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

REVIEWER

OCT 25 1995

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Atrazine Reregistration; Reregistration Case No. 0062; Final Review of Combined Chronic Feeding/Carcinogenicity Study in Rats Using G-34048 Technical (Hydroxyatrazine) as the Test Material, Guideline 83-5.

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Tox. Chem. No. 063
PC Code No. 080803
MRID No. 435320-01

FROM: Edwin R. Budd, Toxicologist
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Budd 8/15/95

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M Copley 10/23/95

Please find attached the final Data Evaluation Report for a combined chronic feeding/carcinogenicity study in rats using G-34048 Technical (hydroxyatrazine) as the test material (MRID No. 435320-01). Hydroxyatrazine is known to be a major plant metabolite of the herbicide atrazine. The study was sponsored by Ciba Crop Protection (Ciba-Geigy Corporation, Greensboro, NC) and performed by Ciba-Geigy Corporation Environmental Health Center (Farmington, CT).

Recall that a preliminary Data Evaluation Report for this same study, based on a cursory review of the study report, was previously prepared and forwarded to you. See memorandum from

Edwin R. Budd (HED) to Venus Eagle-Kunst/Walter Waldrop (SRRD), dated July 13, 1995, TB document no. 011603.

EXECUTIVE SUMMARY:

In a 2-year combined chronic feeding/carcinogenicity study, G-34048 technical (hydroxyatrazine) of 97.1% purity was administered in the diet to groups of 70 or 80 male and 70 or 80 female Crl:CD (SD) BR strain rats at dose levels of 0 (control), 10, 25, 200 or 400 ppm (equivalent to 0, 0.388, 0.962, 7.75 or 17.4 mg/kg/day in males and to 0, 0.475, 1.17, 9.53 or 22.3 mg/kg/day in females). Ten or 20 rats/sex/group were sacrificed at 12 months; the remaining 60 animals in each group were scheduled to be sacrificed at 24 months. Due to high mortality in the 400 ppm group, however, the surviving males and females in this group were sacrificed at 18 months. Mortality, clinical signs of toxicity, body weights, food consumption and water consumption were monitored. Ophthalmologic examinations were performed. Hematological examinations, clinical chemistries and urinalyses were also performed. Necropsy examinations were conducted on all animals and organ weight determinations were made on all animals sacrificed at 12, 18 and 24 months. Histopathological examinations were made on a complete set of organs/tissues from all animals in the control, 200 and 400 ppm groups. Histopathological examinations were also performed on a limited set of organs/tissues from the 10 and 25 ppm groups.

At 400 ppm, an excessive treatment-related mortality was observed for both males and females and this dose level group was terminated at 18 months. Severe renal failure was the predominant cause of death for these animals. Prior to death or sacrifice, these animals exhibited emaciation, dehydrated bodies, pallor and other clinical signs of toxicity expected in animals with severe renal failure. Greatly decreased body weights, body weight gains and food consumption were observed in these animals throughout the study (to 18 months). Water consumption was increased during the first year of the study. Changes in hematology parameters (including anemia), in clinical chemistry parameters (indicating renal disturbances) and in urinalysis parameters (including crystalline material in urine samples) were observed in 400 ppm males and females. Gross necropsies, organ weights and histopathology indicated that the kidney and lower urinary tract were the primary target organs in both males and females at 400 ppm. Kidney effects included discoloration, calculi and rough pitted surfaces seen at gross necropsy; increased kidney weights; and severe histopathological changes including deposition of crystalline material within collecting ducts and renal pelvises, calculi, other morphological changes and accelerated chronic progressive nephropathy. In addition, secondary effects in extrarenal tissues reflected the severe renal damage and resulting renal failure in these animals.

At 200 ppm, similar but less severe gross and histopathological effects on the kidneys were observed in both males and females. Secondary effects in extrarenal tissues were generally not observed at this dose level.

At 25 ppm, no treatment-related effects were observed in either male or female rats. An accumulation of interstitial matrix in the papilla of kidneys of female rats was observed at this dose level, but the toxicological significance of this observation, in the absence of any other signs of renal damage or of impaired renal function, was highly questionable.

A treatment-related increased incidence of tumors of any type was not observed in the treated male or female animals in this study. In particular, there was no increase above control levels in the incidence of mammary gland tumors in either males or females. In addition, onset times for mammary gland tumors in female rats were not decreased in this study.

For both male and female rats, the NOEL is 25 ppm (0.962 mg/kg/day for males and 1.17 mg/kg/day for females) and the LOEL is 200 ppm (7.75 mg/kg/day for males and 9.53 mg/kg/day for females), based on gross and histopathological effects in the kidneys.

This study is classified as Core-Guideline as a chronic feeding study and as a carcinogenicity study.

Reviewed by: Edwin R. Budd, M.A.
Review Section III, Toxicology Branch I (7509C) Budd 8/15/95
Secondary Reviewer: Karen Hamernik, Ph.D., Section Head
Review Section III, Toxicology Branch I (7509C) me & KH

DATA EVALUATION REPORT

Study Type: Combined Chronic Feeding/Carcinogenicity Study, Rats
EPA Subdivision F Guideline 83-5

Test Material: G-34048 Technical (Hydroxyatrazine)

Tox. Chem. No.: None (file under Atrazine, Tox. Chem. No. 063)

PC Code No.: None (file under Atrazine, PC Code No. 080803)

MRID No.: 435320-01 (Original Report, 6 volumes, 2599 pages)

Study Title: 2-Year Dietary Chronic Toxicity/Oncogenicity Study With G-34048 in Rats

Testing Laboratory: Ciba-Geigy Corporation
Environmental Health Center (EHC)
Farmington, CT

Lab. Study No.: F-00125

Authors: Edward Chow and Susan G. Emeigh Hart

Final Report Completion Date: January 27, 1995

Sponsor: Ciba Crop Protection
Ciba-Geigy Corporation
Greensboro, NC

Note: A **preliminary** data evaluation report for this same study, based on a cursory review of the study report, was previously prepared. See memorandum from Edwin R. Budd (HED) to Venus Eagle-Kunst/Walter Waldrop (SRRD), dated July 13, 1995, TB document no. 011603.

TB394:HYDATR09.085

I. EXECUTIVE SUMMARY:

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At 400 ppm, an excessive treatment-related mortality was observed for both males and females and this dose level group was terminated at 18 months. Severe renal failure was the predominant cause of death for these animals. Prior to death or sacrifice, these animals exhibited emaciation, dehydrated bodies, pallor and other clinical signs of toxicity expected in animals with severe renal failure. Greatly decreased body weights, body weight gains and food consumption were observed in these animals throughout the study (to 18 months). Water consumption was increased during the first year of the study. Changes in hematology parameters (including anemia), in clinical chemistry parameters (indicating renal disturbances) and in urinalysis parameters (including crystalline material in urine samples) were observed in 400 ppm males and females. Gross necropsies, organ weights and histopathology indicated that the kidney and lower urinary tract were the primary target organs in both males and females at 400 ppm. Kidney effects included discoloration, calculi and rough pitted surfaces seen at gross necropsy; increased kidney weights; and severe histopathological changes including deposition of crystalline material within collecting ducts and renal pelvises, calculi, other morphological changes and accelerated chronic progressive nephropathy. In addition, secondary effects in extrarenal tissues reflected the severe renal damage and resulting renal failure in these animals.



5

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For both male and female rats, the NOEL is 25 ppm (0.962 mg/kg/day for males and 1.17 mg/kg/day for females) and the LOEL is 200 ppm (7.75 mg/kg/day for males and 9.53 mg/kg/day for females), based on gross and histopathological effects in the kidneys. This study is classified as Core-Guideline as a chronic feeding study and as a carcinogenicity study.

II. DETAILED EVALUATION OF STUDY

A. Test Material: G-34048 Technical (hydroxyatrazine). Description: white powder; 97.1% purity; lot no. FL-870869; obtained from Ciba Crop Protection (Greensboro, NC); Storage conditions: stored at room temperature (previously determined to be stable at room temperature for at least 2 1/2 years). NOTE--hydroxyatrazine is known to be a major plant metabolite of the herbicide atrazine.

B. Test Animals: Rats, Crl:CD (SD) BR strain (Sprague Dawley derived), males and females.
Description: obtained from Charles River Laboratories (Raleigh, NC); 4 weeks old when received; acclimated 2 weeks prior to commencement of treatment at 6 weeks of age; males weighed 122.5-163.5 gm and females weighed 110.1-145.4 gm at commencement of treatment.

Environment: All rats were individually housed in an environmentally controlled room under standard environmental conditions; temperature and humidity were monitored; 12 hour light/dark cycle; diet and tap water were available ad libitum during the acclimation period and entire treatment period.

C. Study Design: Animals were assigned to treatment groups as shown below utilizing a randomization procedure in which animals were stratified by body weight. Main study animals were given control or treated diet mixtures for 24 months (except for 400 ppm male and female animals which were sacrificed at 18 months because of high mortality); interim kill animals (20/sex/group at 0 and 400 ppm amd 10/sex/group at 10, 25 and 200 ppm) were sacrificed at 12 months.

| Dose Level G-34048 (ppm) | Main Study | | Interim Kill | |
|---|---|---|---|---|
| | Males | Females | Males | Females |
| 0 | 60 | 60 | 20 | 20 |
| 10 | 60 | 60 | 10 | 10 |
| 25 | 60 | 60 | 10 | 10 |
| 200 | 60 | 60 | 10 | 10 |
| 400 | 60 | 60 | 20 | 20 |

Treatment commenced on August 27-28, 1991.

Based on food consumption and body weight data, the overall mean consumption of test material for each of the treatment groups was later calculated in units of mg/kg/day for the entire duration of the study. For males, the mean consumption of test material was 0.0, 0.388, 0.962, 7.75 and 17.4 mg/kg/day for the control, 10, 25, 200 and 400 ppm groups respectively. For females, the overall mean consumption of test material was 0.0, 0.475, 1.17, 9.53 and 22.3 mg/kg/day for the control, 10, 25, 200 and 400 ppm groups respectively.

D. Rationale for Selection of Dose Levels: Dose levels in this study "were agreed upon in a meeting with EPA officials on July 10, 1991 and were based on results from the 13-week study (Study number MIN 882146) in which rats were fed diets containing 0, 10, 100, 300, or 600 ppm of G-34048." (quoted from page 20 of the study report).

E. Diet Preparation and Analyses of Diet Mixtures: The test material was incorporated directly into ground Certified Rodent Chow #5002 (Purina Mills). Bulk diet mixtures were stored at room temperature for up to 39 days (diet mixtures were previously demonstrated to be stable in bulk storage for at least 39 days).

Stability: Prior to commencement of treatment, 10 ppm diets were demonstrated to be stable at room temperature in open food jars for at least 24 days. Other concentrations of diets were demonstrated in earlier studies to be stable at room temperature.

Homogeneity: Homogeneity was determined for the first 4 blends and monthly therafter. Satisfactory homogeneity of diet mixtures was demonstrated.

Concentration Analyses: All diet mixtures were assayed for G-34048 content in the first 4 blends and monthly therefter. All diets were analyzed and determined to be within acceptable limits before being offered to the animals. The percents of nominal concentrations achieved for the entire duration of the study were 96.4 ± 3.9%, 95.7 ± 2.3%, 95.2 ± 1.7% and 97.1 ± 2.1% for the 10, 25, 200 and 400 ppm groups respectively.

F. Quality Assurance, GLP Compliance and EPA Flagging Statements: A signed and dated Quality Assurance Statement, GLP Statement and EPA Flagging Statement were provided in the study report.

G. Procedures for Statistical Evaluation: Provided on pages 34-35 of the study report.

H. Observations and Results:

1. Mortality: All animals were observed at least twice each day for mortality and morbidity.

Results: The fates of all animals in the study are presented in Table 1 (copied from the study report). Percent survival of males and females at weekly intervals during the study are presented in Figures 1 and 2 respectively (copied from the study report). An excessive treatment-related increase in mortality was observed at 400 ppm for both males and females. At 18 months, this dose level was terminated (due to the high mortality) and the remaining 13 males and 12 females at this dose level were sacrificed. Severe renal failure was determined to be the predominant cause of early death for these animals.

Although the mortality rates in the control groups and remaining test groups were relatively high (particularly during the last 6 months of the study), there were no apparent differences between control and test groups. The adjusted survival rates at 24 months for males were 12/60 (20%), 15/60 (25%), 15/61 (25%) and 17/60 (28%) and for females were 14/60 (23%), 18/60 (30%), 19/61 (31%) and 24/61 (39%) for the 0, 10, 25 and 200 ppm groups respectively.

Conclusion: Greatly increased treatment-related mortality was observed in male and female groups at 400 ppm. This dose level was clearly excessive. At lower

dose levels, mortality rates were comparable between control and test groups.

2. Clinical Signs: All animals were observed at least twice each day for clinical signs of toxicity. The onset and duration of signs were recorded. In addition, all animals were given a general physical examination, including palpation for masses, once each week.

   Results: Clinical signs and palpable masses were summarized and listed for individual animals in the study report. The location and distribution of clinically palpable masses for males and females are presented in Tables 2 and 3 respectively (copied from the study report). Treatment-related clinical signs of toxicity were limited to the 400 ppm groups. These signs were observed in one or both sexes and included emaciation, dehydrated bodies, general pallor, piloerection, increased urine, stained abdominal/pelvic areas, wet coats, anuria and tremors. Many, if not all, of these signs are expected to be seen in animals with severe renal failure. At the highest dose level of 400 ppm, decreases in incidences of clinical signs commonly observed in old age were attributed to the early terminatiion of the male and female groups at 18 months. There were no differences between control and test groups in the distribution of clinically palpable masses or in the incidence of animals exhibiting one or more palpable masses.

   Conclusion: Treatment-related clinical signs of toxicity in males and females in this study were limited to the 400 ppm groups and were generally correlated with severe renal failure. Neither the distribution nor incidence of palpable masses was related to treatment with the test material.

3. Body Weights: Body weights for all rats were recorded prior to treatment, weekly for the first 13 weeks of the study and once every 4 weeks thereafter.

   Results: Mean absolute body weights for males and females at weekly intervals during the study are presented in Figures 3 and 4 respectively (copied from the study report). Mean cumulative body weight gains for males and females are presented in Figures 5 and 6 respectively (copied from the study report). For both males and females at 400 ppm, treatment-related and statistically significant decreases in absolute body weights and cumulative body weight gains were observed throughout the study (to 18 months). These decreases

were consistent and progressive. At 18 months, mean absolute body weights for 400 ppm male and female animals were lower by 28% and 41% than the male and female control groups respectively. At 18 months, mean cumulative body weight gains for these same groups were decreased by 35% and 61% compared to controls. At lower dose levels, no changes in absolute body weights or cumulative body weight gains were observed between treated male or female groups and their respective control groups.

Conclusion: Treatment-related and statistically significant decreases in mean absolute body weights and in mean cumulative body weight gains were observed for both males and females throughout the study at 400 ppm. Treatment-related differences were not observed at lower dose levels.

4. Food Consumption: Food consumption for all rats was recorded weekly for the first 13 weeks of the study, and once every 4 weeks thereafter.

Results: Mean food consumption values for males and females at weekly intervals during the study are presented in Figures 7 and 8 respectively (copied from the study report).

Conclusion: Treatment-related and statistically significant decreases in mean food consumption were observed for 400 ppm males and females during most of the study. Occasional decreases for 200 ppm males and females are not considered to be treatment-related.

5. Feed Efficiency: The authors stated that "feed efficiency was generally lower in the 400 ppm groups than the controls throughout the study and the differences were often statistically significant." No consistent pattern in feed efficiency was noted at the other feeding levels.

Conclusion: Feed efficiency was decreased in male and female groups throughout the study at 400 ppm.

6. Water Consumption: Weekly water consumption was determined for rats from which urine samples were obtained at 1.5, 3, 6, 12, 18 and 24 months.

Results: The authors stated that "statistically significant increases in water consumption were observed in the 400 ppm animals of each sex at all time intervals when measurements were performed (up to week 52). In addition, a significantly elevated amount of

water was consumed by the 200 ppm animals (both sexes) at 28 weeks."

Conclusion: A treatment-related increase in water consumption was observed in 400 ppm males and females during the first year of the study. An equivocal increase was observed in 200 ppm males and females.

7. Ophthalmoscopic Examinations: Ophthalmoscopic examinations, performed on all animals prior to dosing and on selected animals sacrificed at 12, 18 and 24 months, were negative.

8. Hematology: Samples of blood were collected from the orbital sinus (interim bleedings) or from the abdominal aorta (at sacrifice) from 20 rats/sex/group at 3, 6, 18 and 24 months and from 30 rats/sex/group at 12 months. Animals were fasted prior to blood collection. Standard hematology examinations were performed.

Results: The following hematologic changes are considered to be treatment-related.

At 400 ppm

Consistently observed changes

Statistically significant decreases in erythrocyte counts, hemoglobin level, hematocrit, and mean corpuscular hemoglobin concentration (in both sexes) and decreases in mean corpuscular hemoglobin (in females)

Statistically significant increases in mean corpuscular volume (in males)

Changes at selected intervals only

Statistically significant increases in leukocyte counts, platelet counts and absolute segmented neutrophil counts (in both sexes)

Conclusion: See above.

9. Clinical Chemistries: Samples of blood were collected from the orbital sinus (interim bleedings) or from the abdominal aorta (at sacrifice) from 10 rats/sex/group at 6, 12, 18 and 24 months. Animals were fasted prior to blood collection. A full series of standard clinical chemistry examinations were performed.

Results: The following clinical chemistry changes are considered to be treatment-related.

At 400 ppm

Statistically significant decreases in the levels of glucose, total protein and albumin (in both sexes) and decreases in creatine kinase activity (in males), globulin level (in males) and albumin/globulin ratio (in females)

Statistically significant increases in the levels of calcium, phosphorus, blood urea nitrogen and creatinine (in both sexes) and increases in potassium levels (in females) and cholesterol levels (in females).

Conclusion: See above. These changes are consistent with the severe renal damage and renal failure that were observed in these same animals at 400 ppm.

10. Urinalyses: Overnight and fresh samples of urine were collected from 10 rats/sex/group at 1.5, 3, 6, 12, 18 and 24 months. Standard urinalysis parameters were examined.

Results: The following changes are considered to be treatment-related.

Overnight Samples

At 400 ppm

Increased volume at 6 and 12 months (in both sexes)

Statistically significant decreases in pH, specific gravity and color intensity (in both sexes)

In addition, at occasional times:

decreased protein levels (in males) and ketone bodies (in males)

increased protein at 12 months (in females), occult blood (in females), erythrocytes (in females) and leukocytes at 3 months (in males)

Fresh Samples

At 400 ppm

Statistically significant decreases in pH and osmolality (in both sexes)

Macroscopically observable sediments were present in some samples early in the study, but were not seen subsequently. Microscopic examination of these sediments revealed crystalline material resembling ammonium biurate crystals in appearance. Chemical analysis of the crystals indicated they were enriched with G-34048 (hydroxyatrazine).

Conclusion: See above.

11. Necropsy: All animals in this study, regardless of time or manner of death, were given a complete postmortem examination under the direction of a veterinary pathologist in accordance with standard gross dissection and necropsy procedures. Animals sacrificed at 12, 18 and 24 months and animals sacrificed *in extremis* were given i.p. injections of sodium pentobarbital followed by exsanguination.

Results: The following treatment-related effects were observed in both male and female rats unless indicated otherwise. The incidences of selected gross necropsy findings in the kidney and urinary bladder of male and female rats are presented in Table 4.

At 400 ppm (and occasionally also at 200 ppm)

General Observations: increased incidences of dehydrated bodies, emaciated bodies, pale colored bodies, stained coats.

Kidney: increased incidences of calculi, cysts, dilated pelvises, enlarged kidneys (in males only), small kidneys (in females only), pale and/or general discoloration, malformed/misshaped kidneys, rough pitted surface.

Urinary Bladder: increased incidences of calculi (in males only), thickened wall (in males only)

Renal Lymph Nodes: increased incidences of enlarged nodes, discolored nodes

Pituitary Gland: decreased incidences of enlarged pituitary glands, general discoloration

Adrenal Gland: decreased incidences of enlarged adrenal glands (females only)

Parathyroid Gland: increased incidences of enlarged parathyroid glands

Regarding skin masses, decreased incidences were observed in males and females at 400 ppm (probably due to the early termination of this dose level group at 18 months). The following observations were made for skin masses.

Skin Masses: incidences of 17, 28, 22, 17 and 8 in males and of 47, 42, 47, 39 and 15 in females at 0, 10, 25, 200 and 400 ppm respectively.

Regarding mammary glands, decreased incidences of findings were noted in males and females at 400 ppm (probably due to the early termination of this dose level group at 18 months). The following observations were made for mammary glands.

Cyst(s): incidences of 6, 5, 1, 3 and 1 in males and of 38, 26, 29, 20 and 18 in females at 0, 10, 25, 200 and 400 ppm respectively.

Hypertrophy: incidences of 5, 2, 3, 5 and 0 in males and of 38, 38, 39, 38 and 19 in females at 0, 10, 25, 200 and 400 ppm respectively.

Conclusion: See above.

12. Organ Weights, Organ/Body Weight Ratios and Organ/Brain Weight Ratios: For all animals sacrificed at 12, 18 and 24 months, the following organs were weighed and organ/body weight and organ/brain weight ratios calculated.

| | |
|---|---|
| adrenal | kidney |
| brain | liver |
| ovary | thymus |
| testes (without epididymides) | |

Results: At the 12 month interim sacrifice, absolute kidney weights for the 400 ppm animals were increased 19% in males (statistically significant) and 10% (not significant) in females. Increases in kidney/body weight ratios were difficult to interpret due to the greatly decreased body weights in these animals. At

the 18 month sacrifice, it was not possible to compare organ weights for the 400 ppm animals to control values since no control animals were sacrificed at that time. At the 24 month sacrifice, no effects on organ weights were observed for any of the treated animals (highest dose examined at 24 months was the 200 ppm group).

Conclusion: Treatment-related increases in kidney weights were observed in 400 ppm males and females at 12 months. It could not be determined whether kidney weights for this dose level group were also increased at 18 months since no control animals were sacrificed at this time.

13. Collection, Fixing and Processing of Tissues/Organs: Full sets of tissues/organs were collected from all animals at the time of necropsy and most were fixed in 10% neutral buffered formalin. Special care was taken to collect samples of inguinal skin (mammary area) from all animals, inguinal mammary gland from females and gross lesions, tissue masses and other tissues specified by the pathologist from all animals. Following fixation, representative samples or the whole of the tissues/organs were trimmed, blocked in paraffin, sectioned, and stained with hematoxylin and eosin (H & E) according to standard histologic techniques. In addition, selected tissues were stained with special stains.

14. Microscopic Examination: Full sets of tissues/organs were microscopically examined for all rats in the control, 200 and 400 ppm groups. In addition, all kidneys, livers, gross lesions and urinary bladders were examined for all male animals in all dose groups; these same tissues, plus inguinal skin, ovaries and mammary glands were examined for all females in all dose groups. Numerous tissues were peer reviewed by a second pathologist and the final report represented a consensus opinion of both pathologists. The severity of non-neoplastic tissue lesions was graded.

NON-NEOPLASTIC FINDINGS

Results: Selected non-neoplastic microscopic findings for male and female rats are presented in Tables 5 and 6 respectively. The primary target organs were the kidney and the lower urinary tract in both males and females. Treatment-related and dose-related effects in the kidney were observed at 400 and 200 ppm in both sexes. At 400 ppm, as previously noted, the severe renal damage and resulting renal failure caused numerous early deaths in the high dose level group and



15

the remaining 13 males and 12 females in this group were sacrificed at 18 months, rather that at 24 months as were the survivors in the control and remaining dose level groups. At 400 ppm, in addition to direct effects on the kidney and lower urinary tract, secondary effects were observed in these and other organs/tissues. These latter effects were caused by the renal damage/failure per se and therefore were considered to be indirect, rather than direct, effects of the test material.

At 400 ppm, treatment-related morphological damage to the kidney and urinary bladder was first observed in the male and female rats that died early in the study at 4-6 months. Renal failure was the cause of death in these animals and in many additional 400 ppm animals that died or were sacrificed during the remainder of the study (up to 18 months when this dose level group was terminated). At 200 ppm, pathological damage to the kidney was first observed in male and female rats at the 1-year interim sacrifice. At that time, increased interstitial matrix was observed in the kidney papilla of males, and increased dilatation with crystal deposits in the kidney and increased interstitial fibrosis in the kidney papilla were observed in females (see below). More severe kidncy lesions were observed in 200 ppm animals that died or were sacrificed after 1 year of treatment, although the overall rate of mortality in this dose level group was not affected by treatment.

Primary Effects in the Kidney and Lower Urinary Tract

Kidney lesions typically involved the deposition of a "yellowish green to slightly basophilic, transparent, amorphous to crystalline material within collecting ducts, renal pelvises, and occasionally distal tubules" and was summarized in the pathology narrative and tables as "dilatation with crystal deposits". Deposition of this material was observed in the kidneys of male and female rats at 200 and 400 ppm. It was also observed in the ureter, urinary bladder and/or urethra of some male and female rats at 400 ppm. The crystalline component of the material was deduced by its birefringence under polarized light. Subsequent treatment of the crystals with anti-hydroxyatrazine monoclonal antibody indicated the crystals were enriched with hydroxyatrazine. Additional special staining of the amorphous material demonstrated a polysaccharide component (probably glycoprotein), that was possibly derived from Tamm-Horsfall mucoprotein, a

membrane-associated glycoprotein secreted by the ascending limb of the loop of Henle.

In kidneys containing intratubular crystalline material, the tubular epithelium of the collecting ducts or distal tubules was missing or hyperplastic and the tubules sometimes contained a purulent inflammatory infiltrate. This condition was characterized as "acute inflammation". In kidneys containing crystalline material in the pelvis, erosion and/or ulceration of the renal pelvic transitional cell epithelium was observed. The condition was summarized as "transitional cell--erosion". In ureters, urinary bladders and urethra contining crystal deposits (a few 400 ppm animals only), the deposition was often accompanied by similar hyperplasia of the urothelium and again by the presence of inflammatory infiltrates.

In renal papilla, the papillary interstitium was often thickened by the presence of densely collagenous fibrous connective tissue at 200 ppm and particularly at 400 ppm, where it was observed in nearly all animals in the study. This condition was called "papilla-interstitial fibrosis". In addition, at 200 ppm in males and at 25 ppm and 200 ppm in females (but not at 400 ppm in either sex), a separate lesion in the renal papilla was characterized as "papilla-accumulation interstitial matrix". This latter lesion described swollen and slightly increased eosinophilia of the interstitial cells accompanied by an accumulation of a hyaline (myxoid) basophilic material which stained positively with Alcian blue. This staining indicated an accumulation of acid sulfated mucosubstances (which make up the ground substance of the interstitial matrix). In male rats, the incidence was 4, 3, 2, 32 and 0 in the control, 10, 25, 200 and 400 ppm groups respectively. The increase at 200 ppm was statistically significant at $p < 0.01$. In female rats, the incidence was 17, 10, 26, 26 and 0 in the control, 10, 25, 200 and 400 ppm groups respectively. The increase at 25 ppm, but not at 200 ppm, was statistically significant at $p < 0.05$ and the decrease at 400 ppm was statistically significant at $p < 0.01$. The occurrence of this lesion in female rats at 25 ppm (26/68), although statistically significant ($p < 0.05$), was not attributed to treatment with the test material. A similar occurrence at the next highest dosage level (26/69) was not statistically significant. Furthermore, at 25 ppm, no treatment-related effects of any kind were observed in either male or female rats. In the absence of any signs of renal damage (as evidenced by organ weight changes, gross and



17

microscopic pathologic findings) or of impaired renal function (as evidenced by clinical chemistry and urinalysis results), the toxicological significance of this observation was highly questionable. This same interpretation of the results in this study regarding the NOEL for renal lesions was also independently arrived at by Lucas H. Brennecke, DVM, DACVP, pathology consultant (Pathology Associates International, Frederick, Maryland) to EPA. See Attachment #1 at the end of this DER.

In the renal papilla, an increase in the incidence of transitional cell hyperplasia, characterized as "transitional cell-hyperplasia" was observed in both male and female rats at 400 ppm.

In the renal cortex of male rats, chronic progressive nephropathy was observed in nearly all control and test animals in the study. The severity score for males at 400 ppm, however, was significantly increased (2.5, 2.9, 3.0, 2.5 and 4.6 for the control, 10, 25, 200 and 400 ppm groups respectively). In female rats, a statistically significant increase in the incidence of chronic progressive nephropathy was observed at 200 and 400 ppm.

Secondary Effects in Other Organs and Tissues

A frequently observed secondary effect resulting from severe renal damage and renal failure in the 400 ppm male and female rats was metastatic mineralization of various organs and tisues throughout the animal body. This effect was caused by the calcium-phosphorus imbalance produced as a result of chronic renal failure. Mineralization was typically observed in the tubular epithelia and basement membranes of the kidneys, in the tunica muscularis of the aorta, in the intrinsic arteries of several organs (including the kidney, heart, ovaries, pancreas, salivary glands, spleen, thymus, urinary bladder and some lymph nodes) and in other organs (including the heart, lungs, stomach and colon). Mineralization in the kidney was more severe in females than in males.

Additional secondary effects, other than mineraliztion, were also observed in the male and female rats at 400 ppm in this study. These effects were considered to be caused by the severe renal failure and/or chronic debilitation in these animals. These effects included the following:

bone
    fibrous osteodystrophy
duodenum/pancreas/lymph nodes/testes/epididymides
    polyarteritis nodosa in intrinsic arteries
heart
    progressive cardiomyopathy
parathyroid glands
    hyperplasia
renal lymph nodes
    accumulation of pigmented macrophages
    congestion
    sinusoidal ectasia
testes
    degeneration/atrophy
epididymides
    spermatidic giant cells
    oligospermia

Other Lesions Not Related to the Test Material

In male rats, an apparent increase in ultimobranchial cysts in the thyroid gland at 400 ppm was probably not related to the test material, but rather to the early demise of animals in this group. Such cysts occur normally in younger animals and gradually disappear with increasing age. Statistically significant decreases in the incidence of several other lesions were also observed in male and/or female rats at 400 ppm. These differences were also attributed to the early demise of the animals in this group and not to any effect of the test material. These differences included the following: adrenal gland--lipoid degeneration in the cortex, telangiectasis; brain--atrophy of the mammary bodies; epididymides--chronic inflammation; liver--fatty change, peliosis hepatis, spopngiosis hepatica, basophilic cell focus; ovaries--hyperplasia of Sertoli cells; pancreas--islet cell hyperplasia; prostate--fibrosis; sciatic nerve--radiculoneuropathy; skeletal muscle (thigh)--atrophy; spinal cord--radiculoneuropathy, axonal dystrophy; spleen--extramedullary hematopoiesis; thyroid gland--C cell hyperplasia.

Other lesions observed in the animals in this study occurred with similar incidences in control and treated groups and were not considered to be related to the test material. These lesions were those commonly associated with older rats of this strain in experimental studies.

Summary of Non-neoplastic Effects Induced by the Test Material

At 400 ppm (in both males and females; effects first observed at 4-6 months in animals that died)

Kidneys: deposition of amorphous to crystalline material within collecting ducts and renal pelvises and occasionally in distal tubules (often accompanied by dilated ducts and tubules which were either devoid of epithelium or lined by hyperplastic tubular epithelium and which contained an inflammatory infiltrate); transitional cell erosion/hyperplasia in pelvises and/or papilla; interstitial fibrosis in the papilla; accelerated chronic progressive nephropathy (often accompanied by mineralization of renal tissues)

Lower Urinary Tract: occasional deposition of same amorphous to crystalline material in ureters, urinary bladders and/or urethra (often accompanied by transitional cell hyperplasia, submucosal fibrosis, or inflammation of the urinary bladder)

Extrarenal Organs and Tissues: secondary metastatic mineralization of various organs and tissues such as aorta, heart, lungs, stomach, ovaries, pancreas, salivary glands, spleen, thymus, some lymph nodes, and urinary bladder in animals with nephropathy; other secondary effects such as changes in the renal lymph nodes, parathyroid hyperplasia, fibrous osteodystrophy in the bones, polyarteritis nodosa in various organs, progressive cardiomyopathy, and testicular degeneration and atrophy.

Note--The decreased incidence at 400 ppm of several non-neoplastic lesions frequently observed in aging rats of both sexes was attributed to the early deaths of the animals in this dose level group.

At 200 ppm (in both males and females; effects first observed at the 1-year interim sacrifice)

Kidneys: deposition of amorphous to crystalline material within collecting ducts and renal pelvises and occasionally in distal tubules (often accompanied by dilated ducts and tubules which were either devoid of epithelium or lined by hyperplastic tubular epithelium and which contained an inflammatory infiltrate); transitional cell erosion/hyperplasia in pelvises and/or papilla; interstitial fibrosis in the papilla; accelerated chronic progressive nephropathy in females only (often accompanied by mineralization of renal

tissues), accumulation of interstitial matrix in the renal papilla.

At 25 ppm

No treatment-related effects in either males or females.

Conclusion: The primary target organs were the kidney and the lower urinary tract in both males and females. Treatment-related and dose-related histopathological effects in the kidney were observed in both sexes at 400 and 200 ppm. Treatment-related histopathological effects in the lower urinary tract were confined to the males and females at 400 ppm only. In addition to direct effects on the kidney and lower urinary tract, secondary effects were observed in these and several other organs/tissues in males and females at 400 ppm. These latter effects were caused by the renal damage/failure per se and therefore were considered to be indirect, rather than direct, effects of the test material.

NEOPLASTIC FINDINGS

Results: Selected neoplastic findings for male and female rats are presented in Tables 7 and 8 respectively. Incidences are given for mammary gland, pituitary gland, thyroid gland, adrenal gland, testes, ovaries, kidneys and urinary bladder. A treatment-related increased incidence of tumors of any type was not observed in any of the treated male or female animals in this study. In particular, although some mammary gland tumors were observed in female groups, the incidences were not significantly higher than in the female control group. The lower incidences of some tumor types at 400 ppm (e.g. mammary gland fibroadenomas in females and pituitary gland adenomas of the pars distalis in males and females) were attributed to the decreased survival rate for this dose level group, which resulted in lower incidences of some tumor types frequently observed in aging rats.

With regard to mammary gland tumors in female rats, there was also no decrease in tumor onset time that could be attributed to treatment with G-34048. Onset curves for mammary adenomas, fibroadenomas, adenocarcinomas, benign mammary tumors, malignant mammary tumors and all mammary tumors are presented in Figures 9 through 14 (copied from the study report). Statistical analyses of the onset times for each of the mammary tumor types listed above are presented in Table

9 (copied from the study report). Analyses of onset times for the 400 ppm group were not performed because of the early deaths in this group (due to nephrotoxicity).

Conclusion: A treatment-related increased incidence of tumors of any type was not observed in the treated male or female animals in this study. In particular, there was no increase above control incidences in the incidence of mammary gland tumors in either males or females. In addition, onset times for mammary gland tumors in female rats were not decreased in this study.

## III. DISCUSSION

The report for this study included Discussion and References sections which have been copied in their entirety on the following 5 pages. The discussion presents a hypothesis and supporting data/information that relates nearly all of the treatment-related primary and secondary effects observed in this study to an initial (and chronically occurring) insolubilization of hydroxyatrazine in the form of crystals and/or calculi in the kidney and lower urinary tract of the 400 and 200 ppm animals in this study. The discussion is well-written and researched and, in the opinion of this reviewer, should be seriously considered in the evaluation and interpretation of the results in this study.

It should be noted that the authors of this study report considered the accumulation of interstitial matrix in the papilla of kidneys of female rats at 25 ppm could be a treatment-related effect. As discussed previously on page 14 of this DER, this finding was not considered by TB-1 to be a treatment-related effect.

Atrazine

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Table 4. Selected Gross Necropsy Findings in the Kidney and Urinary Bladder for Male and Female Rats Given G-34048 in the Diet for up to 24 Months [1]

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| MALES | | | | | |
| Kidney | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 80 |
| Calculus | 0 | 1 | 1 | 4 | 54 |
| Cyst(s) | 12 | 8 | 15 | 16 | 73 |
| Dilation, pelvis | 11 | 22 | 16 | 15 | 48 |
| Enlarged | 10 | 7 | 14 | 7 | 21 |
| General discoloration, pale | 1 | 5 | 5 | 4 | 12 |
| Malformed/ misshaped | 0 | 0 | 0 | 4 | 8 |
| Rough pitted surface | 6 | 8 | 10 | 6 | 52 |
| Small | 0 | 0 | 0 | 1 | 1 |
| Urinary Bladder | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 80 |
| Calculus | 1 | 8 | 6 | 14 | 21 |
| Thickened wall | 0 | 0 | 0 | 0 | 9 |
| FEMALES | | | | | |
| Kidney | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 80 |
| Calculus | 0 | 0 | 1 | 2 | 51 |
| Cyst(s) | 4 | 3 | 5 | 8 | 63 |
| Dilation, pelvis | 0 | 2 | 1 | 4 | 49 |
| Enlarged | 1 | 0 | 1 | 1 | 3 |
| General discoloration, pale | 0 | 1 | 3 | 0 | 10 |
| Malformed/ misshaped | 0 | 0 | 0 | 8 | 18 |
| Rough pitted surface | 1 | 0 | 1 | 10 | 68 |
| Small | 0 | 0 | 0 | 1 | 12 |
| Urinary Bladder | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 80 |
| Calculus | 1 | 0 | 0 | 1 | 2 |
| Thickened wall | 0 | 0 | 0 | 1 | 2 |

[1] Data extracted from Table 9.29.5 (pp. 215-226) and Table 9.30.5 (pp. 248-258) in MRID 435320-01.

Table 5. Selected Non-Neoplastic Microscopic Findings for Male Rats Given G-34048 in the Diet for up to 24 Months [1]

| MALES | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Aorta | | | | | |
| No. Exam. | 80 | 46 | 48 | 70 | 80 |
| Mineralization | 4 | 5 | 9 | 4 | 27** |
| Bone | | | | | |
| No. Exam. | 80 | 46 | 46 | 70 | 80 |
| Osteodystrophy, fibrous | 3 | 3 | 6 | 1 | 25** |
| Duodenum | | | | | |
| No. Exam. | 77 | 43 | 42 | 68 | 75 |
| Intrinsic Arteries, polyarteritis nodosa | 0 | 0 | 0 | 0 | 3* |
| Epididymides | | | | | |
| No. Exam. | 80 | 46 | 48 | 70 | 80 |
| Giant Cells, spermatidic | 14 | 8 | 8 | 9 | 27* |
| Intrinsic Arteries, polyarteritis nodosa | 0 | 0 | 0 | 1 | 7** |
| Oligospermia | 8 | 5 | 12 | 13 | 24** |
| Heart | | | | | |
| No. Exam. | 80 | 46 | 46 | 70 | 80 |
| Intrinsic Arteries, mineralization | 5 | 5 | 9 | 3 | 28** |
| Mineralization | 4 | 5 | 7 | 5 | 22** |
| Kidneys | | | | | |
| No. Exam. | 79 | 69 | 70 | 70 | 80 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 5** | 79** |
| Inflammation, acute | 0 | 1 | 1 | 1 | 14** |
| Intrinsic Arteries, mineralization | 1 | 2 | 3 | 4 | 10** |
| Mineralization | 7 | 5 | 6 | 7 | 21** |
| Nephropathy, progressive | 75 | 67 | 64 | 65 | 80[2] |

Table 5. (Continued)

MALES

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Kidneys (continued) | | | | | |
| Papilla--accumulation interstitial matrix | 4 | 3 | 2 | 32** | 0 |
| Papilla--fibrosis interstitial | 1 | 2 | 1 | 11** | 80** |
| Pelvis--dilatation with crystal deposits | 0 | 0 | 0 | 5 | 60** |
| Transitional cell erosion | 0 | 0 | 0 | 1 | 8** |
| Transitional cell hyperplasia | 6 | 7 | 12 | 10 | 19* |
| Lungs | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 80 |
| Alveolus--mineralization | 5 | 5 | 7 | 4 | 19* |
| Pancreas | | | | | |
| No. Exam. | 79 | 44 | 47 | 70 | 78 |
| Intrinsic Arteries, polyarteritis nodosa | 2 | 0 | 1 | 0 | 14** |
| Parathyroid Gland | | | | | |
| No. Exam. | 77 | 47 | 44 | 68 | 77 |
| Hyperplasia | 6 | 9 | 8 | 4 | 39** |
| Renal Lymph Node | | | | | |
| No. Exam. | 80(?) | 59(?) | 59(?) | 70(?) | 80(?) |
| Accumulation, Macrophage pigmented | 7 | 2 | 4 | 2 | 35** |
| Congestion | 4 | 3 | 4 | 2 | 34** |
| Ectasia, sinusoidal | 2 | 4 | 1 | 2 | 29** |
| Stomach | | | | | |
| No. Exam. | 79 | 47 | 46 | 69 | 77 |
| Mineralization | 6 | 5 | 10 | 5 | 28** |

Table 5. (Continued)

| MALES | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Testes | | | | | |
| No. Exam. | 79 | 46 | 48 | 70 | 80 |
| Degeneration/ atrophy | 11 | 12 | 16 | 14 | 41** |
| Intrinsic Arteries, polyarteritis nodosa | 11 | 3 | 5 | 3 | 24* |
| Thyroid Gland | | | | | |
| No. Exam. | 80 | 49 | 49 | 70 | 79 |
| Cyst, ultimobranchial | 14 | 9 | 5 | 12 | 30** |
| Ureter | | | | | |
| No. Exam. | 0 | 1 | 1 | 0 | 7 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 0 | 7 |
| Urethra (Prostatic) | | | | | |
| No. Exam. | 80 | 46 | 47 | 70 | 80 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 0 | 8** |
| Urinary Bladder | | | | | |
| No. Exam. | 79 | 70 | 69 | 70 | 78 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 0 | 2 |

(1) Data extracted from Table 9.33.5 (pp. 358-407) in MRID 435320-01.
(2) Significantly increased severity score (2.5, 2.9, 3.0, 2.5 and 4.6 in control, 10, 25, 200 and 400 ppm groups respectively).

* statistically significant at $p < 0.05$
** statistically significant at $p < 0.01$

Table 6. Selected Non-Neoplastic Microscopic Findings for Female Rats Given G-34048 in the Diet for up to 24 Months [1]

FEMALES

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| **Aorta** | | | | | |
| No. Exam. | 80 | 42 | 42 | 70 | 80 |
| Mineralization | 3 | 2 | 2 | 4 | 48** |
| **Bone** | | | | | |
| No. Exam. | 80 | 42 | 42 | 70 | 80 |
| Osteodystrophy, fibrous | 1 | 0 | 0 | 2 | 24** |
| **Colon** | | | | | |
| No. Exam. | 75 | 41 | 42 | 65 | 72 |
| Mineralization | 0 | 0 | 0 | 0 | 3* |
| **Heart** | | | | | |
| No. Exam. | 80 | 43 | 43 | 70 | 80 |
| Cardiomyopathy, progressive | 40 | 30 | 28 | 44 | 60** [2] |
| Intrinsic Arteries, mineralization | 2 | 2 | 2 | 5 | 47** |
| Mineralization | 2 | 1 | 0 | 3 | 36** |
| **Kidneys** | | | | | |
| No. Exam. | 79 | 70 | 68 | 69 | 80 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 15** | 78** |
| Inflammation, acute | 0 | 0 | 0 | 3 | 12** |
| Intrinsic Arteries, mineralization | 2 | 0 | 0 | 1 | 13** |
| Mineralization | 7 | 7 | 7 | 9 | 42** |
| Nephropathy, progressive | 36 | 32 | 34 | 50** | 79** |
| Papilla--accumulation interstitial matrix | 17 | 10 | 26* | 26 | 0** |
| Papilla--fibrosis interstitial | 0 | 0 | 0 | 20** | 79** |
| Pelvis-dilatation with crystal deposits | 0 | 0 | 0 | 9* | 40** |
| Transitional cell erosion | 0 | 0 | 0 | 0 | 11** |

Table 6. (Continued)

FEMALES

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Kidneys (continued) | | | | | |
| Transitional cell hyperplasia | 3 | 2 | 5 | 8 | 35** |
| Lungs | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 80 |
| Alveolus--mineralization | 3 | 1 | 0 | 2 | 34** |
| Lymph Node, unspecified | | | | | |
| No. Exam. | 80 | 62 | 61 | 70 | 80 |
| Intrinsic Arteries, mineralization | 1 | 0 | 0 | 0 | 9** |
| Intrinsic Arteries, polyarteritis nodosa | 1 | 0 | 0 | 0 | 4 |
| Ovaries | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 79 |
| Intrinsic Arteries, mineralization | 0 | 0 | 0 | 0 | 8** |
| Pancreas | | | | | |
| No. Exam. | 77 | 42 | 41 | 68 | 79 |
| Intrinsic Arteries, mineralization | 1 | 1 | 0 | 1 | 14** |
| Intrinsic Arteries, polyarteritis nodosa | 1 | 1 | 0 | 1 | 20** |
| Parathyroid Gland | | | | | |
| No. Exam. | 78 | 44 | 42 | 68 | 77 |
| Hyperplasia | 3 | 1 | 2 | 3 | 33** |
| Renal Lymph Node | | | | | |
| No. Exam. | 80(?) | 62(?) | 61(?) | 70(?) | 80(?) |
| Accumulation Macrophage pigmented | 0 | 0 | 3 | 1 | 10** |
| Congestion | 0 | 0 | 2 | 1 | 13** |
| Ectasia, sinusoidal | 0 | 0 | 1 | 0 | 7** |

Table 6. (Continued)
FEMALES

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Salivary Gland, Mandibular | | | | | |
| No. Exam. | 80 | 42 | 42 | 70 | 80 |
| Intrinsic Arteries, mineralization | 0 | 0 | 0 | 0 | 6** |
| Spleen | | | | | |
| No. Exam. | 80 | 43 | 45 | 70 | 80 |
| Intrinsic Arteries, mineralization | 0 | 0 | 0 | 0 | 6** |
| Stomach | | | | | |
| No. Exam. | 80 | 46 | 43 | 69 | 78 |
| Mineralization | 3 | 1 | 2 | 4 | 44** |
| Thymus | | | | | |
| No. Exam. | 80 | 39 | 40 | 66 | 75 |
| Intrinsic Arteries, mineralization | 0 | 0 | 0 | 0 | 3* |
| Ureter | | | | | |
| No. Exam. | 0 | 0 | 0 | 0 | 6 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 0 | 3 |
| Urethra | | | | | |
| No. Exam. | 0 | 0 | 0 | 1 | 1 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 0 | 1 |
| Urinary Bladder | | | | | |
| No. Exam. | 80 | 70 | 70 | 69 | 78 |
| Dilatation with crystal deposits | 0 | 0 | 0 | 0 | 0 |
| Intrinsic Arteries, mineralization | 0 | 0 | 0 | 1 | 5** |

(1) Data extracted from Table 9.34.5 (pp. 487-525) in MRID 435320-01.
(2) Increased severity score (1.3, 1.3, 1.4, 1.5 and 2.0 in control, 10, 25, 200 and 400 ppm groups respectively).
* statistically significant at $p < 0.05$
** statistically significant at $p < 0.01$

Table 7. Selected Neoplastic Microscopic Findings for Male Rats Given G-34048 in the Diet for up to 24 Months [1]

| MALES | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Mammary Gland | | | | | |
| No. Exam. | 65 | 35 | 42 | 61 | 78 |
| Adenocarcinoma | 0 | 0 | 0 | 1 | 0 |
| Fibroadenoma | 0 | 2 | 0 | 1 | 1 |
| Lymphoma | 0 | 1 | 0 | 0 | 0 |
| Pituitary Gland | | | | | |
| No. Exam. | 79 | 63 | 63 | 70 | 79 |
| Adenoma, pars distalis | 35 | 29 | 33 | 35 | 13 |
| Adenoma,pars intermedia | 0 | 1 | 0 | 0 | 0 |
| Carcinoma, pars distalis | 3 | 2 | 0 | 2 | 0 |
| Leukemia | 0 | 1 | 1 | 0 | 0 |
| Lymphoma | 0 | 0 | 1 | 0 | 0 |
| Thyroid Gland | | | | | |
| No. Exam. | 80 | 49 | 49 | 70 | 79 |
| Adenocarcinoma, follicular cell | 0 | 0 | 1 | 0 | 0 |
| Adenoma, C cell | 5 | 5 | 5 | 5 | 2 |
| Adenoma, follicular cell | 0 | 0 | 1 | 1 | 0 |
| Carcinoma, C cell | 2 | 0 | 0 | 0 | 1 |
| Leukemia | 1 | 0 | 0 | 0 | 0 |
| Sarcoma, histiocytic | 0 | 0 | 1 | 0 | 0 |
| Adrenal Gland | | | | | |
| No. Exam. | 80 | 50 | 49 | 70 | 79 |
| Adenocarcinoma, cortical | 0 | 1 | 0 | 0 | 0 |
| Adenoma, cortical | 1 | 1 | 0 | 0 | 0 |
| Leukemia (cortex) | 1 | 0 | 0 | 0 | 0 |
| Lymphoma | 2 | 1 | 2 | 0 | 1 |
| Ganglioneuroma (medulla) | 2 | 0 | 0 | 0 | 0 |
| Pheochromocytoma (benign) | 8 | 1 | 5 | 1 | 2 |

Table 7. (Continued)

MALES

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Adrenal Gland (continued) | | | | | |
| Pheochromocytoma (malignant) | 1 | 0 | 1 | 2 | 0 |
| Sarcoma, histiocytic | 0 | 0 | 0 | 1 | 0 |
| Testes | | | | | |
| No. Exam. | 79 | 46 | 48 | 70 | 80 |
| Interstitial cell tumor | 1 | 1 | 1 | 0 | 0 |
| Lymphoma | 0 | 1 | 0 | 0 | 0 |
| Mesothelioma | 0 | 0 | 0 | 0 | 1 |
| Sarcoma, histiocytic | 0 | 0 | 0 | 1 | 0 |
| Kidney | | | | | |
| No. Exam. | 79 | 69 | 70 | 70 | 80 |
| Adenocarcinoma, renal tubular | 0 | 1 | 0 | 0 | 0 |
| Adenoma, renal tubular | 1 | 0 | 1 | 1 | 0 |
| Leukemia | 1 | 1 | 1 | 0 | 0 |
| Lymphoma | 0 | 1 | 2 | 0 | 1 |
| Papilloma, transitional cell | 0 | 1 | 0 | 0 | 0 |
| Sarcoma, histiocytic | 0 | 0 | 1 | 0 | 0 |
| Sarcoma, lipo | 2 | 0 | 1 | 0 | 0 |
| Urinary Bladder | | | | | |
| No. Exam. | 79 | 70 | 69 | 70 | 78 |
| Carcinoma, transitional cell | 0 | 0 | 1 | 1 | 1 |
| Leukemia | 0 | 1 | 0 | 0 | 0 |
| Lymphoma | 0 | 1 | 2 | 0 | 0 |
| Papilloma, transitional cell | 0 | 0 | 0 | 1 | 0 |

(1) Data extracted from Table 9.33.5 (pp. 358-407) in MRID 435320-01.

Table 8. Selected Neoplastic Microscopic Findings for Female Rats Given G-34048 in the Diet for up to 24 Months [1]

FEMALES

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| **Mammary Gland** | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 79 |
| Adenocarcinoma | 17 | 14 | 10 | 10 | 7 |
| Adenoma | 6 | 4 | 2 | 3 | 5 |
| Carcinosarcoma | 1 | 0 | 0 | 0 | 0 |
| Fibroadenoma | 40 | 36 | 41 | 35 | 6 |
| Fibroma | 2 | 3 | 4 | 2 | 0 |
| Lymphoma | 0 | 0 | 0 | 1 | 0 |
| Sarcoma, fibro | 0 | 0 | 1 | 0 | 0 |
| Sarcoma, histiocytic | 1 | 0 | 0 | 0 | 0 |
| **Pituitary Gland** | | | | | |
| No. Exam. | 80 | 65 | 67 | 70 | 80 |
| Adenoma, pars distalis | 55 | 39 | 46 | 48 | 16 |
| Carcinoma, pars distalis | 3 | 6 | 9 | 6 | 2 |
| Pars distalis-Sarcoma, fibro | 0 | 0 | 1 | 0 | 0 |
| **Thyroid Gland** | | | | | |
| No. Exam. | 80 | 45 | 44 | 70 | 80 |
| Adenoma, C cell | 6 | 3 | 2 | 2 | 0 |
| Carcinoma, C cell | 2 | 2 | 1 | 5 | 0 |
| Lymphoma | 0 | 0 | 0 | 1 | 0 |
| **Adrenal Gland** | | | | | |
| No. Exam. | 80 | 51 | 50 | 70 | 80 |
| Adenocarcinoma, cortical | 0 | 1 | 2 | 1 | 0 |
| Adenoma, cortical | 0 | 1 | 1 | 2 | 0 |
| Leukemia | 0 | 1 | 0 | 0 | 0 |
| Pheochromocytoma (benign) | 3 | 0 | 2 | 3 | 0 |
| Pheochromocytoma (malignant) | 0 | 0 | 0 | 1 | 0 |

Table 8. (Continued)

FEMALES

| | 0 ppm | 10 ppm | 25 ppm | 200 ppm | 400 ppm |
|---|---|---|---|---|---|
| Ovaries | | | | | |
| No. Exam. | 80 | 70 | 70 | 70 | 79 |
| Adenoma, tubulostromal | 0 | 1 | 0 | 0 | 0 |
| Granulosa/theca cell tumor | 1 | 0 | 0 | 0 | 0 |
| Lymphoma | 0 | 0 | 0 | 1 | 0 |
| Sertoliform tubular adenocarcinoma | 0 | 1 | 0 | 0 | 0 |
| Sertoliform tubular adenoma | 0 | 0 | 1 | 0 | 1 |
| Kidney | | | | | |
| No. Exam. | 79 | 70 | 68 | 69 | 80 |
| Adenocarcinoma, renal tubular | 0 | 0 | 0 | 1 | 0 |
| Leukemia | 0 | 1 | 1 | 1 | 0 |
| Lymphoma | 0 | 0 | 0 | 1 | 0 |
| Papilloma, transitional cell | 0 | 0 | 1 | 0 | 0 |
| Sarcoma, lipo | 0 | 1 | 0 | 0 | 0 |
| Urinary Bladder | | | | | |
| No. Exam. | 80 | 70 | 70 | 69 | 78 |
| Papilloma, transitional cell | 0 | 0 | 1 | 0 | 0 |

(1) Data extracted from Table 9.34.5 (pp. 487-525) in MRID 435320-01.

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Attachment #1

**MEMORANDUM**

SUBJECT: NOEL for the Combined Chronic Toxicity/Oncogenicity Study with G-34048 in Rats

TO: Edwin R. Budd, Toxicologist
Review Section III, Toxicology Branch I
Health Effects Division (7509C)

cc: Esther Rinde, Ph.D.
Carcinogenicity Peer Review Manager
Science Analysis Branch
Health Effects Division (7509C)

FROM: Lucas H. Brennecke, DVM, DACVP
Pathology Consultant
Health Effects Division (7509C)

DATE: 2 August 1995

Action Requested: Provide comments regarding the NOEL for the Combined Chronic Toxicity/ Oncogenicity Study with G-34048 in Rats

Based upon review of the pathology findings from this study, the most significant conclusions are:

- There were no treatment-related neoplastic lesions.
- The 400 ppm dose exceeded the MTD in males and females
- The kidneys and lower urinary tract were the target tissues for G-34048 in rats.
- The NOEL for males and females (based upon renal lesions) is 25 ppm.

Although the pathology data and summary reflect a very thorough evaluation of the gross and microscopic pathology findings, the significance of the findings is largely obfuscated and complicated by the inordinately large number of redundant and overlapping morphologic diagnoses, particularly for the kidneys. Most of the diagnoses for the kidneys could have and should have been "lumped" under the diagnosis, "nephropathy, progressive". With this in mind, part of the last sentence at the bottom of P. 14 of the pathology summary was the most concise and significant statement. ". . . renal lesions included . . . accelerated chronic progressive nephropathy in males at 400 ppm and in females at ≥ 200 ppm."

The incidences of interstitial fibrosis and tubular dilatation (with or without crystal deposits), two of the many components of chronic progressive nephropathy were increased in males at 200 ppm and 400 ppm. In females the incidences of progressive nephropathy as well as (the redundant components of progressive nephropathy) papillary interstitial fibrosis and papillary dilatation (with or without crystals) were increased at the 200 ppm and 400 ppm levels.

With regard to the increased incidence of papillary interstitial matrix in 25 ppm females and 200 ppm males, no convincing evidence could be found which equates this finding with a deleterious lesion or even a lesion at all. The pathologist stated (on P. 14 of the SUMMARY) that the toxicological significance of the accumulation of interstitial matrix in males at 200 ppm and in females at 25 ppm was unclear. Further on P. 47 of the DISCUSSION, the pathologist stated that ". . .the toxicological significance of the minimal to moderate accumulation of this matrix in females at 25 ppm in the absence of signs of tubular degeneration, necrosis, or impairment of renal function (evidenced by clinical chemistry results) at that feeding level is questionable."



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