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

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JUL 13 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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

DP Barcode D211911 — Tox. Chem. No. 063
Case 819248 — PC Code No. 080803
Submission S481457 — MRID No. 435320-01

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Please find attached a preliminary Data Evaluation Report (DER) 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 (Farming ton, CT).

This DER is a preliminary evaluation of the submitted study, based on a cursory review of the study report. A full and complete DER will be sent to you at a later time.

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SUMMARY OF PRELIMINARY EVALUATION:

In an 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 or 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 necropsy; increased kidney weights; and severe histopathological changes including deposition of material within collecting ducts and renal pelvises, calculi, other morphological changes and 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 histopathological effects on the kidneys and urinary bladder were observed in both males and females. Secondary effects in extrarenal tissues were generally not observed at this dose level.

At 25 ppm, an accumulation of interstitial matrix in the papilla of kidneys of females was observed. The toxicological significance of this finding was unclear.

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.

For female rats, the tentative NOEL in this study is 10 ppm (0.475 mg/kg/day) and the LOEL is 25 ppm (1.17 mg/kg/day), based on the increase in interstitial matrix observed in the kidneys. For male rats, the tentative NOEL is 25 ppm (0.962 mg/kg/day) and the LOEL is 200 ppm (7.75 mg/kg/day), based on histopathological effects in the kidneys and urinary bladder.

This study will be classified for Core status when the full and complete DER for this study is completed.

Reviewed by: Edwin R. Budd, M.A.
Review Section III, Toxicology Branch I (7509C)
Secondary Reviewer: Karen Hamernik, Ph.D., Section Head
Review Section III, Toxicology Branch I (7509C)

Budd 5/8/95
6/7/95 K. Hamernik

PRELIMINARY 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

This DER is a preliminary evaluation of the submitted study, based on a cursory review of the study report. A full and complete DER for this study will be prepared at a later time.

TB294:HYDATR01.055

I. SUMMARY OF PRELIMINARY EVALUATION:

In an 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 or 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 necropsy; increased kidney weights; and severe histopathological changes including deposition of material within collecting ducts and renal pelvises, calculi, other morphological changes and 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 histopathological effects on the kidneys and urinary bladder were observed in both males and females. Secondary effects in extrarenal tissues were generally not observed at this dose level.

At 25 ppm, an accumulation of interstitial matrix in the papilla of kidneys of females was observed. The toxicological significance of this finding was unclear.

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.

For female rats, the tentative NOEL in this study is 10 ppm (0.475 mg/kg/day) and the LOEL is 25 ppm (1.17 mg/kg/day), based on the increase in interstitial matrix observed in the kidneys. For male rats, the tentative NOEL is 25 ppm (0.962 mg/kg/day) and the LOEL is 200 ppm (7.75 mg/kg/day), based on histopathological effects in the kidneys and urinary bladder.

This study will be classified for Core status when the full and complete DER for this study is completed.

II. PRELIMINARY EVALUATION OF STUDY

A. Test Material: G-34048 Technical (hydroxyatrazine).
Description: white powder; 97.1% purity; lot no. FL-470869; 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 20.3 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 9 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.

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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). The authors stated that 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 of these signs were said to be expected in animals with severe renal failure. Decreases in other signs commonly observed in old age were attributed to the early terminatiion of the 400 ppm 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 from 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. Note: At week 104, male group mean body weightr and group mean cumulative body weight gains were statistically significantly greater than the control group at 200 and 25 ppm (see attached Tables A and B). The biological significance of this is unknown.

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. Differences that could clearly be related to treatment 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 were considered by the authors of the study report 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. Standard clinical chemistry examinations were performed.

Results: The following clinical chemistry changes were considered by the authors of the study report 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.

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

Results: The following changes were considered by the authors of the study report 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)

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Fresh Samples

At 400 ppm

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

Macroscopically observable sediments were present in some samples at 1.5 months. Microscopic examination of these sediments revealed crystalline material resembling ammonium biurate crystals in appearance. Chemical analysis of the sediments indicated they were enriched with G-34048.

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 direct supervision of a 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 at 400 ppm unless indicated otherwise.

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, rough pitted surface (also at 200 ppm in females only)

Urinary Bladder: increased incidences of calculi (in males only, also at 200 ppm), 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)

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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 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 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.

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

The following discussion of non-neoplastic findings in this study is essentially the interpretation of the study authors. A cursory inspection of the data for non-neoplastic findings in this study did not indicate any meaningful discrepancies between the interpretation by the study authors and by the EPA reviewer.

Results: The primary target organs were the kidneys and the lower urinary tract in both males and females. In addition, secondary effects in other tissues were observed which reflected the severe renal damage and resulting renal failure.

At 400 ppm (in both males and females)

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); accelerated chronic progressive nephropathy (often accompanied by mineralization of renal tissues)

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

Extrarenal Tissues: Mineralization of various tissues such as aorta, heart, lungs, stomach, ovaries and urinary bladder in animals with nephropathy [mineralization of extrarenal tissues was said by the authors to be a common consequence of calcium phosphate imbalance which results from chronic renal failure]; other secondary effects such as changes in the renal lymph nodes, parathyroid hyperplasia, fibrous osteodystrophy in the bones, polyarteritis nodosa in various organs, arterial fibromuscular proliferation, progressive cardiomyopathy, and testicular degeneration and atrophy [and possibly thyroid C-cell hyperplasia-males].

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.

<u>At 200 ppm</u>

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); accelerated chronic progressive nephropathy (often accompanied by mineralization of renal tissues), in females only; accumulation of interstitial matrix, in males only (toxicological significance unclear)

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

At 25 ppm

Kidneys: accumulation of interstitial matrix, in females only (toxicological significance unclear)

NEOPLASTIC FINDINGS[1]

The following discussion of neoplastic findings in this study is the interpretation of the EPA reviewer and is based on an independent and detailed evaluation of the neoplastic findings in this study.

Results: Selected neoplastic findings for male and female rats are presented in Tables 4 and 5 respectively (data extracted by EPA reviewer from study report). 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 6 (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.

[1] Note: The following histopathology summary tables taken from the study report are attached: TABLE C, TABLE 9.33.5, and TABLE 9.34.5.

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Page____ is not included in this copy.

Pages 18 through 34 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

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____ Description of quality control procedures.

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____ Sales or other commercial/financial information.

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Table 4. Selected Neoplastic Microscopic Findings for Male Rats Given G-34048 in the Diet for 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 4. (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 5. Selected Neoplastic Microscopic Findings for Female Rats Given G-34048 in the Diet for 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 dist-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 5. (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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