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

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MEMORANDUM

SUBJECT: Atrazine: Review of a 21-Day Dermal Study (MRID 420899-02)

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

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Tox Chem 063
PC Code 080803

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Attached is the review of a 21-day dermal study performed with Atrazine technical. The conclusions as stated in the DER are as follows:

Atrazine technical was administered dermally to 30 New Zealand White rabbits 6 hours/day for 25 days. Dose levels were 0, 10, 100, or 1000 mg/kg/day (5 rabbits/sex/dose).

The NOEL for systemic toxicity is 100 mg/kg/day.

The LOEL for systemic toxicity is 1000 mg/kg/day based on statistically significant reductions in food consumption, mean body weight, and percent body weight gain in both sexes, statistically significant increased absolute and relative spleen weights in both sexes, and slight changes in excretion (i.e. few and/or mucoid feces). The increased absolute and relative spleen weights in high-dose animals were not accompanied by histological findings; however, statistically significant reductions in red blood cell counts and hematocrit levels were noted in high-dose females. Further findings included statistically significant

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($p<0.01$) reductions in total protein and chloride in males and significantly increased cholesterol and triglyceride levels in females.

Dermal Effects: minimal to moderate acanthosis, hyperkeratosis, and focal subacute inflammation of treated skin in high-dose females and limited to slight erythema and scaling in some high dose animals.

FINAL

DATA EVALUATION REPORT

Atrazine Technical

Study Type: 21-day Dermal Toxicity Study in Rabbits

Prepared for:

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September 1993

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Contract Number: 68D010075
Work Assignment Number: 1-88
Clement Number: 1-88/91-317
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Guideline Series 82-2: 21-day Dermal Toxicity in Rabbits

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DATA EVALUATION REPORT

STUDY TYPE:	Guideline series 82-2, 21-day dermal toxicity study in rabbits
STUDY NUMBER:	MIN 882035
TOX CHEM NUMBER:	063
MRID NUMBER:	420899-02
PC NUMBER:	080803
TEST MATERIAL:	Atrazine technical
SYNONYMS:	AAtrex; Atranex; Gesaprim
SPONSOR:	Agricultural Division Ciba-Geigy Corporation Greensboro, NC
TESTING FACILITY:	Division of Toxicology/Pathology Ciba-Geigy Corporation Summit, NJ
TITLE OF REPORT:	Atrazine Technical 21-day Dermal Toxicity Study in Rabbits
AUTHOR:	K.R. Huber
REPORT ISSUED:	December 1, 1989

QUALITY ASSURANCE STATEMENT: A GLP certificate, signed January 3, 1990, a flagging statement, and a Quality Assurance Statement, signed November 20, 1989, were provided.

CONCLUSION: Atrazine technical was administered dermally to 30 New Zealand White rabbits 6 hours/day for 25 days. Dose levels were 10, 100, or 1000 mg/kg/day (5 rabbits/sex/dose).

NOEL for systemic toxicity is 100 mg/kg/day

LOEL for systemic toxicity is 1000 mg/kg/day based on statistically significant reductions in food consumption, mean body weight, and percent body

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weight gain in both sexes, statistically significant increased absolute and relative spleen weights in both sexes, and slight changes in excretion (i.e., few and/or mucoid feces). The increased absolute and relative spleen weights in high-dose animals were not accompanied by histological findings; however, statistically significant reductions in red blood cell counts and hematocrit levels were noted in high-dose females. Further findings included statistically significant ($p<0.01$) reductions in total protein and chloride in males and significantly increased cholesterol and triglyceride levels in females.

Dermal application of the test material resulted in ~~limited-to-mild~~ minimal or moderate acanthosis and focal subacute inflammation of treated skin in high-dose females. Dermal irritation included limited-to-slight (grade 1) erythema and scaling in 1 high-dose female at days 17–25. Erythema (grade 1) was observed in 1 high-dose male at day 18.

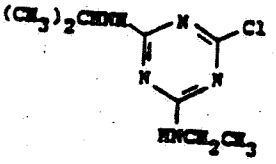
The study authors reported a NOEL of 10 mg/kg/day and a LOEL of 100 mg/kg/day, based on slight transient reductions in mean percent body weight gain in mid-dose females at days 7 & 14, ~~and 21.~~ Because the reductions in female body weight gain at 100 mg/kg/day were slight, [redacted], and without corresponding reductions in food consumption or absolute body weight, the reviewers assessed that the changes were of equivocal biological importance.

CORE CLASSIFICATION: Core Guideline. This study satisfies the Guideline series 82-2 requirements for a 21-day dermal toxicity study in rabbits.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Atrazine technical

Structure: 

Lot number: FL 841802

Purity: 97.6%

Physical property: Solid, color not reported

Stability: Not reported

2. Diet Preparation and Analysis

The purity of the test material was reported by the sponsor to be 97.6%. Stability of the test material was not reported. Stability of the sterile water used for injection was reported to be at least 7 months under the conditions of this study.

3. Animals

Male and female New Zealand White rabbits (22/sex) were received from H.A.R.E., Inc., Hewitt, New Jersey. Upon arrival animals were uniquely identified by Monel ear tags, housed individually, and acclimated to environmental conditions for three weeks. During acclimation and dosing, temperature and relative humidity were 65° ± 5°F and 50% ± 20%, respectively. A 12-hour dark/light cycle was maintained. Animals were provided with tap water and Purina Rabbit Chow #5325 *ad libitum*.

During the 3-week acclimation period all animals received physical, auditory, and ophthalmological examinations and hematology/clinical chemistry tests. Healthy animals were randomly assigned treatment groups (5/sex/dose) by the Bechman TOXSYS® computer program. Just prior to initiation of dosing rabbits were 13–14 weeks old and weighed 2.34–3.06 kg (sexes combined.

Dose Group (5/sex/dose)	Dose Level (mg/kg/day)[1]
Group 1 (control)	0[2]
Group 2 (low dose)	10
Group 3 (mid dose)	100
Group 4 (high dose)	1000

[1] Dose levels calculated from body weights determined each week.
[2] Controls were dosed with dermal applications of sterile water (1.0 mL/kg/day).

Rationale for dose selection: A previous acute dermal toxicity study of atrazine technical in rabbits (Stillmeadow, Inc., project number 5567-88) reported a dermal LD_{50} greater than 2010 mg/kg. The dermal dose levels for the current study were based on the earlier LD_{50} and 21-day dermal toxicity studies of other triazine herbicides at high doses that reported no overt toxicity.

4. Test Procedure

Hair was removed (by clipping) from the flank and back of each rabbit prior to treatment and thereafter when necessary. The shaved portion constituted approximately 5–10% of the total body surface. The appropriate amount of the test material (adjusted according to the weekly body weight determination) was moistened with sterile water and applied to intact skin. Control groups were similarly treated with sterile water (1.0 mL/kg/day) instead

of the test material. A gauze dressing was applied over the test site and secured with adhesive wrapping (Vetrap, 3M). Following dosing, Elizabethan collars were fitted to each rabbit to prevent contact with the test site. Animals were exposed to the test material or vehicle control approximately 6 hours/day for 25–26 days. At the end of the daily exposure period the gauze dressing was removed and the test sites were washed with tap water and dried with a paper towel.

5. Statistical Methods

Statistical analyses were performed on food consumption, clinical chemistry, body weight, and organ weight data. ANOVA was used to test the data collected prior to atrazine or vehicle exposure for each group of rabbits. Dunnett's analysis of variance was used to determine the statistical significance of data collected after atrazine or vehicle exposure for treated groups as compared to the controls. Fisher's exact test was used in the statistical analysis of the pathology data for each sex.

In cases of variance heterogeneity or in the presence of outliers, statistical analyses were conducted using either a series of transformations, nonparametric tests, or analysis of variance.

6. General Observations

(a) Mortality/moribundity

Results - There were no unscheduled deaths during the study.

(b) Clinical observations

Observations for overt signs of toxicity (appearance, behavior, and excretion) were made daily during the acclimation process. After initiation of dosing, observations were made just prior to dosing, within 1 hour postdose, and approximately 2–4 hours postdose.

Results - Table 1 summarizes selected clinical observations. Treatment-related changes in excretion included sporadic (test days 4–21) instances of mucoid and/or few feces in high-dose males and females. Excretion was normal in low- and mid-dose animals. Alopecia was observed at days 15 and 16 in one high-dose male and one female, but was considered an incidental finding.

(c) Body weight/food consumption

Body weight--Body weights were measured during the acclimation period (day -8), just prior to initiation of dosing at day 1, weekly during dosing, and at termination.

Results - Tables 2 and 3 summarize mean body weight and percent mean body weight gain data. Treatment-related

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TABLE 1. Selected Clinical Observations in Rabbits Dermally Exposed to Atrazine Technical[a]

Findings[b]	Number of Animals with Finding: Group 1 (0 mg/kg/day)	Group 2 (10 mg/kg/day)	Group 3 (100 mg/kg/day)	Group 4 (1000 mg/kg/day)
		Males[c]		
Alopecia	0	0	0	1
Mucoid feces	0	0	0	2
Few feces	0	0	0	4
		Females[c]		
Alopecia	0	0	0	1
Mucoid feces	0	0	0	2
Few feces	0	0	0	5

[a] Data extracted from Study No.882035, Table 7.2, page 36.
[b] All findings were transient and were noted prior to termination.
[c] Total number exposed = 5 rabbits/group.

TABLE 2. Mean Body Weights (kg ± S.E.) at Representative Intervals for Rabbits Dermally Exposed to Atrazine Technical[a]

Dose Level (mg/kg/day)	Mean Body Weight (kg ± S.E.) at Day: -7	0	7	14	21	25[b]
			Males			
0	2.350 ± 0.053	2.538 ± 0.046	2.632 ± 0.053	2.774 ± 0.082	2.782 ± 0.105	2.773 ± 0.092
10	2.414 ± 0.050	2.572 ± 0.052	2.600 ± 0.018	2.74 ± 0.024	2.762 ± 0.033	2.740 ± 0.077
100	2.534 ± 0.087	2.720 ± 0.108	2.754 ± 0.103	2.884 ± 0.111	2.954 ± 0.129	2.898 ± 0.103
1000	2.426 ± 0.076	2.586 ± 0.081	2.360 ± 0.092* (91%)[c]	2.444 ± 0.096* (95%)	2.474 ± 0.102 (96%)	2.451 ± 0.079* (95%)
			Females			
0	2.364 ± 0.105	2.596 ± 0.112	2.680 ± 0.110	2.832 ± 0.121	2.806 ± 0.143	2.820 ± 0.134
10	2.344 ± 0.046	2.532 ± 0.037	2.660 ± 0.019	2.806 ± 0.043	2.860 ± 0.068	2.826 ± 0.043
100	2.476 ± 0.083	2.684 ± 0.105	2.680 ± 0.109	2.792 ± 0.119	2.832 ± 0.161	2.771 ± 0.161
1000	2.408 ± 0.044	2.586 ± 0.064	2.182 ± 0.044** (84%)	2.206 ± 0.139** (85%)	2.282 ± 0.136* (88%)	2.277 ± 0.095** (88%)

[a] Data extracted from Study No.882035, Table 7.4, pages 38–58.
[b] Fasted weights.
[c] Values in parentheses represent percent control

* Significantly different from control value, $0.01<p\leq0.05$ (two-tailed Dunnett T test).
** Significantly different from control value, $p\leq0.01$ (two-tailed Dunnett T test).

TABLE 3. Percent Mean Body Weight Gain (% ± S.E.) at Representative Intervals for Rabbits Dermally Exposed to Atrazine Technical[a]

Dose Level (mg/kg/day)	Percent Mean Body Weight Gain (% ± S.E.) at Day: 7	14	21
		Males	
0	3.7 ± 0.744	9.247 ± 1.892	9.520 ± 2.819
10	1.203 ± 1.422	6.656 ± 1.669	7.506 ± 1.832
100	1.290 ± 0.426	6.065 ± 0.895	8.579 ± 1.701
1000	-8.804 ± 1.204**	-5.568 ± 0.927**	-4.415 ± 1.387**
		Females	
0	3.322 ± 1.592	9.188 ± 2.165	7.999 ± 2.058
10	5.146 ± 1.715	10.923 ± 2.421	12.963 ± 2.231
100	-0.152 ± 1.134	4.047 ± 2.145	5.491 ± 4.268
1000	-15.441 ± 2.482**	-14.333 ± 6.196**	-11.479 ± 5.731**

[a] Data extracted from Study No.882035, Table 7.4, pages 38–58.
* Significantly different from control value, $0.01<p\leq0.05$ (two-tailed Dunnett T test).
** Significantly different from control value, $p\leq0.01$ (two-tailed Dunnett T test).

changes included statistically significant ($p<0.05$ in males, $p<0.01$ in females) reduced mean body weights in high-dose animals. Body weights were 91–96% and 84–88% of controls for males and females, respectively.

Treatment-related changes in percent mean body weight gain included statistically significant ($p<0.01$) reductions in high-dose animals. The study authors established a LOEL of 100 mg/kg/day from slight ~~transient~~ reductions in percent mean body weight gain in mid-dose females at days 7 & 14, ~~and 21.~~ However, the reviewers assessed that the changes were of equivocal biological importance because the reduction was slight [redacted], transient, and without corresponding reductions in food consumption or absolute body weight.

Food consumption--Food consumption was measured daily during the last week of the acclimation period and weekly thereafter.

Results - Table 4 presents mean food consumption data. Treatment-related changes included statistically significant ($p<0.01$) reduced food consumption at days 7 and 14 in high-dose males (33% and 71% of controls, respectively) and high-dose females (15% and 41% of controls, respectively). Food consumption at day 21 was 72% of controls in males and 63% of controls in females.

(d) Dermal effects--Erythema, edema and other dermal changes were evaluated just prior to dosing, 30 minutes after dosing (after washing), and before necropsy.

Results - Treatment-related effects were limited-to-slight (grade 1) erythema and scaling in 1 high-dose female at days 17–25. Erythema (grade 1) was observed in 1 high-dose male at day 18.

(e) Ophthalmoscopic/auditory--Ear and eye examinations were performed during the acclimation period (day -16) and again at days 20 and 21, respectively.

Results - No treatment-related effects were observed.

7. Clinical Pathology

Blood samples for hematology and clinical chemistry analyses were taken from all animals once during the acclimation period (day -15 or -14) and at termination (day 22 or 23). Samples were taken before daily dosing from the auricular artery of fasted rabbits. The parameters marked by an "X" below were examined.

TABLE 4. Mean Food Consumption (g/week ± S.E.) at Representative Intervals for Rabbits Dermally Exposed to Atrazine Technical[a]

Dose Level (mg/kg/day)	Mean Food Consumption (g/week ± S.E.) at Day: 0	7	14	21
		Males		
0	1259.400 ± 96.316	1347.800 ± 44.244	1378.000 ± 75.792	1255.000 ± 105.792
10	1281.400 ± 73.369	1113.000 ± 118.247	1198.200 ± 61.718	1104.600 ± 42.834
100	1351.800 ± 90.107	1121.800 ± 71.737	1292.200 ± 92.375	1342.600 ± 87.173
1000	1250.800 ± 86.810	409.800 ± 80.440** (33%)[b]	883.800±75.826** (71%)	901.000 ± 75.870* (72%)
		Females		
0	1288.400 ± 91.519	1201.200 ± 84.578	1250.600 ± 109.787	1194.000 ± 108.046
10	1153.200 ± 46.614	1131.400 ± 88.307	1154.200 ± 76.199	1194.200 ± 42.040
100	1296.600 ± 146.551	1105.000 ± 136.904	1171.200 ± 159.715	1109.400 ± 141.284
1000	1306.800 ± 89.738	201.600 ± 77.832** (15%)	532.000 ± 189.100** (41%)	821.400 ± 164.096 (63%)

[a] Data extracted from Study No.882035, Table 7.4, pages 38–58.
[b] Values in parentheses represent percent control.

* Significantly different from control value, $0.01<p\leq0.05$ (two-tailed Dunnett T test).
** Significantly different from control value, $p\leq0.01$ (two-tailed Dunnett T test).

(a) Hematology

X Heinz bodies**
X Differential WBC count*
X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Platelet count*
X Prothrombin time
X RBC count*
X Red cell morphology
X Reticulocytes**
X WBC count*

* Recommended by Subdivision F (November 1984) Guidelines
** Parameters were tested for Groups 1 and 4 only

Results - Selected hematology parameters are presented in Table 5. Treatment-related changes included statistically significant ($p<0.05$) reductions in hematocrit and red blood cell counts in high-dose females, which corresponded to treatment-related statistically significant increased relative spleen (to brain and body) weights in high-dose animals.

(b) Blood (clinical) chemistry

Electrolytes

X Calcium*
X Chloride*
Magnesium*
X Phosphorus*
X Potassium*
X Sodium*

Other

X Albumin*
X Albumin/globulin ratio
X Creatinine*
X Blood urea nitrogen*
X Cholesterol
X Glucose*
X Total bilirubin*
X Total protein*
X Triglycerides
X LDH
X Urea

Enzymes

X Alkaline phosphatase (ALP)
X Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)
X Serum aspartate aminotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)

*Recommended by Subdivision F (November 1984) Guidelines

Results - Selected clinical chemistry data are presented in Table 6. Treatment-related changes included statistically significant ($p<0.01$) reductions in total protein (93% of control) and chloride (95% of control) in high-dose males. Other treatment-related changes included significantly increased cholesterol and triglyceride levels (201% and 155% of control, respectively) in high-dose females. However, no microscopic/gross liver changes or significant changes in absolute/relative liver weights were observed, except for slightly reduced absolute and relative liver (to brain) weights in high-dose males (78% and 75% of controls, respectively).

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TABLE 5. Selected Hematology Values (Mean ± S.E.) for Rabbits Dermally Exposed to Atrazine TEchnical[a,b]

Parameter	Dose Level (mg/kg/day) 0	10	100	1000
		Males		
Eosinophils (%)	1.200 ± 0.490	0.400 ± 0.245	0.200 ± 0.200	0.000 ± 0.000*
Red blood cells (10^6/ccm)	6.224 ± 0.073	6.498 ± 0.096	6.442 ± 0.131	5.832 ± 0.317
Hematocrit (%)	41.400 ± 0.748	43.400 ± 0.510	41.800 ± 0.970	38.000 ± 2.049
Hemoglobin (g/dL)	13.940 ± 0.209	14.460 ± 0.147	14.060 ± 0.326	12.980 ± 0.766
		Females		
Eosinophils (%)	1.000 ± 0.548	2.000 ± 0.949	0.800±0.374	0.400 ± 0.400
Red blood cells (10^6/ccm)	6.448 ± 0.136	6.636 ± 0.212	6.286±0.122	5.742 ± 0.212*
Hematocrit (%)	42.600 ± 0.980	42.600 ± 1.568	41.000±1.095	37.400 ± 0.812*
Hemoglobin (g/dL)	14.360 ± 0.337	14.160 ± 0.548	13.780 ± 0.365	12.840 ± 0.393

[a] Data extracted from Study No. 882035, Table 7.5, pages 59–107.
[b] Data are values measured at termination of the study (day 21).
* Significantly different from control value, $0.01<p\leq0.05$.

TABLE 6. Selected Clinical Chemistry Values (Mean ± S.E.) for Rabbits Dermally Exposed to Atrazine TEchnical[a,b]

Parameter	Dose Level (mg/kg/day)			
	0	10	100	1000
		Males		
Cholesterol (mg/dL)	37.2 ± 3.007	49.000 ± 4.111	38.400 ± 3.140	40.800 ± 4.091
Triglycerides (mg/dL)	47.800 ± 2.800	47.400 ± 7.527	41.600 ± 3.234	53.200 ± 11.043
Total protein (gm/dL)	5.380 ± 0.073	5.300 ± 0.063	5.340 ± 0.087	5.000 ± 0.071** (93%)[c]
Chloride (meq/L)	106.200 ± 0.800	105.800 ± 1.068	105.400 ± 0.510	101.400 ± 0.400** (95%)
		Females		
Cholesterol (mg/dL)	37.800 ± 3.527	45.800 ± 4.488	60.400 ± 7.026	76.000 ± 17.590** (201%)
Triglycerides (mg/dL)	40.200 ± 3.426	45.600 ± 3.385	43.600 ± 5.546	62.200 ± 10.399* (155%)
Total protein (gm/dL)	5.260 ± 0.169	5.200 ± 0.114	5.340 ± 0.121	5.000 ± 0.100
Chloride (meq/L)	105.400 ± 1.030	105.400 ± 1.568	102.600 ± 1.122	104.600 ± 1.122

[a] Data extracted from Study No. 882035, Table 7.6, pages 108–174.
[b] Data are values measured at termination of the study (day 21)
[c] Values in parentheses represent percent control.

* Significantly different from control value, $0.01<p\leq0.05$.
** Significantly different from control value, $p\leq0.01$.

Non-treatment related ~~effects~~ findings included statistically significant increased total bilirubin (168% of control) in low-dose males only.

8. Sacrifice and Pathology

At the end of the treatment period fasted animals were anesthetized, exsanguinated, and necropsied. Samples of the tissues listed below were taken from all animals and preserved in 10% neutral buffered formalin. Tissues indicated by an "X" below were taken from all animals and examined microscopically. In addition, organs from all animals indicated by "XX" were also weighed.

Digestive System	Cardiovascular/ Hematologic	Neurologic
X Tongue	X Aorta	XX Brain
XX Salivary glands	XX Heart	X Sciatic nerve
X Esophagus	X Bone marrow	X Eyes (optic n.)
X Stomach	X Lymph nodes	X Spinal cord (three levels)
X Duodenum	XX Spleen	XX Pituitary
X Jejunum	XX Thymus	
X Ileum		
X Cecum	Urogenital	
X Colon		Glandular
X Rectum	XX Kidneys*	
XX Liver*	X Urinary bladder	XX Adrenals
X Gall bladder	XX Testes*	X Lacrimal gland
X Pancreas	XX Epididymides	XX Thyroids/ parathyroids
	X Mammary gland	
Respiratory	XX Prostate	
	X Vagina	
X Trachea	XX Ovaries	
XX Lung	XX Uterus	

Other

X Bone (sternum and femur)
X Skeletal muscle (thigh)
X Skin (treated and untreated)*
X All gross lesions and masses*

* Recommended by Subdivision F (November 1984) Guidelines

(a) Gross pathology

No treatment-related gross lesions were found.

(b) Organ weights and body weight ratios

Tables 7 and 8 summarize selected absolute and relative organ weight data. Treatment-related changes included

TABLE 7. Selected Absolute (g ± S.E.) Organ Weights of Rabbits Dermally Exposed to Atrazine Technical[a,b]

Organ	Dose Level (mg/kg/day)			
	0	10	100	1000
		Males[c]		
Adrenal glands	0.252 ± 0.021	0.214 ± 0.012	0.230 ± 0.035	0.220 ± 0.022
Liver	71.236 ± 6.461	62.020 ± 2.577	68.990 ± 5.221	55.798 ± 3.916 (78%)[d]
Spleen	1.178 ± 0.196	1.298 ± 0.161 (110%)	1.020 ± 0.110 (86%)	2.136 ± 0.439* (181%)
Salivary glands	1.344 ± 0.073	1.300 ± 0.142	1.392 ± 0.080	1.318 ± 0.127
Thymus	3.918 ± 0.250	4.204 ± 0.526	3.954 ± 0.445	2.990 ± 0.254
		Females[c]		
Adrenal glands	0.174 ± 0.012	0.198 ± 0.023	0.242 ± 0.020	0.214 ± 0.029
Liver	59.266 ± 2.538	60.552 ± 2.138	59.160 ± 5.483 (95%)	56.366 ± 1.382
Spleen	1.192 ± 0.165	1.944 ± 0.127 (163%)	1.542 ± 0.223 (129%)	2.212 ± 0.401* (186%)
Salivary glands	1.142 ± 0.034	1.232 ± 0.078	1.324 ± 0.067	1.276 ± 0.061
Thymus	3.274 ± 0.300	3.620 ± 0.480	3.486 ± 0.448	2.270 ± 0.342
Uterus	5.590 ± 0.589	5.030 ± 0.326	4.954 ± 0.820	3.134 ± 0.216**
Ovaries	0.276 ± 0.036	0.222 ± 0.011	0.272 ± 0.021	0.178 ± 0.026*

[a] Data extracted from Study No.882035, Table 7.7, page 175.
[b] Findings noted at termination (day 25).
[c] Five rabbits/group.
[d] Values in parentheses represent percent control.

* Significantly different from control value, $0.01<p\leq0.05$ (two-tailed Dunnett T test).
** Significantly different from control value, $p\leq0.01$ (two-tailed Dunnett T test).

TABLE 8. Selected Relative (% ± S.E.) Organ Weights of Rabbits Dermally Exposed to Atrazine Technical[a,b]

Organ	Dose Level (mg/kg/day) 0	10	100	1000	
			Males[c]		
Adrenal glands					
% brain weight	2.624 ± 0.242	2.255 ± 0.186	2.432 ± 0.429	2.200 ± 0.208	
% body weight	0.009 ± 0.001	0.008 ± 0.000	0.008 ± 0.001	0.009 ± 0.001	
Liver					
% brain weight	743.792 ± 76.998	650.754 ± 35.330	724.164 ± 65.718	559.756 ± 39.971	(75%)[d]
% body weight	2.551 ± 0.162	2.263 ± 0.092	2.372 ± 0.116	2.271 ± 0.110	(89%)
Spleen					
% brain weight	12.324 ± 2.225	13.514 ± 1.515	10.809 ± 1.420	21.498 ± 4.420	(174%)
% body weight	0.042 ± 0.006	0.047 ± 0.006	0.035 ± 0.004	0.086 ± 0.015**	(205%)
Salivary glands					
% brain weight	13.981 ± 0.906	13.553 ± 1.306	14.503 ± 0.643	13.149 ± 1.120	
% body weight	0.049 ± 0.003	0.047 ± 0.005	0.048 ± 0.004	0.054 ± 0.004	
Thymus					
% brain weight	40.840 ± 3.236	44.012 ± 5.505	42.019 ± 6.067	29.855 ± 2.227	
% body weight	0.142 ± 0.008	0.153 ± 0.019	0.136 ± 0.014	0.121 ± 0.007	
			Females[c]		
Adrenal glands					
% brain weight	1.829 ± 0.114	2.099 ± 0.263	2.671 ± 0.147	2.370 ± 0.354	
% body weight	0.006 ± 0.000	0.007 ± 0.001	0.009 ± 0.001	0.009 ± 0.001*	
Liver					
% brain weight	623.669 ± 25.522	638.448 ± 20.779	662.798 ± 75.173	620.675 ± 21.142	(100%)
% body weight	2.104 ± 0.035	2.144 ± 0.075	2.121 ± 0.096	2.496 ± 0.141	(119%)
Spleen					
% brain weight	12.591 ± 1.805	20.572 ± 1.600	17.041 ± 2.322	24.315 ± 4.334*	(194%)
% body weight	0.042 ± 0.005	0.069 ± 0.004	0.055 ± 0.006	0.095 ± 0.016*	(226%)
Salivary glands					
% brain weight	12.015 ± 0.316	12.940 ± 0.534	14.817 ± 1.188*	14.033 ± 0.664	
% body weight	0.041 ± 0.001	0.044 ± 0.003	0.048 ± 0.002	0.056 ± 0.002*	
Thymus					
% brain weight	34.562 ± 3.398	39.370 ± 5.409	38.675 ± 4.690	24.905 ± 3.653	
% body weight	0.116 ± 0.009	0.128 ± 0.016	0.125 ± 0.014	0.099 ± 0.013	
Uterus					
% brain weight	58.676 ± 5.669	52.946 ± 2.971	56.649 ± 10.967	34.513 ± 2.564*	
% body weight	0.197 ± 0.013	0.179 ± 0.014	0.178 ± 0.027	0.137 ± 0.006	
Ovaries					
% brain weight	2.874 ± 0.334	2.348 ± 0.148	3.047 ± 0.301	1.969 ± 0.313	
% body weight	0.010 ± 0.001	0.008 ± 0.000	0.010 ± 0.001	0.008 ± 0.001	

[a] Data extracted from Study No.882035, Table 7.7, page 175.
[b] Findings noted at termination (day 25).
[c] Five rabbits/group.
[d] Values in parentheses represent percent control.
* Significantly different from control value, $0.01<p\leq0.05$ (two-tailed Dunnett T test).
** Significantly different from control value; $p\leq0.01$ (two-tailed Dunnett T test).

statistically significant ($p<0.05$) increases in absolute spleen weights that were 181% and 186% of control values for high-dose males and females, respectively. Other treatment-related effects included significantly increased relative spleen (to brain and body) weights in high-dose animals. Absolute and relative spleen weights in high-dose males were 174% and 205% of controls, respectively. Absolute and relative spleen weights in high-dose females were 194% and 226% of controls, respectively. The changes in spleen weights were thought to be associated with the statistically significant ($p<0.05$) reductions in hematocrit and red blood cell counts in high-dose females.

Other findings were reduced absolute and relative liver (to brain) weights in high-dose males that were 78% and 75% of controls, respectively. In addition, decreasing trends in absolute and relative thymus weights were observed in high-dose animals. Decreased mean absolute and relative uterus and ovary weights were observed in high-dose females. Because of the lack of corresponding gross or microscopic changes in these organs, the reviewers considered the ~~toxicological significance of~~ these organ weight changes to be ~~minimal~~ & no toxicological concern. Kurt 11/22/93

(c) Microscopic pathology

Table 9 summarizes selected histological findings. Treatment-related dermal changes included minimal-to-moderate acanthosis and increased focal subacute lymphocytic inflammation of the skin in 3 of 5 high-dose females. In addition, acanthosis was observed in a single low-dose female and lymphocytic inflammation was observed in both a control and low-dose female. No dermal changes were seen in control, low-, mid-, or high-dose males.

B. DISCUSSION

This study is rated Core Guideline and satisfies the guideline requirements (82-2) for a 21-day dermal toxicity study in rabbits.

Atrazine technical was administered dermally to New Zealand White rabbits (5/sex/dose) 6 hours/day for 25 days at target dosage levels of 10, 100, and 1000 mg/kg/day. The NOEL for systemic toxicity was 100 mg/kg/day. The LOEL for systemic toxicity was 1000 mg/kg/day based on statistically significant reductions in food consumption, mean body weight, and percent mean body weight gain in both sexes; statistically significant increased absolute and relative spleen weights in both sexes; and slight changes in excretion (i.e., few and/or mucoid feces). The increased absolute and relative spleen weights in high-dose animals were not accompanied by histological findings; however, statistically significant reductions in red blood cells and hematocrit levels were noted in high-dose females. Other treatment-related findings included

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TABLE 9. Selected Histopathological Observations in Rabbits Dermally Exposed to Atrazine Technical[a]

Findings[b]	Number of Animals with Finding: Group 1 (0 mg/kg/day)	Group 2 (10 mg/kg/day)	Group 3 (100 mg/kg/day)	Group 4 (1000 mg/kg/day)
		Males[c]		
Treated skin (back region)				
Acanthosis	0	0	0	0
Hyperkeratosis	0	0	0	0
Subacute lymphocytic inflammation	0	0	0	0
		Females[c]		
Acanthosis	0	1	0	3
Hyperkeratosis	0	0	0	1
Subacute lymphocytic inflammation	1	1	0	3

[a] Data extracted from Study No.882035, Section 8.3, page 295.
[b] All findings were transient and were noted prior to termination.
[c] Total number exposed = 5 rabbits/group.

statistically significant ($p<0.01$) reductions in total protein and chloride in males and significantly increased cholesterol and triglyceride levels in females.

Reduced absolute and relative liver (to brain) weights were observed in high-dose males (78% and 75% of controls, respectively). Changes in absolute and/or relative organ weights were also observed for adrenal glands, thymus, uterus, ovaries, salivary glands, and brain; however, these changes did not appear to be biologically significant.

KLH 11/23/93

Dermal effects included ~~limited-to-mild~~ minimal to moderate acanthosis, hyperkeratosis and focal subacute inflammation of treated skin in high-dose females. Dermal irritation was limited-to-slight (grade 1) erythema and scaling in 1 high-dose female on days 17–25. Erythema (grade 1) was observed in 1 high-dose male on day 18.

The study authors reported a NOEL of 10 mg/kg/day and a LOEL of 100 mg/kg/day, based on slight transient reductions in mean percent body weight gain in mid-dose females on days 7 and 14. Because the reductions in body weight gain at 100 mg/kg/day were slight, [redacted], transient, and without corresponding reductions in food consumption or absolute body weight, the reviewers did not feel that they were of significant biological importance. KLH