6-17-83

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: William Miller/M. Mautz
PM Team #16
Insecticide Branch/Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head RBJ 6/17/83
Review Section #1
Toxicology Branch/HED (TS-769)

SUBJECT: Azodrin, miscellaneous data reviewed - neurotoxicity.
Reg. No. 201-157

Conclusions and Recommendations:

1. Toxicology Branch recommends the neurotoxicity data be added to the data files in support of Azodrin uses.

2. Toxicology Branch concludes that both a range-finding study and a 90 day subchronic study do not demonstrate a delayed neurotoxicity effect in chickens.

Review:

Study: 14-day Neurotoxicity study of Azodrin® in chicken hens (range-finding). By: FDRL for Shell Development Co. Shell Protocol No. WTP-11. Dated: July 11, 1980. Lab. No. 6535-I. Acc. No. 246436.

Material Tested:

1. Technical Azodrin, SD 9129 77.4% E - isomer with [redacted] trimethyl phosphate.

2. TOCP purity unstated.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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Methods:

110 hens were acclimated for 13 days prior to treatment during which Purina Layena® chicken feed and tap water was available ad lib. Dosing was via gelatin capsule containing 0.0, 0.03, 0.1, 0.3 or 1.0 mg/kg of Azodrin. Positive controls were given either 50 or 100 mg/kg of TOCP in capsules. Body wt., enzyme and egg production determinations were made on 5 animals per dosage. Plasma or RBC cholinesterase determinations were made both at 1 day pretreatment and at days 1, 7 and 14 of treatment. Brain cholinesterase activity was determined after the last dosage. Observations of clinical status and determinations of neurotoxic esterase activity were recorded.

Results:

Body wt. changes occurred in all dosage groups. However, only the high dose group showed a 16.9% wt. loss compared to controls. The 0.3 mg/kg dosage group also lost about 18% body wt. Losses are considered biologically significant to this reviewer.

Data from Table 2., Summary of Egg Production indicate that treatment with Azodrin at 1, 0.3 and 0.1 mg/kg causes a significant reduction in egg reproduction ($p < .05$). The NOEL for chemical effects on egg production is 0.03 mg/kg and an LEL of 0.1 mg/kg.

Plasma cholinesterase determinations for each group, based on the values at day - 1, indicate that at day 14 a statistical reduction of 23% occurred at 0.3 mg/kg, while no depression occurred at 0.1 mg/kg using the Ellman colorimetric method. Plasma cholinesterase values, using the Michel method (ΔpH), were lowered at both 0.3 and 0.1 mg/kg by 33% and 24.8%, respectively, at 14 days when compared to day -1. A NOEL for plasma ChE in the chicken is considered to be 0.03 mg/kg, with an LEL of 0.1 mg/kg.

Brain cholinesterase values using the Michel method showed 18% and 6.8% reduction at 0.3 and 0.1 mg/kg, respectively, compared to a control group. Brain cholinesterase reduction at 6.8% is a threshold NOEL (0.1 mg/kg) with an LEL of 0.3 mg/kg.

Brain neurotoxic esterase levels were unchanged in Azodrin treated groups when compared to the control group. Neurological scores of individual hens to day 14 indicated only 1 hen at 0.3 mg/kg on day 14 which showed an unsteady gait score of 1. The effect can not be ruled out from being cholinesterase inhibition.

Adequate as a range finding study.

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90-day Subchronic Neurotoxicity Study:

Study: Neurotoxicity Evaluation of Azodrin® Insecticide. By FDRL for Shell Development Co. #6535-II. Dated: April 2, 1981. Acc. No. 246435.

Material Tested:

Azodrin® 77.4% E-isomer (technical) with [redacted] trimethyl phosphate.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

Animal Tested:

Specific Pathogen free - Cofal, Marek negative adult hens from SPAFAS, Inc. Norwick, Ct., 9 months of age. Weighing 1.35 - 2.10 kg.

Methods:

After 19 days of acclimation the 10 animals/group were individually penned, fed a commercial layer feed from Purina and tap water ad lib. Dosing was by capsule containing ground feed with 0.03, 0.1, 0.3, and 0 mg/kg b. wt. of Azodrin, or 7.5 mg/kg TOCP in acetone, which was evaporated. At day 79 of the 96 day test the TOCP dosage was raised to 10 mg/kg and the Azodrin dosage of 0.3 mg/kg was raised to 0.5 mg/kg for the remainder of the study.

Observations Made:

1. Clinical observations were made at least once daily.

2. Egg producition and body wts. were recorded and reported on a weekly basis.

3. Enzyme activity for cholinesterase in plasma and RBC was determined before and on days 1, 30, 58 and at termination. Brain enzyme activity of the test animals was determined at termination.

4. Histology/Pathology slides were graded with regard to severity in: brain, spinal cord, optic nerves, peripheral nerves (sciatic, tibial, perineal) and dorsal root ganglia by either frontal, sagittal, cross or longitudinal sections with H&E, Luxol fast blue on Holmes silver stains.

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Statistics:

Reported were means, ± SD; most groups contained 10 birds. A oneway analysis of variance was used on egg production, body wt., and enzyme activity data. Scheffe's test was used to check differences between groups. A chi-square test of Mantel (1963) evaluated neurological data.

Results:

Significant body wt. changes were seen only in the 0.3 mg/kg test group of Azodrin treated animals.

Egg production was reduced from 2 weeks to 41 days at 0.3 mg/kg and recovered slightly until days 84-97. The dosage of Azodrin was increased to 0.5 mg/kg on day 79. A NOEL of 0.1 mg/kg is demonstrated, with an LEL of 0.3 mg/kg.

Neurological scoring was zero for each azodrin treated animal. The TOCP group had 3 animals which showed clinical effects.

ChE Inhibition:

Biologically and statistically significant decreases in plasma cholinesterase of 26.2% and 34.5% are noted at 0.1 mg/kg and 0.3 mg/kg dosages, respectively, by 30 days of treatment.

RBC cholinesterase activity of treated groups is not considered to be different from the control animals.

Brain cholinesterase was not determined.

Histopathology:

Brain to body weight is significantly increased ($p < .05$) over controls in the azodrin group of 0.3 mg/kg (2.07 ± 0.29% vs. 1.69 ± 0.20% in controls).

There were no adverse effects on the optic nerves, dorsal root ganglia, peripheral nerves, or spinal cord. Azodrin showed no demyelination effects in the treated hens. Adnormal tissues (nerve sections) were sparse and observed in negative controls in an inconsistent manner which included swollen axons (minimal numbers) and a few eosinophilic bodies of 1-2.

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Conclusions:

1. Toxicology Branch considers the data adequate to show that azodrin, under the conditions of the study did not exhibit neurotoxicity at 0.3 mg/kg b.wt.

2. Core: Minimum data.

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