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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

AUG 24 1994

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Terbuthylazine

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Health Effects Division (7509C)
and
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Review Section 4, Toxicology Branch I
Health Effects Division (7509C)
and
Esther Rinde, Ph.D. E. Rinde
Manager, Peer Review Committee for Carcinogenicity
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TO: Marshall Swindell
Product Manager #31
Registration Division (7505C)
and
Bruce Sidwell, Manager
PM Team 53
Special Review and Reregistration Division
Reregistration Division (7508W)

THROUGH: Stephanie R. Irene, Ph.D. Stephanie R. Irene
Acting Deputy Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on May 25, 1994 to discuss and evaluate the weight-of-the-evidence on terbuthylazine with particular reference to its carcinogenic potential. The CPRC concluded that terbuthylazine should be classified as Group D - not classifiable as to human carcinogenicity. This decision was based on the finding of tumors only in the rat which were significantly increased only at a dose which the CPRC believed to be excessively toxic, but which were the same tumor types induced by closely related analogs.

SUMMARY

Administration of terbuthylazine in the diet to (Tif:RAIf) rats resulted in statistically significant increases in benign interstitial cell tumors of the testes in the male. In the female rats, there was a statistically significant increase in mammary gland carcinomas. The CPRC concluded that the tumors in both sexes were associated with the administration of the chemical, and that the types of tumors are the same as are seen with other chemicals of this class (triazines), suggesting a common mode of action.

Significant increases in tumors in the rat occurred only at the highest dose in this study. The CPRC considered the highest dose to be excessive, based on severe weight gain depression and that the rats in the highest dose group were compromised and "physiologically abnormal." There was no apparent increase in tumor incidence when terbuthylazine was administered in the diet to Rif:MAGf (SPF) mice at doses considered adequate for carcinogenicity testing. Terbuthylazine is a member of a class of chemicals which are frequently associated with mammary tumors in the female Sprague-Dawley rat and sometimes associated with interstitial cell tumors of the testes in male rats. Terbuthylazine does not appear to have mutagenic activity (evidence for mutagenicity for the triazine class is generally weak).

The consensus of the CPRC was that the highest dose tested (750 ppm) was excessive in both sexes. Weight gain decrements (with respect to controls) of $\geq$ 10% were observed throughout the study in both sexes and at 54 weeks were 49% for males, and 53% for females; at 105 weeks they were up to 61% in females. Significantly decreased organ weights and changes in urine specific gravity, pH and volume were also observed, although there were no adverse effects on survival (males had increased survival at the top dose). The CPRC considered that the rats in the highest dose group in this study were compromised and not physiologically normal. [Details are provided in Section F. "The Weight of Evidence".]

The classification of Group D was based on the difficulty in determining the relevance to humans of tumors which were significantly increased only at a dose considered excessively toxic to the rat, but which were the same tumor types induced by closely related analogs.

A. Individuals in Attendance at the meetings:

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

Penny Fenner-Crisp

William Burnam

Karl Baetcke

Marcia Van Gemert

Richard Hill

Elizabeth Doyle

Hugh Pettigrew

Esther Rinde

Yin Tak Woo

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

Linnea Hansen[1]

Marion Copley

Lori Brunsman

Lucas Brennecke[2]
(PAI/Clement)

3. Other Attendees:

Bernice Fisher

[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

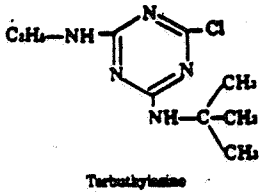
[2]Signature indicates concurrence with pathology report.

B. Material Reviewed

The material available for review consisted of DER's, one-liners and other data summaries prepared and/or supplied by Dr. Linnea Hansen and William Greear, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background Information

Terbuthylazine is registered for use as an algicide. Its current uses are limited to commercial and industrial water cooling tower systems, evaporative condenser water systems, ornamental ponds, fountains and aquaria, and formulation of aquatic noncrop use products. Its chemical structure is shown below:



Terbuthylazine

Its PC Code No. is 080814, the Tox Chem No. is 125b and the CAS No. is 5915-41-3. Its chemical name is 2-(tert-butylamino)-4-chloro-6-(ethylamino)-s-triazine. Other names include 6-chloro-N-(1,1-dimethylethyl)-N'-ethyl-1,3,5-triazine-2,4-diamine; s-triazine, 2-(tert-butylamino)-4-chloro-6-(ethylamino)-; 1,3,5-triazine-2,4-diamine, 6-chloro-N-(1,1-dimethylethyl)-N'-ethyl-; GS 13529; Gardoprim; Primatol M; Primatol M80; and Sorgoprim.

D. Evaluation of Carcinogenicity Evidence

1. Rat Chronic/Carcinogenicity Study #1

Reference: Gfeller, W.; Basler, W; Zakke, F.; Hess, R. "Lifetime Carcinogenicity and Chronic Toxicity Study in Rats: GS 13529", June 16, 1983. MRID No. 00156486, Study No.: 785196; Testing Facility: Ciba-Geigy Ltd. Sisseln Facility, Stein, Switzerland.

a. Experimental Design

Terbuthylazine (96.8%) was administered to a total of 80 male and 80 female (Tif:RAIf) rats in the diet at concentrations of 0, 30, 150 or 750 ppm. Ten animals/sex from each dose group were sacrificed at 12 months and 20 at 24 months; the other 50 were intended for terminal sacrifice at 112 weeks (males) and 122 weeks (females). The dosed terminal sacrifice groups were given untreated diet after Week 104, allowing a recovery period of 8 weeks for males and 18 weeks for females. (The recovery period does not affect tumor

counts. Histopathology and other parameters were measured at several intervals prior to sacrifice). Male rats at 30, 150 or 750 ppm groups received average daily doses of 1.24, 6.97 or 41.47 mg/kg/day and female rats received 1.37, 7.81 or 52.80 mg/kg/day, respectively.

b. Discussion of Tumor Data

Table 1 shows the incidence of benign interstitial cell tumors of the testes. There was a statistically significant increased incidence of benign testicular interstitial tumors at 750 ppm (13%) vs. controls (4%) by pair-wise comparison, as well a significant dose-related trend (both $p<0.05$).

Table 1 Incidence (%) of Benign Interstitial Cell Tumors of the Testes in Male Rats[+] and Peto Prevalence Test Results (p values)[1]

	Dose Level (ppm)				
	0	30	150	750	Historical controls
Benign Interstitial Cell Tumors	3/78(4)	4[a]/79 (5)	2/77 (3)	10/79 (13)	range 0 - 7.5% mean 2.74%
p =	0.019*	0.148	0.666[n]	0.034*	—

1 - Data on benign interstitial cell tumors in male (Tif.RAIf) rats and statistical analysis were abstracted from L. Brunsman memorandum dated April 19, 1994 (see Attachment 5).
+ - Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of first tumor.
n - Negative change from control
a - First benign tumor observed at week 53, dose 30 ppm
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$.

Historical control data provided by the sponsor included the incidence of benign interstitial cell tumors of the testes in male rats from 15 studies lasting up to 104 weeks conducted between October 1978 and May 1988. The incidence of benign interstitial cell tumors ranged from 0/79 (0%) to 6/80 (7.5%). The mean incidence was 31/1131 (2.74%). The incidence of benign interstitial cell tumors in the 750 ppm group (13%) therefore was outside the range observed in historical controls.

Table 2 shows the incidence of female mammary gland tumors. There was a statistically significant ($p <0.01$) dose-related trend for increased incidence of mammary carcinomas and also a significant difference ($p <0.01$) in the pair-wise comparison of controls to the 750 ppm group. However, combined benign/malignant mammary tumor incidence was not increased (it is considered appropriate to combine malignant and benign tumors of this type). No malignant tumors were observed at the 12 month sacrifice. At 24 months 1, 2, 0 and 2 were observed (0, 30, 150 and 750 ppm, respectively).

Table 2 Incidence (%) of Mammary Gland Tumors[+] in Female Rats and Fisher Exact Test and Exact Trend Test Results (p values)[1]

	Dose Level (ppm)				
	0	30	150	750	Historical Controls
Adenomas (%)	3/70 (4)	4/70 (6)	2/69 (3)	1/64 (2)	Range 0%-31.25% Mean 4.32%
p =	0.135	0.500	0.507[n]	0.344[n]	---
Fibroadenomas (%)	16/70 (23)	17/70 (24)	9/69 (13)	8/64 (12)	Range 11.11%-57.14% Mean 34.60%
p =	0.043[n*]	0.500	0.099[n]	0.090[n]	---
Carcinomas (%)	4/80 (5)	9/80 (11)	3/79(4)	14/75 (19)	Range 2.56%-16.46% Mean 9.62
p =	0.003[**]	0.123	0.507[n]	0.007[**]	---
Combined (%)	23/80 (29)	30/80 (38)	14/79 (18)	23/75 (31)	Range 22.78%-67.14% Mean 48.63
p =	0.492	0.157	0.072[n]	0.466	---

1 - Data on mammary gland tumors in female (Tif.RAIf) rats and statistical analysis were abstracted from L. Brunsman memorandum dated April 19, 1994.
\+ - Number of tumor bearing animals/number of animals examined, excluding those that died or were sacrificed before Week 43 for carcinomas and combined, and before week 54 for adenomas and fibroadenomas. First carcinoma observed at Week 43 (750 ppm); first adenoma observed at Week 94 (30 ppm) and first fibroadenoma at Week 72 (750 ppm).
n - Negative trend or negative change from control.
* - $p < 0.05$; ** - $p < 0.01$

The sponsor provided historical control data on the incidence of mammary tumors in female Tif.RAIf rats from 15 studies lasting up to 104 weeks and conducted between October 1978 and May 1988. The incidence of mammary gland carcinoma ranged from 2/78 (2.56%) to 13/79 (16.5%) with a mean of 109/1133 (9.62%). The incidence of mammary gland carcinoma in the 750 ppm group (19%) was just outside historical control range. Although the first carcinoma at 750 ppm was observed at Week 43 (moribund sacrifice), animals that developed malignant mammary gland tumors did not show significantly reduced survival or decreased tumor latency. Single incidences of mammary gland carcinosarcoma were observed at 150 and 750 ppm.

- c. Non-neoplastic Lesions

There were no adverse effects on survival in treated rats. In males at 750 ppm, survival was greater than controls (35%, 46%, 54% and 73% at week 105 at 0, 30, 150 and 750 ppm, respectively; excludes Week 53 sacrifice group). In females, survival at 0 and 750 ppm was similar (59%, 69%, 70% and 61% at week 105 at 0, 30, 150 and 750 ppm, respectively). There were dose-related decreases in mean body weight and body weight gain in treated animals compared to controls which were

sustained throughout the study. At 54 weeks, body weight gain of males in the 30, 150 and 750 ppm groups was decreased by 10%, 28% and 49% compared to controls, respectively. Females had comparable decreases in body weight gain: at 54 weeks, 12%, 32% and 47% at 30, 150 and 750 ppm, respectively, and by Week 105, 16%, 35% and 61%. At termination, the decrease in mean body weight of both sexes at 750 ppm was less pronounced than during treatment (but still significant) due to increased weight gain of high dose animals and body weight decreases of controls during the recovery period. Food consumption was decreased in males and females, particularly during the initial weeks of the study. At Week 1, decreases in food consumption (on a g/animal basis) of -35% and -22% in males and females, respectively, were observed at 750 ppm but at later times, consumption was generally ≤20% (males) or ≤10% (females) less than controls. There were slight, dose-related decreases in erythrocyte parameters in females at 150 and 750 ppm during the first 18 months. At 150 and 750 ppm, specific gravity of urine was increased (1%), pH decreased (1 pH unit) and volume decreased (at 750 ppm, ~46% at 52 weeks) in males and females during the first 18 months. Decreased absolute liver, kidney and heart weights at 150 and 750 ppm were related to decreased body weight. Nonneoplastic microscopic changes observed at 750 ppm are summarized below in Table 3.

Table 3 Incidence (%) of Selected Nonneoplastic Lesions in Rats[a]

	Males/Dose (ppm)				Females/Dose (ppm)			
	0	30	150	750	0	30	150	750
No. of Animals:	69	69	67	69	70	70	69	64
Lesion:								
Lung								
Inflammatory cell infiltration	13 (18.8)	19 (27.5)	7 (10.4)	23 (33.3)*	7 (10.0)	11 (15.7)	11 (15.9)	5 (7.8)
Foam cells	24 (34.8)	24 (34.8)	23 (33.3)	46 (66.7)*	8 (11.4)	12 (17.1)	14 (20.3)	35 (46.9)*
Liver								
Biliary cysts	1 (1.4)	0	3 (4.5)	2 (2.9)	4 (5.2)	9 (18.0)	10 (14.5)	14 (21.9)*
Thyroid								
Nodular hyperplasia	1 (1.4)	2 (2.9)	1 (1.5)	1 (1.4)	0	2 (2.9)	1 (1.4)	4 (6.3)*
Testes: •								
No. of Animals	69	69	74	77				
Interstitial Leydig cell nodular hyperplasia	6 (8.7)	3 (4.3)	5 (7.5)	21 (27)**	—	—	—	—

a - Number of animals affected are indicated for each lesion, excluding animals that died or were sacrificed before observation of the first lesion. Number in parentheses is percent incidence.

* - significantly different from controls at $p \leq 0.05$

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The high dose of 750 ppm was considered excessive for assessing the carcinogenic potential of terbuthylazine due to large decreases in body weight gain (-47% and -61% of controls in males and females, respectively, by Week 105) and altered urinalysis parameters. However, there were no adverse effects on survival in treated males and females; in males, survival was greater than controls, in females, survival was comparable. Body weight gain decreases were sustained throughout treatment. The decreased body weight gain appeared to result from systemic toxicity rather than palatability alone, based on the following considerations: firstly, food consumption was not significantly reduced if considered on a g/body weight bases instead of g/animal (as expressed in the study report). Secondly, although food consumption was comparable in females at 150 and 750 ppm, body weight gain was reduced to a greater extent at 750 ppm. This is supported by the results of the rat developmental toxicity study (MRID 491627-01), where decreased body weight and food consumption were observed even though terbuthylazine was administered by gavage and not in the diet. Decreased urine volume and pH and increased urine specific gravity were also observed at 750 ppm, suggesting that metabolism of these animals was altered. Organ weight decreases paralleled the decreased body weights. In addition, there were increased incidences of lesions in the lung and testes of male rats and in lung, liver and thyroid of female rats.

2. Rat Chronic/Carcinogenicity Study #2

Reference: Gfeller, W.; Basler, W.; Zak, F.; Hess, R. "Lifetime Carcinogenicity and Chronic Toxicity Study in Rats," June 17, 1983. MRID No. 00157342, Study No. 791229, Testing Facility: Ciba-Geigy Ltd. Sisseln Facility, Stein, Switzerland.

a. Experimental Design

Terbuthylazine (98%) was administered to a total of 80 male and 80 female (Tif:RAIf,SPF) rats in the diet at concentrations of 0, 6 or 30 ppm. Ten of these animals/sex/dose were sacrificed at 12 months and 20 at 24 months. The remainder (50/sex/dose) were treated until Week 98. Thereafter, the remaining animals received untreated diet until sacrifice at week 112 for males and 121 weeks for females (recovery period of 14 weeks, males and 23 weeks, females). Mean compound intake was 0.35 and 1.6 mg/kg/day for males and 0.36 and 1.6 mg/kg/day for females in the 6 and 30 ppm groups, respectively. The study was undertaken to determine a NOEL for the previously discussed rat study.

b. Discussion of Tumor Data

There was no increase in the incidence of compound-related neoplastic lesions observed in the study.

c. Non-neoplastic Lesions

Mortality in all dosed animal groups was similar to controls. Body weight gains at 6 ppm were reduced by less than 2% compared to controls for most of the study and were 4% less than controls at week 105. At 30 ppm, body weight gain in males was comparable or decreased by less than 5% below controls throughout most of the study, gradually increasing to about 10% less than controls by week 105 (statistically significant during weeks 2-26). Body weight gain in females at 6 ppm was comparable to or reduced by less than 4% of controls throughout most of the study but during the last months increased (to 10% at week 105). At 30 ppm, body weight gain in females was about 10% less than controls until week 67, gradually decreasing to -15% by week 105 (statistically significant from weeks 18-98). Food consumption was significantly lower in males and females in the 30 ppm group during weeks 1-13. There were no effects on survival, hematology, clinical chemistry, urinalysis, mean organ weights, gross lesions or histopathology.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The minimal toxicity observed (slight decreases in body weight, mostly less than 10% of control, and in food consumption in the 30 ppm group) is considered inadequate for testing the carcinogenic potential of terbuthylazine. No other effects were observed.

3. Mouse Chronic/Carcinogenicity Study

Reference: Gfeller, W. "Chronic Toxicity and Carcinogenicity Study in Mice," August 1982, MRID No. 00156487, Study No: 781595 (GU), Testing Facility: Ciba-Geigy, Ltd., Sisseln Facility, Stein, Switzerland.

a. Experimental Design

Terbuthylazine (98%) was administered to groups of 50 male and 50 female Tif:MAGf (SPF) mice at dose levels of 0, 30, 150 or 750 ppm for a period of 24 months. Mean daily compound intake was 3.28, 16.99 and 86.76 mg/kg/day for male mice and 3.22, 16.6 and 88.54 mg/kg/day for females in the 30, 150 and 750 ppm groups, respectively.

b. Discussion of Tumor Data

No compound-related neoplastic lesions were observed.

c. Non-neoplastic Lesions

Survival was not adversely affected by compound administration. Males in the 750 ppm group had a higher survival rate than controls (50% vs 20%). Female survival at termination was ≈40% (controls and 750 ppm groups). Body weight gain of males in the 750 ppm group was decreased by less than 10% of controls throughout the study. Body weight gain of females in the 750 ppm groups was decreased by 23% at Week 105 compared to controls. Statistically significant decreases in mean body weight representing body weight gain as much as 34% less than controls were observed in high dose females during most of the study (Week 9 through 101). Food consumption was decreased in males in the 750 ppm group by approximately 20% compared to controls throughout most of the study. Increased HGB, HCT and RBC in males in the 750 ppm group were within normal limits and not considered biologically significant. There were no treatment related differences in urinalysis parameters, absolute/relative organ weights, gross observations or microscopic lesions.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Dosing was considered adequate for assessing the carcinogenic potential of terbuthylazine in females based on statistically significant body weight gain decreases (23-34% throughout most of the study. There were no significant adverse effects in males in the 750 ppm group (20% decrease in food consumption). Although dosing in males may not have achieved an MTD, it is considered adequate for assessing the carcinogenic potential of terbuthylazine in male mice since triazine herbicides, as a group, do not appear to cause an increase in neoplastic lesions in mice.

E. Additional Toxicology Data on Terbuthylazine

1. Metabolism

When rats are fed 3.6 mg of ^{14}C-ring labeled terbuthylazine, radioactivity is rapidly excreted: 52.9% and 65.9% in urine and 52.0% and 33.8% in feces of male and female rats, respectively. Major routes of metabolism involve dechlorination/hydroxylation and mono-or didealkylation, possibly followed by hydroxylation. The triazine ring is not degraded. Up to 15 and 25 mostly polar products have been separated in urine and feces, respectively, indicating extensive metabolism of the parent compound. Unchanged parent

compound was not found in the urine or feces. Two urine fractions found in relatively high amounts (12% and 3.4% of applied dose) have been identified as metabolites with one methyl group of the butyl moiety retained but the rest replaced by a carboxyl group. In addition, a chloro-deethylated derivative is present in small amounts. Ammeline and ammelite, products of dealkylation and/or hydroxylation, are present in feces in small amounts. Radioactivity did not accumulate in tissues.

2. Mutagenicity

Terbuthylazine has been tested in several mutagenicity studies. No positive mutagenic response was observed in any study. Acceptable studies fulfill all 3 categories for mutagenicity testing. The following studies are available:

TABLE 4: MUTAGENICITY STUDIES ON TERBUTHYLAZINE

STUDY	STATUS
Gene Mutation	
Ames No. 1 (Salmonella - strains TA98, TA100, TA1535 and TA1537) Tested at up to 500 ug/plate (activated) and 50 ug/plate (non-activated) (MRID Nos. 00108817 and 00140816, Study No. PH-2.632, 7/20/77). NEGATIVE	Acceptable Doc. No. 002994
Ames No. 2 (Salmonella - strains TA1535, TA1537, TA98 and TA100) Tested at up to 5000 ug/plate w/wo metabolic activation. (MRID No. 416340-01 Study No. 874192, 8/20/87) NEGATIVE	Acceptable Doc. No. not yet assigned
Chromosomal aberrations	
In Vitro Chromosomal Aberrations (Human lymphocytes). Tested at up to 1000 ug/ml, w/wo metabolic activation. (MRID No. 414181-01, Study No. 860127, 1/22/87. Reported to be NEGATIVE	Unacceptable Doc. No. 08077
Micronucleus (Mouse). Tested at levels up to 5000 mg/kg. (MRID Nos. 414181-02, 420598-05, Study No. 891393, 10/16/89). NEGATIVE	Unacceptable - Doc. No. 008077 Acceptable - Doc. No. 009492
Other Genotoxic Effects	
DNA Repair (Rat hepatocytes in vitro). Tested at levels up to 125 ug/ml. (MRID No. 00151619, Study No. 8311174, 6/18/84). NEGATIVE	Unacceptable - Doc. No. 005210 Acceptable - Doc. No. 006810
DNA Repair (Human fibroblasts). Tested at levels up to 125 ug/ml. (MRID No. 00151620, Study No. 831175) NEGATIVE	Unacceptable - Doc. No. 005210 Acceptable - Doc. No. 006810
UDS (Rat hepatocytes in vitro). Tested at levels up to 1000 ug/ml. (MRID Nos. 413918-01, 420598-06). NEGATIVE	Acceptable Doc. Nos. 008509, 009680

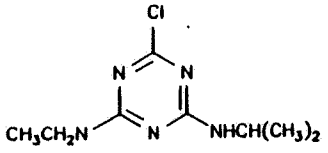
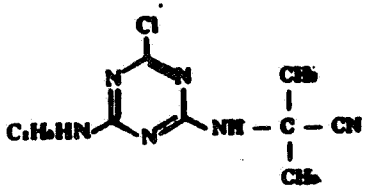
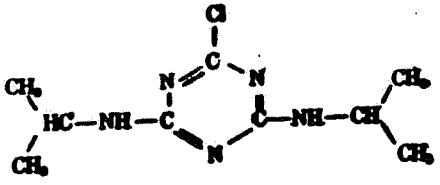
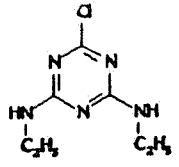
3. Structure Activity Relationship

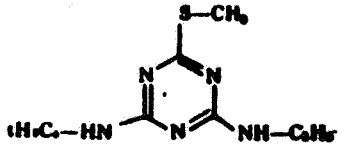
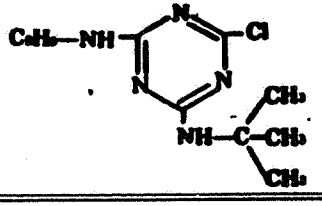
Terbuthylazine is an s-triazine compound that is structurally related to atrazine, cyanazine, propazine, simazine and terbutryn. Comparison of structures, genotoxicity and carcinogenicity is presented in Table 5.

A structure-activity relationship (SAR) analysis of s-triazine herbicides was prepared by Dr. Yin-Tak Woo of the Office of Toxic Substances (memorandum from J. Cotruvo to P. Fenner-Crisp, January 7, 1991). The following conclusions from this analysis, quoted from the memorandum, are relevant to terbuthylazine:

> "1. The carcinogenic activity of any given s-triazine compound is greatly dependent on the nature of the substituents at the 2-, 4-, and 6- positions. Even among closely related compounds, a significant difference in carcinogenic activity may occur as a result of minor structural changes.
>
> 2. Presence of N-alkyl group(s) appears to be crucial for carcinogenic activity of s-triazine herbicides and related compounds. It appears that s-triazine compounds containing two or more unalkylated amino groups may lack chemical carcinogenic activity (e.g., Cyromazine, Melamine).
>
> 3. The nature of the substituent at the 2-position plays an important modifying role on the carcinogenic potency of 4,6-bis-alkylamino-s-triazines. The relative activities follow the order: 2-chloro> 2-alkylthio> 2-alkoxy. Whereas information on 2-hydroxy derivatives is not available, it is speculated that the activity of 2-hydroxy derivatives should be less than or equal to the corresponding 2-alkoxy derivative because of easier excretion and because of the negative data on cyanuric acid (trihydroxy-s-triazine)."

TABLE 5: COMPARATIVE CARCINOGENICITY PROFILES OF STRUCTURALLY RELATED TRIAZINE COMPOUNDS

CHEMICAL NAME	STRUCTURE	TUMOR SITE(S)	EVIDENCE OF GENOTOXICITY	CLASSIFICATION/Q_1^* (HED Cancer Peer Review)
Atrazine		Mammary gland adenomas and carcinomas, female rat Benign interstitial tumors in testes (within historical control range) Mouse negative	-	C 2.2 x 10exp-1(mg/kg/day)exp-1 (based on mammary gland carcinomas in female rats at HDT and benign at several dose levels, positive mutagenicity data)
Cyanazine		Mammary gland adenomas and carcinomas, female rat Mouse negative	+ (mouse lymph. gene mut.; UDS)	C 8.4 x 10exp-1(mg/kg/day)exp-1 (based on mammary gland adenomas/carcinomas in female rats at 2 dose levels, positive mutagenicity data)
Propazine		Mammary gland adenomas, female rat Mouse negative	+ (CHO gene muta.)	C/NO (based on mammary gland adenomas in female rats at HDT, positive mutagenicity data)
Simazine		Mammary and pituitary gland carcinomas, female rat Mouse negative	+ (Published studies: Mouse lymph. gene mut.)	C 1.2 x 10exp-1(mg/kg/day)exp-1 (based on mammary and fatal pituitary gland carcinomas in female rats at HDT and 2 dose levels, respectively, positive mutagenicity data)

Terbutryn		Mammary gland and liver adenomas/carcinomas, female rat Testicular interstitial cell adenomas and thyroid adenomas/carcinomas, male rat Mouse negative	-	C/NO (based on increased adenomas and carcinomas in several tissues in males and females at HDT exceeding MDT)
Terbuthylazine		Mammary gland carcinomas, female rats Testicular interstitial cell benign tumors, male rat Mouse negative	-	D

4. Carcinogenicity in animals -- Terbuthylazine

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concluded that exposure to terbuthylazine resulted in an increased incidence of benign interstitial cell tumors of the testes in male rats and increases in mammary gland malignant carcinomas in female rats. The induction of testicular interstitial cell tumors in male rats and mammary gland tumors in female rats is consistent with induction of these same tumor types in male and female rats by closely related structural analogs, other 2-chloro substituted s-triazines (atrazine, cyanazine, propazine). The relevance of the tumor data to an evaluation of terbuthylazine's potential for human carcinogenicity is discussed elsewhere in this report.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on terbuthylazine in a weight-of-the-evidence determination of carcinogenic potential:

1. Toxicity at the highest dose tested, 750 ppm, was considered to be excessive based on pronounced decreases in body weight gain in both sexes throughout the study and on altered urinalysis parameters. Decreased food consumption was observed at 750 ppm in both sexes. Increased urine specific gravity and decreased urine pH and volume may have reflected altered metabolism. Significantly decreased liver, kidney and heart weights were related to the decreased body weights. Dose-related, decreased body weight gains were also observed at low and mid-doses in males and females.

2. Terbuthylazine was associated with a statistically significantly increased incidence of benign interstitial cell tumors of the testes in male rats at high dose (750 ppm). The incidence was outside the range observed in historical control data from the same laboratory for this strain of rat. The tumors did not affect survival and time to onset of tumors was not decreased due to treatment with terbuthylazine.

3. Terbuthylazine was associated with a statistically significantly increased incidence of mammary gland carcinomas in female rats at high dose (750 ppm). The incidence was slightly outside the range observed in historical control data from the same laboratory for this strain of rat. These tumors did not affect

survival. Terbuthylazine did not decrease the time to onset of tumors. However, total mammary tumors (combined adenomas/fibroadenomas/ carcinomas; considered appropriate to combine benign and malignant lesions for this tumor type) were not increased.

4. Terbuthylazine was not associated with increased incidence of neoplasms in mice at dietary doses up to 750 ppm (~88 mg/kg/day). Dosing in male mice may not have achieved an MTD but was considered adequate for evaluation of carcinogenic potential of terbuthylazine since the s-triazine herbicides, as a group, do not appear to cause an increase in the incidence of neoplastic lesions in mice.

5. Terbuthylazine was not genotoxic in several mutagenicity assays.

6. Terbuthylazine is structurally related to the s-triazine herbicides atrazine, cyanazine, propazine, simazine and terbutryn. All of these compounds have been classified as Group C carcinogens, based on increased incidence of malignant and/or benign mammary gland tumors in female Sprague-Dawley rats. Pituitary gland carcinomas, benign testicular interstitial cell tumors, thyroid adenomas/carcinomas and/or liver adenomas/carcinomas were also observed for some of these compounds. Quantitation of cancer risk using a low-dose extrapolation method was determined to be appropriate only for atrazine, cyanazine and simazine. Evidence for mutagenicity for the triazine class is generally weak, although some of the s-triazine compounds have demonstrated genotoxic potential in one or more assays.

G. Classification of Carcinogenic Potential:

The CPRC considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

Administration of terbuthylazine in the diet to (Tif:RAIf) rats resulted in statistically significant increases in benign interstitial cell tumors of the testes in male rats, and a statistically significant increase in mammary gland carcinomas in females. However, when carcinomas were combined with adenomas and fibroadenomas of the mammary gland there was no significant increase in total mammary tumors. All increases in tumors that were statistically significant occurred only at a dose which the CPRC considered excessively toxic to the rat.

Terbuthylazine is a member of a class of chemicals which are frequently associated with mammary tumors in female Sprague Dawley rats and sometimes with interstitial cell tumors of the testes in males.

There was no apparent increase in tumor incidence when terbuthylazine was administered in the diet to Rif:MAGf (SPF) mice at doses considered adequate for carcinogenicity testing.

Terbuthylazine does not appear to have mutagenic activity (evidence for mutagenicity for the triazine class is generally weak).

The CPRC therefore concluded that terbuthylazine should be classified as Group D - not classifiable as to human carcinogenicity. This decision was based on statistically significant increases in tumors only in the rat, only at a dose which the CPRC considered excessively toxic, but which were the same tumor types induced by closely related analogs.