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

AUG 6 1996

12011

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Review of Special 1-year Study with Atrazine in Female Rats (MRID 43934402).

DP Barcode: D224157 Submission: S501421
PC Code: 080803 Tox Chem No: 063

TO: Kathryn Boyle
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

FROM: Kit Farwell
Section 3, Toxicology Branch I
Health Effects Division (7509C)

Kit Farwell 7-22-96

THRU: Edwin Budd, Acting Section Head
Section 3, Toxicology Branch I
Health Effects Division (7509C)

Budd 7/22/96 KB

Attached is the Data Evaluation Report (DER) for a special 1-year dietary study with atrazine in female rats. This special study was designed by the registrant to collect data related to possible mechanisms of mammary tumor development in female rats.

Dietary levels of 0, 15, 30, 50, 70 or 400 ppm corresponded to 0.8, 1.7, 2.8, 4.1, or 23.9 mg/kg/day. No effects upon clinical signs or mortality were noted. Body weight and body weight gain were significantly decreased in the 400 ppm group beginning at week 2 and continuing throughout the study. Mammary gland adenocarcinomas were increased in high-dose females compared to controls (6/55 vs 1/55), mammary gland adenomas were similar in incidence in high-dose animals compared to controls (1/5 vs 0/55), and mammary gland fibroadenomas were only slightly increased in high-dose females in comparison to controls (4/55 vs 2/55). The increase in mammary neoplasms was statistically significant ($p \leq 0.05$) only when the 3 types of neoplasms were combined. There were no significant differences for onset time among treatment groups when the mammary neoplasms were considered separately, however, there was a significant positive trend ($p \leq 0.05$) when fibroadenomas were combined with either adenomas or

cc: Melba Morrow, Toxicology Branch I
Lori Brunsman, Science Analysis Branch

adenomas and adenocarcinomas. The NOEL is 70 ppm (4.1 mg/kg/day) and the LOEL is 400 ppm (23.9 mg/kg/day) in females based on decreased body weight, body weight gain, and increased mammary gland adenocarcinomas.

The study is classified supplementary, does not satisfy the 83-1 Guideline requirements for a chronic study in rats, and cannot be upgraded because only female rats were used, not all required tissues were examined microscopically, liver and kidneys were not weighed, and no clinical chemistry, urinalysis, or hematology testing was performed. Blood samples for hormone analysis were taken but results were not reported in the study report. Vaginal smears for estrous cycle evaluation were taken with results for individual animals reported but no summary tables were provided. An analysis of the plasma hormone and estrous cycle data are to be reported at a later date.

This study will be considered at the Carcinogenicity Peer Review Meeting presently scheduled for 7/31/96.

ATTACHMENT

EPA Reviewer: Kit Farwell Kit Farwell, Date 7-18-96
Review Section 3, Toxicology Branch 1 (7509C)
EPA Secondary Reviewer: Edwin Budd Edwin Budd; Date 7/22/96
Review Section 3, Toxicology Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Special 1-Year Dietary Study in Female Rats

DP BARCODE: D224157
P.C. CODE: 080803
SUBMISSION CODE: S501421
TOX. CHEM. NO.: 063

TEST MATERIAL (PURITY): Atrazine (97.1%)

SYNONYMS:

CITATION: Pettersen, JC; Turnier, JC (1995). 1-year chronic toxicity study with atrazine technical in rats. Ciba-Geigy Corp. Environmental Health Center (Farmington, CT). Study No. F-00171. Study Date: 12/8/95. MRID 43934402. Unpublished.

SPONSOR: Ciba-Geigy Corporation, Greensboro, NC

EXECUTIVE SUMMARY: This special toxicity study (MRID 43934402) was designed to determine the effects of 12 months of dietary exposure of atrazine to female CD rats on mammary glands, pituitary glands, estrous cycle, and plasma hormones. Estrous cycle evaluation (by vaginal smear and histology) and plasma hormone (estradiol, progesterone, prolactin, and luteinizing hormone) concentrations are to be reported later.

Technical atrazine (97.1% a.i.) was administered in the diet to 55 female Crl:CD(SD)BR rats per dose group at dose levels of 0, 15, 30, 50, 70 or 400 ppm, corresponding to 0.8, 1.7, 2.8, 4.1, or 23.9 mg/kg/day. Ten females per dose group had trunk blood collection and estrous cycle evaluation made at interim sacrifices of 3, 6, 9, or 12 months. Fifteen females per dose group had interim orbital blood samples and estrous cycle evaluations made at 3, 6, 9, and 12 months followed by sacrifice at 12 months. No effects upon clinical signs or mortality were noted. The 400 ppm group had statistically significant decreases in mean body weight compared to, controls beginning at week 2 (96% of controls), decreasing to 88-92% of controls for the last 10 months of the study. The 400 ppm group had statistically significantly decreased mean body weight gain from weeks 2-46 with mean values ranging from 82-89% of controls. Food consumption for the 400 ppm group ranged from 88-101% of controls, statistically significant at 6 weekly intervals in the first 11 weeks. The 400 ppm group had food consumption close to that of controls for the last 9 months of the study. Food efficiency for the 400 ppm group was decreased in comparison to controls during the first 12 weeks of the study. After 12 weeks, the 400 ppm group had similar, or occasionally increased food

efficiency in comparison to controls. Mammary gland hypertrophy (11/55 vs 6/55) and skin masses (9/55 vs 4/55, apparently associated with mammary tumors) were increased in high-dose females compared to controls. Mammary gland adenocarcinomas were increased in high-dose females compared to controls (6/55 vs 1/55), mammary gland adenomas were similar in incidence in high-dose animals compared to controls (1/5 vs 0/55), and mammary gland fibroadenomas were only slightly increased in high-dose females in comparison to controls (4/55 vs 2/55). The increase in mammary gland adenocarcinomas in high-dose females was not statistically significant, however the increase of combined mammary gland adenomas, adenocarcinomas, and fibroadenomas (11/55 vs 3/55 combined) was significant ($p \leq 0.05$). There were no significant differences for onset time among treatment groups when mammary gland adenomas, adenocarcinomas, and fibroadenomas were considered separately, however, there was a significant positive trend ($p \leq 0.05$) when fibroadenomas were combined with either adenomas or adenomas and adenocarcinomas.

The NOEL is 70 ppm (4.1 mg/kg/day) and the LOEL is 400 ppm (23.9 mg/kg/day) in females based on decreased body weight, body weight gain, and increased mammary gland adenocarcinomas.

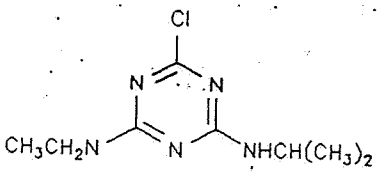
This special study is classified **supplementary**, does not satisfy the guideline requirement for a chronic oral study in the rat, and cannot be upgraded. The following guideline deficiencies were noted: only females were tested; no clinical chemistry, hematology, urinalysis, or ophthalmology testing; liver and kidneys were not weighed; microscopic exam only included the pituitary, ovaries, uterus, vagina, inguinal skin with mammaries, and masses; and not all results were reported (hormone analysis and estrous cycle evaluations).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Atrazine Technical
   Description: white powder
   Lot #: FL-881692, EHC Lot # 0173-10
   Purity: 97.1% a.i.
   Expiration date: 3/6/95
   CAS #:
   Supplied by Ciba Geigy Crop Protection, Greensboro, NC.
   Stored at room temperature.

Structure: 

2. Vehicle and/or positive control: N/A

3. Test animals:
   Species: Female Rats
   Strain: Crl:CD(SD)BR
   Age and wt. at study initiation: 6 weeks, 146 g
   Source: Charles River Laboratories, Raleigh, NC
   Housing: individual polycarbonate cages
   Diet: Purina (PMI) Rodent Chow 5002 ad lib, ground meal.
   Water: ad lib
   Acclimation: 14 days
   Environment:

Temperature:	19-24°C
Humidity:	40-60%
Air changes:	15/hr
Photoperiod:	12 hr cycle

   NOTE: There were also 14 male rats housed in the animal room to support maintenance of regular estrous cycling.

B. STUDY DESIGN: The stated purpose of this special study with female rats was described in the study protocol as follows: "This study is designed to determine the effects of chronic (12 month) dietary administration of atrazine Technical to female CD rats on the mammary and pituitary glands, the estrous cycle, and plasma levels of estradiol, luteinizing hormone (LH), progesterone and prolactin. An attempt will be made to correlate the plasma hormone levels and estrous cycle effects with the onset of mammary tumor development (if any). This study is also designed to provide a no-observable-effect level and does not unnecessarily duplicate a previous study."

1. In life dates - start: 3/16/93 end: 4/1/94

2. Animal assignment

Animals were assigned to study groups with similar mean weights as shown in Table 1.

TABLE 1: STUDY DESIGN

Conc. in Diet (ppm)	Dose to animal mg/kg/day	# of Females/Month of Sacrifice[1]			
		3	6	9	12
0	0	10	10	10	25
15	0.8	10	10	10	25
30	1.7	10	10	10	25
50	2.8	10	10	10	25
70	4.1	10	10	10	25
400	23.9	10	10	10	25

[1]Ten rats in each dose group had vaginal smears made near the time of sacrifice and trunk blood samples taken for hormone analysis at time of sacrifice (months 3, 6, 9, or 12). An additional 15 rats in each dose group had orbital blood samples and vaginal smears taken at 3, 6, and 9 months, and when sacrificed at 12 months.

3. Dose selection rationale: In two studies with CD rats (MRID 4220444-01 and 420850-01, 425471-07, 427439-02), decreased body weight gain, increased mortality, and mammary tumors in females were reported by the study authors at a dietary concentration of 400 ppm.

4. Diet preparation and analysis: Diet was prepared every 2 weeks by mixing appropriate amounts of test material with Purina (PMI) Certified Rodent Chow 5002 and was stored at 4°C. No adjustment was made for purity. Concentration and homogeneity were tested at least monthly. Animals were given fresh feed jars weekly.

Results:

Concentration and Homogeneity: 99-103%

Stability: 94.4-109.9% when stored at 4°C for up to 41 days and 90.1-100.8% when stored at room temperature in open feed jars for up to 14 days.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics - A copy of statistical methods is attached.

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C. METHODS:

1. Observations: Animals were inspected at least twice daily for signs of toxicity and mortality.

2. Body weight: Animals were weighed weekly for the first 13 weeks and every 4 weeks thereafter. Final body weights were determined at necropsy.

3. Food consumption and compound intake: Food consumption for each animal was determined and mean weekly food consumption was reported as g/day. Food efficiency (body weight gain in kg/food consumption in kg per unit time X 100) and compound intake (mg/kg/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic examination was NOT done.

5. Urinalysis was NOT performed in this study.

6. Vaginal smears and estrous cycle evaluation: Vaginal smears to determine the stage of estrous were made at 3, 6, 9, and 12 months. Smears were made for 14-22 days for each animal near the time of sacrifice or interim blood sampling. A protocol amendment says that estrous cycle analysis will be reported at a later date.

7. Blood was NOT collected for hematology and clinical analysis.

Blood samples for hormone analysis were taken from 10 rats in each dose group at time of sacrifice (months 3, 6, 9, or 12). The females were sacrificed and trunk blood samples taken during the first proestrus after at least 14 days of daily vaginal smears or on the last day of the 22 day vaginal smearing interval if proestrus was not seen. Blood samples taken at sacrifice were obtained by decapitation without anesthesia so as to minimize effects on hormone concentrations. The trunk blood samples were collected between 11:00 a.m. and 1:00 p.m. using an oxalate rinsed funnel with heparinized centrifuge tubes.

An additional 15 rats in each dose group had orbital blood samples taken at 3, 6, 9, and 12 months. These blood samples were taken without anesthesia from the right eye if possible, or, if necessary, from the left eye. The orbital blood samples were taken between 11:00 a.m. and 1:00 p.m. using heparinized centrifuge tubes. Blood samples were taken during the first

proestrus after at least 14 days of daily vaginal smears or on the last day of the 22 day vaginal smearing interval if proestrus was not seen. Terminal sacrifice of the animals bled from the orbital plexus was by i.p. injection of sodium pentobarbital.

The female rats were removed one at a time from their home cage and carried to a separate room for sacrifice or blood sampling. Plasma hormones to be tested were estradiol, luteinizing hormone, progesterone, and prolactin. A protocol amendment says that results of hormone analysis will be reported at a later date.

8. Sacrifice and Pathology:

All animals that died and those sacrificed on schedule were subjected to gross pathological examination. The checked (X) tissues were collected for histological examination and the (XX) organs were also weighed, as shown in Table 2. Ovaries, uterus, and vagina were only evaluated for stage of estrous and senescent changes.

TABLE 2 HISTOPATHOLOGY AND ORGAN WEIGHTS

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue		Aorta*		Brain*
	Salivary glands*		Heart*		Periph.nerve*
	Esophagus*		Bone marrow*		Spinal cord (3 levels)*
	Stomach*		Lymph nodes*		
	Duodenum*		Spleen*	XX	Pituitary*
	Jejunum*		Thymus*		Eyes (optic n.)*
	Ileum*		UROGENITAL		GLANDULAR
	Cecum*		Kidneys*+		Adrenal gland*
	Colon*		Urinary bladder*		Lacrimal gland
	Rectum*		Testes*+		Mammary gland*
	Liver*+		Epididymides	X	Parathyroids*
	Gall bladder*		Prostate		Thyroids*
	Pancreas*		Seminal vesicle		OTHER
	RESPIRATORY	XX	Ovaries*+		Bone*
	Trachea*	XX	Uterus*		Skeletal muscle*
	Lung*	X	Vagina		All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

* Required for chronic studies based on Subdivision F Guidelines.
\+ Organ weight required in chronic studies.
NOTE: Brain was weighed but not examined microscopically.

II. RESULTS

A. Observations:

1. Toxicity - No clinical signs of toxicity attributed to treatment were seen. Frequency of clinical signs (chromodachryorrhea, dehydration, hair thinning, ocular opacity, stained hair coat) was similar between control and treatment groups.

2. Mortality - Mortality was similar between control and treatment groups. There were 1, 2, 0, 1, 2, and 2 unscheduled deaths in the control, 15, 30, 50, 70, and 400 ppm groups respectively. Kaplan-Meier adjusted survival rates were reported to be 98%, 93%, 100%, 96%, 96%, and 96% for the 0, 15, 30, 50, 70, and 400 ppm groups, respectively.

B. Body weight: Body weights are shown in Table 3. Mean body weights for the 15, 30, and 50 ppm groups were similar to control weights.

The 70 ppm group had slight decreases in mean body weight compared to controls (statistically significant only from weeks 9-12). Mean body weights for the 70 ppm group were 95% of controls at week 9 decreasing to approximately 91% of controls during the last 2 months of the study. Mean body weights for the 70 ppm group were decreased only slightly (5-7% less than controls) for the first 10 months of the study, were not statistically significant except for weeks 9-12, and are not considered toxicologically significant.

The 400 ppm group had statistically significant decreases in mean body weight compared to controls from weeks 2-42. Mean body weights for the 400 ppm group were 96% of controls at week 2, decreasing to 91% of controls by week 9, and were 89-91% of controls for the remainder of the study. The NOEL/LOEL for decreased body weight in females is 70/400 ppm.

Atrazine **Special 1-Year Dietary Study in Female Rats**

TABLE 3 MEAN WEEKLY BODY WEIGHTS (grams)

WEEK	0 ppm	15 ppm	30 ppm	50 ppm	70 ppm	400 ppm
initial	146.31	148.50	146.88	145.95	145.37	145.34
1	171.63	176.76	173.60	172.08	166.88 (97.2%)	167.23 (97.4%)
2	196.34	200.66	196.73	198.06	193.16 (98.4%)	189.10* (96.3%)
3	218.93	223.52	218.82	218.62	214.05 (97.8%)	209.75* (95.8%)
4	237.54	243.02	235.74	236.51	232.02 (97.7%)	225.97** (95.1%)
5	251.44	255.95	250.63	251.93	245.03 (97.4%)	236.55** (94.1%)
6	264.17	267.44	262.11	264.26	257.87 (97.6%)	249.10** (94.3%)
7	273.69	276.91	271.40	273.28	265.29 (96.9%)	254.66** (93.0%)
8	283.32	285.25	281.10	279.78	271.89 (96.0%)	260.72** (92.0%)
9	293.35	293.75	288.04	284.84	279.40* (95.2%)	266.33** (90.8%)
10	299.76	300.36	295.63	293.80	285.04* (95.1%)	273.26** (91.2%)
11	306.85	303.81	299.40	297.13	289.15** (94.2%)	276.45** (90.1%)
12	309.40	309.07	304.94	302.13	295.36* (95.4%)	280.65** (90.7%)
13	312.34	314.79	310.41	304.75	301.46 (96.5%)	285.85** (91.5%)
14	320.10	320.60	315.90	312.12	307.10 (95.9%)	293.71** (91.8%)
18	339.77	338.30	335.02	329.44	325.54 (95.8%)	310.57** (91.4%)
22	357.01	352.56	350.48	341.49	337.74 (94.6%)	322.60** (90.4%)
26	364.66	367.39	357.77	349.82	343.00 (94.0%)	327.62** (89.8%)
30	382.99	384.74	374.24	373.45	356.88 (93.2%)	340.67** (90.0%)
34	394.69	399.44	387.74	386.39	367.97 (93.2%)	359.73* (91.1%)
38	409.70	418.59	403.69	400.46	383.65 (93.6%)	372.71* (91.0%)

TABLE 3 MEAN WEEKLY BODY WEIGHTS (grams)

WEEK	0 ppm	15 ppm	30 ppm	50 ppm	70 ppm	400 ppm
42	431.38	432.88	415.78	418.56	394.11 (91.4%)	381.40* (88.4%)
46	447.24	450.99	432.53	438.87	404.14 (90.4%)	398.32 (89.1%)
50	460.03	464.54	456.65	453.58	423.44 (92.0%)	408.27 (88.7%)

From Table 9.6, pages 48-50 of study report, MRID 43934402.
*p≤0.05 **p≤0.01
NOTE: Numbers in parentheses are % of control value as calculated by reviewer.

Body weight gains are shown in Table 9.7, copied from the study report. Mean body weight gains for the 15, 30, and 50 ppm groups were similar to controls. The 70 ppm group had statistically significantly decreased mean body weight gain from weeks 8-12 (90-92% of controls). Weight gains were not statistically significant for the 70 ppm group after week 12, values ranging between 87-94% of control weights for the remainder of the study.

The 400 ppm group had statistically significantly decreased mean body weight gain from week 2 until the end of the study. Mean values for body weight gain ranged from 82-89% of controls for the 400 ppm group. The NOEL/LOEL for decreased body weight gain in females is 70/400 ppm.

C. Food consumption and compound intake:

1. Food consumption - Mean weekly food consumption is shown in Table 9.8, copied from the study report. Food consumption for the 15, 30, and 50 ppm groups was similar to controls. Food consumption in the 70 ppm group ranged from 93-100% of controls. Food consumption for the 400 ppm group ranged from 88-101% of controls and was statistically significant principally from weeks 6-11. The 70 and 400 ppm groups had food consumption close to that of controls for the last 9 months of the study.

2. Food efficiency: Mean weekly food efficiency is shown in Table 9.9, copied from the study report. Food efficiency for the 400 ppm was decreased in comparison to controls during the first 12 weeks of the study. After 12 weeks, the 400 ppm group had similar, or occasionally increased food efficiency in comparison to controls.

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3. Compound consumption: Compound consumption is shown in Table 1. Dietary concentrations of 30, 50, 70, and 400 ppm were calculated to be equivalent to 0.8, 1.7, 2.8, 4.1, and 23.9 mg/kg/day.

D. Ophthalmoscopic examination: Ophthalmoscopic examination was NOT performed.

E. Blood work:

1. Hematology - Hematological parameters were NOT determined.

2. Clinical chemistry - Clinical chemistry parameters were NOT determined.

3. Hormone analysis - Blood samples were taken to measure plasma hormone levels (estradiol, progesterone, prolactin, and luteinizing hormone). A protocol amendment says results will be reported at a later date.

F. Urinalysis - Urinalysis was NOT performed.

G. Sacrifice and Pathology:

1. Organ weight - There was no evidence of a treatment-related effect upon brain, ovarian, pituitary, or uterine weights, absolute or relative. Liver and kidneys were not weighed.

2. Gross pathology - Table 4 shows gross necropsy lesions. Mammary gland hypertrophy (11/55 vs 6/55) and skin masses (9/55 vs 4/55) were increased in high-dose females compared to controls. Although not explicitly stated, the skin masses were apparently associated with mammary tumors as the only skin samples reported taken were inguinal skin with mammary gland. Also increased in high-dose animals in comparison to controls were mammary gland cysts (19/55 vs 14/55) and abnormal uterine contents (4/55 vs 1/55), the latter lesions are not believed to be of toxicological significance. Although enlarged pituitary was reported increased in the 400 ppm group compared to controls (9/55 vs 5/55), this is not believed to be treatment related due to lack of a dose-response relationship.

TABLE 4 NECROPSY OBSERVATIONS - ALL ANIMALS

CONDITION	DIETARY CONCENTRATION (ppm)					
	0	15	30	50	70	400
NUMBER OF FEMALES	55	55	55	55	55	55
SKIN						
Mass(es)	4	4	4	4	6	9
MAMMARY GLAND(S)						
Cysts	14	11	11	14	12	19
Hypertrophy	6	2	7	6	6	11
PITUITARY						
Enlarged	5	6	7	2	4	9
UTERUS						
Abnormal contents	1	1	1	2	0	4

From Table 9.12.6 pages 70-73 of the study report, MRID 43934402.

3. Microscopic pathology: Table 5 shows selected histopathological findings. Only results for histological exam of pituitary, inguinal skin, and mammary gland were reported in this study.

a) Non-neoplastic - No increase in non-neoplastic lesions associated with treatment was seen microscopically.

b) Neoplastic - Mammary gland adenocarcinomas were increased in high-dose females compared to controls (6/55 vs 1/55) while mammary gland adenomas were similar in incidence in high-dose animals compared to controls (1/5 vs 0/55). Mammary gland fibroadenomas were only slightly increased in high-dose females in comparison to controls (4/55 vs 2/55). A peer review to verify mammary gland and pituitary neoplasm diagnoses confirmed the initial report.

The increase in mammary gland adenocarcinomas in high-dose females was reported not statistically significant. The increase of combined mammary gland adenomas, adenocarcinomas, and fibroadenomas was significant ($p \leq 0.05$, 3/55 vs 11/55 combined).

There were no significant differences for onset time among treatment groups when mammary gland

adenomas, adenocarcinomas, and fibroadenomas were considered separately. However, there was a significant positive trend ($p \leq 0.05$) when fibroadenomas were combined with either adenomas or adenomas and adenocarcinomas.

The study author points out that there was no evidence of pituitary neoplasms alone or when combined with telangiectasis which may be associated with pituitary adenomas.

As noted in the study deficiencies section, not all required tissues were examined microscopically.

TABLE 5 HISTOPATHOLOGICAL FINDINGS - ALL ANIMALS

CONDITION	DIETARY CONCENTRATION (ppm)					
	0	15	30	50	70	400
NUMBER OF FEMALES	55	55	55	55	55	55
MAMMARY GLAND						
Adenoma	0	0	1	0	1	1
Adenocarcinoma	1	2	0	1	1	6
Fibroadenoma	2	2	2	1	4	4
COMBINED TUMORS	3→	4	3	2	6	11*
NUMBER OF FEMALES	54	55	53	54	55	54
PITUITARY GLAND						
Adenoma	2	5	6	4	1	5
Telangiectasis	0	0	1	1	2	2

*different from control group, $p \leq 0.05$ →positive trend, $p \leq 0.05$

From Table 9.13.6, pages 82-84 and Table 6.2, page 568 of the study report, MRID 43934402.

H. Vaginal Smears and Estrous Cycle Evaluation - Estrous cycle evaluations were not reported in this report but will be presented at a later date. Vaginal smear data for individual animals were reported, but no summary tables were presented in this report. According to the Materials and Methods section (attached), after a preliminary evaluation

of the original estrous cycle data, it was decided that the slides should be re-evaluated. Although mentioned in a protocol amendment, it was not clear why the smears had to be re-evaluated.

III. DISCUSSION AND STUDY DEFICIENCIES:

A. Discussion: The blood samples and time of sacrifice were intended to be in the proestrus phase of the estrous cycle as determined by the vaginal smears. However, the estrous cycle evaluations and plasma hormone concentrations were not reported. According to a protocol amendment, estrous cycle evaluation (by vaginal smear and histology) and plasma hormone concentrations are to be reported later. The principal treatment-related effects reported in this study were decreased body weight and gains in 400 ppm females and increased adenocarcinomas in 400 ppm females.

Mean body weights for the 70 ppm group were close to those of the 400 ppm group for the last 2 months of the study. However, body weights for the 400 ppm group were statistically significant from weeks 2-42 and were decreased as much as 12% below controls. In contrast, body weights for the 70 ppm group were statistically significant only from weeks 9-12, were decreased less than 10% of controls, and are not considered toxicologically significant. The NOEL/LOEL for decreased body weight is 70/400 ppm. Similarly, body weight gain was significant from weeks 2-42 for the 400 ppm females and was significant only from weeks 8-12 in the 70 ppm group. The NOEL/LOEL for decreased body weight gain is 70/400 ppm.

Mammary gland adenocarcinomas were increased in high-dose females compared to controls (6/55 vs 1/55), mammary gland adenomas were similar in incidence in high-dose animals compared to controls (1/5 vs 0/55), and mammary gland fibroadenomas were only slightly increased in high-dose females (4/55 vs 2/55). The increased mammary adenocarcinomas in the 400 ppm group were not statistically significant while the incidence of the combined 3 tumor types in the 400 ppm group was significantly increased ($p \leq 0.05$) compared to controls. Onset time for mammary gland adenomas, adenocarcinomas, and fibroadenomas was not decreased. However, there was a significant positive trend for onset time ($p \leq 0.05$) when fibroadenomas were combined with either adenomas or adenomas and adenocarcinomas.

The NOEL is 70 ppm (4.1 mg/kg/day and the LOEL is 400 ppm (23.9 mg/kg/day) in females based on decreased body weight, body weight gain, and increased mammary gland

adenocarcinomas. Although this study does not satisfy the guideline requirement for a chronic oral study in the rat due to the numerous deficiencies noted below, it does provide supplementary information about the toxicity and carcinogenicity of atrazine in female Crl:CD(SD)BR rats.

B. Study deficiencies: This special toxicity study in the female rat is classified supplementary and cannot be upgraded due to numerous guideline deficiencies: Only females were tested; no clinical chemistry, hematology, urinalysis, or ophthalmology testing; liver and kidneys were not weighed; not all results were reported (hormone analysis and estrous cycle evaluations); and limited microscopic exam (not examined microscopically were salivary glands, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, gall bladder, pancreas, trachea, lung, aorta, heart, bone marrow, lymph nodes, spleen, thymus, kidneys, urinary bladder, brain, peripheral nerves, spinal cord, eyes, adrenal gland, parathyroids, thyroids, bone, and skeletal muscle). The reported skin masses were apparently associated with mammary tumors, but were not described nor were "abnormal" uterine contents described. The report says that after a preliminary evaluation of the estrous cycle data, it was decided to re-evaluate the vaginal smear slides. Although mentioned in a protocol amendment, it was not clear why the smears had to be re-evaluated.

One animal mistakenly received 15 ppm diet for 1 week rather than 30 ppm. At the 3-month interim sacrifice, 13 females in different dose groups did not have terminal body weights recorded. Terminal body weights for another 10 females at the 3-month interim sacrifice were not used because weights were mistakenly recorded post-exsanguination. The incorrect diet for 1 week and the omissions in body weight at the 3-month sacrifice did not alter the conclusions of the study.