10/30/91

PEER REVIEW FILES

CHEMICAL NAME: Simazine
CASWELL NO.: 740
CAS NO.: 122-34-9
REVIEWER: Spencer

CURRENT AGENCY DECISION

C; 1.2 x 10-1 (HED)
C (SAP)

TUMOR TYPE / SPECIES

Pituitary gland carcinomas; Mammary gland carcinomas; Sprague-Dawley rats (F)

REVIEWER PEER REVIEW PACKAGE	PEER REVIEW MEETING DATE	PEER REVIEW DOCUMENTS	PEER REVIEW CLASSIFICATION
5. / /	5. / /	5. / /	5.
4. / /	4. / /	4. / /	4.
3. / /	3. / /	3. / /	3.
2. 10/18/89	2. 10/25/89	2. 05/24/90	2. C; 1.2 x 10-1
1. 05/04/89	1. 05/17/89	1. 07/31/89	1. C(q)

	SAP MEETING	SAP CLASSIFICATION
	2. 09/28/89	2. C
	1. 07/08/85	1.

QUALITATIVE RISK ASSESSMENT DOCUMENT	QUANTITATIVE RISK ASSESSMENT DOCUMENT	GENETIC TOXICITY ASSESSMENT DOCUMENT
3. / /	3. / /	1. / /
2. / /	2. / /	
1. 05/05/89	1. 05/13/89	

MISCELLANEOUS:

#PR-008512

1 OF 67

CD8512

Peer Review Documents

FILE [illegible] 008512

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

008512

MAY 24 1990

MEMORANDUM

SUBJECT: Peer Review Meeting on Simazine Following SAP Review.

FROM: Henry Spencer, Ph.D. Hen Spencer 4/26/90
Review Section II
Toxicology Branch I
Health Effects Division (H7509C)

TO: Jude Andreasen
Special Review Branch
Special Review and Reregistration Division (H7508C)

The Health Effects Division (HED) Peer Review Committee met on October 25, 1989, to reconsider the evaluation of simazine following the presentation to the Scientific Advisory Panel (SAP) (Panel Meeting September 28, 1989.

A. Peer Review Committee Individuals in Attendance: (Signatures indicates concurrence unless otherwise stated).

Penelope A. Fenner-Crisp	Penelope A. Fenner-Crisp
Esther Rinde	Esther Rinde
John D. Quest	John A. Quest
Kerry Dearfield	Kerry Dearfield
Karl Baetcke	Karl J. Baetcke
Reto Engler	Reto Engler
Bill Burnam	Wm L Burnam
Bill Sette	Bill Sette
Marion Copley	Marion Copley
Julie Du	
Rich Levy	Richard Levy

2. Scientific Reviewer: (non-panel member responsible for data).

Henry Spencer

3. Peer Review Members in Absentia: (Members who were unable to attend the discussion, signatures indicate concurrence unless stated).

Richard Hill

Yin-Tak Woo

Robert Beliles

Marcia Van Gemert

George Z. Ghali

4. Other attendees: (Observers).

Hugh Pettigrew

Albin Kocialski

B. Conclusion:

The SAP agreed with the Peer Review of simazine classifying it as a C carcinogen based on tumors in females in one species (rat). The SAP also volunteered that a Q_1* should not be used to quantitate risk for the chemical.

However, the Peer Review Committee in attendance considered it appropriate to use the Q_1* to quantitate risk until the registrant provides data showing hormonal induction of tumors. This classification is consistent with action on similar chemicals, i.e., atrazine. In addition the Peer Review Committee recommended that the Agency ask for further mutagenicity testing to include a mouse lymphoma assay, an in vivo micronucleus assay and a cell transformation assay.

The Weight of the Evidence used to determine the classification remains the same as excerpted below from the original peer review document, dated July 31, 1989 by Esther Rinde, Ph.D

"F. Weight of Evidence Considerations:

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

1. Simazine was not associated with increases in neoplasms when fed in the diet to CD-1 mice, at doses up to 4000 ppm. The study was considered to have been adequately conducted.

2. Simazine was associated with statistically significant increases in carcinomas of the pituitary gland (at the HDT) and mammary gland (at the mid (100 ppm) and highest dose) in the female Sprague-Dawley rat, when fed in the diet at doses up to 1000 ppm. The incidence of mammary gland tumors at the HDT was well outside the range reported for historical controls at the testing facility. The incidence of pituitary gland tumors was just outside the historical control range; however, it exceeded (considerably) the incidences reported for 6 out of 7 studies.

3. The pituitary tumors in the female rats were fatal with a possibly accelerated onset, and the mammary carcinomas also contributed to the increased mortality at the HDT, according to the study authors.

4. Although the HDT may have exceeded the MTD, the mid-dose was well below, and the mammary tumors in the female rat were statistically significantly increased at both the mid and high dose. There was also too great an interval between the mid and high doses: 100 and 1000 ppm, respectively.

5. While a hormonal influence was suggested based on the pituitary and mammary gland tumors, supporting evidence was not presented.

6. There was some evidence of genotoxicity.

7. The mammary tumor response is consistent with that seen with other triazines. Both Atrazine and Propazine, triazines with structures closely related to Simazine, were associated with mammary gland tumors in the female rat.

8a. The incidence of kidney tubule adenomas at the HDT in the female rat, although not statistically significant, exceeded that reported for historical controls (zero) in all seven studies at the testing facility. While this tumor incidence fits the NTP definition of a "rare" tumor (≤1% incidence), Dr. Slaughter offered, that based on his experience, the historical incidence of rat kidney tumors is more accurately defined as "uncommon").

8b. The incidence of kidney tubule carcinomas in male rats was less clearly defined (because of sporadic occurrences of the same tumor in control animals).

G. Classification of Oncogenic Potential:

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying a carcinogen were considered.

The Committee evaluated all of the evidence listed in part F (above) and concluded that Simazine should be classified as a Category C Oncogen (possible human carcinogen), based on evidence in one species, one sex. The Committee also called for a quantitative risk assessment for Simazine, quantification to be based on the mammary tumors in the female rat. The arguments for quantification were given as follows:

1a. The tumors in both the pituitary and mammary glands of the female rat were malignant.

1b. Pituitary tumors in female rats were fatal with a possible accelerated onset (analysis to be provided).

2a. Mammary tumors were statistically increased at 2 doses, albeit one above the MTD; however, there was too large a spread between the mid and high doses.

2b. Evidence of progression was suggested by mammary hyperplasia at the HDT, which correlated with tumors at that dose.

3. There was no supporting evidence for demonstrating an hormonal influence.

4. There was equivocal evidence of kidney tumors ("rare" or at least "uncommon" tumor type) in both sexes.

5. SAR was strongly supportive. Other closely-related triazines (Atrazine and Propazine) were also associated with mammary gland tumors in the female rat.

6. There was some evidence of genotoxicity."

SIMAZINE Female Rat Tumor Rates:

	Dose			
	0	10	100	1000
Mammary Gland				
Adenoma only	1/90	0/80	1/80	2/80
Fibroadenoma only	21/90	18/80	10/80	19/80
Adenoma and/or fibroadenoma only	23/90	20/80	11/80	21/80
Carcinoma	16/90	13/80	20/80	40/80
Adenoma/Fibroadenoma/ Carcinoma	39/90	33/80	31/80	61/80
Pituitary				
Adenoma only	73/90	57/80	63/79	61/80
Carcinoma	1/90	3/80	0/79	6/80
Adenoma and/or Carcinoma	74/90	60/80	63/79	67/80
Kidney Tubules				
Adenomas	0/90	0/80	0/80	2/80

7/31/89

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FILE COPY

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

JUL 31 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Simazine

FROM: Esther Rinde, Ph.D. E. Rinde 6/16/89
Science Analysis and
Coordination Branch
Health Effects Division (TS-769c)

TO: James Yowell
Product Manager #23
Registration Division (TS-767c)

The Health Effects Division Peer Review Committee met on May 17, 1989 to discuss and evaluate the weight-of-the-evidence on Simazine with particular reference to its oncogenic potential.

A. Individuals in Attendance:

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

Penelope A. Fenner-Crisp	Penelope A. Fenner-Crisp
William L. Burnam	
Reto Engler	
Edwin R. Budd	Edwin R. Budd
Marcia Van Gemert	
Karl Baetcke	
Marion Copley	
Kerry Dearfield	
Richard Levy	

A. 1. Peer Review Committee (contd.)

John Quest — John A. Quest

Esther Rinde — Esther Rinde

William Sette — William Sette

Lynnard Slaughter — L. J. Slaughter

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Henry Spencer — Henry Spencer

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Richard Hill

Robert Beliles — Robert P Beliles

George Ghali — G. Ghali

4. Other Attendees:

Esther Saito (HED) was also present.

B. Material Reviewed:

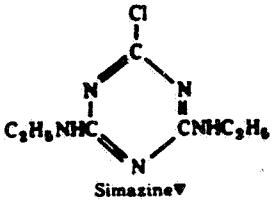
The material available for review consisted of DER's, one-liners, and other data summaries prepared by Dr. Henry Spencer; tables and statistical analysis by Dynamac. The material reviewed is attached to the file copy of this report.

C. Background Information:

Simazine is one of several triazine compounds which are used in agriculture as herbicides to control annual grasses and broadleaf weeds in corn, alfalfa, orchards of cherries, peaches, citrus, apples, pears and asparagus as well as ornamentals and nursery stock. Simazine is also registered for use in controlling algae in ponds. Little of the Simazine parent chemical is found as residues in food and feed crops.

Following the Data-Call-In Notice of the first Registration Standard of 1984, new chronic toxicity studies were received; these were evaluated by the Onco Peer Review Committee.

Structure of Simazine:



Simazine▼

D. Evaluation of Oncogenicity Evidence for Simazine:

1. CD-1 Mouse Oncogenicity Study

Reference: Hazelette, JR and JD Green: "Simazine Technical; 95-week Oral Toxicity/Oncogenicity Study in Mice.", April 4, 1988. Accession/MRID Number: 406144-04, Lab. Study Number: 842121. Testing Facility: Pharmaceuticals Division, Ciba-Geigy Corp., Summit, NJ.

Simazine technical was administered in the diet to groups of 60 male and 60 female Crl:CD1(ICR)BR mice at 0 (control), 40, 1000 or 4000 ppm for 95 weeks.

There were no increases in neoplasms reported for any dosed group.

There was no evidence of a compound-related effect on survival or target organ toxicity.

The dosing was considered to be adequate for assessing the oncogenic potential of Simazine, based on body weight gain depressions of 14% in males and 19% in females seen at 1000 ppm.

D. Evaluation of Oncogenicity Evidence (contd.)

2. Sprague-Dawley Rat Oncogenicity Study

Reference: McCormick, CC and AT Arthur: "Simazine-Technical: 104-Week Oral Chronic Toxicity and Carcinogenicity Study in Rats." , April 12, 1988. MRID Number: 406144-05. Study Number: 2-0011-09. Testing Facility: Pharmaceuticals Division, Ciba-Geigy Corp., Summit, NJ.

Simazine technical was administered in the diet to groups of 50 male and 50 female rats at 0 (control), 10, 100 or 1000 ppm for 2 years. Additional groups (30-40/sex/dose) were also treated.

> In female rats there was a statistically significant increase in mortality, and in male rats there was a statistically significant decrease in mortality, with increasing doses of Simazine.

Neoplastic lesions which occurred with statistically significant increases were reported as follows:

In female rats, there was a statistically significant dose-related trend ($p<.01$) for mammary gland carcinomas and combined adenomas/fibromas/carcinomas; however, when the shortened life-span of the female rats was included in the statistical evaluation, the incidences of carcinoma alone at both the 100 and 1000 ppm (HDT) dosage groups were statistically significantly increased as well ($p<.05$ and $p<.01$, respectively). The upper limit of the historical control incidence reported for mammary carcinoma (Table 1) was exceeded at 100 ppm, and greatly exceeded at 1000 ppm (HDT). The incidence of cystic glandular hyperplasia in the mammary gland was statistically significantly increased at the HDT, which correlates with the observed high tumor incidence at that dose.

There was a statistically significant dose-related trend for kidney tubule adenomas ($p<.05$); however (as in the case of the male rats) tumors occurred only at the HDT and the incidence (3.6%) was not statistically significant by pairwise comparison with that in the concurrent control. The incidences for adenomas and/or carcinomas reported for historical female controls (Table 1) were zero in all 7 studies (Table 1).

TABLE 1

HISTORICAL CONTROL TUMORINCIDENCE DATA
NUMBER OF TUMOR-BEARING ANIMALS - SPRAGUE-DAWLEY RATS

Submitted by Ciba-Geigy

COMPOUND	83 A	JAN 83 B	NOV 83 C	84 D	85 E	85 F	85 G
SITE: NEOPLASM	NUMBER OF NEOPLASMS						
MAMMARY GLAND (FEMALES):	(65)	(60)	(70)	(70)	(60)	(70)	(70)
NUMBER OF SITES EXAMINED							
ADENOMA	6	6	8	2	5	3	2
FIBROADENOMA	18	16	26	21	12	23	22
ADENOMA/FIBROADENOMA (COMBINED)	22	18	30	22	15	25	23
ADENOCARCINOMA	7	4	5	11	9	15	14
ALL MAMMARY TUMORS (COMBINED)	25	22	34	30	20	34	32
PITUITARY GLAND (FEMALES):	(63)	(60)	(69)	(69)	(60)	(70)	(70)
NUMBER OF SITES EXAMINED							
ADENOMA	52	49	55	59	49	62	62
CARCINOMA	0	2	2	2	6	2	1
ADENOMA AND CARCINOMA (COMBINED)	52	51	57	61	55	64	63
KIDNEY (MALES AND FEMALES):	(65/65)	(60/59)	(70/70)	(70/70)	(60/60)	(70/70)	(70/70)
NUMBER OF SITES EXAMINED	M F	M F	M F	M F	M F	M F	M F
ADENOMA	0 0	0 0	2 0	1 0	0 0	0 0	0 0
CARCINOMA	0 0	0 0	0 0	1 0	0 0	0 0	0 0
ADENOMA AND CARCINOMA (COMBINED)	0 0	0 0	2 0	2 0	0 0	0 0	0 0
ADRENAL GLAND (FEMALES):	(65)	(60)	(70)	(70)	(60)	(70)	(70)
NUMBER OF SITES EXAMINED							
ADENOMA	1	3	4	2	3	2	8
LIVER (MALES):	(65)	(60)	(70)	(70)	(60)	(70)	(70)
NUMBER OF SITES EXAMINED							
ADENOMA	0	2	0	2	10	4	1
CARCINOMA	0	1	1	6	2	1	0

D. Evaluation of Oncogenicity Evidence (contd.)

2. Sprague-Dawley Rat Oncogenicity Study (contd.)

In female rats, there were also statistically significant dose-related trends for adenomas, carcinomas and combined adenoma/carcinomas of the pituitary gland ($p<.01$). Pairwise comparisons were significant only for carcinomas at 1000 ppm ($p<.05$) and only when time adjusted, assuming fatal tumor context, to account for the effect of mortality disparity in the animals (the mortality in female rats was statistically significantly increased compared to controls at 100 and 1000 ppm). The incidence of pituitary gland carcinoma at 1000 ppm (HTD) only slightly exceeded the upper bound of the historical control range; however, it greatly exceeded the incidence reported in 6 out of 7 studies.

Tables 4, 5 and 6 (from the Dynamac "..Qualitative Risk Assessment...." 10/18/88, attached) summarize these findings; a fatal tumor analysis was performed on the female rat pituitary gland tumors, as described on pg. 8 of that memo.

Historical control tumor incidence data for Sprague-Dawley rats at the testing facility are given in Table 1.

In male rats, the incidences of liver tumors were statistically significantly increased for carcinoma and for combined adenoma/carcinoma at 100 ppm and 1000 ppm (HDT), respectively ($p<.05$); however, these incidences fell within the range reported for historical controls at the testing facility.

There was also a statistically significant dose-related trend for kidney tubule carcinomas ($p<.05$), and for combined adenoma/carcinoma ($p<.01$); however, tumors occurred only at the HDT and neither the carcinoma (3%) nor the combined adenoma/carcinoma (5%) incidence was statistically significant by pairwise comparison with that in the concurrent control (2% in both cases).

Tables 7 and 9 (from the attached Dynamac memo) present data for the tumor incidences (adjusted for mortality differences) in liver and kidney, respectively. The rationale for the tumor analysis is presented on page 8 of the Dynamac memo.

Table 4. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Female Mammary Gland Tumor Rates* and Peto Prevalence Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000	Historical Control Range
Adenoma Fibroadenoma	23/89 (26)	20/78a (26)	11/71 (15)	21/75 (28)	(27-37)
	p= 0.0689	p= 0.302	p= 0.177	p= 0.123	
Carcinoma	16/89 (18)	13/80 (16)	20/75b (27)	40/78 (51)	(7-21)
	p< 0.0001**	p= 0.4740	p= 0.0392*	p< 0.0001**	
Adenoma Carcinoma	39/89 (44)	33/80 (41)	31/75 (41)	61/78 (78)	
	p< 0.0001**	p= 0.4064	p= 0.2229	p< 0.0001**	

a First Adenoma observed at 48 weeks in dose 10 ppm and the first Fibroadenoma observed at 52 weeks in dose 0, 10, and 1000 ppm.

b First carcinoma observed at 48 weeks in dose 100 ppm.

Table 5. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Female Kidney Tubule Tumor Rates* and Cochran-Armitage Tre Test and Fisher's Exact Test

DOSE(PPM)	0.000	10.000	100.000	1000.000	Historical Controls
Adenoma	0/74 (0.0)	0/62 (0.0)	0/54 (0.0)	2/55c (3.6)	(all 0)
	p= 0.0062**	p= 1.0000	p= 1.0000	p= 0.1799	

c First Adenoma observed at 71 weeks in dose 1000 ppm. No carcinomas were coded.

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before the observation of the first tumor or animal not examined).

( ) Per cent

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with contr denoted at Dose level. * denotes p < 0.05 and ** denotes p < 0.01

TABLE 6. SIMAZINE, SPRAGUE-DAWLEY RAT Study--FEMALE Pituitary Gland Tumor Rates*, Fatal Tumor Analysis and Generalized K/W Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000	Historical Control Range
Adenoma	73/89	57/80	63/77 a	61/79	
	(82.0)	(71.2)	(81.8)	(77.2)	(80-89)
	p= 0.0013**	p= 0.9944	p= 0.0206*	p= 0.0030**	
Carcinoma	1/73	3/61	0/52	6/53 b	
	(1.4)	(4.9)	(0.0)	(11.3)	(0-10)
	p= 0.0010**	p= 0.2351	p= 0.4565	p= 0.0153*	
Adenoma Carcinoma	74/89	60/80	63/77	67/79	
	(83.1)	(75.0)	(81.8)	(84.8)	(83-92)
	p= 0.0005**	p= 0.8351	p= 0.0251*	p=0.0005**	

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before the first tumor or animals not examined).

( ) Per cent

a First Adenoma observed at 35 weeks in dose 100 ppm.

b First Carcinoma observed at 72 weeks in dose 1000 ppm.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p > 0.01$

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Table 7. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Male Liver Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000	Historical Control Range
Adenoma	1/88	2/79a	0/80	3/80	
	(1.1)	(2.5)	(0.0)	(3.8)	(0-17)
	p= 0.0824	p= 0.4594	p= 0.5238	p= 0.2752	
Carcinoma	0/88	2/79	4/80b	3/80	
	(0.0)	(2.5)	(5.0)	(3.8)	(0-9)
	p= 0.2169	p= 0.2223	p= 0.0496*	p= 0.1058	
Adenoma Carcinoma	1/88	4/79	4/80	6/80	
	(1.1)	(5.1)	(5.0)	(7.5)	
	p= 0.0643	p= 0.1519	p= 0.1554	p= 0.0449*	

a First Adenoma observed at 52 weeks in dose 10 ppm.
b First Carcinoma observed at 99 weeks in dose 100 ppm.

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before 52 weeks animals not examined).

( ) Per cent

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

Table 9. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Male Kidney Tubule Tumor Rates* and Peto Prevalence Test Results--

DOSE(PPM)	0.000	10.000	100.000	1000.000	Historical Control Range
Adenoma	0/51 (0)	0/46 (0)	0/48 (0)	1/57a (2)	(0-3)
	p= 0.0543	p= 1.0000	p= 1.0000	p= 0.5278	
Carcinoma	1/66 (2)	0/62 (0)	0/64 (0)	2/65b (3)	(0-1)
	p= 0.0332*	p= 0.1660	p= 0.1821	p= 0.2091	
Adenoma Carcinoma	1/66 (2)	0/62 (0)	0/64 (0)	3/65 (5)	(0-3)
	p= 0.0056**	p= 0.1410	p= 0.1721	p= 0.1087	

a First Adenoma observed at 92 weeks in dose 1000 ppm.

b First Carcinoma observed at 78 weeks in dose 1000 ppm

c The p values for Adenomas were calculated using the Cochran-Armitage Trend Test and Fisher's Exact Tes since the Peto Prevalence method collapsed to one interval.

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before the observation of the first tumor or animals not examined).

( ) Per cent

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

D. Evaluation of Oncogenicity Evidence (contd.)

2. Sprague-Dawley Rat Oncogenicity Study (contd.)

The Committee agreed that the highest dose exceeded the MTD for female rats, based on excess deaths and body weight gain reductions of 28-45% (days 7-728). The highest dose in males appeared to have exceeded the MTD, as well, based on body weight gain reductions of 27-36% (days 7-728). The Committee also felt that there was too great an interval between the mid and high doses (100 to 1000 ppm).

E. Additional Toxicology Data on Simazine:

1. Metabolism

Simazine exhibits increased binding affinity for red blood cells following oral dosing in the rat. Almost all of orally administered Simazine was excreted in the feces and urine 96 hours after administration to rats.

2. Mutagenicity

Three mutagenicity tests have been submitted in support of the registration for Simazine. Simazine was negative in an acceptable Salmonella assay using strains TA98, TA100, TA1535, TA1537 and TA1538, with and without activation. The other two tests were found to be unacceptable: a cytogenetics assay with cultured human lymphocytes and an unscheduled DNA synthesis (UDS) assay with primary rat hepatocytes. Therefore, of the three categories of mutagenicity testing, only the gene mutation category is minimally fulfilled with data gaps in the structural chromosomal aberrations and other genotoxic effects categories.

The negative Salmonella results are consistent with published literature and results with other s-triazine herbicides. However, it is reported in the literature that Simazine is positive for gene mutations in the mouse lymphoma assay (Waters et al., Basic Life Sci 21: 275-326, 1982), the Drosophila sex-linked recessive lethal assay (ibid; also reported by the U.S. EPA Gene-Tox Program), cell transformation in Syrian hamster embryo cells (reported by the U.S. EPA Gene-Tox Program), and plant cytogenetic assays (for review see Plewa et al., Mutat Res: 136 233-245, 1984). Simazine was also reported in the literature as being negative in several other assays including yeast assays, UDS with a human cell strain, sister chromatid exchanges and a mouse micronucleus (an unacceptable protocol) (Waters et al., 1982). It was also reported negative in two assays for aneuploidy (see Dellarco et al., Mutat Res 167: 149-169, 1986).

E. 2. Mutagenicity (contd.)

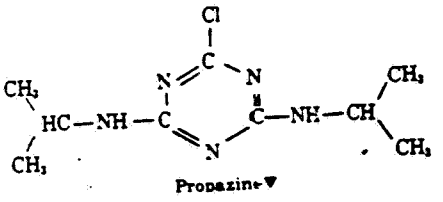
It appears then that Simazine has genotoxic potential and this would provide some support for an oncogenicity concern. Tests for submission to satisfy data gaps and to examine in more detail this genotoxic potential should include a mouse lymphoma assay, an in vivo micronucleus test and a cell transformation assay.

3. Developmental Toxicity

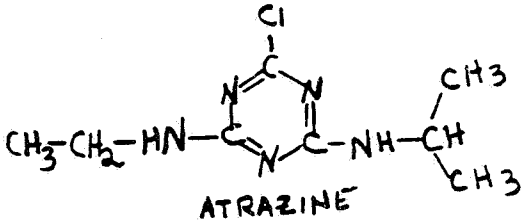
Simazine did not produce terata in the rat, when given by gavage at doses up to 600 mg/kg or in the rabbit at doses up to 200 mg/kg, by gavage; however, maternal toxicity and fetotoxicity (incomplete ossification) were observed in both species.

4. Structure-Activity Correlations

Simazine is structurally related to Atrazine, Propazine, Cyanazine, Ametryn and Prometryn. Atrazine was associated with increased mammary gland tumors in the female albino rat and was categorized as a "C(q)" oncogen by the HED Peer Review Committee. Propazine was also associated with increased mammary gland tumors in the female CD-1 rat and was categorized by the Committee as a "C" oncogen. Ametryn, Prometryn and Cyanazine have not yet been evaluated.



Propazine▼



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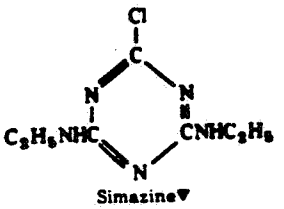

Simazine▼

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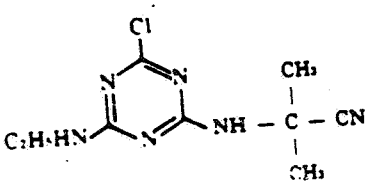

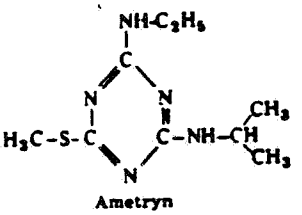

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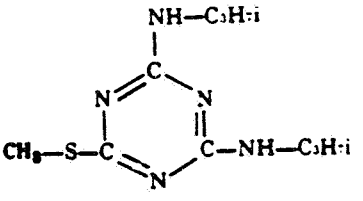

F. Weight of Evidence Considerations:

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

1. Simazine was not associated with increases in neoplasms when fed in the diet to CD-1 mice, at doses up to 4000 ppm. The study was considered to have been adequately conducted.

2. Simazine was associated with statistically significant increases in carcinomas of the pituitary gland (at the HDT) and mammary gland (at the mid (100 ppm) and highest dose) in the female Sprague-Dawley rat, when fed in the diet at doses up to 1000 ppm. The incidence of mammary gland tumors at the HDT was well outside the range reported for historical controls at the testing facility. The incidence of pituitary gland tumors was just outside the historical control range; however, it exceeded (considerably) the incidences reported for 6 out of 7 studies.

3. The pituitary tumors in the female rats were fatal with a possibly accelerated onset, and the mammary carcinomas also contributed to the increased mortality at the HDT, according to the study authors.

4. Although the HDT may have exceeded the MTD, the mid-dose was well below, and the mammary tumors in the female rat were statistically significantly increased at both the mid and high dose. There was also too great an interval between the mid and high doses: 100 and 1000 ppm, respectively.

5. While a hormonal influence was suggested based on the pituitary and mammary gland tumors, supporting evidence was not presented.

6. There was some evidence of genotoxicity.

7. The mammary tumor response is consistent with that seen with other triazines. Both Atrazine and Propazine, triazines with structures closely related to Simazine, were associated with mammary gland tumors in the female rat.

F. Weight of Evidence (contd.)

8a. The incidence of kidney tubule adenomas at the HDT in the female rat, although not statistically significant, exceeded that reported for historical controls (zero) in all seven studies at the testing facility. While this tumor incidence fits the NTP definition of a "rare" tumor (≤1% incidence), Dr. Slaughter offered, that based on his experience, the historical incidence of rat kidney tumors is more accurately defined as "uncommon").

8b. The incidence of kidney tubule carcinomas in male rats was less clearly defined (because of sporadic occurrences of the same tumor in control animals).

G. Classification of Oncogenic Potential:

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying a carcinogen were considered.

The Committee evaluated all of the evidence listed in part F (above) and concluded that Simazine should be classified as a Category C Oncoge- (possible human carcinogen), based on evidence in one species, one sex. The Committee also called for a quantitative risk assessment for Simazine, quantification to be based on the mammary tumors in the female rat. The arguments for quantification were given as follows:

1a. The tumors in both the pituitary and mammary glands of the female rat were malignant.

1b. Pituitary tumors in female rats were fatal with a possible accelerated onset (analysis to be provided).

2a. Mammary tumors were statistically increased at 2 doses, albeit one above the MTD; however, there was too large a spread between the mid and high doses.

2b. Evidence of progression was suggested by mammary hyperplasia at the HDT, which correlated with tumors at that dose.

3. There was no supporting evidence for demonstrating an hormonal influence.

4. There was equivocal evidence of kidney tumors ("rare" or at least "uncommon" tumor type) in both sexes.

5. SAR was strongly supportive. Other closely-related triazines (Atrazine and Propazine) were also associated with mammary gland tumors in the female rat.

6. There was some evidence of genotoxicity.

SAP Executive Summary

9/28/89

OC8512

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

OCT 16 1989

MEMORANDUM

SUBJECT: Transmittal of the Final FIFRA Scientific Advisory Panel Report on the September 28-29, 1989 Meeting

FROM: R. Bruce Jaeger
Executive Secretary
FIFRA Scientific Advisory Panel

TO: Douglas D. Campt, Director
Office of Pesticide Programs

The above mentioned meeting of the FIFRA Scientific Advisory Panel (SAP) was an open meeting held in Arlington, Virginia to review the following topics:

1. A set of Scientific Issues Being Considered by the Agency in Connection with the Proposed Guidelines for Neurotoxicity Testing Under FIFRA.

2. A set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Acetochlor as a Class B2 Oncogen.

3. A set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of DDVP as a Class C Oncogen.

✓4. A set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Simazine as a Class C Oncogen.

5. A set of Scientific Issues Being Considered by the Agency in Connection with the Proposed Guidelines for Mutagenicity Testing Under FIFRA.

Please find attached the Panel's final report on the agenda items discussed at the meeting.

Attachments

cc: Panel Members
Linda J. Fisher
Victor J. Kimm
Jim Roelofs
Susan H. Wayland
Anne Barton
Edwin Tinsworth
Penny Fenner-Crisp
Al Heier
Mary Beatty
EPA Participants
Don Barnes

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Simazine as a Class C Oncogen

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency in connection with the peer review of Simazine. The review was conducted in an open meeting held in Arlington, Virginia, on September 28, 1989. Panel members present for the review were Dr. James Tiedje, Dr. Edward Bresnick and Dr. Robert Anthony. In addition, Dr. Ernest E. McConnell of Raleigh, NC served as a Special Government Employee on the Panel.

Public notice of the meeting was published in the Federal Register on August 25, 1989.

Oral statements were received from Dr. James Stevens and Dr. Lawrence Wetzel of CIBA-GEIGY.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Simazine

The SAP has reviewed the weight of evidence and the suggested classification of Simazine as a category C carcinogen and we agree with this action. The position of the SAP is based upon: a) the presence of mammary carcinomas in female rats in a dose-related manner, b) the appearance of pituitary adenomas and carcinomas in the rat although not in any dose-related manner, c) the structural relationship between Simazine and several compounds with known oncogenic potential, and d) the equivocal mutagenicity data, i.e., most tests were negative. We do not recommend the calculation of a quantitative risk assessment.

The SAP recognizes that the incidence of mammary tumors in the Sprague-Dawley rat is high, e.g., 50%. Consequently, data on compound-induced mammary tumorigenesis are difficult to evaluate. A parameter that has proven more useful in such an evaluation than the percent incidence is the number of mammary tumors per rat. In the spontaneous situation, the number of tumors/rat is low. The SAP would suggest that the latter parameter be employed in assessing the classification for oncogenicity.

The SAP wishes to comment on the presentation by the respondents, at the public hearing, of data that have not been previously seen by the Agency. We strongly encourage the Agency to obtain and review any and all data addressed by the registrant as it specifically relates to the genesis of mammary tumors in rodents. At this juncture, however, no recommendations or conclusions can be made from the information presented by the respondents to EPA and the Panel strongly discourages the presentation of data which have not been presented to the Agency for review.

The SAP recognizes that substances may induce mammary cancer formation in animal species by many ways. The SAP believes that certain insecticides, herbicides, etc., may actually alter the endocrine physiology of the host and so influence the incidence of mammary cancer. We would recommend that the Agency formulate a position for considering oncogenicity data based upon the alteration of the host's endocrinological milieu and for establishing the classification of such a substance. Such information could be incorporated in proposed revisions to the Agency's risk assessment guidelines as they relate to carcinogenicity data.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Robert B. Jaeger
Executive Secretary
FIFRA Scientific Advisory Panel

Date: October 16, 1989

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

SCIENTIFIC ADVISORY PANEL

Review of the Notice of Intent to Cancel Registrations of Certain Simazine Pesticides

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a Notice of Intent to Cancel Registrations of Certain Simazine Pesticides. The review was conducted in an open meeting held in Alexandria, Virginia, on July 8, 1985. This portion of the meeting was chaired by Dr. Christopher Wilkinson. All Panel members except Dr. Ernest Hodgson and Dr. Rosmarie von Rumker were present for the review.

Public notice of the meeting was published in the Federal Register on Friday, June 21, 1985.

Written and oral statements were received from CIBA-GEIGY Corporation.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency and CIBA-GEIGY, the Panel unanimously submits the following report:

REPORT OF SAP RECOMMENDATIONS

The Scientific Advisory Panel (SAP) recognizes that there are both legal and scientific aspects of EPA's proposed cancellation of simazine registrations. However, since the Panel does not consider regulatory or legal recommendations to be among its statutory duties, and does not have professional expertise in these areas, it feels obliged to limit its comments to the scientific aspects of the issue.

Issue:

Given the data available on Simazine, is it likely to leach into groundwater? Are there significant gaps in the chronic toxicity data?

Response:

The SAP believes that simazine has the potential to leach into ground water, but that more data are required before it can be established that this is occurring extensively at the present time at levels that should be considered of serious concern.

The Panel agrees that there are gaps in the toxicology data base for simazine. However, the SAP believes that the limited existing data are adequate until more detailed studies can be completed and reviewed. Currently there is no indication of any toxic effects to humans after 27 years of extensive use. Further, there is no indication that the environmental load of simazine would increase significantly if use is continued until ongoing chronic studies are completed and reviewed.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Philip H. Gray, Jr.
Executive Secretary
FIFRA Scientific Advisory Panel

Date: July 26 '85

[redacted]

008512

Qualitative/Quantitative Risk Assessment

00851[illegible]

FILE COPY

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

[illegible]AY 1991

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Cyanazine (188C), Atrazine (63) and Simazine (7[illegible]) Quantitative Risk Assessment Comparisons on Malignant Mammary Gland Tumors only in Rats.

From: Bernice Fisher, Biostatistician
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

Bernice Fisher 5/13/91

To: Karl Baetcke, Ph.D., Chief
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Thru: Esther Rinde, Ph.D., Acting Section Head
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)
and
Reto Engler, Ph.D., Chief
Scientific Analysis & Corrdination Branch
Health Effects Division (H7509C)

E.R.

Estimated+ $Q_1^*(mg/kg/day)^{-1}$ for Cyanazine, Atrazine and Simazine in Sprague-Dawley Female Rats

	Tumors in the Mammary Gland	Rat $Q_1^*(mg/kg/day)^{-1}$	In Human Equiv.++ $Q_1^*(mg/kg/day)^{-1}$
Cyanazine	Carcinoma, Adenocarcinoma & Fibrosarcoma	1.66×10^{-1}(a)	8.8×10^{-1}
Atrazine[1]	Carcinoma	1.72×10^{-2}(b)	9.2×10^{-2}
Simazine	Carcinoma	2.25×10^{-2}(b)	1.2×10^{-1}

+ Based on results from Statox computer program
++Derived by the use of surface area correction - (Human Wt./ Rat Wt.)$^{1/3}$

(a) Multi-Stage Model (Global86)
(b) Time-to-tumor Multi-Stage Model (Weibull83)

1 HED's previous estimate of Q_1^* was 2.2×10^{-1} based upon both benign & malig[illegible]nt mammary gland tumors. For the puposes of comparison with Cyanazine & Simazine, only malignant tumors were [illegible]ed in the estimation of the unit risk, Q_1^*.

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008512

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

FILE COPY

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Cyanazine (186C), Atrazine (63) and Simazine (740) Quantitative Risk Assessment Comparisons on Malignant Mammary Gland Tumors only in Rats. Revised Comparisons as of July, 1991.

From: Bernice Fisher, Biostatistician
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)

Bernice Fisher 7/8/91

To: Karl Baetcke, Ph.D., Chief
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Thru: Kerry L. Dearfield, Ph.D., Acting Section Head
Science Support & Special Review Section
Science Analysis & Coordination Branch
Health Effects Division (H7509C)
and
Reto Engler, Ph.D., Chief
Scientific Analysis & Coordination Branch
Health Effects Division (H7509C)

Kerry Dearfield 7.8.91

HED's previous estimate of cyanazine's Q_1^* of 8.8×10^{-1} was based upon malignant mammary gland tumors including fibrosarcomas. For comparative purposes with atrazine and simazine, malignant tumors including adenocarcinomas, carcinomas and carcinosarcomas only are used in the estimation of the unit risk, Q_1^*.

Animals with fibrosarcomas in the cyanazine study are excluded from the group for the estimate of Q_1^*. The reason for this exclusion is due to advice given by Dr. Brennecke (HED's consultant in pathology) that fibrosarcomas do not originate from epithelial cell tissues as do the carcinomas. The carcinosarcomas, which originate from both the epithelial and mesenchymal cell tissues, found in both the atrazine and cyanazine mammary gland malignant tumor data can be retained for the estimate of Q_1^*.

cc Kathy Pearce SRRD

Reviewer's Peer Review Package for 2nd Meeting

10/18/89

000512

FILE COPY

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

OCT 18 1989

MEMORANDUM

SUBJECT: Reevaluation of SIMAZINE following SAP Review OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

FROM: Esther Rinde, Ph.D. E.R.
Manager, ONCO Peer Review
Health Effects Division (H7509C)

TO: Addressees

On September 28, 1989, the SAP reviewed the evidence for 3 pesticide chemicals (ACETOCHLOR, DDVP & SIMAZINE) which had been previously evaluated by the Peer Review Committee.

The SAP agreed with the Committee's classification on all 3 chemicals, but disagreed with respect to the quantification of risk - SIMAZINE (SAP said quantification was not appropriate). A copy of the Peer review document and SAP report for SIMAZINE is attached (ACETOCHLOR & DDVP do not require further evaluation since SAP raised no issues for these 2 chemicals).

A meeting to discuss the issue of quantification of risk for SIMAZINE is scheduled for Wednesday, October 25 (immediately following the discussion of APOLLO (Clofentezine).

Attachment

ADDRESSEES:

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
K. Baetcke
R. Beliles
M. Copley
K. Dearfield
J. Du
G. Ghali
R. Levy
J. Quest
R. Rinde
W. Sette
M. Van Gemert
Y. Woo
H. Spencer
B. Fisher

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Simazine as a Class C Oncogen

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency in connection with the peer review of Simazine. The review was conducted in an open meeting held in Arlington, Virginia, on September 28, 1989. Panel members present for the review were Dr. James Tiedje, Dr. Edward Bresnick and Dr. Robert Anthony. In addition, Dr. Ernest E. McConnell of Raleigh, NC served as a Special Government Employee on the Panel.

Public notice of the meeting was published in the Federal Register on August 25, 1989.

Oral statements were received from Dr. James Stevens and Dr. Lawrence Wetzel of CIBA-GEIGY.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Simazine

The SAP has reviewed the weight of evidence and the suggested classification of Simazine as a category C carcinogen and we agree with this action. The position of the SAP is based upon: a) the presence of mammary carcinomas in female rats in a dose-related manner, b) the appearance of pituitary adenomas and carcinomas in the rat although not in any dose-related manner, c) the structural relationship between Simazine and several compounds with known oncogenic potential, and d) the equivocal mutagenicity data, i.e., most tests were negative. We do not recommend the calculation of a quantitative risk assessment.

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The SAP wishes to comment on the presentation by the respondents, at the public hearing, of data that have not been previously seen by the Agency. We strongly encourage the Agency to obtain and review any and all data addressed by the registrant as it specifically relates to the genesis of mammary tumors in rodents. At this juncture, however, no recommendations or conclusions can be made from the information presented by the respondents to EPA and the Panel strongly discourages the presentation of data which have not been presented to the Agency for review.

The SAP recognizes that substances may induce mammary cancer formation in animal species by many ways. The SAP believes that certain insecticides, herbicides, etc., may actually alter the endocrine physiology of the host and so influence the incidence of mammary cancer. We would recommend that the Agency formulate a position for considering oncogenicity data based upon the alteration of the host's endocrinological milieu and for establishing the classification of such a substance. Such information could be incorporated in proposed revisions to the Agency's risk assessment guidelines as they relate to carcinogenicity data.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Robert B. Jaeger
Executive Secretary
FIFRA Scientific Advisory Panel

Date: October 16, 1989

ATTACHMENT 1

Reviewer's Peer Review Package for 1st Meeting

5/4/89

008512

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

FILE COPY

MAY 4 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review on Simazine.

FROM: Esther Rinde, Ph.D. E. Rinde
Manager, ONCO Peer Review
Health Effects Division (TS-769c)

TO: Addressees

Attached for your review is a package on Simazine, prepared by Henry Spencer.

A meeting to consider the classification of Simazine s scheduled for 5/17/89 at 10:00 in Room 821, CM2.

Addressees

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
B. Beliles
D. Beal
J. Hauswirth
M. Van Gemert
M. Copley
J. Quest
L. Slaughter
K. Dearfield
R. Levy
W. Sette
G. Ghali
B. Fisher
H. Spencer

008512

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Submission of Peer Review data for evaluation of Oncogenicity of Simazine by the Peer Review Group.

FROM: Henry Spencer, Ph.D., 4/21/89
Toxicology Branch I, (IRS), Section II
Health Effects Division, (H7509-C)

TO: Reto Engler, Ph.D., Chief,
SACB Branch
Health Effects Division (H7509-C)

THRU: Marion Copley, DVM, Section Head Marion Copley
Review Section II
Toxicology Branch I (IRS) (H7509-C)

A registration standard on Simazine was produced in 1984 and a subsequent DCI notice was transmitted to the registrant, CIBA-Geigy Corp.. New studies to evaluate the oncogenic potential of Simazine were submitted to the Agency and have been reviewed.

This submission contains the results of reviews of those new studies.

Only a chronic rat study shows an increase in female mammary tumors and male liver tumors, while the chronic mouse study appears negative for treatment related tumors. Since only one specie, the rat, appears positive for any increases in the incidence of tumor formation, the Toxicology Branch I, requests determination/confirmation whether the male and female rats both bear treatment related tumors and whether Simazine should be classified as greater than a C oncogen.

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RECEIVED 4/27/89

Index of Peer Review on Simazine

Submission of Oncogenicity Data on Simazine to the Peer Review Committee

Submitted By: Henry Spencer
Section II, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., Section Head
Toxicology Branch I - IRS (H7509C)

Issue

The Peer Review Committee is requested to evaluate the oncogenicity data submitted by the registrant, Ciba-Ceigy Corporation, to determine if simazine produces oncogenic effects in the test animals. Supporting data are supplied for this review.

Background

Simazine is one of several s-triazine compounds [(s) meaning symmetrical] which are used in agriculture as herbicides to control most annual grasses and broadleaf weeds in corn, alfalfa, orchards of cherries, peaches, citrus, apples, pears, and asparagus as well as ornamentals and nursery stock. Nonselective weed control in industrial settings can be achieved by using higher rates of application.

Simazine is often used in combination with other herbicides including paraquat, atrazine, and amitrole. Formulations are available as wettable powders, granulars, and liquids.

Simazine is also registered for use in controlling algae in ponds. Little of the simazine parent chemical is found as residues in food and feed crops.

The Health Effects Division (HED) of OPP has received new toxicity studies on simazine following the Data Call-In Notice of the first Registration Standard of 1984. Reviews of these studies indicate that increased incidences of mammary tumors in female rats are associated with exposure to simazine in the diet.

Toxicology Branch I (IRS) of HED submits the data reviews for evaluation and asks for Peer Review determination of the appropriate oncogenic classification of the compound.

Acute Toxicity

Simazine technical has a low acute toxicity with the rat oral LD_{50} > 5 g/kg (Toxicity Category IV) and another rabbit dermal LD_{50} > 2.0 g/kg in "limit tests."

Inhalation data in rats show that at 1.71 mg/L (the sustained maximum generated) minimal toxicity signs were evident following a 4-hour exposure (Toxicity Category IV).

Simazine is only very slightly irritating to the skin of rabbits after a 4-hour exposure (Toxicity Category IV), and is not a dermal sensitizer to guinea pigs.

Developmental Toxicity

A rat teratology study using dosages by gavage of 0, 30, 300, or 600 mg/kg exhibited maternotoxicity and fetotoxicity at 300 mg/kg and above. No malformations were reported; toxicity to the fetuses was characterized by incomplete ossification. The NOEL for the study was 30 mg/kg. Toxicity was also reported in a rabbit teratology study as nonossification of bones and reduced fetal weights; the NOEL was 75 mg/kg. Maternal toxicity was reported at 75 mg/kg. Terata formation was not evident in the study.

Subchronic (90-Day) Studies

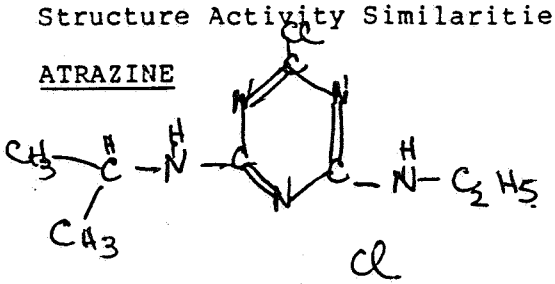
Rodent - Technical grade simazine was fed to rats in groups of 10/sex in a powdered feed mixture at 0, 200, 2000, or 4000 ppm. Reductions in feed intake and mean body weights occurred at 2000 ppm and above. A NOEL for males based on a reduction in red blood cells (RBC) counts was less than 200 ppm (LDT). Cholesterol and inorganic phosphate levels were elevated in both sexes. Renal stones were increased at 200 ppm and above when compared to controls. The LEL was less than 200 ppm (LDT) (Attachment 1).

Nonrodent - Beagle dogs in groups of 4/sex were exposed to dietary mixtures of 0, 200, 2000, or 4000 ppm simazine for 13 weeks. Clinical chemistries and hematological determinations were made midway and at termination of the study. Body weights, food and water intake, and clinical observations were also recorded.

Results - Tremors were present from 9 weeks to termination at 4000 ppm. Body weights and food consumption were reduced at 2000 ppm and above in both sexes. Reduced erythrocyte counts occurred at high doses. A NOEL was based upon reduced albumin and increased globulin levels in males. The MTD was less than 2000 ppm in both sexes based on the reduced body weights and food consumption values (Attachment 2).

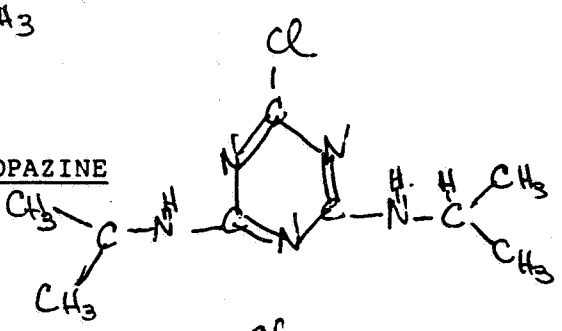
Structure Activity Similarities:

ATRAZINE



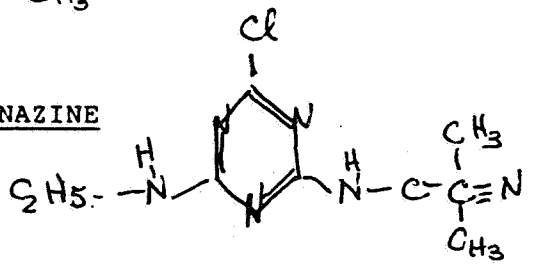
Animal Response
Increased female mammary gland tumors in the albino, rat. Peer reviewed as a "C Q*" oncogen.

PROPAZINE



Increased female CD-1 rat mammary gland tumors. Peer reviewed as a "C Q*" oncogen.

CYANAZINE



Not evaluated due to inadequate data.

Metabolism - Rats were fed 1.5 mg/kg ^{14}C ring-labeled simazine or metabolites obtained from fish fed simazine. The simazine-treated rats excreted 41 percent of the radioactivity in the feces and 49 percent in the urine. Animals fed the fish metabolites excreted 48 to 93 percent activity in the feces and 17 to 31 percent in the urine. Very small amounts of ^{14}C activity remained in the rats after 96 hours (Attachment 3).

A further study in rats indicated that simazine remained attached to RBC preferentially following oral dosing of the animals (Attachment 4).

Mutagenicity (Attachments 5, 6, 7)

Recent studies using simazine in mutagenicity evaluations have been received and provide information that an Ames assay using five doses ranging from 10 to 250 micrograms (ug)/plate was assayed at the maximum test doses possible with no evidence of mutagenic effect. Strains TA1535, TA100, TA1538, TA98, and TA1537 were used with and without S9 microsomal activation.

Structural chromosomal aberration tests were completed using human lymphocytes in vitro. The studies used both activation and nonactivation with S9 materials at concentrations of 6.25, 12.5, 25, 50, and 100 ug/mL. However, the studies were considered unacceptable because they could have been run at higher levels and posttreatment harvest time was extended beyond an optimal time period.

Unscheduled DNA repair in primary rat hepatocytes was evaluated but used too short incubation periods and presented insufficient information on dosage selection to be usable in the assay. The study was unacceptable to properly evaluate UDS.

Chronic Toxicity

Mice - Simazine was fed in the diet at levels of 0, 40, 1000, or 4000 ppm to groups of CD-1 mice containing 60 animals/sex for oncogenicity evaluation, and additional groups of 10/sex/dose for interim sacrifices at 26 and 52 weeks. Animals were observed daily and failed to show effects related to treatment at any dosage. Body weight gains were reduced at 1000 ppm and above in both sexes. Hematologic (Hct, Hgb, and RBC) changes were noted in females at 1000 ppm and above. Females appeared to be more sensitive to ingestion of simazine since most hematological effects in males were noted at 4000 ppm. Decreased organ to body weight ratios and absolute organ weights generally paralleled the lowered body weights observed in the test animals.

Neoplastic lesions were not increased significantly over values reported in control animals.

The study showed a NOEL of 40 ppm with no evidence for oncogenic potential (Attachment 8).

Rats - A chronic feeding study in Sprague-Dawley rats was used to examine simazine for oncogenic potential. Fifty rats/sex/dose were exposed to 0, 10, 100, or 1000 ppm of simazine in the diet and examined after 2 years for oncogenicity. Additional groups (30 to 40/sex/dose) were treated to determine toxicity endpoints (Attachment 9).

Survival - Male rats at the highest dose survived better than controls but females had a 20 percent survival rate compared to 34 percent in the controls.

Non-neoplastic Toxicity

Reduced body weight gains were seen in mid- and high-dose animals of both sexes. Food consumption was reduced signifi- significantly at 1000 ppm in both sexes but only occasionally at 100 ppm. Hematological parameters (Hgc, RBC, Hct) were variously depressed throughout the study at the mid- and high-dose levels in females. Clinical chemistry determinations show that glucose levels were lower at the mid and high doses in females when compared to controls. Other chemistry parameter changes were either not biologically significant or were not discernible as treatment-related.

Organ weight to body weight or brain weight changes were quite severe in the kidneys and livers of females on diets of 1000 ppm simazine. However, the great loss in body weights confounded the results. More likely, the absolute liver weights or percent of the brain weight would represent real changes in the organ weights from treatment. Therefore, the LEL for these effects was considered to be 100 ppm in females.

Neoplastic Changes (Excerpted from the TB review, Attachment 9)

Table 7. Summary of Histopathological Lesions - Male Rats

Histopathological Observation[1/]	Dose (ppm) 0	10	100	1000
Neoplastic Lesions				
Adrenal - Cortical adenoma	0/69[2/]	0/70	1/69	2/69
Kidney - Adenoma	0/70	0/70	0/70	1/70
- Carcinoma (primary)	0/70	0/70	0/70	2/70
Liver - Hepatocellular adenoma	1/70	1/70	1/70	3/70
- Hepatocarcinoma	0/70	2/70	4/70	3/70
- Combined adenoma and/or carcinoma	1/70	3/70	4/70	6/70
Thyroid - C-Cell adenoma	2/70	5/69	5/69	6/70
- C-cell carcinoma	2/70	1/69	1/69	3/70
- Combined adenoma and/or carcinoma	4/70	6/69	6/69	9/70

1/Main study only (interim sacrifice and recovery groups not included).
2/Number of rats with specified observation/total number of tissues examined.

HISTORICAL CONTROL TUMORINCIDENCE DATA
NUMBER OF TUMOR-BEARING ANIMALS - SPRAGUE-DAWLEY RATS

Submitted by Ciba-Geigy

COMPOUND	83 A	JAN 83 B	NOV 83 C	84 D	85 E	85 F	85 G
SITE: NEOPLASM			NUMBER OF NEOPLASMS				
MAMMARY GLAND (FEMALES): NUMBER OF SITES EXAMINED	(65)	(60)	(70)	(70)	(60)	(70)	(70)
ADENOMA	6	6	8	2	5	3	2
FIBROADENOMA	18	16	26	21	12	23	22
ADENOMA/FIBROADENOMA (COMBINED)	22	18	30	22	15	25	23
ADENOCARCINOMA	7	4	5	11	9	15	14
ALL MAMMARY TUMORS (COMBINED)	25	22	34	30	20	34	32
PITUITARY GLAND (FEMALES): NUMBER OF SITES EXAMINED	(63)	(60)	(69)	(69)	(60)	(70)	(70)
ADENOMA	52	49	55	59	49	62	62
CARCINOMA	0	2	2	2	6	2	1
ADENOMA AND CARCINOMA (COMBINED)	52	51	57	61	55	64	63
KIDNEY (MALES AND FEMALES): NUMBER OF SITES EXAMINED	(65/65) M F	(60/59) M F	(70/70) M F	(70/70) M F	(60/60) M F	(70/70) M F	(70/70) M F
ADENOMA	0 0	0 0	2 0	1 0	0 0	0 0	0 0
CARCINOMA	0 0	0 0	0 0	1 0	0 0	0 0	0 0
ADENOMA AND CARCINOMA (COMBINED)	0 0	0 0	2 0	2 0	0 0	0 0	0 0
ADRENAL GLAND (FEMALES): NUMBER OF SITES EXAMINED	(65)	(60)	(70)	(70)	(60)	(70)	(70)
ADENOMA	1	3	4	2	3	2	8
LIVER (MALES): NUMBER OF SITES EXAMINED	(65)	(60)	(70)	(70)	(60)	(70)	(70)
ADENOMA	0	2	0	2	10	4	1
CARCINOMA	0	1	1	6	2	1	0

Males - Male rats exhibited a significant dose-related trend for kidney tubule carcinomas ($p < .05$) or combined adenomas and carcinomas ($p < .01$). Pairwise comparisons were not significant for kidney tumors. Table 7, Summary of Lesions, uses all animals on study while the statistical evaluation uses fewer animals in the C.J. Nelson memorandum (Attachment 10). The liver tumor incidence was statistically significant in the C.J. Nelson evaluation in the Fisher's Exact test for carcinomas at 100 ppm and in the combined adenomas and carcinomas at 1000 ppm ($p < .05$). These values are considered of questionable significance when viewed in light of the historical control data submitted by Ciba-Geigy for compounds D, E, and F in the historical control tumor incidence table on page 6.

Females - Dose-related trends for the adenomas, carcinomas, or combined tumors of the pituitary gland were statistically significantly ($p < 0.03$) in each case. Pairwise comparisons were significant when examined for the effect of being a fatal tumor in the animals. Table 6 shows that increased significance at the 100 and 1000 ppm dosages occurs primarily as adenomas increase. Only at 1000 ppm is there a lifetime adjusted *increase of* carcinomas ($p < .05$).

Prior to additional statistical evaluation, no significant increases in either tumor type are seen in the TB review (Table 6).

The lack of historical control data on the onset of the pituitary tumor with time does not allow its use in this evaluation.

Mammary gland carcinomas and combined adenomas/fibroadenomas and carcinomas exhibited a significant dose-related trend ($p < .0001$) see Table 8.

However, when the shortened life span of the female rats is included in the statistical evaluation, both 100 and 1000 ppm dosage groups show significance at $p = .039$ and $p < .0001$, respectively, when compared to controls (see Attachment 9).

Data supporting an effect of simazine on tumorigenicity is the fact that cystic glandular hyperplasia was increased significantly at the HDT (1000 ppm) and only equivocally at 100 ppm when compared to controls.

Table 6. Simazine, Sprague-Dawley Rat Study--Female Pituitary Gland Tumor Rates+, Fatal Tumor Analysis and Generalized K/W Test Results (extracted from T.B. review, Attachment 9)

Dose (ppm)	0.000	10.000	100.000	1000.000
Adenoma	73/89 (82.0)	57/80 (71.2)	63/77[a] (81.8)	61/79 (77.2)
	p = 0.0033**	p = 0.9944	p = 0.0206*	p = 0.0030**
Carcinoma	1/73 (1.4)	3/61 (4.9)	0/52 (0.0)	6/53[b] (11.3)
	p = 0.0010**	p = 0.2351	p = 0.4545	p = 0.0153*
Adenoma/ Carcinoma	74/89 (83.1)	60/80 (75.0)	63/77 (81.8)	67/79 (84.8)
	p = 0.0005**	p = 0.8351	p = 0.0251*	p = 0.0005**

+Number of tumor-bearing animals/number of animals at risk (excluding animals that died before the first tumor or animals not examined).
() = Percent
[a]First adenoma observed at 35 weeks in dose 100 ppm.
[b]First carcinoma observed at 72 weeks in dose 1000 ppm.

Note: Significance of trend donated at control. Significance of pairwise comparison with control denoted at dose level.
*Denotes $p < 0.05$.
**Denotes $p < 0.01$.

Table 8. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Female Mammary Gland Tumor Rates and Peto Prevalence Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000
Adenoma Fibroadenoma	23/89 (26)	20/78a (26)	11/71 (15)	21/75 (28)
	p= 0.0689	p= 0.302	p= 0.177	p= 0.125
Carcinoma	16/89 (18)	13/80 (16)	20/75b (27)	40/78 (51)
	p< 0.0001**	p= 0.4740	p= 0.0392*	p< 0.0001**
Adenoma Carcinoma	39/89 (44)	33/80 (41)	31/75 (41)	61/78 (78)
	p< 0.0001**	p= 0.4066	p= 0.2229	p< 0.0001**

a First Adenoma observed at 48 weeks in dose 10 ppm and the first Fibroadenoma observed at 52 weeks in dose 0, 10, and 1000 ppm.

b First carcinoma observed at 48 weeks in dose 100 ppm.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

Due to the presence of mortality differences in both sexes of rats, the Peto prevalence test was used for incidental tumor rates to test for increasing incidence with increasing dose levels and for pair-wise differences between controls and treated rats. If the Peto prevalence method reduces to too few intervals then the Cochran-Armitage method is used to test for trends and the Fisher's exact test to test for pair-wise differences. If the tumors are considered fatal, the Thomas, Breslow, and Gart procedure is used to analyze for trends and pair-wise differences.

In the female rats, M. Copley suggested that the mammary gland adenomas and fibroadenomas be analyzed together as benign tumors, since about 50% of the rats with fibroadenomas also had carcinomas. There were no significant pair-wise comparisons or a trend noted. There was a significant dose-related trend for mammary gland carcinomas and for combined mammary gland adenomas/fibroadenomas and carcinomas ($p < 0.0001$). The incidence of mammary gland carcinomas in the 100 ppm and 1000 ppm dose groups were significantly increased ($p = 0.0392$ and $p < 0.0001$, respectively) compared to the controls. The incidence of combined mammary gland adenomas/fibroadenomas and carcinomas in the 1000 ppm dose group was significantly increased ($p < 0.0001$) compared to the controls (Table 8).

Weight-of-the-Evidence

Data on simazine, although sparse, do not indicate a strong mutagenic potential. Chronic data in rat and mice studies indicate that simazine affects body weight gains and hematological parameters in the two species. The rat showed a NOEL of 0.5 mg/kg; the mouse exhibited a NOEL of approximately 6 mg/kg.

The mouse was negative for oncogenic effects associated with exposure to simazine at up to 4000 ppm in the diet.

The effects of simazine on the mammary glands of the female rat indicate increased oncogenic potential in that sex and species. There was also a significant increase in pituitary tumors. The mechanism of tumorigenicity was not discernible from the data submitted.

The male rat data showed an increase in kidney tumors as well as liver tumors.

In summary, one species, the rat, exhibited increased incidences of female mammary tumors and pituitary tumors. The male rat exhibited a dose-related trend for increased kidney tumors and significant numbers (Fisher's Exact test) of liver tumors.

Attachments

Attachment #10 [illegible] 00851

008512

OCT 25, 88

EPA: 68-D8-0565
DYNAMAC No. 1-16
October 18, 1988

SIMAZINE - Qualitative Risk Assessment from a Rat Two Year Oral Chronic Toxicity and Oncogenicity Study

Caswell No. 740

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SUMMARY:

Simazine technical was fed to male and female Sprague-Dawley rats at doses of 0, 10, 100, or 1000 ppm in a 104 week chronic toxicity/oncogenicity study.

For female rats, there was a statistically significant increase in mortality with increasing doses of Simazine and mortality was significantly increased in both the 100 and 1000 ppm dose groups compared to the controls.

The incidence of mammary gland carcinomas and combined adenomas and carcinomas had a significant dose-related trend. The incidence of mammary gland carcinomas was significantly increased compared to the controls at the 100 and the 1000 ppm groups; the combined adenomas and carcinomas was significantly increased compared to the controls for the 1000 ppm group.

The pituitary gland tumors were considered fatal (reference page 1460 of the Ciba-Geigy report, attached), all three tumor groups (adenomas, carcinomas, and combined adenomas and carcinomas) showed significant dose-related trends. The incidence of pituitary adenomas and combined tumors was significantly increased compared to controls at the 100 and 1000 ppm groups; the incidence of carcinomas was significant at the 100 ppm group only.

There was a significant dose-related trend for kidney tubule adenomas.

For male rats, there was a statistically significant decrease in mortality with increasing doses of Simazine and mortality was significantly decreased in the 1000 ppm group compared to the controls.

There were no significant dose-related trends for liver adenomas, carcinomas, and combined adenomas and carcinomas. The incidence of liver carcinomas in the 100 ppm group was significantly increased compared to the controls. The incidence of combined liver adenomas and carcinomas was significantly increased compared to the controls in the 1000 ppm group. There were no significant dose-related trends or pair-wise differences for thyroid C-cell adenomas, carcinomas, and combined adenomas and carcinomas.

There was a significant dose-related trend for kidney tubule carcinomas and combined adenomas and carcinomas. There were no significant pair-wise differences for any of the kidney tubule tumors.

BACKGROUND:

Simazine technical was fed to male and female Sprague-Dawley rats at doses of 0, 10, 100, or 1000 ppm in a 104 week chronic toxicity/carcinogenicity study. Approximately 10 animals in each sex were sacrificed after 52 weeks of continuous dosing in each dose group. Only 9 animals were sacrificed in the male 10 ppm dose group and in the female 100 and 1000 ppm dose groups. This was due to deaths on study which occurred before the scheduled sacrificed since the animals to be sacrificed were selected prior to the beginning of the study. Also ten animals from the 1000 ppm group are not included in this analysis. These animals were dosed for 52 weeks and then maintained for 52 additional weeks on an untreated (control) diet. They were designated as a recovery group. A supplementary table of the results from these animals and their assigned controls was prepared (attachment 1). There were only 2 kidney tumors in the males, one adenoma in the control group and one carcinoma in the 1000 ppm group. In the females, there were 4 mammary gland adenomas in the controls and 2 in the 1000 ppm group. There was 1 mammary gland carcinoma in the controls and 4 in the 1000 ppm group. There were no pituitary gland carcinomas in either group but there were 9 adenomas in both groups.

The study was conducted by Ciba-Geigy Corporation, Pharmaceutics Division, Summit, NJ for the Ciba-Geigy Corporation. The TOX Chemical No. is 740, the MRID No. is 406144-05, and the Study No. is 2-011-09. Data was extracted from a final report dated April 12, 1988. Test animals were assigned randomly to the following dose groups:

Table 1. Experimental Design for Rat Chronic/Carcinogenicity Study

Dose (ppm)	Phase	Total Number		Time of Sacrifice 52 Weeks		Least Number of Dose Weeks
		Male	Female	Male	Female	
Control	Chronic c	10	10	10	10	52
		10	10			52 + 52-wk recovery
		20	20			104
	Carcinogenicity	50	50			104
10	Chronic c	10	10	10a	1'	52
		20	20			104
	Carcinogenicity	50	50			104
100	Chronic c	10	10	10	10a	52
		20	20			104
	Carcinogenicity	50	50			104
1000	Chronic c	10	10	10	10a	52
		10b	10b			52 + 52-wk recovery
		20	20			104
	Carcinogenicity	50	50			104

a Only 9 animals were actually sacrificed in these dose groups.
b These 10 animals were excluded from analysis.
c The chronic animals were also used for hematology, biochemistry, and urinalysis.

SURVIVAL ANALYSIS:

In female rats, a statistically significant increasing trend in mortality was observed with increasing doses of Simazine ($p = 0.0036$). Mortality was significantly increased in the 100 ppm and the 1000 ppm dose group compared to the controls ($p = 0.0058$ and $p = 0.0006$ respectively). (Table 2).

In male rats, a statistically significant decreasing trend in mortality was observed with increasing doses of Simazine ($p = 0.0016$). Mortality was significantly decreased in the 1000 ppm dose group compared to the controls ($p = 0.0077$) (Table 3) .

Tests for mortality were made using the Thomas, Breslow, and Gart procedure. The earlier deaths occurred in the mid and high dose groups and the K/W test gives more weight to earlier deaths. Hence, all mortality test reported are the generalized K/W test.

TABLE 2. SIMAZINE, SPRAGUE-DAWLEY RAT Study--FEMALE Mortality Rates• and Generalized K/W Test Results

DOSE(PPM)	WEEKS 1-26	27-52	52a	53-78	79-106a	TOTAL
0.000	0/90 (0)	1/90 (1)	10/10	13/79 (16)	39/66 (59)	53/80** (66)
10.000	0/80 (0)	2/80 (2)	10/10	18/68 (26)	27/50 (54)	47/70 (67)
100.000	1/80 (1)	8/79 (10)	9/9	18/62 (29)	26/44 (59)	53/71** (75)
1000.000	0/80 (0)	5/80 (6)	9/9	21/66 (32)	31/45 (69)	57/71** (80)

TABLE 3. SIMAZINE, SPRAGUE-DAWLEY RAT Study--MALE Mortality Rates• and Generalized K/W Test Results

DOSE(PPM)	WEEKS 1-26	27-52	52a	53-78	79-106a	TOTA
0.000	0/90 (0)	2/90 (2)	10/10	12/78 (15)	34/66 (52)	48/80 (60)
10.000	0/80 (0)	1/80 (1)	9/9	8/70 (11)	38/62 (61)	47/71 (66)
100.000	0/80 (0)	0/80 (0)	10/10	6/70 (9)	33/64 (52)	39/7((56)
1000.000	0/80 (0)	0/80 (0)	10/10	6/70 (9)	22/64 (34)	28/7((40)

• Number of animals that died during the interval/Number of animals alive at the beginning of the interval.

( ) Per cent

a Interim sacrifice was conducted at 52 weeks. Final sacrifice occurred at week 106.

Note: Time intervals were selected for display purposes only. Significance of trend denoted at Control Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ ** denotes $p > 0.01$

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TUMOR ANALYSIS:

Due to the presence of mortality differences in both sexes of rats, the Peto prevalence test was used for incidental tumor rates to test for increasing incidence with increasing dose levels and for pair-wise differences between controls and treated rats. If the Peto prevalence method reduces to too few intervals then the Cochran-Armitage method is used to test for trends and the Fisher's exact test to test for pair-wise differences. If the tumors are considered fatal, the Thomas, Breslow, and Gart procedure is used to analyze for trends and pair-wise differences.

In the female rats, M. Copley suggested that the mammary gland adenomas and fibroadenomas be analyzed together as benign tumors, since about 50% of the rats with fibroadenomas also had carcinomas. There were no significant pair-wise comparisons or a trend noted. There was a significant dose-related trend for mammary gland carcinomas and for combined mammary gland adenomas/fibroadenomas and carcinomas ($p < 0.0001$). The incidence of mammary gland carcinomas in the 100 ppm and 1000 ppm dose groups were significantly increased ($p = 0.0392$ and $p < 0.0001$, respectively) compared to the controls. The incidence of combined mammary gland adenomas/fibroadenomas and carcinomas in the 1000 ppm dose group was significantly increased ($p < 0.0001$) compared to the controls (Table 4).

There was a significant dose-related trend for kidney tubule adenomas ($p = 0.0042$) by the Cochran-Armitage trend test (Table 5). The Cochran-Armitage trend test was used since the Peto prevalence procedure reduced to one interval. There were no significant pair-wise differences found using the Fisher's exact test for pair-wise differences.

A fatal tumor analysis was performed on female rat pituitary gland tumors (reference page 1460 of the Ciba-Geigy report, attached) and the generalized K/W analysis test results reported. There was a significant dose-related trend for pituitary gland adenomas only, carcinomas, and combined adenomas and carcinomas ($p = 0.0033$, $p = 0.0010$, and $p = 0.0005$ respectively) (Table 6). The incidence of pituitary gland adenomas in the 100 ppm and the 1000 ppm dose group was significantly increased ($p = 0.0206$ and $p = 0.0030$ respectively). The incidence of pituitary gland carcinomas was significantly different from the controls in the 1000 ppm dose group ($p = 0.0153$). The 100 ppm and 1000 ppm dose group of combined pituitary adenomas and carcinomas was significantly different from the controls ($p = 0.0251$ and $p = 0.0005$ respectively).

From an examination of the Kaplan-Meier survival curves (copies available), the pituitary adenoma/carcinoma lesions appear 4 to 15 weeks earlier in the 100 ppm and 1000 ppm dose

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groups than they do in the 10 ppm dose or control groups. The incidence of the mid and high group remain higher than the other two groups until near the end of the study.

In the male rats, there were no dose-related trends for liver adenomas, carcinomas, or combined liver adenomas and carcinomas by the Cochran-Armitage trend test (Table 7). The incidence of liver carcinomas in the 100 ppm group was significantly increased ($p = 0.0494$) compared to the controls by the Fisher exact test. The incidence of combined liver adenomas and carcinomas in the 1000 ppm group was significantly increased ($p = 0.0449$) compared to the controls. The Cochran-Armitage trend test and the Fisher's exact test were used because only one interval was calculated using the Peto prevalence test. For the liver carcinomas, animals that died before 52 weeks were excluded from analysis, although the first carcinoma appears at week 99. It was assumed that 52 weeks was an adequate time period for liver tumors to appear.

There were no significant pair-wise differences or dose-related trends for thyroid C-cell adenomas, carcinomas or combined thyroid C-cell adenomas and carcinomas (Table 8).

There was a significant dose-related trend for kidney tubule carcinomas and combined kidney tubule adenomas and carcinomas ($p = 0.0332$ and $p = 0.0056$, respectively) (Table 9). There were no significant pair-wise differences between treated groups and the controls for kidney adenomas, carcinomas or combined adenomas and carcinomas. Analysis of kidney tubule adenoma was done with the Cochran-Armitage trend test and Fisher's exact test since the Peto prevalence procedure resulted in only one interval.

Table 4. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Female Mammary Gland Tumor Rates* and Peto Prevalence Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000
Adenoma				
Fibroadenoma	23/89	20/78a	11/71	21/75
	(26)	(26)	(15)	(28)
	p= 0.0689	p= 0.302	p= 0.177	p= 0.123
Carcinoma	16/89	13/80	20/75b	40/78
	(18)	(16)	(27)	(51)
	p< 0.0001**	p= 0.4740	p= 0.0392*	p< 0.0001**
Adenoma				
Carcinoma	39/89	33/80	31/75	61/78
	(44)	(41)	(41)	(78)
	p< 0.0001**	p= 0.4064	p= 0.2229	p< 0.0001**

a First Adenoma observed at 48 weeks in dose 10 ppm and the first Fibroadenoma observed at 52 weeks in dose 0, 10, and 1000 ppm.

b First carcinoma observed at 48 weeks in dose 100 ppm.

Table 5. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Female Kidney Tubule Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test

DOSE(PPM)	0.000	10.000	100.000	1000.000
Adenoma	0/74	0/62	0/54	2/55c
	(0.0)	(0.0)	(0.0)	(3.6)
	p= 0.0062**	p= 1.0000	p= 1.0000	p= 0.1799

c First Adenoma observed at 71 weeks in dose 1000 ppm. No carcinomas were coded.

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before the observation of the first tumor or animal not examined).

( ) Per cent

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

TABLE 6. SIMAZINE, SPRAGUE-DAWLEY RAT Study--FEMALE Pituitary Gland Tumor Rates*, Fatal Tumor Analysis an Generalized K/W Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000
Adenoma	73/89	57/80	63/77 a	61/79
	(82.0)	(71.2)	(81.8)	(77.2)
	p= 0.0033**	p= 0.9944	p= 0.0206*	p= 0.0030**
Carcinoma	1/73	3/61	0/52	6/53 b
	(1.4)	(4.9)	(0.0)	(11.3)
	p= 0.0010**	p= 0.2351	p= 0.4565	p= 0.0153*
Adenoma Carcinoma	74/89	60/80	63/77	67/79
	(83.1)	(75.0)	(81.8)	(84.8)
	p= 0.0005**	p= 0.8351	p= 0.0251*	p=0.0005**

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before the first tumor or animals not examined).

( ) Per cent

a First Adenoma observed at 35 weeks in dose 100 ppm.

b First Carcinoma observed at 72 weeks in dose 1000 ppm.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p > 0.01$

Table 7. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Male Liver Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000
Adenoma	1/88	2/79a	0/80	3/80
	(1.1)	(2.5)	(0.0)	(3.8)
	p= 0.0824	p= 0.4594	p= 0.5238	p= 0.2752
Carcinoma	0/88	2/79	4/80b	3/80
	(0.0)	(2.5)	(5.0)	(3.8)
	p= 0.2169	p= 0.2223	p= 0.0494*	p= 0.1058
Adenoma Carcinoma	1/88	4/79	4/80	6/80
	(1.1)	(5.1)	(5.0)	(7.5)
	p= 0.0643	p= 0.1519	p= 0.1554	p= 0.0449*

a First Adenoma observed at 52 weeks in dose 10 ppm.
b First Carcinoma observed at 99 weeks in dose 100 ppm.

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before 52 we animals not examined).

( ) Per cent

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

Table 8. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Male Thyroid C-Cell Tumor Rates* and Peto Prevalence Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000
Adenoma	2/52 (4)	7/52a (13)	5/51 (10)	6/58 (10)
	p= 0.3355	p= 0.0606	p= 0.1082	p= 0.0870
Carcinoma	2/34 (6)	1/31 (3)	1/36 (3)	3/45b (7)
	p= 0.1762	p= 0.1082	p= 0.2881	p= 0.4183
Adenoma Carcinoma	4/52 (8)	8/52 (15)	6/51 (12)	9/58 (16)
	p= 0.1924	p= 0.1965	p= 0.2261	p= 0.1505

a First Adenoma observed at 89 weeks in dose 10 ppm.

b First Carcinoma observed at 102 weeks in dose 1000 ppm.

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before the observation of the first tumor or animals not examined).

( ) Per cent

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with contro denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

Table 9. SIMAZINE SPRAGUE-DAWLEY RAT Study-- Male Kidney Tubule Tumor Rates* and Peto Prevalence Test Results

DOSE(PPM)	0.000	10.000	100.000	1000.000
Adenoma	0/51	0/46	0/48	1/57a
	(0)	(0)	(0)	(2)
	p= 0.0543	p= 1.0000	p= 1.0000	p= 0.5278
Carcinoma	1/66	0/62	0/64	2/65b
	(2)	(0)	(0)	(3)
	p= 0.0332*	p= 0.1660	p= 0.1821	p= 0.2091
Adenoma Carcinoma	1/66	0/62	0/64	3/65
	(2)	(0)	(0)	(5)
	p= 0.0056**	p= 0.1410	p= 0.1721	p= 0.1087

a First Adenoma observed at 92 weeks in dose 1000 ppm.

b First Carcinoma observed at 78 weeks in dose 1000 ppm

c The p values for Adenomas were calculated using the Cochran-Armitage Trend Test and Fisher's Exact since the Peto Prevalence method collapsed to one interval.

* Number of tumor bearing animals/Number of animals at risk (excluding animals that died before the observation of the first tumor or animals not examined).

( ) Per cent

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with contr denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

REFERENCES:

Thomas, D.G., N. Breslow, and J.J. Gart, Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381, 1977.

Cochran, W.G. Some Methods for Strengthening the Common x2 Test. Biometrics 10, 417-451, 1954.

Armitage, P. Test for Linear Trends in Proportions and Fequencies. Biometrics 11, 375-386, 1955.

Peto, R., M Pike, P Day, P Gray, S Parish, J Peto, S Richard, and J Wahrendorf Guidelines for Simple, Sensitive, Significant Tests for Carcinogenic effects in Long-term Animal Experiments. Monograph on the Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal. International Agency on Research on Cancer Monograph - Supplement 2, 311-426, 1980.

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ATTACHMENT 1. SIMAZINE Female Rat Tumor Rates in rats fed 1000 ppm fo 52 weeks and then allowed a 52-week recovery period compared to their matching control groups.

Tumor	Dose(ppm)	0	1000	0	1000
Mammary Gland:		FEMALES		MALES	
Adenoma and/or Fibroadenoma		4/10	2/10		
Carcinoma		1/10	4/10		
Adenoma/Fibroadenoma/ Carcinoma Combined		5/10	6/10		
Pituitary:					
Adenoma only		9/10	9/10		
Carcinoma		0/10	0/10		
Adenoma and/or Carcinoma		9/10	9/10		
Kidney Tubules:					
Adenomas		0/10	0/10	0/10	1/10
Carcinoma				1/10	0/10
Adenoma and/or Carcinoma				1/10	1/10
Liver:					
Adenoma only				0/10	0/10
Carcinoma				0/10	0/10
Adenoma and/or Carcinoma				0/10	0/10
Thyroid C-Cell:					
Adenomas				0/10	0/10
Carcinoma				0/10	0/10
Adenoma and/or Carcinoma				0/10	0/10

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

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PESTICIDES AND TOXIC SUBSTANCES

Subject: Cyanazine (188C), Atrazine (63) and Simazine (740)
Quantitative Risk Assessment Comparisons on Malignant
Mammary Gland Tumors only in Rats. Revised Comparisons
as of July, 1991.

From: Bernice Fisher, Biostatistician
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Bernice Fisher 7/8/91

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Thru: Kerry L. Dearfield, Ph.D., Acting Section Head
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Kerry Dearfield 7.8.91

HED's previous estimate of cyanazine's Q_1^* of 8.8×10^{-1} was based upon malignant mammary gland tumors including fibrosarcomas. For comparative purposes with atrazine and simazine, malignant tumors including adenocarcinomas, carcinomas and carcinosarcomas only are used in the estimation of the unit risk, Q_1^*.

Animals with fibrosarcomas in the cyanazine study are excluded from the group for the estimate of Q_1^*. The reason for this exclusion is due to advice given by Dr. Brennecke (HED's consultant in pathology) that fibrosarcomas do not originate from epithelial cell tissues as do the carcinomas. The carcinosarcomas, which originate from both the epithelial and mesenchymal cell tissues, found in both the atrazine and cyanazine mammary gland malignant tumor data can be retained for the estimate of Q_1^*.

cc Kathy Pearce SRRD

Table on Estimated[+] Q_1^* $(mg/kg/day)^{-1}$ for Cyanazine, Atrazine and Simazine in Sprague-Dawley Female Rats

	Tumors in the Mammary Gland	Q_1^* $(mg/kg/day)^{-1}$ Rat	In Human Equiv.[++]
Cyanazine	Carcinosarcomas & Adenocarcinoma	1.59×10^{-1}(a)	8.4×10^{-1}(c)
Atrazine	Adenocarcinoma & Carcinosarcoma	$1.72 \times 10^{-}2$(b)	$9.2 \times 10^{-}2$(c)
Simazine	Carcinoma	$2.25 \times 10^{-}2$(b)	1.2×10^{-1}(c)

[+] Based on results from Statox computer program
[++] Derived by the use of surface area correction - $(\text{Human Wt.}/\text{Rat Wt.})^{1/3}$

(a) Multi-Stage Model (Global86)
(b) Time-to-Tumor Multi-Stage Model (Weibull83)
(c) Cyanazine - This Q_1^* is the estimate to be used for Risk Characterization.
Atrazine - This Q_1^* is the estimate for comparative purposes only of the three chemical compounds and is not the one that is used for Risk Characterzation (actual estimate used is 2.2×10^{-1} based upon both benign and malignant mammary gland tumors).
Simazine - This Q_1^* is the estimate that has been and is still being used for Risk Characterization.