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

005190

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPTC (EPTAM) - Studies Submitted by PPG for Registration Nos. 748-223 and 748-222

Caswell No. 435

FROM: Irving Mauer, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

THRU: Jane E. Harris, Ph.D., Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: PPG Industries, Pittsburgh PA.

Action Requested:

(405) Review and evaluation of the following studies:

1. Two-Year Oral Feeding Study of the Oncogenicity and Chronic Toxicity of EPTC in Rats - One-Year Status Report (performed by Hazleton Labs America, Inc., Study No. HLA-6100-106, dated February 19, 1985).

2. A Three-Month Subchronic Oral Dietary Toxicity Study of EPTC in Beagle Dogs (performed by Bio/dynamics, Inc., Study No. 83-2781, dated February 15, 1985).

3. Acute Delayed Neurotoxicity Study with EPTC Technical in the Domestic Hen (performed by Huntington Research Center, England, HRC Report No. PPG-12/84676, dated December 28, 1984).

TB Conclusions:

Evaluations of data reported in these three studies are as follows:

Study	Salient Findings	Core-Grade
(1) One-Year Interim (Rat), of Two-Year Chronic feeding (Doses: 0, 9, 18, 36, 72 mg/kg/day)	(1) Decrease in body weight in all dose groups (2) Increased BUN in mid- and high-dose females (3) Increased AST levels in high-dose males and in all but low-dose females. (4) Increase in relative liver weight at the HDT (both sexes). (5) Progressive degenerative cardiomyopathy at all doses in males, and all but lowest dose in females	Supplementary (No NOEL)
(2) Subchronic feeding - Dog (Doses: 0, 200, 600, 1800 ppm)	(1) Depression (25%) in plasma AChE activity in high-dose males only.	Minimum
(3) Acute delayed neurotoxicity - Hen (Doses: 0 - 5000 mg/kg)	No evidence of delayed neurotoxicity at the LD_{50} (4674 mg/kg).	Guidelines

005190

TOXICOLOGY BRANCH DATA REVIEW

Caswell No.: 435
EPA Chem. No.: 041401

Chemical: EPTC

Study Type: Chronic (2-year) feeding/oncogenicity - Rat, 1-year interim.

Citation: One-Year Status Report. Two-Year Oral Feeding Study of the Oncogenicity and Chronic Toxicity of EPTC in Rats.

Accession No./MRID No.: 257015

Sponsor/Testing Lab: PPG/Hazleton Labs America (HLA), Madison, WI.

Study No./Date: HLA 6100-106/February 19, 1985.

Test Material: EPTC technical (no other information provided in this report).

Procedures:

Charles River CD (Sprague-Dawley) rats of both sexes (90/sex/treatment) were fed test material from 2 weeks post-weaning at dietary concentrations providing 0, 9, 18, 36, and 72 mg/kg/day. Body weights and food consumption were recorded weekly through Week 14, at Week 16, and every fourth week thereafter. Clinical laboratory values in blood and urine were determined prior to necropsy on 10/sex/group at 6 months, and again at 12 months. Hearts of all animals sacrificed at 12 months were examined histologically. This report summarizes data collected through 12 months on test in accordance with FIFRA Guidelines. (It was noted that this study is on the HLA EPA-master schedule.)

Results:

Except for low-dose females, dose-related decreases in mean body weight and cumulative body weight gain were recorded in all EPTC groups, as summarized below from the report:

Body Weight Data at Week 52

	Treatment (mg EPTC/kg BW)				
	0	9	18	36	72
Males					
Body weight (g)	750	703*	679*	626*	569*
Percent of control	-	94	91	83	76
Females					
Body weight (g)	442	422	404*	370*	341*
Percent of control	-	96	91	84	77

* Significantly different from control using Dunnett's test. Significance level is 0.05.

Significant differences in food consumption were also noted for both sexes in the two higher dose groups. An increased incidence of animals with singular (49 vs. 35 in controls) and multiple (36 vs. 22) palpable tissue masses was reported in high-dose females.

No consistent differences from controls were recorded at 12 months for hematological or the majority of clinical chemistry values. However, there were increases in BUN levels for females in the 36 and 72 mg/kg groups, as well as in aspartate aminotransferase (AST) levels in high-dose males and in all but the low-dose female groups. Plasma, erythrocyte, and brain cholinesterase activities were comparable to controls in all test groups at 12 months.

Changes in mean organ weights reflected significant decreases in body weights, except for significant increases in mean relative liver weight at 6 and 12 months for both sexes at the HDT. No treatment-related gross lesions were recorded.

Histopathological examination of the hearts of all animals sacrificed at 1 year revealed a dose-related "progressive degenerative cardiomyopathy, consisting of both acute and chronic lesions" (suggesting an ongoing process), as summarized below (from the Report):

Incidence of Degenerative Cardiomyopathies

	Treatment (mg EPTC/kg BW)				
	0	9	18	36	72
Males					
Number examined	10	10	10	10	10
Number with lesions	1	7	10	10	10

4

	Treatment (mg EPTC/kg BW)				
	0	9	18	36	72
Females					
Number examined	10	10	10	10	10
Number with lesions	1	2	6	9	10

Representative photomicrographs of heart slides from high-dose males depicted myocardial fibre degeneration and necrosis, and long-standing mononuclear cell infiltration and fibrosis. The pathologist's summary also noted that both acute and chronic lesions were evident together, as well as apart, in all anatomical sites of atria and ventricles, but were most commonly present in the intraventricular septum. Males appeared to be more severely affected than females at all dose levels; decreased severity and incidence in low-dose females only was considered by the authors a no-effect level after 12 months on test. An additional finding in EPTC males was the presence of pigment in or near myocardial lesions (1 each at 18 and 36 mg/kg, 2 at the HDT).

TB Evaluation/Core:

Core-Supplementary Data (as an Interim Report).

Histopathologic evidence of a progressive degenerative (chronic) cardiopathy after 12 months treatment with EPTC supports and extends the findings from a 3-month rat study (HLA-6100-105), which revealed similar but less severe (acute) lesions.

5

005190

TOXICOLOGY BRANCH DATA REVIEW

Caswell No.: 435
EPA Chem. No.: 041401

Chemical: EPTC

Study Type: Subchronic (3-month) feeding - Dog.

Citation: A 3-Month Subchronic Oral Dietary Study of EPTC in Beagle Dogs.

Accession No./MRID No.: 257016

Sponsor/Testing Lab.: PPG/Bio/dynamics, Inc., NJ.

Study No./Date: 83-2781/February 15, 1985

Test Material: EPTC technical, Lot No. 518-996, 98.4% ai, an amber liquid.

Procedures:

Six-month-old Beagle dogs (6/sex/treatment) were fed diets containing test compound at levels of 0 (Purina Canine #5007), 200, 600, and 1800 ppm for approximately 3 months (7 days a week, January 25 through May 1, 1984). Animals were observed for clinical signs twice daily, weighed weekly, and bled for hematological and clinical chemistry determinations once before treatment and again at Study Week 7 and at termination. Ophthalmoscopic examinations were performed 1 week before treatment began, and again at termination. Complete necropsies were performed on all animals, organs weighed, and histopathological evaluation conducted of the Guidelines roster of tissues from all controls and high-dose animals; in addition, livers and kidneys from all low- and mid-dose animals were examined.

Results:

Except for consistently excessive salivation in one high-dose male, no clinical signs considered to be dose- or treatment-related were observed in test animals throughout the study.

Mean body weights of high-dose males were consistently lower than controls throughout the study, attributed to emaciation (of undetermined cause) in two animals. One low-dose male was also emaciated during the 13 weeks treatment, but its weight loss did not skew the mean value for the group significantly. Transient decrease in food consumption (Test Day 1 only) in high dose males and females was suggestive of an initial palatability problem at this level, which was resolved thereafter, since values increased thereafter to control levels in females, but remained slightly reduced in males.

6

Except for one mid-dose male which exhibited hypertrophy and prolapse of the third lid of the right eye (considered a common lesion in Beagles), no ocular abnormalities attributable to treatment were recorded.

No treatment-related changes in hematological or the majority of clinical chemistry values were recorded. However, mean plasma cholinesterase activity in high-dose males was slightly but significantly reduced (about 25% of controls) at Week 7 and at termination, but in no other group. Erythrocyte and brain cholinesterase values, on the other hand, were apparently not affected by EPTC treatment. An increase in BUN was recorded in the two emaciated high-dose males.

No gross, organ weight, or histological changes were found in EPTC-treated animals.

Conclusions:

Except for depression in plasma cholinesterase values in high-dose males (1800 ppm), no effects related to dietary administration of EPTC for 3 months to Beagle dogs were observed.

TB Evaluation: Core-Minimum

NOEL = 600 ppm (15 mg/kg/day)
LEL = 1800 ppm (45 mg/kg/day),
reduced plasma cholinesterase.

7

005190

TOXICOLOGY BRANCH DATA REVIEW

Caswell No.: 435
EPA Chem. No.: 041401

Chemical: EPTC

Study Type: Acute delayed neurotoxicity - Hen.

Citation: Acute Delayed Neurotoxicity Study With EPTC Technical In The Domestic Hen.

Accession No.: 257014

Sponsor/Testing Lab.: PPG/Huntingdon Res. Ctr., England.

Study No./Date: HRC Report No. PPG-12/84676/December 28, 1984.

Test Material: EPTC technical, Lot No. 518-996, 98.4% ai, a pale yellow liquid.

Procedures:

1. LD_{50} Determination: Adult (12-months-old) female hens (described as "a hybrid brown laying strain") were intubated once with test material (groups of 10 birds given 988, 1481, 2222, 3333, and 5000 mg/kg) and observed 14 days.

2. Neurotoxicity Assessment: Additional groups of 10 birds of the same age and source were intubated once with 4674 mg/kg test material (4 groups), 5 mL/mg corn oil or 500 mg/kg tri-orthocresyl phosphate (TOCP, as positive control) and observed for 21 days. The test and corn oil birds were then given a second single dose, and observed for a further 21 days. TOCP-treated birds were not redosed. Postmortem examinations were carried out according to FIFRA Guidelines (1982).

Results:

1. LD_{50} Determination: The following deaths were recorded: 2 in the corn oil controls, 1 in the 3333 mg/kg group (Day 4) and 6 given 5000 mg/kg (1 each on Days 1, 3, 4, and 6; 2 on Day 5). Marked weight loss preceded death at the two highest dose levels.

2. Neurotoxicity Assessment: During the 7-day period following initial dosing, all EPTC-treated birds lost weight, became "subdued" and/or "unsteady", and seven deaths were recorded (4, 1, 1, and 1 in

the 4 groups). All surviving birds recovered by Day 7, and remained in reportedly good health for the rest of the first 21-day observation period. Two hours after the second dose of EPTC (Study Day 22), all birds again became subdued and/or unsteady, and a few in each group were described as "weak" at the end of the dosing-day. Marked decreases in body weight were recorded for the first 3 days, and 2 deaths were recorded, one each on days 23 and 24. All surviving birds were reported as having recovered by the end of Day 26. By contrast, all except two TOCP-treated birds displayed increasing grades of ataxia (and decreased body weight) from the tenth day after dosing, (the two exceptions started to show ataxic signs beginning on Days 17 and 20), progressing to Grade 7 (by Days 17, 18, and 21) when these were sacrificed. (The remaining seven TOCP-treated birds were sacrificed on Day 22).

No birds on EPTC treatment which died during the study were examined postmortem. Compared to the corn oil control group, no increased incidence or severity of gross or histological changes (Grades I and II) were found in brain, spinal cord, and peripheral nerve preparations of survivng EPTC-treated groups, as summarized in Table A4 from the Report (following page of this review). By contrast, all 10 birds of the TOCP group exhibited Grade III changes or higher (significant neurological degeneration) in one more spinal cord levels, as well in peripheral nerves.

Conclusions:

1. LD_{50} Determination: Based on the incidence of mortality in the toxicity study, the acute oral LD_{50} was calculated by probit analysis to be 4674 (3922-7081) mg/kg.

2. Neurotoxicity Assessment: Oral administration of the EPTC LD_{50} dose to four groups of birds twice, 21 days apart, did not produce clinical or histopathological evidence of neurotoxicity.

TB Evaluation: Core-Guideline Data. No observed delayed neurotoxicity at the LD_{50} (4674 mg/kg).

9

APPENDIX 4
(continued)

TABLE A4

Summary of neuropathological gradings
(number of slides in each grade)

Group	Treatment	No. of birds examined	Brain			Spinal cord					Peripheral nerve					
			I	II	Total	I	II	III	IV	Total	I	II	III	IV	V	Total
1	Negative control (corn oil)	10	20	0	20	38	2	0	0	40	28	2	0	0	0	30
2	Positive control (TOCP 500 mg/kg)	10	18	0	18	18	18	4	0	40	11	5	10	4	0	30
3, 4 5 & 6	EPTC (4674 mg/kg)	10	20	0	20	38	2	0	0	40	28	2	0	0	0	30

APPENDIX 4
(continued)

TABLE A4

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Group	Treatment	No. of birds examined	Brain			Spinal cord					Peripheral nerve					
			I	II	Total	I	II	III	IV	Total	I	II	III	IV	V	Total
1	Negative control (corn oil)	10	20	0	20	38	2	0	0	40	28	2	0	0	0	30
2	Positive control (TOCP 500 mg/kg)	10	18	0	18	18	18	4	0	40	11	5	10	4	0	30
3, 4 5 & 6	EPTC (4674 mg/kg)	10	20	0	20	38	2	0	0	40	28	2	0	0	0	30