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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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

EPA No. 3125-GLR
Record No. 167963

Project No. 1414
Tox. Chem. No. 266E

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John Whalan 5-1-86

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Budd 5/5/86 5/5/86

Mobay Chemical Corporation submitted a Neurotoxicity Study of the Effect of FCR 1272 on Neurotoxic Esterase (Neurotoxic Target Enzyme) in Hens. This study was requested by John Doherty and Edwin Budd (ref. PP 4F3046/FAP 4H5427 and EPA Reg. No. 3125-GLR; 2-15-85)

This study was reviewed by the Toxicology Branch and was classified Core Supplementary. The study was poorly reported and had many deficiencies. There were no indications of significant inhibition of neurotoxic esterase.

Since the report was not signed by either the contributing scientists or the Quality Assurance officer, the validity of the report is in doubt. In the Doherty/Budd review, the failure of the Registrant to submit signed reports was mentioned along with the warning that studies would be classified Invalid unless signed reports were submitted. This warning has gone unheeded, but will be enforced on all future studies.

The Doherty/Budd review requested the Registrant to resolve several questions. The following text is quoted from that review:

> 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:
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> - 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.

NEUROTOXICITY STUDY OF THE EFFECT OF FCR 1272 ON NEUROTOXIC ESTERASE (NEUROTOXIC TARGET ENZYME) IN HENS

Bayer AG Institute of Toxicology; Report No. 13821; September 16, 1985; Accession No. 261433

PROTOCOL: Neurotoxic esterase (NTE) activity was assessed by the method of M.K. Johnson (Arch. Toxicol. 37, 1977, 113-115). Adult White Leghorn chickens (1.25-1.70 kg; 7-10 months old) were randomly assigned to three groups of 15 hens/group. One group was dosed by stomach tube with 20 ml/kg of a 25% (w/v) solution of FCR 1272 (92.9% purity) in polyethylene glycol 400 (PEG 400) at a dose of 5000 mg/kg/day for 3 days. This dose, which was a maximum attainable dose, was based on previous studies in which "clear signs and possibly mortalities" [sic] were observed after a single dose. The intent of this study was not to observe delayed neurotoxicity, but rather to detect NTE inhibition (an early indicator of delayed neurotoxicity) 24 hours after administration of one or two potentially lethal doses. A positive control group was dosed with TOCP (triorthocresylphosphate) in PEG 400 at a dose of 100 mg/kg/day. A third group constituted a vehicle control group and was dosed with PEG 400. Food and water were available ad libitum.

All hens were observed several times each day for clinical signs. They were weighed on day 1 only. They were all examined for gross lesions at the time of death or sacrifice. There were no histopathologic examinations performed. Three hens from each group were sacrificed by decapitation 24 hours after the first and second dosings. Their brains, spinal cords, and sciatic nerves were removed and evaluated for NTE activity.

RESULTS: The study was to last for 14 days, but all surviving hens were sacrificed on day 3 since all the hens dosed with FCR 1272 had died by then. The cumulative mortality (%) was as follows:

	Day 1	Day 2	Day 3
FCR 1272	0	25	100
TOCP	8	9	9
PEG 400	0	11	11

The vehicle and positive control compounds caused some lethality, but the test article was totally lethal. Clinical signs included fluffed plumage, lassitude, shrunken comb, spasms, salivation, dyspnea, and vocalization in hens treated with FCR 1272; slightly fluffed plumage and shrunken comb in the positive controls (TOCP); and slightly fluffed plumage, lassitude, apathy, and shrunken comb in the vehicle controls (PEG 400). There was no mention of the number of dead, moribund, or viable hens in any group. Gross lesions were seen only in the hens that died. Gross lesions seen in hens dosed with the test article included crops distended and filled with fluid, lungs distended and filled with fluid, and patchy livers. Gross lesions in the positive controls included crops distended and filled with fluid, and well-filled gall bladders. Gross lesions in the vehicle controls included crops distended and filled with fluid, patchy livers, and yellowish discoloration of the mucosa of the glandular stomach.

NTE activity in the brain, spinal cord and sciatic nerve in the test article group and vehicle control group were typically low 24 hours after the first and second doses. One hen, which was sacrificed 24 hours after the first dose of FCR 1272, had 53.3% NTE inhibition in the sciatic nerve. This value was approaching the 80% inhibition criteria that indicates the onset of delayed neurotoxicity. NTE activity in the positive control group (TOCP) was inhibited 80.4 to 94.6% 24 hours after the first and second doses, demonstrating the efficacy of the protocol. Thus, the test article did not significantly inhibit NTE.

This study is CORE SUPPLEMENTARY. All assays should have been performed in duplicate, but there was no evidence that this was done. The reference date for the method used in performing this study was incorrectly reported as 1972. The appendix, which contained the FCR 1272 and TOCP stability data, was missing from the report. Dose concentration analyses were apparently not performed. There was no way to determine the number of dead, moribund, or viable hens in each group. Room humidity was poorly regulated, and ranged from 50-90%. The report was signed by the translator, but not by the contributing scientists. A Quality Assurance statement was included in the report, but it too was unsigned. Considering the overall poor quality of the report presentation, it was obvious that the report was never reviewed for Quality Assurance, and is therefore of questionable validity. The Core classification of this study may be upgraded when the above deficiencies are resolved (including an explanation for the wide fluctuations in room humidity).

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