



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

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FEB - 9 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Transmittal of reviews of Carcinogenicity Studies in
Sprague Dawley and Fischer 344 rats with Atrazine.. MRID
422044-01 and MRID # 422270-01

D 175031, and D 175473
S 412435, and S 413045
PC Code 080803
Tox Chem 063

TO: Venus Eagle
PM # 71
Reregistration Branch
SRRD, (H7508W)

FROM: Henry Spencer, Ph.D. *H.S. 1/14/94*
Review Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

THRU: Karen Hamernik, Ph.D. *K. Hamernik to 1/14/94*
Section Head
Review Section 3
Toxicology Branch 1
Health Effects Division (H7509C) *KA 2/17/94*

CONCLUSIONS:

The two studies in the Sprague Dawley rat and the Fischer 344 rat with atrazine have been reviewed and are submitted to the SRRD for filing. Individually, the Sprague Dawley rat study (MRID 42204401) data indicated a shortening of the latency period for the appearance of mammary tumors in the females treated at 400 ppm in the diet. The Fischer 344 rats did not show indications of any mammary gland tumorigenicity at any dose level in the study (MRID# 42227001). Executive Summaries for the two DERS are attached.



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EXECUTIVE SUMMARY:

Atrazine technical was given in the diet to groups of 60 female Sprague-Dawley rats for 24 months at concentrations of 0, 70, or 400 ppm, (approximating 0, 3.79 and 23.01 mg/kg/day respectively). Water and food were available ad libitum. Test doses were selected following a 2 year study using 0, 70, 500, or 1000 ppm of Atrazine in the diet (MRID# 00262714-00262727).

A slight reduction (a negative trend) in survival found amongst the dosed groups was considered to be equivocal because the data were statistically significant ($p < 0.05$) by the Gehan Breslow test but not by the Cox-Tarone test. No treatment related increases in clinical signs were noted in the study. Body weight gains were statistically significantly reduced relative to controls (approx. 12 to 13%) only at 400 ppm during weeks 0-76. Food consumption was only minimally reduced at the highest dose. Slight alteration in red blood cell shapes and incidence of nucleated RBCs were transient in occurrence. Spleen weights were slightly increased but the increase was not statistically significant. Other organ wt. and organ:bwt values from the 400 ppm group were not significantly different from controls. Nonneoplastic lesion findings were comparable in controls and treatment groups. Palpation times for tumors confirmed histologically indicated an early onset of mammary tumors. Total numbers of tumors over the length of the study were statistically significantly increased for the combined incidence of fibroadenomas and carcinomas only when adjustments for survival were made.

A NOEL for systemic toxicity is 70 ppm (calculated by the reviewer to be approximately 3.79 mg/kg/day). The LEL is 400 ppm (approximately 23 mg/kg/day) based on the body weight gains of this group being 12-13 less than controls as well as statistically significant decreases in body weights in the 0-76 week period. Also, a reduction in survival considered to be equivocal is reported at 400 ppm. An MTD and effect level was determined in a previous chronic feeding study (MRID 00262714-00262727). The study is classified Core:Minimum. This study (MRID 42204401) alone does not fulfill Guideline requirements 83-2a for carcinogenicity evaluation because only 2 dose levels were tested. Other studies have completed this Guideline requirement.

EXECUTIVE SUMMARY:

Atrazine technical (97% ai) was fed in the diet to groups of 60 per sex F-344 rats at 0, 10, 70, 200, or 400 ppm (calculated as 0, 0.49, 3.43, 9.87, 20.17 and 0, 0.61, 4.35, 12.71, 26.18 mg/kg/day for males and females respectively) for a period of 24 months. Water and feed were available ad libitum. Survival was not compromised in the study. Clinical observations were those seen in older rats and only the incidence of "thinness" in the highest dosed females was increased above that of controls. Body weight gains were significantly decreased relative to controls at 200 ppm (8%) in both sexes and at 400 ppm dose level by 11% and 16% in females and males respectively for the 0-76 week period. Food consumption was reduced in males at 400 ppm throughout the study but only in the 1-13 week period for the females. Food efficiencies were not significantly different between test groups. Alterations in hematology were sporadic, and not considered compound related. Gross observations reported enlarged spleens noted only in low and high dosed females, but organ weights were not statistically different from controls and were not considered treatment related. Tumor incidences in mammary and pituitary glands of both sexes of treatment groups were not significantly different from the controls. Times of first appearance of the small number of tumors reported were not consistently shorter than the times noted for controls and not dose related in occurrence.

A NOEL can be established at 70 ppm (3.43 mg/kg/day for males and 4.35 mg/kg/day for females). An LEL is established at 200 ppm (9.87 mg/kg/day for males and 12.71 mg/kg/day for females) based on decreased body weight gains in both sexes.

The study is classified as core Guideline and satisfies guideline requirement 83-2 for oncogenicity. MRID# 42227001

NOTE: WITH REGARD TO THE ATTACHED DER FOR THE FOLLOWING STUDY

ONCOGENICITY STUDY IN SPRAGUE-DAWLEY RATS WITH ATRAZINE
TECHNICAL. STUDY NO. HWA 483-275. MRID # 42204401.

CLEMENT ASSOCIATES PERFORMED THE PRIMARY REVIEW OF THE STUDY.
TOXICOLOGY BRANCH 1 REVIEWERS THEN INDEPENDENTLY MADE SOME
AMENDMENTS TO THE CLEMENT'S PRIMARY REVIEW.

Primary Review by: Henry Spencer, Ph.D. *WHS 12/2/93*
Pharmacologist, Review Section III,
Toxicology Branch I/HED

Secondary Review by: Karen Hamernik, Ph.D. *KRH 12/22/93*
Section Head, Review Section III,
Toxicology Branch 1/HED

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity study Rats (83-2)

TEST MATERIAL: Atrazine Technical

TOX CHEMICAL NO: 063

SYNONYMS: 2-chloro-4-ethylamino-6-isopropylamino-s-triazine

MRID NO: 422044-01

STUDY NUMBER: HWA483-275

SPONSOR: Agricultural Division
CIBA-GEIGY Corporation
Post Office Box 18300
Greensboro, NC 27419

TESTING FACILITY: Hazleton Washington, Inc.
9200 Leesburg Turnpike
Vienna, Virginia 22182

TITLE OF REPORT: Oncogenicity Study in Sprague-Dawley Rats with
Atrazine Technical:

AUTHORS: Ajit K. Thakur, Ph.D.

REPORT ISSUED: January 27, 1992

SUMMARY:

Atrazine technical, was administered in the diet to groups of 60 female Sprague-Dawley rats for 24 months at concentrations of 0, 70, or 400 ppm, (approximating 0, 3.79 and 23.01 mg/kg/day respectively). Water and food was available ad libitum. Test doses were selected following a 2 year study using 10, 70, 500, or 1000 ppm of Atrazine in the diet. A slight reduction (a negative trend) in survival found amongst the dosed groups was considered to be equivocal because the data were statistically significant ($p < 0.05$) by the Gehan Breslow test but not by the Cox-Tarone test. No treatment related increases in clinical signs were noted in the study. Body weight gains were statistically significantly reduced relative to controls (approx 12 to 13 %) only at 400 ppm

during weeks 0-76. Food consumption was only minimally reduced at the highest dose. Slight alterations in red blood cell shapes and incidence of nucleated RBCs were transient in occurrence. Spleen weights were slightly increased but the increase was not statistically significant. Other organ wt. and organ/bwt values from the 400 ppm group were not significantly different from controls. Nonneoplastic microscopic alterations were not statistically significantly different from controls in any treatment group for the pituitary, mammary glands, uterus, and ovaries. Nonneoplastic lesion findings were comparable in controls and treatment groups. Palpation times for tumors confirmed histologically indicated an early onset of mammary tumors. Total numbers of tumors over the length of the study were statistically significantly increased for the combined incidence of fibroadenomas and carcinomas only when adjustments were made for survival.

A NOEL for systemic toxicity is 70 ppm (calculated by reviewer to be approximately 3.79 mg/kg/day). The LEL is 400 ppm (approximately 23 mg/kg/day) based on the body weight gains of this group being 12-13% less than controls as well as statistically significant decreases in body weights in the 0-76 week period. Additionally, a reduction in survival found to be statistically significant is reported at 400 ppm. An MTD and effect level was determined in a previous chronic feeding study (MRID 00262714-00262727). The study is classified as CORE MINIMUM.

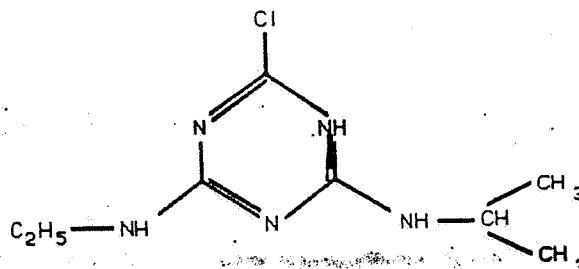
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I. MATERIALS, METHODS AND RESULTS

A. Test Article Description

Name: Atrazine Technical

Formula:



Batch Number: D3413J10 (FL-850612)

Purity: 97%

Physical Property: white powder

Stability: stable at room temperature

B. Test Article Analyses for Purity and Stability

The purity of atrazine technical was reported to be 97% at the beginning of the study; the diets were not adjusted for purity. No further analyses for purity were conducted. No contaminants were reported in the test material.

Homogeneity and room temperature stability analyses of the atrazine technical/diet mixture were reportedly performed by the laboratory during the conduction of a prior study. Homogeneity analyses were performed only for the Week 57 and 86 mixes due to a change in batch size. The homogeneity analyses, conducted for the previous study and at Weeks 57 and 86 of this study, used samples taken from the top, middle, and bottom of the mixtures and revealed concentrations no less than 96% of target at all levels. The results of the stability analyses reveal 98% (of target concentration) stability after 7 days, 92% stability after 14 days, and only 89% stability after 21 days. Since the diets were to be mixed weekly, no stability problems were expected.

Batches of diets were mixed weekly at dietary concentrations of 0, 70, and 400 ppm. After final mixing, two samples from each mixed batch were taken. One set was sent to Analytical Chemistry and one set was frozen. Routine concentration analyses were performed on weekly mixes for Weeks 1, 4, 6, 10, 16, 18, 27, 31, 33, 35, 39, 42, 50, 57, 60, 61, 79, 80, 81, 82, 88, 89, 90, 93, 103, and 104 to insure that dietary concentrations of atrazine technical were maintained. The analyses were performed prior to presentation

of the diets to animals and the diet was released for use only if the measured concentration was $\pm 15\%$ of the target concentration.

C. Animals

Two hundred twenty-one female Sprague-Dawley rats, aged approximately 4 weeks, were purchased from Charles River Labs, Raleigh, North Carolina. Upon receipt, the rats were housed two/cage in stainless-steel cages and acclimated to laboratory conditions for approximately 2 weeks prior to the initiation of dosing.

The feed used was Purina Certified Rodent Chow #5002 which was analyzed by the manufacturer and certified to be free of contaminants. Feed and water were available ad libitum. Water was routinely analyzed for specified pesticides and metals. There were no known contaminants in either the food or water that were expected to interfere with the study.

Following the acclimation period, animals were examined for health status by a staff veterinarian and those judged to be acceptable were assigned to the study with the use of a computer-generated-weight-randomization program. Animals selected for the study were assigned unique permanent animal numbers and housed individually in stainless steel cages. Sixty female rats were assigned to each group: 1 (control), 2 (70 ppm) and 3 (400 ppm).

D. Dosing

Atrazine technical was administered to female Sprague-Dawley rats in the diet at concentrations of 0, 70, or 400 ppm for 104 weeks. The test article was administered at a constant concentration (ppm) in the diets. The rationale used in the selection of these doses was not explained. The registrant should provide an explanation of dose selection including data from the applicable range-finding study, if conducted. *The study used to select test doses in the present study was American Bioorganics Corp. 410-1102, dated 4/29/86 (MRID # 00262714 - 00262727), was submitted to the Agency.*

E. Statistical Analyses

Absolute body weights, body weight changes, total food consumption, hematology data, and terminal body weight and organ weight data of the control group were compared to data of treated groups for homogeneity of variance prior to use of one-way analysis of variance (ANOVA) techniques. Group comparisons were performed at the 5.0% two-tailed probability level using Dunnett's t-test. Survival was analyzed by life table techniques consisting of Kaplan-Meier product limit estimates, Cox-Tarone binary regression on life tables, and Gehan-Breslow nonparametric methods (Thomas et al. 1977). Initially tumor incidences and nonneoplastic lesions were analyzed by Cochran-Armitage method for trend and Fisher-Irwin exact test for control versus treatment comparisons (Thakur et al. 1985). The incidental tumor method consisted of logistic regression of tumor prevalences. The palpable tumors were analyzed by life table techniques using the first palpation times of histomorphologically verified lesions as their onset times.

F. General Observations

1. **Mortality/Moribundity/Survival** - The animals were observed twice daily for mortality and moribundity. The survival of the animals at the termination of the study is reported in Table 1. The study author used the Gehan-Breslow, Kaplan Meier, and Cox-Tarone tests for survival. Using the Gehan-Breslow test, there was a statistically significant negative trend in survival among the dose groups. However, using the Cox-Tarone test, the differences were not found to be significant, nor was any trend detected. Therefore, the reviewer finds that, based on these tests alone, the decrease in survival was equivocal.

Table 1

SURVIVAL OF ANIMALS AT THE END OF THE TWO-YEAR ONCOGENICITY STUDY IN FEMALE SPRAGUE-DAWLEY RATS

	Group 1 (0 ppm)	Group 2 (70 ppm)	Group 3 (400 ppm)
Total animals	60	59 ^a	60
# Surviving at Terminal Sacrifice	31	25 ^a	22 ^{**}
Survival (%)	52	42	37

Data taken from Table 2, pages 66-69 of the Report.

^a Adjusted for accidental death.

^{**} Statistical significance - $p < 0.05$ using Gehan-Breslow test, only.

2. **Clinical Observations** - All animals were observed daily for signs of overt toxicity. Thorough physical examinations were conducted weekly. No treatment-related increases in the incidence of any clinical signs were observed in female rats following exposure to atrazine technical. The author noted that the observations in exposed and control animals included palpable masses and other sporadic changes typical of rats of this strain.

3. **Body Weights/Food Consumption/Test Material Intake** - Body weights were measured prior to the initiation of the study, weekly for the first 16 weeks, and every fourth week thereafter. Terminal body weights were recorded prior to necropsy. As noted in Table 2, decreases in mean body weight gain were noted for Group 3 during the study. By the end of the study, however, the mean body weight gain of Group 3 was only about 4% less than that of the controls. Group 2 animals gained more weight than controls over the course of the study. No decrease in overall weight gain was seen in either dose group, compared to controls.

Table 2

MEAN BODY WEIGHTS IN FEMALE SPRAGUE-DAWLEY RATS (G)

Weeks	Group 1 (0 ppm)	Group 2 (70 ppm)	Group 3 (400 ppm)
0	177.0	177.4	177.5
4	255.8	254.4	246.3*
13	326.0	323.6	308.1*
24	361.5	362.1	340.1*
52	409.2	424.4	389.4
76	449.6	460.1	414.5*
104	459.5	502.8	448.6
Gain (% vs. control)			
Weeks 0 - 4	78.8	77.0 (-2.3)	* 68.8 (-12.7)
Weeks 0 - 13	149.0	146.2 (-1.9)	* 130.6 (-12.4)
Weeks 0 - 24	184.5	184.7 (+0.1)	* 162.6 (-11.9)
Weeks 0 - 76	272.6	282.7 (+3.7)	* 237.0 (-13.1)
Weeks 0 - 104	282.5	325.4 (+15.2)	271.1 (-4.0)

Data taken from Table 4a, pp. 72-75, ~~77~~ of the Report.

* Statistical significance - $p < 0.05$

Food consumption was determined at the same intervals as body weight. Significant decreases in food consumption were noted in Group 3 at the 1 to 4 week and 1 to 13 week intervals. This decrease in food consumption may explain the initial decrease in mean body weight gain seen in this dose group. All other weekly food consumption values among treated and control groups were comparable throughout the study. (see table 5 B appended).

The mean consumption of atrazine technical in mg/kg/day over the course of the study was 3.99 for Group 2 and 24.13 for Group 3 (Calculated using data for Weeks 1, 4, and every fourth week thereafter). The decreased food consumption seen in Group 3 during weeks 1 through 13 resulted in decreased compound consumption during that period.

4. Ophthalmoscopic examination - No details about ophthalmoscopic examinations were included in the Methods section of this study. However,

ophthalmic endpoints, such as opaque eyes and exophthalmia, were included in the evaluation of clinical signs. The incidences of ophthalmic endpoints in treated groups were comparable to controls.

G. Clinical Pathology

1. Hematology - According to the study protocol, blood smears were obtained from all surviving animals at Weeks 52, 78, and 104 of the study. These smears were analyzed for leukocyte differential count and cell morphology. The following parameters were examined within these headings.

Leukocyte Differentials

Blast cells
Metamyelocytes
Band neutrophils
Segmented neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Promyelocyte/myelocyte

Cell Morphology

Reactive lymphocytes
Anisocytes
Polychromatophilic cells
Echinocytes
Acanthocytes
Hypochromic cells
Target cells
Schistocytes
Poikilocytes
Howell-jolly bodies
Microcytes
Nucleated RBCs

Although the report indicates that clinical hematology analyses were to be performed on all surviving animals, only Groups 1 and 3 were evaluated at Weeks 52, 78, and 104. Clinical hematology data for Group 2 were analyzed only in cases where the animal was sacrificed in moribund condition.

The only significant change observed in Group 3 was a significant increase in nucleated red blood cell count at Week 52. This finding was deemed incidental by the authors because the increase was slight and the value declined to a level comparable to controls by Week 78. In addition, a slight increase in mean echinocytes (irregularly shaped red blood cells) was detected in Group 3 at Week 52. This value also declined to a level comparable to controls by Week 78. There were no other significant differences between Groups 1 and 3.

H. Sacrifice and Pathology

Necropsies were performed on all animals which died during the course of the study and on all surviving animals at terminal sacrifice. Animals were sacrificed using sodium pentobarbital and exsanguination. The pituitary, mammary glands, uterus, and ovaries from all animals were embedded in paraffin, sectioned, and stained with hematoxylin and eosin, prior to microscopic examination. Histopathological evaluation was performed by the study pathologist using coded slides in order to avoid bias.

[illegible]^a = weights obtained post fixation

A significant number of animals in Group 3 were found to have enlarged spleens (Table 3). Of the 15 animals in Group 3 exhibiting enlarged spleen, 14 of them died prior to the end of the study. The first animal to die with enlarged spleen died during week 44 of the study; 6 more died prior to week 78. (see Organ/BW table, 9a^B appended and "Discussion" section of this vol.).

Table 3

ANIMALS EXHIBITING ENLARGED SPLEENS DURING THE TWO-YEAR ONCOGENICITY STUDY IN FEMALE SPRAGUE-DAWLEY RATS

Dose Group	1 (0 ppm)	2 (70 ppm)	3 (400 ppm)
Number with enlarged spleen (# at terminal sacrifice)	5 (1)	3 (1)	15* (1)
Total number of animals	60	60	60

* Statistical significance - $p < 0.05$ using Fisher's exact test.

* terminal sacrifice only

A large number of palpable mammary masses were observed in all groups. While the overall number of masses was comparable, the masses in treated animals were palpated earlier than masses in controls. The first mammary masses in Groups 2 and 3 were palpated at 34 and 20 weeks, respectively, while the first mammary mass in the controls were palpated at 46 weeks. No other relevant differences were noted between the controls and treated animals. (See appended Text Table for mammary tumor onset times).

2. Organ weights and organ-to-body weight ratios

At terminal sacrifice the selected organs were weighed. As previously mentioned, the mean terminal body weight of the Group 2 animals was significantly higher than that of the controls. Consequently, the mean brain-to-body weight ratio of this group was decreased significantly relative to controls. The absolute mean brain weights were comparable to controls. Although organs of animals which died or were sacrificed prior to terminal sacrifice were not weighed, it is expected that Group 3 animals with enlarged spleens also had increased absolute spleen weights and/or spleen-to-body weight ratios. No other relevant differences were noted in organ weights or in organ-to-terminal body weight ratios. (see Tables 4 & 5 appended)

3. Microscopic

Only the pituitary, mammary glands, uterus, and ovaries were examined for all animals microscopically. The spleens were not examined microscopically. No statistically significant treatment related microscopic changes were detected in any group for non-neoplastic lesions.

Non-Neoplastic

Non-neoplastic responses observed in treated and control animals were comparable and not considered treatment-related.

Neoplastic

Neoplastic lesions were reported in the pituitary and mammary glands, ovaries, and uteri of many of the treated and control animals. For evaluation purposes, the author treated pituitary, ovarian, and uterine tumors as incidental.

The mammary tumors were treated as palpable masses with the first palpation time taken as the onset time.

All groups had comparable incidences of pituitary tumors. Overall, Groups 1 and 3 had comparable numbers of mammary gland tumors, while Group 2 had fewer tumors (Table 4). The author conducted statistical analyses of the data and found the combined incidence of fibroadenomas and carcinomas, after survival adjustment, to be significant. Having reevaluated the data, the reviewer confirmed this finding. When fibroadenomas and carcinomas are combined, the Life Table, Cox-Tarone, and Gehan-Breslow tests (all of which adjust for survival) indicate a significant increase in the incidence of tumors in Group 3.

Table 4

**NEOPLASTIC MAMMARY GLAND LESIONS
FOUND IN FEMALE SPRAGUE-DAWLEY RATS**

	Group 1			Group 2			Group 3		
Mammary Gland	UD	TS	Total	UD	TS	Total	UD	TS	Total
Number examined	29	31	60	34	25	59	38	22	60
Number fibroadenomas alone	20	19	39	12	18	30	24	17	41
Number of carcinomas alone	9	8	17	7	6	13	12	10	22
Number of fibroadenomas and carcinomas combined	24	22	46	15	19	34	30	19	49 ¹

UD = Unscheduled Deaths TS = Terminal Sacrifice

Data taken from Report Text Table 4, page 39. *See also appended Test Tables 2 & 3 for Terminal*

¹ Statistical significance $p < 0.05$ using Life Table tests.

The Reviewer has the following comment regarding the Materials, Methods, and Results:

CLASSIFICATION: Core Minimum. The study may not be upgraded to Guideline due to the fact that it was not designed to examine all organs histopathologically and therefore does not meet the Guideline requirements for an oncogenicity study.

A brief description of the statistical analyses employed was included in the report.

A Good Laboratory Practice Compliance Statement, a Quality Assurance Statement, and a list of Quality Assurance inspections were included.

II. DISCUSSION

This study has been classified as Core Minimum. The study may not be upgraded to Guideline due to the fact that it was not designed to examine all organs histopathologically and therefore does not meet the Guideline requirements for an oncogenicity study.

One important significant macroscopic change detected during the study was enlarged spleen. The incidence of enlarged spleen in Group 3 was significantly increased relative to controls. Unfortunately 14 of the 15 animals exhibiting this change died prior to terminal sacrifice and their organs were not weighed. It is assumed that this enlargement was accompanied by increased absolute spleen weights and/or spleen-to-body weight ratios. *However, the increased spleen weights at TSacrifice were not significantly greater than controls. This increase in spleen size relationship to treatment is unknown and is considered incidental biologically.*

Prior to adjustment for survival there were no significant increases in the incidence of either mammary fibroadenomas or carcinomas in either group treated with atrazine technical. When fibroadenomas and carcinomas were combined and adjusted for survival, Group 3 had significantly more tumors than the other groups. Pituitary tumors were not significantly increased in treated groups compared to controls and did not correlate as a prerequisite for the incidence of mammary tumors (see report text Tables 1,4,5,6 appended).

The study authors cite decreased body weight gain and decreased survival as indicators that the Maximum Tolerated Dose (MTD) was reached in this study. Body weight gain decrease seen in the 0-76 week period, however was not significantly decreased at the end of the study and is not considered by the reviewer to be indicative that the MTD was actually reached. Results of the statistical analyses of survival alone are considered only equivocally positive since only 1 of several statistical methods reached significance at ($P < 0.05$). Therefore, based on decreased survival, and toxicity reported in other studies at only slightly higher doses, the reduction in body weight gain for a significant portion of the study and the statistically significant increase in the incidence of mammary gland fibroadenomas and carcinomas combined, when adjusted for survival in Group 3, the reviewer concurs that the highest dose tested was adequate to challenge the test animals for carcinogenic activity in this study.

Trt Review 010771

Page _____ is not included in this copy.

Pages 16 through 26 are not included.

The material not included contains the following type of information:

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- ☐ Identity of product impurities.
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- ☐ A draft product label.
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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

NOTE: WITH REGARD TO THE ATTACHED DER FOR THE FOLLOWING STUDY:

ONCOGENICITY STUDY IN FISCHER-344 RATS WITH ATRAZINE
TECHNICAL. STUDY NO. HWA 483-277. MRID # 422270-01.

CLEMENT ASSOCIATES PERFORMED THE PRIMARY REVIEW OF THE STUDY.
TOXICOLOGY BRANCH 1 REVIEWERS THEN INDEPENDENTLY MADE SOME
AMENDMENTS TO THE CLEMENT'S PRIMARY REVIEW.

FINAL

DATA EVALUATION REPORT
ATRAZINE TECHNICAL
ONCOGENICITY STUDY IN FISCHER-344 RATS
WITH ATRAZINE TECHNICAL

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer

Annette M. Shipp Date 12-18-92
Annette M. Shipp

Independent Reviewer

William L. McLellan Date 12-18-92
Bill McLellan

QA/QC Manager

Sharon A. Segal Date 12-21-92
Sharon Segal

Contract Number: 68D10075

Work Assignment Number: 1-88

Project Officer: James Scott, Ph.D.

EPA Work Assignment Manager: Hank Spencer, Ph.D.

Primary Review by: Dr. Henry Spencer
Review Section III,
Toxicology Branch I/HED

Signature Henry Spencer
Date 4/20/93

Secondary Review by: Dr. Karen Hammernik
Section Head, Review Section III,
Toxicology Branch I/HED

Signature K. Hammernik
Date 2/2/94

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity study - Rats (§ 83-2)

TEST MATERIAL: Atrazine Technical

TOX. CHEM. NO.: 063

SYNONYMS: 2-chloro-4-ethylamino-6-isopropylamino-s-triazine

MRID NO.: 422270-01

STUDY NUMBER: HWA 483-277

SPONSOR: Ciba-Geigy Corporation
Agricultural Division
P.O. Box 18300
Greensboro, North Carolina 27419

TESTING FACILITY: Hazleton Washington, Inc.
9200 Leesburg Turnpike
Vienna, Virginia 22182

TITLE OF REPORT: Oncogenicity Study in Fischer-344 Rats with Technical Atrazine

AUTHORS: Ajit K. Thakur, Ph.D.

REPORT ISSUED: February 18, 1992

CONCLUSIONS:

Atrazine Technical, administered in the diet to Fischer-344 rats for at least 104 weeks at concentrations of 0, 10, 70, 200, and 400 ppm, had the following effects:

- 400 ppm - A decrease in body weight gain of approximately 11% was observed in both males and females over the study duration.
- 200 ppm - LEL as approx 8% (statistically signif.) decrease in body wt. gain in both sexes. (weeks 0-76).
- 70 ppm - No effects. = NOEL
- 10 ppm - No effects.

No carcinogenic effects were attributable to compound intake. An increase in hematoneoplasia mononuclear cell leukemia was observed in females in the 10 ppm dose group only. This increase is not considered to be due to treatment with atrazine technical. Incidences of mammary and pituitary gland neoplasms were not statistically different from controls.

The only statistically significant non-neoplastic findings occurred in the liver. These included an increase in leukemia-associated hepatopathy in females in the 10 and 400 ppm group and an increase in basophilic cellular alteration in males in the 70 ppm group. These findings are not believed to be due to treatment with atrazine technical.

The NOEL for this study is ⁷⁰200 ppm. *4/20/93 HLB*

The LOEL in this study is ²⁰⁰400 ppm *4/20/93 HLB* based on a decrease in body weight gain in males and females.

This study is classified Core-Guideline for carcinogenicity.

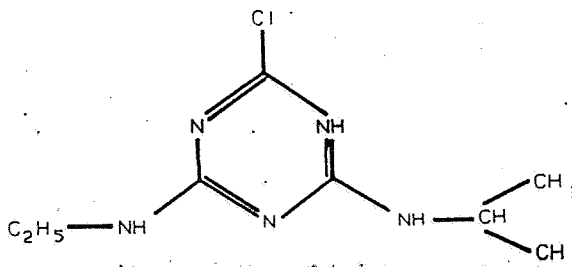
This study satisfies Guideline requirement (§83-2) for an oncogenicity study.

I. MATERIALS, METHODS AND RESULTS

A. Test Article Description

Name: Atrazine Technical

Formula:



Lot Number: D3413J10 (FL-850612)

Purity: 97.0%

Physical Property: white powder

Stability: Stable at room temperature

B. Test Article Analyses for Purity and Stability

The purity of atrazine technical was reported to be 97.0%. Diets were prepared weekly and sampled 1 week prior to feeding to verify concentration. Before dosing began, homogeneity and room temperature stability analyses were performed on days 0, 7, 14, and 21 for the 10 and 400 ppm dose levels since this range included all of the doses to be used. Homogeneity analyses were also conducted at week 56 due to a change in batch size. Results from homogeneity and room temperature stability analyses were within 10% of target, except for stability analyses on day 21 for the 400 ppm group which was within 15% of target (See Tables 1 and 2).

Diets were stored at room temperature. Diet concentration analyses were performed for 26 weekly preparations which were randomly selected by computer. These weeks were 1, 4, 6, 10, 16, 18, 27, 31, 33, 35, 39, 42, 50, 57, 60, 61, 79, 80, 81, 82, 88, 89, 90, 93, 103, and 104. Diet concentration analyses revealed that the prepared diets were generally within 10% of the target concentration. (see Table 4).

C. Animals

CrI:CDF(F344) rats (372 male and 351 female) approximately 4 weeks of age were obtained from Charles River Laboratories, Raleigh, North Carolina. Animals were housed two per sex per cage in stainless-steel, hanging, wire mesh cages and were allowed to acclimate to laboratory conditions for 3 weeks prior to initiation of dosing. Food and water were available ad libitum. The feed was analyzed by the manufacturer for specified heavy metals, aflatoxin, chlorinated hydrocarbons, organophosphates, and specified nutrients. The water was routinely analyzed for specified pesticides and heavy

Table 1

RESULTS OF HOMOGENEITY ANALYSES FOR ATRAZINE TECHNICAL

Week	Target Dose Level (ppm)	Food Level Assayed	Assayed Level (ppm)	Percent Target
Pretest	10	Top	9.76	97.6
		Middle	9.81	98.1
		Bottom	9.62	96.2
	400	Top	383.5	95.9
		Middle	383.0	95.8
		Bottom	385.0	96.3
56	10	Top	10.00	100.0
		Middle	9.98	99.8
		Bottom	9.62	96.2
	400	Top	395.5	99.2
		Middle	386.5	96.7
		Bottom	376.0	94.1

Table 2

RESULTS OF STABILITY TESTS FOR ATRAZINE TECHNICAL

Target Dose Level (ppm)	Assayed Level (ppm)				Percent Target			
	Day 0	7	14	21	Day 0	7	14	21
10	9.73	9.99	9.17	9.14	97.3	99.9	91.7	91.4
400	383.5	386.5	367.5	348	96.0	96.7	91.9	87.0

metals. The results from this analysis were not included in the report, but are on file at the testing laboratory. According to the authors, no contaminants were known to be present at levels which would interfere with the study objectives.

The temperature and relative humidity in the animal room were monitored and were reported to range from 65 to 80°F (18.3-26.7°C) and 18 to 81%, respectively. A 12-hour light/dark cycle was maintained.

After the animals acclimated to laboratory conditions, health status was established by a veterinarian. Animals were ranked by weight and those animals with

weights not within 2 S.D. of the mean were eliminated. The remaining animals whose health was judged to be acceptable were assigned to dose groups (60 animals/sex/dose group) using a computerized weight randomization program (see Table 3). Group assignments were analyzed by analysis of variance techniques to assure homogeneity of group variances and means. The animals were then assigned unique permanent identification numbers and housed individually.

Table 3

NUMBER OF ANIMALS AND THEIR TREATMENT
DURING A STUDY IN RATS WITH ATRAZINE TECHNICAL

Concentration in Diet (ppm)	Females Number of Animals	Males Number of Animals
0	60	60
10	60	60
70	60	60
200	60	60
400	60	60

D. Dosing

Atrazine technical was administered to male and female Fischer-344 rats in the diet at concentrations of 0, 10, 70, 200, or 400 ppm for 104 to 106 weeks depending on week of sacrifice. All dose levels were prepared by premixing the test substance with 200 g of feed for 2 to 3 minutes and then adding the premix to the appropriate amount of feed and mixing for an additional minute (Table 4). No experimental data were given to justify dose selection, however, the authors stated that the dose levels were selected to provide a gradient of effects based on previously conducted studies and on discussions with EPA personnel. Diets were not adjusted for purity before feeding to rats approximately 7 weeks old at study initiation.

E. Statistical Analysis

Body weight, body weight changes, food consumption, leukocyte differential data, and organ weights were analyzed by one-way analysis of variance (ANOVA). Survival was analyzed by life table techniques including Kaplan-Meier product limit estimates, Cox-Tarone binary regression on life tables, and Gehan-Breslow non-parametric methods. Statistical analysis of non-neoplastic and neoplastic lesions was conducted using Cochran-Armitage to assess trend and the Fisher-Irwin exact test for control versus treatment comparisons. In all analyses, statistical significance was indicated when a p-value of 0.05 or less was obtained.

Table 4

RESULTS OF DIET CONCENTRATION ANALYSES
FOR ATRAZINE TECHNICAL

Target Dose Level (ppm)		Corrected Value	Percent of Target
10	Mean S.D. N	9.78 0.39 52	97.8
70	Mean S.D. N	67.4 1.79 52	96.3
200	Mean S.D. N	195 5.47 52	97.5
400	Mean S.D. N	393 13.5 52	98.4

Data extracted from a table located on Report page 21.
Average of sampling over course of study.

F. General Observations

1. Mortality/Moribundity/Survival - The animals were observed twice daily for mortality and moribundity. The survival of the animals at study termination is reported in Table 5. The survival rates for the 0, 10, 70, 200, and 400 ppm groups were 70, 78, 77, 75, and 68% for males and 78, 83, 75, 82, and 73% for females. No significant survival problems were apparent.
2. Clinical Observations - Thorough physical examinations were performed prior to the initiation of dosing and once weekly thereafter. Cageside observations were made once daily for indications of overt toxicity. Clinical observations noted were typical of those observed in this strain of rat. Common findings ^{in all dose groups} included a thin, hunched appearance, soft feces, urine staining of fur, hair loss, body sores, chromodacryorrhea, and lacrimation. Tissue masses in various areas of the body occurred but no dose-related increase in incidence was found. *The highest dosed females appeared to exhibit a clinical effect of thinness which could be the result of chemical exposure.*
3. Body Weights/Food Consumption - Individual body weights were recorded prior to initiation of dosing, weekly through study week 16, and then every 4 weeks thereafter. Terminal body weights were recorded following an overnight fast.

Table 5

**INCIDENCE OF MORTALITY IN FISCHER-344 RATS
ADMINISTERED ATRAZINE TECHNICAL**

	0 ppm	10 ppm	70 ppm	200 ppm	400 ppm
MALES					
Number per group	60	60	60	60	60
Total unscheduled deaths	18	13	14	15	19
Percent mortality	30	22	23	25	32
FEMALES					
Number per group	60	60	60	60	60
Total unscheduled deaths	13	10	15	11	16
Percent mortality	22	17	25	18	27

Data extracted from Report Text Tables 2A and 2B, page 22.
mortality through study week 104. Adjusted survival for 104 weeks was similar

Statistically significant differences were observed in mean body weights and in body weight gain in males and females at various doses (Table 6). At the end of the study, week 104, body weight was statistically significantly reduced in both males and females in the high-dose group. Body weight was also significantly decreased for males and females receiving 400 ppm at weeks 4, 13, 24, 52, and 76 and in males receiving 200 ppm at weeks 4, 24, 52, and 76. Females receiving 200 ppm had statistically significantly reduced body weights at weeks 4, 13, 24, 52, and 76. Body weight was significantly decreased in lower dose groups at various time points but was not significant at terminal sacrifice.

Body weight gain was statistically significantly decreased in males and females in the high-dose group for weeks 0-104. The average decrease in body weight gain in males and females receiving 400 ppm was 16 and 14%, respectively, ^{relative to controls} for the first 13 weeks of the study and 11% over the entire study (0-104 weeks). Body weight gain in both males and females administered 200 or 400 ppm was statistically significantly decreased ^{relative to c} for weeks 0-4, 0-13, 0-24, 0-52, and 0-76 and in the 400 ppm dose group for weeks 0-104. Transient decreases in body weight gain were observed early in the study in lower dose group animals.

Food consumption was determined weekly for weeks 1-16 and once every 4 weeks thereafter. Mean chemical consumption was calculated for each consumption interval. Mean cumulative food consumption was significantly decreased in males receiving 400 ppm during study week intervals 1-13, 1-24, 1-52, 1-76, and 1-104 and in females during week intervals 1-4 and 1-13, compared to controls. No effects on food consumption were observed at any other dose group. Although food consumption was decreased in the (see attached table 5B).

Table 6

**GROUP MEAN BODY WEIGHTS AND BODY WEIGHT GAINS
RAT ONCOGENICITY STUDY WITH ATRAZINE TECHNICAL**

Week	Males					Females				
	0 ppm	10 ppm	70 ppm	200 ppm	400 ppm	0 ppm	10 ppm	70 ppm	200 ppm	400 ppm
BODY WEIGHTS - g										
1	147.6	147.7	146.2	149.5	150.2	105.3	104.2	105.3	106.8	105.6
4	245.4	246.2	240.6*	237.1*	232.8*	154.5	150.0*	151.5*	148.5*	146.2*
13	308.3	306.4	297.1*	301.3	285.4*	180.2	177.3	177.3	172.6*	170.1*
24	339.2	335.8	328.4*	329.0*	312.8*	194.0	189.0*	190.9	187.1*	183.2*
52	365.3	363.9	358.9	353.1*	335.3*	210.2	207.4	207.0	201.0*	195.9*
76	372.1	375.2	365.6	355.9*	337.6*	235.7	236.5	232.9	227.5*	221.7*
104	328.1	333.3	325.6	318.6	310.0*	235.2	231.0	234.5	230.9	220.2*
BODY WEIGHT GAINS - g										
0-4	97.8	98.4	94.4	87.6*	82.6*	49.2	45.8*	46.2*	41.7*	40.6*
0-13	160.7	158.7	150.9*	151.8*	135.2*	74.9	73.1	72.0	65.8*	64.5*
0-24	191.6	188.1	182.2*	179.5*	162.6*	88.7	84.8*	85.6	80.3*	77.7*
0-52	217.5	216.2	212.7	203.6*	185.3*	104.8	103.2	101.7	94.2*	90.4*
0-76	224.4	227.5	219.4	206.3*	187.5*	130.2	132.4	127.6	120.3*	116.2*
0-104	180.6	185.9	179.6	168.7	160.1*	130.1	127.3	129.6	123.7	115.0*

Statistical Significance: $p \leq 0.05$ = *

Data extracted from Report Tables 4A and 4B, pages 86-94.

high dose group, actual food consumption per gram of body weight gain over the study duration was greater than in controls. Control and high-dose males consumed 25.2 and 27.1 grams of food per gram of body weight gain, respectively, while control and high-dose females consumed 26.8 and 29.9 grams of food per gram of body weight gain, respectively. This suggests that the decrease in body weight gain was not a result of decreased food consumption.

4/20/93
Ophthalmic histologic examination - For all animals in the control and high-dose group, and for those animals that died during the study, both eyes were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically. No significant treatment-related findings were reported.

G. Clinical Pathology

1. Hematology - Blood smears were obtained from all surviving animals at weeks 52, 78, and 104 of treatment and from moribund animals prior to sacrifice when possible. Leukocyte differential counts and cell morphology were evaluated for control and high-dose animals and from moribund animals where samples could be obtained.

In females administered 400 ppm atrazine technical in the diet, a statistically significant decrease in the percentage of lymphocytes and a significant increase in segmented neutrophils was reported at week 52 and a significant increase in band neutrophils was observed at week 78. These effects were not considered to be related to treatment with atrazine technical due to the fact that these changes were not observed at other time intervals or at lower doses.

H. Sacrifice and Pathology

Necropsies were performed on all unscheduled deaths and on all surviving animals at terminal sacrifice. Animals were anesthetized with sodium pentobarbital and then sacrificed by exsanguination following an overnight fast.

The CHECKED (x) parameters were examined microscopically from all animals in the control and high-dose groups and in all animals which died during the study. The pituitary, lungs, liver, kidneys, mammary gland, and gross lesions were examined for all animals. The CHECKED (xx) organs were weighed and examined microscopically.

Digestive System		Respiratory		Urogenital	
x	Salivary glands*	x	Trachea*	xx	Kidneys*
x	Esophagus*	x	Lungs*	x	Urinary bladder*
x	Stomach*			xx	Testes*
x	Duodenum*		Cardiovasc./Hemat.	xx	Epididymides
x	Jejunum*	x	Aorta*	x	Prostate
x	Ileum*	xx	Heart*	xx	Seminal vesicles
x	Cecum*	x	Bone Marrow*	xx	Ovaries
x	Colon*	x	Lymph Nodes*	xx	Uterus*
x	Rectum*	xx	Spleen*		
xx	Liver*	x	Thymus*		
x	Pancreas*				

Neurologic		Glandular		Other	
xx	Brain*	xx	Adrenals*	x	Bone*
x	Peripheral Nerve* (sciatic)	x	Mammary gland*	x	Muscle*
x	Spinal Cord*	xx	Parathyroid* ^a	x	Skin*
xx	Pituitary* ^a	xx	Thyroid* ^a	x	All gross lesions and masses*
x	Eyes*				
x	Vagina				

* = EPA Guideline §83-2 Requirement

^a = weights obtained post fixation

1. Macroscopic -

With the exception of a statistically significantly increased incidence of enlarged spleen in females in the low- and high-dose group, no gross findings were noted which were not of the type commonly seen in this species and strain of rat. The incidence of enlarged spleen was 5/60, 13/60, 11/60, 8/60, and 14/60 for the 0, 10, 70, 200, and 400 ppm groups, respectively. The increased incidence of enlarged spleen was not dose-related and was only seen in females; therefore, it is not believed to be related to atrazine-technical treatment. Other findings were similarly distributed among the dose groups in both sexes.

2. Organ weights and organ-to-body weight ratios -

At terminal sacrifice, the kidney, liver, adrenals, thyroid/ parathyroid, pituitary, and testes/seminal vesicles or ovaries were weighed from all animals. Organ/body weight ratios were calculated using the fasted body weight recorded on the day of sacrifice. The organ weights and organ-to-body weight ratios with significant changes in males or females are reported in Table 7.

A statistically significant decrease in absolute thyroid and parathyroid weights and in the relative thyroid and parathyroid weights were observed in females administered 70 and 200 ppm atrazine technical. These decreases were not dose-related and were not observed in males; therefore, they are not believed to be treatment related. Several other organ-to-body weight ratios, but not absolute organ weights, were statistically significantly increased in the high-dose animals as a result of the decreased mean body weight in these animals.

3. Microscopic

Non-Neoplastic

Leukemia-associated hepatopathy was statistically significantly increased in females of the low- and high-dose group (10 and 400 ppm). In males administered 70 ppm, an increase in basophilic cellular alteration of the liver was reported. The incidence of these lesions is shown in Table 8. These lesions are not considered to be biologically significant because they were only found in one sex and no dose response was observed.

Neoplastic

A statistically significant increase in the incidence of hematoneoplasia-mononuclear cell leukemia was observed in females at the low-dose only (See Table 8). Although the incidence of this lesion was higher in the treated groups compared to the control group, the incidence was not statistically significant and no dose-response relationship was observed. The highest incidence of hematoneoplasia-mononuclear cell leukemia observed in this study was 30% in the low dose group, which is within the range of historical control values reported. Therefore, this effect is not considered to be treatment-related. No other statistically significant increases in neoplastic lesions were observed.

Histopathological examination of the pituitary and mammary gland indicated no significant difference in neoplasms from that of the controls (at $p \leq 0.05$) (Table 8) when the carcinomas and fibroadenomas were statistically analyzed, even though the time to first tumor occurred earlier in some of the treated groups than in the controls. Mammary gland carcinomas occurred in females only of the 70 and 200 ppm groups at an earlier time than controls (Table 9). A pituitary gland adenoma occurred in females of the 200 ppm group and a pituitary gland carcinoma occurred in the 200 and 400 ppm groups before these tumors were found in the controls. In males, the only pituitary or mammary gland neoplasm to occur earlier in treated animals than in controls was pituitary adenoma in the 200 ppm group. In addition, one mammary gland carcinoma was found in males administered 10 ppm atrazine technical, while none were found in the male controls or other dose groups.

Table 7

GROUP MEAN ORGAN WEIGHTS OF RATS ADMINISTERED
ATRAZINE TECHNICAL

	MALES					FEMALES				
	0 ppm	10 ppm	70 ppm	200 ppm	400 ppm	0 ppm	10 ppm	70 ppm	200 ppm	400 ppm
No. organs weighed	41	47	46	44	40	47	50	45	49	43
Body weight g	307.5	312.8	302.0	298.2	290.3*	218.6	214.7	219.0	215.6	204.3*
Brain g	2.08	2.09	2.07	2.08	2.04	1.91	1.89	1.90	1.88	1.89
rel. to BW %	0.684	0.673	0.694	0.702	0.708	0.877	0.889	0.875	0.876	0.934*
Heart g	1.17	1.19	1.16	1.17	1.16	0.91	0.89	0.92	0.91	0.91
rel. to BW %	0.382	0.382	0.390	0.394	0.403	0.416	0.418	0.422	0.424	0.448*
Kidneys g	2.66	2.62	2.59	2.67	2.63	1.85	1.86	1.88	1.86	1.89
rel. to BW %	0.875	0.840	0.865	0.901	0.912	0.848	0.877	0.862	0.865	0.932*
Liver g	9.60	9.72	9.77	9.49	9.08	6.75	6.90	6.97	6.73	6.94
rel. to BW %	3.151	3.120	3.251	3.199	3.143	3.089	3.232	3.188	3.129	3.421*
Testes/Epididymis g	5.94	5.89 ^a	5.84	6.08	6.67	NA	NA	NA	NA	NA
rel. to BW %	1.924	1.880	1.934	2.028	2.290*	NA	NA	NA	NA	NA
Thyroid/parathyroid g	0.032 ^b	0.032	0.032	0.028	0.030	0.025	0.025	0.021*	0.020*	0.023
rel. to BW %	0.0105	0.0103	0.0111	0.0096	0.0102	0.0116	0.0119	0.0099*	0.0093*	0.0115

Statistical Significance: $p < 0.05$ =
Data extracted from Report Tables 9 and 10, pages 172-178.

^a N = 46
^b N = 40

Table 8

**MICROSCOPIC NON-NEOPLASTIC AND NEOPLASTIC PATHOLOGY
IN MALE AND FEMALE RATS ADMINISTERED ATRAZINE TECHNICAL**

	0 ppm	10 ppm	70 ppm	200 ppm	400 ppm
Non-Neoplastic					
<u>MALES</u>					
Basophilic cellular alteration of liver	33/60	39/60	44/60*	32/60	31/60
<u>FEMALES</u>					
Leukemia-associated hepatopathy	5/60	16/60*	11/60	10/60	13/60*
Neoplastic					
<u>FEMALES</u>					
Hematoneoplasia-mononuclear cell leukemia	8/60	18/60*	14/60	11/60	15/60
** Mammary gland fibroadenoma	2/60	5/60	5/60	7/60	6/59
** Mammary gland carcinoma	2/60	0/60	2/60	3/60	2/59
Pituitary gland adenoma	22/60	26/60	20/58	19/59	13/59
Pituitary gland carcinoma	1/60	2/60	0/58	1/59	2/59
<u>MALES</u>					
Mammary gland fibroadenoma	2/55	0/54	0/52	0/52	1/58
Mammary gland carcinoma	0/55	1/54	0/52	0/52	0/58
Pituitary gland adenoma	15/59	14/60	15/60	11/60	8/59
Pituitary gland carcinoma	0/59	0/14	0/60	0/60	0/59

Statistical Significance: $p < 0.05 = *$

Data extracted from Table 11C, pages 215-235.

** Combination statistically analyzed - not significant.

Table 9

WEEK AT WHICH FIRST TUMORS FOUND
FOLLOWING ATRAZINE TECHNICAL ADMINISTRATION TO RATS

	0 ppm	10 ppm	70 ppm	200 ppm	400 ppm
FEMALES					
<u>Mammary Gland</u>					
Fibroadenoma	58	103	105	105	84
Carcinoma	97	NF	65	69	105
<u>Pituitary Gland</u>					
Adenoma	79	92	85	74	100
Carcinoma	89	105	NF	72	28
MALES					
<u>Mammary Gland</u>					
Fibroadenoma	103	NF	NF	NF	106
Carcinoma	NF	105	NF	NF	NF
<u>Pituitary Gland</u>					
Adenoma	86	87	92	78	96
Carcinoma	NF	NF	NF	NF	NF

NF - None found.

The Reviewer has the following comment regarding the Materials, Methods, and Results:

This study is to be considered Core Guideline.

A brief description of the statistical analyses employed was included in the report.

A Good Laboratory Practice Compliance Statement, a Quality Assurance Statement, and a list of Quality Assurance inspections were included.

II. DISCUSSION

Significant decreases in mean body weight were observed in males and females in the high-dose group throughout the study. At 200 ppm, body weight was decreased in males and females at various observation times but the decrease was not significant at terminal sacrifice. These decreases in body weight resulted in a decrease in body weight gain of approximately 11% for the entire duration of the study in both males and females of the high-dose group. For the first 13 weeks of the study, body weight gain was decreased 16 and 14% for males and females, respectively, administered 400 ppm atrazine technical.

In the high dose group only, food consumption was decreased in males over the study duration and in females over the first 13 weeks. Although food consumption was decreased on a per gram basis, food consumption was actually greater on a grams consumed per gram of body weight gain basis. This suggests that the decrease in body weight gain observed is not due to a decrease in food consumption but rather to compound consumption.

Microscopic evaluation identified a statistically significant increase compared to controls of leukemia-associated hepatopathy in females administered 10 or 400 ppm. The incidence of this lesion was increased compared to controls in females in the 70 and 200 ppm groups as well; however, there was no dose-response and the increases were not statistically significant in the 70 and 200 ppm groups. No information was provided by the authors on the historical incidence of leukemia-associated hepatopathy.

The only statistically significant increase in neoplastic lesions was in hematoneoplasia-mononuclear cell leukemia in females administered 10 ppm. The incidence of this lesion was also increased at higher doses compared to controls but these increases were not statistically significant. According to the historical control data provided by the authors, these incidences are within normal control values. Since no dose-response was observed and the incidence of this lesion was apparently within historical control range, this increase is not considered to be related to atrazine technical treatment.

Since interim sacrifices were not performed, it is difficult to determine whether tumors developed earlier in treated animals compared to controls. In females, the time to first pituitary carcinomas in the two highest dose groups (200 and 400 ppm) was decreased compared to controls. The incidence of pituitary carcinomas was 1/60, 2/60, 0/58, 1/59, and 2/59 for the 0, 10, 70, 200, and 400 ppm dose groups, respectively. The other pituitary carcinoma in the high dose group was found at terminal sacrifice. The incidence of this tumor is low and was not statistically significantly increased in any of the dose groups. Survival was not affected by atrazine technical administration. A decrease in latency for pituitary carcinomas did not occur as a result of atrazine technical administration. Also in females, mammary gland carcinomas were found earlier than in controls in the 200 and 70 ppm dose groups, but not in the highest dose group. This decrease in time to first tumor is not dose-related and once again the incidence of this tumor type is not statistically significant. A decrease in latency for mammary gland

To of Review 010771

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Pages 45 through 46 are not included.

The material not included contains the following type of information:

- ☐ Identity of product inert ingredients.
- ☐ Identity of product impurities.
- ☐ Description of the product manufacturing process.
- ☐ Description of quality control procedures.
- ☐ Identity of the source of product ingredients.
- ☐ Sales or other commercial/financial information.
- ☐ A draft product label.
- ☐ The product confidential statement of formula.
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