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DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: OPPTS 870.3100 [§82-1a]; Subchronic (90-day) Oral Toxicity Study in Mice

Work Assignment No. 4-1-128 C (MRID 46808222)

Prepared for
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Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: 90-Day Oral Toxicity [feeding]-[mice]; OPPTS 870.3100 [§82-1a] (rodent); OECD 408.

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

TEST MATERIAL (PURITY): XDE-570 (Florasulam; 99.2% a.i.)

SYNONYMS: *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: Redmond, J. M., and K. A. Johnson. (1996) XDE-570: 13-week dietary toxicity in B6C3F1 mice. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID: DR-0312-6565-010, January 30, 1996. MRID 46808222. Unpublished.

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

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 46808222), XDE-570 (Florasulam; 99.2% a.i.; Lot No. 930910) was administered in the diet to ten B6C3F1 mice/sex/dose at dose levels of 0, 20, 100, 500, or 1000 mg/kg/day (time-weighted intake was 0/0, 22/20, 110/101, 549/503, and 1125/1007 mg/kg/day [males/females]) for 13 weeks.

No adverse treatment-related effects were observed on mortality, clinical signs, body weights, body weight gains, food consumption, food efficiency, ophthalmoscopic examination, hematology, clinical chemistry, organ weights, or gross or microscopic pathology. Very slight multi-focal bilateral hypertrophy was observed in the collecting ducts of the kidney in 10/10 males at 500 and 1000 mg/kg/day and in 8/10 females at 1000 mg/kg/day. There were no significant clinical chemistry or histopathological findings to corroborate the observed kidney effects.

The LOAEL is not determined and the NOAEL is 1000 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in mice.

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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 subchronic oral toxicity study in mice. A detailed DER completed by the Canadian Pest Management Regulatory Agency (PMRA) is attached.

COMMENTS:

PMRA selected 500 mg/kg/day as the LOAEL, based on hypertrophy in the kidneys in males. There were no organ weight changes, clinical chemistry, gross or histopathological changes observed in the kidney. Therefore, this kidney observation is not considered an adverse effect. The LOAEL is not determined and the NOAEL is 1000 mg/kg/day.

46808222.PMRA.der
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Reviewer: Tom Morris , **Date** March 7, 2000

STUDY TYPE: Subchronic Oral Toxicity [feeding]-[mice]; OPPTS 870.3100 (rodent); OECD 408.

TEST MATERIAL (PURITY): XDE-570 (Purity - 99.2%)

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

CITATION: Redmond, J. M. and Johnson, K. A. January 30, 1996. **XDE-570: 13-Week Dietary Toxicity in B6C3F1 Mice**. Performing Laboratory: The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, Michigan, 48674. Laboratory Project Study ID: DR-0312-6565-010. Unpublished

SPONSOR: Dow AgroSciences Canada Inc. (DAS).

EXECUTIVE SUMMARY: In a subchronic toxicity study, XDE-570 (Purity - 99.2%) was administered to 10 B6C3F1 mice/sex/dose *ad libitum* in the diet at dose levels of 0, 20, 100, 500, or 1,000 mg/kg bw/d (time weighted average test substance intake for ♂/♀ was 0/0, 22/20, 110/101, 549/503 or 1,125/1,007 mg/kg bw/d) for 13 weeks. The control group received untreated diet (*ad libitum*) throughout the study.

There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, ophthalmoscopy, haematology, clinical chemistry, organ weights or gross pathology. Histopathological examination revealed a very slight, multi-focal bilateral hypertrophy of the epithelial cells of the collecting ducts of the kidney in 10/10 males at 500 and 1,000 mg/kg bw/d and in 8/10 females at 1,000 mg/kg bw/d. The hypertrophied cells were compatible with the intercalated cells which are normally involved in the regulation of acid-base balance through the modulation of bicarbonate resorption and hydrogen ion secretion in the collecting ducts. Functional abnormalities of the collecting duct manifest primarily as an acidification defect and impaired concentrating ability, however, urinalysis was not performed. There were no toxicologically relevant clinical chemistry findings (serum creatinine, nitrogen or electrolyte levels) to correlate with the histopathological findings in the kidney or to indicate an impairment of renal function and there was no cellular degeneration or necrosis evident in the kidneys.

The LOAEL is 500 mg/kg bw/d based on histopathological findings in the kidneys (hypertrophy of the epithelial cells of the collecting ducts) in males. The NOAEL is 100 mg/kg bw/d.

This subchronic toxicity study in the mouse is acceptable / guideline and satisfies the guideline requirement for a subchronic oral study (OPPTS 870.3100; OECD 408) in mice.

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

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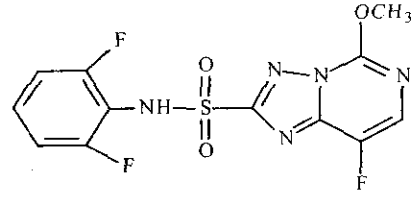
I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** XDE-570 as named in the study. Chemical Name (CA nomenclature): N-(2,6-difluropheny1)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-c)pyrimidine-2-sulphonamide

Description:	White powdery solid
Lot/Batch #:	TSN 100298 (Lot # 930910)
Purity:	99.2 % a.i. (determined by HPLC with ultra-violet detection, Certificate of Analysis, GHE-3395, Analysis Reference 93030/DA, February 1994, S. Boothroyd).
Compound Stability:	The test substance was determined to be stable in the feed for at least 35 days. The compound was stable for the duration of the study (until Feb 1995)
CAS #:	145701-23-1
Structure	



2. **Vehicle and/or positive control:** Dietary admixture.

3. **Test animals:**

Species:	Male and female mice	
Strain:	B5C3F1	
Age/weight at study initiation:	At study initiation, the rats were ≈45 days of age with a body weight range of 22.2 to 27.4 g for males and 16.4 to 20.3 g for females (animals were born on February 7, 1994).	
Source:	Charles River Laboratories, Portage, Michigan.	
Housing:	The animals were individually housed.	
Diet:	Certified Rodent Chow #5002 (Purina Mills Inc., St. Louis, MO) in meal form *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 1 °C
	Humidity:	40-70%
	Air changes:	10-12 changes/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least 7 days.	

B. STUDY DESIGN:

1. **In life dates** - Start: March 29, 1994 (day 1). End: male and females sacrificed on June 28/29, 1994, respectively (study days 92 and 93).

2. **Animal assignment**: Animals were randomly assigned to the study groups using a computer-generated randomization program based on body weights as summarized in Table 1. The test substance was administered (*ad libitum*) in the feed for 13 weeks. The animals were sacrificed and necropsied on study days 92 (males) and 93 (females). The control group animals received untreated diet throughout the study.

TABLE 1: Study design.

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Test Group	Dose Levels (mg/kg bw/d)	Time-Weighted Average Test Substance Intake (mg/kg bw/d)		Number of Animals	
		Males	Females	Males	Females
1	0	0	0	10	10
2	20	22	20	10	10
3	100	110	101	10	10
4	500	549	503	10	10
5	1,000	1,129	1,007	10	10

In a two-week dietary study, 5 B6C3F1 mice/sex/dose were administered XDE-570 in the diet at doses of 0, 100, 500 or 1,000 mg/kg bw/d (Szabo, J.R. and Davis, N.L., February 20, 1992. Laboratory Project Study ID: DR-0312-6565-002, study submitted but a full review was not completed). At 1,000 mg/kg bw/d, females exhibited lower food consumption with subsequent decreases in body weights and secondary organ weight changes suggestive of a slight degree of unpalatability of the diet. There were no treatment-related findings in males up to and including 1,000 mg/kg bw/d. The NOAEL for male and female B6C3F1 mice was 1,000 mg/kg bw/d. The dose levels selected were based on the following: 1) the high-dose, 1,000 mg/kg bw/d, represents the limit dose based on acceptable guidelines (OPPTS 870.3100 and OECD 408) and 2) the lower dose levels were expected to provide dose-response data for any toxicity observed in the high-dose group animals and to ensure the definition of a no-observed-effect level (NOEL) for the test substance.

3. **Diet preparation and analysis** Diets were prepared by serially diluting a concentrated test substance-feed mixture (premix) with ground feed. Premixes were prepared approximately every four weeks. Initial targeted concentrations of the test substance in the diet were calculated from pre-study body weights and historical feed consumption data. Subsequently, test diets were prepared weekly throughout the dosing period based upon the most recent body weight and feed consumption data. The diets were stored at ambient temperature. The stability of the test substance in the diet was determined in the 13-week dietary study in rat (Laboratory Project Study ID - DR-0312-6565-011). The homogeneity of the test material in the low dose level was analysed concurrent with the conduct of the study. Analysis by HPLC of the test substance-feed mixtures to verify the concentration of the test substance in the diet was conducted prior to the beginning of the study (test day 1) and at weeks 7 and 13 of the dosing period. Reference samples (1/dose/sex) from each pre-mix and diet mix were retained and stored at ambient room temperatures.

Results - **Homogeneity Analysis:** The diet with a target concentration of 0.009525% (w/w) from the female 20 mg/kg bw/d dose group was shown to be homogenous, with a standard deviation (SD) of 0.00112 and percent relative standard deviation (%RSD) of 11.8% (mean observed concentration 0.00953% w/w). The SD and %RSD for homogeneity were considered within acceptable limits.

Stability Analysis: XDE-570 was shown to be stable in the diet for at least 30 days at a concentration of approximately 0.00953% (w/w). The concentration was equivalent to the concentration of the female 20 mg/kg bw/d XDE-570 diet. The percent of day zero concentration varied from 91-98% over the 35 day period, but not in a time-dependent manner. The variation was considered within the error of analytical methodology.

Concentration Analysis: Results indicated an acceptable agreement between actual and target levels, with mean percent of target for all diets and premixes ranging from 95 to 109%.

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Dose level (mg/kg bw/d)	Range (% of target concentration)		Mean ± SD (% of target concentration)	
	Males	Females	Males	Females
20	94-103	100-116	97 ± 5	109 ± 8
100	101-108	95-113	104 ± 4	103 ± 9
500	93-96	94-102	95 ± 2	98 ± 4
1,000	94-98	88-103	97 ± 2	97 ± 8
Premix	90-101		96 ± 6	

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. Statistics - Descriptive statistics only (means and standard deviations) were reported for feed consumption, feed efficiency, white blood cell differential counts and red blood cell indices. Body weights, organ weights, clinical chemistry data and appropriate haematological data were evaluated by Bartlett's test for equality of variances. Based on the outcome of Bartlett's test, exploratory data analysis was performed by parametric or non-parametric analysis of variance (ANOVA) followed respectively by Dunnett's test or Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons. Statistical outliers were identified by a sequential test, but routinely excluded only from feed consumption statistics. Because numerous measurements were compared statistically on the same group of animals, the frequency of false positive (Type I) error was unknown, but was considered to be much greater than the nominal alpha.

C. METHODS:

1. Observations: Clinical examinations were conducted on all animals prior to the start of the study and at weekly intervals throughout the duration of the study. A daily cageside examination was made each day of the work week, except on the days when a clinical examination was performed, since the clinical examination was more thorough. An additional observation for moribundity, mortality and the availability of feed and water was made each day of the work week as well as twice daily on weekends and holidays.

2. Body weight: All animals were weighed prior to the start of the study and at weekly intervals during the dosing period.

3. Food consumption and compound intake: Data were collected from all animals and calculations were made weekly during the dosing period by weighing the feeders at the start and end of a measurement cycle. Animals for which food wastage was noted on cage side exams were excluded from the food consumption calculation. From these data, food consumption (g/animal/d) was calculated. Food efficiency (g feed consumed/g bw gain/d) and compound intake (mg/kg bw/d) values were also calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic examination: Eyes were examined on all animals prior to the start of the study using pen-light illumination. At scheduled necropsy, ophthalmological examinations were conducted on all animals using a moistened slide/fluorescent light technique.

5. Haematology & Clinical Chemistry: All animals (10 animals/sex/dose, non-fasted) were anaesthetized with methoxyflurane and blood samples were collected at scheduled necropsy by puncture of the orbital sinus. Haematology samples were mixed with EDTA and blood smears were prepared and stained with Wrights stain. Clinical chemistry samples were collected and serum separated from cells as soon as possible following blood collection. The haematological and clinical chemistry parameters marked with an (X) in tables (a) and (b), respectively, were examined.

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a. Haematology

X	Haematocrit (HCT)*	X	Leukocyte differential count*
X	Haemoglobin (HGB)*		Mean corpuscular Haemoglobin (MCH)
X	Leukocyte count (WBC)*		Mean corpuscular Haemoglobin Concentration (MCHC)
X	Erythrocyte count (RBC)*		Mean corpuscular volume (MCV)
X	Platelet count (PLT)*		Reticulocyte count (RETIC)
	Blood clotting measurements*	X	Erythrocyte Morphology
	(Partial Thromboplastin time)	X	Leukocyte Morphology
	(Thrombin Clotting time)	X	Platelet Morphology
	(Prothrombin time)		

* Recommended for subchronic rodent studies based on Guideline 870.3100
X Examined

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium* (Ca)	X	Albumin* (ALB)
X	Chloride* (Cl)	X	Blood creatinine* (CREAT)
	Magnesium (Mg)	X	Blood urea nitrogen* (UREA)
X	Phosphorus* (P)	X	Total Cholesterol (CHOL)
X	Potassium* (K)	X	Globulins (GLOB)
X	Sodium* (Na)	X	Glucose* (GLUC)
	ENZYMES	X	Total bilirubin (TBILI)
X	Alkaline phosphatase (AP)	X	Total serum protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides (TRIG)
X	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine amino-transferase (ALAT) (also SGPT)*		
X	Serum aspartate amino-transferase(ASAT) (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase (GDH)		

* Recommended for subchronic rodent studies based on Guideline 870.3100
X Examined

6. Urinalysis* Not performed. Urinalysis not required for subchronic dietary studies in rodents according to OECD Guideline 408.

7. Sacrifice and Pathology At the scheduled necropsy, each animal (non-fasted) was weighed, anaesthetized with methoxyflurane, the trachea was exposed and clamped to prevent artifactual aspiration of blood, and the animal was humanely sacrificed via decapitation. The animals were examined externally and were then systematically dissected. The necropsy included *in situ* examination of the eyes by a glass slide technique using fluorescent light illumination. Internal organs were first viewed *in situ* and then removed, incised as appropriate and examined. The organs/tissues, in whole or in part, marked with an (X) in the following table were fixed in neutral, phosphate-buffered 10% formalin. Organs/tissues marked with an (XX) in the table below were weighed prior to fixation. The lungs were infused with buffered formalin to their approximately normal inspiratory volume and the nasal cavity was flushed with formalin delivered via the pharyngeal duct to ensure rapid fixation. A complete histopathological examination (except auditory sebaceous glands and bone joint) of the organs/tissues marked with an (X) in the following table was conducted on all animals from the control and high-dose groups and on all unscheduled deaths. Histopathological examination of the organs/tissues from animals in the low- and mid-dose groups was limited to the liver, kidneys, lungs and grossly-observed lesions. Tissue examined histopathologically were processed by conventional techniques, sectioned at approximately 6 µm and stained with hematoxylin and eosin.

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	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	X	*Thymus*+*		GLANDULAR
X	Ileum*			X	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland T
X	Colon*	XX	Kidneys*+	X	Mammary gland*
X	Rectum*	X	Urinary bladder*	X	Parathyroid*
XX	Liver*+	XX	Testes*+	X	Thyroid*
X	Gall bladder*	X	Epididymides*+		OTHER
X	Pancreas*	X	Prostate*	X	Bone
	RESPIRATORY	X	*Seminal vesicles**	X	Skeletal muscle
X	Trachea*	X	Ovaries*+	X	Skin
X	Lung*	X	Uterus*+	X	All gross lesions and masses*
X	Nose*	X	Oviducts		
X	Pharynx*	X	Cervix		
X	Larynx*	X	Vagina		

* Recommended for subchronic rodent studies based on Guideline 870.3100
+ Organ weights required for rodent studies.
T = required only when toxicity or target organ
X Organ fixed.
XX Organ weighed prior to fixation.

II. RESULTS

A. Observations :

1. Clinical signs of toxicity - There were no treatment-related clinical observations at any dose level.

2. Mortality - There were no treatment-related mortalities. One female at 20 mg/kg bw/d died on study day 7. Prior to death there were no treatment-related clinical observations. Gross pathological findings were limited to a mottled liver, all other tissues appeared normal. The cause of death was not determined.

B. Body weight and weight gain: There were no significant treatment-related changes in body weight or body-weight gain in either sex up to and including 1,000 mg/kg bw/d (limit dose). Body weight and overall body-weight gain (weeks 0-13) are summarized in Table 2.

TABLE 2. Average body weights and body weight gains during 13-weeks of treatment. (a)

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Dose Level mg/kg bw/d	Body Weights (g ± SD)					Overall Body-Weight Gain (weeks 0-13)
	Week 0	Week 3	Week 6	Week 9	Week 13	g ± SD
Male (n = 10 animals/dose)						
0	25.2 ± 1.1	27.5 ± 1.2	28.3 ± 0.8	29.5 ± 0.9	31.4 ± 1.3	6.2 ± 2.0
20	24.8 ± 1.1	27.0 ± 1.1	28.0 ± 1.4	29.4 ± 1.4	30.1 ± 1.3	5.3 ± 1.1
100	24.9 ± 1.1	27.5 ± 1.2	28.2 ± 1.3	29.5 ± 1.4	30.8 ± 1.7	5.9 ± 1.2
500	25.0 ± 1.2	27.3 ± 1.4	28.6 ± 1.3	29.8 ± 1.1	30.2 ± 1.1	5.2 ± 1.1
1,000	25.2 ± 1.0	27.7 ± 1.0	28.5 ± 0.9	29.9 ± 1.0	30.3 ± 0.9	5.1 ± 0.9
Female (n = 10 animals/dose, unless indicated otherwise)						
0	19.3 ± 0.8	22.7 ± 1.4	23.4 ± 1.3	25.2 ± 1.8	25.6 ± 1.6	6.3 ± 1.3
20	18.6 ± 0.7	22.9 ± 0.9 (n = 9)	23.2 ± 1.1	25.4 ± 2.0	25.7 ± 1.5	6.9 ± 1.5 (n = 9)
100	18.5 ± 0.8	22.0 ± 1.0	23.1 ± 1.0	25.3 ± 1.7	25.2 ± 1.5	6.7 ± 1.2
500	18.3 ± 0.8	22.1 ± 1.0	23.2 ± 1.4	25.1 ± 1.4	25.7 ± 2.0	7.3 ± 1.8
1,000	18.5 ± 1.0	21.7 ± 1.1	22.3 ± 1.0	23.9 ± 1.6	24.3 ± 1.5	5.9 ± 1.2

(a) Data obtained from pages 41-44 in the study report for body weight and pages 45-50 for body-weight gain.

C. Food consumption and compound intake:

1. Food consumption - Food consumption was comparable between the treated groups and the controls throughout the study for both sexes up to and including 1,000 mg/kg bw/d (limit dose).

2. Compound consumption Time-weighted average test substance intakes (mg/kg bw/d) and diet concentration (ppm) are summarized in Table 3.

TABLE 3. Time-weighted average test substance intake (mg/kg bw/d) and diet concentration (ppm) in males and females during 13-weeks of treatment. (a)

Dose Level (mg/kg bw/d)	0	20	100	500	1,000
Males					
Average test substance intake (mg/kg bw/d)	-	22	110	549	1,129
Average diet concentration (ppm)	-	105	507	2,589	5,415
Females					
Average test substance intake (mg/kg bw/d)	-	20	101	503	1,007
Average diet concentration (ppm)	-	80	408	1,945	3,970

(a) Data obtained from pages 55-58 of the study report.

3. Food efficiency Food efficiency was comparable between the treated groups and the controls throughout the study for both sexes up to and including 1,000 mg/kg bw/d (limit dose).

D. Ophthalmoscopic examination - There were no treatment-related ophthalmoscopic findings.

E. Blood analyses

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1. Haematology - There were no treatment-related alterations in haematological parameters in either sex up to and including 1,000 mg/kg bw/d (limit dose). Red blood cell, white blood cell and platelet morphology appeared normal for all animals examined.

2. Clinical Chemistry - There were no toxicologically relevant treatment-related clinical chemistry findings. Statistically significant findings included decreased serum urea nitrogen in males at 500 and 1,000 mg/kg bw/d and decreased cholesterol in males at 500 mg/kg bw/d (Table 4). These findings were within the normal range of historical control data for animals of this age and strain from this laboratory and there was no clear dose-response relationship; therefore, in the absence of any corroborating gross pathological, histopathological or other findings were not considered to be toxicologically relevant.

TABLE 4. Significant clinical chemistry findings in males following 13-weeks of treatment. (a)

Dose Level (mg/kg bw/d)	0	20	100	500	1,000
Male (following 13 weeks of treatment) (n = 10 animals/dose)					
Urea Nitrogen (mg/dL)	33 ± 3	31 ± 4	30 ± 3	28 ± 4 *	29 ± 5 *
Cholesterol (mg/dL)	94 ± 7	91 ± 7	95 ± 8	86 ± 5 *	90 ± 6

(a) Data obtained from pages 71 to 74 of the study report.
* Statistically different from control mean by Dunnett's test, $p \leq 0.05$.

F. Urinalysis - Not performed. Urinalysis not required for subchronic dietary studies in rodents according to OECD Guideline 408.

G. Sacrifice and Pathology:

1. Organ weight - Organ weights were unaffected by treatment in both sexes up to and including 1,000 mg/kg bw/d (limit dose).

2. Gross pathology - There were no treatment-related gross pathological observations in either sex at any dose level up to and including 1,000 mg/kg bw/d (limit dose). Incidental findings included an ovarian mass in one control female and a lung nodule, observed at the time of trimming of fixed tissues, in one male at 1,000 mg/kg bw/d. Gross pathological findings in the female at 20 mg/kg bw/d dying on study day 7 were limited to a mottled liver, all other tissues appeared normal.

3. Microscopic pathology -Treatment-related histopathological findings were observed in the kidney in males at 500 mg/kg bw/d and in both sexes at 1,000 mg/kg bw/d (Table 5). A very slight, multi-focal bilateral hypertrophy of the epithelial cells of the collecting ducts was observed in 10/10 males at 500 and 1,000 mg/kg bw/d and in 8/10 females at 1,000 mg/kg bw/d. The hypertrophy of the collecting ducts was characterized by enlargement of the epithelial cells lining the collecting ducts, principally of the inner stripe of the outer zone of the medulla. The hypertrophied cells exhibited a granular, pale, eosinophilic cytoplasm with numerous mitochondria and were compatible with the intercalated cells which are normally involved in the regulation of acid-base balance through the modulation of bicarbonate resorption and hydrogen ion secretion in the collecting ducts. Functional abnormalities of the collecting duct manifest primarily as an acidification defect and impaired concentrating ability, however, urinalysis was not performed. There were no toxicologically relevant clinical chemistry findings (serum creatinine, nitrogen or electrolyte levels) to correlate with the histopathological findings in the kidney or to indicate an impairment of renal function and there was no cellular degeneration or necrosis evident in the kidneys. Morphologically, the lesions were essentially the same as those reported in Fischer 344 rats following 13-weeks of treatment at similar dose levels (Dow Chemical Company Laboratory Project Study ID - DR-0312-6565-011) where urinalysis findings indicative of impaired concentrating and an acidification defect were observed (reduced urinary specific gravity and urinary acidification, respectively). There were no treatment-related histopathological findings in either sex at 20 and 100 mg/kg bw/d or in females at 500 mg/kg bw/d.

TABLE 5. Significant histopathological findings (values expressed as # animals with findings/total # animals

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examined). (a)

Dose Level (mg/kg bw/d)		0	20	100	500	1,000
Males (following 13 weeks of treatment) (n = 10 animals/dose)						
Kidney	- hypertrophy, epithelial cells of collecting ducts (multi-focal, bilateral, very slight)	0/10	0/10	0/10	10/10	10/10
Males (following 13 weeks of treatment) (n = 10 animals/dose)						
Kidney	- hypertrophy, epithelial cells of collecting ducts (multi-focal, bilateral, very slight)	0/10	0/10	0/10	0/10	8/10

(a) Data obtained from pages 78-83 of the study report.

III. DISCUSSION

A. Investigators' conclusions (extracted from page 26 of the study report): "XDE-570 administered to male ane female B6C3F1 mice for thirteen weeks at dosages of 20, 100, 500 or 1000 mg/kg bw/day caused no adverse systemic effects. The only effect attributed to XDE-570 ingestion was a very slight hypertrophy of the cells of the collecting ducts of the kidneys. This change, probably a physiological response, was noted in both sexes given 1000 mg/kg bw/day and males given 500 mg/kg bw/day. Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) was 1000 mg/kg bw/day in male and female B6C3F1 mice, while the no-observed-effect-level (NOEL) was 100 or 500 mg/kg bw/day in male and female B6C3F1 mice, respectively."

B. Reviewer comments: There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, ophthalmoscopy, haematology, clinical chemistry, organ weights or gross pathology. Histopathological examination of the kidney, revealed a very slight, multi-focal bilateral hypertrophy of the epithelial cells of the collecting ducts in 10/10 males at 500 and 1,000 mg/kg bw/d and in 8/10 females at 1,000 mg/kg bw/d. The hypertrophied cells were compatible with the intercalated cells which are normally involved in the regulation of acid-base balance through the modulation of bicarbonate resorption and hydrogen ion secretion in the collecting ducts. Functional abnormalities of the collecting duct manifest primarily as an acidification defect and impaired concentrating ability, however, urinalysis was not performed. There were no toxicologically relevant clinical chemistry findings (serum creatinine, nitrogen or electrolyte levels) to correlate with the histopathological findings in the kidney or to indicate an impairment of renal function and there was no cellular degeneration or necrosis evident in the kidneys.

The LOAEL is 500 mg/kg bw/d based on histopathological findings in the kidneys (hypertrophy of the epithelial cells of the collecting ducts) in males. The NOAEL is 100 mg/kg bw/d.

C. Study deficiencies: OECD Guideline 408 (Subchronic Oral toxicity - Rodent: 90-day Study) recommend that adrenal gland weights be determined, in this study adrenal glands were not weighed although there were no significant gross pathological or histopathological findings in the adrenal glands. Urinalysis was not performed, however, urinalysis is not required for subchronic dietary studies in rodents according to OECD Guideline 408. These deficiencies should not impact on the outcome of this study; therefore, this study is considered acceptable and satisfies the guideline requirement for a subchronic oral study (OPPTS 870.3100; OECD 408) in mice.

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