RD-770
TXR-2917

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

002917

4/25/1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert Taylor (25)
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

SUBJECT: Atrazine Registration Standard

Submission of the Toxicology Branch evaluation of Atrazine toxicity data consists of:

1. Reviews of previously unreviewed studies.

2. Data Evaluation Reports for each relevant toxicity study.

3. "One-Liners" for the data base.

4. Data Summary, a bibliography which discusses the toxicological data gaps and measures taken to fill them.

Toxicology Chapter

Acute Testing

81-1 Oral LD_{50}

Atrazine is a chlorotriazine herbicide which has a low toxicity from acute exposure. Both rats and mice have been studied and found to have acute oral LD_{50} values of 2,850 mg/kg BW (MRID #00027097), and 3,992 mg/kg BW, (MRID# 00024727), respectively. A second and third rat study were found to have LD_{50} values of 1869 mg/kg BW, (MRID #00024706) and 2030 mg/kg BW, respectively (Greear review MRID #).

Data are sufficient to place the chemical in toxicity category III, and are adequate for registration requirements.

1/8.41

002917

81-2 Dermal LD_{50}
81-4 Dermal Irritation
81-5 Eye Irritation

Dermal exposure to rats did not produce toxicity and it was determined that the LD_{50} was greater than 2000 mg/kg BW (MRID# 00027097). The LD_{50} in rabbits was 7550 mg/kg BW (Greear review MRID# ____). Rabbits exposed to technical atrazine failed to show dermal irritation after 24 hours, (MRID# 00027096). The dermal toxicity studies are sufficient to place the chemical in dermal toxicity category III and are also sufficient for registration requirements. Aqueous suspension of technical atrazine has been tested for eye irritation properties in white rabbits (Greear Review MRID#___). Corneal opacity of a minimal severity was present at 1 hour through 72 hrs. after exposure. Complete reversibility occurred before seven days. The study is adequate to place the chemical in toxicity category II and further testing is not necessary for registration requirements.

81-3 Inhalation LC_{50}

Exposure of rats in an experiment to determine the acute toxicity of Atrazine by the inhalation route revealed that the LC_{50} was greater than a nominal value of 167 mg/L/1 hr (Greear MRID# _____).

The data are adequate to indicate that Atrazine does not possess a high toxicity via inhalation; and when considered with the oral LD_{50} data are sufficient to place the chemical in toxicity category IV for inhalation. No further testing is required for registration.

83-1 Chronic Testing
Chronic toxicity - Non Rodent

A two year feeding study in beagle dogs (MRID# 0005213) using 80W in which 4/sex/dose were fed up to 1415 ppm (35 mg/kg BW). Body weights were lowered at the HDT, which was not noted at the mid dose level. Muscular tremors also occurred at the high dose after 6 months. Relative thyroid, liver, heart and adrenal wts. were increased in the high dose group females and relative prostate wts. in males at the high dose were decreased. Since a reduction in food intake was reported, adequate statistical evaluation of these changes is difficult to make. Watery lacrimation occurred only in treated animals at all levels. The study is considered Supplementary due to missing a statement of chemical purity, questionable hematology data and lack of individual feeding and observation records, which if supplied may upgrade study to minimum. This study does not fulfill the needs for registration and is considered to be a data gap.

002917

Chronic Toxicity - Rodent

A second species chronic feeding study in rats. (MRID# 00059211) was reported which used Atrazine 50 W (4 doses, 30 M/30 F per dose). After 65 weeks the lowest dose (1 ppm) was elevated to 1000 ppm for the remainder of the study. Body weights of females at 1000 ppm were reduced as was food intake. Other changes included indications of severly infected animals with numbers of animals dying, unrelated to dosage and probably due to the intercurrent infection, reported in the study. The study does not delineate the oncogenic potential of the compound due to the extremely few number of animals surviving to the end of the study. Feed was not analyzed. The study is consider to be supplementary and does not fulfull the need for a chronic or oncogenic study in rodents and is considered to be a data gap.

83-2 Chronic Testing
Oncogenicity Study - Rat.

See chronic toxicity - rodent above. The rat study does not fulfill oncogenicity requirements for registration and is considered to be a data gap.

Oncogenicity study - 2nd species.

No second species oncogenicity study has been reviewed. This requirement is considered a data gap.

83-3 Teratogenicity, 2 species

(a) The NCI testing program included atrazine exposure to the C3H, BL6 and AKR strains of mice (MRID# 00023558). Subcutaneous injections of 46.4 mg/kg of Atrazine in DMSO on days 6-14 of pregnancy resulted in increased fetal mortality in the C_3H and AKR strains.

Due to the confounding effects of DMSO and insufficient litter data the study is considered supplementary, does not fulfill registration needs, and is considered to be a data gap.

(b) A second species study in rats (MRID#00038041) with treatment at 100, 500 and 1000 mg/kg on days 6-15 of gestation showed an increase in embryonic and fetal resorptions at 500 mg/kg. Ossification centers were delayed in formation at the highest dosage. A NOEL for maternal toxicity and feto-toxicity

(embryonic resorptions) was noted as 100 mg/[illegible] not observed at any dosage up to and including [illegible] (HDT).

Core: Minimum Study, partially fulfills the requirement for 2 species to be tested:

83-4 · Reproduction

The effect of Atrazine as an 80% W.P. on the reproductive performance of rats was examined in a 3-generation study where the HDT was 100 ppm (5 mg/kg body weight) in the diet. No adverse reproductive effects were noted. Study is considered Supplementary due to the alteration in the diets at important maturation period of neonates, and because only 2 dosage levels were used which are considered to be too low and which did not elicit observable toxicity. The lack of toxicity at the highest dose is not in itself sufficient reason to downgrade a study. However, considering the fact that the 2-year rat feeding study and rat teratology study used up to 50 mg/kg and 1000 mg/kg, respectively, this reproduction study, tested at 5 mg/kg, is inadequate to assess the toxicity on reproductive performance.

Special Testing
85-1 Metabolism

Atrazine was fed to the Long-Evans strain of rat and was excreted by as much as 71% in a 48 hour period. Less than 0.1% was exhaled as $^{14}CO_2$. From 12% to 15% of the dose was excreted in the feces and up to 57% in the urine. After 48 hrs: blood levels (6-8 ppm) were greater than 2X those found in kidney and liver tissues. Only 0.3 ppm of residues were found in fat. The study is minimum data for an excretion study but inadequate to determine metabolite moieties (MRID# 0080634).

85-1

A second report, MRID# 00080632, was carried out by feeding either atrazine or hydroxyatrazine to rats and determining the type of metabolites found in the urine and feces. Only a relatively small amount (33%) of fecal metabolites were recovered when atrazine was fed. However, 94% or more of the ^{14}C activity was recovered in both urine and feces of animals fed hydroxyatrazine. Hydroxyatrazine is not found in the urine after the feeding of atrazine. This is a supplemental study which did not adequately determine metabolites and does not fulfull the need of a metablism study for registration.

002917

A data gap exists for a metabolism study which identifies and quantitates the metabolites.

84-2 Mutagenicity

Ames studies using TA 1535, TA 1537, TA 1538, TA 98 and TA 100, with and without activation, did not indicate a mutagenic response at up to 5000 ug/plate (MRID# 00060642). These studies partiallly fulfill data needs for registration.

Additional mutagenicity studies other than Ames studies are required under Reg. requirements 158.135 and are considered data gaps.

Tolerance Reassessment

Tolerances have been established for Atrazine on a number of different food and forage crops. The acceptable daily intake (ADI) was originally established using a two-year dog no-observed-effect-level (NOEL) of 150 ppm (3.75 mg/kg) (Coberly, 1968 MRID# _____). A 100 fold safety factor was used and the current percentage of ADI utilized is 3.42. The Agency has since reevaluated the ADI based on the dog chronic feeding study and has determined that too few animals were examined, effects were noted at the lowest dosage and therefore a NOEL can not be determined for the study. At present there are no adequate long term feeding studies for establishing an ADI.

Data which were evaluated and determined to be adequate did not demonstrate adverse acute toxicity or teratogenicity. There are insufficient data however to determine reproductive effects, mutagenicity and oncogencity potentials, and long-term chronic effects. These data are pivotal and necessary for determination of an ADI. These data are also necessary for continuance of existing tolerances and for consideration of additional tolerances. [TB recommends a statutory requirement or deadline be placed on the registrant(s) for submission of such data before revocation of existing tolerances or withdrawal of existing registrations is considered necessary].

Henry W. Spencer, Ph.D. 4/25/83
Review Section #1
Toxicology Branch/HED (TS-769)

TS-769:SPENCER:sll:X73710:2/24/83 card 5

DATA SUMMARY

CHEMICAL: ATRAZINE

CASWELL: 63

Study/Lab/Study#/Date	MRID	Material *	Accession Number	Results	Tox. Cat.	CORE Classification
Acute Testing : 81-1 to 81-7						
Oral LD_{50} - rat Consultox. Labs. Ltd. #C174:46:996E April, 1974	00027797	95% ai.	Not reported	2,850 mg/kg	III	Minimum
Oral LD_{50} - rat Ciba - Geigy #4569 04/15/1975	00024706	Technical purity not reported	230303	1869 mg/kg both sexes.	III	Minimum
Oral LD_{50} - rat Instituto Di. Recerche	Greear Review	Technical purity not reported	231466	2030 mg/kg both sexes. Tremor, ataxia, anorexia loss of b.wt., adrenal degeneration.	III	Minimum
Oral LD_{50} - mouse CIBA-Geigy Ltd. PH 2635 April 7, 1975	00024707	Technical purity not reported	230303	3,992 mg/kg, sedation, dyspnea, ruffed fur.	III	Minimum

*Though purities are not reported for the technical a.i., they are known to exist as 95% a.i. or greater.

002917

Dermal LD_{50}-rat Consultox Lab. Ltd. #CL 74:46:996E April, 1974	00027097	Technical 95% a.i.	Not reported	LD_{50} > 2,000 mg/kg no toxicity noted	III	Minimum
Dermal LD_{50} - rabbit Instituto Di Ricerche (Italy) December, 1976	Greear Review	Technical purity not reported	231446	LD_{50} = 7.55 g/kg anorexia, ataxia, loss of body wt.	III	Minimum
Eye irritation - rabbit	Greear Review	Technical purity not reported	Not reported	Minimal corneal opacity rever- sible by day 7	II	Minimum
Dermal irritation rabbit Hazelton Labs. America, Inc. #915-102 March 5, 1975	00027096	Technical purity not reported	Not reported	Non irritating	IV	Minimum
Inhalation LC_{50} - rat Hazelton Labs. Am. Inc. # 915-100 April 1, 1975	Greear Review 00027095	Technical purity not reported	Not reported	167 mg/L 1 hr. nominal concentra- tion purity not stated	IV	Minimum
Chronic Testing: 83-1 to 83-4						
Chronic feeding non rodent - dog. Woodard Research Corp. Oct. 27, 1964	00059213	Atrazine 80%	Not reported	Not able to set NOEL from study due to questionable analytical practices.	N/A	Supplementary

Chronic feeding Rodent - rat Hazelton Labs. Inc: March 10, 1961	00059211	Atrazine 50W 48.25% a.i.	Not reported	Not adequate to set NOELs	N/A	Supplementary
Oncogenicity study - rat Hazelton Labs. Inc., March 10, 1961	00059211	Atrazine 50W 48.25% a.i.	Not reported	Not adequate to determine oncogenic potential-poor survival (1000 ppm HDT for 1 yr.)	N/A	Supplementary
Teratogenicity - rat Ciba - Geigy Ltd. Basle, Switerland Oct. 29, 1971	00038041	Technical purity not reported	Not reported	Not teratogenic at 1000 mg/kg (HDT), maternal toxicity: LEL = 500 mg/kg for wt. loss. NOEL = 100 mg/kg, Fetotoxicity: LEL = 500 mg/kg as fetal resorptions NOEL = 100 mg/kg	N/A	Minimum
Teratogenicity - mice Bionetics Research Labs. Aug. 1968	00023558	Unknown	Not reported	Use of DMSO and insufficient data on liters; fetuses make evaluation impossible. AKRC3H, decreased number of live fetuses; AKR exhibited reduced fetal wt.	N/A	Supplementary
Reproduction - rat 3-generation Woodard Research Corp. 1966	00024471	Atrazine 80 WP	Not reported	No toxicity to adults - no reproductive toxicity noted. Alteration in dietary regime does not allow a clear NOEL to be set. (100 ppm HDT)	N/A	Supplementary

Mutagenity Testing: 84-2 to 84-4

Gene mutation - Ames Testing. Entomology Dept., P.S.U. by K.A Rashid 1974	00079923	Purity unknown	Not Reported	1. No metabolic activation. 2. Procedure not delineated. 3. Cytotoxicity limit improperty chosen interpretation not acceptable.	N/A	INVALID
Stanford Research Inst. VF Simmon and D. Poole 1977	0006064	Purity not stated	Not Reported	Not mutagenic up to 5000 microgram/plate w/and w/o activation in TA 1535, TA 1537, TA 1538, TA 98, TA 100.	N/A	Acceptable
T_4 Bacteriophage Systems Battelle Memorial Inst. Columbus, Ohio Jan. 30, 1977	00025376	Atrazine unknown purity	Not Reported	No activation was made. The spot test is limited to usefulness.	N/A	INVALID

Special Testing: 85-1

Metabolism - rat CIBA - GEIGY, Corp. Inc. April 3, 1964	00080632	^{14}C Atrazine ^{14}C Hydroxy-atrazine	Not Reported	No ^{14}C hydroxyatrazine is found in urine from ^{14}C atrazine feeding. Almost 100% of ^{14}C hydroxyatrazine is recovered from urine and feces.	N/A	Supplementary
Metabolism - rat Hazelton Labs., Inc. July 15, 1960	00080634	^{14}C Atrazine	Not Reported	67-72% of radioactivity was eliminated within 48 hrs. via urine and feces. Metabolites not determined. Blood samples carried 2x that found in tissues. Minimum only as an excretion study.	N/A	Minimum

002917

Study: MRID 60642 - Final Report: In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals

(I) Results: - In Vitro Assay of Atrazine with Salmonella typhimurium

The test compound, Atrazine, failed to induce any significant increase in the reversion frequency to histidine independence of the five mutant strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100) in the presence and absence of mammalian metabolic activation from rat liver enzymes in this study, and thus, was not mutagenic agent at the dose levels tested (50, 100, 500, 1000, & 5000 ug/plate).

Evaluation:

The In Vitro mutagenesis assay of Atrazine with five tester strains of S. typhimurium appears to have been conducted in a manner adequate to generate valid results. Therefore, the negative responses of the compound as judged by the summarized table II of Revertants are acceptable (50 through 5000 ug/plate).

(II) Results: - Host-Mediated Assay of Atrazine with S.typhimurium (In Vivo)

There was no increase in the average number of revertants per milliliter and in the average number of revertants per 10^8 cells of Astrazine-treated mice as compared with the vehicale control mice. A reasonable low variation of the revertants and mutation frequency from treated mice and control mice groups was demonstrated. The positive controls apparently gave the expected positive responses (DMNA & 2-anthramine). Therefore, it was concluded that the test compound, Atrazine, was not mutagenic in Host-Mediated Assays in mice after the acute and subacute treatments. (275, 550, 1000, 1100, 2000, & 2200 mg/kg).

Evaluation:

The assay used to evaluate the mutagenic activity of the test compound on the microbial cells of Salmonella typhimurium (TA1535 & TA1538) implanted in the male Swiss Webster mice appears to follow the procedures developed by Legator and Malling (1971). The negative responses of the compound as judged by the summarized tables 7, 8, 9, & 10 of mutation frequency in Host-Mediated Assay system are acceptable.

Study: MRID 25376 - Evaluation of Herbicides for Possible Mutagenic Properties

(A) Evaluation of Atrazine Using the Eight Histidine-Requiring Mutants of Salmonella typhimurium

Results:

The test compound, Atrazine (1-5 ul/plate), was found to be non-mutagenic to the eight mutants of Salmonella typhimurium in the spot test assay described by Ames and Whitefield (1966).

Evaluation:

The test design of the mutagensis study using only the spot test technique appears to be inadequate, not conducted according to the accepted procedures of Salmonella/mammalian microsome mutagenicity test (Ames et al, 1975) for general mutagenesis screening purpose, and hence, the results and their interpretations are unacceptable. The following inadequacies in performing the Ames test were noted:

1. The negative response of the test compound to the histidine-requiring mutants of S. typhimurium obtained from the spot test assay is unacceptable to be used as the evidence of a non-mutagen. The spot test study does not permit quantification and is generally much less sensitive than the accepted plate-incorporation procedures of the Ames test. The results are strongly influenced by the diffusibility of the test compound. The spot test should not be used for definite decision to evaluate the mutagenic agent. When negative results are obtained in this test, the test compound should be further evaluated by using the direct-plating proceudres of the Ames test.

2. The assay was not conducted with a mammalian S9 activation system. Bacteria should be exposed to the test compound both in the presence and absence of an appropriate metabolic activation system.

(B) Evaluation of Astrazine on the Induction of rll mutants of T4 Bacteriophage

Results:

The test compound, Atrazine (20 ug/plate) did not increase the frequency of mutation to the rll type of T4 bacteriophage, and thus was not mutagenic in this test system. (Table V)

(C) Evaluation of Atrazine on the Reversion of Mutants of T4 Bacteriophage

Results:

The test compound, Atrazine (1 mg/plate) did not increase the reversion of bacteriophage AP72 and N17 to T4 pheno type, and thus was not mutagenic in this test system (Table X and XI).

(D) Evaluation of Atrazine on the Reversion of λ Temperature-Sensitive Mutants of ϕX 174 to the Wild Type

Results:

The test compound, Atrazine (30 mg/plate), did not increase the reversion of a temperature-sensitive mutants of ϕX 174 to the wild type (non-temperature dependent), and thus, was not mutagenic in this test system (Table XII).

Evaluation of T4 Bacteriophage Systems (B, C, & D):

Because of the limited usefulness of the spot test technique and no mammalian metabolic activation being used in these viral systems, the reversion spot tests in T4 and ϕX174 bacteriophages employed for this study appear to be inadequate for general mutagenesis screening purpose, and hence, the results and their interpretations are unacceptable.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: Dec 22, 1977

002917

SUBJECT: Atrazine Technical
EPA File Symbol
Caswell #63, Shaughnessy #080803

FROM: Toxicology Branch
Registration Division

TO: Robert Taylor
Product Manager #25

Recommendations

The acute oral LD_{50}, dermal LD_{50}, inhalation LC_{50}, eye and skin irritation studies are adequate and will support registration. However, prior to registration it is recommended that the following precautionary statements be incorporated into the label:

Warning: Keep Out of Reach of Children. Causes eye irritation . Do not ge in eyes, on skin, or on clothing. Harmful if swallowed, or absorbed through the skin. Avoid contamination of food.

First Aid: In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes. For eyes, call a physician. Remove and wash contaminated clothing before reuse.

If swallowed, drink promptly a large quantity of milk, egg whites, gelatin solution or if these are not available, drink large quantitites of water. Avoid alcohol. Call a physician.

Classification: It is recommended the product be classified General Use.

* No RPAR criteria have been exceeded,

Review

1. Acute Toxicity of Romianca Technical Atrazine - (Istituto Di Ricerche Biomediche, Dec 76/Jan 77, submitted by Romianca S. p. A. on August 29, 1977 Acc # 231466)

A. Acute Oral LD_{50}

In an initial range finding study 8 groups of 2 male and 2 female Wistar rats per group, weighing 100-150g, were administered 0.300, 0.479, 0.759, 1.202, 1.905, 3.020, 4.786 or 7.586 g/kg of the test material by gavage. Following the results of this study an additional 8 groups of 5 male and 5 female per group were administered 1.202, 1.513, 1.698, 1.905, 2.137, 2.398, 2.691 or 3.019 g/kg of the test material by gavage. During the 14 day observation period, records were made of all mortalities and signs of toxicity. All animals were necropsied.

Results

ALD_5 = 1.202 - 3.020 g/kg
LD_{50} = 2.030 g/kg 95% C.I. (1.83-2.25)g/kg; slope = 1.27

Toxic Signs: tremors, ataxia, anorexia, piloerection, loss of body weight.
Necropsy: congestion of lungs, liver and kidneys; adrenal degeneration.

Tox Category: III

Classification: Core - Minimum Data

1) Body weight and food consumption data were not recorded daily.

B. Acute Dermal LD_{50}

New Zealand White rabbits, weighing 2-3 kg were employed. Animals were distributed into 3 groups of 2(1M + 1F) for the range finding experiment and into 3 groups of 2(1M +1F) for the final experiment. Dermal applications of test material consisted of 3.9., 6.4 or 9.4 g/kg in the range finding experiment and 6.0, 7.5 or 9.506 g/kg in the final experiment. Animals had their backs slipped 24 hours prior to application. The test material was applied to intact skin under an impervious wrapping and left in contact with the skin for 24 hours, after which time, the wrapping was removed and all the residual material wiped off. Mortalities and signs of toxicity were recorced for 14 days. All animals were necropsied.

Results

ALD_{50} = 6.0-9.0 g/kg
LD_{50} = 7.55 g/kg 95% C. I. (5.74-9.94) g/kg; slope = 1.41
Toxic Signs: anorexia, ataxia, loss of body weight.
Necropsies: congestion of lungs, liver and kidneys.
Tox Category: III
Classfication: Core - Minimum Data
1) Body weight and food consumption were not recorded daily.

C. Primary Dermal Irritation

0.5 g of the test material, premoistened with physiological saline was applied to one intact and one abraded skin site on the clipped skin of the backs of six New Zealand White rabbits, weighing 2-3 kg. After 24 hours of exposure, the patches were removed, the residual material wiped off, and the resulting reactions scored according to Draize. Readings were again made at 72 hours.

Results

Tox Category: IV
Classification: Core-Minimum Data
1) readings were not made on 2 intact and 2 abraded skin sites.

D. Primary Eye Irritation

0.1 ml of an aq. suspension containing 50 mg of the test material was instilled into the right eye of each of 6 New Zealand White rabbits. Eyes were scored 1 minute, 1 hour, 24 hours, 72 hours, and 7 and 14 days post-instillation. The Draize scoring system was employed.

Results

Minimal corneal opacity was present at 1 hour up to and including 72 hours. Conjunctivitis was present at 24 and 72 hours. No irritation was observed at 7 and 14 days.

Tox Category: II
Classification: Core-Minimum Data
1) although mean scores were reported, the results are definitive.

E. Acute Inhalation LC_{50}

Wistar strain rats, weighing 100-150g, were employed. Rats in the range finding experiment were divided into 3 groups of 4 animals each (2M + 2F) and exposed to concentrations of 0.5, 1.0 or 2.0 mg/L of the test material for a 4 hour period. Based on the negative results, in the final experiment 4 groups of 10 animals each (5M + 5F) were exposed to 0, 0.5, 1.0 or 2.0 mg/L of the test material for a 4 hour period in a 60L exposure chamber. The atmosphere was generated with a type Dy Faset-Milan atomizer capable of producing particles ranging in size from 0.5 - 7.0 u. Observations for mortality and signs of toxicity were made for 14 days following exposure. All animals were necropsied.

Results
LD50 > 2.0 mg/kg (no deaths observed)
Toxic Signs: none
Necropsy: unremarkable
Tox Category: III
Classification: Core Minimum Data
1) the analytical concentration was not determined.

William Greear

William Greear
B for GEW 11/20/78

002917

Study Two-Year Dietary Administration-Rats
Hazleton Laboratories Inc. March 10, 1961
MRID #0059211

Animals Tested:

Albino rats (strain and supplier not stated).

Material Tested:

Atrazine 50 WP (wettable powder) - light beige color. 25% a.i. by weight.

Methods:

240 rats equally divided by sex:
Males 68-89 gm
Females 63-89 g (age not stated)

After random selection, rats were housed individually and given either 0.0, 1.0, 10, or 100 ppm dosages. At 66 weeks the 1 ppm group received 1000 ppm to completion of the study 30 per sex/dose were treated.

Diets were prepared fresh each week; Access to diets and water ad lib.

At the start of study 5/sex were randomly chosen for sacrifice at 26 wks. and 52 wks. Records of body wts., food consumption, appearance and demeanor were made weekly. Organ wts. of those sacrificed included liver, kidneys, adrenals and testes. Tissues preserved included brain, heart, thyroid, pituitary, lung, kidney, liver, adrenal, stomach, spleen, pancreas, intestines, bladder, testes, bone marrow, ovary, peripheral nerves and skel. muscle. Unusual lesions as well were examined in those (26) sacrificed at termination. At 52 weeks 100 ppm and control tissues examined included liver, thyroid, large and small intestine, stomach, gonads, adrenal and bladder.

Body wts. were evaluated from start to 26 and 52 weeks, 78 weeks and termination. Food consumption was evaluated from 0-13, 40-52 and 66-78 weeks. Hematologic values were determined in 5/sex/dose at 26 and 52 weeks and also for all survivors at study termination. Values determined were microhematocrits and differential WBC.

Urinalysis of over night collections of pooled urines from 3 animals in each sex/dose were made at 26 and 52 weeks, and also from survivors in all groups at study termination. Values determined were: sugar, protein, S.G., pH, and bile pigments. Appearance of urines were recorded.

Autopsy was done on all animals. Selected animals dying during the second year were examined microscopically in pituitary, lung, thyroid, kidney, liver, adrenal, sternum and on all unusual lesions found at autopsy.

Statistics: Survival was analyzed by the Chi square method. Other values were analyzed using the F-test or analysis of variance p values were set at $p<0.05$.

Results:

Only females of Group 2, after changing to 1000 ppm, exhibited slightly lower food consumption from controls. Body wt. changes for females at 1000 ppm after 66 weeks are noted and a conservative NOEL was 100 ppm. Survival rates for all male groups were at 97.2% or greater at 26 week and 94.6% or greater at 52 weeks. At 78 weeks survival was 85.3% or greater in males of all groups. However, the number of male animals surviving to 104 weeks in the 100 and 1000 ppm dosages were 2/20 and 3/20 compared to 4/20 in controls. The last 24 weeks showed numbers of animals expiring which did not relate to increasing dosages in the treated males. Only the females at 1000 ppm showed a lower number of animals surviving (1/20) compared to 4/20 in controls in the last 24 weeks. Only a weak indication of reduction in hematocrits at 100 ppm compared to controls is seen. Too few data were produced at 1000 ppm for comparison.

Urinalysis revealed an increased number of RBC or WBC in both male and female urines at 100 ppm.

26 Weeks:

Liver and kidney to body wt. ratios were not statisically different from controls in all groups of males and females. However, the highest dosage (1000 ppm) appeared to ~~be~~ liver changes consistently greater than controls and other treatment groups. Testes to body weight ratios at the highest dosage also were increased, though not significantly ($p<.05$). Note: (Too few animals organ weights are presented in Table 221 for males at 104 week to discern meaningful wt. changes in organs examined).

Summary of gross autopsy data on males revealed that lungs were infected in 21/29 control animals, with an additional 2/29 presenting possible infections. Similarly, in 1000 ppm animals, 22/31 had lung infections with 2/30 possible infections. At 100 ppm there were 18/30 with lung infections and 2/30 with possible infections; and at 10 ppm, 17/30 had lungs infected with an additional 10/30 possible lung infections.

Female lungs affected:

	Control	10 ppm	100 ppm	1000 ppm
Infections	17/30	17/28	19/29	19/30
adhesions & masses	3/30	1/28	2/29	3/30

Comment: Females were badly infected throughout the study:

		Control	10 ppm	100 ppm	1000 ppm
Infections in 104 wk. termination	Females	4/4	4/5	5/6	-
	Males	2/4	1/3	-	2/3

The detailed summaries of microscopic examination in Tables 225 and 226 for male and females did not show tumors in treated animals at levels greater than those seen in controls in 1)sacrificed at 52 weeks, 2)sacrificed at 104 week, 3)those dying or 4)the totals of 1, 2 and 3.

Note:

Very few animals of either sex remained alive at 104 weeks probably due to the intercurrent infection noted by the laboratory.

Toxicology Branch does not consider this study to be adequate to delineate the oncogenic potential of the chemical due to the paucity of animals examined and the poor viability due to infection rate of those on test. In addtion, the feed was not analyzed for a.i.

Core:

Supplementary. Not adequate to delineate oncogenic potential.

Teratogenicity Study - (Reproduction Study) 002917
Segment II Dated: 29/10/71
Experiment #22710600 - CIBA - GEIGY LTD, Basle
MRID #00038041

Material Tested:

Preparation G30 027, Batch 4314 in 2% carboxymethylcellulose 10 ml/kg.

Dosages:

100, 500, 1000 mg/kg dosed days 6-15 of gestation.

Methods:

Mating of 1 male/3 females; maintained on NAFAC #185. diet and tap water ad lib. Dosages were given on days 6-15 of gestation. On day 21 pups were delivered by C-section.

Results:

The top dose produced 7 deaths in the 30 dams treated. 500 mg/kg resulted in slight weight loss in females.

Pups from 33, 26, 20 and 16 dams from control, 100, 500 and 1000 mg/kg respectively, showed a reduction in mean fetal wts. only at the top two dosages ($p<0.05$).

The number of embryonic and fetal resorptions increased in the two highest dosages.

Dams	Dosage	Implants	Early Embryonic Res.	Late Fetal Resorptions
33	0	480	12 (2.6%)	0
26	100 mg/kg	346	10 (2.9%)	0
20	500 mg/kg	301	12 (4.0%)	19 (6.3%)
16	1000 mg/kg	235	18 (7.7%)	6 (2.5%)

An increase in missing ossification nuclei of hind leg phalangae is also noted only at the top two dosage levels. Ossification centers as bipartite sites increased to 40/92 (43.5%) of examined pups at the 1000 mg/kg dosage, compared to 50/280 (17.8%) in controls. Other groups were not significantly different from controls.

Asymetrically ossified centers increased only at the top dose level in 7/92 or (7.60%) examined and anasarca occurred in 5 pups only at the 1000 mg/kg dosage level.

Maternal LEL = 500 mg/kg for wt. loss.
NOEL = 100 mg/kg.

002917

Teratogenicity - NOEL = 1000 mg/kg (HDT).

Fetotoxicity LEL = 500 mg/kg
NOEL = 100 mg/kg for pup wt. loss., embryonic death and fetal resorptions.

Core: Minimum

002917

Teratology - Mouse with Atrazine.
Bionetics Research Lab., NTIS. Vol. II. Dated: August 1968. MRID: 00023558 (also 00027598)

Test Animals:

Mice - C3H, BL6 and AKR strains.

Test Material:

Atrazine (Listed in NCI oncogenicity testing; purity unknown).

Methods:

Following breeding, treatment on days 6-14 of pregnancy consisted of a S.C. injection of 46.4 mg/kg in 0.1 ml DMSO. At sacrifice on the 19th day of gestation various neonatal parameters were calculated. Statistical significance from control was set at $p < 0.05$ for the student t-test.

Results:

Fetal mortality was increased in C3H and AKR strains to 43% and 21% ($p < .05$) respectively. The number of live fetuses, 4.8 + 1.4 S.E. per litter was decreased in the C3H strain. Fetal weight was lower for the AKR strain while maternal weights were reduced in the BL6 and AKR strains.

Comment:

Due to the confounding effects of DMSO, valid conclusions can not be drawn from the study. Individual data are missing.

Core:

Supplementary due to use of DMSO as a solvent and insufficient data on fetuses in litters.

3-Generation Reproduction Study
Rats with Atrazine 80WP
Woodard Research Corp., 1966
MRID #00024471

A standard 3-generation study with both A and B litters was carried out using 10 males and 20 females per generation.

The test material was Atrazine 80W (80% WP) number FL-2446, ARS 1655A-64. Item 684 from Geigy Chemical Corp. on June 9, 1964.

Dietary levels were 100, 50, and 0 ppm. After receipt animals were fed only 1/2 of the dietary levels for the first 3 week then changed to the stated levels for 74 days. Weaned pups in succeeding generations were placed on control diets for several (unstated number) days then followed as the parents above.

The F_3B litter was sacrificed for histological examination.

Results of Study:

Mean body wts. of male and female parents were not different from controls. Several deaths occurred which were spontaneous and unrelated to dose.

A slight increase in total number of still births occurred in the F_{1a} and F_{1b} litters over controls but are not considered to be significant. Other parameters appeared normal in F2 and F3 generations.

No malformations were noted excepting a club shaped forepaw in 1 control male pup. Major organ wts. of kidney, liver, and heart as well as body wts. of the F_{3b} weanlings were comparable to controls.

Comments:

Data are supplementary because only 2 dosages were used which are considered to be too low, and which were without observable toxicity. Alteration of test material in the diet during important maturation periods of neonates needs to be explained and justified.

Core: Supplementary.

Metabolism of Simazine, Hydroxy-Simazine, Atrazine and Hydroxy-atrazine by Rats. (Technical Bulletin). Ciba Geigy Corp. Dated: April 3, 1964. MRID: 00080632 002917

Data presented result from the C^{14} labeled. Metabolism study on atrazine by Hazleton Laboratories July 15, 1960.

Material tested: Atrazine - C^{14}

Animals tested: Rat

Methods:

Urine and feces from the Hazleton Labs. and Woodard Research Labs. were returned to C-Geigy Labs. for extraction, identification and quantitation of metabolites excreted.

Feces extraction was with chloroform then followed by adding ethanol to 50% solution and separated by column exchange on a Dowex 50 resin with IN NH_4OH in 50% ethanol and concentrated.

After again loading on a cation exchange resin, elution was carried out with gradient, 0.5 N HCl to 3.75 NHCl. Radioactivity in the sample fractions was determined by a continuous scintillation technique.

Paper chromatography was carried out in a butanol: acetic acid: water 4:1:5 system.

Results:

1. Both hydroxy-atrazine and hydroxy-simazine are found in feces after feeding either the chloro-triazine or the hydroxy-triazine.

2. Both hydroxy-atrazine and hydroxy-simazine may be found in the urine of rats after their feeding of these compounds but not after feeding the Cl-triazines.

3. Simazine and atrazine, hydroxy-simazine and hydroxy-atrazine appear to produce common metabolites in the urine.

Atrazine:

Approx. 85% of urinary C^{14}-atrazine activity was recovered but only 33% of the fecal metabolites were recovered.

About 100% of the hydroxy-atrazine C^{14} activity was recovered from urine and a similar value (94%) was recovered from the feces.

The study is adequate to show activity excreted but does not determine whether the rings are dealkylated, deamineated or split.

Supplementary Data.

002917

Metabolism - rat with Atrazine
Hazelton Laboratories. Report dated July 15, 1960
MRID #0080634

Material tested: Atrazine - ^{14}C
spec. act. 18.32 uc/mg

Animal Studied: Long-Evans strain rat
3/sex weighing 93-109 g.

Methods:

Each rat was individually placed in a glass metabolism cage. Urine and feces were specially collected by an anal cup for fecal separaton. Lab chow (SL White Diet, Simenson Labs, Gilroy, Ca.) and water were present ad lib. Cage temp. - 25-30° C. Air flow through cage - 0.52 - 0.74 L/min. and was CO_2 free. Exhaled CO_2 was collected for ^{14}C analysis. After 4 days, 1/sex were kept as controls and the other 2/sex were dosed. Collections were for 48 hr. for: feces and CO_2 at 6, 12, 24, 36 and 48 hr. Collections of urine were each 3 hr. Blood by cardiac puncture was taken at 48 hr. Animals were sacrificed for gross observation.

Dosing:

^{14}C Atrazine was added to 0.5% methyl cellulose to give approx. 23.6 mg/6ml. Dosing was determined by wt. difference in a 1.0 ml syringe and diluting in Diotol-Phosphor counting solution (0.4:50 ml) then (1:100); then a final 1:14 ml dilution to be counted.

Urine:

Dilutions - 1 ml = 1/50 of total sample was counted in 15 ml solution for 2 minutes.

Cage washings were also counted.

Feces were mixed in 50% methanol to 100 ml volume. 1:15 ml dilutions were counted.

Efficiency for urines was 49%
Efficiency for feces was 39.3%
Efficienty for $^{14}CO_2$ was 27.8%

Tissues were homogenized so that 1/5 of the total sample was diluted 1:15 and counted. Control samples were used as blanks. Blood was counted after 30% peroxide (4 dps) was added as a bleaching agent to negate quenching.

Results: (Extracted from study)

RAT NO.	SEX	ADMINISTERED RADIOACTIVITY uc.	DOSE EXCRETED URINE %	FECES %	CO_2 %	TOTAL DOSE EXCRETED %
1	Male	59.8	57.2	14.3	0.05	71.55
2	Male	40.3	57.3	14.5	0.04	71.84
5	Female	42.7	52.3	15.1	0.08	67.48
6	Female	41.4	55.3	12.4	0.09	67.79

Residues in Tissues

	ppm male (2)		ppm female (2)
Blood	6.49 - 8.21		8.39 - 6.85
Kidney	2.88 - 3.74		3.37 - 3.65
Liver	3.64 - 3.18		3.12 - 3.81
Heart	1.72 - 1.49		2.05 - 1.54
Testes	1.39 - 1.36	Ovaries	0.45 - 1.05
Muscle	1.00 - 1.18		1.25 - 0.86
Fat	0.31 - 0.10		0.25 - 0.14

Conclusion:

In 48 hr. approximately 70% of the ^{14}C activity was excreted in urine, feces and CO_2.

In the 4 animals not more than 0.094% of the dose was excreted as CO_2 in 48 hr.

The majority of the fecal residues were found in the first 24 hr. samples.

Generaly, cage washings represented 52 - 57% of the dose.

The fact that blood contained a higher (approx. 2x) level than either kidney or liver suggests that ^{14}C in some form is being held in that compartment before excretion.

Comment:

Core Minimum as an excretion study. (Does not satisfy the need for a metabolism study defining the metabolic products)

002917

January 14, 1983

To: R. Bruce Jaeger; Section Head 1/14/83
Review Section # 1
Toxicology Branch/HED (TS-769)

From: John Chen, DVM
Review Section #1
Toxicology Branch/HED (TS-769)

Subj: Atrazine - Review and Evaluation of Mutagenicity Studies

Review comments are attached for the following mutagenicity study reports:

(1) MRID 79923

Rashid, K.A. (1974) Mutagenesis Induced in Two Mutant Strains of Salmonella typhimurium by Pesticides and Pesticide Degradation Products (Unpublished study received Feb. 23, 1978; prepared by Entomology Dept. of PSU).

(2) MRID 60642

Simmon, V.F. and D. Poole (1977) Final Report: In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals (Unpublished study received Dec. 29, 1977; prepared by Stanford Research Inst.).

(3) MRID 25376

Anderson, K.J., E.G. Leighty, and M.T. Takahashi (1967). Evaluation of Herbicides for Possible Mutagenic Properties (Unpublished study received Jan. 30, 1977; prepared by Battelle Memorial Inst., Columbus Laboratories).

Study: MRID 79923 - Mutagenesis Induced in Two Mutant Strains of Salmonella typhimurium by Pesticides and Pesticide Degradation Products

Results:

The test compound, Atrazine, failed to induce any significant increase in the reversion frequency to histidine independence of the two mutant strains of Salmonella typhimurium (TA 1535, & TA 1538) in the absence of mammalian metabolic activation from rat liver enzymes in this study, and thus, was not mutagenic agent at the dose levels tested (1, 5, 25, 125, & 325 ug/plate).

Evaluation:

The test design of the mutagenesis study by using the agar overlay technique(Ames et al,1973a) was not conducted according to the accepted procedures of Samonella/mammalian microsome mutagenicity test (Ames et al, 1975) for general mutagenesis screening purpose, and hence, the results and their interpretations are unacceptable. The following inadequacies in performing the Ames test were noted:

1. The tester strains of Salmonella typhimurium (TA1535 &TA1538) selected in this study was inadequate for the general mutagenesis screening purpose. At the present time, the three standard tester strains of S. typhimurium (TA 1535, TA 1537, & TA 1538) which contain deep rough character (rfa) and uvrB deletion should be used in combination with the two new R factor strains (TA98 & TA100) in order to detect various mutagens more effectively.

2. The assay was not conducted with a mammalian S9 activation system. Bacteria should be exposed to the test substance both in the presence and absence of an appropriate metabolic activation system. The most commonly used system is a cofactor supplemented postmitochondrial fraction prepared from the livers of rodents treated with the enzyme inducing agents.

3. Individual numerical data for checking the tester genotypes were not given. The specific procedures used to confirm deep-rough character which results in adeficient lipopolysaccharide ~~and~~ and ultraviolet sensitivity of the tester strains should be included.

4. The upper limit of the test concentration was not properly selected according to the cytotoxicity data for this study. Cytotoxicity may be evdenced by a reduction in the number of spontaneous revertants of the treated cultures.

5. *The interpretation of results was not clear and must be clarified. A test compound which produces neither a statistically significant dose-related increase in the number of revertants nor a statistically significant and reproducible positive response at any one of the test points is considered non-mutagenic in this system.*

TABLE A
GENERIC DATA REQUIREMENTS FOR Atrazine

Data Requirement	Composition	1/ Use Patterns	2/ Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology:					
ACUTE TESTING:					
81-1 - Oral LD_{50} - Rat	TGAI	A, B, G,	Yes	00024706 00027097 00024727	No
81-2 - Dermal LD_{50}	TGAI	A, B, G;	Yes	00027097	No
81-3 - Inhalation LC_{50} - Rat	TGAI	A, B, G,	Yes	Greear	No
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI		No	Greear	No
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding - Rodent, Non-rodent	TGAI		No		No
82-2 - 21-Day Dermal	TGAI		No		No
82-3 - 90-Day Dermal	TGAI		No		No
82-4 - 90-Day Inhalation - Rat	TGAI		No		No
82-5 - 90-Day Neurotoxicity-Hen/Mammal	TGAI		No		No

1/ Compositions: TGAI = Technical grade of the active ingredient.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than _____.

TABLE A
GENERIC DATA REQUIREMENTS FOR Atrazine

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?3/
§158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: Rodent and Non-rodent	TGAI	A, B, G	rodent - no non rodent - no	00059211 00059213	Yes Yes
83-2 - Oncogenicity Study - 2 species: Rat and Mouse preferred	TGAI	"	rat - no mouse - no	00059211 None	4/Yes 4/Yes
83-3 - Teratogenicity - 2 species	TGAI	"	(mice) no (rat) yes	00023558 00038041	Yes No
83-4 - Reproduction, 2-generation	TGAI	"	rat - no	00024471	Yes
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	"	Ames- partial	00060642	5/Yes
84-2 - Chromosomal Aberration	TGAI		no		
84-2 - Other Mechanisms of Mutagenicity	TGAI		no		

1/ Composition: TGAI = Technical grade of the active ingredient.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than _____

4/New IBT studies have been submitted, but have not been included in this document because they have not been reviewed.

5/Additional mutagenicity studies other than Ames listed in Reg. 158

TABLE A
GENERIC DATA REQUIREMENTS FOR Atrazine

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?3/
§158.115 Toxicology (continued)					
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	A,B,G	partially	0080634	4/Yes
85-2 - Domestic Animal Safety	Choice		partially	0080632	
Acute testing (continued)					
81-4 Primary eye irritation rabbit	TGAI	A,B,G	yes	Greear	No
81-5 Primary dermal irritation rabbit	TGAI	A,B,G	yes	00027096	No

1/ Composition: PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than
4/ Data indicating the metabolites formed.

002917

Acute Oral Toxicity in Rats.
Consultol Labs. Ltd., Report #CL74:46:996E datedd April 1974.
MRID #00027097

Test Material:

Atrazine
95% a.i.

Animal Tested:

Wistar rats
5/sex/dose weighing 200 ± 2g

Methods:

Oral gavage followed overnight fasting. The test material was suspended in 0.5% aq. Tween 80 as 150 mg/ml. Animals observed for 14 days.

Results:

Signs of salivation, lethargy, by 3 hour; after 24 hour chromodacryorrhea.

Dosage (mg/kg)	Dead/Dosed Combined	% Mortality
1000	0/10	0
2000	2/10	20
3000	5/10	50
4000	9/10	90
5000	10/10	100

LD_{50} = 2850 (95% CL = 2317 - 3506) mg/kg for both sexes.

Core: Minimum data.

Acute Oral LD_{50} in rats with Atrazine.
Ciba-Geigy Limited, Basle, Switzerland. PH 2.635 Project No: Siss 4569. Dated: April 15, 1975. MRID: 00024706.

002917

Material tested:

Technical atrazine (G 30027) Batch No: Mg 6245

Animal tested:

Tif. RAI rats 6 to 7 weeks old, weighed 160 - 180 g.

Methods:

After fasting overnight, 5/sex/dose were administered by gavage as mixtures of 5, 10, 20 or 30% atrazine in 2% CMC. Observations lasted for 14 days. Food and water was provided ad lib.

Results:

Exophthalmos, dyspnea, sedation and ruffled fur were exhibited within 2 hr.

Dosage	Dead/Dosed at 14 days Males	Females
600 mg/kg	0/5	0/5
1000	1/5	2/5
1290	0/5	3/5
1670	2/5	2/5
3170	5/5	1/5
4640	5/5	5/5
6000	5/5	5/5

LD_{50} = 1869 (1405-2487) mg/kg for both sexes by probit analysis.

Core:

Minimum. Purity not stated but known to be 95% a.i. or greater.

Acute Oral LD_{50}.- Atrazine in mouse.
Ciba-Geigy Limited, Basle, Switz. PH 2635. MRID:00024707.
Dated: April 7, 1975. Project No. Siss 4569.

002917

Test Material:

Technical atrazine (G 30027) Batch No. mg 6245 (purity not stated).

Animal Tested:

Tif. MAG mice 30/sex. Aged 5-10 weeks and weight of 20-30g.

Methods:

After being fasted over night treatment was by gavage with 20 or 30% mixture suspended in 2% CMC. Food and water were provided ad lib. Observed for 14 days.

Results:

Sedation , ruffed fur, dyspnea occurred by 2 hr. Sedation was more severe at higher doses.

Dosage	Dead/Dose at 14 days Male	Females
1670	0/5	0/5
2780	0/5	1/5
3590	3/5	1/5
4640	3/5	3/5
5200	4/5	4/5
6000	5/5	5/5

LD_{50} = 3992 (95% CL 3557 - 4479 mg/kg) probit analysis

Core:

Minimum data - no purity given but known to be 95% a.i. or greater.

002917

Acute Dermal Toxicity. - LD_{50} rats.
Consultox Labs Ltd. Report #CL 74:46:996E. Dated: April, 1974. MRID: 00027097.

Test Material:

Atrazine - 95% a.i.

Animal Tested:

Wistar rats 5/sex

Method:

2000 mg/kg was applied to the bare back skin of the rat. Hair was electrically clipped the night before testing. Test material was suspended in 0.5% aq. Tween 80, applied evenly and covered (occluded) by foil lined adhesive tape. Contact was for 24 hr. then the area was washed with detergent and H_2O. Observation was for 14 days.

Results:

No toxicity was observed, no deaths at 2000 mg/kg.

LD_{50} > 2000 mg/kg for both sexes.

Core: Minimum data. Adequate to show the dermal LD_{50} was greater than 2000 mg/kg.

002917

Primary Skin Irritation - Rabbits
Hazleton Laboratories America, Inc.
Project #915-102 Dated: March 5, 1975
MRID: 00027096

Material Tested:

Atrazina Tecnia (Atrazine technical) (assumed by Hazleton to be 100% active ingredient).

Animal Tested:

New Zealand White rabbits from Dutchland Laboratory Animals Inc., Denver, Penna. (Sex not stated).

Methods:

6 rabbits with backs clipped were tested at 2 sites on each 1 site was unabraded and the other was abraded. After moistening w/tap H_2O, 0.5g of test material was placed on each site. The sites were covered with gauze and a binder was applied. Animals remained in stocks for 24 hr. After 24 hr. exposure the test material was rinsed off w/tap H_2O. Readings were by the Draize method.

Results:

Reading at 24 and 72 hr. post application revealed 0 irritation.

Core:

Minimum. No purity stated, but known to be 95% a.i. or greater.

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.

2-Year Chronic Feeding Study in Dogs with Atrazine 80W.
Woodard Research Corp., Oct. 27, 1964.
Submitted 7/29/66.
MRID# 00059213

002917

Material Tested:

Atrazine 80W (purity unknown).

Animal Tested:

Purebred beagles from R.E. Sanders Corp, Richmond, Va. and Animals for Research, Lorton, Va. No age given. Acclimated for 3 weeks.

Methods:

4/sex/dose were given 0, 15, 150 or 1500 ppm in the diet and were dividually housed, given food once a day during the week, and double portions on Saturday and none on Sunday. At week 35 the beef supplement was halved. Due to the initial addition of beef (90g) the ppm values were 10.3, 103, 1030 ppm for the different groups. From 36 weeks to the termination the ppm values were 14.10, 141.5, and 1415.

Physical exams were made weekly. Food consumption, clinical effects and behavioral changes were checked daily. The animals were given the antihelmenthic, tetrachlorethylene at 58 and 85 weeks.

Blood values for ESR, Hct, Hgb. and WBC (differential) were obtained. Clinical chemistry values for BUN, SAP, and SGOT plus urinalyses were obtained on weeks 4, 8, 13, 22, 26, 39, 53, 65, 78, 91, 104. Thirty different tissues including prostate and or uterus were observed histologically.

Results:

No deaths occurred in the study. Wt. losses were noted in both males and females at 1500 ppm but not at lower dosages excepting 1 male at 15 ppm. An LEL for this effect is 1500 ppm and NOEL = 150 ppm (141.5 ppm).

Clinical signs:

Sacral area and rear limb muscular tremors occurred at 1500 ppm in 5/6 animals after 6 months. One male (150 ppm) experienced severe neuromuscular spasms. Watery lacrimation occurred in 3/6 high dose, 3/6 mid dose and 2/6 low dose. LEL = 15 ppm (LDT) (14.1 ppm).

At the highest dosage (1500 ppm) a reduction in food intake and variability in Hct and Hgb values with time are seen. Blood chemistry and urinalysis results were not markedly different from controls.

Relative organ wts. appear to be increased in thyroids of females at 1500 ppm; increased for hearts of females at 1500 and 150 ppm. Liver wts are increased in females at 1500 ppm and 150 ppm while adrenals appear enlarged at 1500 ppm.

Ovaries, appear enlarged at 1500 ppm while testes are equivocally decreased in wt. at 1500 ppm. Prostatic wts, appear slightly decreased at 1500 ppm while uterine wts. are increased. Brain wts. appear to be slightly increased as does the pituitary at 1500 ppm in females.

Comment:

With the changes seen in pigmentation of the spleen (the RBC scavenging organ) one might suspect that the Hgb-Hct changes to be compound induced. However, upon closer scrutiny, one notes changes in Hct which are in obvious error in conjunction w/Hgb. i.e. the MCHC. Time sequences showing marked changes in all groups suggest poor feeding/watering practices and/or poor quality control of methodolgy in Hgb-Hct analysis.

Conservatively: For increased relative organ wts. a NOEL for liver and heart in females is 15 ppm. A NOEL for increased/decreased relative organ wts. of adrenals, prostate and testes in males is 150 ppm.

Toxicology Branch considers this study to be supplementary due to the above questions on hematology and lack of stated purity. These may be rebutted with submission of the daily individual animal feeding and observation records, methodology of hematology and statements of sample purity used.

The question of the watery lacrimation should be addressed by the registrant since that is considered a cholinergic effect as are the neuro-muscular effects reported unless other causes were apparent but unreported.