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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

006938

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

NOV 29 1988

MEMORANDUM

SUBJECT: Atrazine, Review and/or reevaluation of data evaluation reports for FRSTR

TO: Robert Taylor (TS-767C)
Registration Division

FROM: Marion P. Copley, D.V.M., Acting Section Head
Section 2, Toxicology Branch I
Health Effects Division (TS-769C)

THRU: Judith W. Hauswirth, Ph.D., Acting Branch Chief
Section 2, Toxicology Branch I (IRS)
Health Effects Division (TS-769C)
11/29/88

Tox. Chem. No.:63
Proj. No.:NA
Record No.:NA

The following two studies were either reevaluated or initially reviewed for the FRSTR on Atrazine.

Acute inhalation - rats, MRID 0002795
Study # 915-100
Classification Core - Invalid

Initial classification (Registration Standard 1983) was minimum. This study was downgraded due to inadequate methodology.

90-day - dog, MRID 00163339
Study #T-635
Classification Core - Supplementary

NOEL < 200 ppm (5 mg/kg/day) (low dose tested)
LEL ≤ 200 ppm (5 mg/kg/day) based on body weight gain depression in the males.

In addition at 623 ppm (15.8 mg/kg/day) and above in males, there was a slight decrease in RBC, HCT and HGB. There was also a mild to total arrest of spermatogenesis.

At 2000 ppm (50 mg/kg/day) in males, there was decreased food consumption; in females, there was body weight loss, decreased food consumption, and a slight decrease in RBC, HCT and HGB.

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Reviewed by: Marion P. Copley, D.V.M., D.A.B.T. 11/9/88
Sect.2, Acting Section Head, TB I (IRS) (TS-769C)
Secondary reviewer: Judith W. Hauswirth, Ph.D. 11/21/88
Acting Chief, TB I (IRS) (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: 90-day feeding - dog TOX. CHEM NO: 63

MRID NO.: 00163339

TEST MATERIAL: Atrazine

SYNONYMS: Atranex

STUDY NUMBER: T-635

SPONSOR: Agan Chemical Manufacturers Ltd.

TESTING FACILITY: WARF Institute, Inc., Madison, Wisconsin

TITLE OF REPORT: 90-Day subacute feeding study of Atranex in dogs

AUTHOR(S): M. Tisdel, D. Harris

REPORT ISSUED: Not specified, Initiated Jan. 12, 1977

CONCLUSION:

NOEL < 200 ppm (5 mg/kg/day) (low dose tested)
LEL ≤ 200 ppm (5 mg/kg/day) based on body weight gain depression in the males.

In addition at 623 ppm (15.8 mg/kg/day) and above in males, there was a slight decrease in RBC, HCT and HGB. There was also a mild to total arrest of spermatogenesis.
At 2000 ppm (50 mg/kg/day) in males, there was decreased food consumption; in females, there was body weight loss, decreased food consumption, and a slight decrease in RBC, HCT and HGB.

Classification: CORE-SUPPLEMENTARY

Special Review Criteria (40 CFR 154.7) could not be determined since a NOEL was not established.

A. MATERIALS:

1. Test compound: Atrazine technical, Description - not given, Batch # - 7003, Purity - not given %.

2. Test animals: Species: dog, Strain: beagle, Age: not given, Weight: not given, Source: Ridglan Farm, Inc, Mount Horeb, Wisconsin, animals were given a 2 month acclimatization period.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned to test groups based on weight, sex and litter identification (see table 1).

TABLE 1 Experimental Design

Test Group	Dose in diet (ppm)	Est. dose based on 0.025 mg/kg per PPM (mg/kg/day)	Main Study 3 months male	female
1 Cont	0	0	4	4
2 Low (LDT)	200	5	4	4
3 Mid (MDT)	632	15.8	4	4
4 High (HDT)	2000	50	4	4

2. Diet preparation

Diet preparation, storage and analysis for homogeneity, stability and concentration were not discussed.

3. Animals received food (Purina Canine Diet) ad libitum for 1 hour daily and water ad libitum.

4. Statistics - The procedures utilized in analyzing the numerical data are not listed. Means and standard deviations appear to have been used for some numerical parameters, ie. body weight and food consumption. Organ weights were compared using the T-Test.

5. A signed quality assurance statement was not present. In addition, there was no signature page.

C. METHODS AND RESULTS:

1. Observations:

Animals were inspected daily for signs of toxicity and mortality.

Toxicity/Mortality (survival) - There were no mortalities or treatment related clinical signs observed during the study.

2. Body weight

Animals were weighed at study initiation, then weekly and again at termination.

Results - MALES - As can be seen in table 1, there was a decrease in body weight gain and % body weight gain in all groups of males treated with atrazine. This decrease was dose related. Two dogs in each of the LDT, MDT and HDT actually lost weight during the study. Statistics however, were not done for these values. FEMALES - Only the HDT females had a decreased weight gain (actually a weight loss of 6 %, compared to a gain of 24-28% in the other 3 groups).

TABLE 2 Body weight (gm) and % weight gains for 13 weeks

Conc in diet PPM	male day 0	male day 90	male gain	male % gain	female day 0	female day 90	female gain	female % gain
Cont.	8063	10375	2312	29%	6588	8150	1562	24%
200	7600	8539	939	12%	6375	8075	1700	27%
632	6788	7225	437	6%	5538	7075	1537	28%
2000	7738	7363	-375	-5%	6975	6575	-400	-6%

3. Food consumption and compound intake

Consumption was determined daily and reported as weekly totals of mean daily diet consumption. Food consumption in terms of body weight, food efficiency and compound intake were not calculated.

Food consumption - Food consumption was only decreased (estimated at 30 % less than controls) in the HDT males and females. Values in the other groups were variable and could not be attributed to treatment due to the small sample size (n=4). Statistics were not done on these values.

4. Ophthalmological examinations were not reported.

5. Blood was collected before treatment and at 0, 4, 8, and 13 weeks for hematology and clinical analysis from all animals (fasting not specified). The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc. (MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
	Platelet count*		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Results - As can be seen in table 3, there appeared to be a slight decrease in RBC, Hct and Hgb in males at the MDT and HDT and in females at the HDT. Other changes were within expected ranges for the age and species or there was too much within group variation to make any conclusions.

TABLE 3 Select hematology (13 week)

Conc in diet PPM	HCT (%)	HGB (G%)	RBC 10^6 cells/mm^3	HCT (%)	HGB (G%)	RBC 10^6 cells/mm^3
		MALES			FEMALES	
Cont.	43	15.3	6.92	41	15.2	6.97
200	41	14.8	6.57	42	15.0	6.98
632	35	13.0	5.57	39	14.0	6.19
2000	33	12.2	5.46	34	12.8	5.80

b. Clinical Chemistry

X		X	
	Electrolytes:		Other:
X	Calcium*	X	Albumin*
X	Chloride*		Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
X	Phosphorous*		Cholesterol*
X	Potassium*	X	Alb/Globulin ratio
X	Sodium*	X	Glucose*
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum Protein (TP)*
	Cholinesterase (ChE)#		Triglycerides
	Creatinine phosphokinase*^		Serum protein electrophores
	Lactic acid dehydrogenase (LAD)		
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic and chronic studies
# Should be required for OP
^ Not required for subchronic studies

Results - There were no treatment-related changes in clinical chemistry values.

6. Urinalysis^

Urine was collected (fasting not specified) animals at 0, 4, 8 and 13 weeks. The CHECKED (X) parameters were examined.

X		X	
	Appearance*	X	Glucose*
	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH	X	Blood*
	Sediment (microscopic)*		Nitrate
X	Protein*		Urobilinogen

^Not required for subchronic studies
* Required for chronic studies

Results - There were no treatment-related changes.

7. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. (x) Tissues were collected but not examined. The (XX) organs, in addition, were weighed.

X		X		X	
Digestive system		**Cardiovasc./Hemat.**		**Neurologic**	
	Tongue		Aorta*	X	Brain*+
X	Salivary glands*	XX	Heart*	x	Periph. nerve*#
	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen	x	Eyes (optic n.)*#
X	Jejunum*		Thymus*	**Glandular**	
X	Ileum*	**Urogenital**		XX	Adrenal gland*
X	Cecum*	XX	Kidneys*+		Lacrimal gland#
	Colon*	X	Urinary bladder*		Mammary gland*#
	Rectum*	XX	Testes*+		Parathyroids*++
XX	Liver *+		Epididymides	XX	Thyroids*++
X	Gall bladder*	X	Prostate	**Other**	
X	Pancreas*		Seminal vesicle	X	Bone*#
Respiratory		XX	Ovaries*+		Skeletal muscle*#
X	Trachea*	X	Uterus*	x	Skin*#
X	Lung*			X	All gross lesions and masses*
	Nose				
	Pharynx				
	Larynx				

(key on next page)

* Required for subchronic and chronic studies.
# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement.
+ Organ weight required in subchronic and chronic studies.
++ Organ weight required for non-rodent studies.

a. Organ weight - There appeared to be a slight increase in kidney weight (relative) at the HDT in both males and females. The biological significance of this can not be determined since: 1) these values were not significant at $p < 0.05$ level for the T-Test, and 2) there were no unusual renal histologic findings. Absolute testes weight were decreased about 30 % in the HDT males while relative weights were only decreased about 8%. All other organ weights were similar to controls.

b. Gross pathology - There were no treatment-related changes noted at necropsy.

c. Microscopic pathology

All MDT and HDT males had mild to total arrest of spermatogenesis. In addition, some testes had abnormal cells or degenerative tubules. There were no other histologic changes related to treatment.

D. DISCUSSION:

Four beagles/sex/group were exposed for 90 days to atrazine technical in the diet at either 0, 200, 632 or 2000 ppm, resulting in approximate doses of 0, 5, 15.8 and 50 mg/kg/day, respectively.

There were no overt signs of toxicity or mortality due to atrazine treatment. Although the company states that body weight was only affected in the high dose males and females, the data indicate that body weight was decreased at all 3 atrazine treatment levels in males and high dose females. Even when body weight was evaluated for each individual animal (rather than as means), there appeared to by no NOEL for males. As mentioned in the results, 2 males in each atrazine treatment group had weight losses while the lowest weight gain in controls for the 90 day period was 12 %. Changes at the weekly intervals were less informative than the monthly or 90 day changes due to the small sample size (n=4). Body weight losses at the high dose were consistent with decreased food consumption at this dose. The other food consumption data was difficult to interpret since it was reported as g/dog rather than adjusted for body weight (g/kg body weight).

Slight decreases in hematologic indices (RBC, HCT and HGB) suggested a possible anemia in the MDT and HDT males and HDT females. Although this is consistent with findings in other studies, the biological significance could not be determined conclusively since the changes and sample size were small. All other measured laboratory parameters were similar to control values.

Histologic changes were limited to a mild to total decrease in spermatogenesis in all mid and high dose males. The HDT decrease in testicular weight, although consistent with these histologic changes, may have been due in part, or completely to decreased body weight. Other organs (weight and histopathology) appeared unaffected by treatment.

Since this study report was completed in the 1970s, it does not contain information now required in every report. The following items were not present or incompletely reported:

1) date report completed
2) signature page
3) signed quality assurance statement
4) purity of the test compound
5) test diet preparation (frequency) and storage information
6) analysis of homogeneity, stability and concentration of test diet
7) summary of statistical methods used
8) test compound intake, based upon body weight and feed consumption

Due primarily to the lack of a NOEL in the males for body weight depression and the other deficiencies noted above, this study is assigned a core-classification of SUPPLEMENTARY. In addition, at 623 ppm (15.8 mg/kg/day) and above in males, there was a slight decrease in RBC, HCT and HGB. There was also a mild to total arrest of spermatogenesis. At 2000 ppm (50 mg/kg/day) in males, there was decreased food consumption; in females, there was body weight loss, decreased food consumption, and a slight decrease in RBC, HCT and HGB.

NOTE: Although electrocardiography is not required in subchronic dog studies, this is one of the more sensitive parameters reported in an acceptable chronic dog study for atrazine. Therefore, this study should not be used to determine potential subchronic cardiac toxicity from atrazine even though there were no histological cardiac changes.

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Guideline Series: 81-3

Reviewed by: Hank Spencer
Secondary reviewer: R.B. Jaeger
Date: 4/25/83

See MEMORANDA: "Atrazine Registration Standard" (Tox. Chapter dated 4/25/83).

Marion P. Copley D.V.M. 11/22/85
Date

DATA EVALUATION REPORT

CHEMICAL: Atrazine TOX. CHEM. NO.: 63

STUDY TYPE: Acute inhalation - rats

MRID NUMBER: 0002795 TOX. DOC.: 1983 Tox Reg Std

SYNONYMS: Atrozina, Tecnica

SPONSOR: Industria Prodotti Chimici

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: Acute inhalation - rats

AUTHOR(S): Frederick I. Reno

STUDY NUMBER(S): 915-100

REPORT ISSUED: April 1, 1975

CONCLUSION: $AILD_{50}$ for the nominal is > 167 mg/L
$AILD_{50}$ for actual exposure can not be determined.

Core Classification: Invalid for the reasons noted in the discussion.

DISCUSSION: This study and the original DER have been reevaluated and the study reclassified as core-invalid due to inadequate methodology, including, but not limited to the following:
Particle size was not determined, actual exposure to compound was not determined, atmospheric concentrations were not monitored.

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Original DER
From 1983 Rg. Std.

Acute Inhalation - Rats
Hazleton Laboratories America Inc.
Project #915 - 100 Dated: April 1, 1975
MRID: 00027095

Material Tested: Atrozina, Tecnica, (atrazine technical) (purity not stated).

Animal Tested: Male albino rat (254 g - 308 g).

Methods:

10 male rats were exposed to a single dose of 167 mg/L (nominal conc.) for 1 hr. in a 38L glass chamber. Air delivery was 10 L/min.

The rats were housed individually during exposure.

Observations:

Sacrificed on the 15th day after 14 days of daily observation.

Results:

Clinical signs - hypoactivity; excessive salivation; eye; nose, mouth discharge. At 2 days post exposure a slight brown crust exhibited around eyes, nose, mouth by day 4 signs had disappeared.

Tox. Cat. IV

LC_{50} > 167 mg/L 1 hr. (nominal)

Core:

Minimum. Purity of the technical grade is known to tbe 95% a.i. or greater.

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