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

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NOV - 3 1988

CASWELL FILE

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Mevinphos - Review of an Acute Delayed Neurotoxicity Study in Hens

EPA No. 2498-79 Project No. 8-1135
Record No. 230729 Tox. Chem. No. 160B
40 CFR §180.157

TO: William Miller, PM #16
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section I, Toxicology Branch I (IRS)
Health Effects Division (TS-769c)

John Whalan 10-21-88

THRU: Edwin R. Budd, Section Head
Section I, Toxicology Branch I (IRS)
Health Effects Division (TS-769c)

Budd 11/3/88

The Registrant, Amvac Chemical Corporation, submitted an Acute Delayed Neurotoxicity study of Mevinphos in response to a data call in. This study has been reviewed and classified Core Minimum.

There was no evidence of delayed neurotoxicity or histopathologic lesions following two doses of mevinphos, but serious neurotoxicity was observed in the first week after each of two administrations.

Reviewed by: Joi E. Whalan JW 10-21-88
Section I, Tox. Branch I (IRS) (TS-769C)
Secondary reviewer: Edwin R. Budd
Section I, Tox. Branch I (IRS) (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Acute Delayed Neurotoxicity in Hens

ACCESSION NUMBER: 407759-01

TOX. CHEM. NO.: 160B

TEST MATERIAL: Mevinphos
Lot No. 50826 (purity N/A)
Clear liquid

MRID NO.: N/A

SYNONYMS: Phosdrin

STUDY NUMBER(S): 4685-87

SPONSOR: AMVAC Chemical Corporation

TESTING FACILITY: Bio/dynamics Inc. (New Jersey)

TITLE OF REPORT: Acute Delayed Neurotoxicity Study in Mature Hens with Mevinphos

AUTHOR(S): Debra S. Barrett

REPORT ISSUED: July 26, 1988

CONCLUSIONS: Three of ten hens dosed with 12.5 mg/kg of mevinphos and anti-dotal doses of atropine and 2-PAM chloride died. The seven surviving hens were dosed a second time on day 21 at 12.5 mg/kg. Clinical signs observed during the first week included ataxia, hypoactivity, prostration, sitting on hocks, wings outstretched, hypopnea, closed eyes, miosis, leg weakness, and soft stools. Food consumption was decreased, but body weight gain was not affected. There was no evidence of delayed neurotoxicity. No histopathologic lesions of nervous tissue could be found in any hens dosed with mevinphos.

The positive controls were unaffected by tritolyl-phosphate administration on day 0, but classic delayed neurotoxicity was seen following administration with tri-o-cresyl phosphate on day 21. They had axonal swelling in the spinal cord, and axonal fragmentation and a loss of myelin sheath in the peroneal, tibial, and sciatic nerves.

STUDY CLASSIFICATION: This study is classified CORE MINIMUM. Two positive control articles were used: tritolyl-phosphate and tri-o-cresyl phosphate (tri-o-tolyl-phosphate). The reason for using the former is uncertain since it was not neurotoxic in this study. Both these chemicals are typically formulated in corn oil since they are virtually insoluble in water. They were both formulated in water, however, so the actual dose administered is uncertain. This study received Quality Assurance Review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: Twenty mature (1.3-2.0 kg; 8-14 months old), egg-laying White Leghorn Pullet hens from Kerr Hatcheries, NJ were individually housed in wire cages. Food and water were provided ad libitum. They were dosed with distilled water (vehicle controls), and aqueous solutions of tritolyl-phosphate (positive control - a 90% mixture of isomeric tritolyl phosphates excluding tri-o-cresyl phosphate) and tri-o-cresyl-phosphate (positive control - also called tri-o-tolyl phosphate), and mevinphos. The hens were dosed by gastric intubation with boluses of 1 ml/kg. The mevinphos doses slightly exceeded the LD_{50} of 11.0 (3.2-18.8) mg/kg measured in an acute oral study preceding this study. The dosing regimen was as follows:

Test Article	Dose (mg/kg)	Animals Dosed Day 0	Day 21
Distilled Water	-	6	6/6
Tritolyl phosphate*	750	4	4/4
Mevinphos	12.5	10	7/7

* Tritolyl-phosphate was administered on day 0, but was replaced with tri-o-cresyl phosphate (tri-o-tolyl-phosphate) for the day 21 dosing since no neurotoxicity was observed during the first 21 days. The actual dose administered is uncertain since both chemicals are virtually insoluble in water.

On days 0 and 21, all hens dosed with mevinphos were pretreated with subcutaneous injections of atropine (0.625 mg/kg) and pralidoxime chloride (2-Pam chloride; 10 mg/kg). During the 48 hours following their dosings, these same hens received 5 to 17 additional injections of atropine (0.625 mg/kg/injection) as an antidote based on signs of cholinesterase inhibition, and 2-Pam (10 mg/kg) 5 and 11 hours after dosing.

The hens were observed for clinical signs approximately 1, 2, 3, and 4 hours after dosing, and then daily. Prefast body weights were measured 7, 14, 21, 28, 35, and 42 days after dosing. Neuromuscular evaluations were graded on a scale of 0 to 4 twice per week after dosing. On day 42, all surviving hens were sacrificed with sodium pentobarbital, and perfused with 10% neutral buffered formalin for approximately 5 minutes. Hens which died on study were not examined. Sections of medulla oblongata, spinal cord with peripheral nerves, and other peripheral nerves (sciatic, proximal peroneal, and proximal tibial nerves) were preserved and evaluated histopathologically. The slides were stained with hematoxylin and eosin, and with Luxol Fast Blue to highlight demyelination.

RESULTS: Dose concentration analyses showed nearly all mevinphos formulations to be well within 10% of nominal.

Three hens dosed with mevinphos on day 3 died acutely. All others in the three groups survived to study termination. The hens dosed with mevinphos on day 0 had clinical signs of ataxia, hypoactivity, prostration, sitting on hocks, wings outstretched, hypopnea, closed eyes, miosis, leg weakness, and soft stools. These signs occurred at unspecified times during the first

week. Food consumption was decreased (qualitatively) during weeks 1, 4, and 5. There were no significant changes in body weight gain in the hens dosed with mevinphos, and no evidence of delayed neurotoxic effect.

The positive controls dosed with tritolyl-phosphate on day 0 had essentially no clinical signs or changes in body weight gain during the first 21 days. When they were dosed a second time on day 21 with tri-o-cresyl phosphate, there were signs of soft stools and decreased food consumption (qualitative) during the first week; leg weakness and decreased food consumption during the second week; and ataxia, staggering, sitting on hocks, leg weakness, hypoactivity, and decreased food consumption during the third week. A 14% decrease in body weight gain was observed on day 42, 21 days after being dosed with tri-o-cresyl phosphate on day 21.

Neurologic evaluation of the positive controls on days 35, 38, and 42 showed evidence of slight to marked leg weakness, unsteady or altered gait, a tendency to fall back on hocks, an inability to land when dropped from a 4 foot height, loss of balance, use of wings to maintain balance, and a loss of toe grip. Thus, tritolyl-phosphate was innocuous and inappropriate as a positive control, but tri-o-cresyl phosphate did cause delayed neurotoxicity and decreases in body weight gain.

One positive control hen was emaciated; no other gross lesions were reported. No histopathologic lesions of nervous tissue could be found in any hens dosed with mevinphos. The positive controls, however, had minimal axonal swelling in the spinal cord; minimal to moderate axonal fragmentation and a loss of myelin sheath in the peroneal, tibial, and sciatic nerves.

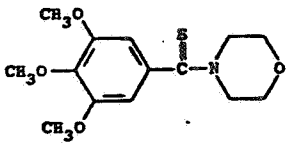
Yellow microcrystals, d 1.33. mp 120-122° in air; 172-174° under nitrogen. Moderately sol in benzene, chloroform, dichloromethane; sparingly sol in cyclohexane; insol in light petroleum. Dissociates extensively in organic solvents.

USE: Catalyst.

9562. Trithiocarbonic Acid. *Carbonotrithioic acid;* dihydrogen thiocarbonate. CH_2S_3; mol wt 110.21. C 10.90%, H 1.83%, S 87.27%. Prepared by the treatment of $BaCS_3$ with ice-cold 10% HCl: v. Halban *et al.*, *Z. Elektrochem.* 29, 445 (1923); Mills, Robinson, *J. Chem. Soc.* 1928, 2326; Gattow, Krebs, *Angew. Chem.* 74, 29 (1962).

Highly refractive red oil. mp −26.9°. bp +57.8°. d_4^{20} 1.483; d_4^{25} 1.476. n_D^{20} 1.8225. Dec by water, alcohol. Addition of sulfur produces tetrathiocarbonic acid CH_2S_4.

9563. Trithiozine. *4-[Thioxo(3,4,5-trimethoxyphenyl)-methyl]morpholine;* 4-(3,4,5-trimethoxythiobenzoyl)morpholine; sulmetozine (rescinded INN); tritiozine; ISF 2001; Tresanil. $C_{14}H_{19}NO_4S$; mol wt 297.37. C 56.55%, H 6.44%, N 4.71%, O 21.52%, S 10.78%. Non-anticholinergic gastric secretion inhibitor. Prepn: G. Pifferi, Ger. pat. 2,102,246 corresp to U.S. pat. 3,862,138 (1972, 1975 both to ISF). Synthesis and pharmacology: G. Pifferi *et al.*, *Chim. Ther.* 8, 462 (1973). HPLC determn in plasma and urine: T. Crolla *et al.*, *J. Chromatog.* 222, 257 (1981). Clinical studies: M. Elakovic *et al.*, *J. Int. Med. Res.* 8, 347 (1980); U. Marini *et al.*, *Clin. Ter.* 92, 399 (1980). Evaluation of gastric acid suppression: K. Gibinski, *Curr. Med. Res. Opin.* 7, 516 (1981).



Pale yellow solid from ethanol. mp 141-143°. LD_{50} in mice: 2000 mg/kg i.p., G. Pifferi *et al.*, *loc. cit.*

THERAP CAT: Antisecretory (gastric).

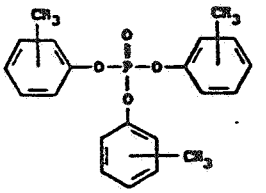
9564. Triticum. Agropyrum; couch grass; dog grass; graminis; quick grass. Dried rhizome and roots of *Agropyron repens* L., Beauv., *Gramineae*, gathered in spring. *Habit.* Europe, Northern Asia; naturalized in the U.S. *Constit.* Triticin, glucose, mannite, inosite.

9565. Tritium. Triterium. T or ^{3}H. at. wt 3.016. Exists in the diatomic state; mol wt 6.032. Naturally occurring radioactive isotope of hydrogen. Under normal conditions the total atmospheric content of molecular T_2 gas is only 11 g. Half-life 12.26 years, low β-emitter. First prepd by the bombardment of deuterophosphoric acid with fast deuterons: M. L. E. Oliphant *et al.*, *Proc. Roy. Soc.* A144, 692 (1934); T. W. Bonner, *Phys. Rev.* 53, 711 (1938). Produced commercially from ^{6}Li by slow neutron bombardment: $^6_3Li + {}^1_0n \rightarrow {}^3_1H + {}^4_2He$. Details of process producing tritium by neutron irradiation of lithium fluoride: Jenks *et al.*, U.S. pat. 3,079,317 (1963). *Reviews:* E. A. Evans, *Tritium and Its Compounds* (Butterworth, London, 1966) 441 pp; Mackay, Dove, "Deuterium and Tritium" in *Comprehensive Inorganic Chemistry* vol. 1, J. C. Bailar Jr. *et al.*, Eds. (Pergamon Press, Oxford, 1973) pp 77-116; J. J. Katz in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 7 (Wiley-Interscience, New York, 3rd ed., 1979) pp 554-564.

Gas, having the properties of hydrogen. mp −254.54° (20.62°K) at 162 mm (triple point). bp −248.12° (25.04°K). Crit temp −232.56°. Crit press. 18.317 atm. Molar density of liquid: 45.35 moles/l (20.62°K).

USE: In fusion-based thermonuclear weapons (hydrogen bombs): energy is released by deuteron bombardment according to the reaction: $^2_1H + {}^3_1H \rightarrow {}^4_2He + {}^1_0n + 18$ Mev. Widely used as a radioactive tracer in chemical, biochemical and biological research.

9566. Tritolyl Phosphate. *Phosphoric acid tris(methylphenyl) ester;* tricresyl phosphate; TCP; PX-917; Celluflex; Kronitex; Lindol. $C_{21}H_{21}O_4P$; mol wt 368.36. C 68.47%, H 5.75%, O 17.37%, P 8.41%. A mixture of isomeric tritolyl phosphates, usually excluding the very toxic *ortho*-isomer as much as possible. Prepd from cresol and phosphoric oxychloride, phosphoric acid or pentachloride: Prahl, U.S. 2,805,240 (1957); Bondy, Gumb, Brit. pat. 890,642 (1962 Coalite and Chem. Prod.); Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 849-853.



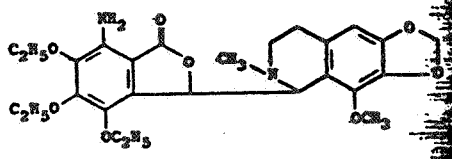
Oily, flame resistant liquid. d_{25}^{25} 1.16; bp_{10} about Pour point −28°. n_D^{25} 1.55. Flash pt (closed cup) Insol in water (<0.002% at 85°). Sp heat 0.38. Misc all the common organic solvents and thinners, linseed china wood oil, castor oil.

USE: As plasticizer in vinyl plastics manuf, as flame-dant, solvent for nitrocellulose, in cellulosic molding co sitions, as additive to extreme pressure lubricants, as a flammable fluid in hydraulic systems, as lead scaveng gasoline: Yust, Barne, U.S. pat. 2,889,212 (1959 to Shell sterilize certain surgical instruments.

9567. Tri-*o*-tolyl Phosphate. Tri-*o*-cresyl phosphate Colorless or pale yellow liquid. *Poisonous!* bp about with slight decompn. Sparingly sol in water; freely in hol, benzene, ether.

USE: As plasticizer in lacquers and varnishes. Ca Ingestion may cause nausea, vomiting, diarrhea. Polyn tis progressing to paralysis of extremities has been se severe poisoning: Fassett in *Industrial Hygiene and To ogy* vol. 2, F. A. Patty, Ed. (Interscience, New York, ed., 1962) pp 1914-1923.

9568. Tritoqualine. *7-Amino-4,5,6-triethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)-1(3H)-isobenzofuranone; 7-amino-4,5,6-triethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)phthalide;* tritocaline; 554L; H stamine; Inhibostamin. $C_{26}H_{32}N_2O_8$; mol wt 500.57 62.39%, H 6.44%, N 5.60%, O 25.57%. Preparation: Fr 1,295,309 (1962 to Lab. de Recherches Biol. Laborec). tivity: Hahn *et al.*, *Arzneimittel-Forsch.* 20, 1490 (1



Crystals, mp 183°.

THERAP CAT: Antihistaminic.

9569. Triuret. *Diimidotricarbonic diamide;* 1,3-bamylurea; carbonyldiurea. $C_3H_6N_6O_3$; mol wt 146.1 24.66%, H 4.14%, N 38.35%, O 32.85%. $H_2NCONHNHCONH_2$. Prepared by the action of phosgene on Schiff, *Ann.* 291, 374 (1896); Blair, *J. Am. Chem. So* 101 (1926); Haworth, Mann, *J. Chem. Soc.* 1943, 603; ner, Gray, *Sci. Proc. Roy. Dublin Soc.* 24, 111 (1946).

Crystals from ammonia water, dec 233°. Freely sol ammonia. Forms a mono- and dipotassium salt, *see loc. cit.*

9570. Troclosene Potassium. *Dichloro-s-triazine-(1H,3H,5H)-trione potassium derivative;* 3,5-dichlorotet dro-2,4,6-trioxo-*s*-triazin-1(2*H*)-yl potassium; potas troclosene; potassium dichloroisocyanurate; ACL-59 $Cl_2KN_3O_3$; mol wt 236.06. C 15.26%, Cl 30.04%, K 1 N 17.80%, O 20.33%. Structure studies and prepn: J son *et al.*, *J. Org. Chem.* 25, 1395 (1960). Prepn from