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DATA EVALUATION RECORD

GLUFOSINATE - AMMONIUM

Study Type: §83-3(b); Testing of Hoe 061517:
For Embryotoxicity in the Himalayan Rabbit After Oral Administration

Work Assignment No. 2-37A (MRID 44076210)

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:
Sandra Daussin

Signature: Sandra Daussin
Date: 12/3/96

Secondary Reviewer:
Michael Norvell, Ph.D.

Signature: Michael Norvell
Date: 12/12/96

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

Signature: Mary L Menetrez
Date: 1/7/97

Quality Assurance:
William Spangler, Ph.D.

Signature: William J Spangler
Date: 01/09/97

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EPA Reviewer: Whang Phang, Ph.D. 2/12/98
Review Section III, Toxicology Branch II (7509C)

EPA Secondary Reviewer: Susan L. Makris, M.S. 6/1/98
Review Section III, Toxicology Branch II (7509C)

012647

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - Rabbit
OPPTS Number: 870.3700 OPP Guideline Number: §83-3(b)

DP BARCODE: D229929 SUBMISSION CODE: S509558
P.C. CODE: 128850 TOX. CHEM. NO.: 580I

TEST MATERIAL (PURITY): Hoe 061517 (99.6%)(a metabolite of glufosinate ammonium)

SYNONYMS: 3-methylphosphinoco-propionic acid

CITATION: Albrecht, M. and Baeder, C. (1994) Testing of Hoe 061517 - Substance Technical (Code: Hoe 061517 0Q ZC99 0003) For Embryotoxicity in the Himalayan Rabbit After Oral Administration. Hoechst Aktiengesellschaft, 6230 Frankfurt am Main 80, Germany. Laboratory Study Numbers, RK0546 & 87.0727; Report Number A52160, February 2, 1994. MRID 44076210. Unpublished.

SPONSOR: AgrEvo USA Company, Little Falls Centre One, 2711 Centerville Road, Wilmington, DE

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44076210) Hoe 061517 (a metabolite of glufosinate ammonium) (99.6% a.i.) in distilled water was administered to 15 Hoe:HIMK (SPFWiga) Himalayan rabbits/dose/group by gavage at dose levels of 0, 50, 100, or 200 mg/kg/day from days 6 through 18 of gestation.

Maternal toxicity was demonstrated at 100 mg/kg/day, as a dose-related increase in abortions (7% vs. 0% in controls) and mortality (7% vs. 0% in controls), clinical signs (disequilibrium), and reductions in food and water consumption, body weight gain, and fecal output. At 200 mg/kg/day, maternal toxicity was demonstrated by treatment-related clinical signs of toxicity (disequilibrium, and/or straddled fore-limbs), increases in abortions (27% vs. 0% in controls) and mortality (33% vs. 0% in controls), reductions in body weight gain, food and water consumption, and fecal output. In addition, treatment-related gross pathology was noted in the kidneys of the high-dose animals and was characterized as uneven, rough surface of one high-dose

dam, and light-brown coloring of the renal cortex of three of the four aborting high-dose dams. Corroborative treatment-related increases in the mean kidney weights was also noted at 200 mg/kg/day.

At 50 mg/kg level, no treatment-related deaths or effects were reported. **The maternal LOEL is 100 mg/kg/day, based on increased abortions and mortality and reductions in food and water consumption, body weight gain, and fecal output. The maternal NOEL is 50 mg/kg/day.**

There were no treatment-related effects noted in developmental parameters at any dose level. **A developmental LOEL was not observed (>200 mg/kg/day). The developmental NOEL is 200 mg/kg/day.**

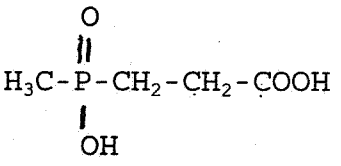
This developmental toxicity study in the rabbit is classified as **Unacceptable/Guideline** and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in the rabbit. In order to upgrade the study, the sponsor must submit data confirming the nominal concentrations of the administered doses and the stability of the test substance in distilled water.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Hoe 061517; 3-methylphosphinoco-propionic acid (a metabolite of glufosinate ammoniun)
   Description: Technical, white powder
   Lot/Batch #: H 404
   Purity: 99.6% a.i.
   CAS #: 77182-82-2
   Structure:



2. Vehicle: Distilled water

3. Test animals: Species: Himalayan rabbit
Strain: Hoe:HIMK (SPFWiga)
Age at mating: 7-8 months
Weight at mating: 2653 ± 164 g
Source: Hoechst breeding colony, Frankfurt, Germany
Housing: Individually (except during mating) in metal-barred cages with wire-mesh floors
Diet: ERKA 6000 standard diet, ad libitum
Water: Tap water, ad libitum
Environmental conditions:
Temperature: 21.0 - 22.5 C
Humidity: 38 - 67%
Air changes: 16-20/hr
Photoperiod: 14 hrs dark/10 hrs light
Acclimation period (P): At least 7 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - Start: 8/11/88 End: 10/26/88

2. Mating: Females in estrous were paired on a 1:1 basis with stock males of the same strain. Animals with sperm in the vaginal smear were mated again after 6 hours to assure that a successful mating occurred. Day 0 of gestation was designated as the day of mating.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. Assignment was random.

Table 1. Animal assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	15
Low (LDT)	50	15
Mid (MDT)	100	15
High (HDT)	200	15

4. Dose selection rationale: In a range-finding study summarized in the current submission, Hoe 061517 (% a.i. not indicated) was administered orally to 2 pregnant rabbits/dose at dosages of 0, 20, 40, 160, 250, 400, or 1250 mg/kg/day on days 6 to 18 of gestation. Dams were sacrificed on day 29 of gestation.

There were no treatment-related findings in either the dams or the fetuses at doses ≤160 mg/kg/day. At 250 mg/kg/day, one dam was found dead on day 13 of gestation following flabbiness, disequilibrium, marked anorexia, and weight loss. The other dam dosed at 250 mg/kg/day lost weight during the first week of treatment but delivered normally developed live fetuses. At 400 mg/kg/day one dam was sacrificed moribund on day 10 of gestation, and the other dam was weak, showed signs of disequilibrium, and aborted by day 10 of gestation. At 1250 mg/kg/day, both dams were found dead on day 8 of gestation.

Based upon these results, the subsequent full developmental toxicity study in rabbits was conducted at dosages of 0, 50, 100, or 200 mg/kg/day.

5. Dosage preparation and analysis: Test substance formulations were prepared daily by mixing appropriate amounts of test substance with distilled water and were administered within 3 hours of preparation. Prior to the start of the study, stability of the test substance in water was evaluated for a period of 5 hours at an unspecified temperature. Concentrations of the formulations were not evaluated or were not reported.

   Results - Stability Analysis: The study report states that the stability of the solutions "was guaranteed for 5 hours after preparation (Analytical Laboratory Hoest AG, statement of 9/7/88)."

   Data are required to confirm the nominal concentration of the administered doses and the stability of the test substance in distilled water.

6. Dosage administration: All doses were administered once daily by gavage, on gestation days 6 through 18, in a volume of 5 ml/kg of body weight/day. Dosing was based on the most recent body weight determination.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked for mortality and clinical signs daily. Body weight data were recorded on gestation days 0, 6, 13, 19, and 29 and food consumption data were recorded for gestation days 0-6, 6-13, 13-19, and 19-29. Dams were sacrificed on day 29 of gestation. Examinations at sacrifice consisted of a gross exam of the thoracic and abdominal cavities and the following organs were weighed: heart, liver, kidneys, and spleen. The reproductive tract was removed and the

following were recorded:
- number of implantation sites
- number of live and dead fetuses
- number of resorptions (early and late)
- number of corpora lutea in each ovary
- placental weights

2. Fetal Evaluations - Each fetus was weighed, examined for signs of life and external abnormalities and the sex was recorded. Fetuses were reared for 24 hours in an incubator at 32°C with a relative humidity of 60%. The number of fetuses that died during this period was recorded. Surviving fetuses were then sacrificed and the crown to rump length was determined. All fetuses were fixed in alcohol and a gross exam of the viscera was performed. According to the report, brain, eyes, heart and both kidneys were removed, fixed in Bouin's fluid, cross-sectioned, and examined. The bodies were then eviscerated, cleared (aqueous KOH), and stained with Alizarin Red S to examine for skeletal alterations.

D. DATA ANALYSIS

1. Statistical analyses: All data collected were subjected to routine appropriate statistical procedures.

2. Indices: Preimplantation and postimplantation loss indices were calculated from cesarean section records of animals in the study. Percent fetal survival at 24 hours after delivery was also calculated. Formulas used for their calculation were not provided.

3. Historical control data: Selected historical data were provided. Historical data for developmental toxicity did not include dates of collection, individual study data, litter incidence, or mean fetal incidence.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: At 100 mg/kg/day, one dam was found dead on day 24 of gestation and one dam was sacrificed on day 22 after hemorrhaging vaginally and aborting. The dam that died was flabby for 7 days prior to death and the dam that aborted exhibited disequilibrium in the 2 days prior to aborting. As a reflection of reduced food consumption, fecal output in these animals was also decreased. The abortion, death, and clinical signs

(flabbiness or disequilibrium) in these animals were treatment-related.

At 200 mg/kg/day, five dams were found dead on days 18-20 of gestation. Four additional high-dose dams were sacrificed on days 16, 17, or 25 after hemorrhaging vaginally and aborting. Treatment-related clinical signs that were noted in the high-dose animals that died or aborted included flabbiness and/or disequilibrium. These observations were persistent, lasting between 1 and 7 days and first appeared between days 12 to 18 of gestation. In addition, one of the high-dose dams that died exhibited straddled fore-limbs. Fecal output was also decreased in the high-dose animals that died or aborted.

In addition, one dam at 200 mg/kg/day aborted on day 3 of gestation (prior to treatment), and one dam at 50 mg/kg/day died from faulty intubation. However, these animals were replaced and were not evaluated further in the study.

No treatment-related clinical findings or deaths were observed at 50 mg/kg/day.

2. Body Weight - Mean body weights and body weight gain data are summarized in Table 2. Body weight gains were not corrected for gravid uterine weights and the data presented only include pregnant animals that survived until the day 29 sacrifice. For these animals, body weight gains were comparable to the controls at all dose levels. For the dams that died and/or aborted in the mid- and high-dose groups, body weight gains were either stagnated or the animals experienced a weight loss during treatment.

Table 2. Maternal body weight and body weight gain (g)

Interval	Dose in mg/kg/day (# of Dams)[a]			
	Control (15)	50 (15)	100 (13)	200 (6)
Pretreatment: Days 0-6	2661±155[b] 21.2[c]	2683±166 41.1	2633±134 24.9	2668±203 43.3
Treatment: Days 6-13	2679±149 14.7	2701±151 -3.8	2649±123 7.4	2680±183 -19.3
Treatment: Days 13-19	2716±143 58.1	2738±114 76.7	2683±116 60.5	2695±193 48.3
Posttreatment: Days 19-29	2817±166 144.8	2840±116 127.6	2785±124 144.5	2799±215 160.3

a Nonpregnant animals, dams aborting, and those not surviving to Day 29 were excluded from the means.
b Mean body weight data excerpted from the report (p. 36) MRID 44076210.
c mean Body weight gain data excerpted from the report (p. 37) MRID 44076210.

3. Food Consumption - Food consumption data for does that survived to cesarean section are summarized in Table 3. Food consumption for the mid- and high-dose dams that died and/or aborted (not included in Table 3) was markedly decreased. These dams typically consumed between 0 and 19 g of food/day in the prior week to the abortion and/or death whereas control animals consumed weekly averages of 87-96 g/day. Water consumption was also decreased in these animals. The data presented in Table 3 do not include dams that died or aborted prior to day 29. Food consumption was comparable to the controls throughout the study at all dose levels for dams that survived to the end of the study and were cesarean sectioned on gestation day 29.

Table 3. Maternal food consumption (g/100 g body weight)[a]

Interval	Dose in mg/kg/day (# of Dams)[b]			
	Control (15)	50 (15)	100 (13)	200 (6)
Pretreatment: Days 0-6	3.40	3.62	3.53	4.18
Treatment: Days 6-13	3.56	3.35	3.32	3.01
Treatment: Days 13-19	3.22	3.14	3.26	3.21
Posttreatment: Days 19-29	3.42	3.16	3.28	3.60

a Data extracted from the study report page 35 (MRID 44076210).
b Nonpregnant animals, dams that aborted, and those not surviving to Day 29 were excluded from the means.

4. Gross Pathology - A gross necropsy was performed and organ weights were determined for all dams in the study except the one dam at 100 mg/kg/day and four of the five dams at 200 mg/kg/day that were found dead. These animals died in the night and a significant degree of general autolysis occurred before a necropsy could be performed. Of the animals examined, gross pathologic lesions noted in the kidneys included light grey retractions on the surface in two controls and one mid-dose dam, uneven, rough surface of one high-dose dam, and light-brown coloring of the renal cortex of three of the four aborting high-dose dams. Other gross findings at 200 mg/kg/day included brown fluid in the vagina and uterus of one dam that aborted and numerous blackish follicles on both ovaries of this same dam.

At 200 mg/kg/day, the mean combined absolute kidney weight

was increased compared to the controls, although the difference was not statistically significant (15.35 g vs. 14.22 g). The increase in the mean kidney weight was primarily due to the relatively high kidney weights of four high-dose dams that were either found dead or aborted (23.5-31.5 g vs. 12.8-20.0 g for the remaining high-dose dams). The mean absolute liver weight of the high-dose dams was also slightly increased compared to the controls (55.8 g vs. 53.7 g) but was not statistically significant. This increase was due to one high-dose dam that was found dead with a liver weight of 107.8 g (liver weights of the remaining high-dose dams were 48.3-79.5 g). The increase in mean liver weight was considered treatment-related.

The study author concluded that the findings in the kidney were not treatment-related at any dose level because similar findings have been observed in the historical controls; however, historical control data to support this assertion were not provided. As renal macroscopic pathology was noted in the animals that aborted and corroborative increases in kidney weights were observed in these same animals, it appears that the kidney is a target organ. Therefore, gross renal pathology and increases in kidneys weights in the high-dose group are considered treatment-related findings.

Heart and spleen weights were comparable to controls at all dose levels and kidney and liver weights were comparable to the controls at the low- and mid-dose levels.

5. Cesarean Section Data - Cesarean section observations are presented in Table 4. The numbers of corpora lutea, implantations, the extent of pre-implantation loss, fetal and placental weights, crown to rump lengths, and the percent males were statistically similar between control and treated groups. In addition, the viability of the delivered fetuses during the first 24-hours after c-section was unaffected by treatment.

Viability as expressed as the number of live fetuses/dam was comparable between the treatment groups and the controls. In the high dose-group, post implantation loss was increased (24.7 vs 18.8 in controls), and the mean number of resorptions/dam was increased also (2.17 vs. 1.13 in controls). The increase in resorptions was not significantly different from the controls. The increase was due to resorptions occurring in three of the six litters examined at cesarean section. The number (percent) of resorptions for each litter were: 9(90.0), 1(25.0), and 3(33.0).

In historical control data for New Zealand white rabbits on study from 1992-1994, published by the Middle Atlantic Reproduction and Teratology Association (MARTA) and the

Midwest Teratology Association (MTA) in 1996, a review of 130 studies demonstrated a mean (±SD) resorption rate of 0.55±0.36 resorption/pregnant femlae or 7.02±5.69%. The resorption rate in the rabbits treated with 200 mg/kg/day of Hoe 061517 exceeded that of the historical controls. It is also noted that the concurrent control resorption rate values for the the study on Hoe 061517 exceeded historical control values, suggesting that the high rate of resorptions in the control does was responsible for the lack of statistical significance for this parameter at the high-dose.

The study authors concluded that this was an indication of a treatment-related increase in the intrauterine death rate at the high-dose. Tox. Branch II agrees with this assessment. The historical control data provided were insufficient and not in an appropriate format for comparing resorptions/dam in this study. The historical data indicated percent of early and late intrauterine deaths and not resorptions/dam.

In support of the conclusion that treatment-related postimplantation loss was occurring at the high dose, a treatment-related increase in abortions was noted in the high- and mid-dose dams and embryotoxicity was noted in most of these dams. At the mid-dose, one dam aborted on day 22. One fetus in this dam was alive and the other seven were undergoing resorption at the time of abortion. At the high-dose, four dams aborted on days 16, 17, or 25. One of the aborting high-dose dams had nine normal conceptuses. The remaining three high-dose dams had 5-8 conceptuses that were all undergoing resorptions.

Additionally, for one of the five high-dose dams and the one mid-dose dam that were found dead, the conceptuses were normal. Of the remaining four high-dose dams that were found dead, the conceptuses were either undergoing resorptions or were severely stunted (severe embryotoxicity).

Table 4. Cesarean section observations[a]

Observation	Dose (mg/kg/day)			
	0	50	100	200
# Animals Assigned (Mated)	15	15	15	15
# Animals Pregnant Pregnancy Rate (%)	15 (100)	15 (100)	15 (100)	15 (100)
# Nonpregnant	0	0	0	0
Maternal Wastage # Died # Died Pregnant # Died Nonpregnant # Aborted # Premature Delivery	 0 0 0 0 0	 0 0 0 0 0	 1 1 0 1 0	 5 5 0 4 0
Total # Corpora Lutea Corpora Lutea/Dam	118 7.9±1.2	126 8.4±1.3	101 7.8±1.2	48 8.0±1.8
Total # Implantations Implantations/Dam	96 6.4±1.8	104 6.9±1.5	81 6.2±1.6	45 7.5±2.2
Total # Litters	15	15	13	6
Total # Live Fetuses Live Fetuses/Dam	79 5.3±2.0	95 6.3±1.5	72 5.5±1.7	32 5.3±2.8
Total # Dead Fetuses Dead Fetuses/Dam	not reported	not reported	not reported	not reported
Total # Resorptions Early Late Resorptions/Dam Early Late Litters with Total Resorptions	17 14 3 1.13±1.06 0.93±1.10 0.20±0.41 0	9 7 2 0.60±1.06 0.47±0.64 0.13±0.52 0	9 7 2 0.69±0.85 0.54±0.52 0.15±0.55 0	13 11 2 2.17±3.54 1.83±3.54 0.33±0.82 0
Mean Fetal Weight (g) b	42.6±2.7	41.4±3.2	42.1±1.8	40.5±2.0
Crown/Rump Length (mm) b	97.1±2.6	97.1±2.4	96.7±2.0	96.0±3.9
Sex Ratio (% Male)	57.0	53.7	51.4	50.0
Preimplantation Loss (%)	19.0	17.3	20.1	7.22
Postimplantation Loss (%)	18.8	8.08	11.0	24.7
Survival rate at 24 hours (%)	94.7	97.4	98.5	100

a Data extracted from the study report pages 38 and 39 (MRID 44076210).
b Data for fetal weights and crown/rump lengths were not presented for each sex separately.

B. DEVELOPMENTAL TOXICITY

1. External, Visceral, and Skeletal Examinations: Fetal examinations included external, internal, and skeletal observations at necropsy and cross-sectioning of the brain, eyes, heart and kidneys. Fetal findings were classified as malformations, minor anomalies, variations, or growth retardation. The study report did not provide an overall

summary for the number of fetuses and litters affected in each evaluation category. However, summaries were provided for the incidence of normal fetuses and litters observed. Table 5 notes the most common findings.

There were no treatment-related malformations, minor anomalies, variations, or growth retardation at any dose level. All fetal findings were observed at incident rates that were statistically comparable to the concurrent controls with the exception of an increased fetal and litter incidence of retarded growth (ossification of less than 13 centers) in the caudal vertebrae of the low dose group (fetal: 24.2% vs. 7.6% in controls, $p<0.05$; litter: 73.3% vs. 33.3% in controls, $p<0.05$). However, this is not considered a treatment-related finding as it was not dose-related.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS The study report concluded that oral administration of Hoe 061517 at 100 and 200 mg/kg/day to pregnant rabbits during organogenesis was associated with treatment-related increases in maternal mortality, abortions, and intrauterine deaths. The maternal deaths and abortions were preceded by treatment-related clinical signs of intolerance (disequilibrium and/or flabbiness), reduced food and water consumption, and body weight reductions. No teratogenic effects were noted at any dose level. Oral administration of Hoe 061517 at 50 mg/kg/day produced no maternal or developmental adverse effects.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: Following oral administration of Hoe 061517 (a metabolite of glufosinate ammonium, 99.6% a.i.) at a dose of 100 mg/kg/day, maternal toxicity was demonstrated by dose-related increases in abortions and mortality, clinical signs of toxicity, and reductions in food and water consumption, body weight gain, and fecal output. One dam was found dead on day 24 of gestation and one dam was sacrificed on day 22 after hemorrhaging vaginally and aborting. The dam that died was flabby for 7 days prior to death and the dam that aborted exhibited disequilibrium in the 2 days prior to aborting. Food and water consumption, and body weight gains for pregnant animals that survived until the day 29 sacrifice were comparable to those in the control group and at all other dose levels. However, for the mid-dose animals that died or aborted, food and water consumption and fecal output were reduced and both animals lost weight in the week prior to sacrifice/death.

Table 5. Summary of noteworthy fetal observations at necropsy[a]

Observations	Dose (mg/kg/day)				Historical controls [b]
	0	50	100	200	
#Fetuses (litters) examined	79 (15)	95 (15)	72 (13)	32 (6)	---
EXTERNAL/VISCERAL and ORGAN CROSS-SECTIONING					
EXTERNAL/VISCERAL #Normal fetuses-(litters)	74 (15)	88 (15)	71 (13)	29 (6)	---
ORGAN CROSS-SECTION #Normal fetuses-(litters)	78 (15)	93 (15)	71 (13)	32 (6)	---
Minor anomalies [c]:					
Lung-Partially or completely fused lobes	0 (0)	3.2 (20.0)	0 (0)	3.1 (16.7)	---
Stomach-enlarged and taut with fluid, transverse position	3.8 (20.0)	3.2 (20.0)	1.4 (7.7)	6.3 (33.3)	---
SKELETON					
#Normal fetuses litters	26(33)[d] 11(73)	27(28) 12(80)	28(39) 10(77)	13(41) 6(100)	---
Major anomalies [c]:					
Scoliosis in region of thoracic vertebra, dysplastic and fused 11th and 12th thoracic vertebral centra, anaplastic 12th thoracic vertebral arch and rib	0 (0)	1.1 (6.7)	0 (0)	0 (0)	0-2.3 (---)
Minor anomalies [c]:					
Skull-unilateral opening in parietal bone	3.8 (20.0)	0 (0)	0 (0)	3.1 (16.7)	---
Caudal vertebral centra-dislocated, fused, longitudinally displaced	3.8 (20.0)	3.2 (20.0)	1.4 (7.7)	3.1 (16.7)	---
Sternebra-longitudinally displaced, fused, dysplasia	5.1 (20.0)	2.1 (13.3)	5.6 (23.1)	6.3 (16.7)	---
Retarded growth [c]:					
Caudal vertebra-<13 centers ossified	7.6 (33.3)	24.2* (73.3*)	8.3 (30.8)	12.5 (50.0)	10.2-22.4 (---)
Sternebra-unossified or partially ossified	54.4 (80.0)	55.8 (93.3)	54.2 (100)	40.6 (83.3)	---

a Data extracted from the study report pages 40-42 (MRID 44076210).
b Historical control values are for the range of % fetal incidence only and were given only for those findings shown.
c Percent affected [Fetal (litter) incidences]
d Percentage
* Statistically significant, $p<0.05$.

At 200 mg/kg/day, maternal toxicity was demonstrated by treatment-related clinical signs of toxicity, increases in abortions and mortality, reductions in body weight gain, reduced food and water consumption, reduced fecal output, increased organ weights, and gross pathology. Five dams were found dead on days 18-20 of gestation. Four additional high-dose dams were sacrificed on days 16, 17, or 25 after hemorrhaging vaginally and aborting. Treatment-related clinical signs of toxicity that were noted in the high-dose animals that died or aborted included flabbiness and/or disequilibrium. These observations were persistent, lasting between 1 and 7 days and first appeared between days 12 to 18 of gestation. In addition, one of the high-dose dams that died exhibited straddled fore-limbs. For the high-dose dams that died or aborted, food and water consumption and fecal output were reduced and body weight gains were either stagnated or the animals experienced a weight loss during treatment.

Treatment-related gross pathologic lesions seen in the kidneys of the high-dose animals were described as uneven, rough surface of one high-dose dam, and light-brown coloring of the renal cortex of three of the four aborting high-dose dams. In addition, a treatment-related increase in mean combined kidney weights at 200 mg/kg/day was noted, although the difference from the controls was not statistically significant (15.35 g vs. 14.22 g). This increase was primarily due to the relatively high kidney weight values of four high-dose dams that were either found dead or aborted (23.5-31.5 g vs. 12.8-20.0 g for the remaining high-dose dams). The study author concluded that the gross findings in the kidney were not treatment-related at any dose level because similar findings have been observed in the historical controls. The reviewer disagrees with this conclusion. As renal marcroscopic pathology was noted in the animals that aborted and corroborative increases in kidney weights were observed in these same animals, it appears that the kidney is a target organ of Hoe 061517.

A treatment-related increase in mean liver weight was also noted at 200 mg/kg/day, although the difference from the controls was not statistically significant (55.8 g vs. 53.7 g). This increase was due to one high-dose dam that was found dead with a liver weight of 107.8 g (liver weights of the remaining high-dose dams were 48.3-79.5 g).

There were no treatment-related deaths, clinical signs of toxicity or gross pathologic findings, changes in body weight gains, food consumption, or organ weights observed in rabbits at the 50 mg/kg/day dose level.

Maternal NOEL = 50 mg/kg/day
Maternal LOEL = 100 mg/kg/day (based on increase in the incidence of abortion, mortality, clinical signs of toxicity, decreased body weight gain, and reduced food and water consumption)

2. DEVELOPMENTAL TOXICITY:

The numbers of corpora lutea, implantations, the extent of pre-and post-implantation losses, fetal and placental weights, crown to rump lengths, and the percent males were similar between control and treated groups. In addition, the viability of the delivered fetuses during the first 24-hours after c-section was unaffected by treatment.at any dose level.

In the high-dose group, there was an increase in post implantation loss (25% vs. 19% in controls), and the mean number of resorptions/dam was also increased (2.2% vs. 1.1% in controls). It is not possible to determine the precise extent to which maternal toxicity was a contributing factor in the intrauterine fetal deaths note at the mid- and high-dose levels (100 and 200 mg/kg/day, respectively). However, because the incidence of postimplantation loss in mid-dose does that survived to cesarean section was less than concurrent and historical controls (MARTA/MTA) values, it is suggested that those intrauterine deaths observed in aborting or moribound does at that dose level were attributed primarily to maternal toxicity. **The mid-dose (100 mg/kg/day), therefore, is established as the developmental NOEL.** At the high-dose (200 mg/kg/day), where postimplantation loss was increased in does that survived to cesarean section, maternal toxicity did not appeared to be the primary contributor to intrauterine death. **The developmental LOEL is, therefore, established at 200 mg/kg/day, based on increased postimplantation loss.**

C. STUDY DEFICIENCIES: This study is not required by the Agency. It is submitted to the Agency for the purpose of verifying the values of LEL and NOEL previously presented to the agency to show that the metabolites of glufosinate ammonium are less toxic than the parent compound.

A major deficiency was that concentrations of the administered formulations were not evaluated or were not reported. Stability data also were not provided although the study report states that the stability of the solutions "was guaranteed for 5 hours after preparation (Analytical Laboratory Hoest AG, statement of 9/7/88)". Without these

data, the developmental study is classified as **Unacceptable/Guideline** and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in rabbits. To upgrade the study the sponsor must submit data confirming the nominal concentrations of the administered doses and the stability of the test substance in distilled water.

Another deficiency was that historical control data provided for resorptions/intrauterine deaths were not in a useful format for comparison with the study report. The historical data indicate percent of early and late intrauterine deaths, however, it is not clear how these values were calculated and individual study data were not provided. In addition, historical control data provided for morphological findings in the fetuses were incomplete and were not in a useful format for comparison with the study data. The historical control data did not include dates of collection, individual study data, litter incidence, or mean fetal incidence. However, as the developmental alterations found were comparable to the concurrent controls or lacked a dose-response and the treatment-related effect noted on resorptions at the high-dose was not the sole end point, these deficiencies did not affect the adequacy of the study to determine developmental or maternal toxicity.

Mean fetal data such as body weight and crown to rump length should be provided for males, females, and combined sexes. If the mean of one sex is statistically significant, it may indicate a developmental effect.

In addition, gravid uterine weights were not presented. However, this is a minor deficiency and does not affect the adequacy of the study to determine developmental and maternal toxicity.