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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Data on Histopathology of the Nervous S[illegible]tem Following Treatment with Isofenphos, Submitted [illegible] a Supplement to a 90-Day Hen Study

Caswell No. 447 AB
HED Project No. [illegible]-1500
Record No. 245[illegible]

MRID 410741-01
ID No. 3125-326

FROM: Sidney J. Stolzenberg, Ph.D. SJS 11/8/89
Review Section I, Tox Branch II (H7509C)

TO: W.H. Miller, PM# 16
Registration Division (H7505C)

THRU Yiannakis M. Ioannou, Ph.D. YM Ioannou
Head, Review Section I, Tox Branch II (H7509C)

and

Marcia van Gemert, Ph.D. M van Gemert 11/9/89
Branch Chief, Tox Branch II
Health Effects Division (H7509C)

APPLICANT: Mobay Corporation
Bayer USA Inc.
Kansas City, MO 64120-0013

ACTION REQUESTED:

Registrant has submitted supplementary data to a subchronic neurotoxicity test. Review the newly submitted material for an update of the toxicology data base.

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CONCLUSION:

This submission contains the nerve tissue histopathology data of a previously reviewed 90-day hen neurotoxicity study (Accession No. 404597-01). Doses of isofenphos administered were 0 (vehicle control), 0.25, 1.0 and 2.0 mg/kg/day; positive controls received triorthocresolphosphate (TOCP). No indications of delayed neurotoxicity due to isofenphos treatment had been previously observed at any of the 3 dose levels. The presently submitted nerve tissue histopathology data indicate that isofenphos did not cause structural damage to the nerve tissues of the brain, spinal cord or peripheral nerves at the highest dose tested, 2.0 mg/kg/day. This confirms the conclusion that isofenphos does not result in delayed neurotoxicity in this test system.

These results support the previously submitted data for this 90-day neurotoxicity test in hens, which has previously been reviewed and classified as core Minimum (MRID 404597-01).

Classification: The 90-day hen neurotoxicity study (MRID 404597-01) is upgraded to core Guideline

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Reviewed by: Sidney Stolzenberg, Ph.D SS 11/8/89
Section I, Tox. Branch II (H7509C)
Sencondary reviewer: Yiannakis M. Ioannau, Ph.D. YMI. 11/9/89
Head, Section I, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 90-Day Hen Neurotoxicity

GUIDELINE: 82-5

MRID NO.: 410741-04

TEST MATERIAL: Isofenphos

HED PROJECT NO.: 9-1500

SYNONYMS: Oftanol

CASWELL NO.: 447 AB

STUDY NUMBER(S): 90231-3

SPONSOR: Mobay Corp.
Bayer USA Inc.
Kansas City, MO 64120-0013

TESTING FACILITY: Bayor AG
Institute of Toxicology
West Germany

TITLE OF REPORT: Subchronic Delayed Neurotoxicity Study (90 Day Study in Hens)

AUTHOR(S): G. Kaliner, D.M.V.

REPORT ISSUED: March 22, 1989

CONCLUSIONS:

This submission contains the nerve tissue histopathology data of a previously reviewed 90-day hen neurotoxicity study (Accession No. 404597-01). Doses of isofenphos administered were 0 (vehicle control), 0.25, 1.0 and 2.0 mg/kg/day; positive controls received TOCP. No indications of delayed neurotoxicity due to isofenphos treatment were observed. The presently submitted nerve tissue histopathology data confirms that isofenphos did not cause damage to the nerve tissues of the brain, spinal cord or peripheral nerves.

Classification: Scientifically acceptable

These results support the previously submitted data for this study which has been reviewed (Accession No. 404597-01) and classified core Minimum.

INTRODUCTION

This study has been previously reviewed under Accession No. 404597-01 and was classified as core Minimum. The present submission is an addendum to the preceding report, consisting of the histopathology findings in the brain, spinal cord and sciatic nerve.

A. MATERIALS

1. TEST COMPOUND: 92.5% pure, technical

2. TEST ANIMAL: Hen. No other details given.

B. STUDY DESIGN.

Animals were assigned 10 per group as follows:

Test Group	Dose mg/kg/day	Number
1. Vehicle Control	0	10
2. Oftanol	0.25	10
3. Oftanol	1.0	10
4. Oftanol	2.0	10
5. TOCP*	5.0	10

*Triorthocresylphosphate, positive control

COMMENT: Only negative control, positive control and high dose treated animals were examined for histopathological effects to the brain, spinal cord and peripheral nerve in the present submission.

C. Procedure (Rewritten from the report).

The brain had been fixed in toto and was sectioned along the median plane. The one half was embedded sagittally. The other half was cross-sectioned into three parts and embedded at right angles to the median plane so that four Paraplast blocks from each hen brain were available for sectioning.

Several connected segments were obtained from the cervical, thoracic, and lumbar regions of the spinal cord. A few connected segments from each spinal cord region were embedded longitudinally and two portions from the same spinal cord region were embedded transversely. Thus, three

tissue blocks from the same spinal cord region of each hen were available for histological sectioning.

From both the left and right sciatic nerves of each hen, the proximal segment and the distal segment with its tibial and common peroneal branches were embedded longitudinally. Thus, histological sections could be prepared from four blocks of the peripheral nervous system of each hen.

All tissues were embedded in Paraplast.

At least three Paraplast sections from three different planes of each spinal cord block were prepared for three different stains.

Histological sections from all Paraplast blocks prepared for the central and peripheral nervous systems were stained with hematoxylin and eosin (H&E) and with Luxol fast blue/cresyl violet (myelin visualization by the method of KLUEVER-BARERRA); axons were visualized by the silver impregnation method of MARSLAND, GLEES, and ERIKSon as modified by E. and G. E. K. NOVOTNY (Stain Technology, 49:273-280, 1974).

Thus, the following numbers of histological sections were available from each hen for microscopic examination:

Brain	12 sections
Spinal cord, cervical	27 sections
Spinal cord, thoracic	27 sections
Spinal cord, lumbar	27 sections
Peripheral Nerves	12 sections

Therefore, there was a total of 105 histological sections per hen.

RESULTS

In the previously submitted report, no signs of delayed neurotoxicity were observed in oftanol treated groups nor in the negative control group. Clinical observations of neurotoxicity were clearly observed in most positive control-TOCP treated hens.

In the present submission, minor degenerations were observed in the peripheral and central nervous systems, occurring in controls and all 3 treated dose groups to the same extent. These were virtually all unilateral and minor in nature, as is usually found in commercially bred stock. Such findings included lymphohistiocytic infiltration in peripheral and central nervous system and minor degree of dogeneration of nerve fibers and gangliotic cells. These were assessed by the pathologist as

"background neuropathological changes", considered generally to be the result of contact with avian viruses.

Hens in the TOCP-positive control group consistently had bilateral degeneration of nerve tract fibres of the funiculi, not seen in any control or oftanol-treated groups. Animals in the TOCP positive control group had ventral funiculi showing a spongy, cribriform appearance because of myelin loss, detected both in cross and longitudinal sections, such as that shown of a segment from the lumber region of the spinal cord in Figure 4 of the report (a photomicrograph). The pathologist also described club-shaped distensions of the axon, vacuolar distension of fibre segments and focal gliosis, also in lumbar sections of spinal cord of TOCP treated hens.

The report contains summary tables of histopathology findings in the brain including medulla oblongata and metencephalon, the cervical, thoracic and lumbar regions of the spinal cord and of the sciatic nerve. In all of these summaries, the total number of animals affected and mean severity of the scores which signify intensities of responsiveness (grades 0-3), were greater for "axon ballons" and "degeneration", only in the TOCP treated group. The responses by the 2 mg/kg oftanol group were similar to control.

These results with TOCP indicate that the hens in this study were responsive to a known neurotoxic substance, TOCP, which caused clinical and histopathological observed changes.

DISCUSSION

In the previously submitted data for this study no indications of delayed neurotoxicity was observed due to oftanol at any of the three dose levels tested. Nevertheless, significant depressions in cholinesterase activity were observed in plasma, erythrocytes and whole blood in the high dose group treated with 2 mg/kg/day (MRID 404597-01),. A significant depression in body weight gain was also observed in the 2 mg/kg/day treated group. The present report which includes histopathology data for the brain, spinal cord and sciatic nerve, confirms that there was no increased structural damage to the nerve tissues at the highest dose tested; i.e. 2 mg/kg/day, in this 90 day hen test.