DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: Non-guideline; Preliminary Developmental Toxicity Study in Rabbits

Work Assignment No. 4-1-128 I (MRID 46808232)

Prepared for
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U.S. Environmental Protection Agency
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This Data Evaluation Record my have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel

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DATA EVALUATION RECORD

STUDY TYPE: Preliminary Prenatal Developmental Toxicity Study - Rabbits; Non-guideline

PC CODE: 129108 **DP BARCODE:** D331116
TXR#: 0054348

TEST MATERIAL (PURITY): XDE-570 (99.3% a.i.)

SYNONYMS: Florasulam; *N*-(2,6-Difluorophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo (1,5-*c*)pyrimidine-2-sulfonamide; XR-570; XRD-570; DE-570

CITATION: Zablotny, C. L., and E. W. Carney (1997) XDE-570: oral gavage teratology probe study in New Zealand White rabbits. The Toxicology Research Laboratories, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID: DR-0312-6565-023, 960014; August 12, 1997. MRID 46808232. Unpublished.

SPONSOR: Dow AgroSciences Canada, Inc., 2100-450 1 St. SW, Calgary, AB, Canada

EXECUTIVE SUMMARY: In a preliminary developmental toxicity study (MRID 46808232), XDE-570 (Florasulam; 99.3% a.i.; Lot No. 940714) in aqueous 0.5% methylcellulose was administered daily via oral gavage to seven naturally mated New Zealand White rabbits/group at a dose volume of 4 mL/kg at dose levels of 0, 100, 300, 600, or 1000 mg/kg/day from gestation day (GD) 7-19. On GD 20, all surviving does were killed and necropsied. The liver and kidneys were removed and weighed, and a detailed examination of the uterus and ovaries was performed.

One 600 mg/kg/day doe died on GD 19, and one 1000 mg/kg/day doe died on each of GDs 10, 13, 17. These animals all exhibited decreased fecal output, body weight loss, and markedly lower food consumption. At necropsy, findings of congested, edematous lungs, decreased ingesta in the digestive tract, a gastric hairball, slight hemorrhage in the vaginal wall, and a distended bladder were noted. Due to increased mortality (43%), the remaining does from the 1000 mg/kg/day group were killed for humane reasons on GD 17, and no further data were collected from this group.
No treatment-related effects were observed on organ weights or gross pathological examinations of animals that survived to scheduled termination.

At 600 mg/kg/day, body weight gains were decreased (not significantly [NS]) during treatment (GD 7-19) by 16%, due to body weight loss during GD 7-10 (-33.1 g vs. 53.1g in controls) and decreased (NS) body weight gains during GD 13-16 (decr. 56%). Food consumption was

decreased (NS) during GD 10-19 (decr. 7-36%).

The maternal LOAEL is 600 mg/kg/day, based on mortality and decreased body weight gains and food consumption. The maternal NOAEL is 300 mg/kg/day.

No treatment-related effects were observed on the numbers of implantations or resorptions, or litter size at up to 600 mg/kg/day. Cesarean section data were not reported for the 1000 mg/kg/day group. Fetuses were not examined in any dose group.

The developmental LOAEL and NOAEL are not determined.

This study is classified as an **acceptable/non-guideline** range-finding developmental toxicity study in rabbits.

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

NOTE: This DER summarizes EPA conclusions regarding effects observed in the preliminary developmental toxicity study in rabbits. A detailed DER completed by the Canadian Pest Management Regulatory Agency (PMRA) is attached.

COMMENTS: EPA concurs with the PMRA toxicology evaluation, no conclusions have been changed.

46808232.PMRA.der
.pdf

Reviewer: Tom Morris , **Date** May 24, 2000.

STUDY TYPE: Prenatal Developmental Study - Rabbit; OPPTS 870.3700; OECD 414.

TEST MATERIAL (PURITY): XDE-570 (Purity - 99.3%)

SYNONYMS: XR-570, XRD-570, DE-570, florasulam.

CITATION: Zablotny, C. L. and Carney, E. W. August 12, 1997. **XDE-570; Oral Gavage Teratology Probe Study in New Zealand White Rabbits.** Performing Laboratory: The Toxicology Research Laboratories, The Dow Chemical Company, Midland, Michigan, 48674. Laboratory Project Study ID: DR-0312-6565-023, 960014. Unpublished

SPONSOR: Dow AgroSciences Canada Inc. (DAS).

EXECUTIVE SUMMARY: In a preliminary developmental toxicity study, XDE-570 (Purity - 99.3%), prepared as a suspension in aqueous 0.5% Methocell (methylcellulose), was administered to 7 naturally mated, adult female New Zealand White rabbits/dose at dose levels of 0, 100, 300, 600 or 1,000 mg/kg bw/d by oral gavage at a dose volume of 4 mL/kg bw from days 7 through 19 of gestation. Sexually mature, virgin adult females were naturally mated with one buck (1 male: 1 female) of the same strain at HRP Inc. prior to shipment to the testing facility. Dosing volume was adjusted daily, based on dam body weight during the dosing period. Due to increased mortality (43%), severe body-weight loss and lower food consumption, all remaining dams at 1,000 mg/kg bw/d were sacrificed on gestation day 17 with no further data being collected on these animals.

One dam at 600 mg/kg bw/d (gestation day 19) and 3 dams at 1,000 mg/kg bw/d (gestation days 10, 13 and 17) died prior to the scheduled necropsy. All of these dams exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to death. The deaths were considered to be treatment-related although the possibility of gavage error could not be eliminated as a possible cause of death since the dam at 600 mg/kg bw/d and 2 dams at 1,000 mg/kg bw/d exhibited edematous lungs. Examination of the uterus indicated that all of these dams were pregnant with normally developing fetuses. At 1,000 mg/kg bw/d, a significant body-weight loss was observed during gestation days 7-10 and 13-16. This was associated with concomitant lower food consumption and reduced faecal output. At 600 mg/kg bw/d, the overall body weight gain during treatment (days 7 through 19 of gestation) was lower (≈16%) compared to controls, this was attributed to a body-weight loss during gestation days 7-10 and a lower body-weight gain (≈56%) during gestation days 13-16. The body-weight loss during gestation days 7-10 was not associated with concomitant lower food consumption. The lower body-weight gain during gestation days 13-16 was associated with concomitant lower food consumption (up to 35% lower). There were no significant treatment-related effects on absolute or relative liver or kidney weights and no treatment-related gross pathological findings in the dams that survived to the scheduled necropsy on day 20 of gestation at 100, 300 or 600 mg/kg bw/d. There were no treatment-related effects on caesarian section parameters examined including pregnancy rate at 100, 300 or 600 mg/kg bw/d (no data collected for dams at 1,000 mg/kg bw/d).

The LOAEL for maternal toxicity was 600 mg/kg bw/d due to one treatment-related mortality, lower body-weight gain and food consumption. The NOAEL for maternal toxicity was 300 mg/kg bw/d.

No fetal evaluation. Dams were sacrificed on day 20 of gestation, one day after the final dosing.

The LOAEL for developmental toxicity was not determined. The NOAEL for developmental toxicity was not determined.

This study is classified as unacceptable and does not satisfy the guideline requirement for a developmental toxicity

study (OPPTS 870.3700; OECD 414) in rabbits. However, the purpose of this developmental/teratology study in the rabbit was to make a preliminary evaluation of the potential maternal toxicity and embryolethality of XDE-570 administered to pregnant New Zealand White rabbits via oral gavage. Results of this study were used to set dose levels for the main gavage developmental/teratology study in rabbits. Although there are no specific testing guidelines for a preliminary developmental/teratology study, this study was conducted in partial compliance with acceptable guidelines (OPPTS 870.3700; OECD 414). This study was conducted in accordance with accepted EPA, OECD and MAFF (Japan) GLP Standards. This study is acceptable for its intended purpose.

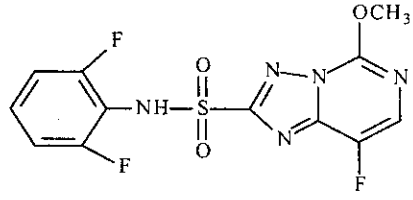
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** XDE-570 as named in the study. Chemical Name (CA nomenclature): N-(2,6-difluorophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-c)pyrimidine-2-sulphonamide

Description:	White powdery solid
Lot/Batch #:	Lot # 940714 / Test Substance # 100511
Purity:	99.3 % a.i. (determined by HPLC).
Compound Stability:	The test substance was re-assayed after study determination and was confirmed at 99.3% (Knowles, et al., 1997, Lab Report Code GHE-P-6448)
CAS #:	145701-23-1
Structure	



2. **Vehicle and/or positive control**: The test substance was administered as a suspension in an aqueous solution of 0.5% Methocell (methylcellulose) such that a dose volume of 4 mL/kg bw yielded the appropriate dose.

3. **Test animals:**

Species:	Adult female time-mated rabbits. Sexually mature, virgin adult females were naturally mated with one buck (1 male: 1 female) of the same strain at HRP Inc.	
Strain:	New Zealand White.	
Age/weight at study initiation:	When naturally mated, the females were ≈5 to 6 months of age with a body weight range of ≈2.5 to 3.5 kg.	
Source:	HRP Inc., Kalamazoo, MI.	
Housing:	The animals were individually housed in suspended cages with flattened tube grid floors.	
Diet:	Animals received 2 oz of Certified Laboratory Rabbit Chow # 5322 (Purina Mills Inc., St. Louis, MO) upon receipt. The amount of food was increased incrementally by 2 oz/day to a total of approximately 8 oz/day.	
Water:	Municipal tap water *ad libitum*	
Environmental conditions:	**Temperature:**	≈20 °C
	Humidity:	40-60%
	Air changes:	12 air changes/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	Approximately 6 days.	

B. PROCEDURES AND STUDY DESIGN

1. **In life dates** - In-life study dates were not provided in study report. However, the observed day of breeding was considered day 0 of gestation. On day 20 of gestation, all surviving dams were euthanised and subjected to a gross pathological examination. Date of study conduct was from 27/08/96 to 27/11/96.

2. **Mating**: Adult females, approximately 5 to 6 months of age and weighing approximately 2.5 to 3.5 kg were naturally mated with one buck (1 male:1 female) of the same strain at HRP Inc. The observed day of breeding was considered day 0 of gestation. Day 0 body weights and records of mating pairs were provided by HRP Inc., and maintained in the study records. The rabbits were shipped on day 0 of gestation.

3. **Animal Assignment**: The time-mated rabbits were randomly assigned to the dose groups, as indicated in Table 1,

using a computer generated procedure designed to achieve similar body weights across the dose groups.

TABLE 1: Animal Assignment.

Dose (mg/kg bw/day)	0	100	300	600	1,000
# Females	7	7	7	7	7

4. Dose selection rationale: No repeat dose oral toxicity studies were available in rabbits. The dose levels were chosen to provide adequate data to establish a maximum tolerated dose (MTD). In addition, the high dose level of 1,000 mg/kg bw/d represented a limit dose as defined by accepted guidelines by (OPPTS 870.3700; OECD 414). As excessive toxicity was observed at the high dose of 1,000 mg/kg bw/d, this dose group was terminated on gestation day 17 with no further data collected.

5. Dosage preparation and analysis The test substance was administered as a suspension in an aqueous vehicle of 0.5% Methocel (methylcellulose) such that a dose volume of 4 mL/kg bw yielded the targeted dose. Dose suspensions were not analysed for concentration, homogeneity or stability. Reference samples of all dose suspensions including control were retained from each mix and stored at ambient temperature in a manner consistent with sample retention policy of accepted GLP procedures.

6. Dosage administration: Doses were administered once daily by oral gavage in aqueous 0.5% Methocel (methylcellulose) on days 7 through 19 of gestation. Dosing volume was adjusted daily, based on current individual dam body weight during the dosing period.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The dams were checked daily for mortality or clinical signs. Body weight data were recorded on day 0 (by supplier), daily during the dosing period and on gestation day 20 prior to sacrifice. Statistical analyses of body weights and body-weight gains were performed using data collected on gestation days 0, 7, 10, 13, 16 and 20. Food consumption was recorded daily during the test period beginning on gestation day 4. On gestation day 20 all surviving females were weighed and sacrificed by decapitation following CO_2 asphyxiation. Immediately after decapitation, the eyes were examined *in situ* by a glass slide technique. A detailed gross pathological examination (necropsy) was performed. Liver and kidney weights were recorded at the time of necropsy and representative sections of liver with gallbladder, kidneys and gross lesions were preserved in neutral, phosphate-buffered 10% formalin. The uterus, uterine contents, cervix, oviducts, ovaries and vagina were preserved in neutral phosphate-buffered 10% formalin until the reproductive data were verified and then were discarded. Microscopic examination of tissues was not conducted. A detailed examination of the uterus for the number of implantations and resorptions, and the ovaries for the number of corpora lutea, was performed. The position and number of early and/or late resorptions and normally developing fetuses was recorded. Corpora lutea were not counted for non-pregnant females or females with totally resorbed litters. The uteri of apparently non-pregnant animals were stained with 10% aqueous solution of sodium sulfide and examined for evidence of early resorptions in order to determined pregnancy status. Dams which died prior to scheduled termination were submitted for a complete necropsy examination. The necropsy was similar to dams sacrificed at the scheduled necropsy except that liver and kidney weights were not determined. Also, the number of corpora lutea and the sex and body weight of the fetuses from these animals were not recorded. The degree to which the implantation site(s) had developed was determined to the extent possible by external examination and then discarded.

2. Fetal Evaluations - No fetal evaluation. Dams were sacrificed on day 20 of gestation, one day after the final dosing.

D. DATA ANALYSIS

1. Statistical analyses: Descriptive statistics (means and standard deviation) were calculated for food consumption. Maternal body weights, body-weight gains and organ weights were evaluated by Bartlett's test for equality of variances. Based on the outcome of the Bartlett's test ($\alpha = 0.01$), a parametric or non-parametric ANOVA ($\alpha = 0.01$ for both) was performed. If the ANOVA was significant, analysis by Dunnett's test ($\alpha = 0.05$, two-sided) or Wilcoxon Rank-Sum test ($\alpha = 0.05$, two-sided) with Bonferroni's correction was performed, respectively. Frequency of pre-implantation loss and resorption among litters and fetal population were analysed using a censored Wilcoxon test ($\alpha = 0.02$, two-sided) with Bonferroni's correction. The number of corpora lutea, number of implantations and litter size were evaluated using a non-parametric ANOVA followed by the Wilcoxon Rank-Sum test with Bonferroni's correction. The number of corpora lutea and implants, and litter size were evaluated using a non-parametric ANOVA followed by the Wilcoxon Rank-Sum test with Bonferroni's correction. Pregnancy rates were analysed using the Fischer exact probability test ($\alpha = 0.05$, two-sided). Non-pregnant females were excluded from the appropriate analysis. Statistical outliers were identified using a sequential method ($\alpha = 0.05$, two-sided), and excluded only if justified by sound scientific reason unrelated to treatment. Because numerous measurements were statistically compared in the same group of animals, the overall false positive rate (Type I errors) was expected to be much greater than the cited alpha level would suggest. Therefore, the final interpretation of the numerical data took into consideration the statistical analyses along with other factors such as dose-response relationships and whether the results were significant in light of other biologic and pathologic findings.

2. Indices: The following indices were calculated from caesarean section records of animals in the study:

$$\text{Pregnancy Rate (\%)} = \frac{\text{\# of females with visible implantations}}{\text{Total \# bred}} \times 100$$

$$\text{Pre-implantation loss} = \frac{\text{\# of corpora lutea - \# implants}}{\text{\# of corpora lutea}} \times 100$$

3. Historical control data: Historical control data were provided for maternal organ weights only. No other historical control data were provided in the study report.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: One dam at 600 mg/kg bw/d (on gestation day 19) and 3 dams at 1,000 mg/kg bw/d (on gestation days 10, 13 and 17) died prior to the scheduled necropsy. At 600 mg/kg bw/d, the dam exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to dying. Necropsy findings in this dam included congested, edematous lungs, decreased ingesta in the digestive tract, a gastric hairball and a distended bladder. Examination of the uterus indicated 8 normal developing fetuses and 2 early resorptions. At 1,000 mg/kg bw/d, all dams dying during the study exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to dying. Necropsy findings in the dam at 1,000 mg/kg bw/d found dead on gestation day 10 included congested, edematous lungs and slight haemorrhage in the vaginal wall. At necropsy, the uterus contained 6 normally developing fetuses. There were no necropsy findings in the dam at 1,000 mg/kg bw/d found dead on day 13 of gestation. In addition, the uterus contained 9 normally developing fetuses. The third dam at 1,000 mg/kg bw/d, found dead on day 17 of gestation, exhibited edema in the lungs. Examination of the uterus indicated five normal developing fetuses and 1 early resorption. Due to increased mortality, severe body-weight loss and lower food consumption, all remaining animals at 1,000 mg/kg bw/d were sacrificed on day 17 of gestation with no further data being collected on these animals. The mortalities at 600 and 1,000 mg/kg bw/d were considered to be treatment-related as gross pathological findings, clinical observations and other signs of maternal toxicity were consistent with treatment-related findings in other animals in this study, although the possibility of gavage error could not be eliminated as the cause of death.

The only treatment-related clinical sign was decreased amount of faeces in the cage pan in 1 dam at 600 mg/kg bw/d and in 5 dams at 1,000 mg/kg bw/d. In 3 dams at 1,000 mg/kg bw/d and in the dam at 600 mg/kg bw/d, this was associated with markedly lower food consumption and body-weight loss just prior to death.

2. Body Weight There were no significant differences in body weight between the controls and the treated animals (Table 2). However, by day 16 (1 day prior to termination of the high-dose dams) body weight at 1,000 mg/kg bw/d was approximately 4% lower compared to controls. At 1,000 mg/kg bw/d, a significant body-weight loss was observed during gestation days 7-10 and 13-16. This was associated with concomitant lower food consumption. Due to increased mortality (43%), severe body-weight loss and lower food consumption, all remaining dams at 1,000 mg/kg bw/d were sacrificed on gestation day 17 with no further data being collected on these animals. At 600 mg/kg bw/d, the overall body weight gain during treatment (days 7 through 19 of gestation) was lower (≈16%) compared to controls, this was attributed to a body-weight loss during gestation days 7-10 and a lower body-weight gain (≈56%) during gestation days 13-16. The body-weight loss during gestation days 7-10 was not associated with concomitant lower food consumption. The lower body-weight gain during gestation days 13-16 was associated with concomitant lower food consumption. There were no treatment-related effects on body weight or body-weight gains at 100 or 300 mg/kg bw/d.

TABLE 2 Maternal Body Weight Gain (g ± SD) (a)

Interval		Dose Level (mg/kg bw/day)				
		0 (n = 7)	100 (n = 7)	300 (n = 6)	600 (n = 7) (b)	1,000 (n = 7) (c)
Body weight (g ± SD)						
Pre-Treatment	Day 0	3197 ± 143	3208 ± 126	3279 ± 205	3231 ± 208	3176 ± 275
	Day 7	3407 ± 172	3552 ± 164	3460 ± 234	3516 ± 200	3525 ± 235
Treatment	Day 10	3461 ± 169	3555 ± 222	3498 ± 228	3483 ± 204	3499 ± 266 (n = 6)
	Day 13	3509 ± 175	3631 ± 240	3578 ± 245	3570 ± 185	3578 ± 312 (n = 5)
	Day 16	3635 ± 183	3741 ± 265	3669 ± 264	3625 ± 179	3490 ± 442 (n = 5)
Post-treatment	Day 20	3719 ± 200	3844 ± 228	3803 ± 251	3753 ± 185 (n = 6)	-
Body-weight gain (g ± SD)						
Pretreatment	Day 0-7	210.2 ± 141.5	344.4 ± 202.9	180.6 ± 130.1	285.4 ± 92.0	348.8 ± 158.2
Treatment	Days 7-10	53.1 ± 39.0	2.5 ± 68.3	38.5 ± 32.3	**-33.1 ± 69.7**	**-41.7 ± 94.7 ***
	Days 10-13	48.6 ± 24.0	76.7 ± 60.6	79.9 ± 60.7	86.7 ± 33.5	69.7 ± 83.8
	Days 13-16	126.3 ± 20.6	109.6 ± 35.5	91.5 ± 51.9	55.2 ± 130.9	**-88.5 ± 179.2 #**
	Days 16-20	83.2 ± 51.1	102.9 ± 61.4	133.2 ± 29.6	106.0 ± 45.3	-
	Days 7-20	311.2 ± 58.7	291.7 ± 86.5	337.9 ± 121.7	260.3 ± 64.5	-
Overall	Days 0-20	521.4 ± 180.7	636.0 ± 243.0	523.7 ± 218.1	562.3 ± 137.7	-

(a) Data extracted from pages 28-29 of the study report. Non-pregnant dams were excluded from analysis.
(b) One dam found dead on gestation day 19. Prior to dying this animal exhibited markedly lower food consumption, a body-weight loss and decreased faecal output.
(c) Three dams at 1,000 mg/kg bw/d died prior to the scheduled necropsy (on gestation days 10, 13 and 17), all exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to dying. Due to increased mortality (43%), severe body-weight loss, markedly lower food consumption and decreased faecal, all remaining dams at 1,000 mg/kg bw/d were sacrificed on gestation day 17 with no further data being collected on these animals.
* Statistically different from control mean by Dunnett's test, $p \leq 0.05$.
# Statistically different from control mean by Wilcoxon test, $p \leq 0.05$.

3. Food Consumption - Maternal food consumption was lower at 600 and 1,000 mg/kg bw/d during the treatment period (Table 3). Overall, average food consumption was approximately 31% lower at 1,000 mg/kg bw/d. In the high-dose dams, lower food consumption was apparent throughout the treatment period and ranged from 10% lower on gestation day 7-8 to a maximum of 59% lower on gestation day 14-15. On the day prior to termination of the high-dose dams (gestation day 15-16), food consumption was approximately 50% lower compared to controls. The

lower food consumption at 1,000 mg/kg bw/d was associated with a concomitant body-weight loss during gestation days 7-10 and 13-16 and decreased faecal output. Overall, average food consumption was approximately 12 % lower at 600 mg/kg bw/d. Lower food consumption was apparent from gestation day 10-11 onwards and reached a maximum on gestation day 14-15, approximately 35% lower compared to controls. Prior to dying, the animal found dead on gestation day 19 exhibited markedly lower food consumption, a body-weight loss and decreased faecal output. If this animal is excluded from food consumption calculations from gestation day 14-15 (1st day of markedly lower food consumption) onwards, food consumption ranged from a maximum of approximately 25% lower on gestation day 14-15 to approximately 4% lower by gestation days 19-20. The lower food consumption in dams at 600 mg/kg bw/d was associated with an overall lower (≈16%) body-weight gain during the treatment period (days 7-19 of gestation). Food consumption was unaffected by treatment at 100 and 300 mg/kg bw/d.

TABLE 3 Maternal Food Consumption (g/animal/day ± SD) (a)

Interval		Dose Level (mg/kg bw/day)				
		0 (n = 7)	100 (n = 7)	300 (n = 6)	600 (n = 7) (b)	1,000 (n = 7) (c)
Pre-Treatment	Day 4-5	196.6 ± 26.6	202.3 ± 10.7	205.5 ± 13.4	194.9 ± 24.6	208.9 ± 13.7
	Day 5-6	194.3 ± 16.8	195.0 ± 15.5	190.0 ± 14.3	206.6 ± 9.7	200.8 ± 10.6
	Day 6-7	188.2 ± 12.2	179.0 ± 7.7	186.1 ± 12.7	193.9 ± 11.3	178.8 ± 18.1
Treatment	Day 7-8	198.4 ± 20.1	204.5 ± 25.7	188.6 ± 30.5	198.4 ± 24.1	178.8 ± 40.2
	Day 8-9	190.7 ± 17.5	189.0 ± 35.7	176.0 ± 30.5	183.2 ± 31.5	131.8 ± 58.1
	Day 9-10	175.9 ± 22.1	179.9 ± 58.2	186.9 ± 23.5	173.6 ± 23.1	122.7 ± 62.7 (n = 6)
	Day 10-11	189.4 ± 29.1	186.7 ± 36.9	185.1 ± 11.5	164.9 ± 31.5	145.6 ± 54.1 (n = 5)
	Day 11-12	178.4 ± 29.1	179.4 ± 32.4	182.1 ± 21.1	158.8 ± 24.3	142.9 ± 48.9
	Day 12-13	172.7 ± 28.7	162.2 ± 42.8	164.6 ± 38.2	146.4 ± 41.3	121.1 ± 66.6
	Day 13-14	160.3 ± 36.8	143.6 ± 63.2	172.1 ± 31.2	149.1 ± 37.4	115.8 ± 70.1
	Day 14-15	199.4 ± 30.5	179.4 ± 36.5	177.0 ± 16.7	128.4 ± 63.5	81.3 ± 66.4
	Day 15-16	190.3 ± 39.3	190.8 ± 33.2	167.2 ± 41.5	147.0 ± 62.7	95.5 ± 78.7
	Day 16-17	188.9 ± 25.1	184.3 ± 29.6	171.7 ± 32.0	148.8 ± 67.7	-
	Day 17-18	197.7 ± 24.2	187.9 ± 33.6	189.4 ± 17.7	157.2 ± 71.6	-
	Day 18-19	195.9 ± 18.5	196.6 ± 19.1	201.3 ± 13.1	181.6 ± 13.1	-
	Day 19-20	175.8 ± 13.6	193.4 ± 27.4	197.8 ± 13.9	168.8 ± 27.3	-

(a) Data extracted from pages 26-27 of the study report. Animals which were non-pregnant were excluded from analysis. There were no statistical comparisons of means.
(b) One dam found dead on gestation day 19. Prior to dying this animal exhibited markedly lower food consumption, a body-weight loss and decreased faecal output.
(c) Three dams at 1,000 mg/kg bw/d died prior to the scheduled necropsy (on gestation days 10, 13 and 17), all exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to dying. Due to increased mortality (43%), severe body-weight loss, markedly lower food consumption and decreased faecal, all remaining dams at 1,000 mg/kg bw/d were sacrificed on gestation day 17 with no further data being collected on these animals.

4. Gross Pathology - There were no treatment-related effects on absolute or relative liver or kidney weights. Absolute and relative kidney weights were approximately 8-11% higher in the treated animals compared to the controls (Table 4). However, this was not statistically significant, not dose-related and was within the range of historical control values for animals of this age and strain from this laboratory; therefore, the difference was not considered to be treatment-related. There were no treatment-related gross pathological findings in the dams that survived to the scheduled necropsy on day 20 of gestation at 100, 300 or 600 mg/kg bw/d. Due to increased mortality (43%), severe body-weight loss and lower food consumption, all remaining dams at 1,000 mg/kg bw/d were sacrificed on gestation day 17 with no further data being collected on these animals. Necropsy findings in the dam at 600 mg/kg bw/d found dead on day 19 of gestation included congested, edematous lungs, decreased ingesta in the digestive tract, a gastric hairball and a distended bladder. Necropsy findings in the dam at 1,000 mg/kg bw/d found dead on gestation day 10 included congested, edematous lungs and slight haemorrhage in the vaginal wall. There were no necropsy findings in the dam at 1,000 mg/kg bw/d found dead on day 17 of gestation. The third dam at 1,000 mg/kg bw/d, found dead on day 17 of gestation, exhibited edema in the lungs.

TABLE 4: Absolute (g ± SD) and relative (g/100 g bw ± SD) organ weights (a)

Organ		Dose Level (mg/kg bw/day)				
		0 (n = 7)	100 (n = 7)	300 (n = 6)	600 (n = 6) (b)	1,000 (n = 6) (c)
Kidneys	Absolute	16.488 ± 1.846	18.330 ± 1.984	18.220 ± 0.705	18.193 ± 2.683	-
	Relative	0.466 ± 0.042	0.483 ± 0.033	0.486 ± 0.034	0.487 ± 0.058	-

(a) Data extracted from pages 30 of the study report. Animals which were non-pregnant were excluded from analysis. There were no statistical comparisons of means.
(b) One dam found dead on gestation day 19. Prior to dying this animal exhibited markedly lower food consumption, a body-weight loss and decreased faecal output. Excluded from organ weight analysis
(c) Three dams at 1,000 mg/kg bw/d died prior to the scheduled necropsy (on gestation days 10, 13 and 17), all exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to dying. Due to increased mortality (43%), severe body-weight loss, markedly lower food consumption and decreased faecal, all remaining dams at 1,000 mg/kg bw/d were sacrificed on gestation day 17 with no further data being collected on these animals. Excluded from organ weight analysis.

5. Caesarean Section Data - The pregnancy rate was 100, 100, 85.7 and 100% at 0, 100, 300 and 600 mg/kg bw/d, respectively (Table 5). All dams sacrificed on gestation day 20 had viable litters. One female at 300 mg/kg bw/d was not pregnant. There were no treatment-related effects on pregnancy rates, number of corpora lutea, implantations, resorptions or litter size at 100, 300 or 600 mg/kg bw/d. No data were collected from the dams at 1,000 mg/kg bw/d that were euthanised on day 17 of gestation. Examination of the uterus of the dam at 600 mg/kg bw/d which died on gestation day 19 indicated 8 normal developing fetuses with 2 early resorptions. Examination of the uterus of the dams at 1,000 mg/kg bw/d dying on gestation day 10, 13 and 17 indicated 6 normally developing fetuses, 9 normally developing fetuses and 5 normal developing fetuses with 1 early resorption, respectively.

TABLE 5 Caesarean Section Observations (a)

Observation		Dose Level (mg/kg bw/day)				
		0	100	300	600 (b)	1,000 (c)
# Animals Assigned (Mated)		7	7	7	7	-
# Animals Pregnant		7	7	6	7	-
Pregnancy Rate (%)		100	100	85.7	100	-
# Nonpregnant		0	0	1	0	-
Maternal Wastage	# Died	0	0	0	1	-
	# Died Pregnant	0	0	0	1	-
	# Died Nonpregnant	0	0	0	0	-
	# Aborted	0	0	0	0	-
	# Premature Delivery	0	0	0	0	-
# Corpora Lutea/Dam		9.7 ± 1.8	9.7 ± 1.3	8.3 ± 1.9	9.3 ± 1.0	-
# Implantations/Dam		9.0 ± 2.2	9.7 ± 1.3	7.3 ± 2.5	8.7 ± 0.5	-
Pre-implantation Loss (%)		8.0 ± 11.7	0 ± 0	13.5 ± 19.6	6.4 ± 9.9	-
# Viable Litters		7	7	6	6	-
# Fetuses/Litter		8.6 ± 1.9	9.4 ± 0.8	7.0 ± 2.8	8.7 ± 0.5	-
Total # Resorptions/Dam		0.4 ± 0.5	0.3 ± 0.8	0.3 ± 0.5	0.0 ± 0.0	-
% Implantations Resorbed (# resorptions/# implantations)		4.8 (3/63)	2.9 (2/68)	4.5 (2/44)	0 (0/52)	- -
% Litters with Resorptions		42.9 (3/7)	14.3 (1/7)	33.3 (2/6)	0 (0/6)	-
Resorptions/Litters with Resorption		1.0 (3/3)	2.0 (2/1)	1.0 (2/2)	0 (0/0)	-

Observation	Dose Level (mg/kg bw/day)				
	0	100	300	600 (b)	1,000 (c)
Litters with Total Resorptions	0	0	0	0	-

(a) Data extracted from page 31 of the study report.
(b) One dam found dead on gestation day 19. Prior to dying this animal exhibited markedly lower food consumption, a body-weight loss and decreased faecal output.
(c) Three dams at 1,000 mg/kg bw/d died prior to the scheduled necropsy (on gestation days 10, 13 and 17), all exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to dying. Due to increased mortality (43%), severe body-weight loss, markedly lower food consumption and decreased faecal, all remaining dams at 1,000 mg/kg bw/d were sacrificed on gestation day 17 with no further data being collected on these animals.

B. DEVELOPMENTAL TOXICITY

1. External Examination - No fetal evaluation. Dams were sacrificed on day 20 of gestation, one day after the final dosing.

2. Visceral Examination - No fetal evaluation. Dams were sacrificed on day 20 of gestation, one day after the final dosing.

3. Skeletal Examination - No fetal evaluation. Dams were sacrificed on day 20 of gestation, one day after the final dosing.

III. DISCUSSION

A. Investigators' conclusions (extracted from page 7 of the study report): "Oral administration of XDE-570 to time-mated female rabbits resulted in treatment-related maternal effects in dams given 600 and 1000 mg/kg/day. At 1000 mg/kg/day, severe maternal toxicity was evidenced by significant maternal mortality (43%) accompanied by decreased feed consumption, body weight gain and fecal output. Due to the severity of the toxicity observed, all remaining rabbits at 1000 mg/kg/day were euthanized on day 17 of gestation with no further data collected. At 600 mg/kg/day, the maternal effects included one death (14%) and slight transient decreases in body weight gains and reduced feed consumption. All other rabbits survived to the scheduled necropsy. No significant maternal effects were observed in rabbits given 100 or 300 mg/kg/day. Therefore, the no-observed-effect level (NOEL) for maternal toxicity was 300 mg/kg/day; the embryonal/fetal NOEL was 600 mg/kg/day."

B. Reviewer's discussion:

1. Maternal toxicity: One dam at 600 mg/kg bw/d (gestation day 19) and 3 dams at 1,000 mg/kg bw/d (gestation days 10, 13 and 17) died prior to the scheduled necropsy. All of these dams exhibited markedly lower food consumption, a body-weight loss and decreased faecal output prior to death. The deaths were considered to be treatment-related although the possibility of gavage error could not be eliminated as a possible cause of death since the dam at 600 mg/kg bw/d and 2 dams at 1,000 mg/kg bw/d exhibited edematous lungs. Examination of the uterus indicated that all of these dams were pregnant with normally developing fetuses. At 1,000 mg/kg bw/d, a significant body-weight loss was observed during gestation days 7-10 and 13-16. This was associated with concomitant lower food consumption and reduced faecal output. At 600 mg/kg bw/d, the overall body weight gain during treatment (days 7 through 19 of gestation) was lower (≈16%) compared to controls, this was attributed to a body-weight loss during gestation days 7-10 and a lower body-weight gain (≈56%) during gestation days 13-16. The body-weight loss during gestation days 7-10 was not associated with concomitant lower food consumption. The lower body-weight gain during gestation days 13-16 was associated with concomitant lower food consumption (up to 35% lower). There were no significant treatment-related effects on absolute or relative liver or kidney weights and no treatment-related gross pathological findings in the dams that survived to the scheduled necropsy on day 20 of gestation at 100, 300 or 600 mg/kg bw/d.

2. Caesarian section: There were no treatment-related effects caesarian section parameters examined including pregnancy rate at 100, 300 or 600 mg/kg bw/d (no data collected for dams at 1,000 mg/kg bw/d).

3. **Developmental toxicity**: No fetal evaluation. Dams were sacrificed on day 20 of gestation, one day after the final dosing.

The LOAEL for maternal toxicity was 600 mg/kg bw/d due to one treatment-related mortality, lower body-weight gain and food consumption. The NOAEL for maternal toxicity was 300 mg/kg bw/d.

The LOAEL for developmental toxicity was not determined. The NOAEL for developmental toxicity was not determined.

C. **Study deficiencies** The purpose of this developmental/teratology study in the rabbit was to make a preliminary evaluation of the potential maternal toxicity and embryolethality of XDE-570 administered to pregnant New Zealand White rabbits via oral gavage. Results of this study were used to set dose levels for the main gavage developmental/teratology study in rabbits. Although there are no specific testing guidelines for a preliminary developmental/teratology study, this study was conducted in partial compliance with acceptable guidelines (OPPTS 870.3700; OECD 414). This study was conducted in accordance with accepted EPA, OECD and MAFF (Japan) GLP Standards. This study is acceptable for its intended purpose, however, this study is classified as unacceptable and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits.