4-1-91

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 1 1991

008311

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Ronilan Fungicide 50W [Vinclozolin] Toxicology Data Submitted under MRID Nos. 417030-01, -02, and 417093-01
ID No. 007969-00053

Chemical (Caswell) No.: 323C
RD Record No.: S-387603
HED Project No.: 1-0337

FROM: Irving Mauer, Ph.D., Geneticist 03/21/91
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Susan Lewis/James Stone, PM Team 21
Herbicide-Fungicide Branch
Registration Division (H7505C)

THRU: Karl P. Baetcke, Ph.D., Chief 3/25/91
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Registrant: BASF Corporation, RTP (NC)

Request

Review and evaluate the following three documents, submitted toward the registration of Ronilan® Fungicide 50W, as well as to report adverse data under FIFRA 6(a)(2):

Submission 1: INTERIM REPORT: Study of the Chronic Toxicity of Registration No. 83-258 (VINCLOZOLIN) in Wistar Rats. Project No. 71S0375/88026, performed by BASF Aktiengesellschaft, Department of Toxicology, Germany, 6700 Ludwigshafen (EPA MRID No. 41703001).

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Submission 2: INTERIM REPORT: In Vitro Study on Dermal Penetration of Registration No. 83-258 (VINCLOZOLIN) [in] Human and Rat Skin. Project No. 11B0481/909008, performed by Inveresk Research International (IRI), Musselburgh (Scotland, UK) (EPA MRID No. 41703002).

Submission 3: A. Report on the Study of the Prenatal Toxicity of Registration No. 83-258 (Vinclozolin) in Rabbits After Oral Administration (Gavage), Project No.: 38R0375/88062, Final Report dated February 14, 1990; study performed by BASF Aktiengessellschaft, Department of Toxicology, D-6700 Ludwigshafen (Federal Republic of Germany) (EPA MRID No. 417093-01).

B. Report on the Supplementary Study of the Prenatal Toxicity of Registration No. 83-258 (Vinclozolin) in Rabbits After Oral Administration (Gavage), Project No.: 40R0375/88077 (Supplementary to the Final Report of Project No. 38R0375/88062), Final Report dated February 22, 1990. (MRID No. 415305-01).

TB Conclusions

Submissions 1 and 2 constitute interim reports of adverse effects reportable under FIFRA 6(a)(2) and are hereby noted, but are considered by the Agency as SUPPLEMENTARY DATA only, pending submission of the Final Reports of these studies (see attached abbreviated TB appraisals). Submission 3 (Developmental Toxicity - Rabbit), consisting of the two reports, A and B above, under submission 3, is fully reviewed and evaluated as CORE-MINIMUM, demonstrating the following parameters (see attached detailed review):

Doses tested: 0, 50, 200, 400, and 800 mg/kg/day administered by oral gavage from gestation days 7 to 28.

Maternal NOEL = 50 mg/kg/day
Maternal LOEL = 200 mg/kg/day
Developmental NOEL = 200 mg/kg/day
Developmental LOEL = 400 mg/kg/day
A/D Ratio = 0.25

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Attachments (DERs)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MAR 2 2

March 20, 1991

MEMORANDUM

SUBJECT: Change of Core Classification of Inhalation Study on the Technical Fortress (IN 43898)

MRID No.: 408837-16
Document No.: 007111

From: Henry Spencer 3/25/91
Head, Review Section III
Toxicology Branch I
Health Effects Division (H7509C)

TO: Ester Saito
SACB
Health Effects Division (H7509C)

THRU: Karl Baetcke, Chief 3/25/91
Toxicology Branch I
Health Effects Division (H7509C)

The study is reclassified as invalid due to the deficiencies noted on (ppt) of the review.

Additionally, rats and rabbits are discussed in the review which should only refer to rats as changed.

A new study is not required as was stated in the original DER in Document 007112.

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Reviewed By: Irving Mauer, Ph.D., Geneticist 03/01/91
Toxicology Branch I - IRS (H7505C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief 3/26/91
Toxicology Branch I - IRS (H7505C)

DATA EVALUATION RECORD
(Abbreviated)

008311

I. SUMMARY

MRID No.: 417030-01
ID No.: 7969-53
RD Record No.: S-387603
Caswell No.: 323C
Project No.: 1-0337

Study Type: (83-1) Chronic Toxicity - Rat

Chemical: Vinclozolin (BASF 83-258)

Synonyms: Ronilan®

Sponsor: BASF, RTP (NC)

Testing Facility: BASF Aktiengeselleschaft, Department of Toxicology, 6700 Ludwigshafen, Germany

Title of Report: INTERIM REPORT: Study of the Chronic Toxicity of Registration No. 83-258 (VINCLOZOLIN) in Wistar Rats, Project No. 71S0375/88026.

Authors: None

Study Number: 71S0375/88026 (Reg. Doc. No. 90/0478)

Date of Issue: September 3, 1990/November 16, 1990

TB Conclusions:

Doses tested: 0, 150, 500, 1500, and 4500 ppm in feed for 24 months; 20 males/20 females per dose group.

Classification (Core-Grade):

CORE-SUPPLEMENTARY. Preliminary results only, summarizing gross pathological findings comprising possible 6(a)(2) data (see attached), namely, anti-androgenic activity and ophthalmological findings.

II. DETAILED REVIEW

A. Test Material - BASF 83-258 (vinclozolin)
[No other description]

B. Test Organism - Rodent

Species: Rat
Strain: Wistar
Age: Not stated
Weights - Males: Not stated
Females: Not stated
Source: Not stated

C. Study Design (Protocol) - This study was designed to assess the chronic toxicity potential of vinclozolin when administered by dietary feed to male and female Wistar rats.

Statements of Quality Assurance measures (inspections/audits) and of adherence of Good Laboratory Practice were both included in this Interim Report.

D. Preliminary TB Evaluation- As described in this Interim Report, compound and/or dose-dependent increases were found in the incidence of cataracts and enlarged/discolored adrenals in both sexes; hepatic nodules/nodular formations (collectively termed "masses"), especially in high-dose males; bilateral testicular lesions, coincident with reductions in size of accessory sex organs; and, uni-/bi-lateral ovarian masses (which the investigators suggested might have included enlarged corpora lutea).

The investigators submitted that the 1500 ppm dose level already represented a maximum tolerated dose (at least for carcinogenicity), and thus the HDT (4500 ppm) was excessive. However, they did not suggest NOELs for non-neoplastic findings, and there does not appear to be any no-effect levels, at least for opthalmological lesions, and potential anti-androgenic effects.

Preliminary Findings (Interim Report) 1/

Observation	Dose level (ppm)									
	0		150		500		1500		4500	
	M	F	M	F	M	F	M	F	M	F
Body weight (g)	684	444	735	440	713	442	593	373	457	309
Cataracts (n)	0	0	0	2	7	14	18	19	20	20
SGGT (Liver)	--	--	--	--	--	--	--	--	Incr	Incr
HEMATOLOGY	--	--	--	--	--	--	Aff	Aft	Incr	Aff
Necropsy: Masses in										
- Liver	1	0	0	2	2	0	2	0	7	2
- Testes	8	--	13	--	17	--	19	--	20	--
- Ovaries	--	1	--	1	--	2	--	4	--	6
Reduced:										
- Epididymis	0	--	2	--	5	--	9	--	13	--
- Prostate	1	--	3	--	4	--	12	--	15	--
- Sem. vesicle	4	--	5	--	5	--	13	--	15	--
Adrenals:										
Discoloration	0	0	1	0	4	6	10	16	19	18
Mass	1	1	1	1	1	--	1	--	--	1
Enlarged	1	5	0	1	1	6	4	15	16	16

Extracted from Tables 1 through 41 of the Interim Report)

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Reviewed By: Irving Mauer, Ph.D., Geneticist 03/01/91
Toxicology Branch I - IRS - (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief 3/25/91
Toxicology Branch I - IRS - (H7509C)

DATA EVALUATION RECORD 008311

(Abbreviated)

I. SUMMARY

MRID No.: 417030-02
ID No.: 7969-53
RD Record No.: S-387603
Caswell No.: 342
Project No.: 1-0337

Study Type: (85-2) Dermal penetration - in vitro

Chemical: Vinclozolin (BASF 83-258)

Synonyms: Ronilan®

Sponsor: BASF, RTP (NC)

Testing Facility: Inveresk Research International (IRI) Musselburgh (UK)

Title of Report: INTERIM REPORT: In Vitro Study on Dermal Penetration of Registration No. 83-258 (VINCLOZOLIN) Human and Rat Skin, Project No. 11B0481/909008.

Authors: None

Study Number: 11B0481/909008

Date of Issue: November 21, 1990

TB Conclusions:

This interim report consists of unrefined raw data from in vitro exposures to rat and human epidermis preparations, at two levels, 2.9 and 200 $\mu g/cm^2$.

Classification (Core-Grade): CORE-SUPPLEMENTARY

II. DETAILED REVIEW

008311

A. Test Material - No details provided.

B. Test Organism - No specifics provided.

C. Study Design (Protocol) - This study was designed to assess the dermal penetration potential of vinclozolin when administered in vitro to human and rat skin samples.

A Statement of Quality Assurance measures (inspections/ audits) was not provided; however, a Statement of Adherence to Good Laboratory Practice was included in this Interim Report.

D. Preliminary TB Evaluation - As summarized by the investigators, there appears to be large species differences in percutaneous transport at both dose levels, based upon compound absorption expressed as percent of the applied dose, with significantly higher values registered for rodent preparations, as follows (given as mean of means, calculated by the reviewer from summary tabulations provided in this Interim Report):

DOSE (ug/cm^2)	SPECIES	ABSORPTION (%) at: 8 HR p/d/	24 HR p.d.
"Low:	Rat	76.6	84.1
2.9)	Human	6.4	13.0
"High"	Rat	32.4	55.1
200.0)	Human	1.2	2.0

However, no definitive conclusions (nor, "margins of exposure/safety") can be drawn from these preliminary data, pending provision (in the Final Report to come) of at least sex of and exact location of the skin specimens, as well as other details of procedure and methods of analysis.

Reviewed By: Irving Mauer, Ph.D., Geneticist 03/01/91
Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief 3/25/91
Toxicology Branch I - IRS (H7509C)

DATA EVALUATION RECORD 002311

I. SUMMARY

MRID No.: 417093-01
ID No.: 7969-53
RD Record No.: S-387603
Caswell No.: 323C
Project No.: 1-0337

Study Type: (83-3) Developmental Toxicity - Rabbit

Chemical: Vinclozolin

Synonyms: Ronilan®

Sponsor: BASF Agricultural, RTP (NC)

Testing Facility: BASF Aktiengeselleschaft, Department of Toxicology, Ludwigshaffen (W. Germany)

Title of Report: Report on the Study of the Prenatal Toxicity of Registration No. 83-258 (Vinclozolin) in Rabbits After Oral Administration (Gavage).

Authors: H.P. Gelbke

Study Number: Project Nos. 38R0375/88062 and 40R0375/88077 (Regis. Doc. Nos. BASF 90/0050 and 90/0051)

Date of Issue: February 14, 1990

TB Conclusions:

Doses tested: 0, 50, 200, 400, and 800 mg/kg/day by gavage from gestation day 7 thru day 28.

Maternal NOEL = 50 mg/kg/day

Maternal LOEL = 200 mg/kg/day (decreased food consumption; increased liver, adrenal weights).

Developmental NOEL = 200 mg/kg/day

Developmental LOEL = 400 mg/kg/day (increased resorptions/decreased live litter size)

In addition, at higher doses (400, 800 mg/kg/day):

- dose-related reductions in maternal body weight
- abortions

A/D Ratio = 0.25

Classification (Core-Grade): CORE-MINIMUM

II. DETAILED REVIEW

A. Test Material - Registration No. 83-2SE vinclozolin)

Description: Solid: white powder
Batch (Lot) No.: N 183
Purity (%): 99.2
Solvent/Carrier/Diluent: Double-distilled water containing 0.5 percent carboxymethyl cellulose (CMC)

B. Test Organism - Lagomorph

Species: Rabbit
Strain: Himalayan (Chbb:HM - outbred)
Age: ("Sexually mature") 25 to 32 weeks
Weight: Females (only): 2715 g
Source: Karl Thomae, Biberach-an-der-Riss (FRG)

C. Study Design (Protocol) - This study was designed to assess the developmentally toxic potential of vinclozolin when administered by oral gavage to pregnant rabbits, according to OECD and EPA Test Guidelines.

Statements of Quality Assurance measures (inspections/audits) and of adherence to Good Laboratory Practice were both provided.

D. Procedures/Methods of Analysis - Following preliminary toxicity testing in both nonpregnant and pregnant NZW females (0, 100, 300, and 900 mg/kg/day for 21 days non-pregnant; 0, 20, 80, and 300 mg/kg/day for only 13 days during early pregnancy in the latter group), three groups of 15 artificially inseminated* females each (pretreated with LH/FSH im) were administered test article (or CMC vehicle) by oral intubation (in a constant volume of 10 mL vehicle) once daily from gestation days 7 through 28. On day 29 gestation, all surviving animals were bled, sacrificed, internal organs examined, and fetuses dissected from uteri.

*With semen from healthy male Himalayans.

Full rosters of maternal parameters* were recorded at necropsy, corpora lutea enumerated, and the number and distribution of implantation sites classified (as live, dead, early, and late resorptions, as well as dead fetuses). Pregnancy rate and ratios of pre- and post-implantation losses were calculated according to standard conventions. All fetuses were sexed, weighed, and examined macroscopically, then sacrificed for soft tissue examination (by Wilson's method), followed by Dawson's method for skeletal assessments.

Fetal external, soft tissue, and skeletal "changes" (defects and/or variations) are classified by these investigators as follows (extracted from text page 19 of the Final Report):

" - Malformations . . . Rare and/or probably lethal [i.e., life-threatening] changes . . . [such as] (exencephaly, atresia ani, hernia umbilicus).

" - Variations . . . Changes which occur regularly [in test] as well as in control groups and have generally no adverse effect on survival . . . [such as] (dilated renal pelvis).

" - Retardations . . . Delays in skeletal development compared with the norm at the time of examination . . . [such as] (sternebrae not ossified).

" - Unclassified . . . external and soft tissue observations which cannot be classified as malformations, variations, or retardations . . . [such as] (focal liver necrosis).

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*Clinical: body weight (every 2 to 3 days)
- food consumption (same freq.)
- signs (daily)
- mortality (daily)

Hematological: WBC - CBC (differential)
RBC - CBC (differential)
Hct
MCV
MCH
MCHC
Platelets

Gross pathology (incl. organ weights): Liver
Spleen
Adrenals
Uterus
Ovaries

For statistical evaluation of the data, the following tests were applied (with significance recorded at both 5 and 1 percent):

Dunnett's . . . for food consumption, body weight, b.w. change, corrected b.w. gain (net maternal weight change); weights of liver, adrenal, placentae, and uterus; numbers of fetuses, corpora lutea implantations, pre- and postimplantation losses, resorptions, and live fetuses.

Fisher's Exact . . . for conception rate, maternal mortality, and all (other) fetal findings.

Analysis of Variance (ANCVA , followed by Dunnett's . . . for hematological parameters (except for differential counts).

E. Results - In the preliminary 3-week test with virgin females, vinclozolin was severely toxic at the HDT, 900 mg/kg (producing universal lethargy and weakness, coupled with large weight loss), moderately so at the mid-dose (300 mg/kg), and minimally at 100 mg/kg. On the other hand, no maternal or reproductive toxicities were observed at any dose in pregnant does treated for the shorter period; while dose-dependent reductions in both mean whole-litter and individual fetal weights compared to concurrent controls were calculated, no value was outside the range of this lab's historical background control. On the basis of these results, 800 mg/kg was selected as the top dose for the definitive study (expected to produce both maternal and possible fetal effects); 200 mg/kg as the mid-dose (possible minimally toxic for dams and/or fetuses); and 50 mg/kg as an expected NOEL.

[NB: However, due to the fact that only 2 does of the high-dose group (800 mg/kg/day) were available for scheduled sacrifice (and only one of these was pregnant), while all other high-dose animals died or had to be sacrificed intercurrently after abortion, only a limited assessment could be made for this test group.

Hence, a supplemental study was conducted at oral doses of 400 mg/kg administered daily to 20 does from day 7 thru 28 of gestation. The results of this additional assay (BASF Project 40R0375/88077) are incorporated with those from the definitive study (38R0375/88062) in this DER. A summary of selected (significant) data extracted from both

Final Reports is presented on the following page of this DER.]

One mid-dose female of the definitive study (No. 58-478/33) aborted on day 12 of gestation and was sacrificed in extremis a week later; all other mid-dose does survived to scheduled sacrifice. Only 2 of the 15 high-dose animals (800 mg/kg/day) survived to study termination (and only one of these was pregnant); one doe was found dead on day 19, one died after aborting on day 20, and 12 others were sacrificed following abortions during the course of treatment. Although none of the 20 does administered 400 mg/kg/day in the supplementary study died intercurrently, 10 did abort.

Food consumption by high-dosed does (400 and 800 mg/kg) was significantly reduced during the greater portion of their treatment periods; that by 200 mg/kg females only early in treatment, compensated for in the latter portion of the study by increased values. This consistent decreased food intake no doubt contributed to significant decreased mean body weights and weight gains among does at the HDT (800 mg/kg), less so for 400 mg/kg animals (where only a significant deficit in weight gain at midtreatment was observed).

Other clinical manifestations of maternal toxicity during the 21 days of treatment were observed at doses above 50 mg/kg, namely, gastrointestinal disturbances (manifested as reduced/absent defecation and/or discolored urine), lesions in major organs (dilation/discoloration in liver, kidney, and heart), and hemotoxicity (manifested as increased reticulocytes) in both 400 and 800 mg/kg groups; enlarged livers and adrenals (increased absolute weight) in 200, 400, and 800 mg/kg groups.

Concordant with the propensity for compound and dose-related abortion at high dose levels (10/20 at 400 mg/kg; 13/15 at 800 mg/kg) were reproduction and fetal changes at these levels. Some form of adverse changes were found in implantations, leading to significantly increased postimplant loss (approximately 33% and 43%, respectively, at 400 and 800 mg/kg, compared to 5 to 10% in concurrent controls, and a background range for this lab of 4.9 to 18.4%), coincident with decreased percent of live fetuses (54% and 57%). Mean fetal weight was not adversely affected even at the HDT; the apparently increased mean fetal weight among 400-mg/kg-treated pregnancies (= 44.5 g, compared to the concurrent control value of 39.9 g) was ascribable to the lower number of live fetuses in this group (but was within the lab historical range of 31.7 to 49.5 g).

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Clincical, Reproductive, and Fetal Effects of Oral Vinclozolin Administered to Rabbits from Gestation Day 7 Through Day 28[1]/

Observation	Dose Group (mg/kg/day)					
	0[2]	50[2]	200[2]	800[2]/	400[3]/	0[3]/
Maternal clinical data:						
Unscheduled deaths	0	0	0	2[4]/	0	0
Abortions	0	0	1	12	10	0
Mean wt. gain (g):						
- Day 16	2811	2843	2802	2569**	2592	2685
- Day 25	2861	2892	2856	2373**	2711	2740
Mean body wt. (g):						
- To day 16	33.1	49.1	32.0	-110.3**	-19.6*	19.0
- To day 25	43.5	54.7	56.8	-39.1**	17.7	44.7
Reduced activity	0	0	0	2	0	0
Reduced defecation	0	0	1	15	15	0
Discolored urine	0	0	1	13	8	0
Reticulocytes (0/00)	16	16	17	67**	29**	16
Abs. liver wt. (g)	53.55	57.91	81.46**	144.31**	85.56**	50.03
Rel. liver wt. (%)	1.81	1.94	2.69**	5.32**	3.05**	1.78
Abs. adrenal wt. (g)	0.20	0.21	0.24*	0.26*	0.23	0.21
Rel. adrenal wt. (%)	0.01	0.01	0.01	0.01	0.01	0.01
Maternal necropsy/ reproduction data:						
Heart changes	0	0	0	3	7	0
Implant changes	0	0	1	12	10	0
Postimpl. loss (%)	4.9	6.1	8.9	42.9*	32.9*	10.3
Live fetuses (%)	95.1	93.9	91.1	57.1*	53.9*	89.7
Fetal data:						
Mean wt. (g)	40.9	43.7	42.6	38.4	44.5*	39.9
Malformed sternebrae (%)	0	1.1	0	25.0*	0	1.7
Retarded ossification (%)	58.3	57.4	59.6	75.0*	33.3	58.1

1/Selected observations and group data extracted from summary and individual animal data tables in both Final Reports.
2/Main ("definitive") study, BASF Project No. 38R0375/88062 (15/group)
3/Supplemental study, BASF Project No. 40R0375/88077 (20/group)
4/One after aborting
*Significantly different from control, $p < 0.05$
**Significantly different from control, $p < 0.01$

There were no fetuses with either external or soft-tissue malformations considered to be compound-related, even at the HDT. As recorded by the investigators, the only statistically significant fetal finding was malformed sternebrae in one of four fetuses in the one high-dose (800 mg/kg) litter (amounting to 25% of surviving fetuses at this dose). This finding was considered as being without biological relevance on account of the limited number of high dose fetuses which could be evaluated at this dose level, and the occurrence of the same incidence of this finding in the fetuses of test group 1 (50 mg/kg body weight/day), as well as in historical controls (but not present in either 200 or 400 mg/kg fetuses). The only other anomaly recorded was a slight (but significant) increas in overall delayed ossification among the three remaining fetuses of the HDT group.

Other fetal findings (malformations, variations, retardations, or unclassified observations) occurred in all test groups, including the current control, with the similar incidences, as well as in the background (historical control). Specifically (and in contrast to findings in fetal rats), there were no compound-related effects on the genitalia of male fetuses. The investigators concluded that the oral administration of vinclozolin to pregnant rabbits from gestation day 7 through 28 p.i. at dose levels of 50, 200, 400, and 800 mg/kg/day caused dose-related reductions in body weight and food consumption at higher doses (400, 800 mg/kg), accompanied by abortions and other adverse clinical, hematological, and organ changes , as well as increased postimplant loss and possibly fetal skeletal variations.

Since 200 mg/kg does ate less and showed statistically significant increased absolute and relative liver weight as well as increased absolute adrenal weight, 50 mg/kg/day was considered the maternal NOEL.

Embryo/fetotoxicity and/or adverse fetal effects were also found only at higher dosage levels, and none at 200 mg/kg/day which was thus considered the fetal NOEL.

TB Conclusions - CORE-MINIMUM. Although performed in separate assays (due to severe toxicity in the definitive study at the HDT), this investigation in toto satisfies the minimal criteria for a developmental toxicity study of this test substance in the second species (rabbit), and provides the following established parameters:

Doses tested: 0, 50, 200, 400, and 800 mg/kg/day but oral intubation from gestation day 7 through 28.

Maternal NOEL = 50 mg/kg/day
LOEL = 200 mg/kg/day (decr. food consumption; increased liver/adrenal weight)

Developmental/fetal NOEL = 200 mg/kg/day
LOEL = 400 mg/kg/day (incr. resorptions; decreased live litter size).

A/D Ratio = 50/200 = 0.25

Attachments (Summary Data Tables)

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008311

[Two-Sided]

Attachment 1

(Summary Data Tables)

A. MAIN STUDY (Doses:0, 50, 200, 800 mg/kg)

11-DEC-88

88062

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE : 001
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 0 CONTROL GMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAYS 0 TO 1	MEAN	111.0	120.3	113.8	113.7
	S.D.	22.65	23.08	14.93	32.88
	N	15	15	15	14
DAYS 1 TO 2	MEAN	123.0	129.6	126.9	129.3
	S.D.	20.85	18.41	13.51	26.18
	N	15	15	15	14
DAYS 2 TO 3	MEAN	111.6	122.3	114.9	121.5
	S.D.	28.68	22.28	12.63	23.39
	N	15	15	15	14
DAYS 3 TO 4	MEAN	116.0	127.8	119.2	124.8
	S.D.	33.45	18.83	14.65	24.66
	N	15	14	15	14
DAYS 4 TO 5	MEAN	108.1	119.9	106.7	118.6
	S.D.	31.80	22.08	14.78	22.29
	N	15	15	15	14
DAYS 5 TO 6	MEAN	116.1	117.7	106.0	119.1
	S.D.	28.33	22.88	8.96	21.08
	N	15	15	15	14
DAYS 6 TO 7	MEAN	118.5	122.2	109.8	127.8
	S.D.	27.02	21.65	11.77	20.52
	N	15	15	15	13
DAYS 7 TO 8	MEAN	111.1	116.5	88.8a	59.5b
	S.D.	20.65	21.68	16.70	20.05
	N	15	15	15	14
DAYS 8 TO 9	MEAN	114.3	114.9	84.2a	37.8b
	S.D.	15.14	22.82	18.43	16.68
	N	15	15	15	14
DAYS 9 TO 10	MEAN	111.0	113.1	101.3	41.4b
	S.D.	17.63	22.00	17.83	12.35
	N	15	15	15	14
DAYS 10 TO 11	MEAN	111.7	108.9	98.4	48.1b
	S.D.	17.21	21.63	23.40	13.62
	N	15	15	15	14

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

90/0051 0348

83/1

11-DEC-89 TABLE : 002

88062

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAYS 11 TO 12	MEAN	105.8	88.8	83.5	42.6b
	S.D.	17.21	20.81	21.13	17.61
	N	15	15	15	14
DAYS 12 TO 13	MEAN	87.4	87.0	87.3	30.1b
	S.D.	23.25	20.38	23.68	17.14
	N	15	15	15	14
DAYS 13 TO 14	MEAN	86.0	86.8	78.9	12.8b
	S.D.	24.49	23.46	28.78	18.18
	N	15	15	15	14
DAYS 14 TO 15	MEAN	80.9	82.8	70.7	8.5b
	S.D.	32.41	22.03	34.21	11.68
	N	15	15	15	14
DAYS 15 TO 16	MEAN	85.5	90.4	73.0	7.0b
	S.D.	42.66	20.60	34.28	10.00
	N	15	15	15	14
DAYS 16 TO 17	MEAN	82.6	82.8	77.3	8.4b
	S.D.	34.81	17.41	28.72	10.44
	N	15	15	15	14
DAYS 17 TO 18	MEAN	85.1	86.3	80.5	9.2b
	S.D.	30.22	25.37	28.86	12.04
	N	15	14	15	14
DAYS 18 TO 19	MEAN	81.8	81.3	83.9	6.6b
	S.D.	25.83	20.64	26.10	9.88
	N	14	15	15	13
DAYS 19 TO 20	MEAN	87.0	82.8	76.9	7.1b
	S.D.	20.46	23.88	33.12	13.64
	N	15	15	15	13
DAYS 20 TO 21	MEAN	87.4	88.6	84.8	11.5b
	S.D.	22.19	19.84	33.88	18.18
	N	15	15	15	12
DAYS 21 TO 22	MEAN	87.4	82.1	79.1	17.1b
	S.D.	28.58	28.85	33.88	27.88
	N	15	15	15	8

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE : 003
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

			TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAYS 22 TO 23		MEAN	84.4	95.4	89.5	24.6b
		S.D.	22.82	25.25	31.34	44.94
		N	15	15	15	7
DAYS 23 TO 24		MEAN	100.0	100.3	94.2	16.8b
		S.D.	17.65	22.36	33.04	34.94
		N	14	15	15	7
DAYS 24 TO 25		MEAN	104.2	108.9	98.8	30.6b
		S.D.	12.36	18.00	32.84	66.34
		N	15	15	15	5
DAYS 25 TO 26		MEAN	87.0	111.6	114.9	51.6a
		S.D.	22.68	17.03	22.37	87.99
		N	15	15	14	3
DAYS 26 TO 27		MEAN	98.8	112.8	124.7b	148.4a
		S.D.	22.26	17.08	17.83	0.00
		N	15	15	14	1
DAYS 27 TO 28		MEAN	110.8	122.1	138.8b	187.3a
		S.D.	18.63	17.80	18.36	0.00
		N	15	15	14	1
DAYS 28 TO 29		MEAN	113.2	118.0	134.1a	164.8
		S.D.	18.11	24.28	18.63	0.00
		N	15	15	14	1
DAYS 0 TO 7	MEAN OF MEANS	S.D.	114.8	122.8a	113.9	122.1
		N	4.83	4.33	7.43	5.53
			7	7	7	7
DAYS 7 TO 28	MEAN OF MEANS	MEAN	98.7	101.6	91.9	37.5b
		S.D.	8.23	10.67	17.12	43.41
		N	21	21	21	21
DAYS 0 TO 28	MEAN OF MEANS	MEAN	103.1	107.3	98.7	62.3b
		S.D.	10.81	13.14	18.92	55.54
		N	28	28	28	28

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO [illegible], PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAY 0	MEAN	2714	2730	2713	2715
	S.D.	160.3	184.8	112.4	131.7
	N	15	15	15	14
DAY 2	MEAN	2756	2788	2774	2769
	S.D.	173.6	202.7	128.6	124.1
	N	15	15	15	14
DAY 4	MEAN	2749	2778	2761	2770
	S.D.	166.2	211.8	133.2	130.6
	N	15	15	15	14
DAY 7	MEAN	2752	2774	2748	2774
	S.D.	176.4	215.4	131.8	135.3
	N	15	15	15	14
DAY 8	MEAN	2751	2781	2749	2786
	S.D.	162.5	207.5	122.9	146.3
	N	15	15	15	14
DAY 11	MEAN	2748	2773	2740	2742
	S.D.	158.0	210.3	127.6	148.7
	N	15	15	15	14
DAY 14	MEAN	2778	2794	2771	2679
	S.D.	140.0	211.0	140.5	153.8
	N	15	15	15	14
DAY 16	MEAN	2811	2843	2802	2569b
	S.D.	156.8	200.4	148.5	167.7
	N	15	15	15	14
DAY 18	MEAN	2804	2838	2815	2423b
	S.D.	149.1	198.9	160.3	188.0
	N	15	15	15	13
DAY 21	MEAN	2803	2828	2789	2375b
	S.D.	158.2	189.4	166.0	175.4
	N	15	15	15	12
DAY 23	MEAN	2817	2837	2799	2401b
	S.D.	158.4	185.2	185.4	197.4
	N	15	15	15	7

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE : 006
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAYS 0 TO 2	MEAN	42.3	57.8	61.7	53.7
	S.D.	24.01	28.05	33.42	47.44
	N	15	15	15	14
DAYS 2 TO 4	MEAN	-6.9	-8.3	-13.2	1.2
	S.D.	21.08	26.56	18.51	21.42
	N	15	15	15	14
DAYS 4 TO 7	MEAN	2.5	-4.8	-13.0	4.5
	S.D.	27.58	20.69	18.41	26.07
	N	15	15	15	14
DAYS 7 TO 9	MEAN	-1.0	7.2	0.6	11.6
	S.D.	23.24	20.60	26.70	32.05
	N	15	15	15	14
DAYS 9 TO 11	MEAN	-2.1	-7.9	-9.2	-43.7b
	S.D.	18.15	19.38	26.01	39.35
	N	15	15	15	14
DAYS 11 TO 14	MEAN	28.1	28.9	30.9	-62.5b
	S.D.	24.37	28.32	38.95	46.62
	N	15	15	15	14
DAYS 14 TO 16	MEAN	33.1	49.1	32.0	-110.3b
	S.D.	33.38	38.93	43.21	50.26
	N	15	15	15	14
DAYS 16 TO 18	MEAN	-8.9	-4.8	12.4	-143.1b
	S.D.	38.62	28.75	38.55	54.61
	N	15	15	15	13
DAYS 18 TO 21	MEAN	-0.5	-9.8	-25.9	-68.8b
	S.D.	22.99	18.90	33.62	68.48
	N	15	15	15	12
DAYS 21 TO 23	MEAN	13.8	8.9	18.4	-23.8
	S.D.	26.35	24.01	35.83	93.15
	N	15	15	15	7
DAYS 23 TO 28	MEAN	43.8	54.7	56.8	-39.1b
	S.D.	28.33	22.01	36.49	100.51
	N	15	14	15	6

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01

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TABLE : 005

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAY 28	MEAN	2861	2897	2856	2373#
	S.D.	168.1	200.6	204.1	283.9
	N	15	15	15	6
DAY 28	MEAN	2919	2981	2984	2689
	S.D.	164.3	191.2	138.1	0.0
	N	15	15	14	1
DAY 28	MEAN	2950	2994	3026	2717
	S.D.	180.2	191.1	141.5	0.0
	N	15	15	14	1

SIGNIFICANTLY DIFFERENT FROM CONTROL: # = P<0.05; ## = P<0.01.

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PROJECT NO.38K0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 — 007
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAYS 28 TO 28	MEAN	58.1	69.9	94.9a	26.9
	S.D.	30.05	38.37	37.68	0.00
	N	15	15	14	1
DAYS 28 TO 28	MEAN	31.8	31.3	31.3	23.3
	S.D.	31.81	25.12	35.15	0.00
	N	15	15	14	1

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 008

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAYS 0 TO 7	MEAN	37.8	43.7	36.6	50.3
	S.D.	51.03	39.48	35.92	45.31
	N	15	15	15	14
DAYS 7 TO 28	MEAN	187.1	187.6	237.4	36.0
	S.D.	87.44	92.47	117.44	0.00
	N	15	15	14	1
DAYS 0 TO 28	MEAN	238.8	262.8	307.6	59.2
	S.D.	82.11	101.80	129.96	0.00
	N	15	15	14	1

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0375/88082: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN GRAVID UTERINE WEIGHTS AND NET MATERNAL BODY WEIGHT CHANGE -- GRAMS

TABLE : 009

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
GRAVID UTERUS	MEAN	352.8	370.9	374.1	220.5
	S.D.	82.74	84.81	117.44	0.00
	N	15	15	14	1
CARCASS	MEAN	2597.5	2621.6	2651.4	2491.9
	S.D.	158.60	172.31	90.17	0.00
	N	15	15	14	1
NET WEIGHT CHANGE FROM DAY 7	MEAN	-154.1	-152.0	-106.4	-161.2
	S.D.	60.58	68.00	93.08	0.00
	N	15	15	14	1

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

CARCASS WEIGHT = TERMINAL BODY WEIGHT MINUS UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 7 = CARCASS WEIGHT MINUS DAY 7 BODY WEIGHT

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TABLE : 010

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL CLINICAL OBSERVATIONS DURING GESTATION

		DAY OF GESTATION																													
	GROUP#	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	TOTAL
# OF FEMALES EXAMINED	0	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	
	1	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	
	2	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	14	
	3	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	13	8	8	8	6	5	5	2	
NORMAL																																
NO REMARKABLE CLINICAL OBSERVATIONS	0	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
	1	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
	2	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	14	14	14	15	14	14	14	14	14	14	14	14	14	14	15	15
	3	15	15	15	15	15	15	15	15	15	15	13	13	15	12	9	3	2	3	3	3	0	0	0	1	1	1	1	1	1	1	15
DEAD																																
FOUND DEAD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
SACRIFICED AFTER ABORTION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4	1	0	2	1	0	2	0	11
DIED AFTER ABORTION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
BODY POSITION																																
ABDOMINAL POSITION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
ACTIVITY																																
APATHY	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	1	2

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TABLE 1 011

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL CLINICAL OBSERVATIONS DURING GESTATION

		DAY OF GESTATION																													
	GROUP#	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	TOTAL
# OF FEMALES EXAMINED	0	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	
	1	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	
	2	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	14	
	3	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	13	9	8	4	6	5	5	2	
EYES																																
CONJUNCTIVITIS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	0	1	
MISCELLANEOUS																																
ABORTION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4	1	0	3	1	2	0	0	12
VAGINAL HEMORRHAGE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	2
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SKIN/FUR																																
FUR SMEARED WITH URINE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1
STOOL/URINE																																
REDUCED DEFECATION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	0	1	1	1	1	1	0	0	0	1	
	2	0	0	0	0	0	0	0	0	0	0	0	1	2	0	3	4	8	10	8	10	8	8	6	5	4	2	2	1	1	0	15
	3	0	0	0	0	0	0	0	0	0	0	2	2	0	3	4	8	10	8	10	8	8	6	6	5	4	2	2	1	1	0	15
REDDISH-BROWN DISCOLORATION OF URINE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	7	8	8	8	4	9	8	5	4	4	4	3	2	0	0	13
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	7	8	8	8	4	9	8	5	4	4	4	3	2	0	0	13

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PROJECT NO.38R0375/88062. PRENATAL TOXICITY STUDY IN RABBITS — TABLE : 012
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL CLINICAL OBSERVATIONS DURING GESTATION

	GROUP#	DAY OF GESTATION 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	TOTAL
# OF FEMALES EXAMINED	0	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	
	1	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	
	2	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	
	3	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	14	14	13	9	8	8	8	5	5	2	
NO DEFECATION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	1	2	3	3	5	1	0	2	3	3	3	1	1	12

BASF TOXICOLOGY - DATATOX RC.2
PROJECT NUMBER 38R0375/88082 REG. NO. 83 258

GROUP MEANS HEMATOLOGICAL EXAMINATIONS PRINT DATE 6-NOV-89

Nominal days in study 28 p.i.

F E M A L E S		WBC GIGA/L	RBC TERA/L	HGB MMOL/L	HCT L/L	MCV FL	MCH FMOL	MCHC MMOL/L	PLT GIGA/L
GROUP 0									
0 MG/KG	M	6.52	5.33	7.68	0.396	74.23	1.44	19.40	460
	SD	1.24	0.31	0.41	0.022	1.40	0.04	0.34	65
	N	15	15	15	15	15	15	15	15
GROUP 1									
50 MG/KG	M	6.26	5.30	7.75	0.400	75.39	1.46	19.38	321**
	SD	0.88	0.30	0.39	0.019	2.59	0.06	0.38	100
	N	15	15	15	15	15	15	15	15
GROUP 2									
200 MG/KG	M	6.48	5.22	7.56	0.393	75.20	1.45	19.24	324**
	SD	1.73	0.33	0.36	0.020	2.40	0.05	0.27	82
	N	14	14	14	14	14	14	14	14
GROUP 3									
800 MG/KG	M	7.57	4.72	7.48	0.380	80.30	1.58	19.71	453
	SD	0.00	0.00	0.00	0.000	0.00	0.00	0.00	0
	N	1	1	1	1	1	1	1	1

Statistics: Anova + Dunnetts teste (two-sided): * P<0.05 ** P<0.01 (Statistical unit = Animal)

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TABLE 014

BASF TOXICOLOGY
PROJECT NUMBER 30R0375/88062 Reg. No 83 258

GROUP MEANS DIFFERENTIAL BLOOD COUNT 6 NOV 89

Nominal days in study 28 p.i.

FEMALES

		WBC GIGA/L	EOS %	BASO %	BAND %	POLY %	LYMP %	MONO %
GROUP 0								
0 mg/kg								
	M	6.52	0.67	2.60	0.13	40.60	52.53	3.47
	SD	1.24	0.72	2.20	0.35	11.87	10.69	1.60
	N	15	15	15	15	15	15	15
GROUP 1								
50 mg/kg								
	M	6.26	0.93	3.27	0.13	41.47	51.40	2.80
	SD	0.99	0.88	1.44	0.35	11.60	12.16	1.47
	N	15	15	15	15	15	15	15
GROUP 2								
200 mg/kg								
	M	6.48	0.50	2.43	0.00	38.43	54.64	4.00
	SD	1.73	0.76	1.65	0.00	12.77	12.59	3.01
	N	14	14	14	14	14	14	14
GROUP 3								
800 mg/kg								
	M	7.87	1.00	0.00	0.00	42.00	52.00	5.00
	SD	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	N	1	1	1	1	1	1	1

BASF TOXICOLOGY
PROJECT NUMBER 38R0375/88082 Reg. No. 83 258

GROUP MEANS DIFFERENTIAL BLOOD COUNT 6-NOV-89

Nominal days in study 28 p.i.

F E M A L E S

		WBC GIGA/L	EOS GIGA/L	BASO GIGA/L	BAND GIGA/L	POLY GIGA/L	LYMP GIGA/L	MONO GIGA/L
GROUP 0								
0 mg/kg	M	6.52	0.04	0.16	0.01	2.72	3.35	0.23
	SD	1.24	0.05	0.13	0.03	1.38	0.67	0.12
	N	15	15	15	15	15	15	15
GROUP 1								
50 mg/kg	M	6.26	0.06	0.20	0.01	2.63	3.18	0.17
	SD	0.88	0.06	0.09	0.02	0.99	0.77	0.09
	N	15	15	15	15	15	15	15
GROUP 2								
200 mg/kg	M	6.48	0.03	0.15	0.00	2.48	3.59	0.23
	SD	1.73	0.05	0.10	0.00	1.12	1.51	0.17
	N	14	14	14	14	14	14	14
GROUP 3								
800 mg/kg	M	7.57	0.08	0.00	0.00	3.18	3.94	0.38
	SD	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	N	1	1	1	1	1	1	1

TABLE 016

BASF TOXICOLOGY - DATATOX RC.2
PROJECT NUMBER 38R0378/89062

REG. NO. 83 258

GROUP MEANS

RETICULOCYTES

PRINT DATE 6-NOV-89

Nominal days in study 28 p.i.

F E M A L E S .		RETI 0/00
GROUP 0		
0 MG/KG	M	16
	SD	5
	N	16
GROUP 1		
50 MG/KG	M	16
	SD	5
	N	15
GROUP 2		
200 MG/KG	M	17
	SD	6
	N	14
GROUP 3		
800 MG/KG	M	67**
	SD	0
	N	1

Statistics: Anova + Dunnetts tests (two-sided): * P<0.05 ** P<0.01 (Statistical unit = Animal)

BASF Department of Toxicology

REG. NR. 83 258 , PRENATAL TOX. STUDY,
ADMINISTRATION BY GAVAGE IN RABBITS
ABSOLUTE WEIGHTS - MEAN VALUES

	Sacrifice group / Sex / Dose group		F1 0	1	2	3
Body weight	B	M	2858.4	2892.6	3025.643	2712.
		SD	188.885	181.036	141.354	
		n	15.	15.	14.	1.
Liver	B	M	83.540	87.005	81.456**	144.31
		SD	7.414	8.143	14.935	
		n	15.	15.	14.	1.
Adrenal glands	B	M	0.202	0.214	0.236*	0.26
		SD	0.038	0.033	0.04	
		n	15.	15.	14.	1.

Dunnett test
* P < 0.05 ** P < 0.01
two sided (statistical unit = animal)

Tab. 018

BASF Department of Toxicology

REG. NR. 83 258 . PRENATAL TOX. STUDY.
ADMINISTRATION BY GAVAGE IN RABBITS
RELATIVE WEIGHTS - MEAN VALUES

1
JHR0375/88062
Nov/03/1989 KOPE
GLOBAL   System
psn:002

			Sacrifice group	F1			
			Sex	F			
			Data group	0	1	2	3
Body weight	%	M		100.	100.	100.	100.
		SD					
		N		15.	15.	14.	1.
Liver	%	M		1.811	1.836	2.686**	8.321
		SD		0.18	0.172	0.433	
		N		15.	15.	14.	1.
Adrenal glands	%	M		0.007	0.007	0.008	0.01
		SD		0.001	0.001	0.001	
		N		15.	15.	14.	1.

Dunnett test
* P < 0.05 ** P < 0.01
two sided (statistical unit = animal)

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PROJECT NO.38R0375/88082: PRENATAL TOXICITY STUDY IN RABBITS TABLE : 019
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL NECROPSY OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAMS EXAMINED	N	15	15	15	15
NOTHING ABNORMAL DETECTED	N	15	15	14	0
	%	100.0	100.0	93.3	0.0
POST MORTEM AUTOLYSIS	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
ANEMIA	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
HEART: DILATION	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
HEART: DISCOLORATION	N	0	0	0	2
	%	0.0	0.0	0.0	13.3
LUNGS: EDEMA	N	0	0	0	2
	%	0.0	0.0	0.0	13.3
LIVER: NECROSIS	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
LIVER: FOCUS	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
LIVER: PROMINENT ACINAR PATTERN	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
GLANDULAR STOMACH: ULCER	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
GLANDULAR STOMACH: FOCUS	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
KIDNEYS: DISCOLORATION	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
CECUM: DYSENTERIA	N	0	0	0	1
	%	0.0	0.0	0.0	6.7

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TABLE : 020

PROJECT NO.38R0375/8806?: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL NECROPSY OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
DAMS EXAMINED	N	15	15	15	15
PARTICULAR FIND.ON IMPLANTS IN DAMS SACR.MOBIB./DIED INTERC.	N	0	0	0	1
	%	0.0	0.0	0.0	6.7
PARTICULAR FINDINGS ON IMPLANTS IN DAMS WHICH ABORTED	N	0	0	1	12
	%	0.0	0.0	6.7	80.0

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PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 021
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Females Mated	N	15	15	15	15
Pregnant	N	15	15	15	14
	%	100	100	100	93
Aborted	N	0	0	1	12
Premature Births	N	0	0	0	0
Dams with Viable Fetuses	N	15	15	14	1
Dams with all Resorptions	N	0	0	0	0
Female Mortality	N	0	0	1	13b
	%	0.0	0.0	6.7	87
Pregnant at C-section	N	15	15	14	1b
	%	100	100	93	6.7
Corpora Lutea	MEAN	7.8	8.1	8.4	7.0
	S.D.	1.41	1.22	1.28	0.00
	TOTAL	112	121	118	7
Implantation Sites	MEAN	6.7	6.7	7.1	7.0
	S.D.	1.44	1.78	2.02	0.00
	TOTAL	101	101	99	7
Preimplantation Loss	MEAN%	8.8	17.1	15.6	0.0
	S.D.	14.32	14.66	21.77	0.00
Postimplantation Loss	MEAN%	4.8	6.1	8.9	42.8a
	S.D.	7.42	10.73	19.12	0.00

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 022

PROJECT NO.38R0376/88062, PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Pregnant at C-section	N	15	15	14	1
Resorptions, Total	MEAN	0.3	0.5	0.4	3.0b
	S.D.	0.49	0.83	0.63	0.00
	TOTAL	5	7	5	3
	MEAN%	4.8	6.1	8.8	42.9b
	S.D.	7.42	10.73	19.12	0.00
Early	MEAN	0.1	0.3	0.2	3.0b
	S.D.	0.35	0.46	0.58	0.00
	TOTAL	2	4	3	3
	MEAN%	2.1	3.8	7.1	42.9b
	S.D.	5.73	6.66	19.30	0.00
Late	MEAN	0.2	0.2	0.1	0.0
	S.D.	0.41	0.56	0.36	0.00
	TOTAL	3	3	2	0
	MEAN%	2.8	2.3	1.8	0.0
	S.D.	6.90	6.71	4.84	0.00
Dead Fetuses	N	0	0	0	0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0375/88062; PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF REPRODUCTION DATA

TABLE : 023

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Dams with Viable Fetuses	N	15	15	14	1
Live Fetuses	MEAN	6.4	6.3	6.7	4.0
	S.D.	1.40	1.67	2.46	0.00
	TOTAL	96	94	94	4
	MEAN%	95.1	93.9	91.1	57.1a
	S.D.	7.42	10.73	10.12	0.00
Females	MEAN	3.9	3.0	3.4	3.0
	S.D.	1.41	1.20	2.21	0.00
	TOTAL	58	45	48	3
	MEAN%	57.6	46.2	44.4	42.9
	S.D.	15.77	20.70	28.18	0.00
Males	MEAN	2.5	3.3	3.3	1.0
	S.D.	1.30	1.62	1.60	0.00
	TOTAL	38	49	46	1
	MEAN%	37.6	47.6	46.7	14.3
	S.D.	16.02	21.38	20.62	0.00
PER CENT LIVE FEMALES		60.4	47.9	51.1	75.0
PER CENT LIVE MALES		39.6	52.1	48.9	25.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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83062

PROJECT NO 38ND3/D/83062. PHENATAL TOXICITY STUDY IN RABBITS — TABLE 1 — 024
ORAL ADMINISTRATION (GAVAGE)
MEAN PLACENTAL AND FETAL BODY WEIGHTS

		TEST GROUP 0 CONTROL (MI	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
PLACENTAL WEIGHTS UNITS: GRAMS					
of all Viable Fetuses	MEAN	4.7	4.8	4.9	4.2
	S.D.	0.54	0.46	1.23	0.00
	N	15	15	14	1
of Male Fetuses	MEAN	4.8	4.8	5.0	4.7
	S.D.	0.70	0.61	1.23	0.00
	N	15	15	14	1
of Female Fetuses	MEAN	4.7	4.8	4.4	4.0
	S.D.	0.65	0.31	0.52	0.00
	N	15	14	12	1
FETAL WEIGHTS UNITS: GRAMS					
of all Viable Fetuses	MEAN	40.9	43.7	42.6	38.4
	S.D.	2.58	2.21	5.52	0.00
	N	15	15	14	1
of Male Fetuses	MEAN	41.1	43.6	42.7	42.6
	S.D.	3.94	3.04	5.59	0.00
	N	15	15	14	1
of Female Fetuses	MEAN	40.7	44.0b	40.6	36.9
	S.D.	2.30	1.60	3.88	0.00
	N	15	14	12	1

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 025

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL EXTERNAL OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	86	84	84	4
Live	N	86	84	84	4
Dead	N	0	0	0	0
TOTAL MALFORMATIONS					
Fetal Incidence	N	1	0	0	0
	%	1.0	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	6.7	0.0	0.0	0.0
Affected Fetuses/Litter	MEANS	1.7	0.0	0.0	0.0
	S.D.	6.46	0.00	0.00	0.00
TOTAL VARIATIONS					
Fetal Incidence	N	1	1	0	0
	%	1.0	1.1	0.0	0.0
Litter Incidence	N	1	1	0	0
	%	6.7	6.7	0.0	0.0
Affected Fetuses/Litter	MEANS	0.8	0.7	0.0	0.0
	S.D.	3.23	2.68	0.00	0.00

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0378/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 — 0/6
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL EXTERNAL MALFORMATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	86	84	84	4
Live	N	86	84	84	4
Dead	N	0	0	0	0
OLIGODACTYLY					
Fetal Incidence	N	1	0	0	0
Litter Incidence	N	1	0	0	0
	%	6.7	0.0	0.0	0.0
TOTAL FETAL EXTERNAL MALFORMATIONS					
Fetal Incidence	N	1	0	0	0
Litter Incidence	N	1	0	0	0
	%	6.7	0.0	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO. 38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL EXTERNAL VARIATIONS

TABLE : 027

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	96	94	94	4
Live	N	96	94	94	4
Dead	N	0	0	0	0
PSEUDOANKYLOSIS (FORELIMB)					
Fetal Incidence	N	1	1	0	0
	%	1.0	1.1	0.0	0.0
Litter Incidence	N	1	1	0	0
	%	6.7	6.7	0.0	0.0
TOTAL FETAL EXTERNAL VARIATIONS					
Fetal Incidence	N	1	1	0	0
	%	1.0	1.1	0.0	0.0
Litter Incidence	N	1	1	0	0
	%	6.7	6.7	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE : 028
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL EXTERNAL UNCLASSIFIED OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 4 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	86	84	64	4
Live	N	86	84	64	4
Dead	N	0	0	0	0
TOTAL FETAL EXTERNAL UNCLASSIFIED OBSERVATIONS					
Fetal Incidence	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Litter Incidence	N	0	0	0	0
	%	0.0	0.0	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE : 029
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL SOFT TISSUE OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	86	94	94	4
Live	N	86	94	94	4
Dead	N	0	0	0	0
TOTAL MALFORMATIONS					
Fetal Incidence	N	1	3	1	0
	%	1.0	3.2	1.1	0.0
Litter Incidence	N	1	3	1	0
	%	6.7	20.0	7.1	0.0
Affected Fetuses/Litter	MEANS	1.1	3.5	0.9	0.0
	S.D.	4.30	7.43	3.34	0.00
TOTAL VARIATIONS					
Fetal Incidence	N	33	24	26	1
	%	34.4	25.5	27.7	25.0
Litter Incidence	N	14	11	11	1
	%	83.3	73.3	78.6	100.0
Affected Fetuses/Litter	MEANS	38.8	28.3	31.0	25.0
	S.D.	28.88	21.81	27.32	0.00

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 030

PROJECT NO.38A0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SOFT TISSUE MALFORMATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	86	84	84	4
Live	N	86	84	84	4
Dead	N	0	0	0	0
TRUNCUS ARTERIOSUS COMMUNIS					
Fetal Incidence	N	0	1	0	0
	%	0.0	1.1	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	6.7	0.0	0.0
HERNIA DIAPHRAGMATICA					
Fetal Incidence	N	0	1	0	0
	%	0.0	1.1	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	6.7	0.0	0.0
AGENESIA OF SPLEEN					
Fetal Incidence	N	0	1	0	0
	%	0.0	1.1	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	6.7	0.0	0.0
AGENESIA OF GALLBLADDER					
Fetal Incidence	N	1	1	1	0
	%	1.0	1.1	1.1	0.0
Litter Incidence	N	1	1	1	0
	%	6.7	6.7	7.1	0.0
TOTAL FETAL SOFT TISSUE MALFORMATIONS					
Fetal Incidence	N	1	3	1	0
	%	1.0	3.2	1.1	0.0
Litter Incidence	N	1	3	1	0
	%	6.7	20.0	7.1	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

PROJECT NO.38R0375/88082: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SOFT TISSUE VARIATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	96	94	84	4
Live	N	96	94	84	4
Dead	N	0	0	0	0
SEPARATED ORIGIN OF CAROTIDS					
Fetal Incidence	N	21	14	25	0
	%	21.8	14.9	29.8	0.0
Litter Incidence	N	11	8	11	0
	%	73.3	53.3	78.6	0.0
HEART: TRACES OF INTERVENTRIC.FORAMEN/SEPTUM MEMBRANACEUM					
Fetal Incidence	N	13	6	2b	1
	%	13.5	6.4	2.1	25.0
Litter Incidence	N	7	4	2	1
	%	46.7	26.7	14.3	100.0
HYPOPLASIA OF GALLBLADDER					
Fetal Incidence	N	0	3	0	0
	%	0.0	3.2	0.0	0.0
Litter Incidence	N	0	2	0	0
	%	0.0	13.3	0.0	0.0
DILATED RENAL PELVIS					
Fetal Incidence	N	1	1	0	0
	%	1.0	1.1	0.0	0.0
Litter Incidence	N	1	1	0	0
	%	6.7	6.7	0.0	0.0
TOTAL FETAL SOFT TISSUE VARIATIONS					
Fetal Incidence	N	33	24	26	1
	%	34.4	25.5	27.7	25.0
Litter Incidence	N	14	11	11	1
	%	93.3	73.3	78.6	100.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 032

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SOFT TISSUE UNCLASSIFIED OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	14	15	14	1
Fetuses Evaluated	N	88	94	84	4
Live	N	88	94	84	4
Dead	N	0	0	0	0
LIVER: FOCAL NECROSIS					
Fetal Incidence	N	0	1	1	0
	%	0.0	1.1	1.1	0.0
Litter Incidence	N	0	1	1	0
	%	0.0	6.7	7.1	0.0
BLOOD COAGULUM AROUND BLADDER					
Fetal Incidence	N	0	1	4	0
	%	0.0	1.1	4.3	0.0
Litter Incidence	N	0	1	4a	0
	%	0.0	6.7	28.6	0.0
TOTAL FETAL SOFT TISSUE UNCLASSIFIED OBSERVATIONS					
Fetal Incidence	N	0	2	5a	0
	%	0.0	2.1	6.3	0.0
Litter Incidence	N	0	2	5a	0
	%	0.0	13.3	35.7	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL SKELETAL OBSERVATIONS

TABLE : 033

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	96	94	94	4
Live	N	96	94	94	4
Dead	N	0	0	0	0
TOTAL MALFORMATIONS					
Fetal Incidence	N	1	1	1	1
	%	1.0	1.1	1.1	25.0
Litter Incidence	N	1	1	1	1
	%	6.7	6.7	7.1	100.0
Affected Fetuses/Litter	MEANS	1.0	0.8	0.7	25.0b
	S.D.	3.88	3.23	2.67	0.00
TOTAL VARIATIONS					
Fetal Incidence	N	6	7	5	0
	%	6.3	7.4	5.3	0.0
Litter Incidence	N	5	6	5	0
	%	33.3	40.0	35.7	0.0
Affected Fetuses/Litter	MEANS	7.3	7.3	7.3	0.0
	S.D.	12.34	10.67	13.76	0.00
TOTAL RETARDATIONS					
Fetal Incidence	N	56	54	56	3
	%	58.3	57.4	59.6	75.0
Litter Incidence	N	14	15	14	1
	%	93.3	100.0	100.0	100.0
Affected Fetuses/Litter	MEANS	57.9	57.3	63.2	75.0
	S.D.	27.10	27.68	31.08	0.00

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01

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TABLE 1 034

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL MALFORMATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	18	18	14	1
Fetuses Evaluated	N	86	84	84	4
Live	N	86	84	84	4
Dead	N	0	0	0	0
THORACIC VERTEBRA ABSENT					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	1.1	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	7.1	0.0
LUMBAR VERTEBRA ABSENT					
Fetal Incidence	N	1	0	0	0
	%	1.0	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	6.7	0.0	0.0	0.0
STERNEBRAE WITH VARIOUS MALFORMATIONS					
Fetal Incidence	N	0	1	0	1a
	%	0.0	1.1	0.0	25.0
Litter Incidence	N	0	1	0	1
	%	0.0	6.7	0.0	100.0
RIB(S) ABSENT					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	1.1	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	7.1	0.0
TOTAL FETAL SKELETAL MALFORMATIONS					
Fetal Incidence	N	1	1	1	1
	%	1.0	1.1	1.1	25.0
Litter Incidence	N	1	1	1	1
	%	6.7	6.7	7.1	100.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01

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PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS — TABLE . 035
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	88	84	84	4
Live	N	88	84	84	4
Dead	N	0	0	0	0
SPLITTING OF SKULL BONE(S)					
Fetal Incidence	N	0	4	0	0
	%	0.0	4.3	0.0	0.0
Litter Incidence	N	0	3	0	0
	%	0.0	20.0	0.0	0.0
EPACTAL BONE BETWEEN PARIETAL BONES					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	1.1	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	7.1	0.0
ACCESSORY THORACIC VERTEBRA					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	1.1	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	7.1	0.0
CLAVICULA DEFORMED					
Fetal Incidence	N	1	0	0	0
	%	1.0	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	6.7	0.0	0.0	0.0
ACCESSORY STERNEBRA					
Fetal Incidence	N	1	2	0	0
	%	1.0	2.1	0.0	0.0
Litter Incidence	N	1	2	0	0
	%	6.7	13.3	0.0	0.0
STERNEBRAE FUSED					
Fetal Incidence	N	2	3	0	0
	%	2.1	3.2	0.0	0.0
Litter Incidence	N	2	3	0	0
	%	13.3	20.0	0.0	0.0
STERNEBRA(E) OF IRREGULAR SHAPE					
Fetal Incidence	N	0	1	1	0
	%	0.0	1.1	1.1	0.0
Litter Incidence	N	0	1	1	0
	%	0.0	6.7	7.1	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

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TABLE 1 036

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	86	84	84	4
Live	N	86	84	84	4
Dead	N	0	0	0	0
ACCESSORY 13TH RIB(S)					
Fetal Incidence	N	0	0	3	0
	%	0.0	0.0	3.2	0.0
Litter Incidence	N	0	0	3	0
	%	0.0	0.0	21.4	0.0
12TH RIB(S) ABSENT					
Fetal Incidence	N	1	0	0	0
	%	1.2	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	6.7	0.0	0.0	0.0
RUDIMENTARY CERVICAL RIB(S)					
Fetal Incidence	N	1	0	0	0
	%	1.2	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	6.7	0.0	0.0	0.0
TOTAL FETAL SKELETAL VARIATIONS					
Fetal Incidence	N	6	7	5	0
	%	8.3	7.4	6.3	0.0
Litter Incidence	N	5	6	5	0
	%	33.3	40.0	35.7	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 037

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 50 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 800 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	96	94	94	4
Live	N	96	94	94	4
Dead	N	0	0	0	0
SKULL INCOMPLETELY OSSIFIED					
Fetal Incidence	N	3	0	4	1
	%	3.1	0.0	4.3	25.0
Litter Incidence	N	2	0	4	1
	%	13.3	0.0	28.6	100.0
INTERPARIETAL BONE REDUCED IN SIZE					
Fetal Incidence	N	0	1	0	0
	%	0.0	1.1	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	6.7	0.0	0.0
STERNEBRA(E) NOT OSSIFIED					
Fetal Incidence	N	37	37	33	2
	%	38.6	39.4	35.1	50.0
Litter Incidence	N	13	12	9	1
	%	86.7	80.0	64.3	100.0
STERNEBRA(E) INCOMPLETELY OSSIFIED OR REDUCED IN SIZE					
Fetal Incidence	N	17	16	23	1
	%	17.7	17.0	24.5	25.0
Litter Incidence	N	11	11	12	1
	%	73.3	73.3	85.7	100.0
TOTAL FETAL SKELETAL RETARDATIONS					
Fetal Incidence	N	56	54	56	3
	%	58.3	57.4	59.6	75.0
Litter Incidence	N	14	15	14	1
	%	93.3	100.0	100.0	100.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE 038

PROJECT NO.38R0375/88062: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL EXTERNAL, SOFT TISSUE, AND SKELETAL OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 200 MG/KG BW/DAY	TEST GROUP 3 600 MG/KG BW/DAY
Litters Evaluated	N	15	15	14	1
Fetuses Evaluated	N	98	94	94	4
Live	N	98	94	94	4
Dead	N	0	0	0	0
TOTAL MALFORMATIONS					
Fetal Incidence	N	3	4	2	1
	%	3.1	4.3	2.1	25.0
Litter Incidence	N	3	3	2	1
	%	20.0	20.0	14.3	100.0
Affected Fetuses/Litter	MEANS	3.7	4.3	1.6	25.0a
	S.D.	8.01	8.04	4.11	0.00
TOTAL VARIATIONS					
Fetal Incidence	N	37	30	30	1
	%	38.6	31.9	31.9	25.0
Litter Incidence	N	15	12	12	1
	%	100.0	80.0	85.7	100.0
Affected Fetuses/Litter	MEANS	40.6	32.6	37.3	25.0
	S.D.	26.71	24.39	25.88	0.00
TOTAL RETARDATIONS					
Fetal Incidence	N	88	84	88	1
	%	89.8	89.4	93.6	25.0
Litter Incidence	N	14	15	14	1
	%	93.3	100.0	100.0	100.0
Affected Fetuses/Litter	MEANS	57.8	57.3	63.2	75.0
	S.D.	27.10	27.68	31.08	0.00

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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B. SUPPLEMENTAL STUDY (Doses: 0, 400 mg/kg)

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TABLE : 001

PROJECT NO.40RD375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAYS 0 TO 1	MEAN	124.7	121.1
	S.D.	17.07	18.81
	N	19	20
DAYS 1 TO 2	MEAN	124.4	127.6
	S.D.	18.86	22.71
	N	19	19
DAYS 2 TO 3	MEAN	124.6	117.0
	S.D.	20.83	20.83
	N	19	20
DAYS 3 TO 4	MEAN	119.4	118.7
	S.D.	20.18	23.10
	N	19	20
DAYS 4 TO 5	MEAN	116.1	114.4
	S.D.	17.48	18.48
	N	19	19
DAYS 5 TO 6	MEAN	113.2	105.8
	S.D.	21.18	24.96
	N	19	20
DAYS 6 TO 7	MEAN	109.2	105.7
	S.D.	19.84	27.25
	N	19	20
DAYS 7 TO 8	MEAN	101.4	92.2b
	S.D.	20.81	18.95
	N	19	20
DAYS 8 TO 9	MEAN	98.0	46.8b
	S.D.	23.84	21.62
	N	19	20
DAYS 9 TO 10	MEAN	93.4	87.6b
	S.D.	22.41	20.78
	N	19	20
DAYS 10 TO 11	MEAN	81.9	83.8b
	S.D.	23.64	23.68
	N	19	20

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01

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TABLE : 002

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAYS 11 TO 12	MEAN	80.2	53.5b
	S.D.	23.37	38.28
	N	19	20
DAYS 12 TO 13	MEAN	80.1	50.8b
	S.D.	19.43	42.09
	N	19	20
DAYS 13 TO 14	MEAN	83.0	52.7a
	S.D.	22.03	47.41
	N	19	20
DAYS 14 TO 15	MEAN	70.8	60.3
	S.D.	20.29	43.01
	N	19	20
DAYS 15 TO 16	MEAN	75.2	54.8
	S.D.	20.16	44.38
	N	19	20
DAYS 16 TO 17	MEAN	81.6	60.9
	S.D.	23.05	43.41
	N	19	20
DAYS 17 TO 18	MEAN	90.8	62.0a
	S.D.	15.99	45.26
	N	19	20
DAYS 18 TO 19	MEAN	87.8	66.3
	S.D.	22.68	53.67
	N	19	19
DAYS 19 TO 20	MEAN	84.8	61.3
	S.D.	23.21	46.04
	N	19	18
DAYS 20 TO 21	MEAN	83.1	60.1
	S.D.	23.33	45.39
	N	19	18
DAYS 21 TO 22	MEAN	83.4	60.0
	S.D.	17.09	42.87
	N	19	18

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 8U3

PROJECT NO.40R0378/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

			TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAYS 22 TO 23		MEAN	89.7	76.2
		S.D.	19.05	48.25
		N	18	14
DAYS 23 TO 24		MEAN	81.6	78.6
		S.D.	16.07	48.63
		N	18	14
DAYS 24 TO 25		MEAN	100.3	93.1
		S.D.	20.03	40.65
		N	18	13
DAYS 25 TO 26		MEAN	100.8	96.8
		S.D.	20.18	48.88
		N	18	13
DAYS 26 TO 27		MEAN	104.2	116.0
		S.D.	19.71	44.44
		N	18	10
DAYS 27 TO 28		MEAN	100.1	127.8
		S.D.	18.46	38.65
		N	18	10
DAYS 28 TO 29		MEAN	103.8	124.8
		S.D.	21.38	37.88
		N	18	10
DAYS 0 TO 7	MEAN OF MEANS	MEAN	118.6	118.7
		S.D.	6.28	8.88
		N	7	7
DAYS 7 TO 28	MEAN OF MEANS	MEAN	98.3	88.8b
		S.D.	8.68	21.33
		N	21	21
DAYS 0 TO 28	MEAN OF MEANS	MEAN	97.8	91.9a
		S.D.	15.82	20.66
		N	28	28

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE . 004

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAY 0	MEAN	2584	2578
	S.D.	129.7	118.2
	N	19	20
DAY 2	MEAN	2666	2660
	S.D.	144.4	130.5
	N	19	20
DAY 4	MEAN	2659	2656
	S.D.	142.3	135.2
	N	19	20
DAY 7	MEAN	2660	2654
	S.D.	138.8	141.1
	N	19	20
DAY 9		2656	2638
		146.6	139.3
		19	20
DAY 11	MEAN	2643	2628
	S.D.	150.3	143.7
	N	19	20
DAY 14	MEAN	2662	2658
	S.D.	157.2	174.8
	N	19	20
DAY 16	MEAN	2685	2692
	S.D.	156.9	212.6
	N	19	20
DAY 19	MEAN	2669	2687
	S.D.	135.3	189.9
	N	19	19
DAY 21	MEAN	2676	2597
	S.D.	141.8	186.8
	N	19	18
DAY 23	MEAN	2695	2671
	S.D.	135.9	140.4
	N	19	14

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.408078/88077; PREMATAL TOXICITY STUDY IN RABBITS

TABLE 1 005

ORAL ADMINISTRATION (GAVAGE)

MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

	TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAY 15		
MEAN	3119	3111
S.D.	140.4	91.1
N	10	13
DAY 20		
MEAN	2705	2674
S.D.	143.3	103.7
N	10	10
DAY 29		
MEAN	2815	2810
S.D.	150.1	105.8
N	10	10

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE 1. 006

PROJECT NO.40R0375/88077; PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAYS 0 TO 2	MEAN	87.8	80.5
	S.D.	28.63	46.63
	N	19	20
DAYS 2 TO 4	MEAN	-7.8	-12.7
	S.D.	20.58	30.18
	N	19	20
DAYS 4 TO 7	MEAN	0.3	-1.3
	S.D.	20.08	32.20
	N	19	20
DAYS 7 TO 9	MEAN	-4.0	-15.7
	S.D.	22.17	37.71
	N	19	20
DAYS 9 TO 11	MEAN	-12.9	-11.1
	S.D.	16.23	18.84
	N	19	20
DAYS 11 TO 14	MEAN	19.8	-19.8*
	S.D.	20.32	64.28
	N	19	20
DAYS 14 TO 16	MEAN	23.2	-16.1
	S.D.	21.01	64.14
	N	19	20
DAYS 16 TO 19	MEAN	4.8	-12.2
	S.D.	33.61	77.39
	N	19	18
DAYS 19 TO 21	MEAN	-14.8	-33.8
	S.D.	17.24	57.55
	N	19	18
DAYS 21 TO 23	MEAN	18.4	-7.8
	S.D.	19.06	54.89
	N	19	14
DAYS 23 TO 25	MEAN	44.7	17.7
	S.D.	28.48	58.09
	N	19	13

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

PROJECT NO.40R0376/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CHC	TEST GROUP 1 400 MG/KG BW/DAY
DAYS 18 TO 18	MEAN	18.3	33.8
	S.D.	47.41	101.91
	N	18	18
DAYS 20 TO 20	MEAN	19.4	8.8
	S.D.	19.88	20.17
	N	18	18

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE 1 008

PROJECT NO.4DR0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAYS 0 TO 7	MEAN	78.2	78.4
	S.D.	30.65	67.13
	N	10	20
DAYS 7 TO 20	MEAN	138.8	140.7
	S.D.	74.89	184.42
	N	10	10
DAYS 0 TO 20	MEAN	231.2	220.4
	S.D.	82.72	176.10
	N	10	10

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.4UR0375/88U77: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 — 009
ORAL ADMINISTRATION (GAVAGE)
MEAN GRAVID UTERINE WEIGHTS AND NET MATERNAL BODY WEIGHT CHANGE -- GRAMS

		TEST GROUP 0 CONTROL CHC	TEST GROUP 1 400 MG/KG BW/DAY
GRAVID UTERUS	MEAN	328.6	259.6
	S.D.	114.68	102.43
	N	10	10
CARCASS	MEAN	2488.2	2550.0
	S.D.	134.64	130.02
	N	10	10
NET WEIGHT CHANGE FROM DAY 7	MEAN	-171.6	-109.1
	S.D.	76.88	85.06
	N	10	10

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

CARCASS WEIGHT = TERMINAL BODY WEIGHT MINUS UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 7 = CARCASS WEIGHT MINUS DAY 7 BODY WEIGHT

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TABLE 1

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL CLINICAL OBSERVATIONS DURING GESTATION

		DAY OF GESTATION																													
	GROUP#	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	TOTAL
# OF FEMALES EXAMINED	0	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	
	1	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	19	18	18	18	17	16	14	14	13	10	10	
NORMAL																																
NO REMARKABLE CLINICAL OBSERVATIONS	0	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	
	1	20	20	20	20	20	20	20	20	16	15	15	15	13	12	12	13	14	12	10	11	11	11	10	10	11	10	9	9	9	20	
DEAD																																
SACRIFICED AFTER ABORTION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	2	0	1	3	0	0	9	
DIED AFTER ABORTION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	
MISCELLANEOUS																																
ABORTION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2	2	0	1	1	2	0	0	10
BLOOD IN BEDDING	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	0	2
STOOL/URINE																																
REDUCED DEFECATION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	4	5	5	5	6	5	6	7	5	6	6	7	5	4	7	5	2	3	2	1	1	16
NO DEFECATION	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3	2	0	0	1	0	0	1	2	0	1	0	0	0	0	0	6
REDDISH-BROWN DISCOLORATION OF URINE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	1	1	2	3	4	6	6	5	2	2	1	1	1	0	0	8

TABLE 011

BASF TOXICOLOGY - DATATOX RC.2
PROJECT NUMBER 40A0378/88077 REG. NO. 83 258

GROUP MEANS HEMATOLOGICAL EXAMINATIONS PRINT DATE 12-OCT-89

Nominal days in study 29 p.i.

FEMALES GROUP		WBC GIGA/L	RBC TERA/L	HGB MMOL/L	HCT L/L	MCV FL	MCH FMOL	MCHC MMOL/L	PLT GIGA/L
0 MG/KG	M	8.80	8.42	7.91	0.402	74.10	1.46	19.70	412
	SD	0.88	0.34	0.46	0.023	2.43	0.05	0.47	97
	N	10	10	10	10	10	10	10	10
GROUP 1									
400 MG/KG	M	7.32	8.18	7.76	0.384	76.40*	1.51*	19.70	423
	SD	1.03	0.30	0.52	0.030	2.63	0.06	0.40	134
	N	10	10	10	10	10	10	10	10

Statistics: Anova + Students t-tests (two-sided); * P<0.05; ** P<0.01; *** P<0.001 (Statistical unit = Animal)

BASF TOXICOLOGY
PROJECT NUMBER 40R0375/88077 Reg. Nr. 83 258 (Vinclozolin)

GROUP MEANS DIFFERENTIAL BLOOD COUNT 13-OCT-89

Nominal days in study 28 Pole

FEMALES

		WBC GIGA/L	EOS %	BASO %	BAND %	POLY %	LYMP %	MONO %
GROUP 0 0 MG/KG	M	8.68	0.37	3.00	0.37	38.79	55.05	2.42
	SD	8.89	0.68	1.83	0.60	8.63	8.80	1.80
	N	19	19	19	19	19	19	19
GROUP 1 480 MG/KG	M	7.32	0.80	2.60	0.80	42.20	50.70	2.80
	SD	1.63	0.79	1.26	0.98	8.65	8.56	1.32
	N	10	10	10	10	10	10	10

TABLE 013

BASF TOXICOLOGY
PROJECT NUMBER 40R0378/88077 Reg. Nr. 83 258 (Vinclozolin)

GROUP MEANS DIFFERENTIAL BLOOD COUNT 13-OCT-89

Nominal days in study 28 p.i.

F E M A L E S

		WBC GIGA/L	EOS GIGA/L	BASO GIGA/L	BAND GIGA/L	POLY GIGA/L	LYMP GIGA/L	MONO GIGA/L
GROUP 0								
0 MG/KG								
	M	8.88	0.03	0.15	0.02	2.53	3.66	0.16
	SD	0.89	0.05	0.12	0.04	0.55	0.86	0.12
	N	10	10	10	10	10	10	10
GROUP 1								
400 MG/KG								
	M	7.32	0.06	0.19	0.07	3.13	3.68	0.20
	SD	1.03	0.06	0.10	0.07	0.97	0.84	0.09
	N	10	10	10	10	10	10	10

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TABLE 014

BASF TOXICOLOGY - DATATOX RC.2
PROJECT NUMBER 40R0375/88077 REG. NO. 83 258

GROUP MEANS RETICULOCYTES PRINT DATE 12-OCT-89

Nominal days in study 28 P.I.

F E M A L E S		RETI 0/00
GROUP 0		
0 MG/KG	M	16
	SD	6
	N	19
GROUP 1		
400 MG/KG	M	28**
	SD	15
	N	18

Statistics: Anova + Students t-tests (two-sided): * P<0.05; ** P<0.01; *** P<0.001 (Statistical unit = Animal)

Tab. 015

BASF Department of Toxicology

REG. NO. 03 250, PRENATAL TOX STUDY,
ABSOLUTE WEIGHTS - MEAN VALUES

Sacrifice group	F1			
Sex	F			
Dose group	0			
Body weight	0	20	2814.047	2817.0
		20	140.000	105.741
Liver	0	20	80.030	85.5550
		20	6.17	6.417
Adrenal glands	0	20	0.21	0.227
		20	0.034	0.034

Dunnett test
* P ≤ 0.05 ** P ≤ 0.01
two sided statistical unit = animal

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Tab. 016

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REG. NR. 83 250. PRAENATAL. TOX STUDY.
ADMINISTRATION BY GAVAGE IN RABBITS
RELATIVE WEIGHTS - MEAN VALUES

Sacrifice group			F1	
Sex			F	
Dose group			0	1
Body weight	%	M	100.	100.
		SD		
		n	10.	10.
Liver	%	M	1.777	3.05 **
		SD	0.186	0.203
		n	10.	10.
Adrenal glands	%	M	0.007	0.008
		SD	0.001	0.001
		n	10.	10.

Dunnett test
* P < 0.05 ** P < 0.01
two sided (statistical unit = animal)

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PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 — 017
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF MATERNAL NECROPSY OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
DAMS EXAMINED	N	20	20
NOTHING ABNORMAL DETECTED	N	20	2
	%	100.0	10.0
HEART: DILATION	N	0	1
	%	0.0	5.0
HEART: DISCOLORATION	N	0	6
	%	0.0	30.0
LUNGS: EDEMA	N	0	2
	%	0.0	10.0
LIVER: DISCOLORATION	N	0	8
	%	0.0	40.0
LIVER: PROMINENT ACINAR PATTERN	N	0	1
	%	0.0	5.0
KIDNEYS: DISCOLORATION	N	0	1
	%	0.0	5.0
PARTICULAR FINDINGS ON IMPLANTS IN DAMS WHICH ABORTED	N	0	10
	%	0.0	50.0
UTERUS: DIVERTICULUM	N	0	1
	%	0.0	5.0

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PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF REPRODUCTION DATA

TABLE : 018

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Females Mated	N	20	20
Pregnant	N	19	20
	%	95	100
Aborted	N	0	10
Premature Births	N	0	0
Dams with Viable Fetuses	N	19	8
Dams with all Resorptions	N	0	2
Female Mortality	N	0	10b
	%	0.0	50
Pregnant at C-section	N	19	10b
	%	95	50
Corpora Lutea	MEAN	7.9	7.4
	S.D.	1.84	1.43
	TOTAL	151	74
Implantation Sites	MEAN	6.7	5.3
	S.D.	2.16	2.26
	TOTAL	127	53
Preimplantation Loss	MEAN%	17.2	30.2
	S.D.	17.87	22.71
Postimplantation Loss	MEAN%	10.3	32.9a
	S.D.	18.53	37.71

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE 1 018

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 CONTROL CNC	TEST GROUP 1 400 MG/KG BW/DAY
Pregnant at C-section	N	10	10
Resorptions: Total	MEAN	1.5	1.1
	S.D.	0.96	0.88
	TOTAL	10	11
	MEAN%	10.3	32.9a
	S.D.	18.83	37.71
Early	MEAN	0.4	0.8
	S.D.	0.83	0.88
	TOTAL	7	8
	MEAN%	7.8	26.2
	S.D.	17.08	31.85
Late	MEAN	0.2	0.2
	S.D.	0.37	0.42
	TOTAL	3	2
	MEAN%	2.4	6.7
	S.D.	5.67	16.18
Dead Fetuses	N	0	0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 6

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Dams with Viable Fetuses	N	19	8
Live Fetuses	MEAN	6.2	5.3
	S.D.	2.67	1.98
	TOTAL	117	42
	MEAN%	89.7	83.8
	S.D.	18.53	14.77
Females	MEAN	3.3	3.4
	S.D.	1.80	1.92
	TOTAL	63	27
	MEAN%	50.3	64.3
	S.D.	18.88	28.34
Males	MEAN	2.8	1.9
	S.D.	1.95	1.55
	TOTAL	54	15
	MEAN%	39.4	28.7
	S.D.	18.42	21.25
PER CENT LIVE FEMALES		53.8	64.3
PER CENT LIVE MALES		46.2	35.7

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE 1 021

PROJECT NO.40R0378/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
MEAN PLACENTAL AND FETAL BODY WEIGHTS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
PLACENTAL WEIGHTS UNITS: GRAMS			
of all Viable Fetuses	MEAN	4.4	4.7
	S.D.	0.78	0.75
	N	10	8
of Male Fetuses	MEAN	4.3	4.7
	S.D.	0.88	1.16
	N	10	8
of Female Fetuses	MEAN	4.4	4.8
	S.D.	0.88	0.58
	N	10	8
FETAL WEIGHTS UNITS: GRAMS			
of all Viable Fetuses	MEAN	39.8	44.8a
	S.D.	3.83	4.15
	N	10	8
of Male Fetuses	MEAN	39.8	44.8a
	S.D.	4.38	5.67
	N	10	8
of Female Fetuses	MEAN	40.1	43.5a
	S.D.	4.07	3.42
	N	10	8

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 02
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL EXTERNAL OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL MALFORMATIONS			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0
Affected Fetuses/Litter	MEANS	0.7	0.0
	S.D.	2.87	0.00
TOTAL VARIATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0
Affected Fetuses/Litter	MEANS	0.0	0.0
	S.D.	0.00	0.00

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 02

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL EXTERNAL MALFORMATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
CHEILOSCHISIS			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0
TOTAL FETAL EXTERNAL MALFORMATIONS			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE 1

PROJECT NO.40A0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL EXTERNAL VARIATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL FETAL EXTERNAL VARIATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

PROJECT NO.40R0378/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL EXTERNAL UNCLASSIFIED OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL FETAL EXTERNAL UNCLASSIFIED OBSERVATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

88077 PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL SOFT TISSUE OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL MALFORMATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0
Affected Fetuses/Litter	MEANS	0.0	0.0
	S.D.	0.00	0.00
TOTAL VARIATIONS			
Fetal Incidence	N	23	20b
	%	19.7	47.6
Litter Incidence	N	11	7
	%	57.9	87.5
Affected Fetuses/Litter	MEANS	20.2	53.8b
	S.D.	25.40	32.93

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.40R0378/88077: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 — 027

ORAL ADMINISTRATION (GAVAGE)

SUMMARY OF FETAL SOFT TISSUE MALFORMATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL FETAL SOFT TISSUE MALFORMATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SOFT TISSUE VARIATIONS

		TEST GROUP 0 CONTROL CNC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
SEPARATED ORIGIN OF CAROTIDS			
Fetal Incidence	N	12	15b
	%	10.3	35.7
Litter Incidence	N	9	6
	%	47.4	75.0
HEART: TRACES OF INTERVENTRIC.FORAMEN/SEPTUM MEMBRANACEUM			
Fetal Incidence	N	11	6
	%	9.4	14.3
Litter Incidence	N	5	3
	%	26.3	37.5
HYPOPLASIA OF GALLBLADDER			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0
TOTAL FETAL SOFT TISSUE VARIATIONS			
Fetal Incidence	N	23	20b
	%	19.7	47.6
Litter Incidence	N	11	7
	%	57.9	87.5

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.40R0376/88077: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 020
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SOFT TISSUE UNCLASSIFIED OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL FETAL SOFT TISSUE UNCLASSIFIED OBSERVATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS — TABLE : 030
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL SKELETAL OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL MALFORMATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0
Affected Fetuses/Litter	MEAN%	0.0	0.0
	S.D.	0.00	0.00
TOTAL VARIATIONS			
Fetal Incidence	N	14	6
	%	12.0	14.3
Litter Incidence	N	8	3
	%	42.1	37.5
Affected Fetuses/Litter	MEAN%	13.1	12.5
	S.D.	19.72	17.43
TOTAL RETARDATIONS			
Fetal Incidence	N	68	14b
	%	58.1	33.3
Litter Incidence	N	16	5
	%	84.2	62.5
Affected Fetuses/Litter	MEAN%	54.8	33.3
	S.D.	35.09	38.73

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

PROJECT NO.40RD375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL MALFORMATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL FETAL SKELETAL MALFORMATIONS			
Fetal Incidence	N	0	0
	%	0.0	0.0
Litter Incidence	N	0	0
	%	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE : 032

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 CONTROL CNC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
SPLITTING OF SKULL BONE(S)			
Fetal Incidence	N	4	0
	%	3.4	0.0
Litter Incidence	N	4	0
	%	21.1	0.0
EPACTAL BONE BETWEEN NASAL AND FRONTAL BONES			
Fetal Incidence	N	2	0
	%	1.7	0.0
Litter Incidence	N	2	0
	%	10.5	0.0
ACCESSORY THORACIC VERTEBRA			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0
CLAVICULA DEFORMED			
Fetal Incidence	N	0	1
	%	0.0	2.4
Litter Incidence	N	0	1
	%	0.0	12.5
STERNEBRA(E) OF IRREGULAR SHAPE			
Fetal Incidence	N	2	0
	%	1.7	0.0
Litter Incidence	N	2	0
	%	10.5	0.0
STERNEBRA(E) BIPARTITE			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0
STERNEBRAE FUSED			
Fetal Incidence	N	2	1
	%	1.7	2.4
Litter Incidence	N	2	1
	%	10.5	12.5

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1 033
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL VARIATIONS

		TEST GROUP 0 CONTROL CNC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
ACCESSORY 13TH RIB(S)			
Fetal Incidence	N	4	2
	%	3.4	4.8
Litter Incidence	N	3	1
	%	15.8	12.5
FLYING RIB(S)			
Fetal Incidence	N	0	2
	%	0.0	4.8
Litter Incidence	N	0	1
	%	0.0	12.5
12TH RIB(S) ABSENT			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0
TOTAL FETAL SKELETAL VARIATIONS			
Fetal Incidence	N	14	6
	%	12.0	14.3
Litter Incidence	N	8	3
	%	42.1	37.5

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS — TABLE 1
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
SKULL INCOMPLETELY OSSIFIED			
Fetal Incidence	N	5	2
	%	4.3	4.8
Litter Incidence	N	5	2
	%	26.3	25.0
STERNEBRA(E) NOT OSSIFIED			
Fetal Incidence	N	36	7
	%	30.8	16.7
Litter Incidence	N	12	3
	%	63.2	37.5
STERNEBRA(E) INCOMPLETELY OSSIFIED OR REDUCED IN SIZE			
Fetal Incidence	N	31	6
	%	26.5	14.3
Litter Incidence	N	13	4
	%	68.4	50.0
TOTAL FETAL SKELETAL RETARDATIONS			
Fetal Incidence	N	68	14b
	%	58.1	33.3
Litter Incidence	N	16	5
	%	84.2	62.5

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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TABLE 1

PROJECT NO.40R0375/88077: PRENATAL TOXICITY STUDY IN RABBITS
ORAL ADMINISTRATION (GAVAGE)
SUMMARY OF ALL CLASSIFIED FETAL EXTERNAL, SOFT TISSUE, AND SKELETAL OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 400 MG/KG BW/DAY
Litters Evaluated	N	19	8
Fetuses Evaluated	N	117	42
Live	N	117	42
Dead	N	0	0
TOTAL MALFORMATIONS			
Fetal Incidence	N	1	0
	%	0.9	0.0
Litter Incidence	N	1	0
	%	5.3	0.0
Affected Fetuses/Litter	MEANS	0.7	0.0
	S.D.	2.87	0.00
TOTAL VARIATIONS			
Fetal Incidence	N	32	22b
	%	27.4	52.4
Litter Incidence	N	13	7
	%	68.4	87.5
Affected Fetuses/Litter	MEANS	28.5	86.6a
	S.D.	28.88	30.75
TOTAL RETARDATIONS			
Fetal Incidence	N	68	14b
	%	58.1	33.3
Litter Incidence	N	16	5
	%	84.2	62.5
Affected Fetuses/Litter	MEANS	54.0	33.3
	S.D.	35.08	36.73

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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