2-9-88

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

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FEB 9 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Assure®: Review of Dose-Range Finding Teratology Study and Final Teratology Study with Rabbits

Caswell No.: 215D EPA Accession No.: 403705-01
403705-02

EPA ID No.: 352-UUR / 5F3252 / 6H5479

TO: R. Taylor / V. Walters, PM (25)
Registration Division (TS-767c)

FROM: Whang Phang, Ph.D. 12/28/87
Pharmacologist
Toxicology Branch / HED (TS-769c)

THROUGH: Marcia van Gemert, Ph.D. 1/4/88
Head, Section III
&
William Burnam, Deputy Branch Chief 1/5/88
Toxicology Branch / HED (TS-769c)

The Registrant, E. I. du Pont de Nemours, has submitted a dose-range-finding teratology study and a final teratology study on Assure® with rabbits. The data evaluation reports of these two studies are attached, and the conclusions are the following:

1). Dose-range-finding study:

Groups of New Zealand White female rabbits (6/group) were artificially inseminated. They were then intubated with Assure at doses of 0, 7, 25, 60, and 75 mg/kg from gestation days 7 to 19. On gestation day 29, fetuses were delivered with cesarean section from the surviving females prior to sacrifice.

During the treatment period (gestation days 7-19), the body weight and food consumption of 75 mg/kg females were decreased relative to the controls. Increased incidence of abortion was found in 60 and 75 mg/kg females compared to the controls (control, 0/6; 60 mg/kg, 1/6; 75 mg/kg, 3/6). No indications of treatment related developmental toxicity was observed during fetal examinations.

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Based upon these data, 60 mg/kg was chosen as the highest dose in a full teratology study. Since the study is a dose-range-finding study, it is classified as a supplementary study.

2). Final teratology study:

When groups of 16 presumed pregnant rabbits were intubated with Assure at doses of 0, 7, 20, and 60 mg/kg from gestation days 7-19, no evidence of developmental toxicity was observed. The NOEL for developmental toxicity was 60 mg/kg (HDT).

Decreases in food consumption and body weight gain were observed in 60 mg/kg does. Based upon these findings, the LEL for maternal toxicity was 60 mg/kg; NOEL, 20 mg/kg. The study is classified as Core Minimum.

Reviewed by: Whang Phang, Ph.D. 12/25/88 006598
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D. 12/28/88
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Teratology: Range-Finding Study-Rabbit

ACCESSION NUMBER: 403705-01 TOX. CHEM. NO.: 215D

TEST MATERIAL: Assure or NC-302 (Technical)
(99.1% pure; white solid)

CITATION: Morseth, S.L. (1987). Range-Finding Rabbit Teratology Study. Hazleton Laboratories America, Inc.; HLA Study No. 2096-131. Study Sponsor: Nissan Chemical Industries, Ltd., Japan. Submitted by E.I. du Pont de Nemours and Co. Inc. (Sept 30, 1987).

CONCLUSIONS:

Groups of New Zealand White female rabbits (6/group) were artificially inseminated. They were then intubated with Assure at doses of 0, 7, 25, 60, and 75 mg/kg from gestation days 7 to 19. On gestation day 29, fetuses were delivered with cesarean section from the surviving females prior to sacrifice.

During the treatment period (gestation days 7-19), the body weight and food consumption of 75 mg/kg females were decreased relative to the controls. Increased incidence of abortion was found in 60 and 75 mg/kg females compared to the controls (control, 0/6; 60 mg/kg, 1/6; 75 mg/kg, 3/6). No indications of treatment related developmental toxicity was observed during fetal examinations.

Based upon these data, 60 mg/kg was chosen as the highest dose in a full teratology study. Since the study is a dose-range-finding study, it is classified as a supplementary study.

A. MATERIALS:

Test animals: HRA: New Zealand White SPF female rabbits

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose Levels (mg/kg/day)	Dosing Schedule Day of Gestation	No. of Inseminated Female Rabbits
1 (Veh. Con)	0	7-19	6
2	7	7-19	6
3	25	7-19	6
4	60	7-19	6
5	75	7-19	6

2. Insemination of Does

Each female was intravenously administered 0.25 ml of human chorionic gonadotropin (HCG) to induce ovulation. Approximately 1 hr after HCG administration, the females were artificially inseminated with semen from a male of similar strain. Three hrs after HCG administration a second insemination was also carried out with semen from the same buck. The day of insemination was designated as "Day 0" of gestation.

3. Dose preparation

The test compound, Assure, was ground, and a desired amount was added to the vehicle which consisted of 0.5% carboxymetyhlcellulose, 0.1% Tween® 80, and a small amount of distilled water. The dosing suspension was freshly prepared daily.

The animals were intubated with the above dosages at 5 ml/kg/day on gestation days 7-19. Samples of the dosing suspension was analyzed periodically for stability and homogeneity.

The data indicated that the samples remained stable for at least 24 hrs and the concentration ranged from 83.6% to 108% of the targeted dose levels for Assure.

4. Maternal Observations:

All does were observed twice daily for any toxic effects. Individual body weights and food consumption were recorded on gestation days 0, 7, 9, 10, 12, 14, 20, 24, and 29.

During late gestation, females, which showed signs of abortion or premature delivery, were sacrificed and grossly examined for thoracic, abdominal, and pelvic abnormalities. Uteri and ovaries were examined for implantation and corpors lutea, respectively. Does, which were found dead, were also examined for the above parameters. Similar examinations were conducted at sacrifice time (gestation day 29).

5. Fetal Examination:

On gestation day 29, all surviving does were weighed and sacrificed and examined as described above. uterus from each gravid female was excised, weighed, and examined for the number and location of the implantation sites, the number of live or dead fetuses, the number of resorptions, and any of the abnormalities of the placenta.

All fetuses were weighed and examined for abnormalities. After sacrifice (by sodium pentobarbital injection), the fetuses were preserved in 10% neutral buffered formalin. After fixation each fetus was examined for any visceral and skeletal abnormalities. "Gross external, visceral, and skeletal findings were judged to be either variations or malformations."

C. Results and Discussion

1). Maternal Toxicity

During the treatment period, the mean body weights of the 75 mg/kg does were decreased (Table 1). Also, the mean body weight changes showed treatment-related drops in 25, 60, and 75 mg/kg females (Table 2). However, when the treatment stopped, the animals began to gain weight. The mean food consumption data showed decreases in food consumption in the 25, 60 and 75 mg/kg females from gestation days 12 to 24 of the study (Table 3).

Table 4 presents the data on the gravid uterus weights, carcass weights, and the net body weight changes. Although there were differences in the gravid uterus weight and no difference in the net body weight changes between the controls and the highest dose females, the small sample size of the high dose animals renders these data of little use.

Table 5 shows necropsy observations. During the post-treatment period, abortion occurred in 3/6 females of 75 mg/kg group 1/6 females of 60 mg/kg group. No abortion was seen in other test groups. Increased incidence of gallbladder enlargement was observed in 75 mg/kg females (4/6) relative to the controls (0/6), and this effect appeared to be treatment related.

2. Developmental Toxicity

a). Cesarean Section Data

The data on cesarean section are summarized in Table 6. The pregnancy rates, number of litters with resorptions, number of dead fetuses/litter, number of early or late resorptions/litter, and mean live fetal weight were similar between the control and treated groups. The mean implantation efficiencies of 60 and 75 mg/kg females were noticeably lower than that of the controls. However, the number of animals of these 2 groups at sacrifice was fewer than that of the controls (control,6; 60 mg/kg, 4; 75 mg/kg, 2). In addition, the number of implantation sites of one of the 75 mg/kg does (2 implantation sites) was far below the range of that of the control females (6-14 implantation sites).

b). Fetal Data

The incidences of external variations and malformations are summarized in Tables 7 and 8. No incidence of variations or malformation found in any fetus of the treated or control does.

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Table 1*
Mean Maternal Body Weights During Gestation (kg)
Range-Finding Rabbit Teratology Study

Gestation Day	Group: / Dose Level: (mg/kg/day)	1 / 0	2 / 7	3 / 25	4 / 60	5 / 75
0	Mean:	4.31	4.51	4.47	4.43	4.26
	S.D.:	.147	.265	.163	.067	.211
	N:	6	6	6	6	6
7	Mean:	4.38	4.63	4.56	4.58	4.40
	S.D.:	.126	.282	.201	.116	.209
	N:	6	6	6	6	6
9	Mean:	4.42	4.71	4.60	4.58	4.44
	S.D.:	.124	.266	.168	.045	.190
	N:	6	6	6	6	6
10	Mean:	4.39	4.68	4.58	4.53	4.39
	S.D.:	.109	.245	.215	.062	.185
	N:	6	6	6	6	6
12	Mean:	4.40	4.70	4.60	4.51	4.36
	S.D.:	.131	.281	.224	.139	.160
	N:	6	6	6	6	6
14	Mean:	4.46	4.71	4.56	4.47	4.21
	S.D.:	.143	.291	.150	.177	.133
	N:	6	6	6	6	6
20	Mean:	4.48	4.64	4.30	4.33	3.91
	S.D:	.125	.302	.173	.351	.148
	N:	6	6	6	6	6
24	Mean:	4.59	4.54	4.35	4.38	3.84
	S.D.:	.136	.199	.279	.498	.213
	N:	6	6	5	6	6
29	Mean:	4.51	4.47	4.29	4.64	4.11
	S.D.:	.201	.221	.363	.024	.120
	N:	6	6	5	4	2

* DATA TAKEN FROM SUBMISSION.

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Table 2 *
Mean Maternal Body Weight Changes During Gestation (kg)
Range-Finding Rabbit Teratology Study

Gestation Day	Group: / Dose Level: (mg/kg/day)	1 / 0	2 / 7	3 / 25	4 / 60	5 / 75
0-7	Mean:	.07	.12	.09	.15	.14
	S.D.:	.038	.029	.086	.078	.021
	N:	6	6	6	6	6
7-20	Mean:	.10	.02	-.26	-.25	-.48
	S.D.:	.127	.091	.276	.423	.160
	N:	6	6	6	6	6
20-29	Mean:	.04	-.17	-.00	.11	.15
	S.D.:	.144	.214	.248	.229	.078
	N:	6	6	5	4	2
0-29	Mean:	.20	-.04	-.13	.22	-.06
	S.D.:	.196	.226	.487	.093	.035
	N:	6	6	5	4	2
7-29	Mean:	.14	-.15	-.20	.10	-.19
	S.D.:	.205	.239	.442	.093	.014
	N:	6	6	5	4	2

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Table 3 *
Mean Maternal Food Consumption During Gestation (kg)
Range-Finding Rabbit Teratology Study

Gestation Day	Group: / Dose Level: (mg/kg/day)	1 / 0	2 / 7	3 / 25	4 / 60	5 / 75
0-7	Mean:	1008	1161	1156	1300	1131
	S.D.:	149.7	73.6	287.3	109.0	215.6
	N:	6	6	6	6	6
7-9	Mean:	291	414	321	311	306
	S.D.:	43.8	115.2	59.8	64.6	62.9
	N:	6	6	6	6	6
9-10	Mean:	138	199	150	132	116
	S.D.:	18.6	56.1	23.1	67.1	52.8
	N:	6	6	6	6	6
10-12	Mean:	270	365	293	210	210
	S.D.:	49.6	77.7	77.8	160.3	133.1
	N:	6	6	6	6	5
12-14	Mean:	239	295	219	173	90
	S.D.:	63.8	111.5	117.4	147.2	78.7
	N:	6	6	6	6	6
14-20	Mean:	797	750	408	482	125
	S.D.:	146.5	284.1	375.1	499.7	213.5
	N:	6	6	6	6	6
20-24	Mean:	473	177	247	318	51
	S.D.:	54.4	205.1	213.5	252.8	79.5
	N:	6	5	5	6	5
24-2_	Mean:	309	174	248	442	469
	S.D.:	149.3	254.4	144.3	352.4	137.2
	N:	6	5	5	4	2

* DATA TAKEN FROM Submission

TABLE 4*

RANGE-FINDING RABBIT TERATOLOGY STUDY

SUMMARY OF UTERINE AND NET BODY WEIGHTS (grams)

	DOSAGE	0 MG/KG/DAY	7 MG/KG/DAY	25 MG/KG/DAY	60 MG/KG/DAY	75 MG/KG/DAY
GRAVID UTERUS	MEAN	522.58	437.05	428.98	502.58	268.15a
	S.D.	123.082	77.758	134.055	79.767	179.110
	N	6	6	5	4	2
CARCASS	MEAN	3989.08	4034.62	3863.02	4139.92	3836.85
	S.D.	147.702	205.430	253.866	81.093	58.890
	N	6	6	5	4	2
NET BODY CHANGE FROM DAY 0	MEAN	-320.92	-472.05	-562.98	-280.08	-323.15
	S.D.	139.999	198.315	384.489	96.116	214.465
	N	6	6	5	4	2

CARCASS WEIGHT = TERMINAL BODY WEIGHT MINUS GRAVID UTERINE WEIGHT

NET WEIGHT CHANGE FROM DAY 0 = CARCASS WEIGHT MINUS DAY 0 BODY WEIGHT

* DATA TAKEN FROM THE submission.

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TABLE 5 *
RANGE-FINDING RABBIT TERATOLOGY STUDY
SUMMARY OF PARENTAL NECROPSY OBSERVATIONS

	DOSAGE	0 MG/ KG/DAY	7 MG/ KG/DAY	25 MG/ KG/DAY	60 MG/ KG/DAY	75 MG/ KG/DAY
DAMS	N	6	6	6	6	6
FOUND DEAD-PREGNANT	N	0	0	1	1	1
ABORTION/PREMATURE DELIVERY	N	0	0	0	1	3
SCHEDULED KILL-PREGNANT	N	6	6	5	4	2
LUNGS-PALE	N	0	0	0	0	1
LIVER-PALE	N	0	0	0	2	1
GALLBLADDER-ENLARGED	N	1	2	1	2	4
STOMACH-HAIR/MATERIAL	N	0	0	0	0	1
KIDNEY(S)-PALE	N	0	0	0	1	0
CECUM-DISTENDED	N	0	0	0	0	1

* DATA TAKEN FROM THE SUBMISSION

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Table 6 *
Summary of Cesarean Section Data
Range-Finding Rabbit Teratology Study

Group:	1	2	3	4	5
Dose Level: (mg/kg/day)	0	7	25	60	75
Number of females mated	6	6	6	6	6
Number of pregnant females	6	6	6	6	6
Pregnancy rate (%)	100	100	100	100	100
Number (%) of females surviving to Day 29 cesarean section	6 (100)	6 (100)	5 (83)	4 (67)	2 (33)
Number of females found dead	0	0	1	1	1
Number (%) of females aborting[a]	0 (0)	0 (0)	0 (0)	1 (17)	3 (50)
Number of litters with only resorptions	0	0	0	0	0
Number of litters with live fetuses	6	6	5	4	2
Mean number (%) of:					
Corpora lutea	13.2	13.5	11.8	15.0	8.0
Implantations	10.0	9.3	9.8	8.8	5.0
Live fetuses	9 (91)	7.5 (83)	8.4 (87)	7.5 (87)	5.0 (100)
Dead fetuses	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Early resorptions	0.5 (5)	1.0 (9)	1.2 (12)	1.0 (11)	0.0 (0)
Late resorptions	0.5 (4)	0.8 (8)	0.2 (2)	0.3 (3)	0.0 (0)
Total resorptions	1.0 (9)	1.8 (17)	1.4 (13)	1.3 (14)	0.0 (0)
Mean implantation efficiency (%)[b]	76	~~71~~ 68	~~88~~ 83.1	~~68~~ 58.7	~~57~~ 62.5
Mean live fetal weight (g)	38.7	36.9	32.7	41.4	37.0

[a] Includes premature delivery.

b. Some reported computations were incorrect; Reviewers calculations were presented next to the reported data

* DATA TAKEN FROM Submission

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Table 7 *
Summary of Fetal External Variations[a]
Range-Finding Rabbit Teratology Study

	Group:	1	2	3	4	5
	Dose Level: (mg/kg/day)	0	7	25	60	75
Litter evaluated	N	6	6	5	4	2
Fetuses evaluated	N	54	45	42	30	10
Live	N	54	45	42	30	10
Dead	N	0	0	0	0	0
Total fetal external variations						
Fetal incidence	N	0	0	0	0	0
	%	0	0	0	0	0
Litter incidence	N	0	0	0	0	0
	%	0	0	0	0	0

[a] Includes females at scheduled cesarean section only.

* DATA TAKEN FROM SUBMISSION

Table 8 *
Summary of Fetal External Malformations[a]
Range-Finding Rabbit Teratology Study

	Group:	1	2	3	4	5
	Dose Level: (mg/kg/day)	0	7	25	60	75
Litter evaluated	N	6	6	5	4	2
Fetuses evaluated	N	54	45	42	30	10
Live	N	54	45	42	30	10
Dead	N	0	0	0	0	0
Total fetal external malformations						
Fetal incidence	N	0	0	0	0	0
	%	0	0	0	0	0
Litter incidence	N	0	0	0	0	0
	%	0	0	0	0	0

[a] Includes females at scheduled cesarean section only.

* DATA TAKEN From Submission

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Reviewed by: Whang Phang, Ph.D. Whang Phang 12/28/87
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C) M van Gemert 1/4/88

DATA EVALUATION REPORT

STUDY TYPE: Teratology Study-Rabbit

ACCESSION NUMBER: 403705-02 TOX. CHEM. NO.: 215D

TEST MATERIAL: Assure or NC-302 (Technical)
(99.1% pure; white solid)

CITATION: Morseth, S.L. (1987). ~~Range-Finding~~ Rabbit Teratology Study. Hazleton Laboratories America, Inc.; HLA Study No. 2096-132. Study Sponsor: Nissan Chemical Industries, Ltd., Japan. Submitted by E.I. du Pont de Nemours and Co. Inc. (Oct 8, 1987).

CONCLUSIONS: When groups of 16 presumed pregnant rabbits were intubated with Assure at doses of 0, 7, 20, and 60 mg/kg from gestation days 7-19, no evidence of developmental toxicity was observed. The NOEL for developmental toxicity was 60 mg/kg (HDT).

Decreases in food consumption and body weight gain were observed in 60 mg/kg does. Based upon thses findings, the LEL for maternal toxicity was 60 mg/kg; NOEL, 20 mg/kg. The study is classified as Core Minimum.

A. MATERIALS:

Test animals: HRA: New Zealand White SPF female rabbits which were obtained from Hazleton Research Products, Inc., Denver, PA.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly "via a weight randomization Program" to the following groups:

Test Group	Dose Levels (mg/kg/day)	Dosing Schedule Day of Gestation	No. of Inseminated Female Rabbits
1 (Veh. Con)	0	7-19	16
2 (Low)	7	7-19	16
3 (Mid)	20	7-19	16
4 (High)	60	7-19	16

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2. Insemination

Each female was intravenouly administered 0.25 ml of human chorionic gonadotropin (HCG) to induce ovulation. Approximately 1 hr after HCG administration, the females were artificially inseminated with semen from a male of similar strain. Four hrs after HCG aministration a second insemination was also carried out with semen from the same buck. Prior to insemination, the semen was evaluated for viability and motility. The day of insemination was designated as "Day 0" of gestation.

3. Dose preparation

Doses of Assure were selected based upon the findings of a dose-range-finding study (EPA Accession No. 403705-01). In that study, dose levels of 0, 7, 25, 60, and 75 mg/kg were used. Females of 75 mg/kg showed decreased food consumption and body weight. Increased incidence of abortion was also observed in 60 and 75 mg/kg does relative to the controls (Control, 0/6; 60 mg/kg, 1/6; 75 mg/kg, 3/6). Based upon these observations, it appeared that 60 mg/kg was appropriately chosen as the highest dose for this study.

The test compound, Assure, was ground, and a desired amount was added to the vehicle which consisted of 0.5% carboxymetyhlcellulose, 0.1% Tween® 80, and a small amount of distilled water. The dosing suspension was freshly prepared daily.

The animals were intubated with the above dosages at 5 ml/kg/day on gestation days 7-19. Samples of the dosing suspension was analyzed periodically for stability and homogeneity.

The data indicated that the samples remained stable for at least 24 hrs and the concentration ranged from 88% to 101% of the targeted dose levels.

4. Maternal Observation:

All females were observed daily for for mortalicy and toxicity. Individual body weights were recorded on gestation days 0, 7, 9, 10, 15, 20, 24, and 29. Food consumption was recorded on gestation days 0, 7, 9, 11, 15, 20, 24, and 29.

During late gestation, does exhibiting signs of abortion or premature delivery were sacrificed and examined grossly for

abnormalities of the thoracic, abdominal, and pelvic viscera. Uteri and ovaries were examined for number of implantations and corpora lutea, respectively. In addition, the number of early and late resorptions, dead fetuses, or apparently normally developing fetuses was recorded. Does which were found dead were also examined in a similar manner as described above.

5. Cesarean Section:

On day 29 of gestation, all surviving does were weighed, sacrificed, and examined as decribed above. In addition, the uterus from each pregnant female was excised, weighed, and examined as previously described.

Each fetus was weighed and examined for external anomalies. Subsequent to external examination, each fetus was sacrificed and examined for skeletal and visceral variations and malformations. The procedures used are presented in the Attachment A.

6. Statistical Analyses:

The statistical analyses of the data are presented in attachment B.

RESULTS:

Materanl Toxicity

1. Clinical Observations: No treatment-related effects were observed except sporadic findings such as alopecia, soft feces, and ocular discharge (lacrimation and clear discharge) in all groups of the experimental animals.

2. Body Weights, Body Weight Changes, and Food Consumption: In 60 mg/kg females, there was a decrease in mean maternal body weight gain during the dosing period (gestation days 7-20). During the post-treatment period (gestation days 20-29), the mean body weight gain was significantly elevated relative to the controls (Table 1).

Accordingly, during the dosing period there was a drop in food consumption in the 60 mg/kg females relative to the controls (Table 2). The decrease in food consumption durig dosing period and a significant increase in body weight gain during the post-treatment period in 60 mg/kg animals indicated a compound-related effect.

3. Uterine Weight: Although the mean gravid uterine weights of 20 and 60 mg/kg rabbits were decreased relative to the controls, no dose-related trend or statistical significance in uterine weight changes was observed (Table 3).

4. Gross Pathology: No treatment-related gross pathology was observed in treated rabbits relative to the controls (Table 4).

CESAREN RESULTS

Pregnancy rates, mean number of corpora lutea, and mean number of implantations were comparable between treated and control animals (Table 5).

FETOXICITY:

Mean number of live fetuses in 20 and 60 mg/kg animals appeared to be decreased relative to the controls, but the decrease is not statistically significant (Table 5).

No difference was observed in fetal weights when the mean body weight was compared to that of the controls (Table 5).

No fetal external malformations or variations were reported.

The incidence of soft tissue variations and malformations was comparable between treated and control groups (Table 6).

For fetal skeletal variations, there was a statistically significant increase in incidence of 26-presacral vertebrae in the fetuses of 7 and 20 mg/kg groups (Table 7); however, this increase was not dose-related, and the increase in 60 mg/kg fetuses was marginal. Therefore, this incidence could not be considered as a treatment-related effect.

The incidence of fetal skeletal malformation in treated animals was similar to that of the controls (Table 8).

DISCUSSION:

Based upon the reported data, there was no evidence of developmental toxicity in fetuses of treated females; the NOEL for developmental toxicity was 60 mg/kg (HDT). The females of 60 mg/kg showed decreases in food consumption and body weight gain during the treatment period (gestation days 7-19). Based upon these observations, the LEL for maternal toxicity was 60 mg/kg; NOEL, 20 mg/kg.

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Table 1 +
Mean Maternal Body Weight Change Values During Gestation (kg)
Rabbit Teratology Study

Cestation Days	Group: / Dose Level: (mg/kg/day)	1 / 0	2 / 7	3 / 20	4 / 60
0-7	Mean	.12	.13	.10	.12
	S.D.	.061	.071	.062	.061
	N	14	14	13	15
7-9	Mean	.03	-.002	.61	.04
	S.D.	.060	.092	.057	.067
	N	14	14	13	15
7-20	Mean	.17	.07	.14	.08
	S.D.	.087	.168	.152	.232
	N	13	14	13	15
20-29	Mean	.12	.14	.12	.22*
	S.D.	.087	.080	.062	.142
	N	13	14	12	15
0-29[a]	Mean	.40	.34	.39	.42
	S.D.	.108	.178	.100	.214
	N	13	14	12	15
7-29	Mean	.29	.21	.28	.30
	S.D.	.121	.166	.111	.186
	N	13	14	12	15

* Significantly different from control value, $p \leq 0.05$.
a Statistical analysis was performed on rank-transformed data.

+ TAKEN FROM submission

Table 2 +
Mean Maternal Food Consumption During Gestation (g/interval/animal)
Rabbit Teratology Study

Gestation Days	Group: / Dose Level: (mg/kg/day)	1 / 0	2 / 7	3 / 20	4 / 60
0-7	Mean	1162.0	1135.1	1023.1	1045.4
	S.D.	163.99	132.88	171.70	139.02
	N	13	14	13	15
7-9	Mean	334.9	325.6	317.2	303.7
	S.D.	106.28	42.53	43.84	94.42
	N	14	14	13	15
9-11[a]	Mean	319.4	335.4	329.1	261.6
	S.D.	29.68	69.11	44.56	119.31
	N	13	14	13	15
11-15	Mean	597.2	585.9	583.1	542.7
	S.D.	70.00	160.85	80.97	187.75
	N	13	14	13	15
15-20	Mean	780.2	687.5	653.2	680.5
	S.D.	133.30	252.13	216.86	294.24
	N	13	13	13	15
20-24	Mean	570.3	514.0	516.3	636.5
	S.D.	97.67	155.97	219.59	230.05
	N	13	14	13	15
24-29	Mean	513.7	524.7	513.7	608.5
	S.D.	143.87	170.14	187.05	136.56
	N	13	14	12	15
7-20	Mean	2025.8	1943.1	1882.5	1788.8
	S.D.	257.56	472.95	310.72	627.27
	N	13	13	13	15

[a] Statistical analysis was performed on rank-transformed data.

+ TAKEN FROM Submission

TABLE 3+
RABBIT TERATOLOGY STUDY
SUMMARY OF UTERINE AND NET BODY WEIGHTS (grams)

	DOSAGE	0 MG/KG	7 MG/KG	20 MG/KG	60 MG/KG
GRAVID UTERUS	MEAN	432.27	420.83	362.25	391.85
	S.D.	95.900	118.258	123.439	112.557
	N	11	11	10	12
CARCASS	MEAN	3415.00	3329.17	3317.75	3308.98
	S.D.	196.366	274.720	343.089	261.453
	N	11	11	10	12
NET BODY WEIGHT CHANGE FROM DAY 0	MEAN	-37.73	-69.01	14.75	90.65
	S.D.	127.378	178.649	147.746	131.985
	N	11	11	10	12

NOTE: Excludes animals with no viable fetuses.

+DATA TAKEN FROM Submission.

TABLE 4 +
RABBIT TERATOLOGY STUDY
SUMMARY OF PARENTAL NECROPSY OBSERVATIONS

DOSAGE		0 MG/KG	7 MG/KG	20 MG/KG	60 MG/KG
DAMS	N	16	16	16	16
FOUND DEAD-PREGNANT	N	1	0	0	0
ACCIDENTAL DEATH-NOT PREGNANT	N	0	0	1	0
ABORTION/PREMATURE DELIVERY	N	0	0	1	0
SCHEDULED KILL-PREGNANT	N	13	14	12	15
SCHEDULED KILL-NOT PREGNANT	N	2	2	2	1
LUNGS-DARK AREAS	N	1	0	0	0
LUNGS-INFLATED	N	1	0	0	0
STOMACH-HAIR/MATERIAL	N	1	0	1	0
CYST(S)	N	1	2	0	0
UTERUS-STAINED POSITIVE	N	0	0	1	0

+ TAKEN FROM SUBMISSION

Table 5+
Summary of Cesarean Section Data
Rabbit Teratology Study

Group:	1	2	3	4
Dose Level: (mg/kg/day)	0	7	20	60
Number of females mated	16	16	16	16
Number of pregnant females	14	14	13	15
Pregnancy rate (%)	88	88	81	94
Number of females surviving to Day 29 cesarean section (%)	15(94)	16(100)	14(88)	16(100)
Number of females found dead	1	0	0	0
Number of females aborting (%)	0	0	1(8)	0
Number of accidental deaths	0	0	1	0
Number of litters with only resorptions	2	3	2[a]	3
Number of litters with live fetuses	11	11	10	12
Mean number (%) of:				
Corpora lutea	9.2	9.9	9.4	9.8
Implantations	7.0	6.8	6.3	7.1
Live fetuses (includes all pregnancies)	5.8(78)	5.6(71)	4.8(73)	5.2(65)
Live fetuses in litters with live fetuses	6.9(93)	7.2(90)	5.7(87)	6.5(82)
% male fetuses	(54)	(46)	(49)	(43)
Dead fetuses	0 (0)	0 (0)	0 (0)	0 (0)
Early resorptions	1.0(20)	1.1(28)	1.4(24)	1.9(35)
Late resorptions	0.2 (2)	0.1 (1)	0.2 (3)	0.0 (0)
Total resorptions	1.2(22)	1.1(29)	1.6(27)	1.9(35)
Mean implantation efficiency (%)	(77)	(67)	(69)	(74)
Mean live fetal weight - grams	43.9	40.4	44.6	41.8
Mean live male fetal weight - grams	43.9	39.6	46.6	41.7
Mean live female fetal weight - grams	43.8	40.9	42.7	41.6

[a] Group 3 female Number E44135 determined to be pregnant by staining of uterus.

+ TAKEN FROM SUBMISSION

TABLE 6
RABBIT TERATOLOGY STUDY
SUMMARY OF FETAL SOFT TISSUE VARIATIONS + Malformations

	DOSAGE	0 MG/KG	7 MG/KG	20 MG/KG	60 MG/KG
Litters Evaluated	N	11	11	10	12
Fetuses Evaluated	N	76	79	57	78
Live	N	76	79	57	78
Dead	N	0	0	0	0
VARIATION(S) OF THE MAJOR VESSELS					
Fetal Incidence	N	3	1	6	0
	%	3.9	1.3	11	0.0
Litter Incidence	N	2	1	3	0
	%	18	9.1	30	0.0
HEART AND/OR GREAT VESSEL VARIATION					
Fetal Incidence	N	0	3	0	1
	%	0.0	3.8	0.0	1.3
Litter Incidence	N	0	2	0	1
	%	0.0	18	0.0	8.3
INTERMEDIATE LOBE OF LUNG MISSING/SMALL					
Fetal Incidence	N	2	4	2	1
	%	2.6	5.1	3.5	1.3
Litter Incidence	N	2	3	2	1
	%	18	27	20	8.3
TOTAL FETAL SOFT TISSUE VARIATIONS					
Fetal Incidence	N	5	8	8	2
	%	6.6	10	14	2.6
Litter Incidence	N	4	6	4	2
	%	36	55	40	17
TOTAL FETAL SOFT TISSUE MALFORMATIONS					
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

Data taken from submission

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TABLE 7

TABLE 7
RABBIT TERATOLOGY STUDY
SUMMARY OF FETAL SKELETAL VARIATIONS

DOSAGE		0 MG/KG	7 MG/KG	20 MG/KG	60 MG/KG
Litters Evaluated	#	11	11	10	12
Fetuses Evaluated	#	76	79	57	78
Live	#	76	79	57	78
Dead	#	0	0	0	0
UNOSSIFIED HYOID BODY					
Fetal Incidence	#	1	0	0	0
	%	1.3	0.0	0.0	0.0
Litter Incidence	#	1	0	0	0
	%	9.1	0.0	0.0	0.0
ANGULATED HYOID WING(S)					
Fetal Incidence	#	1	7	0	2
	%	1.3	8.9	0.0	2.6
Litter Incidence	#	3	1	0	2
	%	27	16	0.0	17
ACCESSORY BONE(S) IN SKULL					
Fetal Incidence	#	3	1	1	5
	%	3.9	1.3	1.8	6.4
Litter Incidence	#	0	1	1	4
	%	0.0	9.1	10	33
26 PRESACRAL VERTEBRAE					
Fetal Incidence	#	0	1	0	2
	%	0.0	1.3	0.0	2.6
Litter Incidence	#	0	1	0	2
	%	0.0	9.1	0.0	17
24 PRESACRAL VERTEBRAE					
Fetal Incidence	#	3	20*	9*	2
	%	3.9	25	16	2.6
Litter Incidence	#	3	8	5	5
	%	27	73	50	42
BIPARTITE VERTEBRAL CENTRUM(A)					
Fetal Incidence	#	0	0	0	1
	%	0.0	0.0	0.0	1.3
Litter Incidence	#	0	0	0	1
	%	0.0	0.0	0.0	8.3
HEMICENTRUM(A)					
Fetal Incidence	#	0	0	0	1
	%	0.0	0.0	0.0	1.3
Litter Incidence	#	0	0	0	1
	%	0.0	0.0	0.0	8.3
LESS THAN 16 CAUDAL VERTEBRAE OSSIFIED					
Fetal Incidence	#	1	0	0	1
	%	1.3	0.0	0.0	1.3
Litter Incidence	#	1	0	0	1
	%	9.1	0.0	0.0	8.3
MISALIGNED OR BIPARTITE CAUDAL VERTEBRA(E)					
Fetal Incidence	#	1	1	0	1
	%	1.3	1.3	0.0	1.3
Litter Incidence	#	1	1	0	1
	%	9.1	9.1	0.0	8.3
5TH STERNEBRA UNOSSIFIED					
Fetal Incidence	#	8	8	4	14
	%	11	10	7.0	18
Litter Incidence	#	5	3	1	6
	%	45	27	10	67
13TH UNILATERAL FULL RIB					
Fetal Incidence	#	7	3	3	3
	%	9.2	3.8	5.3	3.8
Litter Incidence	#	6	3	2	3
	%	55	27	20	25
13TH RUDIMENTARY RIB(S)					
Fetal Incidence	#	4	7	6	12
	%	5.3	8.9	11	15
Litter Incidence	#	5	6	6	6
	%	45	55	60	50
14TH RIBS, ONE FULL, ONE RUDIMENTARY					
Fetal Incidence	#	0	0	0	1
	%	0.0	0.0	0.0	1.3
Litter Incidence	#	0	0	0	1
	%	0.0	0.0	0.0	8.3
THICKENED RIB(S)					
Fetal Incidence	#	4	0	0	0
	%	5.3	0.0	0.0	0.0
Litter Incidence	#	3	0	0	0
	%	27	0.0	0.0	0.0
TOTAL FETAL SKELETAL VARIATIONS					
Fetal Incidence	#	52	62	41	55
	%	68	78	72	71
Litter Incidence	#	11	11	9	12
	%	100	100	90	100
6TH STERNEBRA UNOSSIFIED					
Fetal Incidence	#	2	2	3	1
	%	2.6	2.5	5.3	1.3
Litter Incidence	#	1	1	2	1
	%	9.1	9.1	20	8.3
FUSED STERNEBRAE (POINT/CHAIN)					
Fetal Incidence	#	2	1	0	1
	%	2.6	1.3	0.0	1.3
Litter Incidence	#	2	1	0	1
	%	18	9.1	0.0	8.3
STERNEBRAE ASSYMETRICALLY OSSIFIED					
Fetal Incidence	#	0	1	2	0
	%	0.0	1.3	3.5	0.0
Litter Incidence	#	0	1	2	0
	%	0.0	9.1	20	0.0
13 FULL PAIRS RIBS					
Fetal Incidence	#	25	16	20	17
	%	33	20	35	22
Litter Incidence	#	7	8	8	9
	%	64	73	80	75
13TH RIBS, ONE FULL, ONE RUDIMENTARY					
Fetal Incidence	#	4	5	7	11
	%	5.3	6.3	12	14
Litter Incidence	#	3	3	6	9
	%	27	27	60	75

* Significantly different from control value, $p \leq 0.05$.

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TABLE 8
RABBIT TERATOLOGY STUDY
SUMMARY OF FETAL SKELETAL MALFORMATIONS

DOSAGE		0 MG/KG	7 MG/KG	20 MG/KG	60 MG/KG
Litters Evaluated	N	11	11	10	12
Fetuses Evaluated	N	76	79	57	78
Live	N	76	79	57	78
Dead	N	0	0	0	0
FUSED CERVICAL VERTEBRA(E)					
Fetal Incidence	N	1	0	0	0
	%	1.3	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0
	%	9.1	0.0	0.0	0.0
VERTEBRAL ANOMALY WITH/WITHOUT ASSOCIATED RIB ANOMALY					
Fetal Incidence	N	1	3	3	0
	%	1.3	3.8	5.3	0.0
Litter Incidence	N	1	3	3	0
	%	9.1	27	30	0.0
MISALIGNED LUMBAR AND/OR SACRAL VERTEBRA(E)					
Fetal Incidence	N	0	1	0	0
	%	0.0	1.3	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	9.1	0.0	0.0
BENT/TWISTED CLAVICLE					
Fetal Incidence	N	0	1	0	0
	%	0.0	1.3	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	9.1	0.0	0.0
FORKED/FUSED RIB(S)					
Fetal Incidence	N	0	1	0	0
	%	0.0	1.3	0.0	0.0
Litter Incidence	N	0	1	0	0
	%	0.0	9.1	0.0	0.0
TOTAL FETAL SKELETAL MALFORMATIONS					
Fetal Incidence	N	1	4	3	0
	%	1.3	7.4	5.3	0.0
Litter Incidence	N	1	4	3	0
	%	9.1	36	30	0.0

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