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

JUN 6 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Peer Review of Atrazine

From: Judith W. Hauswirth, Ph.D. *Judith W. Hauswirth 3/1/88*
Section Head, Section VI
Toxicology Branch/HED (TS-769C)

To: Robert Taylor/Clare Grubbs
Product Manager #25
Registration Division (TS-767C)

The Toxicology Branch Peer Review Committee met on September 10, 1987 to discuss and evaluate the weight of the evidence on atrazine, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Theodore M. Farber

Theodore M. Farber

William Burnam

Wm F Burnam

John A. Quest

John A. Quest

Esther Rinde

Esther Rinde

Richard Levy

Richard Levy

Donald Barnes

Donald Barnes

Judith W. Hauswirth

Judith W. Hauswirth

2. Peer Review Committee Members in Absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Reto Engler

Reto Engler

Robert Beliles

Robert Beliles

Anne Barton

Anne Barton

Diane Beal

Diane Beal

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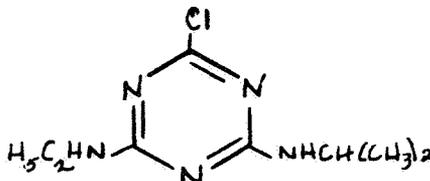
B. Material Reviewed:

The material available for review consisted of a package prepared by Dr. Hauswirth containing data evaluation of a rat oncogenicity study, an interim report on a IARC rat study, statistical analysis of rat mammary gland tumor data, historical control data and Toxicology Branch "one-liners".

C. Background Information:

Atrazine is a selective herbicide used for season-long weed control in corn, sorghum and other crops. It is used at the highest rate for non-selective weed control in noncropped areas.

The chemical name of atrazine is 2-chloro-4-ethylamino-6-isopropylamino-S-triazazine. The structure is as follows:



A peer review of the atrazine data was requested by the Office Director of OPP in the absence of a mouse oncogenicity data because of a possible ground water contamination problem with atrazine.

D. Evaluation Oncogenicity Studies:

1. Rat Oncogenicity Study - Ciba Geigy

Ref.: Twenty-four month combined chronic oral toxicity and oncogenicity study in rats utilizing atrazine technical. Mayhew, DA, Taylor, GD, Smith, SH and Banas, DA. Conducted by American Biogenics Corporation for Ciba-Geigy Corp. Study No. 410-1102. Accession No. 262714-262727. April 29, 1986.

Sprague-Dawley [Cr1:COBS CD(SD)BR] rats were started on diets containing atrazine at 37-38 days of age. The dosage levels of atrazine used for the chronic toxicity and oncogenicity portions of the study were 0, 10, 70, 500 and 1000 ppm. Twenty rats per sex per group were used for the chronic toxicity group, i.e. rats used to measure blood parameters and clinical chemistries and urinalysis. Fifty rats per sex per group were used for the oncogenicity study and were maintained on diets for 24 months. An additional 10 rats per sex were placed on control and high dose (1000 ppm) diets for a twelve month interim sacrifice and another 10 per sex (control and high dose, 1000 ppm) for a 13 month sacrifice (the 1000 ppm group was placed on control diet for one month prior to sacrifice). The total number of animals/sex in the control and HDT groups was 90 and 70 for the 10, 70, and 500 ppm groups. Histopathology was performed on all animals.

The incidence of relevant neoplastic pathology seen in this study can be found summarized in Table 1.

Incidence of Relevant Neoplastic Pathology

Tissue	Dose (ppm)				
	0	10	70	500	1000
<u>Females</u>					
Mammary Gland					
fibroadenoma ¹	29/89** (32)	29/65(45)	36/70(51)	39/68(57)	45/88** (51)
fibroadenoma ² (only)	20/79(25)	24/65(37)	21/69(30)	21/66(32)	19/75(25)
adenoma ¹	1/57(2)	0/51(0)	1/57(2)	1/54(2)	2/50(4)
adenoma ² (only)	1/45(2)	0/43(0)	0/49(0)	0/42(0)	1/33(3)
adenocarcinoma plus carcino- sarcoma ³	15/90** (17)	16/68(23)	27/70* (39)	27/68* (40)	45/90** (50)
TBA ⁴	36/90** (40)	40/68(59)	47/70(67)	48/68(71)	65/90** (72)
<u>Males</u>					
Testes					
interstitial cell tumor	1/58* (2)	3/59(5)	2/59(3)	2/60(3)	7/64* (11)

Note: Significance of trend denoted at Control.
 Significance of pairwise comparison with control denoted at Dose level.
 *p<0.05, **p<0.01.

- 1 Including animals that may also have a carcinoma
- 2 Excluding animals that may also have a carcinoma
- 3 Two animals in the high dose group had carcinosarcomas.
- 4 Total tumor bearing animals - # of animals with at least one type of mammary tumor.

Tumors were analyzed by Peto Prevalence since survival differences were observed in both male and female rats.

The following tumor incidences were statistically significantly elevated in atrazine treated rats:

1. In females:
 - a. The incidence of fibroadenomas (including animals that may also have a carcinoma) was increased at the high dose. This increase was associated with a significant dose-related trend;
 - b. The incidence of adenocarcinomas (including two rats at the high dose with carcinosarcomas) was increased at 70, 500, and 1000 ppm. This increase was associated with a significant dose-related trend; and
 - c. The total number of rats with at least one type of mammary tumor was increased at the high dose. This increase was associated with a significant dose-related trend.

2. In males, the incidence of testicular interstitial cell tumors was increased at the high dose. This increase was associated with a significant dose-related trend (driven by a high dose effect).

There were also indications of reduced latency of mammary gland adenocarcinomas, since at the 12 month interim kill there were 0/20 adenocarcinomas in the control group and 6/20 in the high dose group.

The historical control range for fibroadenomas was reported by the performing laboratory to be 36-48%. The incidence of fibroadenomas at the high dose in the atrazine study was just outside of the historical control range. The incidence of adenocarcinomas was outside of the historical control range (3-19%) for all treated groups. The number of animals with mammary gland tumors of any type was also outside of the historical control range (28-51%) for all treated groups. The incidence of testicular interstitial cell tumors was within the historical control range (0-12%).

The Committee felt that the MTD had been exceeded in female rats at 1000 ppm based upon a statistically significant increase in mortality, a 26% decrease in body weight gain at week 13 of the study, and non-neoplastic pathology including a significant increase in centrilobular necrosis of the liver and bone marrow myeloid hyperplasia. The MTD was reached at 500 ppm based upon body weight gain decrement of 18% at week 13 and an increase in bone marrow myeloid hyperplasia.

In male rats, the MTD was exceeded at 1000 ppm based upon a 25% decrease in body weight gain at week 13 of the study which remained at this same percentage decrement for the remainder of the study. Other non-neoplastic pathology seen at 1000 ppm was mammary gland acinar hyperplasia, kidney pelvic calculi, epithelial hyperplasia of the prostate and degeneration of muscle. As was seen in females, the MTD was reached at 500 ppm due a 17% decrease in body weight gain.

2. Chronic Feeding/Oncogenicity Study in Fischer 344/LATI rats conducted for IARC:

Since the full report of this study was not available for the Committee's review it was not considered in the weight-of-the-evidence for atrazine.

E. Additional Toxicology Information:

1. Mutagenicity:

Atrazine was negative in the following acceptable assays used to determine mutagenic potential: Ames Salmonella assay, rec assay in Bacillus subtilis, reverse mutation in E. coli and unscheduled DNA synthesis assay in rat hepatocytes.

2. Reproduction and Teratology:

Atrazine is not teratogenic in the rat or rabbit. In the rat, an increased incidence of runts was seen at all dosage levels (NOEL<10mg/kg). In the rabbit, administration of atrazine (75 mg/kg) was associated with

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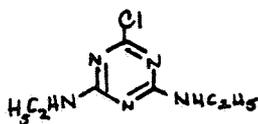
increased resorptions, reduced fetal weights for both sexes, and increases in delayed ossification. In an unacceptable 3-generation reproduction study, no adverse reproductive effects were seen up to 1000 ppm, the highest dose tested.

3. Metabolism:

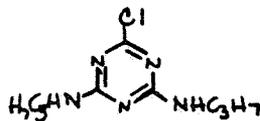
When a single oral dose of ^{14}C -atrazine was given to Long-Evans rats, 52-57% was excreted in the urine and 12-15% in the feces within 48 hours. Less than 0.1% was excreted in expired CO_2 . The highest tissue residues were found in the liver and kidney. No metabolite identification was done in this study.

4. Structure Activity Relationship:

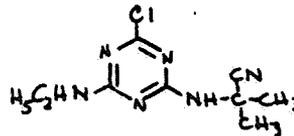
Atrazine is structurally related to simazine, cyanazine, propazine, and terbutryn, the structures of which are shown below.



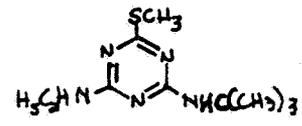
Simazine



Propazine



Cyanazine



Terbutryn

a. Simazine

Simazine is rapidly metabolized in the rat. Eighty-six percent of the labelled compound is excreted within 14 hours in the urine and feces. Oncogenicity studies are currently underway.

b. Cyanazine

In rats, 89% of labelled cyanazine is eliminated within 4 days, 42% in urine and 47% in feces. The major metabolic pathways are dechlorination and deethylation. Cyanazine did not produce chromosomal aberrations in bone marrow of mice and did not appear to be oncogenic to CD mice. Adequate oncogenicity studies the rat are not available; however, a new study in the rat is presently being conducted.

c. Propazine

Forty-two percent of ^{14}C -propazine was eliminated in the urine and 28% in the feces. Mostly unchanged propazine was found in the feces. Hydroxypropazine was identified both in urine and feces.

Propazine has been found to be positive for mutagenicity in V79 Chinese hamster cells both with and without metabolic activation. However, the response was weaker in the presence of metabolic activation. It was negative in a nucleus anomaly assay and in a DNA repair assay in rat hepatocytes.

Propazine was negative for oncogenicity in the CD-1 mouse but caused a statistically significant increase in mammary gland tumors in female CD rats. Propazine has recently been presented to the Toxicology Branch Peer Review Committee for classification of oncogenic potential and has been classified as a category C oncogen.

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d. Terbutryn

Eighty-five percent of ring-labelled ^{14}C -terbutryn is excreted within 72 hours in the urine (39%) and feces (46%) of rats. The major metabolic pathways are desulfuration, N-deethylation and S-demethylation.

Terbutryn is not mutagenic in the Ames Salmonella assay and the micronucleus assay and does not cause chromosomal aberrations in vivo in hamsters.

Terbutryn is negative for oncogenicity in the CD-1 mouse. When administered in the diet to female Charles River CD rats, terbutryn induced a statistically significant increase in combined mammary gland adenomas and adenocarcinomas and in combined hepatocellular adenomas and carcinomas. In males, terbutryn induced an increase in combined thyroid follicular cell adenomas and carcinomas and in testicular interstitial cell adenomas. The Toxicology Branch Peer Review Committee has classified terbutryn as a category C oncogen.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Atrazine to be of importance in a weight of the evidence determination of oncogenic potential.

1. Administration of Atrazine to female Sprague-Dawley rats was associated with a statistically significant increase in mammary gland fibroadenomas at 1000 ppm, in mammary gland adenocarcinomas (including two carcinosarcomas at the HDT) at 70, 500, and 1000 ppm, and in total mammary gland tumor bearing animals at 1000 ppm. Each of these increases was associated with a statistically significant dose-related trend and was outside of the high end of the historical control range. In addition, there was evidence for decreased latency for mammary gland adenocarcinomas at the 12 month interim sacrifice.

2. A statistically significant increase in testicular interstitial cell tumors was seen in male Sprague-Dawley rats at 1000 ppm; however, this increase was within the historical control range.

3. In both males and females the highest dose tested exceeded the MTD based upon body weight gain decrement in males and increased mortality, liver necrosis, and bone marrow myeloid hyperplasia in the females. The MTD was reached in males and females at 500 ppm.

4. Testing for oncogenicity in the mouse is underway but has not been completed.

5. Atrazine was negative in three acceptable assays for mutagenicity.

6. Atrazine was not teratogenic in rats or rabbits and caused no reproductive toxicity in rats up to 1000 ppm.

7. Complete metabolism studies are not available; however, atrazine has been shown to be excreted mainly in the urine.

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8. Atrazine is structurally related to simazine, cyanazine, propazine and terbutryn. Both propazine and terbutryn have been found to induce mammary tumors in rats and have been classified as category C oncogens by the Toxicology Branch Peer Review Committee. In addition, cyanazine, propazine and terbutryn have been found to be negative for oncogenicity in the CD-1 mouse.

G. Classification of Oncogenic Potential:

The Committee concluded that the data available for atrazine provided limited evidence for the oncogenicity of the chemical in rats. According to EPA Guidelines for Carcinogen Risk Assessment (CFR, September 24, 1986), the Committee classified Atrazine as a Category C oncogen (possible human carcinogen).

That is, administration of atrazine to Sprague-Dawley rats was associated with an increased incidence of mammary gland fibroadenomas and adenocarcinomas in female rats. The increase in testicular interstitial cell tumor seen at the high dose in male rats was not considered to be treatment-related by the Committee since the incidence was within the historical control range and was seen at a dosage level that exceeded the MTD. Atrazine has not shown any mutagenic activity in any assays available to the Committee; however, it is structurally related to propazine and terbutryn which induce mammary gland tumors in female rats and have been classified as category C oncogens.

The classification of atrazine as a possible human carcinogen was tentative pending receipt of an acceptable oncogenicity study in the mouse. The Committee concluded that a quantitative risk assessment should be performed due to (1) the induction of malignant mammary gland tumors and possible decreased latency for their appearance and (2) positive SAR data for mammary gland tumors.

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