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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

FILE COPY

JAN 10 1989
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OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

2nd PR

MEMORANDUM

SUBJECT: Peer Review of Propazine - Re-Evaluation

FROM: Esther Rinde, Ph.D. E. Rinde 12/14/88
Science Analysis and Coordination Branch (TS-769c)

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

The Health Effects Division (HED) Peer Review Committee met on Nov. 22, 1988 to re-evaluate the classification of Propazine, based on the submitter's re-reading of the slides.

A. Individuals in Attendance:

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

William L. Burnam
Reto Engler
Robert Beliles
Judith W. Hauswirth
Marcia Van Gemert
Lynnard Slaughter
Marion Copley
Kerry Dearfield
Richard Levy
William Sette
Esther Rinde

A. 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

C.J. Nelson (Statistics) C J Nelson

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, —

Diane Beal —

John A. Quest John A. Quest

George Ghali G. Ghali

B. Conclusions

Propazine was originally classified by the Toxicology Branch Peer Review Committee as a Group C (potential human carcinogen) (Memo, 8/10/88). The HED Peer Review Committee subsequently reviewed the additional data (see memos from Dykstra, 11/10 and 11/19/88, attached to file copy of this report) and concluded that Propazine should remain classified as a Group C (potential human carcinogen), but without quantitative risk assessment.

C. Evaluation of Oncogenicity Evidence for Propazine

There have been three histologic evaluations of the rat mammary gland tumor slides, all by the same pathologist.

The most recent histologic evaluation was requested by the company due to disparities between the OPP reviewer's tumor counts and those of the company, and to clarify some discrepancies between the first and second histologic evaluations. For this most recent evaluation, the pathologist re-examined only those slides (15) which showed a discrepancy between the first and the second reading. In this group of 15 (3 from the controls and 12 from the high-dose group) most of the carcinomas in the treated group were rediagnosed as adenomas (Dykstra memo 11/10/88). Table 3x (taken from C.J. Nelson memo, 11/17/88) represents the final overall evaluation of the mammary glands from this study.

The Peer Review Committee had originally called for a quantification of risk for Propazine. On reconsideration of all of the available information including the new additional data, it was decided that a quantitative risk assessment was not warranted, since the tumors did not show a dose-related response, occurred in only one sex, were mostly benign, and were significantly increased only at the highest dose.

* * * * * * *

It was noted that the registration of Propazine has been withdrawn by the manufacturer. In light of the discrepancies in the tumor counts, should the manufacturer ever decide to bring this chemical back to market, a complete independent re-reading of all of the slides will be required.

Most-recent re-evaluation

TABLE 3x. PROPAZINE, RAT Study-- FEMALE Mammary Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE		0.000	3.000	100.000	1000.000
Benign		19/53	16/55	22/59 a	25/54
	(%)	(36)	(29)	(37)	(46)
		p= 0.0463*	p= 0.2931	p= 0.5158	p= 0.1837
Malignant		9/53 c	17/55	10/58	15/53 c
	(%)	(17)	(31)	(17)	(28)
		p= 0.1876	p= 0.0706	p= 0.5861	p= 0.1228
Combined Benign and Malignant		28/53	33/55	32/59	40/54
	(%)	(53)	(60)	(54)	(74)
		p= 0.0087**	p= 0.2888	p= 0.5161	p= 0.0184*

c) First Carcinoma occurred at 75 weeks in dose 1000 ppm (Papillary carcinoma) and dose 0 (adenocarcinoma).

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

8/10/87

FILE COPY

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

AUG 10 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 Kasza	Louis Kasza
Robert Beliles	Robert 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

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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).

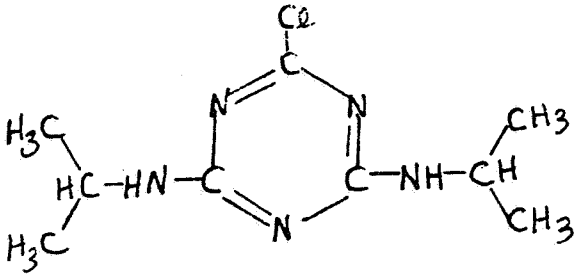
B. Material Reviewed:

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 I

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	31	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

3a

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 II

†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:

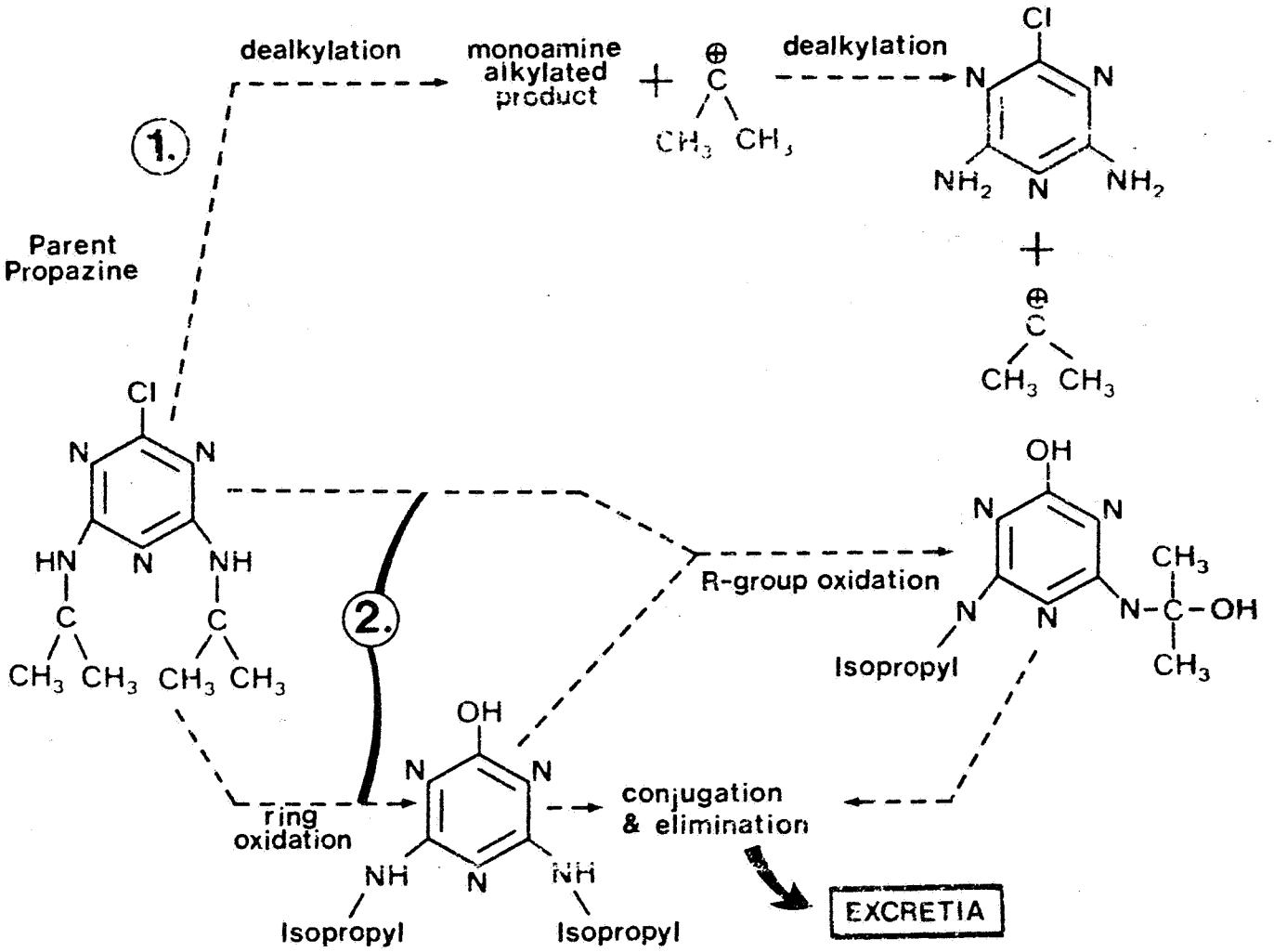


FIGURE 1

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>.)

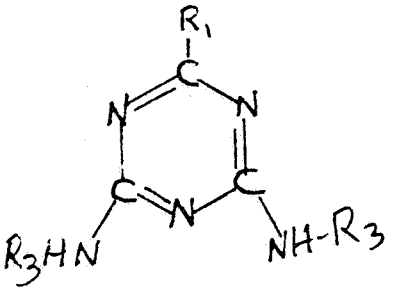
E. 4. Structure-Activity Correlations

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.

Simazine - 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	$-Cl$	$-C_2H_5$	$-CH(CH_3)_2$
Simazine	$-Cl$	$-C_2H_5$	$-C_2H_5$
Cyanazine	$-Cl$	$-C_2H_5$	$-C(CH_3)_2-C\equiv N$
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].

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

OCT 25 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT : Ad Hoc Committee Meeting on Longterm Studies of Propazine CASWELL#184

Date : October 17, 1984

Committee: √William Dykstra (reviewer)
Christine Chaisson (Section Head)
Gene Paynter
Louis Kasza
Bertram Litt
Jack Quest
Reto Engler
William Burnam (not present)
Caroline Gordon (Program Analyst)

The reviews of Propazine (June 16, 1984) were referred to the committee on September 25, 1984 for obtaining a consensus opinion on the further evaluation of the longterm effects, including oncogenicity of Propazine.

At this meeting it was the consensus of the committee that a decision cannot be reached based on the material (review) presented. Both rat and mouse studies were referred back to the review cycle with instructions (oral and written) to present the data in more detail, and present interrelationships of gross, clinical, necropsy and histological observations and expand the reporting of mammary tumors to show which animals have single or multiple types of tumors.

The committee is expecting to reevaluate Propazine upon completion of the additional reviews.

Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769C)

cc: Committee members
Caswell File
J. Akerman

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