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DATA EVALUATION RECORD

GLUFOSINATE AMMONIUM (HOE 099730)

Study Type: 83-3b; Testing for Embryotoxicity after Oral Administration in Himalayan Rabbits Plus Supplement

Work Assignment No. 2-37C (MRID 44076205)

Prepared for

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DATA EVALUATION RECORD

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

DP BARCODE:	D229929	SUBMISSION CODE:	S509558
P.C. CODE:	128850	TOX. CHEM. NO.:	580I
MRID:	44076205		

TEST MATERIAL (PURITY): HOE 099730 00 ZC92 0001, technical (92.4% a.i.) (a metabolite of glufosinate ammonium)

SYNONYMS: HOE 099730; N-acetyl-glufosinate ammonium.

CITATION: Baeder, C. and Hofmann, T. (1995) Hoe 099730-Substance-Technical (Code: Hoe 099730 ZC92 0001): Testing for Embryotoxicity after Oral Administration in Himalayan Rabbits Plus Supplement, Pharma Development Corporate Technology, Germany. Study No. 93.0112 & RK0669. Laboratory report numbers A52948 & A54431, August 24, 1994 - Supplement on May 26, 1995. MRID 44076205. Unpublished

SPONSOR: AgrEvo USA Company, 2711 Centerville Road, Wilmington, DE

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44076205) HOE 099730 (92.4% a.i.) was administered to 15 Himalayan rabbits/dose in distilled water by gavage at dose levels of 0, 64, 160, or 400 mg/kg/day from days 6 through 18 of gestation.

Minimal maternal toxicity was demonstrated by reduced feed consumption (↓22-24%; $p<0.05$) in the 160 mg/kg/day group and in the 400 mg/kg/day group (↓30-40%; $p<0.05$) during treatment days 6-13 and 13-19. There were no treatment-related effects in mortality, clinical signs, body weight, or cesarean section parameters. **The maternal LOEL was 160 mg/kg/day based on reduced feed consumption. The maternal NOEL was 64 mg/kg/day.**

A uni- or bilateral extra rib at the 13th thoracic vertebra was observed in the 160 mg/kg/day group; **based on this finding the developmental LOEL was 160 mg/kg. The developmental NOEL was 64 mg/kg/day.**

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Usually, data are required to confirm the nominal concentrations of the administered doses. Without these data, the study would have been classified as unacceptable. However, the test substance is a metabolite of glufosinate ammonium which has an adequate developmental toxicity data base. In addition, this study was submitted for verification of the NOEL and LEL provided by the registrant to show that toxicity of various metabolites is less than that of the parent compound. Under the circumstance, this study is considered as **acceptable/nonguideline** for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in rabbits.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: HOE 099730 00 ZC92 0001
   Description: technical, brown liquid
   Lot/Batch #: Lot 2+3 (Fass 1-4)
   Purity: 92.4% a.i.
   CAS #: Not provided
2. Vehicle: Distilled water
3. Test animals: Species: Rabbit
   Strain: Himalayan HIMK(SPFWiga)
   Age at mating: 8-10 months
   Weight at mating: Mean weights at beginning of gestation were 2536-2613 g
   Source: Breeder was Karl Thomae GmbH
   Housing: individually, except when mated (two animals/cage), in steel Type HD 3 cages
   Diet: Pelleted Altromin 2123 rabbit diet (Altromin GmbH, Lage/Lippe, FRG), ad libitum and hay (40-50 g/day)
   Water: tap water, ad libitum
   Environmental conditions:
   Temperature: approximately 22-23 C
   Humidity: 44-74%
   Air changes: 16-20/hr
   Photoperiod: 10 hrs dark/14 hrs light
   Acclimation period (P): at least 7 days

B. PROCEDURES AND STUDY DESIGN

1. In life dates - start: 7/14/93, end: 9/2/93

2. Mating: Each female was mated with a mature male rabbit in the ratio of 1 male:1 female. 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 treatment groups as indicated in Table 1 using a computer-generated algorithm.

Table 1. Animal Assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	15
Low (LDT)	64	15
Mid (MDT)	160	15
High (HDT)	400	15

4. Dose selection rationale: In a range-finding study summarized in the current submission, HOE 099730 (% a.i. not indicated) was administered daily via oral gavage to 2 pregnant female rabbits/dose at dosages of 8.88, 320, 500, 750, or 1,000 mg/kg/day on gestational days 6 through 18. Animals were sacrificed on day 29 of gestation and caesarean sections were performed.

There were no treatment-related findings in either the does or the fetuses at the 8.88 mg/kg/day dose. Dose related maternal toxicity consisting of reduced feed and water consumption and body weight gain, as well as reduced defecation and pultaceous feces, were observed in the 320, 500, and 750 mg/kg/day females. In the females dosed at 1,000 mg/kg/day, there were marked decreases in body weight gain and feed and water consumption as well as vaginal bleeding. One high-dose female was killed on day 22. The second high-dose female delivered one live fetus on day 26 and its uterus contained three live fetuses, four markedly retarded fetuses, one dead fetus, and two conceptuses undergoing resorption. Increased incidences of conceptuses undergoing resorption, and retarded and dead fetuses were also observed at the 500 and 750 mg/kg/day dose levels.

Based on the results of this range-finding study, the doses summarized in Table 1 above were selected for the developmental toxicity study.

5. Dosage preparation and analysis

Test substance formulations were prepared daily immediately prior to dosing. Prior to the start of the study, the homogeneity (top, middle, and bottom) and stability of the test substance in the vehicle (water) was evaluated for a period of 4 hours. It was reported that concentration of the formulations were evaluated between the first and third day of dosing.

Results - Homogeneity and Stability Analyses: The homogeneity and stability of the test substance formulated at 12.8 and 80 g/l were 101-112% of nominal. Neither coefficients of variation nor standard deviations were presented. The storage temperature was not indicated.

Concentration Analysis: It was reported that the test formulations contained the stated amount of the test substance, but the data to support this statement were not submitted.

Data are required to confirm the nominal concentration of the administered doses.

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

C. OBSERVATIONS

1. Maternal Observations and Evaluations - Mortality and clinical observations were made daily. Body weights were recorded on days 0, 6, 13, 19, and 29 of gestation and feed consumption data were recorded for gestation days 0-6, 6-13, 13-19, and 19-29. Does were sacrificed on day 29 of gestation, necropsied, and examined for gross changes especially of the uterus. The fetuses and placentae were weighed and examined for gross external abnormalities and the conceptuses undergoing resorption were measured. The following were recorded:
   - gravid uterine weight
   - number of corpora lutea
   - number of implantations
   - number of resorption sites (early or late)
   - number of live and dead fetuses

2. Fetal Evaluations: Each fetus was weighed, examined for external abnormalities and sexed. 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 of each was measured. All fetuses were fixed in alcohol and grossly examined for visceral abnormalities. According to the study report, the 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 in preparation for skeletal evaluation.

D. DATA ANALYSIS

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

2. Indices: Pre-implantation and post-implantation loss indices were calculated from cesarean section data. Percent fetal survival at 24 hours after delivery was also calculated. The calculations used to determine these indices were not provided.

3. Historical control data: Selected historical control data were provided. Historical control 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: No deaths occurred during the study. Incidences of increased water intake and reduced defecation were observed; these incidences were sporadic, not dose related, and observed in both treated and control animals and were therefore not deemed to be treatment-related.

2. Body Weight - Body weight data are summarized in Table 2. Body weight gains were not corrected for gravid uterine weights and the data presented excluded nonpregnant females, females that had aborted, and females with resorptions only. No statistically significant changes were noted in body weights or in body weight gains at any dose level. During gestation days 13-19, decreased body weight gains were noted in the 64, 160, and 400 mg/kg/day groups compared to concurrent controls. Body weight gains in the treated groups during the post-treatment interval (days 19-29) continued to be lower than the controls. Overall body weight gains (days 0-29) were decreased by 11, 31, and 23% in the low, mid- and high-dose groups. These decreases in body weight gains were not statistically different from the controls and a strict dose-dependence was not displayed; these findings were therefore considered not to be of toxicological concern.

Table 2. Maternal Mean Body Weight[a] and Body Weight Gain[b](g).

Interval	Dose in mg/kg/day (# of Does)[c]			
	Control(15)	64(14)	160(14)	400(15)
day 6 Days 0-6	2611±206 -4.6	2605±142 29.7	2541±214 9.6	2549±196 8.9
Day 13 Days 6-13	2607±200 -2.6	2610±138 -20.1	2539±208 -12.4	2540±201 -27.3
Day 19 Days 13-19	2642±197 72.6	2628±135 56.1	2544±207 22.1	2554±204 55.2
Posttreatment:Day 29 Days 19-29	2760±195 162.6	2724±152 136.9	2625±220 138.7	2651±192 140.1
Overall treatment plus Posttreatment Days 0-29	228.0	202.7	158.0	176.8

a Mean body weight data are presented in the first row of each panel. The data are excerpted from the report (p. 27) and added to this table by EPA reviewer.

b The body weight gain data are presented in the second row of each panel. The data are extracted from the study report page 28.

c Nonpregnant animals, does aborting, and those having resorptions only were excluded from the means.

3. Feed Consumption - Feed consumption data are presented in Table 3 below. A statistically significant ($p < 0.05$) reduction in feed consumption was noted in the mid- and high-dose groups during treatment. During treatment (6-13 and 13-19 days), feed consumption was reduced by 22-24% in the 160 mg/kg/day group and by 30-40% in the 400 mg/kg/day group. Feed consumption by the 64 mg/kg/day animals was slightly decreased, but the reduction was not statistically significant. The reductions in feed consumption in mid- and high dose groups were treatment-related.

Table 3. Maternal Feed Consumption (g/100 g body weight) [a].

	Dose in mg/kg/day (# of Does)[b]			
Interval	Control (15)	64 (13-14)	160 (13-14)	400 (14-14)
Pretreatment: Days 0-6	4.21±0.45	4.23±0.60	4.16±0.50	4.26±0.27
Treatment: Days 6-13	3.69±0.81	3.17±0.82	2.79±0.63*	2.20±0.59*
Treatment: Days 13-19	3.81±0.89	3.41±0.83	2.97±0.65*	2.67±1.26*
Posttreatment: Days 19-29	4.03±0.56	3.90±0.67	3.96±0.48	4.34±0.90

a Data extracted from the study report page 29. Standard deviation added by EPA reviewer.
b Nonpregnant animals, does aborting, and those having resorptions only were excluded from the means.
* $p < 0.05$.

4. Gross Pathology - No treatment-related gross pathologic findings were noted in any of the does. Missing junction of the uterus to the vagina at one side was observed in two females from the low-dose group and one female from the mid-dose group; this was not a dose-dependent finding and was not considered to be treatment-related. Except for uterine weights, which were unaffected by treatment, no organ weight data were reported.

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

   No statistically significant differences were observed in any of the cesarean section parameters. There was one dead fetus in the 64 mg/kg/day group and two each in the 160 and 400 mg/kg/day groups, in addition, there was one abortion each in the 64 and 160 mg/kg/day groups. There were some differences in cesarean section parameters between the 160 mg/kg/day group and controls, but the differences were not dose-related and not statistically significant and were therefore considered not to be of toxicological concern.

Table 4. Cesarean Section Observations[a].

Observation	Dose (mg/kg/day)			
	0	64	160	400
# 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 0	0 0 0 0 1 0	0 0 0 0 0 0
Total # Corpora Lutea Corpora Lutea/Dam	120 8.0±1.4	118 8.4±1.6	100 7.1±1.2	110 7.3±1.3
Total # Implantation Implantation/Dam	95 6.3±2.0	85 6.1±2.5	85 6.1±1.3	99 6.6±1.5
Total # Litters	15	14	14	15
Total # Live Fetuses Live Fetuses/Dam	90 6.0±2.0	82 5.9±2.4	73 5.2±1.6	90 6.0±1.3
Total # Dead Fetuses Dead Fetuses/Dam	0 0	1 0.07±0.27	2 0.14±0.36	2 0.13±0.35
Total # Resorptions Early Late Resorptions/Dam Early Late Litters with Total Resorptions	5 NR NR 0.33±0.62 NR NR NR	2 NR NR 0.14±0.36 NR NR NR	10 NR NR 0.71±0.99 NR NR NR	7 NR NR 0.47±0.92 NR NR NR
Mean Fetal Weight (g) Males Females	42.8±3.2 NR NR	43.0±4.4 NR NR	40.4±3.6 NR NR	39.6±3.0 NR NR
Sex Ratio (% Male)	46.67	47.56	36.99	55.56
Crown/Rump Length (mm)	99.7±3.4	99.3±4.6	97.0±4.4	96.0±3.5
Preimplantation Loss (%)	22.20	27.41	14.73	10.03
Postimplantation Loss (%)	5.94	2.98	14.89	7.98
Survival Rate at 24 Hours (%)	95.3±10.2	99.4±2.2	96.2±10.0	93.9±12.9
Placental Weight (g)	5.35±0.79	5.21±0.68	4.89±0.44	5.01±0.59

a: Data extracted from the study report pages 32 and 33. NR: Not reported.

B. DEVELOPMENTAL TOXICITY Fetal examinations included external, internal, and skeletal observations and cross-sectioning of the brain, eyes, heart and kidneys. Fetal findings were classified as major and minor defects, 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.

All fetal findings were observed at incident rates that were statistically comparable to the concurrent controls with the exception of the fetal and litter incidence of a uni- or bilateral extra rib at the 13th thoracic vertebra in the 160 mg/kg/day group (fetal: 11% vs. 2.2% in controls, $p<0.05$; litter: 50% treated vs. 13.3% in controls, $p<0.05$) and the 400 mg/kg/day group (fetal: 12.2%, $p<0.01$; litter: 33.3%, not statistically significant). According to the historical control data for the performing laboratory for studies conducted between 1990 and 1993, the fetal incidence of extra ribs was within the normal range (0-11.6%) for the 160 mg/kg/day dose group and slightly above the upper limit of the normal range for the 400 mg/kg/day dose group; while the litter incidence was above the upper limit of the normal range (0-15.4%) for the 160 & 400 mg/kg/day dose groups. The mean fetal and litter incidence of 13th thoracic ribs were 2.5% and 6.0%, respectively. Therefore, although the increased incidence of this variation was not strictly dose-related, the fetal incidences fell at the maximum historical incidence level and the litter incidence exceeded the historical control levels, and this variation was judged to be treatment related at 160 & 400 mg/kg/day.

There were no treatment-related defects (major or minor) or growth retardations at any dose level. However, hydrocephalus was observed in one fetus from a 400 mg/kg/day female; this finding was statistically comparable to the concurrent controls and within the range of incidence of the historical controls and was therefore considered not to be of toxicological concern.

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

Observations	Dose (mg/kg/day)				Historical controls [b]
	0	64	160	400	
#Fetuses (litters) examined	90 (15)	82 (14)	73 (14)	90 (15)	--
EXTERNAL/VISCERAL and ORGAN CROSS-SECTIONING					
EXTERNAL Retarded Fetuses	0 (0)	1 (1)	0 (0)	0 (0)	--
EXTERNAL/VISCERAL #Normal fetuses- (litters)	77 (15)	75 (14)	63 (14)	67 (15)	--
ORGAN CROSS-SECTION #Normal fetuses- (litters)	86 (15)	77 (14)	71 (14)	86 (15)	--
Major defects [c]:					
Head- Hydrocephalus, cranium protruding in region of parietal bone	0 (0)	0 (0)	0 (0)	1.1 (6.7)	0-9.1 (--)
Minor defects [c]:					
Eye- Blood in orbital cavity-right or bilateral	0 (0)	0 (0)	1.4 (7.1)	2.2 (13.3)	0-9.4 (--)
Thoracic Cavity- Blood in thoracic cavity	0 (0)	2.4 (14.3)	2.7 (14.3)	3.3 (13.3)	0-2.1 (--)
Thoracic Cavity/Heart/Lung- Thoracic cavity, hollow space; Heart, apex displaced; Lung, deformed lobe	0 (0)	0 (0)	0 (0)	1.1 (6.7)	0-2.2 (--)
Lung- Partially or completely fused lobes or aplasia	2.2 (6.7)	1.2 (7.1)	6.8 (21.4)	5.6 (33.3)	0-17.8 (--)
Stomach- Enlarged and taut with fluid, transverse position	7.9 (40.0)	3.7 (14.3)	4.1 (21.4)	10.0 (46.7)	0-14.7 (--)
Kidney- distended pelvis, left or bilateral	1.1 (6.7)	0 (0)	0 (0)	2.2 (6.7)	0-6.8 (--)

Observations	Dose (mg/kg/day)				Historical controls b
	0	64	160	400	
SKELETON					
#Normal fetuses (litters)	55 (14)	49 (13)	39 (14)	52 (15)	--
Minor defects [c]:					
Skull- unilateral or bilateral opening in parietal bone	0 (0)	3.7 (14.3)	0 (0)	0 (0)	0-8.0 (--)
Sternebra- fused	2.2 (13.3)	1.2 (7.1)	5.5 (28.6)	5.6 (26.7)	0-10.6 (--)
Retarded growth [c]:					
Skull- parietal, slight bilateral ossification	0 (0)	0 (0)	0 (0)	1.1 (6.7)	0-11.3 (--)
Caudal Vertebral Centra- < 13 centers ossified	4.4 (13.3)	12.2 (35.7)	1.4 (7.1)	3.3 (20.0)	4.3-25.6 (--)
Sternebra- unossified or partially ossified	31.1 (66.7)	32.9 (57.1)	30.1 (71.4)	22.2 (46.7)	20.5-86.7 (--)
Variation c:					
Extra rib- at 7th cervical vertebra, left or bilateral	0 (0)	0 (0)	1.4 (7.1)	2.2 (13.3)	0-12.1 (--)
at 13th thoracic vertebra, uni- or bilateral	2.2 (13.3)	0 (0)	11.0 * (50.0 *)	12.2 ** (33.3)	0-11.6 (0-15.4)

a: Data extracted from the study report pages 35-37 and 172-173.
b: Except for historical control data regarding an additional 13th thoracic rib, historical control values (1974-1993) are for the range of % fetal incidence only. For the 13th thoracic rib, historical control values were derived from studies conducted between 1990 and 1993.
c: Fetal (litter) incidence as % affected.
*: $p<0.05$
**: $p<0.01$
--: not reported

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The study authors concluded that oral administration of Hoe 099730 at 160 and 400 mg/kg/day during organogenesis was associated with reduced maternal feed consumption and with statistically significant increases in the incidence of extra thoracic ribs in the offspring. Oral administration of Hoe 099730 at 64 mg/kg/day produced no maternal or developmental adverse effects.

Maternal and Developmental LOEL=160 mg/kg/day
Maternal and Developmental NOEL=64 mg/kg/day

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY: Following oral administration of the test substance Hoe 099730 at 64, 160, or 400 mg/kg/day to pregnant rabbits on days 6-18 of gestation, minimal maternal toxicity was demonstrated by reduced feed consumption (↓22-24%; $p<0.05$) in the 160 mg/kg/day group and in the 400 mg/kg/day group (↓30-40%; $p<0.05$) during treatment days 6-13 and 13-19. Food consumption by the 64 mg/kg/day animals was slightly decreased, but the small reduction was not significantly different from the controls. The 64 mg/kg could be considered as a threshold maternal NOEL. Therefore,

   Maternal NOEL = 64 mg/kg/day
   Maternal LOEL = 160 mg/kg/day

2. DEVELOPMENTAL TOXICITY:
   a. Deaths/Resorptions: There was one dead fetus in the 64 mg/kg/day group and 2 each in the 160 and 400 mg/kg/day groups in addition, there was one abortion each in the 64 and 160 mg/kg/day groups. No statistically significant or treatment-related differences were observed in any of the cesarean section parameters.

   b. Altered Growth: There were no significant reductions or increases in fetal body weights or crown to rump lengths at any dose level.

   c. Developmental Variations: A uni- or bilateral extra rib at the 13th thoracic vertebra was observed in the 160 mg/kg/day group (fetal: 11% vs. 2.2% in controls, $p<0.05$; litter: 50% treated vs. 13.3% in controls, $p<0.05$) and the 400 mg/kg/day group (fetal: 12.2%, $p<0.01$; litter: 33.3%, not statistically significant). Although the increased incidence of this variation was not strictly dose-related, the fetal incidences fell at the maximum historical level and the litter incidence exceeded historical control level, therefore this variation was judged to be treatment-related at 160 & 400 mg/kg/day levels.

d. Malformations: There were no treatment-related developmental malformations noted at any dose level. Hydrocephalus was observed in one fetus from a 400 mg/kg/day female; this finding was statistically comparable to the concurrent controls and within the range of incidence of the historical control values and was therefore considered not to be of toxicological concern.

Based upon the increased incidence of 13th thoracic ribs, the **Developmental LOEL was 160 mg/kg/day** and **Developmental NOEL was 64 mg/kg/day.**

C. STUDY DEFICIENCIES Usually, data are required to confirm the nominal concentrations of the administered doses. Without these data, the study would have been classified as unacceptable. However, the test substance is a metabolite of glufosinate ammonium which has an adequate developmental toxicity data base. In addtion, this study was submitted for verification of the NOEL and LEL provided by the registrant to show that toxicity of various metabolites is less than that of the parent compound. Under the circumstance, this study is considered as **acceptable/nonguideline** for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in rabbits.

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