); however, this effect was not clearly dose-dependent.

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

	Dose (mg/kg/day)			
Interval	0	50	150	450
Pre-treatment: GD 0-6 [b]	49	63	63	37
Treatment GD 6-8	-4±29	-3±33	-10±34	0±33
GD 8-10	9±30	11±37	14±28	0±33
GD 26-28	31±26	25±36	36±39	20±36
Treatment GD 6-18	95±49	78±66 (↓18)	61±80 (↓36)	40±67 (↓58)
GD 6-29	222±80	191±113 (↓14)	195±101 (↓12)	151±98 (↓32)
Gravid uterus (g)	390.7±60.3	305.0±113.1* (↓22)	328.3±118.6	301.4±77.8* (↓23)
Carcass[c] (g)	2444.3±145.8	2507.5±134.2	2490.0±184.5	2458.2±124.4
Net weight change GD 6-29	-168.8±91.6	-113.8±82.3	-132.9±133.7	-150.4±83.8

a Data (n=21-24) were obtained from pages 42-47 of MRID 46020304. Percent difference from controls, calculated by reviewers, is included in parentheses.
b Calculated by the reviewers from mean body weight data on pages 42 and 44 of MRID 46020304.
c Carcass weight = Terminal body weight minus uterine weight.
* Significantly different from the control at $p \leq 0.05$

3. **Food consumption:** No treatment-related decrease was observed on food consumption. An incidental change ($p \leq 0.05$) in food consumption was observed at 450 mg/kg/day on Days 13-14 and at 150 mg/kg/day on Days 28-29. A high occurrence of food spillage was observed in all groups, treated and control.

4. **Gross pathology:** No treatment-related macroscopic findings were observed in the maternal organs/tissues.

5. **Cesarean section data:** Pre-implantation loss was increased at 50 (19.8%) and 450 mg/kg/day (17.9%) vs controls (9.9%), and post-implantation loss was increased at 150 mg/kg/day (15.9%) vs controls (6.9%)(Table 3). The total number of live fetuses was decreased in all treated groups; however, statistical significance ($p \leq 0.05$) was observed at 150 mg/kg/day only. Although there was a dose-dependent decrease in the number of live fetuses/doe observed in all treated groups (↓18-23%), the treated groups were statistically similar to controls. There were no abortions, premature deliveries, or dead fetuses; and no effects of treatment on the number of litters, fetal body weight, or sex ratio.

Table 3. Cesarean section observations in the main study [a]

Observation	Dose (mg/kg bw/day)			
	0	50	150	450
# Animals Assigned (Mated)	25	25	25	25
# Animals Pregnant [b]	22	23	25	24
Pregnancy Rate (%) [c]	88	92	100	96
# Nonpregnant	3	2	0	2
Maternal Wastage				
# Died	0	1	0	0
# Died Pregnant	0	1	0	0
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	0	0
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	192	177	211	179
Corpora Lutea/Doe	8.7±1.8	8.0±1.7	8.4±1.6	7.8±2.5
Total # Implantations	173	142	176	147
(Implantations/Doe)	7.9±1.6	6.5±2.4	7.0±2.0	6.4±2.4
Total # Litters	21	22	24	21
Total # Live Fetuses	161	132	148* (↓8)	129
(Live Fetuses/Doe)	7.3±2.2	6.0±2.5 (↓18)	5.9±2.4 (↓19)	5.6±2.6 (↓23)
Total # Dead Fetuses	0	0	0	0
(Dead Fetuses/Doe)	0	0	0	0
Total # Resorptions [c]	9	10	20	14
Early	5	7	12	4
Late	4	3	8	10
Resorptions/Doe [c]	0.4	0.5	0.8	0.7
Early	0.2±0.6	0.3±1.1	0.5±0.8	0.2±0.4
Late	0.2±0.5	0.1±0.4	0.3±0.9	0.4±0.7
Litters with Complete Resorption	1	0	1	2
Fetal Weight (g)/litter - Total	35.8±2.8	34.3±3.2	35.1±3.7	33.1±4.0
Male	35.7±2.9	34.2±3.4	34.7±5.3	32.8±5.1
Female	35.8±3.7	34.2±3.5	35.1±4.0	32.7±4.9
Sex Ratio (% male)	54.7	46.2	48.0	43.4
Pre-implantation Loss (%)	9.9	19.8**	16.6	17.9*
Post-implantation Loss (%)	6.9	7.0	15.9*	12.2

a Data were obtained from pages 50-51 and 91-94 of MRID 46020304.
b Number pregnant was tabulated from individual data on pages 91-94 of MRID 46020304. The Sponsor reported the number of pregnant does alive at term.
c Calculated by the reviewer
* Significantly different from controls at $p \leq 0.05$
** Significantly different from controls at $p \leq 0.01$

B. DEVELOPMENTAL TOXICITY

1. External examination: External findings are presented in Table 4a. Meningocele and cranioschisis were observed in one fetus (0.8% fetuses; 4.8% litters) at 450 mg/kg. Historical controls were unavailable; however, it is unlikely that the findings in this single fetus are treatment-related.

2. Visceral examination: Selected visceral findings are presented in Table 4b. The following visceral findings were observed at 450 mg/kg (0.8% fetuses; 4.8% litters): (i) small cerebrum, corresponding to meningocele and cranioschiosis observed externally; (ii) markedly dilated renal pelvis and dilated ureter; (iii) discolored (dark red) liver and absent ovary; and (iv) absent abdominal viscera, small spleen, and whitish focus on the liver. Historical control data were unavailable.

3. Skeletal examination: Treatment-related effects on the skeletal system were observed (Table 4c). The incidence of extra sternebral ossification sites (malformations) increased dose-dependently in all treated groups (0.8-2.3 [4.5-14.3]) compared to controls (0 [0]). Supernumerary cervical vertebra and misaligned sternebra(e) (malformations) were observed (% fetuses affected [% litters affected]) at 450 mg/kg/day (0.8 [4.8]) compared to the controls (0 [0]). Full supernumerary (13^{th}) ribs increased dose-dependently ($p \leq 0.001$) in all groups. Additionally, the short supernumerary 13^{th} rib was observed ($p \leq 0.05$) more frequently in all treated groups (8.5-15.2 [38.1-54.5]); however, a dose-dependent relationship may not have existed. At ≥150 mg/kg, unossified rib(s) were observed (1.4-3.1 [8.3-9.5] treated vs 1.2 [4.8] controls), and cartilage was present in the cervical vertebra(e) (0.7-4.7 [4.2-19.0] treated [$p \leq 0.01$ at 450 mg/kg/day] vs 0 [0] controls). Additionally, at 450 mg/kg/day, the following variations/cartilage effects were increased compared to the controls (0 [0]): incomplete ossification of the frontal (0.8 [4.8]), parietal (0.8 [4.8]), cervical vertebra(e) (3.9 [19.0]; $p \leq 0.05$), and rib(s) (0.8 [4.8]); unossified interparietal (0.8 [4.8]), 1^{st} metacarpal (0.8 [4.8]), and talus (1.6 [9.5]); cartilage present in the interparietal (0.8 [4.8]) and metacarpal bone(s) (0.8 [4.8]); fused cartilage of ribs (1.6 [9.5]); and misshapen sternebra(e) (5.4 [19.0]; $p \leq 0.05$). Additionally, incomplete ossification of the 1^{st} to 4^{th} sternebra(e) was observed at 450 mg/kg/day (7.0 [38.1]; $p \leq 0.05$) compared to the controls (1.9 [9.5]).

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

Observations	Dose (mg/kg/day)			
	0	50	150	450
# Fetuses (litters) examined	161 (21)	132 (22)	148 (24)	129 (21)
Malformations				
Meningocele [b]	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Cranioschisis [b]	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Total external malformations	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Variations				
Malrotated paw	0.6 (4.8)	0.8 (4.5)	3.4 (16.7)	2.3 (9.5)
Malrotated limb	0.6 (4.8)	1.5 (9.1)	0.7 (4.2)	0 (0)
Blunt-tipped tail	0 (0)	0 (0)	0.7 (4.2)	0 (0)
Total external variations	1.2 (9.5)	2.3 (13.6)	4.7 (25.0)	2.3 (9.5)

a Data were obtained from pages 53-56 and 238 of MRID 46020304.
b Meningocele and cranioschisis were observed in the same fetus.

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

Observations	Dose (mg/kg/day)			
	0	50	150	450
# Fetuses (litters) examined	161 (21)	132 (22)	148 (24)	129 (21)
Malformations				
Small cerebrum	0 (0)	0 (0)	0 (0)	0.8 (4.8) [b]
Markedly dilated renal pelvis	0 (0)	0 (0)	0 (0)	0.8 (4.8) [c]
Absent ovary	0 (0)	0 (0)	0 (0)	0.8 (4.8) [d]
Absent abdominal viscera	0 (0)	0 (0)	0 (0)	0.8 (4.8) [e]
Total soft tissue malformations	0.6 (4.8)	1.5 (9.1)	4.7* (25.0)	3.9 (19.0)
Variations				
Small spleen	0 (0)	0 (0)	0 (0)	0.8 (4.8) [e]
Liver, whitish focus	0 (0)	0 (0)	0 (0)	0.8 (4.8) [e]
Liver, dark red lobe	0 (0)	0 (0)	0 (0)	0.8 (4.8) [d]
Dilated ureter	0 (0)	0 (0)	0 (0)	0.8 (4.8) [c]
Total soft tissue variations	13.0 (47.6)	15.9 (54.5)	17.6 (58.3)	17.8 (66.7)

a Data were obtained from pages 57-65 and 231-242 of MRID 46020304.
b Meningocele and cranioschisis were observed externally in this fetus, with small cerebrum observed viscerally.
c-e Findings denoted by the same superscript were observed in the same fetus.
* Significantly different from controls at $p \leq 0.05$

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

Observations	Dose (mg/kg/day)			
	0	50	150	450
# Fetuses (litters) examined	161 (21)	132 (22)	148 (24)	129 (21)
Malformations				
Extra sternebral ossification site	0 (0)	0.8 (4.5)	1.4 (8.3)	2.3 (14.3)
Supernumerary cervical vertebra	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Misaligned sternebra(e)	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Total skeletal malformations	10.6 (52.4)	8.3 (36.4)	4.1 (20.8)	10.9 (42.9)
Variations				
Full supernumerary 13th rib(s)	3.1 (19.0)	61.4*** (95.5)***	67.6*** (100)***	71.3*** (100)***
Short supernumerary 13th rib(s)	0.6 (4.8)	15.2*** (54.5)***	9.5*** (41.7)**	8.5** (38.1)*
Incomplete ossification of frontal	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Parietal	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Cervical vertebra(e)	0 (0)	0 (0)	0 (0)	3.9* (19.0)
1st to 4th sternebra(e)	1.9 (9.5)	2.3 (13.6)	2.0 (12.5)	7.0* (38.1)
Rib(s)	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Unossified interparietal	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Rib(s)	1.2 (4.8)	0.8 (4.5)	1.4 (8.3)	3.1 (9.5)
1st metacarpal(s)	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Talus	0 (0)	0 (0)	0 (0)	1.6 (9.5)
Cartilage present in interparietal	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Cervical vertebra(e)	0 (0)	0 (0)	0.7 (4.2)	4.7** (19.0)
Metacarpal bone(s)	0 (0)	0 (0)	0 (0)	0.8 (4.8)
Fused cartilage of ribs	0 (0)	0 (0)	0 (0)	1.6 (9.5)
Misshapen sternebra(e)	0.6 (4.8)	0.8 (4.5)	0 (0)	5.4* (19.0)
Total skeletal variations	77.0 (100)	84.8 (100)	84.5 (100)	84.5 (100)
Total skeletal cartilage	77.6 (100)	36.4 (77.3)	29.1 (87.5)	30.2 (71.4)

a Data were obtained from pages 66-85 of MRID 46020304.
* Significantly different from controls at $p \leq 0.05$
** Significantly different from controls at $p \leq 0.01$
*** Significantly different from controls at $p \leq 0.001$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that the maternal LOAEL was 450 mg/kg/day based on decreased food consumption and body weight gain. The maternal NOAEL is 150 mg/kg/day. The developmental LOAEL is 50 mg/kg/day based on a markedly higher incidence of skeletal variations, particularly the presence of 13 pairs of ribs. The developmental NOAEL was not observed.

B. REVIEWER COMMENTS

1. **Maternal toxicity:** The reviewers disagreed with the Sponsor's conclusions concerning food consumption and body weight gain. No statistically significant difference from controls were observed in body weights or body weight gain. Although body weight gain was decreased by 12-

32% for the treatment interval, the effect on body weight gain, corrected for gravid uterine weight, was unrelated to dose and was similar to the controls in the 450 mg/kg/day group. Gravid uterine weights were decreased ($p \leq 0.05$) at 50 and 450 mg/kg/day (↓22-23%); however, this effect was not clearly dose-dependent. Only incidental change ($p \leq 0.05$) in food consumption was observed at 450 mg/kg/day on Days 13-14, and at 150 mg/kg/day on Days 28-29, and food consumption in the high dose group was similar (↑2%; not statistically significant) to the controls during the treatment period (Days 6-29).

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

2. Developmental toxicity

a. Deaths/Resorptions: A treatment-related adverse effect was not observed. Pre-implantation loss was increased at 50 (19.8%) and 450 mg/kg/day (17.9%) vs controls (9.9%), and post-implantation loss was increased at 150 mg/kg/day (15.9%) vs controls (6.9%). The effect on live fetuses and pre/post-implantation loss seemed unrelated to dose. Although there was a dose-dependent decrease in the number of live fetuses/doe observed in all treated groups (↓18-23%), the treated groups were statistically similar to controls,

b. Altered Growth: At ≥150 mg/kg, unossified rib(s) were observed, and cartilage was present in the cervical vertebra(e). At 450 mg/kg/day, the following variations/cartilage effects were increased compared to the controls: incomplete ossification of the frontal, parietal, cervical vertebra(e), and rib(s); unossified interparietal, 1st metacarpal, and talus; cartilage present in the interparietal and metacarpal bone(s). Additionally, incomplete ossification of the 1st to 4th sternebra(e) was observed at 450 mg/kg/day.

c. Developmental Variations: Full supernumerary (13th) ribs increased dose-dependently ($p \leq 0.001$) in all groups. Short supernumerary 13th rib was observed ($p \leq 0.05$) more frequently in all treated groups; however, a dose-dependent relationship may not have existed.

d. Malformations: The incidence of extra sternebral ossification sites increased dose-dependently in all treated groups compared to controls.

The developmental toxicity LOAEL is 50 mg/kg/day based on an increased incidence of extra sternebral ossification sites and supernumerary 13th rib. The developmental toxicity NOAEL was not observed.

This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental study in the rabbit.

C. STUDY DEFICIENCIES: Historical control data were not provided.

DATA FOR ENTRY INTO ISIS

Developmental Study - rabbit (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	Endpoint(s)	Comments
123009	46020304	developmental	rabbit	GD 6-28	oral	gavage	50-450	0, 50, 150, 450	450	not observed		maternal
123009	46020304	developmental	rabbit	GD 6-28	oral	gavage	50-450	0, 50, 150, 450	not observed	50	skeletal malformations and variations	developmental

Deleted