CASTELLE FILE

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

JAN 31 1985

Castell # 435

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Neurotoxicity Study with EPTC in Chickens,
Action # 476-2140/2165

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)

THRU: Christine F. Chaisson, Ph.D. cfc 1/31/85
Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: Chad B. Sandusky, Ph.D. Chad B. Sandusky 1/31/85
Pharmacologist
Toxicology Branch
Hazard Evaluation Division (TS-769) 1/31/85

Action Requested:

Stauffer Chemical Company has submitted for review an acute delayed neurotoxicity study with technical EPTC (Eptom) in adult hens (study number T-6537). These data were submitted in response to the Registation Standard on EPTC.

Data Review and Conclusions:

A summary review of these data is presented below. A more detailed data evaluation is attached.

Groups of hens (N=12-16) were treated with corn oil, TOCP (500 mg/kg) or technical EPTC (7200 mg/kg). Although both groups of hens treated with TOCP or EPTC lost weight during the 42 observation days, only the TOCP group displayed signs of delayed neurotoxicity, e.g., impaired walking behavior, sciatic nerve swelling and degeneration and axonal degeneration in the brain and spinal cord. The results of this experiment demonstrate that EPTC does not produce TOCP-like delayed neurotoxicity at doses up to 7200 mg/kg. However this dose was sufficient to cause decreased body weight and some pharmocotoxic signs on day of treatment, e.g., diarrhea.

In addition, this study is classified as Core Guideline.

Attachment

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004259

EPA: 68-01-6561
TASK: 89
January 10, 1985

DATA EVALUATION RECORD

EPTAM

Acute Delayed Neurotoxicity Study in Hens

STUDY IDENTIFICATION: Sprague, G.L. Acute delayed neurotoxicity study with Technical Eptam in adult hens. (Unpublished study No. T-6537 by Richmond Toxicology Laboratory for Stauffer Chemical Co., Richmond, CA; dated February 5, 1981, Accession No. 254256.)

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-10-85

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1. CHEMICAL: EPTC (Eptam®).

2. TEST MATERIAL: Technical Eptam Lot #CHK-0601 (98.6%) pure) by weight.

3. STUDY/ACTION TYPE: Acute delayed neurotoxicity study in hens.

4. STUDY IDENTIFICATION: Sprague, G.L. Acute delayed neurotoxicity study with Technical Eptam in adult hens. (Unpublished study No. T-6537 by Richmond Toxicology Laboratory for Stauffer Chemical Co., Richmond, CA; dated February 5, 1981, Accession No. 254256.)

5. REVIEWED BY:

Finis Cavender, Ph.D.
Project Scientist
Dynamac Corporation

Signature: Finis Cavender
Date: 1/11/85

Nicolas Hajjar, Ph.D.
Project Scientist
Dynamac Corporation

Signature: Nicolas P. Hajjar
Date: January 10, 1985

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Technical Quality Assurance
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 1-16-85

Chad Sandusky, Ph.D.
EPA Reviewer

Signature: Chad B. Sandusky
Date: Jan 23, 1985

Chris Chaisson, Ph.D.
Section Head

Signature: C F Chaisson
Date: Jan 29, 1985

7. CONCLUSIONS:

A. EPTC produced some neurotoxic signs in hens as judged by effects on walking ability and histopathologic lesions observed in the brain and spinal cord. EPTC did not produce TOCP-like delayed neurotoxicity.

B. The study was well designed and conducted in an acceptable manner. It meets or exceeds the criteria for a Core Guideline study.

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8. RECOMMENDATIONS:

Not applicable.

9. BACKGROUND:

A preliminary acute oral toxicity study determined the acute oral LD_{50} of EPTC in hens to be 7171 (5921-9051) mg/kg. Pharmacotoxic signs noted in the study included diarrhea, ptosis, and motor incoordination. All deaths occurred within 3 days following dosing.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

Not applicable.

11. MATERIALS AND METHODS (PROTOCOLS):

The complete Materials and Methods section for study T-6537 are given in Appendix A. This information was reproduced as submitted in the original text by the registrant.

A. Materials and Methods:

1. Technical Eptam, Lot # CHK-0601, 98.6% pure by weight, (EPTC).

2. Adult, white Leghorn hens, 12-14 months old, obtained from Feather Hill Farms (Petaluma, CA).

3. Groups of hens were treated with 10 ml/kg corn oil (Mazola), 500 mg/kg practical grade tri-o-tolyl phosphate (TOCP), Eastman Organic Chemicals, (Lot HA7C), or 7200 mg/kg Technical Eptam.

12. REPORTED RESULTS:

Mortality: No hens given corn oil died on study. In contrast, 7/12 hens given TOCP died between days 23-26 on study and 6/16 hens given EPTC died on days 2, 4, or 22 of the study.

Clinical Observations: Pharmacotoxic signs observed during the study are summarized in Table 1. Of the hens receiving EPTC, only one showed signs of being unsteady when standing. The walking behavior of hens during the study is summarized in Table 2. For EPTC-treated hens, walking behavior was affected only on the day of treatment.

Body Weight: Selected body weight data are given in Table 3. Hens receiving TOCP or EPTC lost weight following treatment during the study, and did not recover.

TABLE 1. Incidence of Adverse Signs Observed in Hens Treated with Corn Oil, TOCP, or EPTC[a]

Observed Sign	Incidence of Signs in Hens Treated Twice With Corn Oil (10 ml/kg)	TOCP (500 mg/kg)	EPTC (7200 mg/kg)
Appearance:			
Dry, atrophied comb	6/12	7/12	11/16
Plate comb	0/12	1/12	11/16
Feather loss	12/12	12/12	11/16
Coordination/Leg Strength:			
Unsteady when standing	0/12	12/12	1/16
Sitting on hocks	0/12	10/12	0/16
Unable to stand	0/12	8/12	0/16
Physiological:			
Soft-shelled egg	1/12	0/12	0/16
Diarrhea	4/12	12/12	13/16
Difficulty breathing	0/12	2/12	1/16

[a] This table was reproduced from the original text as submitted by the registrant.

TABLE 2. Walking Behavior for Hens Treated with Corn Oil, TOCP, or EPTC

Treatment (Administered on Day 1 and Day 22)	Walking Behavior [a] on Days						
	-14	1	8	15	22	29	36
Corn oil (10 ml/kg)	0.0	0.3	0.0	0.2	0.5	0.3	0.2
TOCP (500 mg/kg)	0.4	2.8	0.5	6.0	6.8	6.6	11.0
EPTC (7200 mg/kg)	0.2	5.2	0.4	0.2	3.2	0.1	0.2

[a] Walking behavior based on locomotion, posture, equilibrium, and leg strength (perfect score = 0.0).

TABLE 3. Selected Mean Body Weights of Hens Treated with Corn Oil, TOCP, or EPTC

Treatment (Administered on Day 1 and Day 22)	Mean Body Weights (g) on Days					
	-7	1	9	22	30	42
Corn oil (10 ml/kg)	1579	1528	1506	1494	1504	1560
TOCP (500 mg/kg)	1734	1616	1507*	1380*	1316*	1301*
EPTC (7200 mg/kg)	1645	1709	1433*	1433*	1284*	1362*

* Significantly different from base line value at day -7 ($p \leq 0.05$).

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Histopathology: Selected histopathology data are given in Table 4. Noticeable differences in the incidences of axonal degeneration in the brain and spinal cord were noted between TOCP- and EPTC-treated hens.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Adult hens were treated twice with 7200 mg/kg EPTC and did not show signs of delayed motor coordination or central nervous system lesions; therefore, EPTC does not produce TOCP-like delayed neurotoxicity.

B. This study was conducted in an acceptable manner and was inspected in accordance with Good Laboratory Practice regulations. The quality assurance statement was present, signed, and dated March 20, 1980.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. The toxic signs noted in hens receiving EPTC were not supportive of delayed neurotoxicity. In addition, there was no axonal degeneration of the brain and spinal cord or delayed progressive muscle incoordination which affects the hens' ability to stand and walk. Thus, EPTC did not produce TOCP-like delayed neurotoxicity.

B. There were potential neurotoxic signs noted on the day of treatment which indicated a subchronic (reported daily dosing) neurotoxicity test may be required to further evaluate EPTC as a neurotoxin.

C. The study was designed, conducted, and reported in an acceptable manner.

15. COMPLETION OF ONE-LINER FORM FOR STUDY:

- EPTC does not produce TOCP-like delayed neurotoxicity.

16. CBI APPENDIX:

Appendix A - Materials and Methods (reproduced from original text as submitted by the registrant).

TABLE 4. Selected Incidence Data of Histopathologic Findings for Hens Receiving Corn Oil TOCP, or EPTC[a]

Neurological Tissue	Histopathologic Finding	Specified Changes (%) in Hens Treated With TOCP (500 mg/kg)	EPTC (7200 mg/kg)	Corn Oil (10 ml/kg)
Brain	Axonal degeneration in cerebellar peduncles	100.0	0.0	16.7
	Focal gliosis	100.0	30.0	8.3
Spinal Cord Cervical	Axonal degeneration in dorsal funiculi	100.0	0.0	0.0
	Random axonal degeneration	54.5	20.0	8.3
	Focal gliosis	100.0	60.0	58.3
	Neuronal swelling and chromatolysis	18.2	20.0	0.0
Spinal Cord Thoracic	Axonal degeneration in ventral and lateral funiculi	100.0	0.0	8.3
	Random axonal degeneration	45.5	40.0	16.7
	Lymphocytic perivascular cuffing	45.5	30.0	25.0
	Neuronal swelling and chromatolysis	18.2	40.0	25.0
Spinal Cord Sacro-lumbar	Axonal degeneration in ventromedial funiculi	100.0	0.0	8.3
	Random axonal degeneration	36.4	20.0	25.0
	Focal gliosis	100.0	70.0	58.3
	Neuronal swelling and chromatolysis	27.3	50.0	25.0
Sciatic Nerve	Bilateral nerve fiber degeneration	100.0	30.0	0.0
	Swelling of axis cylinders (R/L)[b]	45.5/72.7	10.0/0.0	0.0/8.3
	Presence of perineural or interstitial lymphocytic foci (R/L)	81.8/81.8	80.0/90.0	66.7/66.7

[a] Portions of this table were reproduced from the original report as submitted by the registrant.

[b] (Right/Left).

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Eptam

Page _____ is not included in this copy.

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