DATA EVALUATION RECORD

BAS 670H

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

Work Assignment No. 1-01-11 M (MRID 45902211)

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: 2/9/04

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

Signature: John W Allran
Date: 02/09/04

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

Signature: Mary L Menetrez
Date: 02-09-04

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 2/9/04

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.
Toxicology Branch, Health Effects Division (7509C)
EPA Work Assignment Manager: P. V. Shah, Ph.D.
Registration Action Branch 1, Health Effects Division (7509C)
PMRA Reviewer: Michael Honeyman
Fungicide and Herbicide Toxicological Evaluation Section, Health Evaluation Division

Signature: [signature] **Date** 7/26/2005
Signature: [signature] **Date** 7/27/05
Signature: [signature] **Date** 8/30/05
Template version 11/01

TXR#: 0052097

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 (98.7% a.i.)

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

CITATIONS: Schneider, S., Deckardt, K., and Hellwig, J. (2003) BAS 670H - Prenatal developmental toxicity study in New Zealand white rabbits: oral administration (gavage). Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. Laboratory Project ID: Project No. 40R0124/98170, BASF Registration Document No. 2003/1006257, March 13, 2003. MRID 45902211. Unpublished.

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

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45902211), BAS 670H (Lot/Batch # WH 20089, 98.7% a.i.) 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 [Crl:KBL (NZW)] rabbits/group on gestation days (GD) 6 through 28 at dose levels of 0, 5, 50, or 500 mg/kg. Blood was taken from all does on GD 28 for measurement of serum tyrosine levels. All does were sacrificed on GD 29; their fetuses were removed by cesarean section and examined. Skeletal examinations were not performed.

No effects of treatment were observed on maternal survival, clinical signs, body weights, body weight gains, food consumption, or gross pathology. Significantly increased tyrosine levels were observed in the sera of all treatment groups (↑6-12X). Increased tyrosine levels reached a plateau value at 50 mg/kg/day.

The maternal NOAEL was not observed. The maternal LOAEL was 5 mg/kg/day based on increased tyrosine level.

There were no treatment-related effects on the numbers of litters or fetuses (live or dead). Increased resorptions (early, late, and complete litter) were observed at 500 mg/kg (not significant), resulting in increased ($p \leq 0.05$) post-implantation loss compared to concurrent and historical controls. Increased incidence of unilateral absent kidney and ureter were observed in the 50 and 500 mg/kg fetuses compared to concurrent and historical controls. There were no treatment-related external malformations.

There were no treatment-related external or visceral variations.

Mean gravid uterine weights were decreased ($p \leq 0.05$) at 500 mg/kg; however, fetal weights were comparable to controls. This decrease was considered to be due to a small decrease in the number of fetuses at this dose level.

Under the condition of this study, increased incidence of unilateral absent kidney and ureter was observed at 50 mg/kg/day. However, a NOAEL/LOAEL can not be established because fetal skeletal examination was not performed in this study; skeletal abnormality has been observed at lower dose in other developmental studies.

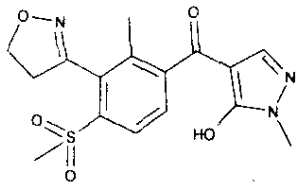
This study is classified as **Unacceptable/guideline (OPPTS 870.3700b)** because fetal skeletons were not evaluated for abnormalities and does not satisfy guideline requirement for a developmental toxicity study.

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:	Light brown powder
Lot/Batch #:	WH 20089
Purity:	98.7% 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 [Crl:KBL (NZW)]	
Age/body weight range on GD 1:	17-19 weeks/2859-4041 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: November 18, 2002 End: December 19, 2002

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 was designated as gestation day (GD) 0. Rabbits were shipped on GD 0 and arrived at the performing laboratory on GD 1.

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

Table 1. Animal assignment [a]

Dose (mg/kg bw/day)	0	5	50	500
# Females	25	25	25	25

a Data obtained from page 22 of the study report.

4. **Dose selection rationale:** It was stated that doses were chosen as follows: 5 mg/kg was expected to be the NOAEL; 50 mg/kg was selected as the intermediate dose level; and 500 mg/kg was expected to cause maternal and possible developmental toxicity. No other information regarding dose selection was provided.

5. **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 was suspended in (doubly-distilled) aqueous 0.5% (w/v) carboxymethylcellulose using a high-speed homogenizer and stirred during dosing. Homogeneity was confirmed by analyses of three samples (top, middle, and bottom) for the low and high dose formulations prepared for use on the first day of treatment. Concentration was confirmed by analysis of samples for all dose formulations prepared at the beginning and toward the end of the administration period. For stability analysis, the test substance (Batch N26; 95.8% a.i.) 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): 2.0-2.4%

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): 84.0-100.6

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 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. On GD 28, non-fasted does were bled by puncture of an ear vein for determination of serum tyrosine concentrations. 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. All rabbits were necropsied, and the numbers of corpora lutea, and the number and distribution of live and dead fetuses, resorptions (early and late), and implantation sites were recorded. Does that died or were sacrificed prematurely were examined according to the same procedures as those killed on schedule, except that gravid uterine weights were not determined.

2. Fetal evaluations: On removal from the uterus, all fetuses were weighed, given a detailed external examination, and viability and the condition of the placentae, umbilical cords, fetal membranes, and fluids were recorded. 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 per doe (and any 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, and the carcasses were stained and archived. Detailed examination of the skeleton and cartilage was not 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 for gravid uterine weight), 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, 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 levels	Non-parametric Kruskal-Wallis (two-sided), followed by Wilcoxon's test (two-sided) if significant

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 section 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 section 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 5.0 mg/kg female was found dead; one control female died following a gavage error; one control female was sacrificed after abortion; and one 500 mg/kg female was sacrificed in moribund condition. No clinical signs were observed in any of these animals prior to death. There were no other deaths.

Table 2. Maternal clinical observations (# animals affected)[a]

Observation	Dose (mg/kg bw/day)			
	0	5	50	500
Found dead	0	1	0	0
Died after gavage error	1	0	0	0
Sacrificed after abortion	1	0	0	0
Sacrificed moribund	0	0	0	1

a Data obtained from pages 36 and 57-59 of the study report; n=25.

2. **Body weight:** Body weight gain data are shown in Table 3. No treatment-related effects were observed on body weights, body weight gains, or body weight gains from GD 6, either uncorrected or corrected for gravid uterus weights. A decrease ($p \leq 0.05$) in gravid uterine weight was observed in the 500 mg/kg does (↓18%). An increase ($p \leq 0.05$) in body weight gain was noted in the 50 mg/kg group on GD 16-19, but this increase was not dose-dependent.

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

Interval	Dose in mg/kg bw/day (# Does)			
	0 (21-22)	5 (23-24)	50 (22)	500 (21-22)
Pretreatment:GD 1-6	275.6±76.17	215.0±112.07	280.6±98.38	265.3±112.43
Treatment: GD 6-9	53.3±45.6	63.5±75.0	65.9±69.1	39.8±83.0
GD 9-11	59.9±34.0	61.6±84.8	61.5±43.3	55.0±40.7
GD 16-19	25.3±97.4	38.2±71.8	85.5±87.6*	37.0±63.1
Treatment: GD 6-28	357.5±120.01	425.7±212.72	458.8±152.82	313.2±260.07
Overall: GD 1-29	629.9±148.68	641.4±242.98	729.7±191.11	602.4±261.24
Gravid uterus	474.4±103.46	483.1±79.15	476.4±86.36	388.2±148.60* (↓18)
Carcass[b]	3499.5±226.75	3422.9±312.05	3573.9±325.86	3536.0±396.07
Net change[c]:GD 6-29	-121.4±143.45	-53.8±204.68	-27.3±140.73	-44.7±290.61

a Data obtained from pages 68-69 of the study report. Percent differences from controls, calculated by reviewers, are included in parentheses.
b Carcass = terminal body weight - gravid uterine weight
c Net weight change = carcass - GD 6 body weight
* Significantly different from controls; $p \leq 0.05$

3. **Food consumption:** No treatment-related effect was observed on food consumption. Sporadic decreases ($p \leq 0.05$) and increases ($p \leq 0.05$) were observed in all treatment groups, but dose-dependency was not observed.

4. **Serum tyrosine concentration:** Serum tyrosine levels were increased (↑638-1281%; $p \leq 0.01$) in the ≥5 mg/kg does (Table 4), reaching a plateau value at 50 mg/kg.

Table 4: Mean (±SD) maternal serum tyrosine concentrations (µmol/L)[a]

Observation	Dose in mg/kg bw/day (# Does)			
	0 (23)	5 (25)	50 (25)	500 (24)
Serum tyrosine (µmol/L)	66.86±18.42	493.17±114.09** (↑638)	923.44±341.31** (↑1281)	921.10±223.68** (↑1278)

a Data obtained from page 75 of the study report. Percent differences from controls, calculated by reviewers, are included in parentheses.

** Significantly different from controls; p≤0.01

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. Early, late, and complete litter resorptions were increased at 500 mg/kg (not significant), resulting in significantly increased post-implantation loss (19.2%; p≤0.05) compared to concurrent (4.5%) and historical (8.4-12.5%) controls. No effects of treatment were noted on numbers of litters, live fetuses, fetal body weight, placental weight, or sex ratio.

Table 5. Cesarean section observations[a]

Observation	Dose (mg/kg bw/day)			
	0	5	50	500
# Animals Assigned (Mated)	25	25	25	25
# Animals Pregnant	23	24	22	22
Pregnancy Rate (%)	92	96	88	88
# Nonpregnant	2	1	3	3
Maternal Wastage				
# Died	2	1	0	1
# Died Pregnant	1	1	0	1
# Died Nonpregnant	0	0	0	0
# Aborted	1	0	0	0
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	205	246	223	198
Corpora Lutea/Doe	9.8±2.07	10.7±1.58	10.1±1.93	9.4±2.20
Total # Implantations	192	225	216	178
(Implantations/Doe)	9.1±2.48	9.8±1.24	9.8±2.02	8.5±2.96
Total # Litters	21	23	22	19
Total # Live Fetuses	183	209	192	146
(Live Fetuses/Doe)	8.7±2.49	9.1±1.76	8.7±1.80	7.7±2.79
Total # Dead Fetuses	0	0	2	0
(Dead Fetuses/Doe)	0.0±0.0	0.0±0.0	0.1±0.4	0.0±0.0
Total # Resorptions	9	16	22	32
Early	6	4	9	13
Late	3	12	13	19
Total Resorptions/Doe	0.4±0.68	0.7±1.33	1.0±1.07	1.5±2.40
Early	0.3±0.64	0.2±0.49	0.4±0.59	0.6±0.86
Late	0.1±0.36	0.5±1.31	0.6±0.85	0.9±2.39
Complete Litter Resorption	0	0	0	2
Mean Fetal Weight (g)/litter	38.9±4.42	36.8±5.35	37.0±4.21	36.7±5.62
Males	39.3±4.69	38.1±5.21	37.1±4.72	37.7±5.75
Females	38.4±4.87	36.1±5.82	36.8±4.50	35.3±4.91
Mean Placental Weight (g)/litter	5.1±0.67	4.8±0.64	5.2±0.80	5.3±1.10
Males	5.1±0.76	4.9±0.68	5.2±0.79	5.3±1.02
Females	5.1±0.68	4.6±0.66	5.2±0.86	5.1±0.96
Sex Ratio (Mean % Male)	56.3	52.2	51.0	50.7
Pre-implantation Loss (%)	7.5±12.76	7.5±11.55	3.0±7.32	12.9±21.25
Post-implantation Loss (%)	4.5±7.36	7.2±12.99	10.4±10.52	19.2±30.03*

a Data obtained from pages 36, 72-74, 76, and 137-140 of the study report.
* Significantly different from controls; $p \leq 0.05$

B. DEVELOPMENTAL TOXICITY

1. External examination: External malformations are presented in Table 6a. No treatment-related external malformations were observed. Gastroschisis was noted in the 50 (0.5% fetuses; 4.5% litters) and 500 (1.4% fetuses; 11.0% litters) mg/kg fetuses compared to 0 concurrent and historical controls. This finding was minor and considered incidental. Acaudate was observed in single 50 (0.5% fetuses; 4.5% litters) and 500 (0.7% fetuses; 5.3% litters) mg/kg fetuses; and

thoracoschisis and cleft palate were each noted in single 500 mg/kg fetuses (0.7% fetuses; 5.3% litters), all compared to 0 concurrent and historical controls. These findings were all considered incidental. Malrotated limb was noted in single 5 (0.5% fetuses; 4.3% litters), 50 (0.5% fetuses; 4.5% litters), and 500 (0.7% fetuses; 5.3% litters) mg/kg fetuses compared to 0 concurrent controls; however, this finding fell within the fetal range of historical controls (0.0-0.9% fetuses; 0.0-3.6% litters). All other external malformations were unrelated to dose. There were no dose-related external variations or unclassified findings.

2. **Visceral examination:** Selected visceral malformations are presented in Table 6b. Unilateral absent kidney and ureter were observed in the 50 (2.6% fetuses; 18.0% litters) and 500 (5.5% fetuses; 21.0% litters) mg/kg fetuses compared to 0 concurrent controls. These findings exceeded the range of historical controls (0.0-0.5% fetuses; 0.0-4.2% litters) and were considered treatment-related. Small lung, absent lobus superior sinister, and diaphragmatic hernia were each noted in single 500 mg/kg fetuses compared to 0 concurrent and historical controls. These findings were considered incidental. All other visceral malformations were unrelated to dose. There were no dose-related visceral variations or unclassified findings.

3. **Skeletal examination:** Fetuses were not examined for skeletal abnormalities.

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

Observations	Dose (mg/kg bw/day)				
	0	5	50	500	Historical controls[b]
# Fetuses (# litters) examined	183 (21)	209 (23)	194 (22)	146 (19)	601 (73)
Gastroschisis	0 (0)	0 (0)	0.5 (4.5)	1.4 (11.0)	Not observed
Acaudate	0 (0)	0 (0)	0.5 (4.5)	0.7 (5.3)	Not observed
Thoracoschisis	0 (0)	0 (0)	0 (0)	0.7 (5.3)	Not observed
Cleft palate	0 (0)	0 (0)	0 (0)	0.7 (5.3)	Not observed
Malrotated limb	0 (0)	0.5 (4.3)	0.5 (4.5)	0.7 (5.3)	0.0-0.9 (0.0-3.6)
Anal atresia	0 (0)	0 (0)	0.5 (4.5)	0 (0)	Not observed

a Data obtained from pages 78-79 in the study report.
b Historical control data obtained from page 220 in the study report.
* Significantly different from controls; $p \leq 0.05$

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

Observations	Dose (mg/kg bw/day)				
	0	5	50	500	Historical controls[b]
# Fetuses (# litters) examined	183 (21)	209 (23)	194 (22)	146 (19)	601 (73)
Absent kidney	0 (0)	0 (0)	2.6 (18.0)	5.5 (21.0)*	0.0-0.5 (0.0-4.2)
Absent ureter	0 (0)	0 (0)	2.6 (18.0)	5.5 (21.0)*	0.0-0.5 (0.0-4.2)
Small lung	0 (0)	0 (0)	0 (0)	0.7 (5.3)	Not observed
Absent lobus superior sinister	0 (0)	0 (0)	0 (0)	0.7 (5.3)	Not observed
Diaphragmatic hernia	0 (0)	0 (0)	0 (0)	0.7 (5.3)	Not observed

a Data obtained from pages 84-87 in the study report.
b Historical control data obtained from page 223 in the study report.
* Significantly different from controls; $p \leq 0.05$

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The NOAEL for maternal toxicity is 500 mg/kg body weight/day. Serum tyrosine levels were increased ($p \leq 0.01$) in the ≥5 mg/kg does; however, in the absence of corroborating data, this finding was not considered adverse. The test substance caused effects on fetal morphology, namely unilateral absent kidneys/ureters, at doses of ≥50 mg/kg. At 500 mg/kg, signs of embryo/fetotoxicity were demonstrated by increased post-implantation loss and decreased mean gravid uterine weight. The developmental NOAEL is 5 mg/kg body weight/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. Significantly increased tyrosine levels were observed in the sera of all treatment groups (↑6-12X). Increased tyrosine levels reached a plateau value at 50 mg/kg/day..

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

The maternal NOAEL was not observed. The maternal LOAEL is 5 mg/kg/day based on increased tyrosine level.

2. **Developmental toxicity:**

a. Deaths/Resorptions: There were no treatment-related effects on the numbers of litters or fetuses (live or dead). Increased resorptions (early, late, and complete litter) were observed at 500 mg/kg (not significant), resulting in increased ($p \leq 0.05$) post-implantation loss (19.2%) compared to concurrent (4.5%) and historical (8.4-12.5%) controls.

b. Altered Growth: Mean gravid uterine weights were decreased (↓18%; p≤0.05) at 500 mg/kg; however, fetal weights were comparable to controls. This decrease was considered to be due to a small decrease in the number of fetuses at this dose level.
c. Developmental Variations: There were no treatment-related external or visceral variations. Fetal skeletons were not evaluated.
d. Malformations: Increased incidence of unilateral absent kidney and ureter were observed in the 50 (2.6% fetuses; 18.0% litters) and 500 (5.5% fetuses; 21.0% litters) mg/kg fetuses compared to concurrent (0) and historical (0.0-0.5% fetuses; 0.0-4.2% litters) controls. There were no treatment-related external malformations.

Under the condition of this study, increased incidence of unilateral absent kidney and ureter was observed at 50 mg/kg/day. However, a NOAEL/LOAEL can not be established because fetal skeletal examination was not performed in this study; skeletal abnormality has been observed at lower dose in other developmental studies.

This study is classified as **Unacceptable/guideline (OPPTS 870.3700b)** because fetal skeletons were not evaluated for abnormalities and does not satisfy the requirements for a developmental study in the rabbit.

C. **STUDY DEFICIENCIES:** The following deficiencies were noted:

- A dose selection rationale was not provided.
- Fetal skeletons were not evaluated for abnormalities.
- 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 to be reviewed 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	45902211	developmental	rabbit	GD 6-28	oral	gavage	5-500	0, 5, 50, and 500	Not established	5	Incr. Tyrosine level	Maternal
123009	45902211	developmental	rabbit	GD 6-28	oral	gavage	5-500	0, 5, 50, and 500	Not established	Not established	Kidney	Developmental

Deleted