CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

005428

AUG 28 1986

MEMORANDUM

SUBJECT: Isophenphos Delayed Neurotoxicity Study(Open Literature); Mobay report # 89024; Caswell # 447AB; Project # 57

TO: William H. Miller
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Registration Division (TS-767C)

FROM: James N. Rowe. Ph.D.
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James N. Rowe 8/19/86

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
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and
Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)
for LDC 8-28-86
8/28/86

ACTION: Review isofenphos neurotoxicity study entitled, "Toxicity of organophosphorus esters to laying hens after oral and dermal administration"; submitted by Mobay Chemical Corporation as study # 89024; A 258240; Cas.# 447AB.

RECOMMENDATIONS:

The severely limited number of animals tested and the lack of neurohistopathology data prevents any definite conclusions regarding the study findings. This study was not intended for submission to satisfy the regulatory requirements for a subchronic delayed neurotoxicity study and is designated Core Supplementary data.

DATA EVALUATION RECORD

STUDY/ACTION TYPE: Delayed neurotoxicity in white leghorn hens

CHEMICAL: Isofenphos: 1-methylethyl 2-[[ethoxy[(1-methylethyl)amino] phosphonothioyl] oxy]benzoate

TEST MATERIAL: Technical material extracted from commercial sample of "Amaze" granular insecticide

STUDY I.D.:

1. Title: "Toxicity of organophosphorus esters to laying hens after oral and dermal administration"

2. Laboratory: Institute for Environmental Studies, Department of Entomology, Department of Veterinary Biosciences, University of Illinois, Urbana IL

3. Sponsor: U.S. Department of Agriculture, North Central Region Pesticide Impact Assessment Program

4. Study #: J. Environ. Sci. Health, B20(1)

5. Date of Report: 1985

6. Study Authors: Francis, B.M. et al.

7. Caswell # 447AB, Accession 258240; EPA ID # 3125-326

METHODS:

Isofenphos was one of 14 organophosphorus esters evaluated for delayed neurotoxicity after administration orally or dermally to white leghorn hens. For oral administration a 10-20% solution (w/v) of the pesticide in corn oil was delivered volumetrically into gelatin capsules via Eppendorf® pipette. For dermal administration, 1% to 2% emulsifiable concentrates were formulated in technical grade xylene containing 2% Triton X-100. Volumes of 0.1 to 0.4 ml were applied to the right or left ventral wing surface at the humerus on alternate days. Hyline white leghorn pullets, obtained from Roth Hatcheries (Watseka, IL) at 20 weeks of age and were provided with food and water ad lib in individual layer cages. A 14:10 hour (light:dark) photoperiod was maintained. The animals were acclimitized for 4-8 weeks before dosing was begun. Concurrent controls were used. Hens were removed from their cages in groups of 3-6 daily and allowed to move freely for 5-10 minutes. They were graded for ataxia and treated. Status was determined by stance, gait and balance.

COMMENTS ON METHODS:

This study was not intended for regulatory review and thus does not have all the attendent raw data required for such a submission. For example, the test compound is not adequately identified nor was neurohistopathology presented. In addition, the age of the hens was not appropriate (6 to 7 months of age as opposed to 8-14 months of age specified in EPA Guidelines) and the number of animals on test was insufficient (4 hens for the oral study and 3 for the dermal study as

opposed to ten animals for each treatment group as specified in the EPA guidelines).

RESULTS:

Oral administration of either 10 or 30 mg/kg (1x) isofenphos to 2 hens per dose resulted in the death of 1 hen in each treatment group on the first day (no mention was made concerning the fate of the other 2 hens). No additional oral doses were administered. Three hens were given a different dermal dosage regimen (see table below). Dermal exposure was reported to produce a rapid and severe weight loss in all the hens (up to 39% by 42 days).

| Hen no. | dosage(mg/kg x days) | total(mg/kg) | Days to Stage: T-2 | T-3 | T-4 | Death |
|---|---|---|---|---|---|---|
| 983 | 4.7 x 32 | 150.0 | 25 | 37 | 43 | 44 |
| 994 | 5.2 x 52 | 265.0 | 57 | -- | 59 | 61 |
| 995 | 4.9 x 18 | 88.2 | 17 | — | 20 | 21 |

T-2= ataxic(staggers); T-3= severely ataxic(rests on hocks) and T-4= paraplegic (unable to walk)

Ataxia was reported for all 3 hens during the dosing period but only 1 hen survived long enough after cession of administration to experience a gradation in the neurotoxic response, i.e., T-3 effects prior to T-4 effects (hen 983).

CONCLUSIONS

The severely limited number of animals tested and the lack of neurohistopathology data prevents any definite conclusions regarding the findings. The observation of apparent ataxia in the 3 hens treated dermally suggests that delayed neurotoxicity might be occurring. On the other hand, this material was shown to be quite acutely toxic via the oral route, and the ataxia seen in hens dosed dermally may have been simply related to cumulative toxicity.

This study was not intended for submission to satisfy the regulatory requirements for a subchronic delayed neurotoxicity study and is designated Core Supplementary data.