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IBT Evaluation Report--Avadex

Neurotoxicity Study with Avadex in Chickens

(IBT No. 8580-09119)

Submitted to:

United States Environmental Protection Agency
Office of Pesticide Programs
Hazard Evaluation Division
Toxicology Branch

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Under:

Contract No. 68-01-6561

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Cipriano Cueto, Project Director

September 20, 1983

IBT EVALUATION REPORT

(1) CHEMICAL: Avadex.

(2) TYPE OF FORMULATION: Liquid.

(3) CITATION: IBT. No. 8580-09119. Neurotoxicity Study with Avadex in Chickens. December 28, 1976.

(4) SPONSOR: Monsanto Company.

(5) EPA ACCESSION NUMBER and or Pesticide Petition No. and/or Registration No. for this IBT Report: Accession No.: 228094; Registration Nos.: 524-119, 524-151, and 524-306.

(6) EVALUATION PERFORMED BY:

Cipriano Cueto, Ph.D.
Department Director
Dynamac Corporation

Signature: William L. McLellan /for
Date: 20 Sept, 1983

Nicolas P. Hajjar, Ph.D.
Acting Program Manager
Dynamac Corporation

Signature: Nicolas P. Hajjar
Date: September 20, 1983

(7) Based upon findings listed in this Dynamac Corporation evaluation report (which included examination of the microfiched raw data, the sponsor validation report, the final test report, and the Canadian validation report), I concur with this determination.

Pharmacologist
Toxicology Branch
HED, EPA

Signature: Lawrence D. Chitlik for W.T.
Date: 11/4/83

Section Head
Toxicology Branch
HED, EPA

Signature: Lawrence D. Chitlik
Date: 11/4/83

(8) TOPIC: This study has information pertinent to the discipline of toxicology; topic, subchronic neurotoxicity. It relates to the Proposed Guidelines data requirement 162.82-5.

(9) EVALUATION REPORT CONCLUSION:

_____ CORE GUIDELINE

_____ CORE MINIMUM

_X_ CORE SUPPLEMENTARY

_____ CORE INVALID

RECOMMENDATIONS

This study is classified as Core Supplementary Data. It presents useful histopathologic data permitting a morphological evaluation of the potential delayed neurotoxicity of the test material in chickens as well as daily observations of clinical neurological signs. The study has been compromised because the raw data did not contain records of dose calculation or administration. Since the dosage of test material administered to the test animals cannot be verified, a compound-related effect level cannot be established. In addition, there were no laboratory records to support body weight data in the final report, and food consumption raw data were present but not reported.

Histologic lesions were present in two of the ten test animals; these consisted of minimal to mild axonal degeneration of the spinal cord and sciatic nerve, with mild demyelination. Similar histologic changes were reported in all positive controls. All test birds displayed neurological signs ranging from slight ataxia and lethargy to paralysis. In the first 21-day test period these signs generally peaked 2 to 3 days after dosing and then subsided; four birds with paralysis recovered. During the second 21-day observation period (test days 27, 28, and 39) three test birds died with paralysis , and one was sacrificed on day 31. Neurologic signs occurred earlier with Avadex than with positive controls; all TOCP treated birds exhibited severe delayed neurotoxicity between days 12 and 16 of the study and were subsequently sacrificed on day 16. Untreated control birds appeared normal throughout the entire study and had no histologic lesions. In conclusion, although Avadex caused some neurologic effects in hens at the dose tested, these appeared shortly after dosing and most of the animals recovered. Histologic lesions, although only mild to minimum in degree, that occurred in two test birds were, nervertheless, characteristic of those accompanying delayed neurotoxicity in positive controls.

BACKGROUND

The Canadian validation report, dated 4/17/79, for this study noted that raw data on body weight and general observations were missing, but concluded that the study was valid since the raw data supported the final report findings on neurotoxicity (clinical neurologic findings and histopathologic findings).

REVIEW

MATERIALS AND METHODS

TEST MATERIAL

- Identification: Avadex Technical.
- Sample Identification and Purity: Not provided.
- Storage: No information provided on storage.
- Batch No. and Date Received: No information was provided.
- Solvent Used: No information was provided.
- Concentration: Undiluted (neat) Avadex was used.
- Stability: Not provided.
- Route of Administration: Orally via gavage.
- Compound Preparation: Doses were volumetrically measured and administered via gavage.

EXPERIMENTAL METHODS

- Test System: Thirty hens over 9 months old were used; groups of 10 hens each served as untreated control, test group, and positive control. They were observed for an unspecified pretest period to determine their suitability as test animals based on general physical condition. The animals were fasted for 16 hours prior to dosing.
- Procedure and Observations: Following the 16-hour fast, the test material was administered to each of ten animals via gavage at a dosage of 0.312 g/kg body weight. Dosing was carried out twice daily for 3 consecutive days and the dosing procedure was repeated on day 22. The total dosage administered was 3.74 g/kg. Vehicle controls received corn oil and positive controls received a single dose of 0.5 g/kg TOCP in corn oil. The dose of Avadex selected was based on a range finding study in which two hens per group were dosed twice a day for three consecutive days with one of six doses of test compound (0.156 - 5.0 g/kg) and observed for mortality. The maximum non-lethal dose was 0.312 g/kg (repeated twice daily for three days). The positive control group received a dosage of tri-o-cresyl phosphate (TOCP) known to produce delayed neurotoxicity.

All animals were observed daily for mortality and neurotoxic reactions. Body weights were recorded on days 0, 21 and 42. After 42 days, the surviving birds were sacrificed and subjected to a gross pathological examination. The brain, sciatic nerve and spinal cord were removed, fixed, stained, and examined microscopically.

- Statistical Analysis: No statistical analysis of the data was performed.

RESULTS

DOSING

There were no raw data to verify that test birds received the required amounts of Avadex. There were no laboratory records of dose calculations or administration. The calculation of dosage required the determinations of body weights of test animals at 0 and 21 days. However, there were no laboratory records of body weights at any interval even though individual weights for test birds were presented in the final report for 0, 21, and 42 days. Body weight data and calculations (based on the weights) for dosing of positive controls were present in the raw data.

GENERAL OBSERVATIONS AND MORTALITY

Clinical observations consisting of daily graded clinical neurological results were available in the raw data and presented in an addendum report.

In the first 21-day period, mild neurological signs (slight ataxia and lethargy) appeared on day three in all test birds, peaked at day 6, and subsequently subsided. Four of 10 birds had severe effects (paralysis).

In the second 21-day period, three test birds died (on days 27, 28, and 39) and one bird was sacrificed in extremis on day 31, these four showed severe neurotoxic signs (paralysis). Seven out of 10 test birds experienced paralysis in one or both of the 21-day test periods (arrows on Reference 1, page 2).

Positive control birds develped mild neurotoxic signs (slight ataxia and lethargy) on day 10-11 and were sacrified in extremis on day 16 because of severe neurotoxic effects such as severe weakness of wings and legs and inability to stand (Reference 1, page 2). Untreated control birds did not have any neurotoxic signs.

BODY WEIGHTS AND FOOD CONSUMPTION

According to the final report, the test birds had depressed body weights on days 21 and 42 when compared to untreated controls. However, body weight raw data were not present for the test birds but were present for untreated controls and positive controls. Food consumption data present in the raw data showed that less food was consumed by Avadex treated birds than by controls, however these data were not presented in the final report.

GROSS PATHOLOGY

Individual pathology observation sheets were present for test and control birds in the raw data, but no diagnostic entries for gross observations were recorded. A gross pathology log in the raw data noted dates of death and sacrifice (e.g., Reference 2). In addition, all test birds had the notations "extremely thin" and "N.A.T.A. (meaning unknown)"; all Avadex treated birds that survived to final sacrifice at day 43 ~~birds~~ had the notation N.A.T.A.

HISTOPATHOLOGY

The brain, spinal cord, and sciatic nerve were examined histologically; lesions were present in 2/10 test birds (both died with paralysis), whereas all untreated controls were normal. One of these test birds had minimum to mild axonal degeneration of the spinal cord and mild multifocal axonal degeneration of the sciatic nerve with mild demyelination, and the other bird had minimum to mild axonal degeneration of the sciatic nerve.

Although the protocol required only 3 positive control birds, raw data were present for 10; and only 4 of these were examined histologically. Three of four had minimum to mild axonal degeneration of the spinal cord with minimum demyelination and moderate to severe multifocal axonal degeneration of the sciatic nerve with mild demyelination. The fourth bird had mild axonal degeneration of the sciatic nerve but no spinal cord lesion.

Other histologic changes in neural tissues found in both control and test birds "were lesions of lymphatomatosis (Marek's disease), a naturally occurring viral disease of chickens." These lesions, minimal to mild perivascular lymphoid infiltration in brain, spinal cord and sciatic nerve and interstitial lymphoid infiltration of the sciatic nerve were noted at about the same frequency in negative controls and test birds.