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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review on Propazine

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

Attached for your review ia a package containing supplementary data for Propazine, submitted by Dr. Dykstra.

Propazine has been previously evaluated by the Peer Review Committee and was classified as a Group C carcinogen. The Committee is now being asked to re-evaluate this classification in light of this new information.

A meeting to reconsider the classification of Propazine is scheduled for Nov. 22 at 11:00A.M. in Room 821 CM-2.

Addresses:

B. Burnam	M. Copley
R. Engler	L. Slaughter
J. Quest	K. Dearfield
J. Hauswirth	B. Dykstra
D. Hill	E. Budd
B. Beliles	R. Levy
D. Beal	B. Sette

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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Propazine; Re-evaluation of Oncogenic Potential by Peer Review Committee

TO: Peer Review Committee

FROM: William Dykstra, Ph.D.
Section I, TOX-IRS
Health Effects Division (TS-769)

William Dykstra
11/10/88

The purpose of the peer review for propazine is to reconsider the oncogenicity issue in the female rat for mammary gland tumors.

The basis for the reconsideration is a re-evaluation of the slides for tumor counts.

A full statistical analysis will be distributed at the peer review meeting.

Based on recent information, the incidence of mammary gland tumors in female rats appears to be as shown below:

DOSE (ppm)	0	3	100	1000
Benign	19/53 36%	16/55 29%	22/59 37%	25/54 46%
Malignant	9/56 16%	17/55 31%	10/58 17%	15/53 28%
Combined benign & Malignant	28/56 50%	33/55 60%	32/59 54%	40/59 67%

Attachments:
Ciba-Geigy Letter of October 27, 1988
EPL Letter of May 5, 1988
IROC Addendum of June 8, 1988
IROC Historical Control Data
Peer Review of Propazine of August 10, 1987

Agricultural Division
CIBA-GEIGY Corporation
P.O. Box 18300
Greensboro, North Carolina 27419
Telephone 919 292 7100

CIBA-GEIGY

October 27, 1988

William Dykstra, Ph.D.
Health Effects Division (TS-769C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall 2 - Room 824C
Arlington, Va 22202

Dear Dr. Dykstra:

Enclosed please find the information you requested for the rat study for propazine. The report is a supplement to the original pathology report from Environmental Pathology Laboratories for the study in question. To aid you in summarizing the data, I am providing the following summary of the tumor incidence data taken from this revised report. Please note that the numbers differ somewhat slighltly from the summary provided to you in March, 1988. I have attempted to explain briefly why this occurred.

Errors in the original pathology report for the Propazine chronic rat study report were identified and corrected in a report addendum dated June 8, 1988. The revised incidence data, which is presented in Table 1, was not sent to the EPA following the decision to cancel the U.S. registration of Propazine. A new statistical analysis of the incidence data was not performed either, so the statistical flags have been deleted from the Table 1.

Table 1

Incidence(%) of Mammary Tumors in Female Rats[1]

Microscopic Diagnosis	Feeding Level (ppm)			
	0	3	100	1000
Adenoma	3(5)	3(5)	5(8)	11(18)
Fibroadenoma	22(34)	22(37)	24(41)	24(40)
Benign Tumors	24(38)	25(42)	26(44)	30(50)
Adenocarcinoma	6(9)	11(19)	8(14)	10(17)
Papillary Carcinoma	4(6)	7(12)	3(5)	8(13)
All Malignant Tumors	9(14)	17(29)	10(17)	15(25)
All Mammary Tumors	28(44)	33(56)	32(54)	41(68)
No. Animals Examined	64	59	59	60

[1]The first palpable mass was found at week 35 in the 1000 ppm female 39789; denominators for tumor incidence were determined on the basis of all animals surviving 35 weeks and longer.

The original version of this table prepared for the canceled SAP meeting (Table 2) is presented for comparison. There are several differences in diagnosis, particularly for the category, papillary carcinomas. It appears that the total mammary tumor incidence would be elevated at 1000 ppm.

Table 2

Incidence(%) of Mammary Tumors in Female Rats[1]

Microscopic Diagnosis	Feeding Level (ppm) 0	3	100	1000
Adenoma	4(6)	3(5)	5(8)	9(15)*
Fibroadenoma	22(34)	22(37)	24(40)	21(34)
Benign Tumors	24(37)	25(42)	26(43)	26(43)
Adenocarcinoma	5(8)	11(18)	8(13)	11(18)
Papillary Carcinoma	3(5)	7(12)	3(5)	11(18)*
All Malignant Tumors	8(12)	17(26)	10(17)	19(31)**
Normalized K-M Incidence[2]	(12)	(24)	(13)	(34)
All Mammary Tumors	27(42)	33(56)	32(53)	39(64)**
Normalized K-M Incidence[2]	(42)	(43)	(38)	(56)
No. Animals Examined	65	59	60	61

[1]The first palpable mass was found at week 35 in the 1000 ppm female 39789; denominators for tumor incidence were determined on the basis of all animals surviving 35 weeks and longer.

[2]Adjusted incidence based on one minus the Kaplan-Meier estimate of animals surviving without known mammary tumors. These incidences were normalized to control levels so that a direct comparison to historical control data is possible.

* Significantly different from control at $p < 0.0_5$ by the Thomas, Breslow, and Gart life table method.

** Significantly different from control at $p < 0.01$ by the Thomas, Breslow, and Gart life table method.

I hope this provides the information you need to finalize your activities with propazine.

Sincerely,

Thomas J. Parshley
Regulatory Specialist

Enclosure

Attachment 1

IRDC's Historical Control Incidence of Mammary Tumors in Sprague Dawley Rats

Study Identification

STUDY	START DATE	END DATE
A	7/21/76	7/21/78
B	4/15/76	4/13/78
C	8/7/74	8/6/76
D	4/28/76	4/28/78
E	3/17/77	3/20/79
F	5/12/76	5/16/78
G	7/14/76	7/14/78
H	1/2/76	5/10/78
I	9/29/75	9/26/77
J	2/18/75	5/27/77
K	9/2/75	9/2/77
L	7/23/75	7/19/77
M	8/9/76	8/10/78
N	11/3/76	11/3/78
O	7/27/76	7/28/78
P	7/30/76	8/2/78
Q	11/9/76	11/10/78
R	10/1/76	10/3/78
S	8/30/76	8/30/78
T	6/23/77	6/26/79
U	4/15/77	4/19/79
V	3/30/76	4/5/78

Attachment 2

IRDC's Historical Control Incidence of Mammary Tumors in Sprague Dawley Rats

Individual Study Incidence Data

STUDY*	ADENOMA		FIBROADENOMA		ADENOCARCINOMA		ANIMALS WITH ONE OR MORE TUMORS	
C	1/47	(.02)	18/47	(.38)	5/47	(.11)	21/147	(.45)
J	7/107	(.07)	75/156	(.48)	20/156	(.13)	95/156	(.61)
L	***		25/42	(.60)	3/42	(.07)	29/42	(.69)
K	***		22/64	(.34)	1/64	(.02)	22/64	(.34)
I	9/74	(.12)	22/74	(.30)	2/74	(.03)	32/74	(.43)
V	21/98	(.21)	42/98	(.43)	6/98	(.06)	67/98	(.68)
B	***		23/60	(.38)	4/60	(.07)	23/60	(.38)
D	12/100	(.12)	47/100	(.47)	1/100	(.01)	52/100	(.52)
H**	5/41	(.12)	19/41	(.46)	12/41	(.29)	28/41	(.68)
F	2/60	(.03)	22/60	(.37)	1/60	(.02)	23/60	(.38)
G	11/97	(.11)	37/97	(.38)	13/97	(.13)	49/97	(.51)
A	6/48	(.13)	20/48	(.42)	10/48	(.21)	25/48	(.52)
O	1/65	(.02)	22/65	(.34)	6/65	(.09)	28/65	(.43)
P	6/64	(.09)	12/64	(.19)	14/64	(.22)	21/64	(.33)
M	***		15/29	(.52)	5/29	(.17)	18/29	(.62)
S	7/50	(.14)	19/50	(.38)	6/50	(.12)	27/50	(.54)
R	4/57	(.07)	21/57	(.37)	8/57	(.14)	24/57	(.42)
N	13/60	(.22)	22/60	(.37)	4/60	(.07)	32/60	(.53)
Q	3/64	(.05)	21/64	(.33)	2/64	(.03)	27/64	(.42)
E	3/55	(.05)	14/55	(.25)	8/55	(.15)	23/55	(.42)
U	9/150	(.06)	53/150	(.35)	41/150	(.27)	82/150	(.55)
T	2/47	(.04)	18/47	(.38)	8/47	(.17)	21/47	(.45)
TOTAL	122/1284	(.10)	589/1528	(.39)	180/1528	(.12)	769/1528	(.50)

* arranged in chronological order
** study ran for 28 months instead of 24
*** no data available

EPL

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.
P.O. BOX 474 HERNDON, VIRGINIA 22070 (703) 471-7060

May 5, 1988

Dr. Edwin I. Goldenthal
International Research and
Development Corporation
500 Main Street
Mattawan, MI 49071

Dear Dr. Goldenthal:

This is in regard to the incidence of mammary gland tumors for female rats as reported in the Propazine Two-Year Rat Study report, IRDC Study Number 382-007. In reviewing our records, there was an initial report of all of the findings on the high dose and control animals followed later by two addendum reports. All mammary glands were re-evaluated from the high and control groups along with mammary glands from the mid and low dose groups as well as a review of the wet tissues for additional mammary gland masses. A few additional slides were prepared following re-evaluation of wet tissues from all the groups. Enclosed are revised Summary Incidence Tables and Histopathology Incidence Tables for the mammary gland/skin which should represent the final overall evaluation of the mammary glands from this study.

With respect to the problems demonstrated by the asterisk on the tables submitted in a letter dated March 16, 1988 from Dr. Charles Breckenridge of CIBA-GEIGY Corporation to you, the following comments should explain the differences:

Animal Number	Group	Changes After Review
39417	Control	Papillar Adenoma (100**) rediagnosed as Papillary Carcinoma
39418	Control	Cystadenoma (95**) rediagnosed as Fibroadenoma
39460	Control	Additional Adenoma added (105*)
39790	High Dose	Additional Adenoma (97**) added to addendum
39792	High Dose	Adenoma (79**) rediagnosed as Fibroadenoma
39798	High Dose	Adenocarcinoma/Carcinoma (65**) rediagnosed as Adenoma
39800	High Dose	Papillary Adenocarcinoma/Carcinoma (95**) rediagnosed as Adenoma
39818	High Dose	Adenocarcinoma/Carcinoma (104**) rediagnosed as Adenoma
39824	High Dose	Two Adenocarcinomas/Carcinoma (67**) one rediagnosed as Fibroadenoma, the other as Adenoma

Animal Number	Group	Changes After Review
39827	High Dose	Adenocarcinoma/Carcinoma (56**) rediagnosed as Adenoma
39829	High Dose	Ductular Adenoma (60**) rediagnosed as Fibroadenoma
39830	High Dose	Papillary Carcinoma added (originally misidentified as 39836)
39834	High Dose	Additional Adenocarcinomas (2) (90**) added to addendum
39836	High Dose	Papillary Adenocarcinoma/Carcinoma (88**) not present at review (see 39830)
39841	High Dose	Papillary Carcinoma (66**) rediagnosed as Adenocarcinoma

Having never seen the final report issued by IRDC to CIBA-GEIGY Corporation, I do not know exactly where any changes to the pathology narrative should be made but a statement should be added to the pathology portion to clarify the fact that the mammary glands were reviewed from the high dose and controls, along with mammary glands from the mid and low doses, and a few additional slides created following re-evaluation of the wet tissues from all the animals. The Histopathology Incidence Tables and Summary Incidence Tables for mammary gland/skin submitted with this letter should represent the final overall evaluation of the mammary glands for this study. If you have any additional questions regarding this table or any aspects of the pathology reports previously submitted, please feel free to contact me.

Sincerely,

LARRY J. ACKERMAN, V.M.D.
Pathologist

LJA/wk
Enclosures

International Research
and Development Corporation
MATTAWAN, MICHIGAN, U.S.A. 49071 TELEPHONE (616) 668-3336

Addendum
to the
Final Report
(Submitted: April 28, 1980)

SPONSOR: Ciba-Geigy Corporation

TEST ARTICLE: Propazine Technical

SUBJECT: Two Year Chronic Oral Toxicity Study in Rats

DATE OF SUBMISSION: June 8, 1988

382-007

Reason for Addendum

By request of the Sponsor, the tabular results of the microscopic examination of mammary gland were reviewed. Subsequent communication with the subcontracted pathology lab (Experimental Pathology Laboratories, Inc., Herndon, Virginia, EPL), which had prepared the tables in question, dictated clarification of the pathology text as well as the microscopic incidence tables for mammary gland.

All mammary glands were re-evaluated from the control and high dose groups along with mammary glands from the mid and low dose groups. The wet tissues were also reviewed for additional mammary gland masses and a few additional slides were prepared. The results were reported in two separate addendum pathology summaries which were included in the final report.

Following the inquiry into the chronology and generation of the mammary gland tables, revised Summary Incidence Tables and Histopathology Incidence Tables for the mammary gland/skin were received from EPL. These tables represent the final overall evaluation of the mammary glands from this study and are added for clarification.

Edwin I. Goldenthal, Ph.D.
Vice President and Director of Research
Study Director

6/8/88
Date

Margery J. Wirth, B.S.
Director of Quality Assurance

6/8/88
Date

382-007

peripheral nerve (sciatic)	spleen
pituitary gland	sternum
prostate	stomach (cardia, fundus, pylorus)
salivary gland (submaxillary)	thyroid gland
skin	trachea
small intestine (duodenum, jejunum and ileum)	urinary bladder
spinal cord	uterus
	any other tissue with gross lesions

The above tissues from rats which were sacrificed at termination or which died or were sacrificed in extremis during the period 12-24 months were delivered to Experimental Pathology Laboratories, Inc., Herndon, Virginia for histologic processing and microscopic examination.

In addition, mammary gland slides from the control and high dose groups for 0-12 months, wet tissues from the 0-12 months, and wet tissues from the low and mid-dose groups from 12-24 months (which had been returned to IRDC), were later shipped to EPL per request from Dr. Ackerman. All mammary glands were re-evaluated and a few additional slides were prepared and examined.

B. RESULTS

1. Gross Pathology (Tables 26-29):

The number of subcutaneous masses and nodules in female rats from the 1000-ppm group was slightly increased when compared to the control group. This increase, which correlated with a statistical significant increase in microscopically diagnosed mammary neoplasms in this group (see below), may have been compound related. No other gross findings at necropsy were considered to have had a compound relationship.

2. Organ Weights (Tables 30-36):

Although statistical variations occurred in sex group mean weights of a number of organs of rats in the treated groups, there was no dose response evident and the organs which had statistical weight variations were not the site of compound related gross or microscopic morphologic lesions. These weight variations therefore were not considered of toxicological significance.

3. Histopathology (Tables 37-43):

12 Month Interim Sacrifices, Deaths 0-12 Months:

No microscopic pathologic lesions which were considered related to Propazine feeding were seen in any tissues examined from rats from the 1000-ppm group which were sacrificed at the 12-month interim or which died or were sacrificed in extremis during the first 12 months of study. Microscopic findings in these rats were those which commonly occur in untreated rats of this age and strain. They were primarily lesions of mild inflammatory conditions or early degenerative changes and they occurred with similar frequency and severity in rats from the control group and the 1000-ppm group.

Mammary gland slides and wet tissues were reviewed/re-evaluated by Larry J. Ackerman, V.M.D. of Experimental Pathology Laboratories, Inc. whose report follows.

Terminal Sacrifices, Deaths 12 Months to Termination:

Microscopic examination of tissues from these rats was done by Larry J. Ackerman, V.M.D. of Experimental Pathology Laboratories, Inc. whose report follows.

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

JUN 1987

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Propazine

FROM: Esther Rinde, Ph.D. E. Rinde 7/10/87
Scientific Mission Support Staff (TS-769c)

TO: Robert Taylor
Product Manager #25
Registration Division (TS-767c)

The Toxicology Branch Peer Review Committee met on May 21, 1987 to discuss and evaluate the weight-of-the-evidence on Propazine 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.)

Theodore M. Farber — Theodore M Farber
William L. Burnam — W L Burnam
Reto Engler — Reto Engler
Louis Rizzo — Louis Rizzo
Robert Beliles — Robert J Beliles
Richard Levy — Richard Levy
Judith W. Hauswirth — Judith W. Hauswirth
Esther Rinde — Esther Rinde

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

William Dykstra (Reviewer) — William Dykstra
Edwin Budd (Section Head) — Edwin Budd

A. 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.)

Anne Barton _____

Richard Hill _____

Diane Beal Diane O. Beal

John A. Quest John A. Quest

4. Other Attendees: Henry Spencer (Tox. Branch).

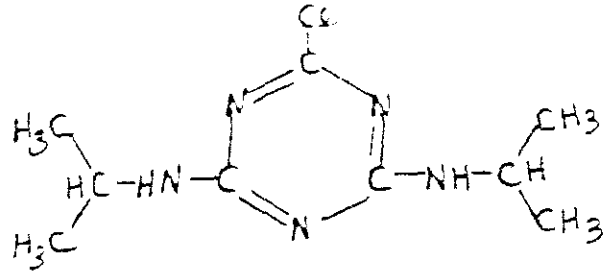
B. Material Reviewed:

The material available for review consisted of data summaries and 1-liners prepared by the reviewer, and a CAG Memo [Assessment of the Carcinogenicity of Propazine, J.Holder, 1/20/87]. A copy of the material reviewed is attached to the file copy of this report.

C. Background Information:

Propazine is a triazine herbicide [2-chloro-4,6-BIS(isopropylamino)-S-triazine] which is used as a preemergent herbicide, pricipally (in the U.S.) for sorghum protection. Propazine was referred to the "Ad Hoc Committee on Long-term Studies" on Sept. 25, 1984. At that time a consensus could not be reached based on the material presented. Additional, more detailed, reviews were requested for both the rat and mouse studies.

Structure:



D. Evaluation of Oncogenicity Evidence of Propazine

1. Two-Year Carcinogenicity Study in CD-1 Mice
(IRDC Report No. 382-004; April 24, 1980)

Sixty male and 60 female (randomized) CD-1 mice were fed propazine in their diets for 2 years at 0, 3, 1000, or 3000 ppm. Mortality, body weight and food consumption were not affected by treatment. Significant incidences of non-neoplastic lesions were observed: hemosiderin-laden macrophages in high-dose males (15/60 vs 3/60 in controls) and myocardial degeneration in high-dose females (17/59 vs 4/60 in controls).

Preliminary evaluation of the reticuloendothelial system, suggested a significant increase in malignant lymphoma in females at 3000 ppm, based on total number of tumors per animal at different sites. Re-evaluation of the incidence of this tumor, based on number of tumor-bearing animals gave the following results: control, 7/60; 3 ppm, 8/60; 1000 ppm, 10/60; 3000 ppm, 6/60 (Table I). No significant dose-related trend and no indication of statistical significance in pairwise comparisons were found for the re-evaluated data and there was no effect on latency.

(In the CAG memo, a positive trend (p=0.02) was noted for both hepatocellular carcinoma and male mouse lung adenomas, neither of which, however, demonstrated a dose-response <J.Holder 1/20/87>.)

The MTD apparently was not achieved, since mortality, body weight, and food consumption were unaffected by treatment, and no overt toxicity was noted, other than that indicated above.

2. Two-Year Study in Charles River Sprague-Dawley Rats
(IRDC Report No, 382-007; April 28, 1980)

Sixty males and 60 females were fed propazine in the diet for 2 years at 0, 3, 100 or 1000 ppm. Body weights of high dose males and females were significantly decreased, compared to controls, at 104 weeks (-13.3% and -11.4%, respectively). There was also a significant decrease in food consumption in high dose males and females, but it was not thought to be entirely responsible for the weight loss, since females only showed a dose-related depression. There were no compound-related effects on clinical chemistry of the blood or urine.

Significant survival disparities were found between female dose-groups: survival in mid-dose group was better than in controls; high dose group survival was statistically significantly lower than in the mid dose group and had the lowest survival of all.

TABLE 1

Incidence of Malignant Lymphomas in Female Mice

0 ppm	Weeks	3 ppm	Weeks	1000 ppm	Weeks	3000 ppm	Weeks
24789*	105[a]	24903	85	25027	81	25149	85
24788	105	24908	76	25032	88	25152	89
24791	105	24922	96	25048	50	25172	20
24806	20	24923	51	25056	86	25174	105
24831	83	24942	105	25059	105	25177	27
24842	93	24951	102	25062	72	25183	84
25203	105	24952	80	25064	82	6	
7		24960	105	25065	105		
		8		25072	90		
				25078	40		
				10			

*Animal number
[a]Weeks on study

D. 2. Two-Year Study in Charles River S-D Rats (continued)

The incidences of mammary tumors (malignant: papillary adenocarcinoma and adenocarcinoma; benign: fibroadenoma, papillary adenoma, cystadenoma and ductular adenoma) were elevated over controls at the high dose (1000 ppm) and a decreased latency was noted in weeks 72-86 (Table II).

Statistically significant dose-related trends were found for both malignant and malignant/benign combined (Peto Prevalence) and statistically significant pairwise comparison was found for high dose versus control for malignant/benign combined.

The MTD was apparently achieved or slightly exceeded in high dose males and females, based on depression of body weight gain of >10% (13.3 and 11.4%, respectively).

Historical Control Information

The incidence of carcinoma in female rats at 1000 ppm (37.7%) exceeded the upper value of the historical control range: 21.4% (1.7% fibrosarcoma in controls). The total tumor incidence at 1000 ppm in female rats (76.4%) also exceeded that for historical controls: 48.3% 517/1071). Historical control data are presented in Table III.

E. Additional Toxicology Data on Propazine:

1. Metabolism

Data is limited. C^{14} propazine fed to rats was recovered unchanged mainly in the feces; hydroxypropazine was found equally in both feces and urine. The general metabolic patterns of propazine are given in Figure 1.

2. Non-Oncogenic Toxicological Effects

Propazine is not very acutely toxic by the oral route in rats (LD_{50}>5gm/kg), but is moderately toxic in rabbits via acute dermal or inhalation exposure (LD_{50}>2gm/kg; LC_{50}>2.1mg/L/4hr). Propazine is a moderate irritant for rabbit eyes and skin (PIS=3.9). Data on dermal sensitization is not available. In subchronic feeding studies in the dog and rat, 80% formula propazine depressed body weight at relatively high doses (1000 ppm).

TABLE 11

†Prevalence of Malignant Mammary Tumors Combined for the Female Rat
( ) = Percent

Dose (ppm)	Weeks 75[a]–103	Weeks 104	Weeks 105	Total
0	2/16 (12.5)	0/1 (0)	8/36 (22.2)	10/53*(18.9)
3	4/17 (23.5)	1/2 (50)	3/37 (8.1)	8/56 (14.3)
100	1/13 (7.7)	0/1 (0)	9/44 (20.5)	10/58 (17.2)
1000	9/26 (34.6)	1/2 (50)	10/25 (40.0)	20/53 (37.7)

[a]First tumor of this type occurred.

†Prevalence of All Mammary Tumors Combined for Female Rats

Dose (ppm)	Weeks 55[a]–71	Weeks 72–86	Weeks 87–95	Weeks 96–105	Final Kill 105	Total
0	0/4 (0)	3/10 (30)	1/3 (33)	2/4 (50)	23/36 (63.9)	29/57**(50.9
3	0/2 (0)	2/3 (66.7)	5/10 (50)	4/6 (66.7)	17/37 (45.9)	28/58 (48.3
100	0/1 (0)	2/3 (66.7)	2/5 (40)	4/6 (66.7)	24/44 (54.5)	32/59 (54.2
1000	1/1 (100)	7/12 (58.3)	4/5 (80)	9/12 (75)	21/35 (60)	42/55**(76.4

[a]First tumor of this type occurred.

†Peto Prevalence dose-related trend test is indicated on controls, pair wise comparisons on the dose groups with:

* for $p < 0.05$
** for $p < 0.01$

TABLE III

Historical Control Data

IRDC Historical Cancer Incidence Data - CD-1 Rat Mammary Gland

Historical Group Size:	1010 Males Examined			1071 Females Examined		
	Males			Females		
Location and Type of Tumors	Total Number of Animals with Tumors	Total Mean Percentage Incidence	Range of % Incidence in Studies	Total Number of Animals with Tumors	Total Mean Percentage Incidence	Range of % Incidence in Studies
Mammary Gland:						
Intraductal papilloma	0	0	--	2	0.2	0- 3.3
Adenoma	3	0.3	0- 3.3	52	4.9	0-21.7
Fibroadenoma	9	0.9	0- 2.9	359	33.5	3.3-47.0
Carcinoma	3	0.3	0- 1.7	102	9.5	1.5-21.4
Fibroma	0	0	--	1	0.1	0- 1.4
Fibrosarcoma	0	0	--	1	0.1	0- 1.7

The general metabolic pathway of propazine in the rat is shown below:

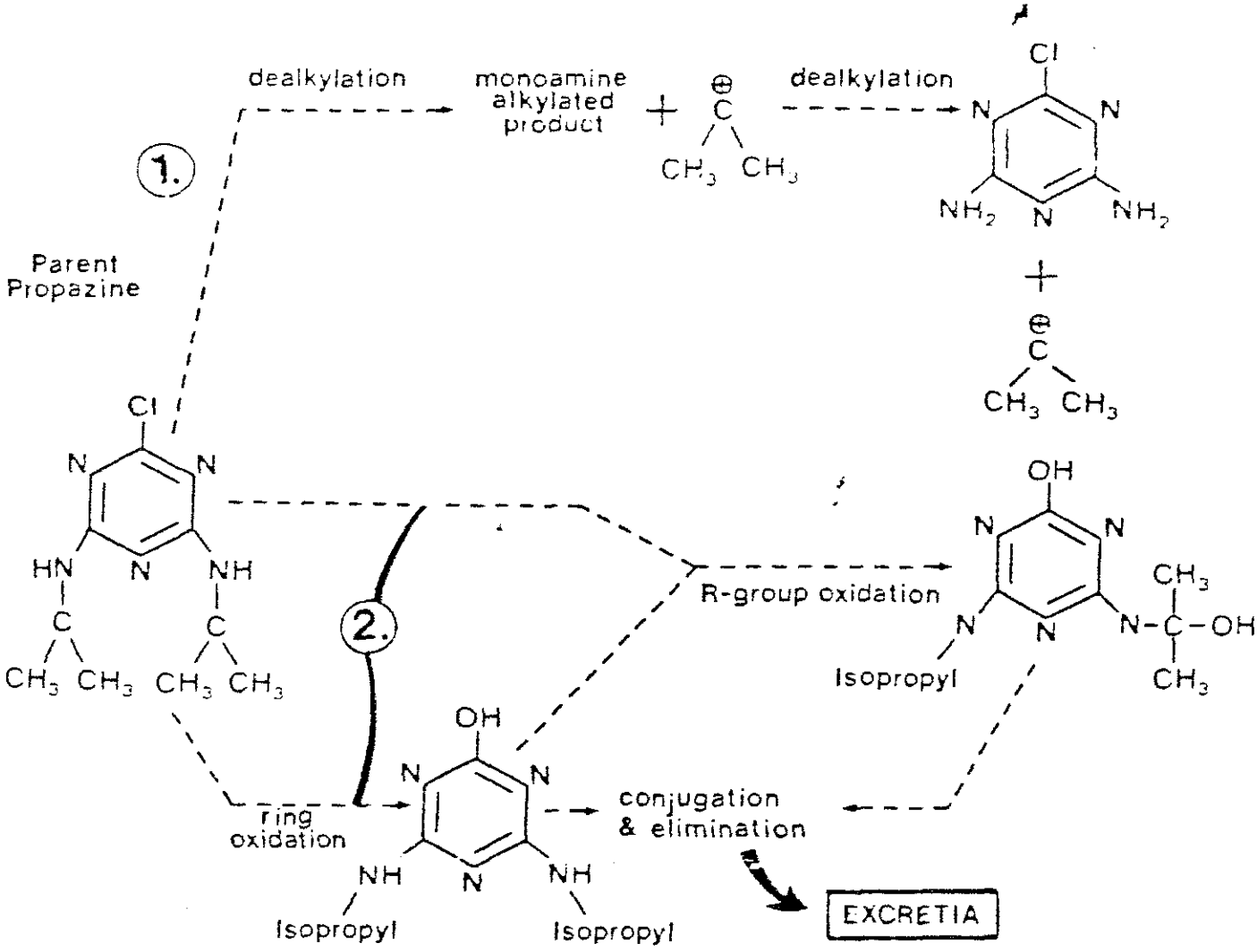


FIGURE 1

E. 2. Non-Oncogenic Toxicological Effects (continued)

In 2 rat oral gavage studies, propazine did not produce any frank teratogenic effects at the HDT (500, 600 mg/kg/d, respectively). Developmental toxicity included an increase in the 14th ribs, incomplete ossification of skeletal or bone structures, and decrease in fetal body weight. (NOEL for fetal and maternal toxicity = 10 mg/kg/d in one study, and 100 mg/kg/d, in the other.)

In a 3 generation reproductive study in the rat, no compound-related effects in fertility of either sex, gestation length, pup variability, or survival were observed from propazine administration. (NOEL for systemic toxicity in pups and adults = 100 ppm.)

3. Mutagenicity

In V79 Chinese Hamster cells, propazine induced a dose-related positive response without metabolic activation, and a weak (non dose-related) positive response with metabolic activation. Propazine was negative in a Nucleus Anomaly assay and in a DNA damage/repair assay in rat hepatocytes. (In the CAG memo, written at a time when the CHO assay was not available to CAG, only negative findings were reported for bacterial mutagenicity (considered inadequate) assays <J.Holder , 1/20/87>.)

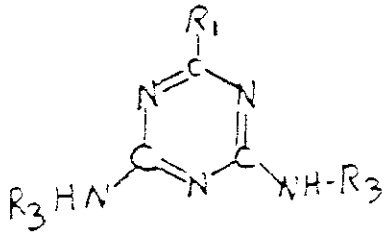
E. 4. Structure-Activity Correlations

Atrazine - Preliminary report of a 2 year rat study shows a dose-related increase in the incidence of adenocarcinoma of the mammary gland in female Charles River S-D rats. No information in mice.

Simizine - Being tested for oncogenicity.

Cyanazine - Negative in CD-1 mice. No information in rats.

Terbutryn - Negative in CD-1 mice. In Charles River S-D rats, produced a statistically significant increase in combined mammary gland adenomas and adenocarcinomas and in combined hepatocellular adenomas and carcinomas in females at 3000 ppm. There was also a significant increase in thyroid follicular adenomas and testicular interstitial cell adenomas in high dose (3000 ppm) males. Terbutryn was classified by the Peer Review Committee as Category C with a Risk Assessment, with a contingency that positive information for mutagenicity and oncogenicity for other structurally related triazines could raise it to a B2.



GENERAL TRIAZINE-TYPE STRUCTURE

	R_1	R_2	R_3
Atrazine	-Cl	$-C_2H_5$	$-CH(CH_3)_2$
Simizine	-Cl	$-CH(CH_3)_2$	$-CH(CH_3)_2$
Cyanazine	-Cl	$-C_2H_5$	$-CH(C\equiv N)CH_3$
Terbutryn	$-SCH_3$	$-C_2H_5$	$-C(CH_3)_3$
Propazine	-Cl	$-CH(CH_3)_2$	$-CH(CH_3)_2$

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on propazine to be important in a weight-of-evidence determination of oncogenicity.

1. Female Charles River CD rats fed propazine in the diet, developed mammary tumors (benign and malignant). Statistically significant dose-related trends were found for both malignant, and malignant and benign tumors, combined; statistically significant pairwise comparison was found for high dose vs control for malignant and benign, combined.

2. Although these tumors were significant only at the high dose, at which the MTD was apparently achieved or slightly exceeded, the Committee agreed that they were, nevertheless, convincing since:

The increase in malignant tumors in females at the high dose, exceeded that of historical controls (37.7% at 1000 ppm vs 21.4% for historical controls), and

The increase in total tumors, in this same group, also exceeded that of historical controls (76.4% at 1000 ppm vs 48.3% for historical controls).

3. Structure activity on related triazines provides support for the association of mammary tumors with this class of chemcals.

4. Propazine induced a dose-related, positive response (without metabolic activation) in V79 Chinese Hamster cells (and a weak non-dose-related one with activation). Propazine was negative in a Nucleus Anomaly assay and in a DNA damage/repair assay in rat hepatocytes.

5. Propazine was negative for oncogenicity in CD-1 mice. For malignant lymphomas in females, multiplicity of tumors per animal (tumor load) was enhanced relative to dose. This suggests that increased or enhanced metastatic factors may be operating in the mouse.

G. Classification of Oncogenic Potential:

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

The Committee unanimously agreed that the classification of propazine should be Group C (potential human carcinogen), based on positive findings for oncogenicity (malignancy) in one species (rat). Additional data from SAR and mutagenicity studies were not thought to provide sufficient support for a higher classification.

The Committee also agreed, unanimously, that a quantitative risk assessment should be performed on Propazine, based on the progression to malignant tumors, the strong SAR of symmetrical triazine herbicides, and the positive response in mutagenicity assays. The potency estimate, Q_1^* of Propazine [c(q)] is 1.7×10^{-1} $(mg/kg/day)^{-1}$, calculated using the Weibull '82 model, and is based on all mammary tumors combined, in female rats [C.J. Nelson memo 6/12/87, attached].

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Chemical:	**Propazine**
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