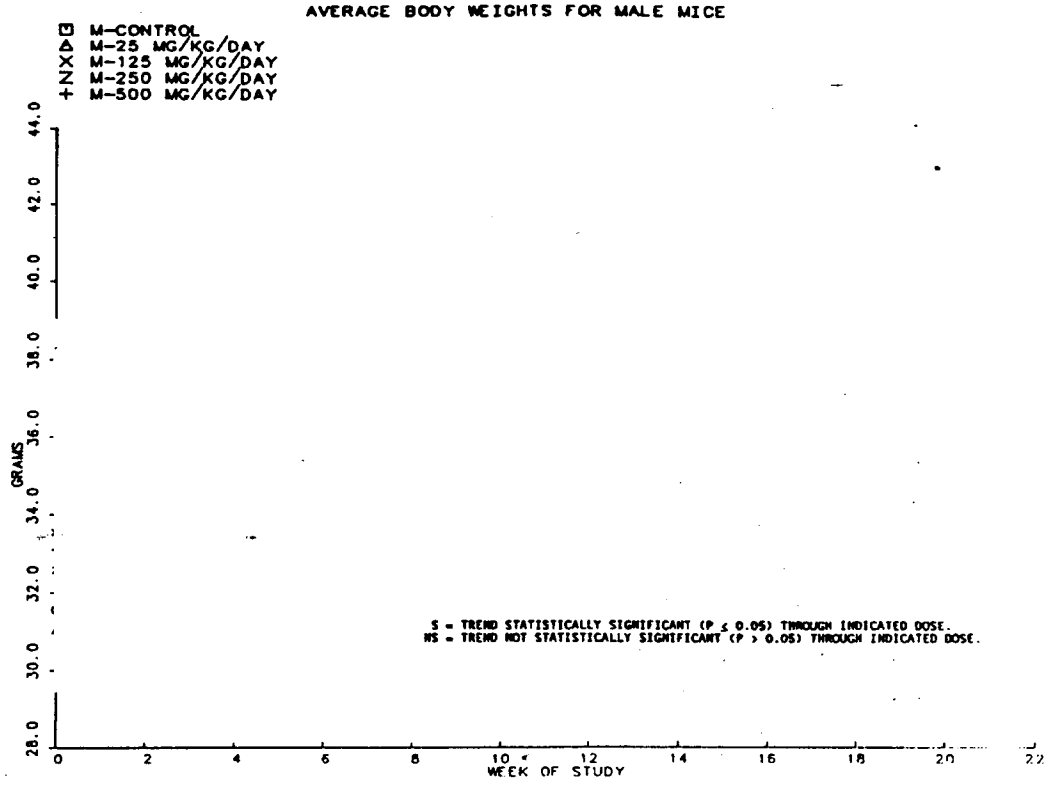
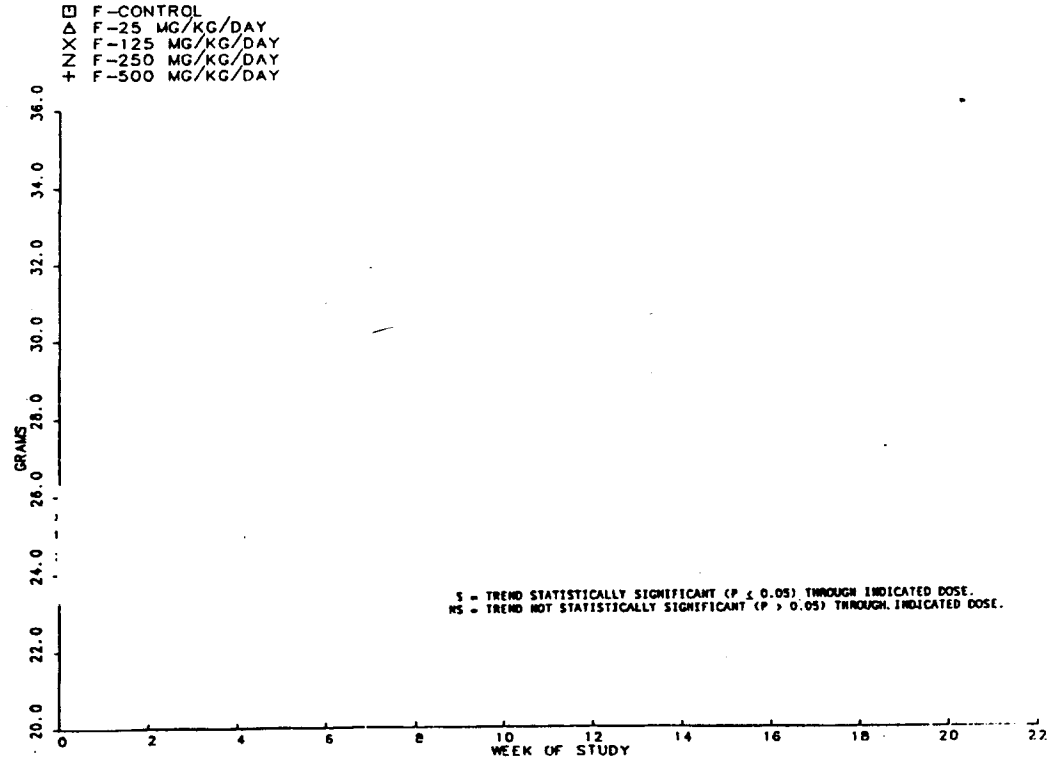
AVERAGE BODY WEIGHTS FOR MALE MICE



AVERAGE BODY WEIGHTS FOR FEMALE MICE



C.2.d. MK-0462: Five-Week Oral Toxicokinetic Study in Mice
(GLP; Report #: TT 93-086-0; Vol. 14)
Conducted by: MRL, West Point, PA Study Dates: 7/15/93 - 8/13/93

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Methods:

The study conditions were essentially identical to those of the 14-week toxicity study (doses: 25, 125, 250, 500 mg/kg). The animals received a total of 29 doses (one per day), and plasma samples were collected 20 min to 24 hrs after the last dose from 4/mice/sex/time point.

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Results:

Mortality: 3 HDM and 1 HDF died during weeks 2-4. Two of the 4 had intestinal distension.

Toxicokinetics:

Drug absorption was prolonged over the period of 20 min to 2 hrs, and plasma levels remained relatively constant. The individual data were highly variable, and the mean value for either the 25 or 125 mg/kg group was spurious. With the omission of the 25 mg/kg TK values, increases in plasma levels are dose proportional.

	25		125		250		500	
	M	F	M	F	M	F	M	F
Cmax (µg/ml)	5 (4)	7 (3)	14	12	31	19	38	25
AUC (µg.hr/ml)	55 (7)	72 (6)	32	31	74	70	162	122

( ) = value calculated with the omission of a possible spurious 8-hr sample

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C.3. Chronic Toxicology

C.3.a. 53-Week Oral Toxicity Study in Rats with a 27-Week Interim Necropsy

(GLP; Report #: TT-93-111-0; Vols. 15-17)
Conducted by: MRL, West Point, PA Study Dates: 8/19/93 - 8/19/94

Summary:

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ON ORIGINAL

RIZ was administered orally by gavage once daily to Sprague-Dawley rats (n = 30/sex/group) for 27 (n = 10) or 53 weeks (n = 20) at doses of 10, 50 or 250 mg/kg/day. RIZ caused a slight, dose-related reduction in body weight that did not exceed 10% at any dose level. Clinical signs were salivation (all groups) and ptosis (MD, HD). The only abnormal clinical pathology associated with treatment was elevated alkaline phosphatase in HD animals. Relative liver weights were increased slightly increased in HDF (21%) and HDM (15%). However, there were no histopathological findings in the liver, or any other tissue. Toxicokinetic analyses indicated slightly less than dose-proportional increases in RIZ plasma exposures based on Cmax, and slightly greater than dose-proportional increases based on AUC. There was no significant gender difference.

The MD (50 mg/kg) is considered the NOAEL for the study, based on hepatic weight changes and AP increases at the HD. The estimate is conservative since the endpoints are of questionable or minimal toxicological significance in the absence of correlative histopathology. Plasma exposures at this level exceeded expected human exposures at the MRHD (30 mg) by 125 times based on AUC.

Methods:

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Animals:	Sprague-Dawley rat, [Crl:CD(SD)BR]; 39 days old; males: females:
N:	30/sex/group (10/sex/group for interim sacrifice; 20/sex/group at termination);
Dosages:	10, 50, 250 mg/kg/day (calculated as the free base) [The sponsor did not provide a rationale for dosage selection; the HD is lower the MTD in the 14-week range-finding study]
Route/Freq:	one daily gavage administration
Vehicle:	0.5% methylcellulose (5 ml/kg)
Lots:	004B010, 004B013, 004B009, 004B014
Feeding:	Rationed (Females 17 g, Males 24 g); water *ad lib*

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Parameters monitored:			
	clinical signs	-	daily
	body wt, food in.	-	1-2X weekly
	ophthalmic exam	-	wks 13, 24, 40, 51 (con & HD)
	hematology*	-	wks 5, 12, 25, 39, 51
	clinical chemistry*	-	wks 5, 12, 25, 39, 51
	urinalysis	-	wks 12, 25, 39, 51
	histopathology*	-	
	plasma levels	-	wk 21 (n=3) @ 0.5-24 hrs post-dose

* parameters are identified in an appendix Table

Results:

Mortality: No treatment-related deaths occurred.

Clinical: No data tables of clinical findings were submitted. The sponsor reports in the text that salivation occurred in all dosage groups with a dose-related increase in incidence, and suggests that this may be related to poor palatability. Ptosis occurred in MD and HD animals with a dose-related incidence.

Body Wt: A slight, but statistically significant reduction in body weight gain was observed for all dose groups (see Sponsor Figures 1 & 2). However, as shown in the Table below, the magnitude of body weight gain reductions were ≥ 10% only in the HD group. The changes in terminal body weight of the HD group were < 10%, and not considered toxicologically significant.

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FEMALES

	pretest	WK 52	Δ	Δ bwg (%)	Δ term bw (%)
Con	150	306	156	-	-
10 mg/kg	149	297	148	-5%	-3%
50 "	148	294	146	-6%	-4%
250 "	153	293	140	-10%	-4%

MALES

	Pretest	WK 52	Δ	Δ bwg (%)	Δ term bw (%)
Con	182	570	388	-	-
10 mg/kg	190	547	357	-8%	-4%
50 "	181	536	355	-9%	-6%
250 "	181	524	343	-12%	-8%

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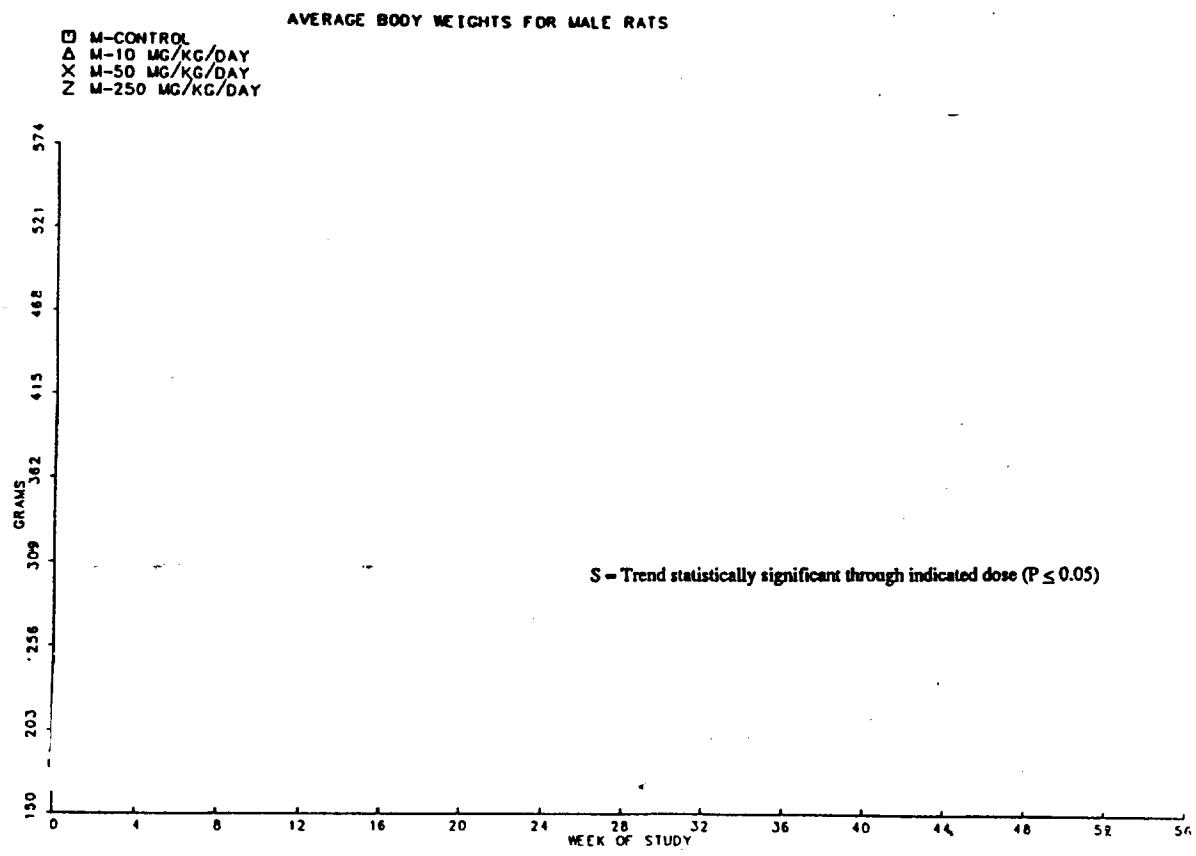
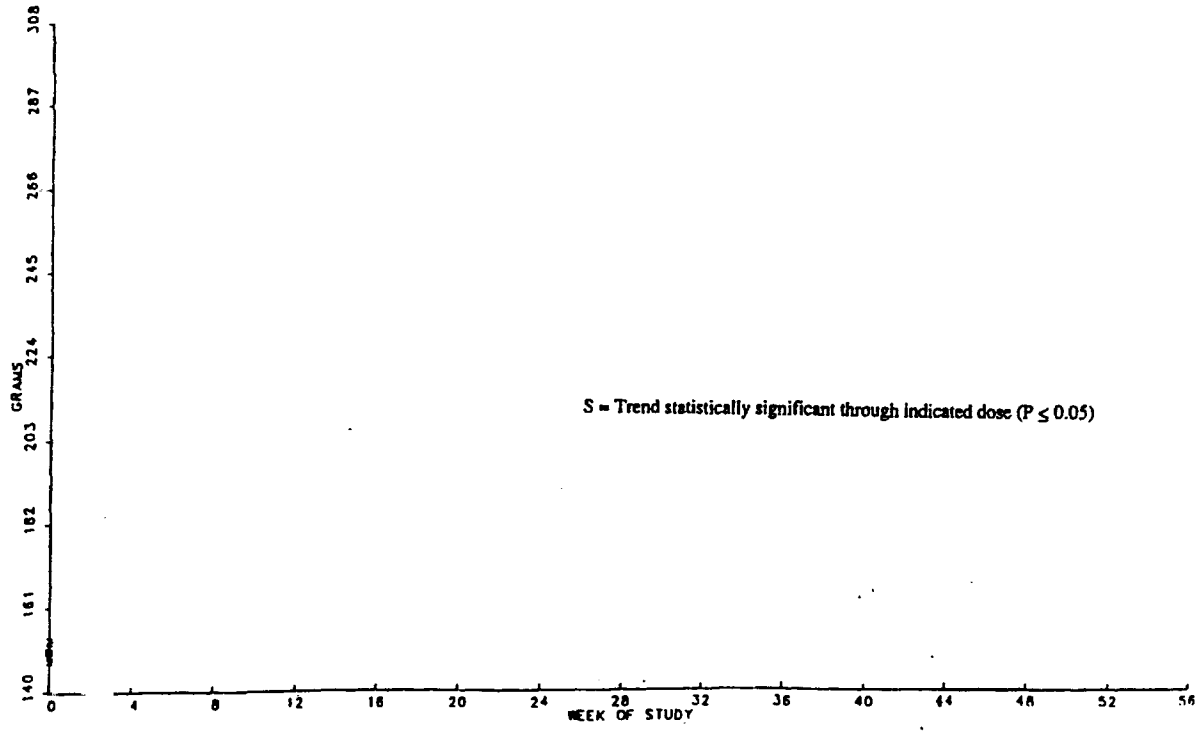
AVERAGE BODY WEIGHTS FOR MALE RATS



AVERAGE BODY WEIGHTS FOR FEMALE RATS



Ophthalm: No treatment-related effects

Hematol: No treatment-related effects

Clin Chem: Mean values of alkaline phosphatase in HDF were approximately double those of concurrent controls at week 12, 25, 39, 51. Ten of 19 HDF had AP levels that exceeded the sponsor's reference at week 51. Mean AP elevations in HDM were less marked (approximately 50%); 5 of 20 animals had values higher than the sponsor reference range. The significance of the finding is uncertain in the absence of corresponding histopathological changes.

Urinalysis: No treatment-related effects

Organ Wts: Relative liver weights were slightly increased in HDM (15%) and HDF (21%). Relative prostate weights were increased in HDM (20%).

Gross Path: No treatment-related findings

Histopath: No treatment-related findings

Toxicokinetic Determinations (week 21):

	MALES			FEMALES		
	10	50	250	10	50	250
Cmax (µg/ml)	2	6	24	2	6	20
AUC (µg.hr/ml)	3	20	116	3	20	105
Tmax (hr)	0.5	1.0	0.5	0.5	0.5	2.0

C.3.b. 53-Week Oral Toxicity Study with a 27-Week Interim Necropsy in Dogs
(GLP; Report #: TT-93-112-0; Vols: 17-19
Conducted by: MRL, West Point, PA Study Dates: 8/26/93 - 8/26/94

Summary:

RIZ was administered by gavage once daily to beagle dogs (n = 8/sex/group) for 27 (n = 4) or 53 weeks (n = 4) at doses of 0.2, 1.0, or 5.0 mg/kg/day. No significant drug-related toxicities were identified by the sponsor. Mydriasis and salivation were common drug-related clinical signs. The sponsor reported that no ophthalmological or ECG alterations were evident but data were not provided. Modest increases in liver weight (24-30%) were evident at termination (not reported by sponsor), but no signs of hypertrophy or hyperplasia were reported by the pathologist. No histopathology findings were considered treatment-related by the sponsor. Interstitial fibrosis of the lung tended to increase in RIZ-treated dogs, but a treatment-relationship is equivocal because of the small sample size, incomplete assessment of LD and MD animals, and presence in some controls.

The MD (1.0 mg/kg) is considered the NOAEL for the study, based on hepatic weight changes. The estimate is conservative since the toxicological significance increased liver weights without histological evidence of hypertrophy or hyperplasia is questionable. The absence of a clear toxicity and toxicokinetic data limits the utility of this study for safety assessment purposes.

Methods:

Animals: Beagle dogs, 46-56 weeks old;
males: , females:
Dosages: 0.2, 1.0, 5.0 mg/kg/day (calculated as the free base)
[The sponsor did not provide a rationale for dosage selection; the doses were the same in the 14-week range-finding study]
N: 8/sex/group (4/sex/group for interim sacrifice; 4/sex/group at termination)
Route/Freq: one daily gavage administration
Vehicle: H_2O (5 ml/kg)
Lots: 004B008
Feeding: Rationed (350-450 g/day); water ad lib

Parameters monitored:			
	clinical signs	-	daily
	body wt	-	1-2X weekly
	food intake	-	3-5X weekly, wks 1-13; then 1-4X monthly
	ophthalmic exam	-	wks 0, 12, 25, 39, 51
	ECG	-	wks 0, 12, 24, 39, 51 (4-6 hrs post-dose)
	hematology *	-	wks 0, 4, 12, 25, 39, 51
	clinical chemistry *	-	wks 0, 4, 12, 25, 39, 51
	urinalysis	-	wks 0, 12, 25, 39, 51
	histopathology *	-	complete exam only of Con & HD animals

* parameters are identified in an appendix Table

Results:

Mortality: No treatment-related deaths occurred. One MDM was sacrificed when a hematoma on the ear flap did not respond to treatment.

Clinical: No data tables of clinical findings were submitted. The sponsor reported mydriasis occurred in all dosage group with a dose-related increase in intensity. Salivation was attributed to poor palatability.

Body Wt: The mean weight gain of control animals (1.5 kg) appeared higher than that of HD animals (0.2 kg), but appeared due to large increases in two animals. In general, the Con, LD, and MD groups had 2-3 dogs that gained > 1 kg, and no HD dogs gained more than 0.5 kg.

Ophth/ECG: No data were provided. The sponsor states that there were no treatment-related effects.

Hematology: No treatment-related effects

Clin Chem: Occasional ALT elevations were observed in 2 LDM and 2 LDF; increased alkaline phosphatase was also observed in one of the LDFs in week 25. The animals with the highest levels (1 F, 1 M) were sacrificed at week 27, but the tissues from these animals were not examined histologically. Since similar elevations were not observed at the higher doses, a treatment relationship is unlikely.

Urinalysis: No treatment-related effects

Organ Wts: The sponsor stated that there were no treatment-related changes. Review of liver data revealed an approximate 30% increase in relative weights in HDF at 27 and 53 weeks, and a 24% increase in HDM at 53 weeks (no increase at 27 weeks). These increases suggest a possible drug effect, but no correlating hypertrophy and/or hyperplasia was observed.

Gross Path: No treatment-related findings

Histopath: No findings were considered treatment-related by the sponsor. Interstitial fibrosis of the lung tended to increase in RIZ-treated dogs, but a relationship to treatment is cannot be conclusively established because of the small sample size, incomplete assessment of LD and MD animals, and presence in controls:

	CON		LD		MD		HD	
	M	F	M	F	M	F	M	F
27 weeks	0/4	0/4	-	0/2	1/2	0/1	2/4	0/4
52 weeks	1/4	1/4	-	1/2	1/1	1/2	2/4	2/4
total	1/8	1/8	-	1/4	2/3	1/3	4/8	2/8
rate	12.5		-	25	50		37.5	

C.4. Reproductive Toxicology

The following table from the sponsor lists the type and doses of reproductive toxicology studies conducted with RIZ. Only the main studies were comprehensively reviewed; essential parts of the range-finding studies were reviewed, and are discussed within the context of the main study.

Table C-1. Reproductive Toxicity - List of Studies

Study Number [Reference Number]*	Species/Sex	Study Type/Dose (mg/kg)	Route
TT #92-708-1 [C-1]	Rat/F	Range-Finding (pregnant) 25, 100, 250, 500	Oral
TT #92-708-0 [C-2]	Rat/F	Developmental Toxicity 2, 10, 100	Oral
TT #92-709-2 [C-3]	Rabbit/F	Range-Finding (non-pregnant) 1, 5, 25, 100	Oral
TT #92-709-1 [C-4]	Rabbit/F	Range-Finding (pregnant) 5, 25, 100	Oral
TT #92-709-0 [C-5]	Rabbit/F	Developmental Toxicity 5, 10, 50	Oral
TT #92-720-0 [C-6]	Rat/F	Fertility Study 2, 10, 100	Oral
TT #93-733-0 [C-7]	Rat/F	Late Gestation/Lactation 2, 10, 100	Oral
TT #93-729-0 [C-8]	Rat/M	Fertility Study 5, 35, 250	Oral
TT #93-737-0 [C-9]	Rabbit/F	Toxicokinetic Study (pregnant) 5, 50	Oral
TT #95-701-0 [C-10]	Rat/F	Toxicokinetic Study (pregnant) 2, 100	Oral

*[ ] See II. References for citations.

C.4.a. Developmental Toxicity in Rats

C.4.a.1. L-705,126: Oral Developmental Toxicity Study in Rats
(GLP; Report #: TT 92-708-0; Vol. 19)
Conducted by: MRL, West Point, PA Study Dates: 7/12/92 - 11/23/92

Summary:

RIZ (0, 2, 10 and 100 mg/kg/day) was given by gavage to mated female rats (25/dose) on days 6-17 of gestation. Doses were based on a range-finding study in which decreased maternal weight at ≥ 100 mg/kg, decreased pup weights during lactation at ≥ 25 mg/kg, and pup deaths at 500 mg/kg were observed. Dams were sacrificed on day 21.

Maternal body weight gain was significantly reduced in HD animals during gestation. No other clinical signs or effects on pregnancy were observed. Possible drug-related embryofetal effects were a slight, but statistically significant decrease in live fetal weight, and increased incidences of cervical and hypoplastic ribs in HD offspring

The NOAELs for maternotoxicity and developmental toxicity is 10 mg/kg/day based on body weight impairments. Toxicokinetic data were not obtained (in the subsequent study) at this level. At the LD, maternal exposures exceeded human exposures at the MRHD (30 mg) by approximately 2-fold.

Methods:

Animals: Crl:CD(SD)BR Rat; 10 wks; 213-301 g;
Dosages: 0, 2, 10, 100 mg/kg/day (Lot: 004B003; calcd. as base) in water.

Doses were selected based on a developmental toxicity range-finding study of 25, 100, 250, 500 mg/kg/day (TT #92-708-1) administered from GD6 to LD20. Maternotoxicity (↓ b.w.g. during gestation) occurred at ≥ 100 mg/kg (sponsor Figs. A1 & A2; Table A2). Pups deaths were significantly increased in the 500 mg/kg group on PND 1-3 (12.1% vs. 1.1% in controls), and pup body weights during lactation were dose-dependently decreased (sponsor Table A-7).

N: 25/group
Regimen: once daily on GD 6-17; all animals sacrificed on GD 21
Route: oral (gavage)

Parameters: *Maternal* - clin signs, body wt, food cons, preg/non-preg, corpora lutea, implants, resorptions, live/dead fetuses, necropsy (thoracic, pelvic, abdominal)
Fetuses - body wt, external exam, visceral exam (1/3 of total), skeletal exam (alizarin red)

RANGE FINDING RESULTS

FIGURE A1. L-705,126: ORAL RANGE-FINDING REPRODUCTION STUDY IN FEMALE RATS. TT #92-708-1
AVERAGE MATERNAL BODY WEIGHTS OF F0 FEMALES DURING GESTATION

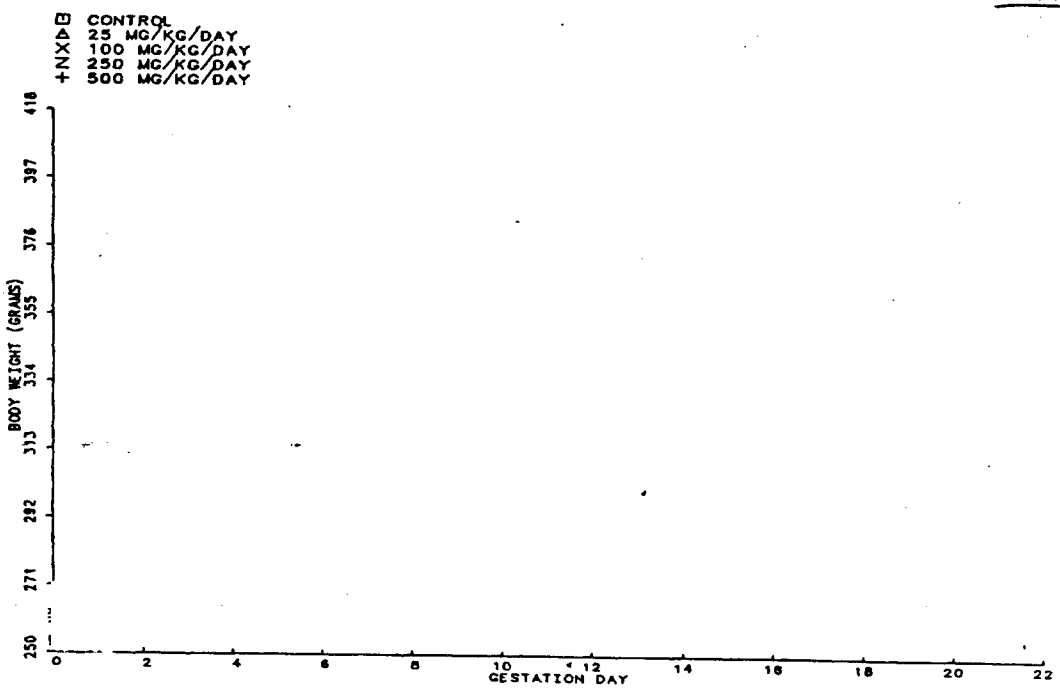
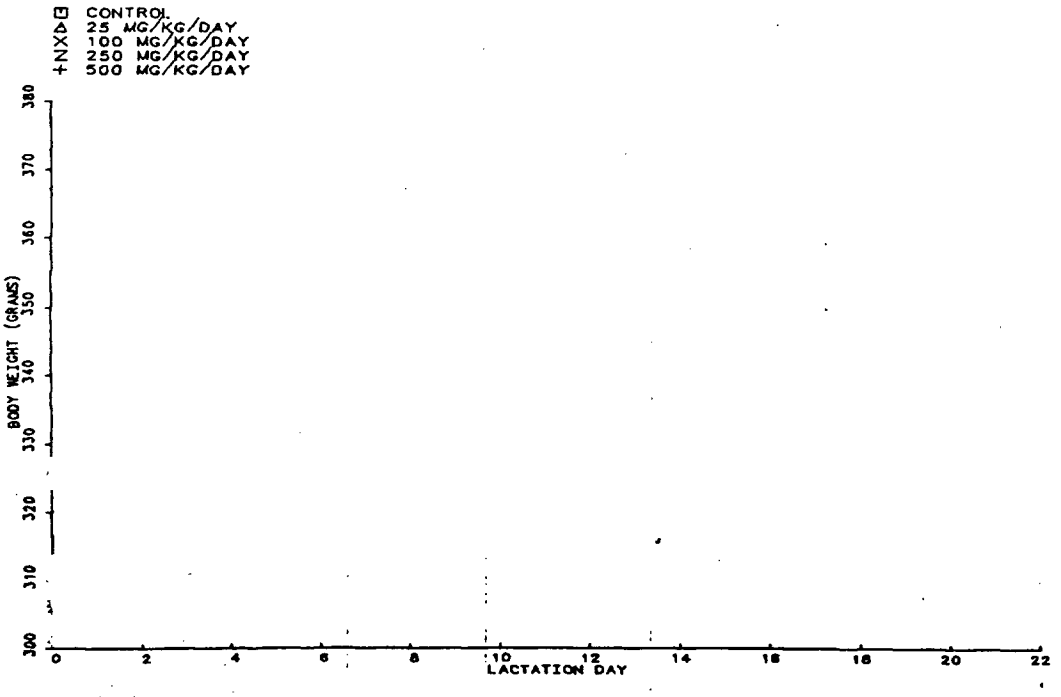


FIGURE A2. L-705,126: ORAL RANGE-FINDING REPRODUCTION STUDY IN FEMALE RATS. TT #92-708-1
AVERAGE MATERNAL BODY WEIGHTS OF F0 FEMALES DURING LACTATION



RANGE-FINDING RESULTS

TABLE A2. L-705,126: ORAL RANGE-FINDING REPRODUCTION STUDY IN FEMALE RATS. TT #92-708-1
AVERAGE MATERNAL BODY WEIGHT CHANGES (GRAMS) OF F0 FEMALES

TREATMENT GROUP:	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG/DA	500 MG/KG/DAY
GESTATIONAL PERIOD					
DAY 6 TO 14	53 (10)	47 (09)	39 (10)	33 (10)	27 (10)
DAY 14 TO 18	36	36	36	35	36
DAY 18 TO 20	33	32	34	30	33
DAY 6 TO 20[A]	122	114 NS	109 S	98 S	96 S
LACTATIONAL PERIOD					
DAY 0 TO 7	24 (10)	19 (09)	25 (10)	18 (10)	16 (10)
DAY 7 TO 14	21	24	21	18	18 (09)
DAY 14 TO 21	-17	-10	-5	-2	-3
DAY 0 TO 21	28	33	41	34	30

(N) = GROUP SIZE AND APPEARS ONLY IF DIFFERENT FROM PREVIOUS N. SEE INDIVIDUAL TABLE FOR EXCLUSIONS.
S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.
NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.
A = TREND ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR GESTATION DAY 6 WEIGHTS.

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TABLE A7. L-705,126: ORAL RANGE-FINDING REPRODUCTION STUDY IN FEMALE RATS. TT #92-708-1
SUMMARY OF STATUS OF F1 GENERATION PRIOR TO WEANING

	CONTROL	25 MG/KG/DAY	100 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY
PARENTAL FEMALES	10	9	10	10	10
IMPLANTS PER FEMALE	14.9	16.7	17.0	15.9	17.4 NS
% POSTIMPLANTATION SURVIVAL (L.M.)	88.1	90.5	93.1	90.2	88.3 NS
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	10	9	10	10	10
FEMALES WITH LIVE PUPS DAY 21 POSTPARTUM	10	9	10	10	9
TOTAL PUPS (FEMALES/MALES)	139(74/ 65)	136(67/ 69)	161(77/ 84)	149(65/ 84)	162(83/ 79)
LIVE PUPS ON POSTNATAL DAY 0	134(71/ 63)	136(67/ 69)	158(76/ 82)	145(62/ 83)	155(82/ 73)
DEAD PUPS ON POSTNATAL DAY 0	5(3/ 2)	0(0/ 0)	3(1/ 2)	4(3/ 1)	7(1/ 6)
LIVE PUPS PER LITTER	13.4	15.1	15.8	14.5	15.5 NS
% LIVE PUPS (L.M.)	95.0	100.0	98.1	97.3	95.3
LIVE PUPS AFTER CULLING ON POSTNATAL DAY 3	80	72	80	80	80
PUP DEATHS (% PUP DEATHS) (L.M.)					
POSTNATAL DAYS 1 - 3	2(1.1)	1(0.8)	3(1.9)	7(5.5) NS	18(12.1) S
POSTNATAL DAYS 4 - 7	1(1.2)	0(0.0)	0(0.0)	0(0.0)	1(1.2)
POSTNATAL DAYS 8 - 14	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
POSTNATAL DAYS 15 - 21	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
POSTNATAL DAYS 4 - 21	1(1.2)	0(0.0)	0(0.0)	0(0.0)	1(1.2) NS
LIVE FEMALE PUP WEIGHT (GM) (L.M.)					
POSTNATAL DAY 0[A]	6.6	6.0 NS	5.8 S	5.8 S	5.5 S
POSTNATAL DAY 7	17.0	16.3 NS	15.7 S	14.5 S	12.9 S
POSTNATAL DAY 14	35.3	34.8 NS	32.5 S	29.7 S	26.4 S
POSTNATAL DAY 21	57.3	57.4 NS	54.5 S	50.8 S	45.0 S
LIVE MALE PUP WEIGHT (GM) (L.M.)					
POSTNATAL DAY 0[A]	6.8	6.4 S	6.2 S	6.2 S	5.9 S
POSTNATAL DAY 7	17.3	16.8	16.5 NS	15.5 S	13.5 S
POSTNATAL DAY 14	35.6	35.4	33.8 NS	31.2 S	27.0 S
POSTNATAL DAY 21	57.8	58.5	57.4 NS	53.2 S	46.3 S

(L.M.) = LITTER MEAN

S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.
NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.
A = TREND ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR LITTER SIZE AND LENGTH OF GESTATION.

Results:

Maternal - There were no mortalities, treatment-related clinical signs or effects on pregnancy parameters (sponsor Table 4). Body weight gain was significantly reduced in the HD group (13%) during the treatment period (GD6-17; sponsor Fig.1). Food consumption in HD appeared low on day 8, but this was not significant (sponsor Fig. 2).

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FIGURE 1. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS.
TT #92-708-0
AVERAGE MATERNAL BODY WEIGHTS DURING GESTATION

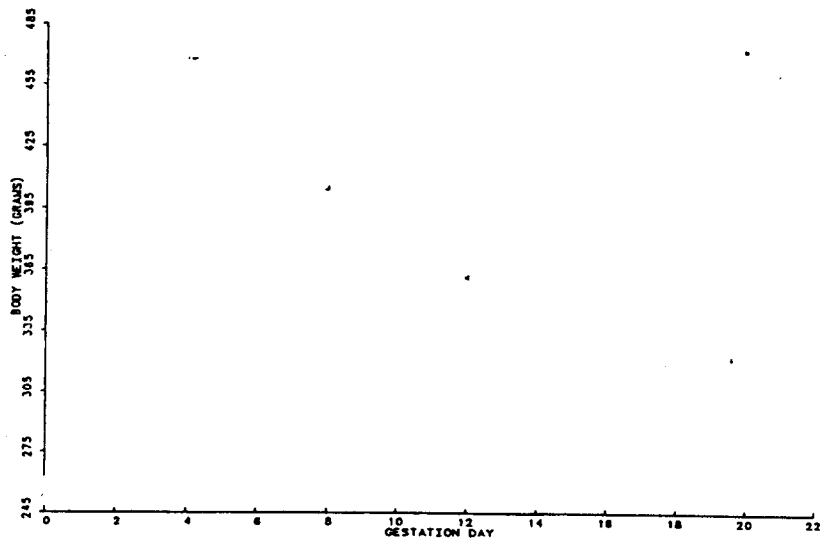
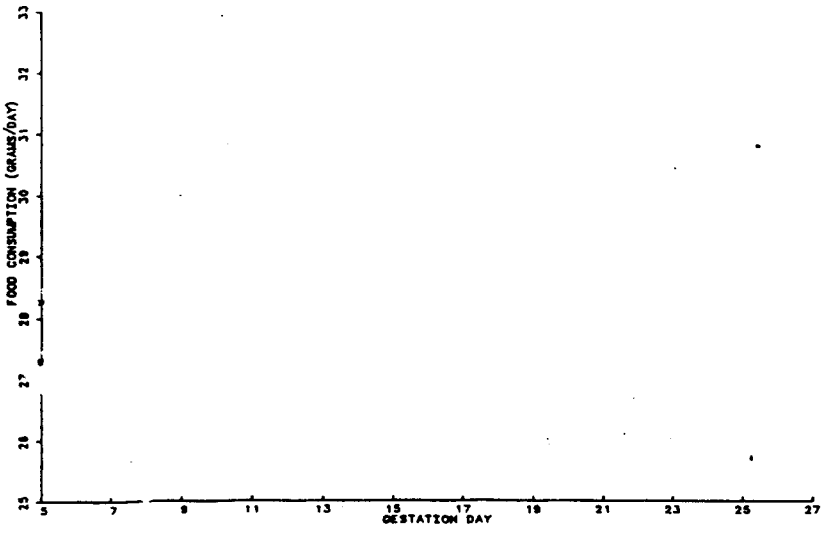


FIGURE 2. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS.
TT #92-708-0
AVERAGE MATERNAL FOOD CONSUMPTION DURING GESTATION



Fetal - A slight, statistically significant decrease in live fetal weight was evident in the HD group (sponsor Table 4). There were no treatment-related effects on embryo survival, or external or visceral examinations (sponsor Tables 5 & 6). In HD fetuses, the fetal incidence of hypoplastic (1.55%) and cervical (2.1%) ribs was higher than controls (0.26, 0.52; sponsor Table 7). The sponsor does not consider these findings treatment-related as the incidence of hypoplastic ribs is within their historical control range (highest incidence = 2.03%), and an increased incidence of cervical ribs was not observed in the C-section component of the female rat fertilty study. However, the observed fetal incidences in this study are higher than the historical incidence MARTA database average (cervical ribs: 0.615; hypoplastic ribs: 1.06).

TABLE 4. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #92-708-0

SUMMARY OF LAPAROTOMY DATA

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
FEMALES				
TOTAL FEMALES	25	25	25	25
PREGNANT	25	22	22	25
EXAMINED LIVE LITTER	25	22	22	25
DIED	0	0	0	0
SACRIFICED	0	0	0	0
ABORTED	0	0	0	0
NOT PREGNANT	0	3	3	0
LIVE	0	3	3	0
DIED	0	0	0	0
SACRIFICED	0	0	0	0
% PREIMPLANTATION LOSS (LITTER MEAN)	6.0	8.2	4.4	6.0
IMPLANTS				
IMPLANTS	400	344	357	405
IMPLANTS/PREGNANT FEMALE	16.0	15.6	16.2	16.2 NS
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	28	22	18	17
% RESORPTIONS/IMPLANTS (LITTER MEAN)	7.4	6.4	5.0	4.0
DEAD FETUSES	0	0	0	1
% DEAD FETUSES/IMPLANTS (LITTER MEAN)	0.0	0.0	0.0	0.2
% (RESORP+DEAD FET)/IMP (LITTER MEAN)	7.4	6.4	5.0	4.3 NS
LIVE FETUSES				
LIVE FETUSES	372	322	339	387
FEMALES	190	161	179	189
MALES	182	161	160	198
SEX RATIO (LITTER MEAN)	0.51	0.52	0.53	0.49
LIVE FETUSES/PREGNANT FEMALE	14.9	14.6	15.4	15.5 NS
LIVE FETAL WEIGHT (GM, LITTER MEAN)				
FEMALES[a]	5.19	5.31	5.20 NS	5.07 S
MALES[a]	5.48	5.55	5.49 NS	5.37 S

% PREIMPLANTATION LOSS = ((NO. CORPORA LUTEA - NO. IMPLANTS) / NO. CORPORA LUTEA) X 100

SEX RATIO = (TOTAL NO. LIVE FEMALE FETUSES/TOTAL NO. LIVE FETUSES)
S = TREND STATISTICALLY SIGNIFICANT THROUGH INDICATED DOSE ($P \leq 0.05$).
NS = TREND NOT STATISTICALLY SIGNIFICANT THROUGH INDICATED DOSE ($P > 0.05$).
a = TREND ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR TIME OF SACRIFICE AND NUMBER OF LIVE FETUSES PER LITTER.

TABLE 5. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #92-708-0

SUMMARY OF EXTERNAL EXAMINATION OF FETUSES

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
LIVE FETUSES/LITTERS EXAMINED		372/25	322/22	339/22	387/25
DEAD FETUSES/LITTERS EXAMINED		0	0	0	1/ 1
FETUSES WITH MALFORMATIONS (%, LM)		1 (0.27)	0	1 (0.27)	0
LITTERS WITH MALFORMATIONS (%)		1 (4.0)	0	1 (4.5)	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	0
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
ANOPHTHALMIA	(M)	0	0	1 (0.27)	0
CLEFT PALATE	(M)	1 (0.27)	0	0	0
TAIL MALFORMATION	(M)	1 (0.27)	0	0	0

(LM) = LITTER MEAN (M) = MALFORMATION

TABLE 6. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #92-708-0

SUMMARY OF VISCERAL EXAMINATION OF FETUSES

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
THORACIC AND ABDOMINAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		134/25	113/22	120/22	138/25
DEAD FETUSES/LITTERS EXAMINED		0	0	0	1/ 1
FETUSES WITH MALFORMATIONS (%, LM)		1 (0.67)	0	0	0
LITTERS WITH MALFORMATIONS (%)		1 (4.0)	0	0	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	1 (0.80)
LITTERS WITH VARIATIONS (%)		0	0	0	1 (4.0)
CORONAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		132/25	113/22	120/22	138/25
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		3 (2.4)	0	0	0
LITTERS WITH VARIATIONS (%)		1 (4.0)	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
HYDROURETER	(M)	1 (0.67)	0	0	0
CAROTID BRANCHING VARIATION	(V)	0	0	0	1 (0.80)
CEREBRAL VENTRIC. ENLARGEMENT	(V)	3 (2.4)	0	0	0

(LM) = LITTER MEAN (M) = MALFORMATION (V) = VARIATION

TABLE 7. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT 692-708-0

SUMMARY OF SKELETAL EXAMINATION OF FETUSES (EXCLUDING OSSIFICATION DATA)

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
TORSO AND LIMB EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		372/25	322/22	339/22	387/25
DEAD FETUSES/LITTERS EXAMINED		0	0	0	1/ 1
FETUSES WITH MALFORMATIONS (%, LM)		8 (2.2)	3 (0.83)	1 (0.35)	6 (1.4)
LITTERS WITH MALFORMATIONS (%)		3 (12)	3 (14)	1 (4.5)	3 (12)
FETUSES WITH VARIATIONS (%, LM)		48 (14)	45 (14)	41 (12)	55 (14)
LITTERS WITH VARIATIONS (%)		18 (72)	18 (82)	13 (59)	19 (76)
HEAD EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		240/25	209/22	219/22	249/25
DEAD FETUSES/LITTERS EXAMINED		0	0	0	1/ 1
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	0
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
THORACIC VERTEBRA MALFORMATION	(M)	0	1 (0.25)	0	0
MISSING VERTEBRA	(M)	1 (0.31)	0	0	0 1.55
HYPOPLASTIC RIB	(M)	1 (0.27)	2 (0.50)	0	6 (1.4)
MISSHAPEN RIB	(M)	6 (1.6)	0	0	0
STERNEBRAL MALFORMATION	(M)	0	1 (0.32)	1 (0.35)	0
LUMBAR VERTEBRA VARIATION	(V)	2 (0.54)	3 (0.83)	0	2 (0.53)
SACRAL VERTEBRA VARIATION	(V)	0	0	2 (0.61)	0
VERTEBRAL COUNT VARIATION	(V)	3 (1.5)	1 (0.32)	0	2 (0.53)
CERVICAL RIB	(V)	2 (0.57)	4 (1.1)	3 (0.92)	8 (2.2) 2.1
SUPERNUMERARY RIB	(V)	45 (13)	39 (12)	37 (10)	46 (12)
STERNEBRAL VARIATION	(V)	1 (0.24)	1 (0.32)	1 (0.35)	1 (0.29)

(LM) = LITTER MEAN (M) = MALFORMATION (V) = VARIATION

TABLE 8. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RATS. TT #92-708-0

SUMMARY OF FETAL OSSIFICATION DATA

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
TORSO AND LIMB EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	372/25	322/22	339/22	387/25
FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)	2 (0.52)	2 (0.56)	4 (1.1)	2 (0.55)
LITTERS WITH INCOMPLETE OSSIFICATION (%)	2 (8.0)	2 (9.1)	4 (18)	2 (8.0)
NUMBER OSSIFIED SACROCAUDAL VERTEBRAE[a] (LITTER MEAN)	9.9	10.1	10.0	9.9
HEAD EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	240/25	209/22	219/22	249/25
FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)	0	1 (0.57)	1 (0.45)	0
LITTERS WITH INCOMPLETE OSSIFICATION (%)	0	1 (4.5)	1 (4.5)	0
SITE AND NUMBER OF FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)				
INCOMP. OSS. THORACIC VERTEBRA	0	1 (0.25)	4 (1.1)	2 (0.55)
INCOMP. OSS. SKULL BONE	0	1 (0.57)	1 (0.45)	0
INCOMP. OSS. STERNEBRA	2 (0.52)	1 (0.30)	0	1 (0.27)

(LM) = LITTER MEAN
a = SEE INDIVIDUAL TABLE FOR EXCLUSIONS.

C.4.a.2. **MK-0462: Oral Toxicokinetic Study in Pregnant Rats with Secretion in Milk**
(GLP; Report #: TT 95-701-0; Vol. 19)
Conducted by: MRL, West Point, PA Study Dates: 1/9/95 - 6/23/95

Summary:

This study was conducted under conditions essentially identical to those of the main study with a different group of rats (n=29/dose), and a different drug lot (004B015). Only the LD and HD of the main study (2 and 100 mg/kg) were evaluated. Animals were dosed once daily from either GD6-GD20 for the toxicokinetic phase, or GD6-LD 14 for the milk secretion phase. Blood samples were collected on GD20 from 4 animals/dose at 0.5, 1, 2, 4, 7 and 24 hrs post-dose. Fetal blood samples were collected from umbilical vessels at 0.5 and 2 hrs. For the milk secretion study, blood and milk were collected at 2 hrs post-dose on LD14 (n=4).

The TK results are shown in sponsor Tab. B-4. Blood samples at the LD were near the limit of detection, particularly at 2 hrs. Maternal plasma levels at the HD suggested greater than dose proportional increases in exposure. Maternal milk:plasma ratios at the HD was 6.43 indicating extensive milk secretion. Fetal:maternal plasma ratios were 0.33-0.47 demonstrating placental transfer of drug.

TABLE B-4. MK-0462: ORAL TOXICOKINETIC STUDY IN PREGNANT RATS WITH SECRETION IN MILK. TT #95-701-0

SUMMARY OF MEAN DRUG TOXICOKINETIC PARAMETERS FOR PREGNANT AND LACTATING RATS TREATED ORALLY WITH MK-0462 AT 2 AND 100 MG/KG/DAY

	2 mg/kg/day[1]	100 mg/kg/day
Maternal Toxicokinetic Phase (GD 20/21)		
Mean Cmax (µg/ml)	0.16	7.40
Tmax (hr)	0.5	1.0
AUC of the Means (µg•hr/ml)	0.31	46.72
Placental Transfer Phase (GD 20)		
0.5 Hour Post-Dose		
Mean Maternal Concentration (µg/ml)	0.16	5.85
Mean Fetal Plasma Concentration (µg/ml)	0	1.15
Ratio (Fetal/Maternal)	0	0.20
2 Hour Post-Dose		
Mean Maternal Concentration (µg/ml)	0.03	4.06
Mean Fetal Plasma Concentration (µg/ml)	0	1.62
Ratio (Fetal/Maternal)	0	0.40
Milk Transfer Phase (2 Hour Post-Dose) (LD 14)		
Mean Maternal Concentration (µg/ml)	0	2.82
Mean Milk Concentration (µg/ml)	0.59	18.13
Ratio (Milk/Maternal Plasma)	NC	6.43

1 = A zero value indicates all individual and mean values were below the limit of quantitation.
NC = not calculated; division by zero.
GD = Gestation Day
LD = Lactation Day

C.4.b. Developmental Toxicity in Rabbits

C.4.b.1. L-705,126: Oral Developmental Toxicity Study in Rabbits

(GLP; Report #: TT 92-709-0; Vol. 20)
Conducted by: MRL, West Point, PA Study Dates: 8/31/92 - 1/15/93

Range Finding Studies:

L-705,126: Oral Range-Finding Study in Non-Pregnant Rabbits (TT #92-709-2).
L-705,126: Oral Range-Finding Study in Pregnant Rabbits (TT #92-709-1).

Summary:

RIZ (0, 5, 10 and 50 mg/kg/day) was given by gavage to mated female rabbits (18/dose) on days 6-18 of gestation. Does were sacrificed on day 28. Dose selection was based on range study findings of maternotoxicity at ≥ 25 mg/kg, one abortion at 100 mg/kg, and fetotoxicity at 100 mg/kg (increased resorptions and dead fetuses, decreased fetal weights).

No deaths or abortions occurred. Mydriasis or slow pupillary reflexes, body weight loss, and decreased food consumption were seen in HD animals. There were no treatment-related effects on pregnancy parameters, fetal weights, external morphology or skeletal examinations. Thus, RIZ was devoid of teratogenic effects in rabbits at a maternotoxic dose of 50 mg/kg.

The NOAEL for F_0 is 10 mg/kg based on body weight loss and decreased food consumption. The NOAEL for F_1 is 50 mg/kg. Toxicokinetics for the LD and HD were determined in a subsequent study (see C.4.b.2.). Maternal plasma exposures at the LD (below the NOAEL for F_0) exceeded expected human exposures at the MRHD (30 mg) by 4 times based on AUC. Maternal plasma exposures at the NOAEL for F_1 exceeded expected human exposures by 148 times based on AUC.

Methods:

Animals: New Zealand premated white rabbits; 23.5 wks, N = 18/group;
Dosages: 0, 5, 10, 50 mg/kg/day (Lot: 004B007; calcd. as base) in water.

Dose selection was based on a developmental toxicity range-finding study of 5, 25 and 100 mg/kg/day administered on days 6-18 of gestation (TT #92-709-1). Maternotoxicity signs were decreased body weight gain and food consumption and slow pupillary reflex at ≥ 25 mg/kg, and weight loss, one abortion and lethargy at 100 mg/kg. Fetotoxicity was evident at the HD level as an increase in resorptions and dead fetuses (see sponsor Table 6&7 from study 92-709-1), and a decrease in fetal weights (33.0g vs. 38.5g in Con). Fetal wastage was attributed to feeding cessation during gestation.

Regimen: once daily by gavage on GD 6-18; all animals sacrificed on GD 28
Parameters: *Maternal* - clin signs, body wt, food cons, preg/non-preg, corpora lutea, implants, resorptions, live/dead fetuses, necropsy (thoracic, abdominal)
Fetuses - body wt, external exam, visceral exam, skeletal exam (alizarin red)

RANGE - FINDING STUDY RESULTS

FIGURE 1. L-705.126: ORAL RANGE-FINDING STUDY IN PREGNANT RABBITS. TT #92-709-1
AVERAGE MATERNAL BODY WEIGHTS

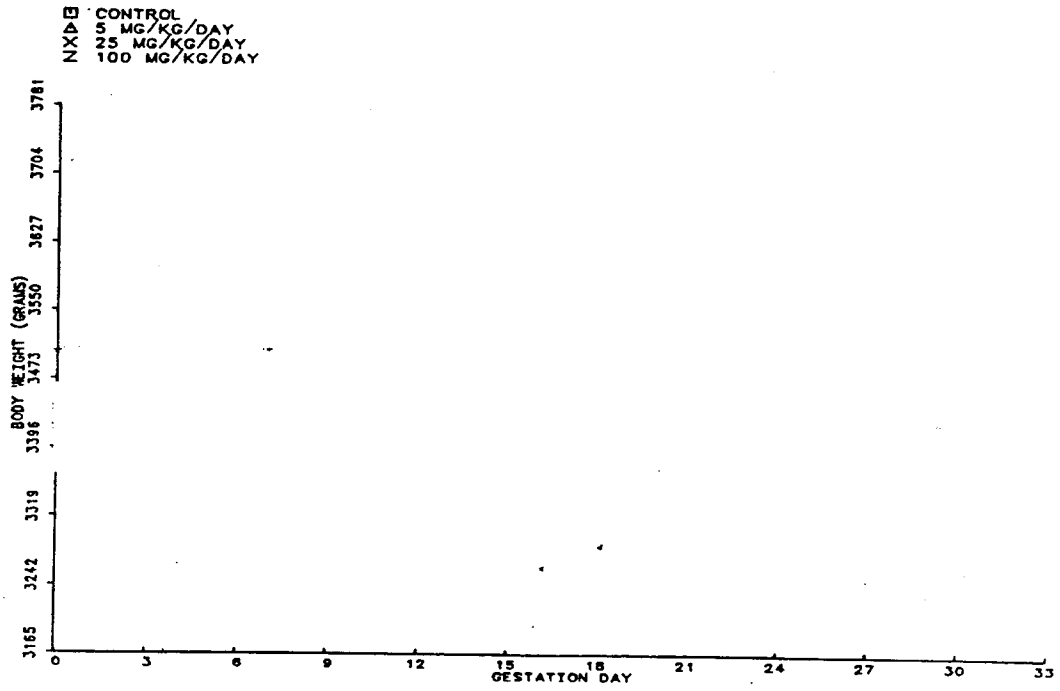


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FIGURE 2. L-705.126: ORAL RANGE-FINDING STUDY IN PREGNANT RABBITS. TT #92-709-1
AVERAGE MATERNAL FOOD CONSUMPTION

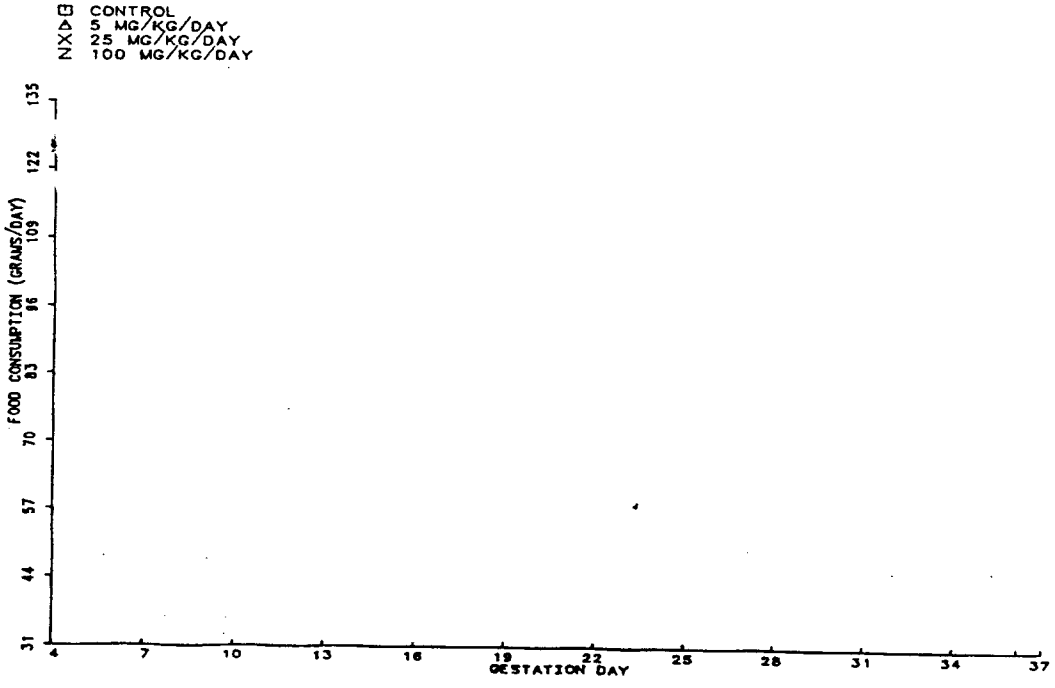


TABLE 6. L-705,126: ORAL RANGE-FINDING STUDY IN PREGNANT RABBITS. TT #92-709-1
SUMMARY OF LAPAROTOMY DATA

TREATMENT GROUP:	CONTROL	5 MG/KG/DAY	25 MG/KG/DAY	100 MG/KG/DAY
FEMALES				
TOTAL FEMALES	10	10	10	10
PREGNANT	10	10	9	10
EXAMINED LIVE LITTER	9	10	9	9
DIED	0	0	0	0
SACRIFICED	1	0	0	0
ABORTED	0	0	0	1
NOT PREGNANT	0	0	1	0
LIVE	0	0	1	0
DIED	0	0	0	0
SACRIFICED	0	0	0	0
IMPLANTS				
IMPLANTS	68	90	76	85
IMPLANTS/PREGNANT FEMALE	7.6	9.0	8.4	9.4^{NS}
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	0	0	3	11
% RESORPTIONS/IMPLANTS (LITTER MEAN)	0.0	0.0	3.7	12.2
DEAD FETUSES	0	0	0	2
% DEAD FETUSES/IMPLANTS (LITTER MEAN)	0.0	0.0	0.0	2.8
% (RESORP+DEAD FET)/IMP (LITTER MEAN)	0.0	0.0	3.7^{NS}	15.0^{S}
LIVE FETUSES				
LIVE FETUSES	68	90	73	72
UNDETERMINED SEX	68	90	73	72
LIVE FETUSES/PREGNANT FEMALE	7.6	9.0	8.1	8.0^{NS}
LIVE FETAL WEIGHT (GM, LITTER MEAN)	38.5	36.1	36.2^{NS}	33.0^{S}

NS = TREND NOT STATISTICALLY SIGNIFICANT THROUGH INDICATED DOSE ($P > 0.05$).
S = TREND STATISTICALLY SIGNIFICANT THROUGH INDICATED DOSE ($P \leq 0.05$).

TABLE 7. L-705,126: ORAL RANGE-FINDING STUDY IN PREGNANT RABBITS. TT #92-709-1

SUMMARY OF EXTERNAL EXAMINATION OF FETUSES

TREATMENT GROUP:		CONTROL	5 MG/KG/DAY	25 MG/KG/DAY	100 MG/KG/DAY
LIVE FETUSES/LITTERS EXAMINED		68/ 9	90/10	73/ 9	72/ 9
DEAD FETUSES/LITTERS EXAMINED		0	0	0	2/ 2
FETUSES WITH MALFORMATIONS (%, LM)		0	1 (0.91)	3 (4.2)	0
LITTERS WITH MALFORMATIONS (%)		0	1 (10)	2 (22)	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	0
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
TAIL MALFORMATION	(M)	0	0	2 (2.8)	0
ECTRODACTYLY	(M)	0	1 (0.91)	0	0
CLUBBED HINDFOOT	(M)	0	0	1 (1.4)	0

(LM) = LITTER MEAN (M) = MALFORMATION

Results:

Maternal - There were no deaths or abortions. Mydriasis or slow pupillary reflexes was the only clinical sign observed in HD animals. Four does lost a large amount of weight during gestation . Mean weight loss was 13g. The weight loss was paralleled by a decrease in food intake (sponsor Figure 1 & 2). There were no treatment effects on pregnancy parameters (sponsor Table 4).

FIGURE 1. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT #92-709-0
AVERAGE MATERNAL BODY WEIGHTS DURING GESTATION

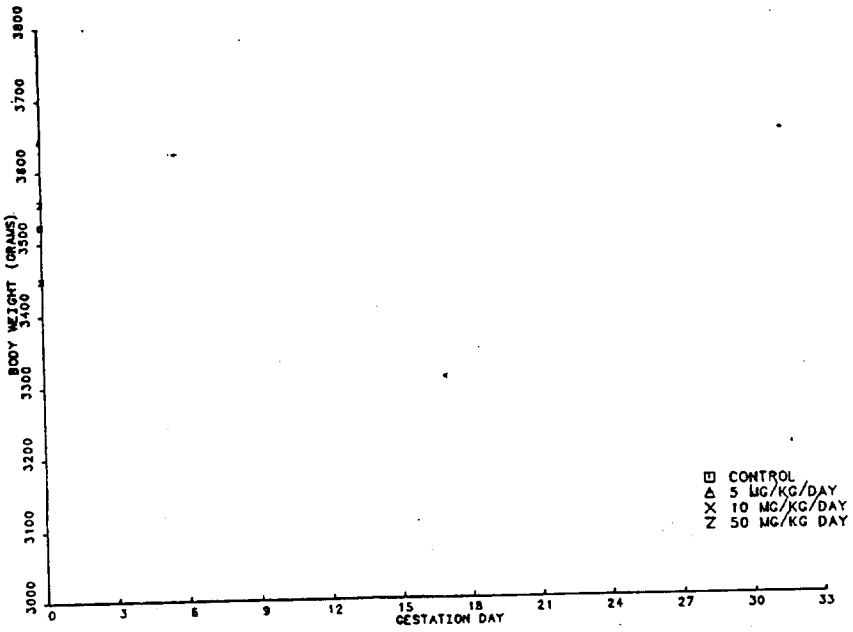
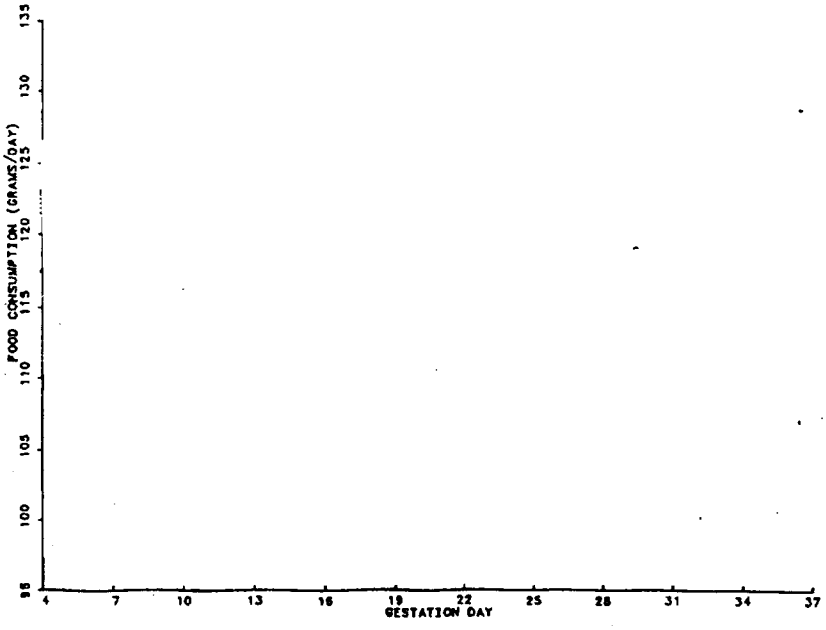


FIGURE 2. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT #92-709-0
AVERAGE MATERNAL FOOD CONSUMPTION DURING GESTATION



Fetal - There were no treatment effects on fetal weights, external morphology, or skeletal examinations (sponsor Tables 4, 5, 7 & 8). Variation in lung lobation was noted only in drug-treated animals, but the incidence did not increase with dose (also noted: the incidence rate was below that in the MARTA historical database).

TABLE 4. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT #92-709-0

SUMMARY OF LAPAROTOMY DATA

TREATMENT GROUP:	CONTROL	5 MG/KG/DAY	10 MG/KG/DAY	50 MG/KG/DAY
FEMALES				
TOTAL FEMALES	18	18	18	18
PREGNANT	18	17	18	18
EXAMINED LIVE LITTER	18	17	18	18
DIED	0	0	0	0
SACRIFICED	0	0	0	0
ABORTED	0	0	0	0
NOT PREGNANT	0	1	0	0
LIVE	0	1	0	0
DIED	0	0	0	0
SACRIFICED	0	0	0	0
CORPORA LUTEA				
CORPORA LUTEA	186	175	179	171
CORPORA LUTEA/PREGNANT FEMALE	10.3	10.3	9.9	9.5
% PREIMPLANTATION LOSS (LITTER MEAN)	18.8	11.4	8.7	10.6
IMPLANTS				
IMPLANTS	151	155	165	151
IMPLANTS/PREGNANT FEMALE	8.4	9.1	9.2	8.4[NS]
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	1	10	4	3
% RESORPTIONS/IMPLANTS (LITTER MEAN)	0.7	6.1	3.7	1.7
DEAD FETUSES	3	1	3	0
% DEAD FETUSES/IMPLANTS (LITTER MEAN)	1.8	0.6	2.4	0.0
% (RESORP+DEAD FET)/IMP (LITTER MEAN)	2.5	6.7	6.1	1.7[NS]
LIVE FETUSES				
LIVE FETUSES	147	144	158	148
FEMALES	78	64	65	66
MALES	69	80	93	82
SEX RATIO (LITTER MEAN)	0.53	0.47	0.39	0.45
LIVE FETUSES/PREGNANT FEMALE	8.2	8.5	8.8	8.2[NS]
LIVE FETAL WEIGHT (GM, LITTER MEAN)				
FEMALES[a]	37.0	36.3	35.3	35.9[NS]
MALES[a]	37.2	36.7	36.9	36.2[NS]

% PREIMPLANTATION LOSS = ((NO. CORPORA LUTEA - NO. IMPLANTS) / NO. CORPORA LUTEA) X 100
SEX RATIO = (TOTAL NO. LIVE FEMALE FETUSES/TOTAL NO. LIVE FETUSES)
NS = TREND NOT STATISTICALLY SIGNIFICANT THROUGH INDICATED DOSE (P > 0.05).
a = TREND ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR NUMBER OF LIVE FETUSES PER LITTER.

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TABLE 5. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT #92-709-0

SUMMARY OF EXTERNAL EXAMINATION OF FETUSES

TREATMENT GROUP:		CONTROL	5 MG/KG/DAY	10 MG/KG/DAY	50 MG/KG/DAY
LIVE FETUSES/LITTERS EXAMINED		147/18	144/17	158/18	148/18
DEAD FETUSES/LITTERS EXAMINED		3/ 3	1/ 1	3/ 3	0
FETUSES WITH MALFORMATIONS (%, LM)		0	1 (0.74)	0	0
LITTERS WITH MALFORMATIONS (%)		0	1 (5.9)	0	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	0
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
GASTROSCHISIS	(M)	0	1 (0.74)	0	0

(LM) = LITTER MEAN (M) = MALFORMATION

TABLE 6. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT #92-709-0

SUMMARY OF VISCERAL EXAMINATION OF FETUSES

TREATMENT GROUP:		CONTROL	5 MG/KG/DAY	10 MG/KG/DAY	50 MG/KG/DAY
THORACIC AND ABDOMINAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		147/18	144/17	158/18	148/18
DEAD FETUSES/LITTERS EXAMINED		3/ 3	1/ 1	3/ 3	0
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		0	6 (4.2)	2 (1.1)	6 (4.1)
LITTERS WITH VARIATIONS (%)		0	5 (29)	2 (11)	4 (22)
CORONAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		147/18	144/17	158/18	148/18
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	0
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
GALLBLADDER REDUCED IN SIZE	(V)	0	1 (0.59)	1 (0.50)	0
VARIATION IN LUNG LOBATION	(V)	0	5 (3.6)	1 (0.62)	6 (4.1)

TABLE 7. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT #92-709-0

SUMMARY OF SKELETAL EXAMINATION OF FETUSES (EXCLUDING OSSIFICATION DATA)

TREATMENT GROUP:		CONTROL	5 MG/KG/DAY	10 MG/KG/DAY	50 MG/KG/DAY
TORSO AND LIMB EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		146/18 [a]	144/17	158/18	148/18
DEAD FETUSES/LITTERS EXAMINED		3/ 3	1/ 1	3/ 3	0
FETUSES WITH MALFORMATIONS (%, LM)		4 (2.3)	1 (0.59)	1 (0.50)	0
LITTERS WITH MALFORMATIONS (%)		4 (22)	1 (5.9)	1 (5.6)	0
FETUSES WITH VARIATIONS (%, LM)		31 (21)	30 (20)	28 (18)	35 (23)
LITTERS WITH VARIATIONS (%)		15 (83)	14 (82)	14 (78)	14 (78)
HEAD EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		146/18	144/17	158/18	148/18
DEAD FETUSES/LITTERS EXAMINED		3/ 3	1/ 1	3/ 3	0
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		0	1 (0.65)	0	0
LITTERS WITH VARIATIONS (%)		0	1 (5.9)	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
STERNEBRAL MALFORMATION	(M)	3 (1.7)	1 (0.59)	1 (0.50)	0
PELVIC BONE MALFORMATION	(M)	1 (0.62)	0	0	0
SKULL BONE VARIATION	(V)	0	1 (0.65)	0	0
CERVICAL RIB	(V)	0	0	0	1 (0.62)
REDUCED 13TH RIB	(V)	30 (21)	30 (20)	28 (18)	33 (22)
STERNEBRAL VARIATION	(V)	1 (0.50)	0	0	0
PELVIC BONE VARIATION	(V)	0	0	0	1 (0.79)

(LM) = LITTER MEAN (M) = MALFORMATION (V) = VARIATION
a = SEE INDIVIDUAL TABLE FOR EXCLUSION.

TABLE 8. L-705,126: ORAL DEVELOPMENTAL TOXICITY STUDY IN RABBITS. TT #92-709-0

SUMMARY OF FETAL OSSIFICATION

TREATMENT GROUP:	CONTROL	5 MG/KG/DAY	10 MG/KG/DAY	50 MG/KG/DAY
TORSO AND LIMB EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	146/18 [a]	144/17	158/18	148/18
FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)	40 (29)	26 (15)	29 (15)	35 (24)
LITTERS WITH INCOMPLETE OSSIFICATION (%)	14 (78)	8 (47)	8 (44)	11 (61)
NUMBER OSSIFIED SACROCAUDAL VERTEBRAE [a] (LITTER MEAN)	19.7	19.6	19.7	19.4
HEAD EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	146/18	144/17	158/18	148/18
FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)	0	1 (0.74)	0	0
LITTERS WITH INCOMPLETE OSSIFICATION (%)	0	1 (5.9)	0	0
SITE AND NUMBER OF FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)				
INCOMP. OSS. LUMBAR VERTEBRA	0	0	0	1 (0.93)
INCOMP. OSS. SKULL BONE	0	1 (0.74)	0	0
INCOMP. OSS. STERNEBRA	13 (11)	9 (5.1)	19 (10)	7 (4.4)
INCOMP. OSS. METACARPAL	31 (20)	20 (11)	14 (7.2)	18 (12)
INCOMP. OSS. PELVIC BONE	2 (1.2)	0	2 (1.0)	13 (8.9)

(LM) = LITTER MEAN
a = SEE INDIVIDUAL TABLE FOR EXCLUSIONS.

C.4.b.2. **MK-0462: Toxicokinetic Study in Pregnant Rabbits**
(GLP; Report #: TT 93-737-0 ; Vol. 22)
Conducted by: MRL, West Point, PA Study Dates: 10/21/93 - 11/8/93

Summary

This study was conducted under conditions essentially identical to those of the main study with a different group of rabbits (n=10/dose), and a different drug lot (004B009). Only the LD and HD of the main study (5 and 50 mg/kg on GD6-18) were evaluated. Blood samples were collected on GD18 from 5 animals/dose at 20 and 40 min, and from the other 5 animals/dose at 1, 2, 4 and 6 hrs.

The TK results are shown in sponsor Tab. B-3. Increases in plasma levels were greater than dose proportional. The absorption period was extended and plasma levels remained high and stable over the course of sample collection. Fetal uptake of drug was significant; at 6 hrs after the HD, fetal tissue concentration exceeded the maternal plasma concentration demonstrating high placental transfer.

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TABLE B-3. MK-0462: TOXICOKINETIC STUDY IN PREGNANT RABBITS. TT #93-737-0

MATERNAL PLASMA MK-0462 GROUP MEAN Cmax, Tmax, AND AUC DATA AND GROUP MEAN FETAL MK-0462 CONCENTRATION DATA

	5 mg/kg/day	50 mg/kg/day
Maternal Plasma		
Group Mean C_{max} (µg/ml)	0.27	6.72
Group Mean T_{max} (hr)	1	0.67
Group Mean AUC[1] (µg•hr/ml)	0.63	23.74
Fetus		
0.67 hr Group Mean Conc. (µg/g)	0.10	3.27
6 hr Group Mean Conc. (µg/g)	0	2.53
Fetus/Maternal Plasma Group Mean Drug Ratio[2]		
0.67 hr group	0.42	0.49
6 hr group	0	1.15

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1 = Group Mean AUC for 0 to 6 hours
2 = Fetus/Maternal Plasma Group Mean Drug Ratio-calculated by dividing the group mean fetal concentration by the group mean maternal plasma concentration.

C.4.c. L-705,126: Oral Fertility Study in Female Rats
(GLP; Report #: TT 92-720-0; Vol. 20)
Conducted by: MRL, West Point, PA Study Dates: 7/13/92-12/11/92

Summary:

RIZ (0, 2, 10 and 100 mg/kg/day) was given by gavage to female rats from day 14 prior to mating through gestation day 20 or lactation day 20 (n = 20/dose/time point). Dose selection was based on range study findings of maternal and developmental toxicities at ≥ 100 mg/kg, and pup deaths at 500 mg/kg.

Mating in the HD group was slightly delayed, possibly due to persistent diestrus. No other effects on the dams were evident (i.e., clinical signs, weight gain, fertility, gestation, parturition, pregnancy parameters). No clearly treatment-related embryofetal abnormalities were evident in the C-section group, although hypoplastic ribs, a possible finding in the Segment II study, were observed in 2 HD fetuses. In the natural delivery group, treatment-related decreases in MD and HD pup body weight were observed during lactation. No other treatment-related developmental impairments were seen in F_1 or F_2 generations.

The NOAEL for F_0 is 10 mg/kg based on possible estrous delays at the HD. The NOAEL for F_1 is 2 mg/kg based on impaired body weight development.

Methods:

Animals: Crl:CD(SD)BR rats; 9 wks; 196-273 g;
N: 40/group (20/group C-section; 20/group natural delivery)
Dosages: 0, 2, 10, 100 mg/kg/day (Lot: 004B006; calcd. as base) in water.

Doses were selected based on the same range-finding study used for selection developmental toxicity study doses (TT #92-708-1; see C.4.a); maternal and developmental toxicities (↓ b.w.g.) were observed at 100-500 mg/kg, and pup deaths occurred at 500 mg/kg.

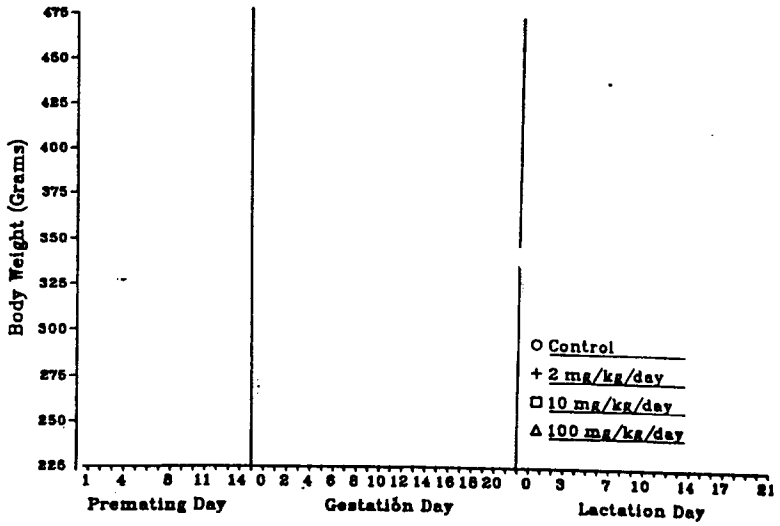
Regimen: once daily from 14 days prior to cohabitation through GD 20 (C-section group) or LD 20.
Route: oral (gavage)

Parameters:
Maternal - clin signs, body wt, food cons
C-sect dams- preg/non-preg, corpora lutea, implants, resorptions, live/dead fetuses, necropsy (thoracic, abdominal)
Fetuses - body wt, external exam, visceral exam (1/3 of fetuses), skeletal exam (alizarin red)
F1 - body wts on PD 0, 7, 14, 21; external exam, clin signs; culled to 8 on PD3; cull to 2M and 2F on PD21; neurobehavioral (acoustic startle on PD 48/49, passive avoidance on PD 62/63, open field behavior on PD 82-84) and reproductive tests (on PD 48/49)
F2 - survival, sex, body wt, external exam; discard on PD 5

Results:

Maternal - There were no deaths, abortions, treatment-related clinical signs or reductions in maternal weight gain (sponsor Fig. 1).

Figure 1. L-705,126: Oral Fertility Study in Female Rats. TT #92-720-0
Average Body Wei ' (Grams) of F_0 Females



There was no drug-related effect on mating incidence, but the time to mating was slightly delayed in the HD group, possibly due to persistent diestrus (sponsor Table 4). The sponsor considered this of uncertain relationship to treatment, and of minimal biological relevance. More than 50% of mated females in the HD group were not pregnant, as compared to 33% in the control group. Again, a treatment relationship is uncertain in the absence of a dose-response effect. No other treatment-related effects on fertility, gestation, parturition, or necropsy were evident.

TABLE 4. L-705,126: ORAL FERTILITY STUDY IN FEMALE RATS. TT 892-720-0
FINAL REPORT
SUMMARY OF REPRODUCTIVE PERFORMANCE OF FO FEMALES

	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
FEMALES COHABITED	40	40	40	40
MATED FEMALES	37	37	39	39
PREGNANT FEMALES	31	27	31	27
DIED OR SACRIFICED PRIOR TO DAY 20	0	0	0	0
CESAREAN SECTIONED	12	9	13	9
FEMALES WITH LIVE PUPS	19	18	18	18
MATINGS PER 4-DAY PERIODS OF COHABITATION:				
DAYS 1 TO 4	32	28	27	25
DAYS 5 TO 8	0	3	3	2
DAYS 9 TO 12	0	3	2	1
DAYS 13 TO 16	3	2	6	7
DAYS 17 OR LATER	2	1	1	4
TIME TO MATING (4-DAY PERIODS)	1.46	1.51	1.74 NS	2.05 S
MATED FEMALES/FEMALES COHABITED, %	92	92	98	98 NS
FECUNDITY INDEX PREGNANT FEMALES/MATED FEMALES, %	84	73	79	69 NS
FERTILITY INDEX PREGNANT FEMALES/FEMALES COHABITED, %	78	68	78	68 NS
FEMALES WITH LIVE PUPS/PREGNANT FEMALES, % (A)	100	100	100	100
LENGTH OF GESTATION (DAYS)	22.1[a]	22.2	22.2	22.0 NS,a

(A) = EXCLUDES ANY FEMALES NOT SURVIVING PAST DAY 20 OF GESTATION
S = TREND STATISTICALLY SIGNIFICANT ($P < 0.05$) THROUGH INDICATED DOSE.
NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.
a = SEE INDIVIDUAL TABLE FOR EXCLUSIONS.

Fetal - C-section - There were no treatment-related effects on pregnancy or embryofetal parameters. A relatively high number of resorptions occurred in the LD group (sponsor Table 5).

TABLE 5. L-705,126: ORAL FERTILITY STUDY IN FEMALE RATS. TT #92-720-0
FINAL REPORT
SUMMARY OF LAPAROTOMY DATA FROM F0 FEMALES

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
FEMALES				
TOTAL FEMALES	21	21	21	21
PREGNANT	12	9	13	9
EXAMINED LIVE LITTER	12	9	13	9
DIED	0	0	0	0
SACRIFICED	0	0	0	0
ABORTED	0	0	0	0
NOT PREGNANT	6	9	7	11
LIVE	6	9	7	11
DIED	0	0	0	0
SACRIFICED	0	0	0	0
NOT BRED	3	3	1	1
CORPORA LUTEA				
CORPORA LUTEA	221	178	236	159
CORPORA LUTEA/PREGNANT FEMALE	18.4	19.8	18.2	17.7
% PREIMPLANTATION LOSS (LITTER MEAN)	9.0	24.5	21.3	8.1
IMPLANTS				
IMPLANTS	200	133	188	146
IMPLANTS/PREGNANT FEMALE	16.7	14.8	14.5	16.2 NS
RESORPTIONS AND DEAD FETUSES				
RESORPTIONS	3	18	10	4
% RESORPTIONS/IMPLANTS (LITTER MEAN)	1.5	12.5	5.9	2.3
DEAD FETUSES	0	0	0	0
% DEAD FETUSES/IMPLANTS (LITTER MEAN)	0.0	0.0	0.0	0.0
% (RESORP+DEAD FET)/IMP (LITTER MEAN)	1.5	12.5	5.9	2.3 NS
LIVE FETUSES				
LIVE FETUSES	197	115	178	142
FEMALES	104	58	80	65
MALES	93	57	98	77
SEX RATIO (LITTER MEAN)	0.53	0.51	0.47	0.45 NS
LIVE FETUSES/PREGNANT FEMALE	16.4	12.8	13.7	15.8
LIVE FETAL WEIGHT (GM, LITTER MEAN)				
FEMALES	4.99	5.09	5.22	4.88 NS
MALES	5.27	5.43	5.34	5.22 NS

% PREIMPLANTATION LOSS = ((NO. CORPORA LUTEA - NO. IMPLANTS) / NO. CORPORA LUTEA) X 100
SEX RATIO = (TOTAL NO. LIVE FEMALE FETUSES/TOTAL NO. LIVE FETUSES)
NS = TREND NOT STATISTICALLY SIGNIFICANT (P > 0.05) THROUGH INDICATED DOSE

There were no treatment-related effects on external or visceral exams (sponsor Tables 6 & 7).

TABLE 6. L-705,126: ORAL FERTILITY STUDY IN FEMALE RATS. TT #92-720-0
FINAL REPORT
SUMMARY OF EXTERNAL EXAMINATION OF FETUSES FROM F_0 FEMALES

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
LIVE FETUSES/LITTERS EXAMINED	197/12	115/ 9	178/13	142/ 9
FETUSES WITH MALFORMATIONS (%, LM)	0	0	0	0
LITTERS WITH MALFORMATIONS (%)	0	0	0	0
FETUSES WITH VARIATIONS (%, LM)	0	0	0	0
LITTERS WITH VARIATIONS (%)	0	0	0	0

(LM) = LITTER MEAN

TABLE 7. L-705,126: ORAL FERTILITY STUDY IN FEMALE RATS. TT 892-720-0
FINAL REPORT
SUMMARY OF VISCERAL EXAMINATION OF FETUSES FROM F_0 FEMALES

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
THORACIC AND ABDOMINAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		70/12	40/ 9	63/13	52/ 9
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		2 (2.8)	0	0	0
LITTERS WITH VARIATIONS (%)		2 (17)	0	0	0
CORONAL EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		70/12	40/ 9	63/13	52/ 9
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	0
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
AZYGOS VEIN VARIATION	(V)	1 (1.4)	0	0	0
URETER VARIATION	(V)	1 (1.4)	0	0	0

(LM) = LITTER MEAN (V) = VARIATION

Low incidences of rib malformations/variations were considered spontaneous occurrences (sponsor Table 8). Hypoplastic ribs were observed in 2 HD fetuses. The fetal incidence rate (1.4%) exceeds the MARTA database average, and is noted as a consistent finding with the Segment II study.

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TABLE 8. L-705,126: ORAL FERTILITY STUDY IN FEMALE RATS. TT 892-720-0
FINAL REPORT
SUMMARY OF SKELETAL EXAMINATION OF FETUSES (EXCLUDING OSSIFICATION DATA) FROM F_0 FEMALES

TREATMENT GROUP:		CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
TORSO AND LIMB EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		197/12	115/ 9	178/13	142/ 9
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	2 (1.4)
LITTERS WITH MALFORMATIONS (%)		0	0	0	2 (22)
FETUSES WITH VARIATIONS (%, LM)		27 (14)	22 (21)	15 (8.7)	8 (6.0)
LITTERS WITH VARIATIONS (%)		7 (58)	7 (78)	5 (38)	4 (44)
HEAD EXAMINATION					
LIVE FETUSES/LITTERS EXAMINED		127/12	75/ 9	115/13	90/ 9
FETUSES WITH MALFORMATIONS (%, LM)		0	0	0	0
LITTERS WITH MALFORMATIONS (%)		0	0	0	0
FETUSES WITH VARIATIONS (%, LM)		0	0	0	0
LITTERS WITH VARIATIONS (%)		0	0	0	0
TYPE AND NUMBER OF FETAL ALTERATIONS (%, LM)	CLASS				
HYPOPLASTIC RIB	(M)	0	0	0	2 (1.4)
SACRAL VERTEBRA VARIATION	(V)	1 (0.49)	0	0	0
VERTEBRAL COUNT VARIATION	(V)	2 (1.2)	2 (1.5)	1 (0.43)	0
CERVICAL RIB	(V)	0	1 (1.0)	0	0
SUPERNUMERARY RIB	(V)	26 (14)	20 (20)	14 (8.3)	8 (6.0)

(LM) = LITTER MEAN (M) = MALFORMATION (V) = VARIATION

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The incidences of ossification delays are noted as higher in drug-treated animals, but of uncertain significance (sponsor Table 9).

TABLE 9. L-705,126: ORAL FERTILITY STUDY IN FEMALE RATS. TT #92-720-0
FINAL REPORT
SUMMARY OF FETAL OSSIFICATION DATA FROM F_0 FEMALES

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
TORSO AND LIMB EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	197/12	115/ 9	178/13	142/ 9
FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)	1 (0.60)	2 (1.4)	1 (0.43)	5 (3.8)
LITTERS WITH INCOMPLETE OSSIFICATION (%)	1 (8.3)	1 (11)	1 (7.7)	4 (44)
NUMBER OSSIFIED SACROCAUDAL VERTEBRAE (LITTER MEAN)	10.4	10.1	10.0	10.1
HEAD EXAMINATION				
LIVE FETUSES/LITTERS EXAMINED	127/12	75/ 9	115/13	90/ 9
FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)	0	0	0	0
LITTERS WITH INCOMPLETE OSSIFICATION (%)	0	0	0	0
SITE AND NUMBER OF FETUSES WITH INCOMPLETE OSSIFICATION (%, LM)				
INCOMP. OSS. THORACIC VERTEBRA	0	2 (1.4)	1 (0.43)	4 (3.1)
INCOMP. OSS. STERNEBRA	1 (0.60)	0	0	1 (0.69)

(LM) = LITTER MEAN

Natural Delivery - Treatment-related decreases in MD and HD pup body weight occurred during lactation (sponsor Fig. 3&4, Table 10). After weaning, body weight was reduced in MDF and HDF, but not dose-dependently.

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TABLE 10. L-705,126: ORAL FERTILITY STUDY IN FEMALE RATS. TT #92-720-0
FINAL REPORT
SUMMARY OF STATUS OF F1 GENERATION PRIOR TO WEANING

	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG /DAY
PARENTAL FEMALES	19	18	18	18
IMPLANTS PER FEMALE	14.9	15.9	17.4	16.1 NS
% POSTIMPLANTATION SURVIVAL (L.M.)	88.4	87.5	93.8	94.2 NS
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	19	18	18	18
TOTAL PUPS (FEMALES/MALES)	253(123/130)	260(142/118)	296(152/144)	277(119/158)
LIVE PUPS ON POSTNATAL DAY 0	251(122/129)	253(137/116)	294(152/142)	274(117/157)
DEAD PUPS ON POSTNATAL DAY 0	2(1/ 1)	7(5/ 2)	2(0/ 2)	3(2/ 1)
LIVE PUPS PER LITTER	13.2	14.1 NS	16.3 S	15.2 S
% LIVE PUPS (L.M.)	99.2	96.2	99.4	99.1
LIVE PUPS AFTER CULLING ON POSTNATAL DAY 3	152	136	144	144
PUP DEATHS (% PUP DEATHS) (L.M.)				
POSTNATAL DAYS 1 - 3	1(0.3)	5(5.9)	4(1.4)	2(0.7) NS
POSTNATAL DAYS 4 - 7	2(1.3)	0(0.0)	1(0.7)	0(0.0)
POSTNATAL DAYS 8 - 14	0(0.0)	0(0.0)	0(0.0)	0(0.0)
POSTNATAL DAYS 15 - 21	0(0.0)	0(0.0)	0(0.0)	0(0.0)
POSTNATAL DAYS 4 - 21	2(1.3)	0(0.0)	1(0.7)	0(0.0) NS
LIVE FEMALE PUP WEIGHT (GM) (L.M.)				
POSTNATAL DAY 0[a]	6.5	6.4 NS	6.1 S	5.9 S
POSTNATAL DAY 7[a]	17.9	18.0 NS	16.6 S	16.2 S
POSTNATAL DAY 14[b]	36.1	36.8 NS	34.8 S	33.1 S
POSTNATAL DAY 21[b]	60.4	60.2 NS	58.0 S	56.0 S
LIVE MALE PUP WEIGHT (GM) (L.M.)				
POSTNATAL DAY 0[a]	6.8	6.7 NS	6.5 S	6.3 S
POSTNATAL DAY 7[a]	18.7	18.9 NS	17.4 S	17.0 S
POSTNATAL DAY 14	37.4	38.3 NS	36.2 S	34.7 S
POSTNATAL DAY 21[b]	62.6	63.1 NS	60.5 S	59.1 S

(L.M.) = LITTER MEAN
% POSTIMPLANTATION SURVIVAL = [(NO. OF LIVE PUPS ON DAY 0)/(NO. OF METRIAL GLANDS OR TOTAL PUPS, IF LARGER)] X 100
S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE
NS = TREND NOT STATISTICALLY SIGNIFICANT ($P < 0.05$) THROUGH INDICATED DOSE
a = STATISTICAL ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR LENGTH OF GESTATION AND NUMBER LIVE PUPS PER LITTER ON ON POSTNATAL DAY 0
b = STATISTICAL ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR LENGTH OF GESTATION

Figure 3. L–705,126: Oral Fertility Study in Female Rats. TT #92–720–0
Average Body Weights (Grams) of F_1 Females

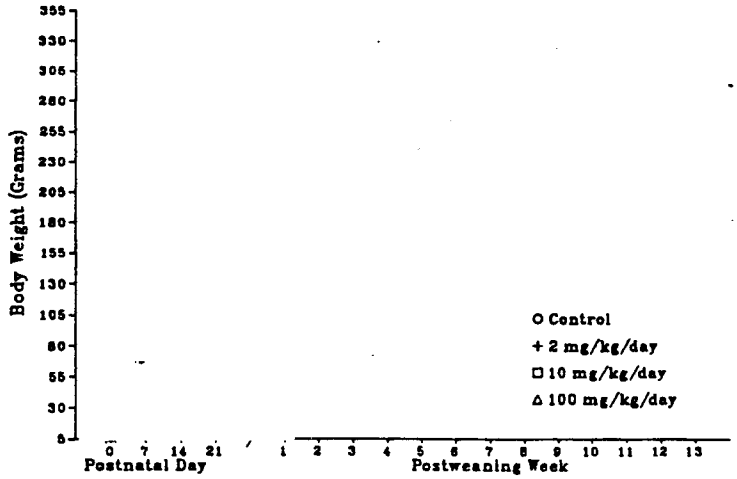
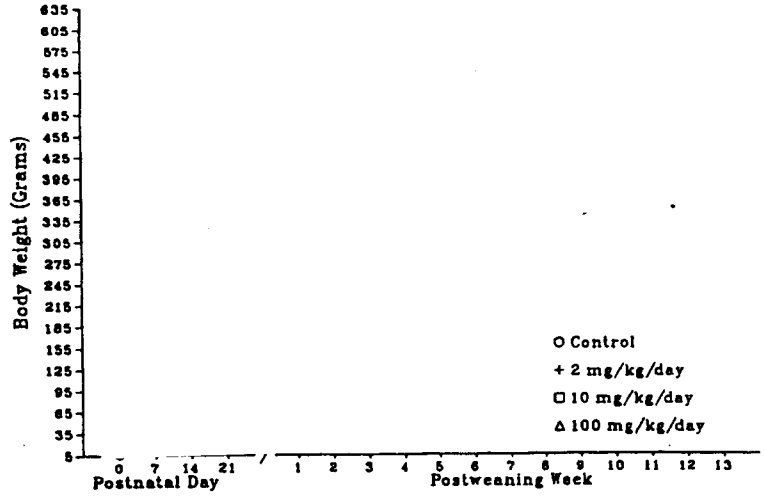


Figure 4. L–705,126: Oral Fertility Study in Female Rats. TT #92–720–0
Average Body Weights (Grams) of F_1 Males



F_1 Devel. - There were no treatment-related impairments of neurobehavioral or reproductive development in the F_1 generation.

F_2 - No treatment-related effects

C.4.d. MK-0462: Oral Late Gestation and Lactation Study in Rats
(GLP; Report #: TT 93-733-0; Vol. 21)
Conducted by: MRL, West Point, PA Study Date: 10/3/93 - 11/22/93

Summary:

RIZ (0, 2, 10 and 100 mg/kg/day) was given by gavage to mated female rats from gestation day 6 to lactation day 20 (n = 20/dose). The only maternotoxicity was transiently reduced body weight gain at the HD. The only developmental impairment was reduced body weights in HD pups throughout lactation, and in MDF on PND 0. There were no dose-related trends suggestive of a treatment-related effect on preweaning survival, but 14 MD pups were dead on PND 0 (sponsor Tab. 5). The deaths were not commented on by the sponsor.

The NOAELs were 10 mg/kg/day for F_0, and 2 mg/kg for F_1 based on decreased body weight gain or development.

Methods:

Animals:	Crl:CD(SD)BR rats; 10 wks;
N:	20/group
Dosages:	0, 2, 10, 100 mg/kg/day (Lot: 004B006; calcd. as base) in water. Dose selection was based on the oral fertility study (TT #92-720-0) in which treatment-related decreases in pup body weight occurred at 10 and 100 mg/kg.
Regimen:	once daily from GD 15 through LD 20; dams necropsied between LD 21-24
Route:	oral (gavage)
Parameters:	*Maternal* - clin signs, body wt, food cons, pregnancy status, necropsy (thoracic and abdominal, including number of metrial glands). *F_1* - body wt, physical signs, external exam

Results:

Maternal - There were no deaths or treatment-related physical signs during the study. Body weight gain was reduced in HD by 16% on days GD 15-20 (sponsor Fig. 1&2, Tab. 2). There were no treatment-related effects on reproductive performance or pregnancy parameters, and no notable necropsy findings.

TABLE 2. MK-0462: ORAL LATE GESTATION AND LACTATION STUDY IN RATS. TT #93-733-0
AVERAGE MATERNAL BODY WEIGHT CHANGES (GRAMS) OF F0 FEMALES

TREATMENT GROUP:	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
GESTATIONAL PERIOD				
DAY 0 TO 15	93 (20)	100 (20)	90 (20)	95 (20)
DAY 15 TO 20[a]	69	71	66 NS	59 S
LACTATIONAL PERIOD				
DAY 0 TO 7	23 (20)	23 (20)	25 (20)	19 (20)
DAY 7 TO 14	29	24	21	22
DAY 14 TO 21	-16	-16	-11	-8
DAY 0 TO 21	36	31	35	34

(N) = GROUP SIZE AND APPEARS ONLY IF DIFFERENT FROM PREVIOUS N.

S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.
NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.
a = TREND ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR MATERNAL BODY WEIGHT CHANGE BETWEEN DAY 0 AND 15.

FIGURE 1. MK-0462: ORAL LATE GESTATION AND LACTATION STUDY IN RATS. TT #93-733-0
AVERAGE MATERNAL BODY WEIGHTS (GRAMS) OF F0 FEMALES DURING GESTATION

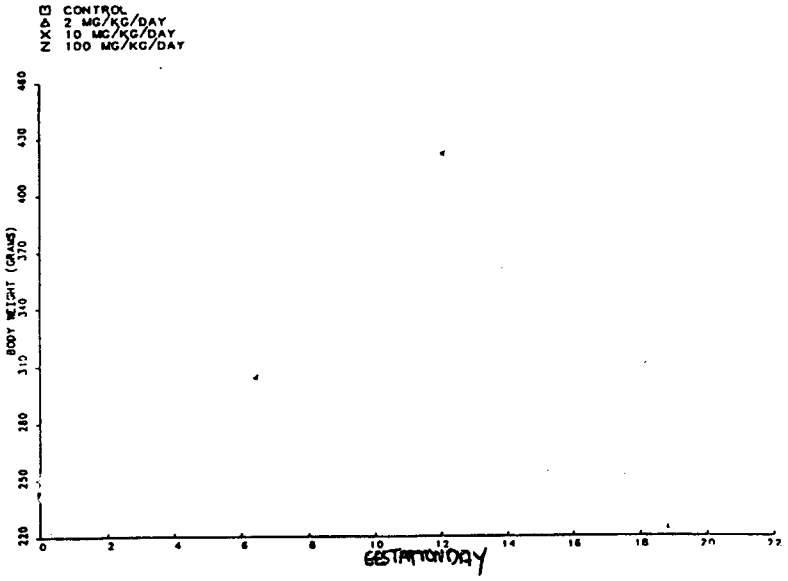
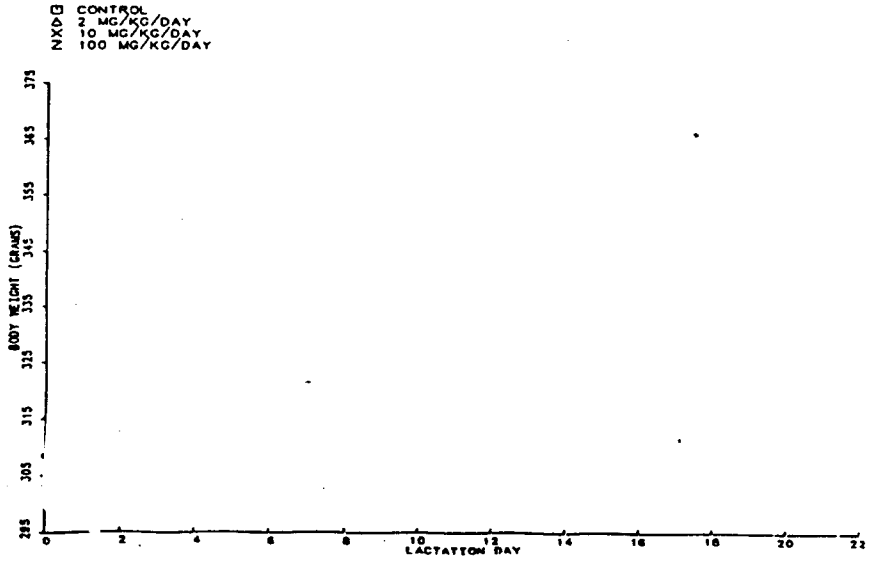


FIGURE 2. MK-0462: ORAL LATE GESTATION AND LACTATION STUDY IN RATS. TT #93-733-0
AVERAGE MATERNAL BODY WEIGHTS (GRAMS) OF F0 FEMALES DURING LACTATION



F_1 - There were no dose-related trends suggestive of a treatment-related effect on preweaning survival, but 14 MD pups were dead on PND 0 (sponsor Tab. 5). These deaths were not commented on by the sponsor. Body weight gain was reduced in HD pups throughout lactation, and in MDF on PND 0 (sponsor Tab. 5). There were no other treatment-related clinical signs or external anomalies.

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TABLE 5. MK-0462: ORAL LATE GESTATION AND LACTATION STUDY IN RATS. TT #93-733-0
SUMMARY OF STATUS OF F1 GENERATION PRIOR TO WEANING

	CONTROL	2 MG/KG/DAY	10 MG/KG/DAY	100 MG/KG/DAY
PARENTAL FEMALES	20	20	20	20
IMPLANTS PER FEMALE	16.8	17.4	16.6	15.8
% POSTIMPLANTATION SURVIVAL (L.M.)	91.1	90.8	89.4	93.1 NS
FEMALES WITH LIVE PUPS DAY 0 POSTPARTUM	20	20	20	20
FEMALES WITH LIVE PUPS DAY 21 POSTPARTUM	20	20	20	20
TOTAL PUPS (FEMALES/MALES)	310(173/135)	318(161/157)	309(157/151)	296(158/138)
LIVE PUPS ON POSTNATAL DAY 0	306(173/133)	317(160/157)	295(153/142)	295(157/138)
DEAD PUPS ON POSTNATAL DAY 0	4(0/ 2)	1(1/ 0)	14(4/ 9)	1(1/ 0)
LIVE PUPS PER LITTER	15.3	15.8	14.8	14.8 NS
% LIVE PUPS (L.M.)	98.7	99.6	95.4	99.6
LIVE PUPS AFTER CULLING ON POSTNATAL DAY 3	160	160	157	160
PUP DEATHS (% PUP DEATHS) (L.M.)				
POSTNATAL DAYS 1 - 3	0(0.0)	6(1.8)	5(1.6) a	3(1.0) NS
POSTNATAL DAYS 4 - 7	2(1.2)	0(0.0)	0(0.0)	0(0.0)
POSTNATAL DAYS 8 - 14	0(0.0)	1(0.6)	0(0.0)	1(0.6)
POSTNATAL DAYS 15 - 21	0(0.0)	0(0.0)	1(0.6)	0(0.0)
POSTNATAL DAYS 4 - 21	2(1.2)	1(0.6)	1(0.6)	1(0.6) NS
LIVE FEMALE PUP WEIGHT (GM) (L.M.)				
POSTNATAL DAY 0[c]	6.3	6.3 b,NS	6.1 S	6.1 S
POSTNATAL DAY 7	18.4	18.4	17.9 NS	16.9 S
POSTNATAL DAY 14	37.5	37.6	36.5 NS	34.6 S
POSTNATAL DAY 21[d]	61.4	60.9	59.0 NS	56.1 S
LIVE MALE PUP WEIGHT (GM) (L.M.)				
POSTNATAL DAY 0[c]	6.6	6.7 b	6.5 NS	6.4 S
POSTNATAL DAY 7	19.3	19.0	18.7 NS	17.8 S
POSTNATAL DAY 14	38.7	38.7	37.7 NS	36.1 S
POSTNATAL DAY 21	64.5	62.9	61.8 NS	59.1 S

(L.M.) = LITTER MEAN
TOTAL INCLUDES PUPS FOR WHICH SEX COULD NOT BE DETERMINED
S = TREND STATISTICALLY SIGNIFICANT ($P \leq 0.05$) THROUGH INDICATED DOSE.
NS = TREND NOT STATISTICALLY SIGNIFICANT ($P > 0.05$) THROUGH INDICATED DOSE.
a = INCLUDES ONE PUP THAT DIED AFTER LIVE WEIGHING ON DAY 0.
b = SEE INDIVIDUAL TABLES FOR EXCLUSIONS.
c = STATISTICAL ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR LENGTH OF GESTATION AND NUMBER OF LIVE PUPS PER LITTER ON POSTNATAL DAY 0.
d = STATISTICAL ANALYSIS WAS PERFORMED WITH AN ADJUSTMENT FOR LENGTH OF GESTATION.

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C.4.e. MK-0462: Oral Fertility Study in Male Rats
(GLP; Report #: TT 93-729-0; Vol. 22)
Conducted by: MRL, West Point, PA Study Date: 8/2/93 - 2/3/94

Summary:

RIZ (0, 5, 35 and 250 mg/kg/day) was administered by gavage to male rats for 70 days prior to mating through the cohabitation period. Body weight gain was significantly reduced in HD animals throughout the treatment period, but no impairments of male reproductive performance or notable necropsy findings were observed. Untreated female partners showed no evidence of altered reproduction or pregnancy, and there was no evidence of treatment-related changes in fetal development.

The NOAEL for toxicity in treated males (decrease body weight gain) was 35 mg/kg. The NOAEL for impairment of male reproductive performance was > 250 mg/kg. These studies suggest that RIZ does not present a significant risk to reproductive performance in male rats.

Methods:

Animals: Crl:CD(SD)BR rats; 9 wks; 328-454g; (treated males, untreated females)
N: 24/group
Dosages: 0, 5, 35, 250 mg/kg/day (Lot: 004B010; calcd. as base) in water.

Doses were selected based on a 14-week toxicity study (TT #92-097-0) in which body weight gain was decreased in males treated with

Regimen: males treated once daily from 70 days prior to cohabitation, through cohabitation, and until sacrifice; untreated mated females were sacrificed on day 21
Route: oral (gavage)

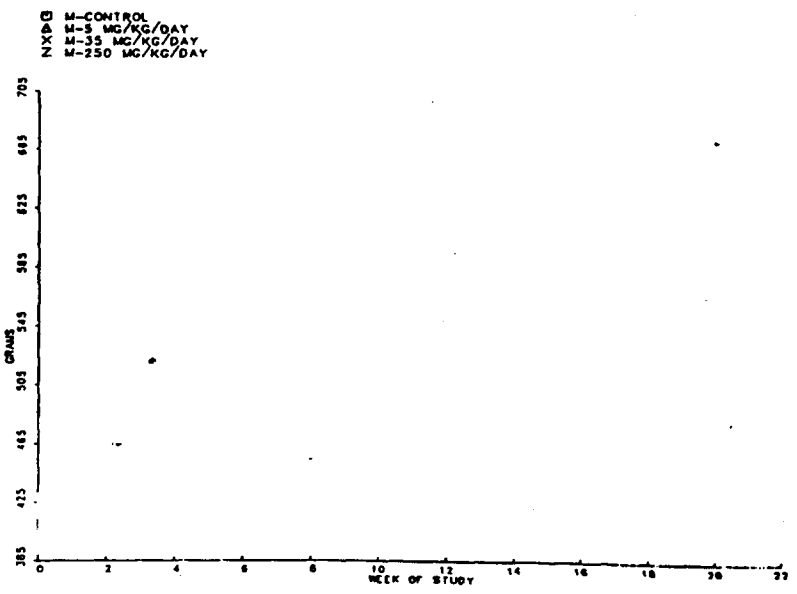
Parameters:

Paternal - clin signs, body wt, food cons, mating performance, necropsy (thoracic and abdominal viscera, testes, epididymides).
Maternal - sac'd on GD21 to assess pregnancy status, # corpora lutea, implant sites
F_1 - body wt, external exam, sex

Results:

Paternal - There were no treatment-related deaths or clinical signs of toxicity. Body weight gain was reduced in HD by 12% on weeks 1-10, and 31% on weeks 11-15 (sponsor Fig.1).

FIGURE 1. MK-0462: ORAL FERTILITY STUDY IN MALE RATS. TT #93-729-0
AVERAGE BODY WEIGHT (GRAMS) OF MALE RATS



There were no effects on male reproductive performance (sponsor Tab. A-6), and no notable necropsy findings.

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TABLE A-6. MK-0462: ORAL FERTILITY STUDY IN MALE RATS. TT #93-729-0
SUMMARY OF REPRODUCTIVE PERFORMANCE OF MALES

	CONTROL	5 MG/KG/DAY	35 MG/KG/DAY	250 MG/KG/DAY
FEMALES COHABITED[a]	24 (1)	24 (1)	24 (2)	24
MALES COHABITED	24	24	24	24
MATED FEMALES	24	24	23	24
PREGNANT FEMALES	23	24	22	24
DIED OR SACRIFICED PRIOR TO DAY 20	0	0	0	0
CESAREAN SECTIONED	23	24	22	24
MATED FEMALES/FEMALES COHABITED, %[b]	100	100	96	100 NS
FECUNDITY INDEX PREGNANT FEMALES/MATED FEMALES, %	96	100	96	100 NS
FERTILITY INDEX PREGNANT FEMALES/FEMALES COHABITED, %[b]	96	100	92	100 NS

NS = TREND NOT STATISTICALLY SIGNIFICANT (P > 0.05) THROUGH INDICATED DOSE.
a = NUMBER IN PARENTHESIS INDICATES FEMALES THAT DID NOT MATE DURING THE FIRST FIVE NIGHTS OF COHABITATION AND THAT WERE REMOVED AND REPLACED FOR THE LAST FIVE NIGHTS.
b = CALCULATION EXCLUDES FEMALES THAT DID NOT MATE DURING THE FIRST FIVE NIGHTS OF COHABITATION.

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