UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM FEB 7 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Franklin D. R. Gee, Product Manager #17
Registration Division (TS-767)

THRU: O. E. Paynter, Chief OEP 2/4/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: EPA Reg. No. 432-487. Resmethrin: Review of Thyroid Pathology Data.

TOX Chem. No. 83E

Note to PM: This memo concerns data packages sent to TOX Branch as follows:

Dec. 3, 1981 -	S. B. Penick's response to Toxicology Branch's review of the rat chronic feeding/oncogenesis study - revised thyroid pathology report by S. W. Thompson. EPA Acc. No. 246214.
August 25, 1982 -	Reanalysis of thyroid data as prepared by S. B. Penick's consultant Dr. Conrad King.
October 26, 1982 -	Additional information regarding thyroid data in rats as provided by Dr. Conrad King for the S. B. Penick Co. EPA Acc. No. 248547.

Background:

The original review (J. Doherty review dated May 19, 1981, see EPA File No. 432-487) of the rat chronic feeding/oncogenesis study with the synthetic pyrethroid Resmethrin indicated that there was a possible oncogenic effect in the thyroid gland. The following table illustrates the incidence of thyroid adenomas as originally presented to EPA (EPA Acc. No. 242783, Path Table 12).

Original Thyroid Data[1]

Dose Level	Males n	Males Adenomas	Males Cysts	Females n	Females Adenomas	Females Cysts
Control	47	2	1	50	1	1
500 ppm	26	4	1	16	1	1
2500 ppm	27	3	2	23	4	0
5000 ppm	47	8	6	48	5	3

n: number of rats examined.

[1] NOTE: Only rats dying after the first year and survivors are included.

The above table also includes the number of incidence of cysts as originally reported. The data as originally presented did not differentiate interstitial adenomas from follicular adenomas.

These data show that there are more incidences of "adenomas" and "cysts" in both the high dose male and female test groups.

The registrant (S. B. Penick Corporation) was asked to reanalyse the thyroid tissue and include those rats from the low and mid dose groups which were not previously examined microscopically. The registrant complied and submitted the revised pathology report by Dr. S. W. Thompson (submission of 12/3/81) and eventually 2 additional submissions, (8/25/82 and 10/26/82). As per the memorandum from Dr. Louis Kasza, DVM, Toxicology Branch (TB) staff pathologist to Edwin Budd, dated 12/7/82, the pathologic effects of Resmethrin in the thyroid (and liver) should be evaluated based on the diagnoses of Dr. Samuel Thompson.

Recommendations and Comments:

1. TB has reviewed the information submitted by the S. B. Penick Corporation regarding the pathology of the thyroid of rats dosed with Resmethrin and has concluded:

   a. The thyroid is affected by the presence of Resmethrin in the diet (either directly or indirectly) and there are statistically significant increases in the frequencies of cysts in the follicules of both males and females in the high dose groups. The female high dose group has a statistically significant increase in thyroid weight. The high dose group males and mid dose group females also have pronounced increases in thyroid weight. A NOEL is set at 2,500 ppm for these effects in the thyroid.

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b. The data (as presented in Dr. Thompson's revised October 29, 1981 thyroid pathology report) do not provide sufficient evidence to conclude that Resmethrin induced thyroid tumors in the rats in this study. The overall magnitude of the response is not sufficient to justify a conclusion that Resmethrin caused an increased incidence of these not uncommon thyroid neoplastic (particularly follicular adenomas) in this study. lesions

Detailed Considerations

Review of Revised Thyroid Pathology Report:

A Lifetime Evaluation of the Dietary Administration of SBP-1382 to Wistar Albino Rats - Supplemental Report (Pathology Report) - Thyroid Pathology.

Food and Drug Research Laboratories, October 29, 1981, Lab No. 5271, (prepared by Samuel W. Thompson, D.V.M.) (EPA Accession No. 246214).

The tissue sections of all specimens of thyroid collected at necropsy for the male and female rats of the control, and high dose groups and the tissues in the low and mid dose that were previously selected for preparation and histology were retrieved from the FDRL. The remaining tissues from the low and mid dose test groups which were not previously selected for histopathology were prepared for examination. In addition, certain specimens of thyroids which may have contained sectioning artifacts were reprepared for histology. All of the tissue samples were reevaluated by Dr. Samuel W. Thompson, then Director of Pathology, FDRL. The criteria which were used to differentiate benign and malignant neoplasms were:

Benign	Malignant
Encapsulated	Non-encapsulated
Non-invasive	Invasive of blood vasculature or capsule of the gland
Little or no anaplasia	Metastases

The statistics used in the report by the sponsor for evaluating the data were the Chi-Square test with Yates correction for 2 x 2 contingency tables. Note: TB used Fisher's Exact test to statistically evaluate some of the data.

Results of the Reanalyses: The following table describes the revised data related to the thyroid tissue.

Comprehensive Table of Data on the Thyroid Glands
from Rats Dosed with SBP-1382[1]

	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Organ Weight n^2	15	18	14	19	19	25	16	23
Absolute (mg)	31 ± 6	33 ± 7	31 ± 7	36 ± 7	22 ± 4	25 ± 5	25 ± 9	29 ± 6*
(as % control)				+ 16%		+ 14%	+ 14%	+ 32%
Relative (% B.W.)	.67±.16	.69±.14	.68±.15	.78±.14	.70±.14	.73±.14	.79±.24**	.98±.21**
(as % control)				+ 16%		+ 4%	+13%	+40%
Gross Necropsy n^3	60	60	60	60	60	60	60	60
other than normal	8	11	12	18	2	5	10	14
as %	13.3	18.3	20.0	30.0	3.3	8.3	16.7	23.3
Histopathology n^3	59	59	60	60	60	59	58	59
Interstitium or other								
hypertrophy	1	0	0	0	1	0	0	0
Capsule	0	0	0	0	1	0	0	0
Lymphocytic inflam	4	2	2	1	2	2	0	1
Interstitial adenoma	4	3	2	3	2	2	0	1
Lymphocytic leukemia	1	0	0	0	0	0	0	0
Follicles								
cysts	0	4	2	18*	2	3	2	8*
hyperplasia	1	0	0	0	2	4	2	1
squamous metaplasia	0	0	2	2	0	0	0	0
necrosis	0	1	0	0	0	0	0	0
Adenomas (follicular)								
polymorphofollicular	1	3	3	4	0	0	4	3
microfollicular	0	0	0	0	0	0	0	1
papillary	0	0	0	1	0	0	0	0
solid	0	0	0	0	1	1	1	0
Carcinomas (follicular)								
microfollicular	1	0	0	0	0	0	0	0
polymorphofollicular	2	0	0	0	0	0	0	2
Total Follicular Neoplasms (Adenomas & Carcinomas)	4	3	3	5	1	1	5	6

1 These data are from the revised report (S. W. Thompson report, 10/29/81, EPA Acc. No. 264214) except for the organ weight data which is from the original report (EPA Acc. No. 242782).

2 Does not include rats with obvious large sizes (i.e. some rats with thyroid cysts and neoplasms).

3 10-13 of these were sacrificed at 53 weeks or died before 53 weeks.

* Statistically significant by Fishers exact test.

** $P < 0.001$ (t test)

The above table indicates that the thyroid gland is affected by high levels of Resmethrin in the diet. Statistically significant increases in the weight (absolute and relative) of this organ are attained for the high dose group females. The mid dose group females and high dose group males are also obviously larger in weight (absolute and relative), but statistical significance was not attained.

There were more rats in both the mid and high dose test groups (male and female) which had evidence of a test chemical effect as noted at gross necropsy.

With the exception of the follicles, histopathology did not reveal indications of there being an adverse effect. In particular, several interstitial adenomas were present but their presence was clearly not related to the test material.

The highest level of Resmethrin in the diet affected the follicular cells of the thyroid. In both sexes, the high dose test group had a statistically significant increase in follicular (colloid) cysts. These cysts are considered to be nonneoplastic and a NOEL for this lesion was set at 2500 ppm. A difference between Dr. Thompson's revised report and the original report is that many more cysts were found by Dr. Thompson than were first reported.

When follicular adenomas in males alone are considered, there are 1/59, 3/59, 3/60 and 5/60 rats affected for the control, low, mid and high dose test groups but these data do not show statistical significance (Fisher's one tailed p statistic as determined by J. Doherty and by the test procedure used by the laboratory). There were a total of 3 follicular carcinomas among the male rats, all of which were in the control group. Combining adenomas with carcinomas in the males resulted in a total of 4/59, 3/59, 3/60 and 5/60 incidences of follicular neoplasms for the control, low, mid, and high dose test groups.

Among the females, polymorphofollicular adenomas were found only in the mid (4 incidences) and high (3 incidences) test dose groups. Statistical significance was not $< .05$ for these data. When adenomas plus the two incidences of carcinomas which occurred in the high dose female group are considered, the high dose test group approaches marginal statistical significance ($p = .054$, as determined by J. Doherty using Fisher's one tailed p statistic). The statistical procedure used by the sponsors statistician also did not show that these data were significant.

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The registrant through its consultant, Dr. Conrad D. King, provided a defense that the thyroid tissue was not an oncogenic target for the effects of Resmethrin. The first report by Dr. King (dated 7/7/82) discusses the possibility that thyroid pathology results secondary to damage to the liver resulting from Resmethrin treatment. TB declines from either concurring or disagreeing with this discussion of a possible physiological basis for the thyroid pathology noted in this study. Dr. King's report recognizes that at 5000 ppm there are observable effects in both males and females. Since those effects were determined by Dr. Thompson to be nonneoplastic in nature, a NOEL of 2500 ppm was set for these lesions by TB.

The second report by Dr. King (EPA Acc. No. 248547) provided several published reports which show that the spontaneous rate of occurrencce of thyroid tumors in Wistar rats is 0-30%. Dr. King indicated that the minor increase in incidences for the adenomas in males and females in this study is still well within what can be expected as a spontaneous rate.

Conclusions:

1. Based upon the diagnosis of S. W. Thompson (10/29/81 report), TB has determined that there is insufficient evidence to conclude that Resmethrin induces a positive oncogenic response in the thyroid. The rats dosed with Resmethrin did not develop thyroid neoplasms in a statistically significantly different frequency than did the controls. The slight increases in thyroid neoplasms in the dosed rats can be shown to be within the spontaneous response for the Wistar strain of rat.

2. A NOEL for nonneoplastic effects in the thyroid is set at 2500 ppm. At 5000 ppm there were statistically significant increases in the frequency of cysts in both males and females and female thyroid weights were increased.

John D. Doherty, Ph.D. 2/2/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

2/4/83

OPP:HED:TOX: J.DOHERTY:sb 12/29/82 re/1/31/83 X73713 Rm 814 #m19

Tox Chem No. 051 Resmethrin

File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade, Doc. No.
ronic Feeding/Oncogenesis rats - Revised liver thology Report (Thompson's eport), FDRL #1 5271 ay 19, 1982	Tech	247579	NOEL < 500 ppm for any response (minimal hypertrophy of hepatocytes at 500 ppm) NOEL = 500 ppm for toxic response LEL = 2500 ppm, increased liver weight and pathological liver lesions Not Oncogenic in rat liver	—	MINIMUM
, Chronic Feeding/Oncogenesis - Revised thyroid port (Thompson's Report) DRL # 5271, t. 29, 1981	Tech	246214	Not oncogenic in rat thyroid NOEL = 2500 ppm LEL = 5000 ppm - cysts and increases in thyroid weight	—	MINIMUM

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