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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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

Thru: O. E. Paynter, Branch Chief OEP 2/14/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

Subject: EPA Registration No. 432-487. Review of Rat Liver Pathology Reports Related to the Chronic Feeding/Oncogenesis Study With Resmethrin. Resolution of the Problem of There Being a Possible Oncogenic Response in the Liver of Females. Assignment of a NOEL for Effects in the Liver.

TOX Chem No. 83E

Background:

The S. B. Penick Corp. (Lyndhurst, New Jersey) previously submitted a rat chronic feeding/oncogenesis study with the synthetic pyrethroid Resmethrin. Toxicology Branch review of this study (see J. Doherty review dated May 19, 1981) indicated that the data as presented showed that Resmethrin was associated with higher frequencies of liver neoplasms in the mid (2500 ppm) and high (5000 ppm) dose test groups in females.

The final report as originally presented to EPA (Acc. No. 242782, 242783, 242784, 242785 and 242786) contained the results of 3 microscopic readings of the liver tissue. There were two readings by Dr. Mark K. Walter who was originally responsible for the diagnosis and a reading by Dr. Peter J. Becci and Dr. George Cox. Dr. Walter's original report gave some indications of a neoplastic effect in the liver of females and subsequently Dr. Becci and Dr. Cox prepared additional slides and made their own diagnoses. Dr. Walter was later asked to reevaluate the slides. A summary of the potential neoplastic findings in female rat liver as reported in each of the three readings is as follows:

1.) Dr. Walter's original diagnosis: (EPA Acc. No. 242783, Table 9 page 324b and Table 12 page 472-3)

	Control	Low	Mid	High
Nodular hyperplasia	0	0	3	8
Nodule, hyperplastic	1	0	0	1
Adenoma	0	0	0	1
Hepatoma	0	0	0	5

2.) Dr. Becci and Dr. Cox's diagnosis: (EPA Acc. No. 242784, Table 17a)

	Control	Low	Mid	High
Nodule, hyperplastic	1	0	5	13
Adenoma	0	0	5	13
Carcinoma	0	0	0	8

3.) Dr. Walter's revised report: (EPA Acc. No. 242784, Table 17b)

	Control	Low	Mid	High
Hyperplasia, nodular	1	0	6	20
Nodule, hyperplastic	1	0	5	12
Hepatoma	0	0	2	5

Note: There were 46-50 rats examined per group. Some rats have more than one type of suspect neoplasm.

The conclusion in the May 19, 1981 TB review that Resmethrin causes an oncogenic effect in rat liver was based largely on the diagnoses of Drs. Becci and Cox, which show the presence of adenomas and carcinomas. The terms "nodular hyperplasia" and "nodule, hyperplastic" and "hepatoma" are ambiguous and Toxicology Branch advised the Penick Corporation that these lesions would be considered as neoplastic unless they were adequately described differently.

Because of the differences in the terminology used and because not all of the liver tissue in the low and mid dose test groups were reanalyzed and because there were different numbers of slides prepared per rat, the registrant was requested to provide an additional reading. The conditions of this additional reading were that equal numbers of slides for all rats should be read and that the same pathologist read all of the slides. The Penick Corporation complied and Dr. Samuel W. Thompson, then staff pathologist at FDRL, made readings of the slides from all female rats (and selected male rats) and an amendment to the rat chronic feeding/oncogenesis study was submitted. This amendment is reviewed below.

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As per the memorandum (attached) from Dr. Louis Kasza, DVM, Ph.D., Toxicology Branch staff pathologist to Edwin Budd dated Dec. 7, 1982, the pathologic effects of Resmethrin in the liver (and thyroid) should be evaluated based on the diagnoses of Dr. Samuel Thompson.

Recommendations and Conclusions

1. Oncogenic response in rat liver.

Toxicology Branch (TB) has concluded that there is insufficient evidence to conclude a frank oncogenic response in rat liver.

The revised pathology report as submitted on June 1, 1982 (report prepared and signed by T. G. Hess, S. W. Thompson, and P. J. Becci, dated May 19, 1982 from FDRL) asserts that there is no oncogenic response in the liver of the rats dosed with Resmethrin. This conclusion was made possible because most of the livers previously diagnosed by Drs. Becci and Cox and reported in the original submission as having adenomas or carcinomas were diagnosed by Dr. Thompson as having nonneoplastic lesion types.

As implied by his signature on the May 19, 1982 document, Dr. Becci concurs with the reclassification of these lesions as described by Dr. Thompson in the revised report. There is no indication as to whether Dr. Cox who was also responsible for the original diagnosis also agrees with the reclassification of these lesions.

An important factor leading to the TB conclusion that there is no neoplastic effect of Resmethrin in rat liver was the explicit description of "hyperplastic nodules" as proliferative rather than as a neoplastic lesions by Dr. Thompson. TB recognizes that there is no agreement at this time among pathologists for the classification of "hyperplastic nodules" as being neoplastic or non-neoplastic in nature. TB also recognizes that diagnosis for adenomas (neoplastic tissue) and hyperplastic nodules is difficult.

2. A NOEL for adverse toxic responses.

The liver pathology data (June 1, 1982 submission) clearly indicate a dose response for increased incidences of "hypertrophy of hepatocytes". The low dose test group (females) was statistically significant at the .012 level (Fisher's one tail P statistic). This type of lesion is not,

however, considered by TB to be a definite toxic response but rather a pharmacological response due to the presence of a xenobiotic (i.e., Resmethrin) inducing increased enzyme activity of the liver.

The NOEL for this study is < 500 ppm for any observable effect. The NOEL for toxic responses is 500 ppm. The LEL is 2500 ppm. At 2500 ppm and above there are increases in liver weight and increases in various types of liver lesions.

3. A summary table and discussion of the neoplasms in tissues other than liver and thyroid for the rat chronic feeding/oncogenesis study with Resmethrin is included in this memo.

4. Any other toxicity data requirements which may exist will be addressed when the individual registrations and/or tolerance requests are submitted by Registration Division to Toxicology Branch for review.

Detailed Considerations

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

Prepared and signed by Frederick G. Hess, Samuel W. Thompson, DVM, and Peter J. Becci. FDRL, Study No. 5271, May 19, 1982. EPA Acc. No. 247579.

Background:

The original review of this study (see J. Doherty review dated May 19, 1981) concluded that the data as originally presented showed that Resmethrin produced an oncogenic effect in the liver as evidenced by the dose related increases in hyperplastic nodules, adenomas and carcinomas. Hyperplastic nodules were included as neoplastic and the registrant was advised to defend their position that these lesion types should not be classified as such. In a subsequent meeting (Nov. 1981) with the registrant it was decided that the female and certain male liver tissues would have to be reexamined and an equal number of slides from each rat must be examined. All slides must be read by the same pathologist.

Results:

The liver samples were prepared and later examined microscopically by Dr. Samuel W. Thompson, DVM, Diplomate, American College of Veterinary Pathologists. A summary table of the important lesions found in the liver of female rats in this study is shown below.

Lesions: (Nonneoplastic):

1. Showing Possible Dose Response

	Females			
Non-Proliferative:	Control	Low	Mid	High
Number Examined	60	60	60	60
Fibrosis	0	2	1	12
Hemorrhage	1	1	0	11
Hemosiderin Pigment Deposits	1	2	3	10
Bile Pigment Deposits	1	0	3	9
Hypertrophy of Hepatocytes	3	12	25	30
Nuclear Hypertrophy	0	1	6	8
Atrophy of cord cells	0	2	1	10
Necrosis of Indiv. Hepatocytes	1	0	2	9
Necrotic Focus	0	1	0	9
Necrotic Area	0	1	2	5
Acute leukocytic inflam	0	0	1	3
Lymphocytosis	0	2	3	5
Microgranuloma	1	2	2	4
Clear cell area alter	0	0	2	3
Acidophilic cell area alter	0	0	2	2
Basophilic cell area alter	0	0	3	9
Mixed cell area alter	1	0	0	4
Proliferative:				
Hyperplastic focus of hepatocytes	0	0	1	3
Hyperplastic nodules of hepatocytes	1	0	4	8(9)*
2. Not showing Dose Response				
Non-Proliferative:				
Subacute lymphatic inflammat.	42	53	37	38
Hematopoiesis, extramedullary	27	32	26	34
Telangiectases	17	15	21	20
Intracytoplasmic microvesicle	52	58	57	54
Intracytoplasmic vacoules	43	51	39	45

Lesions: (Nonneoplastic continued):

Proliferative	Females Control	Low	Mid	High
Number Examined	60	60	60	60
Bile duct without connective tissue	42	42	36	38
Bile duct with connective	38	32	29	28
Bile duct with sclerotic	31	37	23	22
3. Gross Necropsy (showing dose response)				
White nodules and other nodules or white areas and/or spots, masses or cyst-like	4	6	15	41
4. Liver Weight (absolute)	14.09	14.89	17.27** 22.6%†	20.34** 44.4%†
(relative)	4.45	4.41	5.45** 22.5%†	6.84** 53.7%†

† As % increase relative to control

* The report indicated that 8 rats were affected with hyperplastic nodules. Toxicology Branch tabulated 9. The rats involved were #425, 428, 433, 444, 455, 456, 461, 462 and 470.

** Statistically significant ($p \leq 0.05$).

NOTE: Other types of liver pathology were also present but the incidences noted did not reflect a dose response.

As indicated by the above table, the mid and high dose level groups are associated with increased incidences of a variety of lesions both proliferative and non-proliferative. There are also increased incidences of rats with gross necropsy observations. The liver weight of the mid dose group and high dose group females is elevated relative to controls (see original review May 19, 1981).

The data in the table showing the summary of nonneoplastic effects indicates the progression of 3/60, 12/60, 25/60, and 30/60 incidences of "hypertrophy of hepatocytes" among the female controls, low, mid, and high dose test rats. The incidences in the low dose test groups are statistically significant when compared with the control groups ($p = .012$, Fisher's One Tail P statistic). This effect ("hypertrophy of hepatocytes") is not, however, considered by Toxicology Branch to be a definite toxic response but rather an adaptation of the rat to the presence of the xenobiotic.

The NOEL for non-neoplastic toxic effects in the liver is set at 500 ppm. At 2500 ppm (LEL) there is an increase in liver weight, hyperplastic nodules of hepatocytes, nuclear hypertrophy and possibly also other types of liver pathology. At 5000 ppm the effects noted at 2500 ppm are increased in incidence and other types of lesions appear including fibrosis, hemorrhage, pigment deposit and necrosis are evident.

The oncogenic response (incidences) in liver as described by Dr. Thompson is shown in the following Table.

	Males				Females			
Tumor Type	Control	Low	Mid	High	Control	Low	Mid	High
Number examined	48	49	48	47	60	60	60	60
True liver tumors								
Liver cell adenoma	0	0	0	0	0	0	0	2*
Liver cell carcinoma	0	0	0	0	0	0	0	1*
Hemangioendothelioma	0	0	0	0	0	0	0	1
Total	0	0	0	0	0	0	0	4
Others								
Adenocarcinoma-gastric metastasis to liver	0	0	0	0	1	0	0	0
Leukemia infiltrate	1	0	1	0	0	0	1	0
Reticulum cell Sarcoma	0	0	0	1	0	0	0	0

* The revised pathology report indicates that only two rats were affected with liver cell adenoma or carcinoma. These were females in the high dose test group and one of these had both adenoma and carcinoma. A third female in the high dose test group (# 436) was diagnosed as having hemangioendothelioma. Five other rats (total both sexes) had neoplastic tissue in the liver, but the types of tumors were not considered to be frank liver tumors.

The above data do not provide sufficient evidence to conclude that Resmethrin induced an oncogenic response in female rat liver. The revised report as shown also shows that there are no frank liver tumors among the males. Thus, the problem (as indicated in the original review of this study) that there may be an oncogenic effect in males is dismissed.

Summary of Neoplasms in the Rat Chronic Feeding/ Oncogenesis Study With Resmethrin.

The following table indicates the frequency of occurrence of selected neoplasms in tissues other than the liver, thyroid gland and ovary as reported in the revised summary table (EPA Accession No. 247579 pages 43-59).

Incidences of Specific Neoplasms

		MALES				FEMALES			
		Control	Low	Mid	High	Control	Low	Mid	High
Pituitary	n	56	33	32	56	54	41	45	55
adenoma		8	7	7	6	16	18	22	12
carcinoma		1	0	0	0	0	0	0	0
Mammary Gland	n	47	26	26	50	60	29	32	59
Fibroadenoma		0	0	0	0	15	7	12	7
Testis	n	60	42	45	60	-	-	-	-
interstitial cell tumor		9	8	14	6	-	-	-	-
Pancreas	n	60	38	35	60	60	33	31	60
adenomas (3 types)		2	1	3	3	3	0	0	3
adenocarcinomas		1	0	0	0	0	0	0	1
Thymus	n	?	?	?	?	?	?	?	?
(total)		1	0	2	0	3	6	2	0
Adrenals	n	59	34	39	60	60	46	52	60
Adenomas		1	0	0	0	3	0	0	2
pheochromocytoma		1	2	1	0	0	0	0	1

n = Number of animals examined.
? = The total number of tissues examined for the thymus was not provided in the report.

Other examples of tissues not listed in the above table which had neoplasms were the heart (1 incidence of rhabdomyoma), large and small intestines (one each); mouth (1); salivary gland (2, one adenoma each in the low and high dose female groups); kidneys (1 incidence), lungs (1 adenocarcinoma in the low dose (female), two others with systemic tumors); spleen (3 rats with lymphosarcoma, all in the mid dose group, 1 male and 2 females); parathyroid (5 adenomas, 2 in controls (1 male and 1 female), and 3 in the high dose group (2 males, 1 female); brain (7 total, 1 adenoma, control female; 2 astrocytoma, control male; 1 meningioma, low dose group female, 2 glioblastomas both in the high dose group, 1 male and 1 female 1 glioma high dose group male); stomach (3 different types, none in the same group).

Twenty-three incidences (18 males and 5 females) were affected with (various neoplasms in the skin) The neoplasm types included squamous cell carcinoma (1), fibroma (11), lipoma (1), papilloma (3), fibrosarcoma (4), lymphosarcoma (1), hemangiosarcoma (1) and sarcoma (1). None of these showed evidence of being related to Resmethrin in the diet.

There were 11 rats affected with neoplasms in the lymph nodes, these were in the control (5) and in the mid dose group (5) and one high dose test group (1). The neoplastic types were hemangioma, (4) leukemia (1), lymphoma (1) and lymphosarcoma (5).

Pathology of the ovaries: The ovaries are considered separately as below. The following table shows the information related to the ovaries as reported in the original pathology report. (EPA Accession No. 242783)

		FEMALES			
PATHOLOGY (Ovaries)		Control	Low	Mid	High
Gross Necropsy	n	50	49	49	49
Abcessed (nodules, mass, etc.)		4	8	5	8
Color alterations*		1	4	4	6*
Cystic		14	17	16	14
Size alterations		8	10	2	4
Non-neoplastic pathology	n	50	30	23	49
Cystic (various kinds)		12	8	14	12
Interstitial cell hyperplasia		1	0	0	2
Follicular necrosis		2	0	0	0
Abscesses		1	4	3	3
Oophoritis		3	2	3	1
Neoplastic	n	50	30	23	49
Adenoma		0	0	1	0
Granulosa-theca cell tumor*		0	1	0	3*

cont.

Weight	n	16	20	15	22
Absolute	mg	109±35	98±35	118±50	101±22
Relative		.34±.11	.29±.11	.39±.18	.35±.08

* Data are not statistically significant at the .05 level using Fisher's One Tail P Statistic

The rats which developed granulosa-theca cell tumors were a low dose (#343, 113 weeks) and three high dose animals (#443, 100 weeks; #452, 99 weeks; and #473, 113 weeks). All rats affected were aged greater than 99 weeks. None of these rats also had thyroid neoplasms.

Of these four affected rats all but #473 had revealing gross necropsy in the form of abscesses (nodule and/or mass, etc.). There were other rats which had this description at gross necropsy. Many of these were followed up microscopically with diagnoses of oophoritis, abscesses or cysts. There were five rats with gross necropsy indicative of possible neoplasm that were not followed up by a histological description. Three of these were in the control group and one each in the mid and high dose groups.

This apparent increased incidence of neoplasms in the ovary was not considered to be a result of the test chemical because the response in the high dose group was of a low degree of magnitude and because this type of tumor is, although not common, not rare. The increased frequency in the high dose group does not reach statistical significance at the 0.05 level.

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