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CASWELL FILE

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

010352

JUN 22 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: SULFLURAMID - Comments and Rebuttals to Reviews
TO: Mike Mendelsohn
PM Team Reviewer (18)
Registration Division (H7505C)
FROM: Linda L. Taylor, Ph.D. *Linda Lee Page 6/21/93*
Toxicology Branch II, Section II,
Health Effects Division (H7509C)
THRU: K. Clark Swentzel *K. Clark Swentzel 6/21/93*
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. *Marcia van Gemert 6/21/93*
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: Griffin Corporation
Chemical: N-ethyl perfluorooctanesulfonamide
Synonym: GX-071; Sulfluramid
Case No.: 004595
Caswell No.: 454E
Shaughnessy No.: 128992
Submission No.: S436490
Identifying No.: 001812-00327
DP Barcode: D190072
MRID No.: 426335-01 and 426335-02
Action Requested: Please review the enclosed responses to David Liem's reviews of 8/1/92 and 8/2/92.

Comment: The Registrant has submitted (1) an addendum to MRID # 417994-02 [Acute Oral Studies]: Identification of Sulfluramid Containing Salts (MRD 89-470 and MRD 89-471), which was given the MRID # 426335-01 and (2) an addendum to MRID # 417994-08 [Developmental Toxicity Study in Rabbits with Sulfluramid], which was given the MRID # 426335-02.

1) A Certificate of Analysis for both Sulfluramid sodium salts (MRD 89-470 and MRD 89-471) used in two of the acute oral toxicity studies reviewed previously (TB II memo dated 8/2/92) has been provided.

MRD 89-470: Sulfluramid sodium salt, linear isomer - 68.5%
Sulfluramid sodium salt, branched isomer - 31.5%

MRD 89-471: Sulfluramid sodium salt, linear isomer - 84.9%
Sulfluramid sodium salt, branched isomer - 15.2%

The information submitted is adequate, and both studies can be upgraded to Core Supplementary.

2) Two range-finding studies, which were used as the basis for dose selection for the rabbit developmental toxicity study, have been submitted, and each has been reviewed [DER's attached]. Dose levels in the first study proved to be too high (5, 25, 50, and 150 mg/kg/day). Deaths occurred at the two highest dose levels, and body-weight/gain and food consumption were reduced at all dose levels. The second study used doses of 0.3, 1.0, and 3.0 mg/kg, which did not affect survival or pregnancy rate, but overall body-weight change and food consumption at all dose levels was reduced. One abortion occurred at the high dose, which was considered treatment-related, and there appeared to be a dose-related decrease in the number of implants and viable fetuses. Based on the results of both range-finding studies, the dose levels chosen for the definitive developmental toxicity study were 0.1, 0.5, and 1.5 mg/kg. Considering the magnitude of the differences in body weight gain and food consumption in all of the dose groups compared to the control value, these dose levels appear to be appropriate. Based on the above, the rabbit developmental toxicity study can be upgraded to Core Minimum. The maternal and developmental toxicity NOEL's can be set at 1.5 mg/kg, the highest dose tested. The definitive rabbit developmental toxicity study [MRID # 417994-08] satisfies the guideline requirement [83-3(b)] for a developmental toxicity study in the rabbit.

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Reviewed by: Linda L. Taylor, Ph.D.
Section II, Tox. Branch II (H7509C)
Secondary Reviewer: K. Clark Swentzel
Section II Head, Tox. Branch II (H7509C)

Linda Lee Taylor 4/21/93
K. Clark Swentzel 6/21/93

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity rabbit (dose range-finding)

TOX. CHEM. NO.: 454E

SHAUGHNESSY NO.: 128992

MRID NO.: 426335-02

TEST MATERIAL: Sulfluramid

SYNONYMS: N-ethyl perfluorooctanesulfonamide; GX-071

STUDY NUMBER: PH 329DR-GC-001-90

SPONSOR: Griffin Corporation/Valdosta, GA

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Dose-Range-Finding Developmental Toxicity Study in Rabbits

AUTHOR: DJ Margitich

REPORT ISSUED: October 5, 1990

QUALITY ASSURANCE: No quality assurance statement was provided, but a statement was provided in the report [page 3 of 39] that indicates that the study is not required to meet GLP requirements. This conflicts with a GLP statement on page 3 of 82, which indicates that the study was performed in compliance with GLP standards.

CONCLUSIONS: Under the conditions of the study, dose levels of 0.3, 1.0, and 3.0 mg/kg/day did not affect survival or pregnancy rate, but overall body-weight change and food consumption at all dose levels was reduced. One abortion occurred at the high dose, which was considered treatment-related, and there appeared to be a dose-related decrease in the number of implants and viable fetuses. This study was a range-finding study used to determine the dose levels to be used in the definitive developmental toxicity study. Based on the results of both range-finding studies, the dose levels chosen for the definitive developmental toxicity study were 0.1, 0.5, and 1.5 mg/kg. Considering the magnitude of the differences in body weight gain and food consumption in all of the dose groups compared to the control value, these dose levels appear to be appropriate.

Classification: Acceptable. This is a range-finding study, which does not satisfy the guideline requirement (83-3) for a developmental toxicity study in the rabbit nor was it intended to do so.

A. MATERIALS

1. Test Compound: Sulfluramid; Description: white powder (Material Safety Data Sheet lists white color needle-like crystals; bland odor); Batch #: Lot # AN-90247; Purity: % not provided ; Source: Pharmakon Research International, Inc..
2. Test Animals: Species: rabbit; Strain: New Zealand White; Age: ♂♂ 7 months/♀♀ 5.5-6 months at study start; Weight: 3.394-4.340 kg; Source: Hare-Marland, Hewitt, NJ.
3. Statistics: Maternal body weight, weight changes, and food consumption: one way analysis of variance using Dunnett's test to determine significance of differences from control. Non-parametric statistics were used when variances were significantly different using Bartlett's Test. The number of early resorptions, pre-implantation losses, and post implantation losses and the percentages of these resorptions and losses were compared by Kruskal-Wallis and Mann-Whitney U-test to judge the significance of the difference. Statistics were calculated using Systat by Systat, Inc. Evanston, IL.

B. STUDY DESIGN

Groups of four female rabbits [artificially inseminated with semen from untreated proven bucks; prior to insemination were administered chorionic gonadotropin (Lot # 18A013; Lyphomed, Inc.), via the marginal ear vein] were administered (oral intubation) the test material or vehicle control once daily from day 6-18 of gestation. The dose levels were 0, 0.3, 1.0, and 3.0 mg/kg/day administered in a dosing volume of 3 mL/kg. The vehicle control rabbits were administered 0.5% methylcellulose. The rabbits were acclimated for 7 days prior to study initiation, selected according to body weight, and assigned sequentially to a group as they became inseminated. Each female was housed individually. The total dose administered each day was based on day 6 body weights. Throughout the study, Purina Certified Rabbit Chow #5322 (Lot # 1027892A) and tap water were available ad libitum. This is a dose range-finding study; doses were based on the previous range-finding study (Study # PH 329-GC-001-89).

Dose Preparation: The solutions of test material (dosage levels: 0.3, 1.0, and 3.0 mg/kg) were prepared daily. The dosing solutions were not analyzed. Data are available in the definitive study.

RESULTS

Information on the stability and concentration of the test material in the vehicle was not provided in the report. It was stated that the purity, identity, strength, and stability of the test material are the responsibility of the sponsor.

C. Clinical Observations

Each doe was examined at least once daily for mortality, moribundity, general appearance, and behavior, and detailed clinical observations

were recorded. Individual body weights were recorded on gestation days 0, 6, 12, 18, 24, and 29, and food consumption was recorded every two days. Gravid uterine weight, net body weight (day 29 body weight minus the weight of gravid uterus), and actual body weight were recorded on day 29.

D. Terminal Procedures

On Day 29 of gestation, all surviving does were sacrificed via an i.v. injection of Beuthanasia-D Special euthanasia solution.

E. Uterine/Implantation Data

The uterus of each doe was excised, weighed, and the number of corpora lutea on each ovary, the number and location of viable and non-viable fetuses, early and late resorptions, and the total number of implantations were recorded.

F. Fetal Data

Fetuses were examined for gross external morphological observations.

RESULTS

1. Clinical Observations and Survival - Maternal

All does survived to study termination. Clinical signs observed during the study include scant feces for 2 days in one control doe, moderate diarrhea in 1 low-dose doe, scant feces in one low- and three mid-dose does, with one of the latter displaying absences of feces and alopecia also. Two high-dose does displayed slight diarrhea, minimal feces, absence of feces, alopecia, and anorexia.

2. Maternal Body Weight and Body-weight Gain

Body weights were comparable among the groups at study initiation (day 0), and all groups gained weight between days 0 and 6. The high-dose does displayed a decrease in body weight between days 6 and 12 and days 18 and 24. The low- and mid-dose does displayed a decrease in body weight between days 24 and 29. The overall gain was negative for all groups, but the treated groups displayed a deficit that was 300 to 400% of the control value.

Table 1. Body Weight (% of Control)

Day/Dose	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
0	103	101	99
6	101	99	97
12	101	98	95
18	100	97	94
24	98	95	89
29	96	93	91

Table 2. Body-weight Gains [kilograms]

Dose (mg/kg) Time Interval	0	0.3	1.0	3.0
0-6	0.187	0.109	0.120	0.115
6-12	0.051	0.050	0.007	-0.032
12-18	0.146	0.085	0.071	0.060
18-24	0.105	0.030	0.035	-0.098
24-29	0.023	-0.075	-0.070	0.008
6-18	0.197	0.134	0.078	0.028
0-29	0.513	0.198	0.162	0.155
0-29 (corrected)	-0.081	-0.293	-0.267	-0.302

Gravid uterine weight was not provided; however, subtracting corrected body weight from day 29 body weight for the control and 0.3, 1.0, and 3.05 mg/kg dose groups shows a control value of 0.593 kg and 0.490, 0.429, and 0.390, respectively for the treatment groups (83, 72, and 66% of control). The corrected body weight among the groups was comparable.

3. Food Consumption

Food consumption was severely affected (see Table 3) at all dose levels from day 10 on (except at low dose for days 18-20 and mid dose for days 28-29).

Table 3. Food Consumption (% of control value)

Interval/Dose	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
0-2	77	98	96
2-4	78	95	93
4-6	86	96	85
6-8	98	94	91
8-10	102	104	83
10-12	84	82	63
12-14	67	82	55
14-16	68	74	50
16-18	87	72	62
18-20	98	72	46
20-22	88	69	39
22-24	73	69	32
24-26	58	61	57
26-28	60	50	68
28-29	66	140	86

4. Gross Pathological Observations

None were reported.

5. Maternal Observations

Pregnancy rate was 100% in all groups. One high-dose doe aborted on gestation day 25, but there were no premature deliveries. Although there were no statistically significant differences observed with respect to the number of corpora lutea, viable fetuses, implants, resorptions, pre-/post-implantation losses (N=4), a dose-related decrease was noted for the numbers of implants and viable fetuses compared to the concurrent control. The Cesarean section observations

are listed below (only summary data were provided).

Cesarean Section observations

GROUP (mg/kg)	0	0.3	1.0	3.0
# Females inseminated	4	4	4	4
# Pregnant Females	4	4	4	4
Pregnancy Rate (%)	100	100	100	100
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	0	0	0	0
#Aborted	0	0	0	1
#Premature Delivery	0	0	0	0

Table 4. Group Mean Observations

Parameter/Dose	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Total # implants	10.0	8.5	7.8	7.7
# viable fetuses	9.0	8.3	7.0	6.7
# non-viable fetuses	0.5	0.3	0.8	0.7
# early resorptions	0.5	0	0	0.3
# late resorptions	0	0	0	0
# corpora lutea	13.3	10.8	10.8	10.3
Pre-implantation loss [# (%)]	3.3 (23.5)	2.3 (22.0)	3.0 (24.9)	2.7 (32.4)
Post implantation loss [# (%)]	1.0 (9.2)	0.3 (5.0)	0.8 (7.3)	1.0 (9.3)

6. Fetal Observations

Eight fetal deaths (2, 1, 3, 2 from the control, low-, mid-, and high-dose groups, respectively) were observed. Reduced physical development (lack of bone ossification) was observed in the dead fetuses from all groups. Also noted were hydramnios and maceration in all dead fetuses, and the high-dose fetus also displayed a pale placenta and was edematous. No gross malformations were detected, although one fetus from the high-dose group displayed abnormal flexure and inward curvature of the left forepaw.

D. Discussion

The purpose of this study was to determine the appropriate dose levels to be used in a definitive developmental toxicity study. Because of the unexpected toxicity noted in the previous range-finding study (Study # PH 329-GC-001-89), reviewed in a separate DER, the current study was performed. There was no effect of treatment on survival or pregnancy rate. One high-dose doe aborted on day 25, which is considered to be treatment-related. There was a decrease in the overall body-weight change and food consumption at all dose levels during the study. There was a dose-related decrease in the number of implants and viable fetuses, but due to the small number of does/group, statistical significance was not attained.

D. CONCLUSION

Under the conditions of the study, dose levels of 0.3, 1.0, and 3.0 mg/kg/day did not affect survival or pregnancy rate, but overall body-

weight change and food consumption at all dose levels was reduced. One abortion occurred at the high dose, which was considered treatment-related, and there appeared to be a dose-related decrease in the number of implants and viable fetuses. Based on the results of both range-finding studies, the dose levels chosen for the definitive developmental toxicity study were 0.1, 0.5, and 1.5 mg/kg. Considering the magnitude of the differences in body weight gain and food consumption in all of the dose groups compared to the control value, these dose levels appear to be appropriate.

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Section II Head, Tox. Branch II (H7509C)

Linda Lee Taylor 4/21/93
K. Clark Swentzel 6/21/93

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity rabbit (dose range-finding)

TOX. CHEM. NO.: 454E

SHAUGHNESSY NO.: 128992

MRID NO.: 426335-02

TEST MATERIAL: Sulfluramid

SYNONYMS: N-ethyl perfluorooctanesulfonamide; GX-071

STUDY NUMBER: PH 329DR-GC-001-89

SPONSOR: Griffin Corporation/Valdosta, GA

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA

TITLE OF REPORT: Dose-Range-Finding Developmental Toxicity Study in Rabbits

AUTHOR: DJ Margitich

REPORT ISSUED: October 5, 1990

QUALITY ASSURANCE: No quality assurance statement was provided, but a statement was provided in the report [page 3 of 39] that indicates that the study is not required to meet GLP requirements. This conflicts with a GLP statement on page 3 of 82, which indicates that the study was performed in compliance with GLP standards.

CONCLUSIONS: This range-finding study was to be used to determine the dose levels for the definitive developmental toxicity study. Under the conditions of the study, the dose levels chosen [5, 25, 50, and 150 mg/kg] were too high; a second range-finding study was performed using dose levels of 0.3, 1.0, and 3.0 mg/kg.

Classification: Acceptable. This is a range-finding study, which does not satisfy the guideline requirement (83-3) for a developmental toxicity study in the rabbit nor was it intended to do so.

A. MATERIALS

1. Test Compound: Sulfluramid; Description: white powder (Material Safety Data Sheet lists white color needle-like crystals); Batch #: Lot # AN-90247; Purity: % not provided ; Source: Pharmakon Research International, Inc..
2. Test Animals: Species: rabbit; Strain: New Zealand White; Age: ♂♂ 7 months/♀♀ 5.5-6 months at study start; Weight: 3.427-4.153 kg; Source: Hare-Marland, Hewitt, NJ.
3. Statistics: Maternal body weight, weight changes, and food consumption: one way analysis of variance using Dunnett's test to determine significance of differences from control. Non-parametric statistics were used when variances were significantly different using Bartlett's Test. Statistics were calculated using Systat by Systat, Inc. Evanston, IL.

B. STUDY DESIGN

Groups of four female rabbits [artificially inseminated with semen from untreated proven bucks; prior to insemination were administered chorionic gonadotropin (Lot # 18A013; Lyphomed, Inc.), via the marginal ear vein] were administered (oral intubation) the test material or vehicle control once daily from day 6-18 of gestation. The dose levels were 0, 5, 25, 50, and 150 mg/kg/day administered in a dosing volume of 3 mL/kg. The vehicle control rabbits were administered corn oil for 2 days and then 0.5% methylcellulose for the rest of the dosing period. The rabbits were acclimated for 22 days prior to study initiation, selected according to body weight, and assigned sequentially to a group as they became inseminated. Each female was housed individually. The total dose administered each day was based on day 6 body weights. Throughout the study, Purina Certified Rabbit Chow #5322 (Lot # 1027892A) and tap water were available ad libitum. This is a dose range-finding study; it was not stated how the levels were chosen.

Dose Preparation: The solutions of test material (dosage levels: 5, 25, 50, and 150 mg/kg) were prepared daily. The dosing solutions were not analyzed. Data are available in definitive study.

RESULTS

Information on the stability and concentration of the test material in the vehicle was not provided in the report. It was stated that the purity, identity, strength, and stability of the test material are the responsibility of the sponsor.

C. Clinical Observations

Each doe was examined at least once daily for mortality, moribundity, general appearance, and behavior, and detailed clinical observations were recorded. Individual body weights were recorded on gestation days 0, 6, 12, 18, 24, and 29, and food consumption was recorded every two

days. Gravid uterine weight, net body weight (day 29 body weight minus the weight of gravid uterus), and actual body weight were recorded on day 29.

D. Terminal Procedures

On Day 29 of gestation, all surviving does were sacrificed via an i.v. injection of Beuthanasia-D Special euthanasia solution.

E. Uterine/Implantation Data

The uterus of each doe was excised, weighed, and the number of corpora lutea on each ovary, the number and location of viable and non-viable fetuses, early and late resorptions, and the total number of implantations were recorded.

F. Fetal Data

Fetuses were examined for gross external morphological observations.

RESULTS

1. Clinical Observations and Survival - Maternal

Four does died during the study. The death at the 50 mg/kg dose level was thought to be due to a dosing error. The three deaths at the 150 mg/kg dose level were attributed to treatment (days 21, 25, and 27).

Clinical signs were observed in the corn oil vehicle control does (slight diarrhea, minimal feces, and decreased body tone), which were attributed to the corn oil, and the vehicle was changed to methylcellulose. Thereafter the controls appeared normal. The treated does displayed numerous signs of toxicity, which included slight diarrhea, minimal feces, decreased body tone, abnormal stance and gait, decreased activity, and dyspnea and appear to be treatment-related.

2. Maternal Body Weight and Body-weight Gain

Body weights of the treatment groups were 5-7% greater than control at study initiation (day 0). All groups gained weight between days 0 and 6 and displayed a decrease between days 6 and 12. The loss in the control was apparently due to the corn oil. Thereafter, controls displayed a body-weight gain for the remainder of the study. All treatment groups continued to display negative body-weight gain, with the exception of the 5 mg/kg group between days 24 and 28. One doe aborted and one delivered prematurely; therefore day 28 body weight value is for 2 does. Since individual data were not provided, it cannot be determined whether these animals gained weight during this period or the apparent gain is due to the loss of the two does. Negative body-weight gains were displayed at all dose levels throughout the study; control displayed a negative gain during the 6-12 day period.

Table 1. Body Weight (% of Control)

Day/Dose	5 mg/kg	25 mg/kg	50 mg/kg	150 mg/kg
0	105	107	106	105
6	101	106	102	103
12	96	98	91♦	88
18	90	84	78	72
24	86	77♦	68♥	69*
29	95♦	-	-	-

♦ 2 does aborted/delivered early; ♦ 2 does aborted; ♦ 1 doe found dead; ♥ 1 doe aborted; * 2 does aborted/found dead;

Table 2. Body-weight Gains [kilograms]

Dose (mg/kg) Time Interval	0	5	25	50	150
0-6	0.176	0.050	0.149	0.047	0.113
6-12	-0.097	-0.296	-0.419	-0.552*	-0.652*
12-18	0.218	-0.038	-0.316*	-0.305*	-0.437♦
18-24	0.073	-0.085	-0.316	-0.318	-0.398
24-29	0.043	-0.031	-	-	-
6-18	0.121*	-0.334*	-0.735*	-0.857*	-1.089*
0-29	0.413	-0.098	-	-	-
0-29 (corrected)	0.152	0.436	-	-	-

* p<0.05; ♦ statistical significance not given; * marked as significant at p<0.05

Gravid uterine weight was not provided; however, subtracting corrected body weight from day 29 body weight for the control and 5 mg/kg dose groups shows a control value of 0.565 kg and a 5 mg/kg value of 0.338 kg (60% of control). The corrected body weight listed for these groups was comparable (3.480 kg vs 3.507 kg), respectively.

3. Food Consumption

Food consumption was severely affected (see Table 3) at all dose levels from day 6 on, although the 5 mg/kg dose group displayed an apparent intake greater than control during days 24-28, which probably reflects the fact that 2 does were eliminated from the calculations for this group at this time.

Table 3. Food Consumption (grams)

Interval/Dose	0 mg/kg	5 mg/kg	25 mg/kg	50 mg/kg	150 mg/kg
0-2	316	371	411	342	407
2-4	323	338	355	316	395
4-6	301	290	383	316	418
6-8	48	8	18	15	6
8-10	197	105	100	30	19
10-12	247	132	75	6	2
12-14	294	132	17	4	3
14-16	352	97	6	3	3
16-18	358	93	37	5	4
18-20	366	96	4	6	6
20-22	291	95	3	3	11
22-24	204	101	0	2	0
24-26	113	139	2	2	-
26-28	145	171	-	-	-
28-29	82	56	-	-	-

4. Gross Pathological Observations

In the does that died during the study, findings at necropsy included dark fluid-filled lungs in the doe dying from dosing error, hydrothorax, mottled lungs, pale intestines, dark-red sponge-like lungs, multiple stomach lesions, nasal and urogenital discharge, and dark tan discoloration of the stomach mucosa. No assessment of organ weight data was performed.

5. Maternal Observations

Pregnancy rate was 100% at the 5, 25 and 50 mg/kg dose levels and 75% (3 out of 4) for the control and 150 mg/kg dose groups. Seven does aborted during the study (1 at 5 mg/kg, 3 at 25 mg/kg, 2 at 50 mg/kg, and 1 from 150 mg/kg dose groups), and three prematurely delivered (1 each from groups 5, 25, and 50 mg/kg). Only 6 of the 20 does survived to termination (4 control and 2 from the 5 mg/kg dose group). Therefore, effects on uterine contents were not determined. The Cesarean section observations are listed below.

Cesarean Section observations

GROUP (mg/kg)	0	5	25	50	150
# Females inseminated	4	4	4	4	4
# Pregnant Females	3	4	4	4	3
Pregnancy Rate (%)	75	100	100	100	75
Maternal Wastage					
#Died	0	0	0	1	3
#Died/pregnant	0	0	0	1	3
#Non pregnant	1	0	0	0	1
#Aborted	0	1	3	2	1
#Premature Delivery	0	1	1	1	0

Table 4. Group Mean Observations

Parameter/Dose	0 mg/kg	5 mg/kg
Total # implants	9.7	5.0
# viable fetuses	9.7	2.5
# non-viable fetuses	0	2.5
# early resorptions	0	0
# late resorptions	0	0
# corpora lutea	14.7	8.5
Pre-implantation loss [# (%)]	5 (36.3)	3.5 (41.0)
Post implantation loss [# (%)]	0 (0)	2.5 (50)

6. Fetal Observations

Five fetal deaths (all from one 5 mg/kg doe) were observed. One gross malformation (short tail) was detected in the control group (not previously detected in the historical controls).

D. Discussion

The purpose of this study was to determine the appropriate dose levels to be used in a definitive developmental toxicity study. Because of the unexpected toxicity noted in this study, a second range-finding study

was performed (Study # PH 329-GC-001-90), reviewed in a separate DER. In the current study, all dose levels displayed decreased body weight/gain and a negative gain from the start of dosing until termination. Food consumption was reduced severely at all dose levels during the same interval. Deaths occurred at the two highest dose levels (dose-related), and abortion or premature delivery occurred in each treated group but not in the control group.

D. CONCLUSION

The dose levels chosen for this range-finding study were too high; a second range-finding study was performed using dose levels of 0.3, 1.0, and 3.0 mg/kg.