RB-1777

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

008207

DEC 19 1990

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Aliette: Review of a non-guideline 90-day feeding study in rats

TO: S. Lewis / J. Stone, PM Team 21
Registration Division (H7505C)

FROM: Wharg Phang, Ph.D. 12/13/90
Pharmacologist
Tox. Branch II / HED (H7509C)

THROUGH: James Rowe, Ph.D. 12/13/90
Section Head
and
Marcia van Gemert, Ph.D. 12/18/90
Branch Chief
Tox. Branch II / HED (H7509C)

Introduction: In 1986, the Toxicology Branch Peer Review Committee evaluated the toxicology data on fosetyl-Al. Based upon the findings that fosetyl-Al induced an increase in the incidence of urinary bladder tumors (adenomas and carcinomas combined) in male Charles River CD rats which received the test article at dietary concentration of 30,000 ppm for 2 years, fosetyl-Al was classified as a Category C oncogen with out risk assessment. This 90-day feeding study has been specially designed and conducted to provide evidence for the registrant's rebuttal that the urinary bladder tumors were "the result of a disturbance of the phosphorus/calcium imbalance due to an overloading of animals with phosphorus ... which led to an increased incidence of bladder stones and subsequent irritation and proliferation of the bladder epithelium" (Memorandum: J. Quest to H. Jacoby, June 12, 1986).

Discussion: The 90-day feeding study has been evaluated and the conclusion is as follows:

Groups of rats (70/sex/dose) received Fosetyl-Al at dietary concentrations of 0, 8,000, 30,000, and 50,000 ppm. Each dose group was further divided into 7 subgroups each of which received the test article for a different length of time (ranged from 2 weeks to 13 weeks), and some subgroups were then placed on the

normal diet for different recovery periods (ranged from 8 weeks to 21 weeks). The results established that, in male rats, Fosetyl-Al at 30,000 ppm or more produced diuresis, hypercalciuria, acidic urine, uroliths in the kidneys, ureters, and bladder, and histopathological changes in the urinary system. The histopathological changes were characterized by the following:

kidneys: pyelitis, pyelonephritis, papillary necrosis, dilatation of collecting tubules, and transitional hyperplasia.

Ureters: dilatation, ureteritis, and transitional cell hyperplasia.

Urinary bladder: submucosal edema, papillary hyperplasia, cystitis, and transitional cell hyperplasia.

The results also indicated that the histopathological changes in the urinary system were related to the presence of uroliths.

This study is a non-guideline study which is specifically designed to show that the histopathological changes in the urinary bladder seen in an earlier 2-year chronic/oncogenicity study were related to the calculi formation in the bladder. Therefore, it will not be classified according to the Core Classification Guidelines for toxicology studies. However, it is scientifically acceptable.

The results of this study and all available toxicology data on Fosetyl will be presented to the Peer Review Committee on Carcinogenicity of HED which will re-consider the carcinogenic potential of this chemical.

Aliette toxicology review

Page _____ is not included in this copy.

Pages 15 through 39 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewer: Whang Phang, Ph.D. Whang Phang 12/13/90
HFAS/Tox. Branch II/HED (H7509C)

Secondary Reviewer: James Rowe, Ph.D. James Rowe 12/13/90
Section Head
HFAS/Tox. Branch II/HED (H7509C)

DATA EVALUATION REPORT

Chemical: Fosetyl-Al; Aluminum tris(-O-ethyl phosphonate); Aliette®

Study Type: 90-Day feeding study (rats) (Non-guideline, special study)

Note: In 1986, the Toxicology Branch Peer Review Committee evaluated the toxicology data on fosetyl-Al. Based upon the findings that fosetyl-Al induced an increase in the incidence of urinary bladder tumors (adenomas and carcinomas combined) in male Charles River CD rats which received the test article at dietary concentration of 30,000 ppm for 2 years, fosetyl-Al was classified as a Category C oncogen with out risk assessment. This 90-day feeding study has been specially designed and conducted to provide evidence for the registrant's rebuttal that the urinary bladder tumors were "the result of a disturbance of the phosphorus/calcium imbalance due to an overloading of animals with phosphorus ... which led to an increased incidence of bladder stones and subsequent irritation and proliferation of the bladder epithelium" (Memorandum: J. Quest to H. Jacoby, June 12, 1986).

Caswell No.: 12B **HED Proj. No.:** 0-0469

MRID No.: 413152-01 **EPA ID No.:** 264-266

EPA Record No.: 257775

Sponsor: Rhône-Poulenc Ag Co.

Testing Laboratory: Bio-Research Ltd.
87 Senneville Rd
Senneville, Quebec H9X 3R3
Canada

Citation: Osborne, B.E. (1989), A maximum 13-week dietary toxicity study of Fosetyl-Al in the Albino rats with a maximum 21 week recovery period. Bio-Research Ltd.; Lab. Proj. No. 83040. Aug. 9, 1989.

Conclusion: Groups of rats (70/sex/dose) received Fosetyl-Al at dietary concentrations of 0, 8,000, 30,000, and 50,000 ppm. Each dose group was further divided into 7 subgroups each of which received the test article for a different length of time (ranged from 2 weeks to 13 weeks), and some subgroups were then placed on the normal diet for different recovery periods (ranged from 8 weeks to 21 weeks). The results established that, in male rats, Fosetyl-Al at 30,000 ppm or more produced diuresis, hypercalciuria, acidic urine, uroliths in the kidneys, ureters, and bladder, and histopathological changes in the urinary system. The histopathological changes were characterized by the following:

kidneys: pyelitis, pyelonephritis, papillary necrosis, dilatation of collecting tubules, and transitional hyperplasia.

Ureters: dilatation, ureteritis, and transitional cell hyperplasia.

Urinary bladder: submucosal edema, papillary hyperplasia, cystitis, and transitional cell hyperplasia.

The results also indicated that the histopathological changes in the urinary system were related to the presence of uroliths.

This study is a non-guideline study which is specifically designed to show that the histopathological changes in the urinary bladder seen in an earlier 2-year chronic/oncogenicity study were related to the calculi formation in the bladder. Therefore, it will not be classified according to the Core Classification Guidelines for toxicology studies. However, it is scientifically acceptable.

Materials and Methods

Test article: Fosetyl-Al was a fine white powder with Lot No. DA 497, additional Code No. LS 74 783 Ca (39148-24-8); 97.3% purity.

Animals: Sprague-Dawley rats, Crl:CD^{R} (SD) BR strain (330 males and 331 females) were obtained from Charles River Canada Inc., St. Constant, Quebec, Canada. At the initiation of the study, the animals were approximately 6 weeks old, and body weights were 165 to 229 gm for males and 123 to 179 gm for females.

Study Design

It should be reiterated that this study was specially designed to investigate urinary bladder changes seen in rats of an earlier 2-year rat study. In this study, the rats were treated with Fosetyl-Al at dietary levels ranged from 8,000 to 50,000 ppm for up to 13 weeks followed by a recovery period of up to 21 weeks. The

urinary biochemical profile, the development of urinary calculi, and any gross and histopathological changes in the kidneys and urinary tract were examined to establish a possible cause-effect relationship for the increase in the incidence of urinary bladder tumors.

Prior to the initiation of the treatment, 5 rats/sex were randomly selected from the total number of animals for analyzing the baseline values of biochemical parameters of blood, feces, and urine. The animals were then randomly divided into 4 dose groups (70 rats/sex/dose). The dietary concentrations of Fosety-Al tested were 0, 8,000, 30,000, and 50,000 ppm. Each dose group was then further divided into 7 subgroups which were treated for various times and placed on the control diet for different recovery periods. The experimental scheme and the sacrifice schedules are presented below:

No. of animals per subgroup	Treatment Period Weeks	Recover Period Weeks	Sacrifice Week
10	2		2
10	4		4
10	8		8
10[b]	13		13
10[a]	8	8	16
10[a]	8	16	24
10[b]	13	21	34

a: In the report, these groups are referred to as Subpopulation 1.
b: These groups are referred to as Subpopulation 2, in the report.

Test diet preparation: The test diet was prepared weekly by mixing appropriate amounts of the test article with the control diet. The prepared test diet was stored at room temperature. Samples of the test diet were collected and analyzed for the stability and homogeneity.

Clinical Observations: All test animals were examined twice daily for signs of mortality and toxicity.

Body weights: All test animals were weighed weekly during the acclimation and treatment periods. At the scheduled sacrifice, the fasted body weights of the test animals were measured.

Food consumption: The food consumptions were reported to be determined weekly.

Compound intake: The chemical intake was calculated for each interval using the group mean values of the food consumption and the following formula:

$$\text{Average achieved intake (mg/kg/day)} = \frac{\text{dietary con. (mg/kg)}}{\text{mid-wk group mean body weight}} \times \frac{\text{group mean food intake (gm/rat/wk)}}{7}$$

Water consumption: Water consumption was measured on various groups of the test animals.

Hematology & Clinical chemistry: Prior to the initiation of the study, blood samples were collected from 5 rats/sex . During the study period, blood samples were collected from either 5 or 10 rats/sex/dose at various treatment periods.

a: Hematology: The following hematological parameters were examined:

- hematocrit
- hemoglobin
- red blood cell counts
- white blood cell counts (total & differential)
- platelet counts
- Wintrobes constants (MCV, MCHC, & MCH) (calculated)
- blood smear

b. Clinical chemistry: The following clinical chemistry parameters were measured:

- blood urea nitrogen (BUN)
- total protein
- creatinine
- glucose
- albumin
- sodium
- potassium
- calcium
- total CO_2
- inorganic phosphorous
- aluminum

Urinalysis: Urine samples were collected at various times from 5 rats/sex/dose for analyses. The following parameters were assayed:

- color and appearance
- pH
- glucose
- ketones
- blood
- volume
- specific gravity (SG)
- protein
- bilirubin
- urobilinogen
- sodium
- potassium
- calcium
- total phosphorous
- aluminum
- oxalate
- microscopy of centrifuge deposit
- nitrite

Fecal examinations: Fecal samples were collected and analyzed for the following parameters:

aluminum calcium phosphorous

Urinary calculi examination: The details of the experimental methods were not reported, but the following elements were analyzed:

aluminum calcium phosphorous magnesium

Gross pathology: Prior to the initiation of the study, 5 rats/sex were sacrificed, and gross pathological examinations were performed to obtain a baseline evaluation. During the study, gross pathological examinations were conducted in all test animals when possible. " For each animal, necropsy consisted of an external examination, including identification of all clinically recorded lesions, as well as a detailed internal examination. The abdominal cavity was opened and urinary bladder was inflated (but not distended) with Zenker's fluid".

Kidneys and thyroid with parathyroid were removed and weighed. In addition, kidneys, ureters, thyroids with parathyroids, and bones were removed and fixed in buffered 10% formalin. The urinary bladder was fixed in Zenkers's fluid.

Histopathology: Histopathological examinations were conducted on bladder, kidneys, ureters, and thyroids of all animals. In addition, the urinary bladder was examined for any crystalline formation. Representative calculi found in the urinary bladder were photographed. The urinary calculi from 10 rats were removed and assayed.

Statistical analyses: Certain data were analyzed for homogeneity of variance using Bartlett's test. Dunnett's "t" test was used to assess the significance of inter-group differences. Kruskal-Wallis test was used to analyze heterogeneous data.

Quality assurance: A quality assurance statement was signed and included in the report.

Results

a). Mortality: During the study, 10 males of 50,000 ppm and 3 males of 30,000 ppm group died or were sacrificed *in extremis*. Before death, these animals showed signs of "weakness, skin and eye pallor, tremors, hypothermia, and abdominal distension". Wetness and red/brown staining of the abdominal fur were consistently seen, and these signs were related to diuresis which was also observed. These gross pathology examinations showed the presence of calculi in the urinary system (kidneys, ureters, and urinary bladder) and dilatation of the bladder, ureters and/or pelves of kidneys. The histopathology findings were urolithiasis, papillary hyperplasia in the bladder, hydronephrosis, nephritis,

papillary necrosis, and pelvic transitional cell hyperplasia in the kidneys and occasional transitional cell hyperplasia in the ureters. No death was reported in 8,000 ppm rats.

b). Clinical observation: Clinical signs consisted of abdominal wetness, red/brown fur staining and/or yellow fur staining, and diuresis were seen in 30,000 and 50,000 ppm males at various treatment periods. However, the above clinical signs were seen to a lesser extent in females of similar dose groups. The diuresis was reported to subside slightly after 4 weeks or 13 weeks, but the staining of the abdominal fur persisted into 8 or 13 weeks of the recovery periods. Rats which received 8,000 ppm test article did not exhibit these clinical signs.

c). Body weights: The relevant group mean body weight data were excerpted from the report and presented in Table 1. Both male and female rats of 50,000 ppm groups showed statistically decreases in body weights at various treatment periods, and the decreases persisted through the 21 week recovery period (Table 1). A less dramatic decrease in body weights was also seen in 30,000 ppm males, but during the recovery periods, the body weights of these animals were comparable to those of the controls.

The body weights of 30,000 ppm females and of 8,000 ppm males and females were comparable to those of the controls (Table 1).

c). Food consumption: Food consumptions in both 50,000 ppm males and females were significantly decreased at various treatment periods relative to those of the controls. However, after the treatment stopped, the food consumptions returned to the level of the controls (Figure 1). On some occasions of the first 6 weeks of the treatment period, a decrease in food consumptions was seen in 30,000 ppm males. A decrease in food intake in 8,000 ppm males was seen only on isolated occasions. A persistent decrease in food intake was not seen in females of 30,000 or 8,000 ppm groups.

d). Compound intake: The average compound intake during the treatment periods was calculated as follows:

Dietary Concentration of Fosetyl-AL ppm	Average Compound Intake gm/kg/day	
	Male	Female
8,000	0.5	0.6
30,000	2.1	2.5
50,000	3.5	4.2

e). Water consumption: A significant increase in water consumption

was seen in 50,000 ppm males and females and in 30,000 ppm males. This effect persisted in 50,000 ppm males and females after the treatment was ceased. Notable changes were not seen in other dose levels.

f). Hematology: At 2 and 8 weeks of the treatment periods, an increase in the levels of erythrocyte counts, hemoglobin, and platelets was seen in 50,000 ppm males and females. These hematological changes were likely caused by diuresis.

g). Clinical chemistry: The clinical chemistry results at various analysis periods were excerpted from the report and presented in Tables 2A, 2B, 2C, 2D, and 2E. A statistically significant increase in the levels of BUN, phosphorous, and CO_2 was found in 50,000 ppm males and females at various periods of treatments (Tables 2A to 2E). The increase in the BUN level persisted during the treatment and the recovery periods although females showed a slight recovery. The levels of phosphorous and CO_2 returned to the level of the controls at the recovery periods.

An increase in the phosphorous, BUN, and CO_2 levels was also seen in 30,000 ppm animals during the initial periods of the study (Tables 2A and 2B). Significant changes were not seen in other dose levels.

h). Urinalysis: The relevant urinalysis data at various treatment and recovery periods were excerpted from the report and presented in Tables 3A through 3E. All treated males and females showed a decrease in urinary pH and an increase in the urinary Ca++ levels while receiving the test compound. The urinary phosphorous levels were decreased in the treated males and females relative to those of the controls, and this decrease might due to diuresis. Urinary aluminum levels were also elevated in all treated animals during the treatment periods. Urine volumes were consistently increased in 50,000 ppm males and females at different sacrifice periods. When the treatment ceased, some of the changes in the urinary electrolytes virtually returned to the control levels (Table 3E).

i). Fecal analysis: The relevant results of fecal analyses were excerpted from the report and presented in Tables 4A to 4E. There was an overall decrease in fecal Ca++ levels in 50,000 ppm males and females despite an initial increase (at 2 weeks of treatment period) in 50,000 ppm males. A consistent and dose-related increase in fecal aluminum level was seen in all treated males and females. The phosphorous levels were also increased in 50,000 ppm males and females at different treatment durations. However, all these fecal electrolyte changes returned to the control levels after the treatment was stopped (Tables 4A through 4E).

j). Gross pathology: The major gross pathology findings were associated with the presence of calculi in the urinary system. Calculi were found in kidneys, ureter, and urinary bladder of 30,000 and 50,000 ppm males. The kidney calculi were mainly found in the pelves. The ureter calculi often "seen to be causing a virtual obstruction of the duct"; the registrant presented photographic results to support this observation (pages 1387-1402 of the report). The urinary bladder calculi were reported to be in greater number and larger size than the calculi found in the kidneys and ureter. In addition, the number and size of the urinary bladder calculi were also greatest at the 2 week sacrifice; at each subsequent sacrifice the size and number of the urinary bladder calculi progressively decreased. Therefore, the selective gross pathology data of 2 and 4 weeks sacrifices were excerpted from the report and presented in Tables 5A and 5B.

The reduction in the size and number of urinary bladder calculi after 2 weeks of treatment might be associated with the decrease in the pH of the urine causing the dissolution of the urinary bladder calculi.

The recovery animals showed a decrease in the incidence of urinary bladder calculi. The calculi were not found in 8,000 ppm and the control animals. The incidence of urinary bladder calculi was very few in 50,000 ppm females and essentially none in lower dose group females despite the presence of calculi in the kidneys and the ureters (Tables 5A and 5B).

The kidneys of the affected animals often showed dilatation, irregular surface, enlargement, and discoloration. Dilatation of the ureter was frequently seen in the affected animals.

k). Organ weights: The absolute kidney and thyroid weights were not substantially different from the controls in animals treated for less than 13 weeks. The relative kidney weights (organ/body) were increased in 50,000 ppm males and females at various sacrifice periods prior to 13 weeks, but this increase was mainly due to a decrease in the body weights of these animals.

After 13 weeks of treatment, the absolute kidney weights were increased in 30,000 and 50,000 ppm males and 50,000 ppm females relative to those of the controls as indicated below:

	Absolute Kidney Weights (gm)		
	Control	30,000 ppm	50,000 ppm
Males:	2.90 ± 0.39	3.41 ± 0.39a	3.75 ± 0.32b
Females:	1.86 ± 0.14	1.90 ± 0.21	2.10 ± 0.24a

a: $p < 0.05$; b: $p < 0.01$

The kidney weights of recovery animals were essentially comparable to those of the controls.

l). Urinary calculi analysis: Calculi were collected from 30,000 and 50,000 ppm males and females at 2-week sacrifice and analyzed for phosphorous, magnesium, aluminum, and calcium contents. The results are excerpted from the report and presented in Table 6. The results indicated that these calculi consisted of approximately 23% phosphorous, 33% calcium, 0.2% magnesium, and less than 0.1% aluminum (Table 6). The remaining portion was thought to be oxalate which was not analyzed. In this reviewer's opinion, the calculus analysis was scientifically insufficient. The analysis on oxalate, uric acid, protein, and the entire unit of the test chemical should have been included to properly characterize the composition of a calculus.

m). Histopathology: The histopathology findings in the Fosetyl-Al treated animals were closely associated with the presence of the calculi or uroliths in the urinary system. The findings on kidneys, ureter, and urinary bladder at different sacrifice periods were excerpted from the report and presented in Tables 7A through 7E.

1). Kidneys: In the kidneys, an increase in the incidence of uroliths, chronic interstitial nephritis, hydronephrosis, pyelonephritis, transitional cell hyperplasia, and papillary necrosis was commonly seen in 30,000 and 50,000 ppm males and 50,000 ppm females at different sacrifice periods. Some of these incidences were also increased in the recovery males and females (Tables 7A to 7E). The author of the report believed that hydronephrosis and other findings in kidneys were likely to be induced by urine stasis resulting from the obstruction of the urine flow.

The report also noted that a benign transitional cell papilloma was found in a 50,000 ppm male which received Fosetyl-Al for 8 weeks followed by 16 weeks of recovery, but this rat died in week 22.

2). Ureters: An increase in the incidence of ureteritis, the presence of uroliths, dilatation, was seen in

30,000 and 50,000 ppm males and 50,000 ppm females whereas transitional cell hyperplasia was seen predominantly in 50,000 ppm males (Tables 7A through 7E).

3). Urinary bladder: In the urinary bladder. an increase in the incidence of submucosa edema, papillary hyperplasia, the presence of uroliths, and cystitis was seen in 30,000 and 50,000 ppm males at different treatment periods. Some of these findings were also seen during the recovery periods (Table 7E). In contrast, the above findings were rather low in females of similar dose groups; for example, the presence of uroliths was seen in 1/10 females verses 5/9 males which received 50,000 ppm test compound and sacrificed at 8 weeks of treatment (TAble 7C).

Papillary hyperplasia was seen mainly in 30,000 and 50,000 ppm males and 50,000 ppm females, and none was reported in 30,000 ppm females or 8,000 ppm males and females. Papillary hyperplasia was characterized by the "folded processes or expansion of the lamina propria covered by a hyperplastic urothelium of varying thickness and were generally accompanied by a minimal inflammatory infiltrate". When the treat-treatment stopped, a significant decrease in these proliferative changes was found.

Discussion and Conclusion

Groups of rats (70/sex/dose) received Fosetyl-Al at dietary concentrations of 0, 8,000, 30,000, and 50,000 ppm. Each dose group was further divided into 7 subgroups each of which received the test article for a different length of time (ranged from 2 weeks to 13 weeks), and some subgroups were then placed on the normal diet for different recovery periods (ranged from 8 weeks to 21 weeks). The results indicated that Fosetyl-Al at 30,000 and 50,000 ppm produced death and diuresis in males and some females. A decrease in body weight and food consumption was consistently seen in 50,000 ppm males and females and to a lesser extent in 30,000 ppm males. However, during the recovery period the body weights and food con-sumptions were comparable to those of the controls. An increase in water consumption was also seen in 30,000 and 50,000 ppm males and in 50,000 ppm females. Hematological changes were found in 50,000 ppm males and females, but the changes were related to diuresis.

Clinical chemistry data indicated increases in BUN nitrogen, phosphorous, and CO_2 in 50,000 ppm males and females. During the recovery periods, CO_2 and phosphorous levels were comparable to those of the controls, but the increase in BUN level persisted.

The urinalysis results indicated a decrease in the pH values in all treated animals after 2 weeks of treatment and an increase in urinary Ca++ levels in 30,000 and 50,000 males and females. The urinary phosphorous level was decreased in 30,000 and 50,000 ppm males and females; this decrease was related to diuresis. Urinary aluminum level was increased, and it was thought to be due to contamination of the urine samples since the blood level of aluminum was low.

Fecal analysis revealed that there was an overall decrease in the Ca++ level in 50,000 ppm males and females relative to that of the controls. The fecal aluminum level was consistently higher in the treated animals, and this increase was dose-related. The normal level of blood aluminum and the dose-related increase in the fecal aluminum level indicated that aluminum was not absorbed via the intestinal tracts.

Both gross pathology and histopathology data showed that calculi or uroliths were present in kidneys, ureters, and urinary bladder of 30,000 and 50,000 ppm males and of a few 50,000 ppm females. The chemical compositions of the urinary bladder calculi were approximately 23% phosphorous, 33% calcium, 0.2% magnesium, and less than 0.1% aluminum. In the kidneys, the increased incidence of urolithiasis, hydronephrosis, pyelitis, pyelonephritis, papillary necrosis, dilatation of the collecting tubules, and transitional hyperplasia of the pelvis was seen in 30,000 and 50,000 ppm males and 50,000 ppm females. In the ureters, an increase in the incidence of urolithiasis, ureteritis, and dilatation was found in 30,000 and 50,000 ppm males and 50,000 ppm females. In the urinary bladder, an increase in the incidence of urolithiasis, submucosa edema, papillary hyperplasia, and cystitis was seen in 30,000 and 50,000 ppm males at different treatment durations, and some of these finding persisted to the recovery periods. After 13 weeks of treatment, the absolute kidney weights of 30,000 and 50,000 ppm males and 50,000 ppm females were significantly increased ($p < 0.05$).

Based upon the data presented in this report, the histopathological findings in the kidneys, ureters, and urinary bladder were related to the presence of uroliths in these organs because, in 8,000 ppm males and females and 30,000 ppm females, uroliths were virtually absent in their urinary systems, and accordingly the histopathological changes were not seen. Most importantly, an evaluation of the individual animal histopathology and the urinalysis data revealed that the presence of calculus was almost always associated with urinary hypercalciuria, acidic urine, transitional cell hyperplasia and/or papillary hyperplasia of the urinary bladder, ureter, and kidney tubules.

The report did not attempt to offered any explanation for the substantially lower incidence of calculi formation in 50,000 ppm females relative to that of the males.

This study is a non-guideline study which is specifically designed to show that the histopathological changes in the urinary bladder seen in an earlier 2-year chronic/oncogenicity study were related to the calculi formation in the bladder. This study, however, will not be classified according to the Core Classification Guidelines for toxicology studies, but the results of this study and all available toxicology data on Fosetyl will be presented to the Peer Review Committee on Carcinogenicity of HED which will re-consider the carcinogenic potential of this chemical.