OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

CASWELL FILE

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

PC 128831

JAN - 9 1987

005649

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of a Neurotoxicity Study of Baythroid™ in Hens

EPA No. 3125-GLE
Record No. 180761

Project No. 2354
Tox. Chem. No. 266E

TO: George LaRocca (PM Team #15)
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

John E Whalan 12-2-86

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

11/9/87 11/9/86

Mobay Chemical Corporation submitted a Delayed Neurotoxicity Study and Neuro-Toxic Esterase Activity Assessment of FCR 1272 in Hens. This study was sent in response to an EPA review of another Neurotoxic Esterase study (Bayer AG Institute of Toxicology, Report No. 13821) which was Core Classified as Supplementary (Memorandum from John Whalan, EPA No. 3125-GLR, May 8, 1986).

The repeat study was reviewed by the Toxicology Branch and classified Core Minimum. This study fulfills the request for a neurotoxic esterase study. There were no indications of neurotoxic esterase inhibition in hens dosed with FCR 1272, and only mild signs of neurotoxicity at the doses tested. There was no resemblance to the classic delayed neurotoxic signs seen in hens dosed with the organophosphate TOCP.

The study and report received Quality Assurance review, and the report was signed by the contributing scientists. These were key criteria in acceptance of this study for review.

The Whalan memorandum repeated a request to resolve several questions which had first been proposed to the Registrant by John Doherty and Edwin Budd (PP 4F-3046/FAP 4H-5427, and EPA Reg. No. 3125-GLR; February 15, 1985). The following text is quoted from these reviews:

> "The registrant is also requested to provide an explanation and/or rationale for the different results observed in the acute delayed neurotoxicity tests in chickens between the studies performed by Bayer AG Institute of Toxicology (in Germany) and those performed by Mobay Chemical Corporation (in the United States). Some points that should be addressed include:

- Possible differences in the test material

  ° Including a consideration of impurities, contaminants and/or manufacturing by-products in the test material.

  ° Including a consideration of possibly different ratios of active ingredient isomers in the test material.

- Possible differences in the test animals used

  ° Including a consideration of strain, source, etc.

  ° Including a consideration of normal background incidence of nervous system lesions in historical control animals of the same strain and source (if possible).

- Possible differences in investigational techniques employed

- Other"

These questions remain unanswered.

DELAYED NEUROTOXICITY STUDY AND NEUROTOXIC ESTERASE ACTIVITY ASSESSMENT OF FCR 1272 IN HENS

Research & Consulting Company AG; Report No. 93094; April 11, 1986; Accession No. 264955

PROTOCOL: This study was performed in two parts using adult White Leghorn hens (1.2-2.0 kg; approximately 12 months old):

1. Delayed Neurotoxicity - Hens were assigned to five groups and dosed according to the following regimen:

Test Article	Regimen (days)	Dose (mg/kg/day)	Population	Sacrificed
FCR 1272	X1	4300	12	Day 22
FCR 1272	X2 (1,21)	4300	16	Day 57
FCR 1272	X5 (1-5)	1500	10	Day 57
PEG 400	X1	10 ml/kg	7	Day 57
TOCP	X1	500	7	Day 22

The hens were dosed by gavage into the crop with dose volumes of 10 ml/kg. FCR 1272 (93.5% purity) was formulated daily in PEG 400. The positive control, TOCP (triorthocresylphosphate), was formulated in corn oil. Food and water were available ad libitum. All hens were observed daily for clinical signs. Their food consumption and body weights were measured weekly. They were all examined for gross lesions at the time of death or sacrifice. Histopathologic examinations of 6 hens/group were performed on the following tissues:

Brain (cerebrum, cerebellum, medulla oblongata)
Spinal cord (upper, cervical bulb, midthoracic, and lumbosacral regions)
Sciatic nerve (left and right)
Tibial nerve (left and right)

These tissues were stained with hematoxylin and eosin, Bodian's silver stain (axons), and Luxol Fast Blue (myelin sheaths).

2. Neurotoxic Esterase (NTE) Activity - Neurotoxic esterase (NTE) activity was assessed by the method of M.K. Johnson (Arch. Toxicol. 37, 1977, 113-115). NTE was measured spectrophotometrically as the difference in phenyl valerate hydrolyzing activity between paired samples in the presence of paraoxon and paraoxon plus mipafix. Additional hens were dosed for this study as follows:

Test Article	Regimen	Dose (mg/kg	Population
FCR 1272	X1	4300	20
PEG 400	X1	10 ml/kg	20
TOCP	X1	500	20

Five hens from each group were evaluated for brain and spinal cord NTE activity at each of four intervals - 24 hours, 48 hours, 72 hours, and 7 days after dose administration. Other than the NTE measurements, there were no other observations or measurements made for these hens.

RESULTS:

1. Delayed Neurotoxicity - There were two unexplained deaths during the second week - one vehicle control hen, and one hen dosed twice with FCR 1272. In addition there were other hens which died or were sacrificed moribund after loosing 16-55% of their body weight. These included 2 hens dosed twice with FCR 1272 (days 15 and 31), and 3 hens dosed 5-times with FCR 1272 (days 23, 33, and 46). Presumably these hens died from malnutrition; there was no way to determine whether a neurologic inability to eat was involved.

The hens dosed with 4300 mg FCR 1272/kg as a single dose were somnolent on days 4-11, and were emaciated (unspecified interval). Hens dosed with 4300 mg FCR 1272/kg on days 1 and 21 (X2 regimen) were aggressive on days 4-13, somnolent on days 6-12 and 22-36, and emaciated (unspecified interval). One of these hens died on day 15, and was ataxic several days before dying; its death was attributed to an emaciated state. The hens dosed on five consecutive days (X5 regimen) with 1500 mg/kg of FCR 1272 were aggressive on days 10-13, somnolent on days 14-36, and emaciated with cyanosis of the crest on days 12-19. All of the positive control (TOCP) hens had slight ataxia which began on day 3. The neurologic signs progressed through stages of reduced motor activity, stilted gait, stumbling, clumsy landing, sitting on hocks, and shuffling gait. On days 19-22 (last days of the study), all of the positive controls were unable to stand due to total paralysis. In addition the positive controls were aggressive after day 10. The vehicle control (PEG 400) hens had no clinical signs.

Food consumption was severely reduced in all but the vehicle control group. The hens dosed with FCR 1272 were anorectic during weeks 2-3 (X1 and X5 regimens), and weeks 2-3 and 5 (X2 regimen). The positive controls were anorectic during weeks 2-4. These effects were reflected in significant losses in body weight, relative to the vehicle controls:

Test Article	Regimen (days)	Dose (mg/kg/day)	Maximum Mean Weight Loss
FCR 1272	X1	4300	21%
FCR 1272	X2 (1,21)	4300	24%
FCR 1272	X5 (1-5)	1500	21%
TOCP	X1	500	18%

The body weights and food consumption of the hens dosed with the X2 and X5 regimen were approaching those of the vehicle controls during the last week of the study.

There were no compound-related gross lesions in any hens. Histopathologic lesions of nervous tissue were seen almost exclusively in the positive control hens. These lesions included minimal to marked axonal degeneration of the medulla oblongata, spinal cord, and tibial and sciatic nerves. The only histopathologic lesions seen in hens dosed with FCR 1272 were slight axonal degeneration of the sciatic nerve in one hen given a single dose, and slight axonal degeneration of the spinal cord in one hen given two doses. There were no lesions in the hens given five doses of FCR 1272 or in the vehicle controls.

2. Neurotoxic Esterase (NTE) Activity - Neurotoxic Esterase (NTE) activity in the positive control group (TOCP) was reduced as much as 90% in the brain, and 82% in the spinal cord, thus demonstrating the sensitivity of the testing system. The greatest effect was seen at 24, 48, and 72 hours. NTE activity in the brain and spinal cord of the hens dosed once with 4300 mg FCR 1272/kg was similar to that of the vehicle controls at each sampling interval.

CONCLUSIONS: In the Delayed Neurotoxicity study, the highest incidence of death occurred in the hens given 2 or 5 doses of FCR 1272. These deaths were dose-related. Presumably, these hens died because of compound-induced anorexia and weight loss without primary neurologic involvement. Neurologic signs were seen, however, including aggression, somnolence, and cyanosis of the crest. Of far greater severity were the delayed neurotoxic signs seen in the positive controls dosed with TOCP. These hens had a progression of ataxic signs which climaxed in total paralysis of all hens. Histopathologic lesions in these hens included axonal degeneration of the medulla oblongata, spinal cord, and the tibial and sciatic nerves. The few neurologic lesions found in the hens dosed with FCR 1272 were probably spontaneous. Thus, FCR 1272 was mildly neurotoxic to hens at the doses tested, but did not bear any resemblance to the classic delayed neurotoxic signs seen in the hens dosed with the organophosphate TOCP.

In the Neurotoxic Esterase (NTE) Activity study, NTE activity was severely reduced in the brain and spinal cord of hens dosed with TOCP, but NTE activity in the hens dosed with FCR 1272 resembled that of the vehicle controls.

STUDY CLASSIFICATION: This study is Core MINIMUM. The report failed to discuss the cause of death for all but one hen. There were no observations of any kind for the hens used in the NTE study. Since a group of hens in the delayed neurotoxicity study were dosed at the same FCR 1272 and control dose levels, and the FCR 1272 dose was frankly toxic, these data could suffice for NTE interpretation. There is no mention of performing NTE assays in duplicate. Dose concentration analyses demonstrated that the 25% formulation was only 80% of the nominal dose. The study and report received Quality Assurance review, and the report was signed by the contributing scientists. Mean body weight data were not reported.

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Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**01/09/87**
File ID:	***TX005649***
Accession Number:	**412-03-0015**

HED Records Reference Center
09/30/2002