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September 11, 1998

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Attn: TSCA 8(e) Coordinator
TSCA Section 8(e) Supplemental Submission

Dear Sir/Madam:

is submitting the enclosed supplemental notification pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA). This submission is a supplement to an initial submission dated February 18, 1998 for

(No CAS assigned) (Attachment I). The test substance is named

The initial submission was to report toxicology findings from a 28-day oral (gavage) study in rats that was conducted as a range-finding precursor for a 90-day oral study in rats. In the pilot study, conducted at Huntingdon Life Sciences (U.K.), CD rats were administered by gavage for 28 consecutive days at dose levels of 0 (corn oil vehicle control), 100, 500, and 1000 mg/kg/day. Findings reported in the previous submission are described the Attachment I.

This submission reports unaudited findings from the 90-day oral toxicity study in rats, also conducted at Huntingdon Life Sciences (U.K.). In the 90-day study, CD rats (10/sex/group) were dosed by gavage at dose levels of 0 (corn oil vehicle control), 5, 50, and 600 mg/kg/day for 90

Page 2

September 11, 1998

consecutive days (13 weeks). An additional 10 rats/sex/group were dosed at 0 (corn oil) or 600 mg/kg/day for 90 days and retained for 28 days further, without exposure, as "recovery groups." Each rat was subjected to a gross necropsy, blood samples were collected for hematological and blood chemistry evaluation, and individual organ weights were measured. Organ weights were evaluated as the absolute weight, the weight relative to body weight and as the weight adjusted to individual body weight. All weighed tissues and additional tissues were fixed for histological processing. Estrus cyclicity was measured during the last weeks of dosing and/or of the recovery period. Semen parameters were measured at the end of dosing or recovery.

Overall, the data of the 90-day oral toxicity study in rats are similar to findings in the 28-day oral toxicity range-finding pilot study reported earlier. A table of study findings is attached.

During the in-life phase of the study, the following findings were observed in the 600 mg/kg/day group: hairloss (both sexes); brown/yellow staining in the urogenital regions (females); reduced body weight gain (both sexes); reduced food consumption (females, week 1-13); increased incidence of abnormal (irregular or extended estrus) estrus cycles (females).

At 600 mg/kg/day, liver and adrenal weights were increased in both sexes. In males at this dose, reduced weights were recorded for the testes, epididymides, seminal vesicles/prostate, and prostate. In females treated at 600 mg/kg/day, relative kidney weight and kidney weight adjusted to body weight were increased. Microscopic evaluation of organs from the 600 mg/kg/day group noted generalized hepatocyte hypertrophy, periportal hepatocyte vacuolization, adrenal cortical hypertrophy, and increased alveolar macrophages in the lungs. In high dose males, microscopic evaluations also noted reduced colloid in the prostate and seminal vesicles. There were no treatment attributed histological findings in the testes or epididymides. Histopathological findings noted in high dose females were endometrial epithelial hypertrophy and hyperplasia in the uterus, and prominent developing follicles with few corpora lutea in ovaries. Statistically significant blood hematology/chemistry findings at 600 mg/kg/day were: reduced packed cell volume (both sexes); reduced hemoglobins (both sexes); reduced mean cell hemoglobin (females); increased prothrombin time (females); reduced eosinophils, monocytes and leukocytes (males); increased neutrophils (females); increased alkaline phosphatase, glutamic pyruvic transaminase, and gamma glutamyl transpeptidase (both sexes); reduced cholesterol (both sexes); reduced glucose (both sexes); increased albumin and A/G ratio (males); decreased albumin and A/G ratio (females); increased sodium (males); reduced calcium and potassium (females). At 600 mg/kg/day, testosterone was elevated in males and estradiol was reduced in females, but the differences were not statistically significant. Statistical evaluation is not yet available for semen parameters. All treated groups had slightly higher percentages of motile sperm and progressive sperm, slightly lower mean epididymidal sperm counts, and slightly lower percentages of morphologically normal sperm. The data did not display a dose-related trend.

Page 3
September 11, 1998

There was no organ weight or histopathology findings attributed to treatment at 5 or 50 mg/kg/day. At 50 mg/kg/day, findings were limited to hairloss and reduced calcium in the females.

In the recovery group previously treated at 600 mg/kg/day, there was incomplete improvement of hairloss (reduced severity). During the recovery period, body weight gain in males increased over control values while body weight gain in females continued to be reduced when compared to controls. Food consumption in both sexes was similar to control values. In females, there was a reduction in the incidence of abnormal estrus cycles. Statistically significant organ weight changes were liver weight (males); adrenal weight (females); epididymal weight ; ovary weight . Microscopic evaluation of tissues collected at the end of the recovery period noted increased alveolar macrophages in the lungs of female rats. No data are yet available for the microscopic evaluation of the reproductive organs or adrenals. Blood chemistry/hematological findings in females were: reduced packed cell volume; reduced total protein; reduced calcium; reduced cholesterol; increased glucose; increased chloride. In males, glutamic pyruvic transaminase was reduced. Following the recovery period, there were no apparent differences in semen parameters between the control and treated groups.

All data are currently in draft, unaudited form. The toxicological significance of these findings is still being assessed. When we receive the final report for this study, we will submit it to you.

Our Material Safety Data Sheet is under revision to describe these findings.

If you have any questions, please contact Mr. _____ (TSCA Coordinator) at _____ . A sanitized version of this letter and data table is enclosed.

Sincerely,

Encl: Attachment I

Cc:

13-Week Oral Gavage Study in Rats; Preliminary Results

| | mg/kg/day | Males | | | | | Females | | | | | | |
|--------------------------------------|-----------|-------|------|------|--------|------|---------|------|--------|--|--|--|--|
| | | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 | | | | |
| | | | | | | | | | | | | | |
| Mean Body Weight Gain (g) | | | | | | | | | | | | | |
| Weeks (0-13) | | 377 | 379 | 363 | 271** | 165 | 160 | 164 | 143** | | | | |
| % of Control | | | 101 | 96 | 72 | | 97 | 99 | 87 | | | | |
| Recovery Weeks (0-4) | | 16 | | | 54** | 11 | | | 4 | | | | |
| % of Control | | | | | 338 | | | | 36 | | | | |
| (a) Mean Food Consumption (g) | | | | | | | | | | | | | |
| Weeks (1-13) | | 2520 | 2481 | 2364 | 2486 | 1818 | 1772 | 1755 | 2001** | | | | |
| % of Control | | | 98 | 94 | 99 | | 97 | 97 | 110 | | | | |
| Recovery Weeks (1-4) | | 871 | | | 917 | 649 | | | 678 | | | | |
| % of Control | | | | | 105 | | | | 104 | | | | |
| Mean Food Efficiency | | | | | | | | | | | | | |
| Weeks (1-13) | | 6.7 | 6.5 | 6.5 | 9.2 | 11.0 | 11.1 | 10.7 | 14.0 | | | | |
| Recovery Weeks (1-4) | | 54.1 | | | 16.8 | 59.7 | | | 167.8 | | | | |
| Mean Organ Weights (g) | | | | | | | | | | | | | |
| Terminal BW (Week 14) | | 523 | 547 | 531 | 438 | 312 | 304 | 310 | 287 | | | | |
| Terminal BW (Week 18) | | 586 | | | 497 | 324 | | | 294 | | | | |
| Liver - absolute weights (Week 14) | | 18.7 | 18.6 | 18.8 | 21.6 | 12.3 | 12.2 | 12.1 | 16.9 | | | | |
| Liver - adjusted weights (Week 14) | | 18.1 | 16.8 | 17.7 | 25.0** | 11.9 | 12.2 | 11.7 | 17.8** | | | | |
| Liver - absolute weights (Week 18) | | 19.7 | | | 19.2 | 13.2 | | | 12.8 | | | | |
| Liver - adjusted weights (Week 18) | | 17.7 | | | 21.2** | 12.5 | | | 13.4 | | | | |

*p<0.05, **p<0.01

13-Week Oral Gavage Study in Rats; Preliminary Results

| | Males | | | Females | | | | | |
|--|-----------|-------|-------|---------|---------|-------|-------|-------|---------|
| | mg/kg/day | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 |
| (a) Statistical analysis was not possible due to there only being one cage/sex/group. | | | | | | | | | |
| Mean Organ Weights (g) cont'd. | | | | | | | | | |
| Adrenals- absolute weights (Week 14) | 0.065 | 0.062 | 0.062 | 0.062 | 0.075 | 0.075 | 0.079 | 0.077 | 0.097 |
| Adrenals- relative weights (Week 14) | 1.2 | 1.2 | 1.2 | 1.2 | 1.7** | 2.4 | 2.6 | 2.5 | 3.4** |
| Adrenals- adjusted weights (Week 14) | 0.064 | 0.060 | 0.060 | 0.060 | 0.081** | 0.073 | 0.079 | 0.076 | 0.100** |
| Adrenals- absolute weights (Week 18) | 0.072 | | | | 0.070 | 0.086 | | | 0.091 |
| Adrenals- relative weights (Week 18) | 1.2 | | | | 1.4 | 2.7 | | | 3.1** |
| Adrenals- adjusted weights (Week 18) | NP | | | | NP | 0.084 | | | 0.093 |
| Kidneys - absolute weights (Week 14) | 3.70 | 3.67 | 3.76 | 3.76 | 3.64 | 2.18 | 2.25 | 2.27 | 2.42 |
| Kidneys - relative weights (Week 14) | 71 | 68 | 71 | 71 | 84** | 71 | 74 | 74 | 85** |
| Kidneys - adjusted weights (Week 14) | 3.65 | 3.53 | 3.68 | 3.68 | 3.92 | 2.14 | 2.25 | 2.25 | 2.49** |
| Kidneys - absolute weights (Week 18) | 3.78 | | | | 3.49 | 2.38 | | | 2.36 |
| Kidneys - relative weights (Week 18) | 65 | | | | 70 | 74 | | | 81 |
| Kidneys - adjusted weights (Week 18) | 3.49 | | | | 3.77 | 2.31 | | | 2.44 |
| Brain - absolute (Week 14) | 2.15 | 2.13 | 2.11 | 2.11 | 2.07 | 2.00 | 1.93 | 1.93 | 1.97 |
| Brain - relative (Week 14) | 41 | 39 | 40 | 40 | 48** | 65 | 64 | 63 | 69 |
| Brain - adjusted (Week 14) | NP | NP | NP | NP | NP | 1.99 | 1.93 | 1.93 | 1.98 |
| Brain - absolute (Week 18) | 2.10 | | | | 2.19* | 2.03 | | | 1.95 |
| Brain - relative (Week 18) | 36.00 | | | | 44** | 63 | | | 67 |
| Brain - adjusted (Week 18) | NP | | | | NP | 2.00 | | | 1.98 |

13-Week Oral Gavage Study in Rats; Preliminary Results

| | mg/kg/day | Males | | | | Females | | | |
|---|-----------|-------|-------|-------|---------|---------|---|----|-----|
| | | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 |
| *p≤0.05, **p≤0.01 | | | | | | | | | |
| NP= Not presented | | | | | | | | | |
| Mean Organ Weights (g) cont'd. | | | | | | | | | |
| Testes - absolute (Week 14) | | 3.75 | 3.73 | 3.85 | 3.45* | | | | |
| Testes - relative (Week 14) | | 72 | 69 | 74 | 80 | | | | |
| Testes - adjusted (Week 14) | | NP | NP | NP | NP | | | | |
| Testes - absolute (Week 18) | | 3.78 | | | 3.57 | | | | |
| Testes - relative (Week 18) | | 65 | | | 72** | | | | |
| Testes - adjusted (Week 18) | | 3.58 | | | 3.77 | | | | |
| Epididymides (Rt) - absolute (Week 14) | | 0.718 | 0.684 | 0.707 | 0.584** | | | | |
| Epididymides (comb.) - relative (Week 14) | | 27.28 | 24.74 | 26.58 | 26.27 | | | | |
| Epididymides (Lt) - adjusted (Week 14) | | 0.705 | 0.649 | 0.682 | 0.574** | | | | |
| Epididymides (comb.) - absolute (Week 18) | | 1.49 | | | 1.33** | | | | |
| Epididymides - relative (Week 18) | | 25.60 | | | 26.93 | | | | |
| Epididymides- adjusted (Week 18) | | NP | | | NP | | | | |
| Sem. Ves./Prostate - absolute (Week 14) | | 3.113 | 2.728 | 2.955 | 1.831** | | | | |
| Sem. Ves./Prostate - relative (Week 14) | | 60 | 50 | 56 | 42** | | | | |
| Sem. Ves./Prostate - adjusted (Week 14) | | NP | NP | NP | NP | | | | |
| Sem. Ves./Prostate - absolute (Week 18) | | 3.004 | | | 2.689 | | | | |
| Sem. Ves./Prostate - relative (Week 18) | | 52 | | | 54 | | | | |
| Sem. Ves./Prostate - adjusted (Week 18) | | NP | | | NP | | | | |

13-Week Oral Gavage Study in Rats; Preliminary Results

| mg/kg/day | Males | | | | | Females | | | | |
|---|-------|-------|-------|---------|-------|---------|------|----|--------|--|
| | 0 | 5 | 50 | 600 | | 0 | 5 | 50 | 600 | |
| <p>*p≤0.05, **p≤0.01 NP= Not presented</p> | | | | | | | | | | |
| Mean Organ Weights (g) cont'd. | | | | | | | | | | |
| Prostate - absolute (Week 14) | 1.297 | 1.144 | 1.280 | 0.837** | | | | | | |
| Prostate - relative (Week 14) | 25 | 21 | 24 | 19 | | | | | | |
| Prostate - adjusted (Week 14) | NP | NP | NP | NP | | | | | | |
| Prostate - absolute (Week 18) | 1.403 | | | 1.141 | | | | | | |
| Prostate - relative (Week 18) | 24 | | | 23 | | | | | | |
| Prostate - adjusted (Week 18) | 1.275 | | | 1.269 | | | | | | |
| Ovaries - absolute (Week 14) | | | | | 100.5 | 103.4 | 91.4 | | 78.7 | |
| Ovaries - relative (Week 14) | | | | | 3.3 | 3.4 | 3.0 | | 2.7 | |
| Ovaries - adjusted (Week 14) | | | | | 97.0 | 103.0 | 88.8 | | 85.2 | |
| Ovaries - absolute (Week 18) | | | | | 103.2 | | | | 105.0 | |
| Ovaries - relative (Week 18) | | | | | 3.2 | | | | 3.5 | |
| Ovaries - adjusted (Week 18) | | | | | 94.5 | | | | 113.7* | |
| Uterus - absolute (Week 14) | | | | | 0.67 | 0.81 | 0.67 | | 0.62 | |
| Uterus - relative (Week 14) | | | | | 27 | 27 | 22 | | 22 | |
| Uterus - adjusted (Week 14) | | | | | 0.64 | 0.81 | 0.65 | | 0.66 | |
| Uterus - absolute (Week 18) | | | | | 0.63 | | | | 0.74 | |
| Uterus - relative (Week 18) | | | | | 19 | | | | 25 | |

13-Week Oral Gavage Study in Rats; Preliminary Results

| | Males | | | | Females | | | |
|---|-------|------|------|--------|---------|------|------|--------|
| | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 |
| mg/kg/day | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 |
| Uterus - adjusted (Week 18) | | | | | NP | | | NP |
| <p>*p≤0.05, **p≤0.01 NP= Not presented</p> | | | | | | | | |
| Hematology | | | | | | | | |
| Packed Cell Volume (%) (Week 13) | 46.0 | 46.5 | 45.9 | 44.8* | 43.8 | 43.3 | 43.6 | 42.7* |
| Packed Cell Volume (%) (Week 17) | 44.7 | | | 45.2 | 43.9 | | | 42.0* |
| Hemoglobin (g/dl) (Week 13) | 15.5 | 15.5 | 15.5 | 15.0** | 15.0 | 14.9 | 14.9 | 14.5** |
| Hemoglobin (g/dl) (Week 17) | 15.30 | | | 15.4 | 15.2 | | | 14.7 |
| Mean Cell Hemoglobin (pg) (Week 13) | 17.5 | 17.5 | 17.8 | 17.4 | 18.5 | 18.5 | 18.2 | 18.2* |
| Mean Cell Hemoglobin (pg) (Week 17) | 17.60 | | | 18.0 | 19.0 | | | 18.7 |
| Prothrombin Time (s) (Week 13) | 12.5 | 12.6 | 12.8 | 12.7 | 12.9 | 12.5 | 13.3 | 13.3* |
| Prothrombin Time (s) (Week 17) | 12.90 | | | 13.4 | 12.7 | | | 13.3* |
| Eosinophils (Week 13) | 0.15 | 0.13 | 0.15 | 0.10** | 0.09 | 0.09 | 0.09 | 0.10 |
| Eosinophils (Week 17) | 0.17 | | | 0.14 | 0.13 | | | 0.14 |
| Neutrophils (Week 13) | 1.52 | 1.56 | 1.67 | 1.48 | 0.86 | 0.81 | 0.82 | 1.06* |
| Neutrophils (Week 17) | 1.52 | | | 1.59 | 1.03 | | | 0.93 |
| Monocytes (Week 13) | 0.21 | 0.21 | 0.18 | 0.15** | 0.12 | 0.09 | 0.09 | 0.13 |
| Monocytes (Week 17) | 0.23 | | | 0.2 | 0.2 | | | 0.15 |
| Leukocytes (Week 13) | 0.20 | 0.20 | 0.18 | 0.16* | 0.10 | 0.08 | 0.08 | 0.10 |
| Leukocytes (Week 17) | 0.24 | | | 0.21 | 0.16 | | | 0.13 |

13-Week Oral Gavage Study in Rats; Preliminary Results

| | Males | | | | | | Females | | | | | |
|---|-----------|------|------|------|--------|------|---------|------|----|----|--------|-----|
| | mg/kg/day | 0 | 5 | 50 | 600 | 600 | 0 | 5 | 50 | 50 | 600 | 600 |
| Serum Chemistry | | | | | | | | | | | | |
| Alkaline Phosphatase (mU/ml) (Week 13) | | 210 | 214 | 252 | 873** | 111 | 95 | 135 | | | 300** | |
| Alkaline Phosphatase (mU/ml) (Week 17) | | 123 | | | 125 | 82 | | | | | 71 | |
| *p≤0.05, **p≤0.01 | | | | | | | | | | | | |
| NP= Not presented | | | | | | | | | | | | |
| Serum Chemistry cont'd. | | | | | | | | | | | | |
| Glutamic Pyruvic Transaminase (mU/ml) (Week 13) | | 25 | 25 | 25 | 37** | 22 | 19 | 19 | | | 31** | |
| Glutamic Pyruvic Transaminase (mU/ml) (Week 17) | | 26 | | | 23* | 53 | | | | | 38 | |
| Gamma Glutamyl Transpeptidase (mU/ml)(Week 13) | | <1 | <1 | <1 | <2** | <1 | <1 | <1 | | | <3** | |
| Gamma Glutamyl Transpeptidase (mU/ml)(Week 17) | | <1 | | | <1 | <1 | | | | | <1 | |
| Cholesterol (mg/dl) (Week 13) | | 68 | 72 | 71 | 54** | 83 | 84 | 77 | | | 51** | |
| Cholesterol (mg/dl) (Week 17) | | 77 | | | 88 | 120 | | | | | 100* | |
| Glucose (mg/dl) (Week 13) | | 118 | 117 | 118 | 108** | 112 | 112 | 118 | | | 103* | |
| Glucose (mg/dl) (Week 17) | | 125 | | | 132 | 98 | | | | | 114** | |
| Total Protein (Week 13) | | 6.5 | 6.5 | 6.6 | 6.5 | 7.1 | 7.1 | 6.9 | | | 6.8* | |
| Total Protein (Week 17) | | 6.5 | | | 6.6 | 7.5 | | | | | 6.9** | |
| Albumin (Week 13) | | 3.0 | 3.0 | 3.0 | 3.1* | 3.6 | 3.6 | 3.5 | | | 3.3** | |
| Albumin (Week 17) | | 3.0 | | | 2.9 | 3.7 | | | | | 3.4 | |
| Albumin/Globulin (A/G) Ratio (Week 13) | | 0.85 | 0.85 | 0.83 | 0.90** | 1.03 | 1.03 | 1.02 | | | 0.96** | |
| Albumin/Globulin (A/G) Ratio (Week 17) | | 0.83 | | | 0.81 | 0.96 | | | | | 0.94 | |
| Sodium (mEq/l) (Week 13) | | 144 | 145 | 145 | 146** | 144 | 143 | 143 | | | 143 | |
| Sodium (mEq/l) (Week 17) | | 143 | | | 143 | 142 | | | | | 142 | |

13-Week Oral Gavage Study in Rats; Preliminary Results

| | Males | | | | | Females | | | | | | |
|--|--------|--------|--------|--------|-----|---------|------|-------|------|-----|------|-------|
| | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 |
| mg/kg/day | | | | | | | | | | | | |
| Calcium (mEq/l) (Week 13) | 5.5 | 5.5 | 5.5 | 5.5 | 5.6 | 5.5 | 5.4* | 5.4** | 5.4* | 5.5 | 5.4* | 5.4** |
| Calcium (mEq/l) (Week 17) | 5.3 | | | 5.4 | 5.7 | | | 5.3** | | | | 5.3** |
| Potassium (mEq/l) (Week 13) | 4.1 | 4.0 | 4.0 | 4.0 | 3.7 | 3.5 | 3.5 | 3.6* | 3.7 | 3.5 | 3.5 | 3.6* |
| Potassium (mEq/l) (Week 17) | 5.5 | | | 5.4 | 5.6 | | | 5.3* | 5.6 | | | 5.3* |
| *p≤0.05, **p≤0.01 | | | | | | | | | | | | |
| Serum Chemistry cont'd. | | | | | | | | | | | | |
| Chloride (mEq/l) (Week 13) | 102 | 103 | 103 | 103* | 103 | 102 | 103 | 102 | 103 | 102 | 103 | 102 |
| Chloride (mEq/l) (Week 17) | 103 | | | 102 | 101 | | | 103** | | | | 103** |
| Testosterone (ng/ml) (Week 13) | 0.6 | 0.9 | 0.7 | 1.3 | | | | | | | | |
| Testosterone (ng/ml) (Week 17) | 0.9 | | | 0.8 | | | | | | | | |
| Estradiol (pg/ml) (Week 13) | | | | | 17 | 16 | 13 | 7 | | | | |
| Estradiol (pg/ml) (Week 17) | | | | | <7 | | | <8 | | | | |
| Seminology*** | | | | | | | | | | | | |
| Sperm Motility (%) (Week 14) | 79 | 84 | 88 | 87 | | | | | | | | |
| Sperm Motility (%) (Week 17) | 81 | | | 85 | | | | | | | | |
| Progressive Sperm (%) (Week 13) | 33 | 36 | 41 | 41 | | | | | | | | |
| Progressive Sperm (%) (Week 17) | 32 | | | 35 | | | | | | | | |
| Epididymidal Sperm Counts (million/ml) (Week 13) | 1749.8 | 1423.0 | 1339.2 | 1432.6 | | | | | | | | |
| Epididymidal Sperm Counts (million/ml) (Week 17) | 1844.7 | | | 1371.5 | | | | | | | | |
| Testicular Sperm Counts (million/ml) (Week 13) | 116.4 | 116.4 | 129.3 | 118.3 | | | | | | | | |
| Testicular Sperm Counts (million/ml) (Week 17) | 144.0 | | | 160.6 | | | | | | | | |
| Estrous Cyclicity*** | | | | | | | | | | | | |
| Abnormal Estrous Cycle (%) (Week 13) | | | | | 20 | 30 | 40 | 55 | | | | |
| Abnormal Estrous Cycle (%) (Week 17) | | | | | NP | | | 20 | | | | |
| Macroscopic Pathology | | | | | | | | | | | | |

13-Week Oral Gavage Study in Rats; Preliminary Results

| | mg/kg/day | Males | | | | | Females | | | | |
|--------------------------------------|-----------|-------|------|------|------|------|---------|------|-------|--|--|
| | | 0 | 5 | 50 | 600 | 0 | 5 | 50 | 600 | | |
| Alopecia (Week 13) | | 3/10 | 4/10 | 2/10 | 9/10 | 0/10 | 0/10 | 6/10 | 10/10 | | |
| Alopecia (Week 17) | | 2/10 | | | 6/10 | 6/10 | | | 10/10 | | |
| Reduced Adipose Tissue (Week 13) | | 0/10 | 0/10 | 0/10 | 5/10 | 0/10 | 0/10 | 0/10 | 5/10 | | |
| Reduced Adipose Tissue (Week 17) | | 0/10 | | | 0/10 | 0/10 | | | 5/10 | | |
| *p<0.05, **p<0.01 | | | | | | | | | | | |
| *** Statistical analysis is pending. | | | | | | | | | | | |
| Macroscopic Pathology cont'd. | | | | | | | | | | | |
| Enlarged Livers (Week 13) | | 0/10 | 0/10 | 0/10 | 1/10 | 0/10 | 0/10 | 0/10 | 3/10 | | |
| Enlarged Livers (Week 17) | | 0/10 | | | 0/10 | 0/10 | | | 5/10 | | |
| Enlarged Adrenals (Week 13) | | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 5/10 | | |
| Enlarged Adrenals (Week 17) | | 1/10 | | | 0/10 | 2/10 | | | 2/10 | | |
| *p<0.05, **p<0.01 | | | | | | | | | | | |
| NP = Not Presented | | | | | | | | | | | |

February 18, 1998

Document Processing Center
Chemical Information Division
Office of Toxic Substances
U. S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20406

Attn.: TSCA 8(e) Coordinator

TSCA Section 8(e) Submittal

Dear Sir/Madam:

Company is submitting the enclosed notification pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA). This submittal is for

(No CAS assigned).

A 28-day oral (gavage) study in rats was conducted as a range-finding precursor to a 90-day oral study in rats that is yet to be conducted. In this pilot study, conducted at _____, CD rats (5/sex/group) were administered the test substance _____, by gavage at dosages of 0 (corn oil vehicle control), 100, 500, and 1000 mg/kg/day for 28 consecutive days. During the dosing period, all animals were observed daily for clinical signs; body weights and food consumption were measured weekly. All animals were sacrificed on day 29. Each rat was submitted to a gross necropsy, blood samples were collected for hematological and blood chemistry evaluation, and individual organ weights (adrenals, brain, epididymides, heart, kidneys, liver, ovaries, prostate, seminal vesicles, spleen, testes, and uterus) were measured. Organ weights were evaluated as the absolute weight and as the weight adjusted to individual body weight. All weighed tissues and additional tissues were fixed for histological processing.

During the in-life phase of the study, clinical signs observed were limited to hairloss in females at 500 and 1000 mg/kg/day, and males at 1000 mg/kg/day. Males at this high dose also exhibited decreased body weight gain and food consumption. Absolute and/or relative liver weights were increased in both

males and females at 500 and 1000 mg/kg/day. In females at 500 and 1000 mg/kg/day, both absolute adrenal and absolute/adjusted kidney weights were increased, whereas uterine weight decreased (not statistically significant). Absolute brain weight was decreased in females at 1000 mg/kg/day. In males at 1000 mg/kg/day, the weights of the reproductive organs (testes, epididymides, seminal vesicles, and prostate) decreased. Microscopic evaluation noted liver hypertrophy/vacuoles in males and females at 500 and 1000 mg/kg/day. Adrenal hypertrophy was noted in males at 500 and 1000 mg/kg/day, and in females at all dose levels. Males treated at 1000 mg/kg/day were noted to have reduced colloidal secretions of the prostate and seminal vesicles. There were no treatment-attributed histopathological findings for the testes, epididymides, or uteri. Blood chemistry/hematology findings in males treated at 1000 mg/kg/day were: increased total white blood cell count; increased glutamic pyruvic transaminase (GPT), increased urea; and decreased cholesterol. Males treated at 500 mg/kg/day had reduced serum cholesterol. Blood chemistry/hematology findings in females treated at 1000 mg/kg/day were: increased alkaline phosphatase (AP); increased GPT; decreased cholesterol; decreased calcium; and decreased chloride. Females treated at 500 mg/kg/day also had increased AP and GPT, reduced serum cholesterol, and decreased calcium and chloride.

We were informed of the microscopic pathology on January 28, 1998. All data currently available are in draft, unaudited form. The toxicological significance of these findings is uncertain and will not be fully assessed until the report is complete. When we receive the final report, we will submit it to you.

Our Material Safety Data Sheet is under revision to describe these findings.

If you have any questions, please contact _____ (TSCA Coordinator) at _____ Company, _____ . A sanitized version of this letter and data table is enclosed.

Sincerely,

Attachment

cc:

28-Day Oral Gavage Study in Rats; Results From Draft Report

| mg/kg/day | Males | | | | Females | | | |
|---|-------|-------|-------|--------|---------|------|-------|-------|
| | 0 | 100 | 500 | 1000 | 0 | 100 | 500 | 1000 |
| (a) Statistical analysis was not possible due to there only being one cage/sex/group. | | | | | | | | |
| (b) significant when evaluated as an adjusted weight. | | | | | | | | |
| Gross Pathology | | | | | | | | |
| Liver (enlarged) | 0/5 | 0/5 | 0/5 | 0/5 | 0/5 | 0/5 | 0/5 | 3/5 |
| Alopecia (hairloss) | 0/5 | 1/5 | 1/5 | 5/5 | 0/5 | 0/5 | 5/5 | 5/5 |
| Microscopic Pathology | | | | | | | | |
| Seminal Vesicles (reduced colloid) | 0/5 | 0/5 | 1/5 | 2/5 | | | | |
| Prostate (reduced colloid) | 0/5 | 0/5 | 1/5 | 4/5* | | | | |
| Adrenals (hypertrophy) | 0/5 | 0/5 | 1/5 | 2/5 | 0/5 | 2/5 | 5/5 | 5/5 |
| Liver (centrilobular hypertrophy) | 0/5 | 0/5 | 3/5 | 5/5** | 0/5 | 0/5 | 5/5** | 5/5** |
| Liver (periportal vacuolation) | 0/5 | 0/5 | 0/5 | 4/5** | 0/5 | 0/5 | 1/5 | 5/5** |
| Hematology | | | | | | | | |
| Total WBC | 11.09 | 11.04 | 12.97 | 14.25* | 10.14 | 9.14 | 9.07 | 11.43 |
| Serum Chemistry | | | | | | | | |
| Cholesterol (mg/dl) | 97 | 91 | 56** | 51** | 85 | 71 | 61** | 48** |
| Glutamic pyruvic transaminase (mU/ml) | 37 | 40 | 33 | 59* | 22 | 22 | 36* | 64** |
| Calcium (mEq/l) | 5.5 | 5.6 | 5.5 | 5.4 | 5.6 | 5.5 | 5.3* | 5.3* |
| Alkaline phosphatase (mU/ml) | 612 | 775 | 1051 | 845 | 327 | 398 | 552* | 526* |
| Urea (mg/dl) | 17 | 18 | 16 | 25* | 27 | 27 | 25 | 27 |

*p≤0.05, **p≤0.01

28-Day Oral Gavage Study in Rats; Results From Draft Report

| | mg/kg/day | Males | | | | Females | | | |
|---------------------------------|-----------|-------|--------|--------|-------|---------|---------|---------|------|
| | | 0 | 100 | 500 | 1000 | 0 | 100 | 500 | 1000 |
| Mean BW Gain(g)(Days 0-28) | 134 | 121 | 120 | 87** | 58 | 58 | 58 | 57 | |
| % Difference from Control | | 90 | 90 | 65 | 100 | 100 | 100 | 98 | |
| (a) Mean Food Consumption (g) | 27.4 | 26.3 | 28.11 | 23.3 | 17.9 | 18.3 | 18.4 | 20 | |
| % of Control | | 96 | 103 | 85 | 102 | 103 | 103 | 111 | |
| Mean Organ Weights (g) | | | | | | | | | |
| Terminal BW | 333 | 312 | 324 | 262 | 216 | 217 | 213 | 218 | |
| Testes | 3.4 | 3.16 | 3.2 | 2.92* | | | | | |
| Epididymides | 0.71 | 0.73 | 0.66 | 0.60** | | | | | |
| Seminal Vesicles | 0.75 | 0.69 | 0.6 | 0.31** | | | | | |
| Prostate | 0.482 | 0.514 | 0.44 | 0.31** | | | | | |
| Adrenals - absolute weights | 0.051 | 0.048 | 0.059 | 0.055 | 0.053 | 0.062 | 0.071** | 0.074** | |
| (b) Adrenals - adjusted weights | 0.045 | 0.047 | 0.055 | 0.067* | | | | | |
| Liver - absolute weights | 17.5 | 17.1 | 20.7 | 17.3 | 9.9 | 9.8 | 13.1** | 15.9** | |
| (b) Liver - adjusted weights | 15 | 16.7 | 19.0** | 21.9** | | | | | |
| Brain | 1.97 | 1.86 | 1.86 | 1.83 | 1.84 | 1.77 | 1.8 | 1.75* | |
| Kidneys - absolute weights | 2.81 | 2.75 | 3.02 | 2.29 | 1.77 | 1.87 | 2.06** | 2.07** | |
| (b) Kidneys - adjusted weights | 2.62 | 2.72 | 2.9 | 2.62 | 1.77 | 1.86 | 2.09** | 2.05** | |
| Uterus | | | | | 0.61 | 0.55 | 0.36 | 0.39 | |

*p<0.05, **p<0.01