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

MEMORANDUM

DATE: DEC 15 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 432-487. Company Response to the Problem of Amyloidosis Increase in the Mouse Oncogenesis Study with Resmethrin.

TOX Chem. No. 83E

FROM: John Doherty 12/1/81
Toxicology Branch/HED (TS-769)

TO: F. D. R. Gee, PM #17
Registration Division (TS-767)

Background:

The Penick Corporation previously submitted a mouse oncogenesis study with the insecticide resmethrin and review of this study (see J. Doherty review, dated December 11, 1979) indicated that the test chemical may be associated with increased incidences of amyloidosis at all dose levels including the low dose level. The registrant was asked to reexamine tissues in the low and mid dose groups and to provide a demonstration that amyloidosis in the low and mid dose groups was not related to ingestion of resmethrin. NOTE: The testing laboratory already had conceded that the high dose groups (male and female) developed higher frequencies of amyloidosis probably as a non-specific result of the test chemical and that this was related to early deaths of the mice.

Registrants Response:

1. The registrant replied that amyloidosis occurs frequently in mice and its occurrence in this study is not conclusively related to ingestion of resmethrin. They request that a NOEL of 500 ppm be assigned for this lesion.

2. EPA's request to reanalyze certain slides and grade the amyloidosis (i.e. as 1-4 depending on severity) as well as to analyze unread slides was not carried out by the registrant.

3. The registrant provided "Addendum Statement on Amyloidosis" prepared by George E. Cox, M.D., Director of Pathology, at Food and Drug Research Laboratories, Inc. where the study was originally conducted. In this statement Dr. Cox asserted that "although the high level of mortality was real and the amyloidosis (regarded as causative) was a marked finding, it (amyloidosis) is of trivial importance as an indicator of test material toxicity". Dr. Cox indicated that the amyloidosis commonly occurs in this strain of mice, and its predisposition is idiopathic and determined genetically. One of a number of factors which

might accentuate an already extensive ongoing activity, Dr. Cox indicated was a high concentration of various nonspecific test materials in the diet. Thus, the increased incidences of amyloidosis are nonspecific.

4. The registrant consulted Conrad King, DVM, Ph.D. for his "third party" opinion. Dr. King's opinion was that the amyloid findings already presented demonstrate an equivocal effect which would remain equivocal even if a dose related increase in amyloid was found on reexamination. The rationale for his opinion was that the high spontaneous incidence of amyloidosis found in test animals in this study could have been exacerbated by either physiological stress or other nonspecific factors.

Conclusions:

Additional work to quantitate amyloid is not required in light of the explanations provided by Drs. Cox and King above. The increased incidences of amyloid which occur in the low dose groups for some tissues are not considered to be of toxicological concern.

NOTE: A table showing the rates of amyloidosis in all groups is appended.

Attachment

OPP:HED:TOX: J.DOHERTY:sb 11/17/81 X73711 #m6

Table 1

Percent Incidence Amyloid Found per Tissue Examined*

	Control		250		500		1000	
	M	F	M	F	M	F	M	F
Adrenals	63.4 (45/71)	83.8 (62/74)	85.0 (17/20)	73.7 (14/19)	95.0 (19/20)	75.0 (15/20)	86.3 (63/73)	90.5 (67/74)
Epididymides	0 (0/73)	-	0 (0/20)	-	0 (0/20)	-	2.7 (2/73)	-
Heart	55.4 (41/74)	84.9 (62/73)	80.0 (16/20)	65.0 (13/20)	85.0 (17/20)	75.0 (15/20)	89.2 (66/74)	90.7 (68/75)
Lrg. Intestines	5.6 (4/72)	7.0 (5/71)	10.0 (2/20)	10.0 (2/20)	10.0 (2/20)	25.0 (5/20)	13.5 (10/74)	40.0 (30/75)
Sml. Intestines	81.1 (60/74)	95.9 (71/74)	80.0 (16/20)	85.0 (17/20)	95.0 (19/20)	100 (20/20)	94.5 (69/73)	91.9 (68/74)
Kidneys	68.5 (50/73)	87.8 (65/74)	100 (20/20)	85.0 (17/20)	100 (21/21)	100 (21/21)	90.4 (66/73)	94.7 (71/75)
Liver	54.1 (40/74)	69.9 (51/73)	70.0 (14/20)	60.0 (12/20)	55.0 (11/20)	85.0 (17/20)	79.7 (59/74)	92.0 (69/75)
Lungs	6.8 (5/73)	0 (0/74)	20.0 (4/20)	5.0 (1/20)	20.0 (4/20)	0 (0/20)	10.8 (8/74)	1.3 (1/75)
Lymph Nodes	17.7 (11/62)	35.4 (22/62)	26.3 (5/19)	30.0 (6/20)	37.5 (6/16)	33.3 (6/18)	20.3 (13/64)	47.1 (33/70)
Mamm. Gld.	-	4.3 (3/70)	-	5.3 (1/19)	-	0 (0/20)	-	2.9 (2/68)
Mesentery	14.0 (6/43)	74.5 (35/47)	35.7 (5/14)	75.0 (12/16)	46.2 (6/13)	100 (15/15)	32.5 (13/40)	90.2 (46/51)
Ovaries	-	91.5 (65/71)	-	80.0 (16/20)	-	89.5 (17/19)	-	90.7 (68/75)
Pancreas	10.8 (8/74)	9.7 (7/72)	5.0 (1/20)	20.0 (4/20)	5.0 (1/20)	26.3 (5/19)	23.6 (17/72)	56.3 (40/71)
Saliv. Gld.	100 (1/1)	87.5 (7/8)	50.0 (3/6)	100 (5/5)	50.0 (1/2)	100 (2/2)	66.7 (4/6)	71.4 (5/7)
Skin	1.4 (1/74)	1.4 (1/74)	10.0 (2/20)	5.0 (1/20)	0 (0/20)	0 (0/20)	1.4 (1/74)	0 (0/75)
Spleen	20.3 (15/74)	54.8 (40/73)	15.0 (3/20)	45.0 (9/20)	35.0 (7/20)	60.0 (12/20)	46.6 (34/73)	73.6 (53/72)
Stomach	20.5 (15/73)	47.3 (35/74)	10.0 (2/20)	55.0 (11/20)	20.0 (4/20)	73.7 (14/19)	55.4 (41/74)	76.0 (57/75)
Testes	9.5 (7/74)	-	10.0 (2/20)	-	0 (0/20)	-	27.0 (20/74)	-
Thyroid	34.3 (24/70)	77.8 (56/72)	55.0 (11/20)	65.0 (13/20)	50.0 (10/20)	78.9 (15/19)	75.0 (54/72)	86.3 (63/73)
Uterus	-	16.9 (12/71)	-	5.0 (1/20)	-	15.0 (3/20)	-	31.1 (23/74)

* (No. of animals with amyloidosis per number of animals examined)
From FDRL Study No. 5270, Path Table 6