September 16, 1977

Merphos - Neurotoxicity Tests - Oral, Dermal, Hens
FDRL #5297 and #5332 - Mobil Chemical Company

George E. Whitmore, D.V.M.
Toxicology Branch, RD (WH-567)

Robert Taylor - PM #25
Registration Division (WH-567)

Conclusion and Recommendations:

Merphos was demonstrated to be a delayed neurotoxic agent for hens exposed dermally at the MTD. Oral exposure at the LD_{50} did not produce signs of delayed neurotoxicity.

These studies are conditionally acceptable. Before final acceptance, the protocols for the two experiments are needed for review and the mg/kg/bw exposure rate for Merphos needs identification for both experiments and the mg/kg/bw for TOCP needs identification for the dermal test.

Merphos - Oral exposure - hens - FDRL #5297, 4/24/77

Exposure Scheme - mg/kg/bw

	No. Hens	At Day 1	At Day 21
Merphos	40	11 ml (11 mg)?	11 ml (11 mg)?
TOCP	10	500 mg	--
Corn oil	10	11 ml	11 ml

Observations - Neurotoxicity grading

0 - sign free
2 - ? or minor signs
8 - paralytic signs
12 - advanced paralytic signs
16 - death

Results:

	0 - 21 days	21 - 42 days
Merphos	No neurotoxic signs 16 deaths	No neurotoxic signs 11 deaths

	0 - 21 days	21 - 42 days
TOCP	All subjects neurotoxic signs by 16th day 2 deaths 1 @ 16th day 1 @ 21st day	No subjects recovered 1 subject improved 4 survivors
Corn oil	No reactions	No reactions

Comment: This experiment demonstrated that Merphos administered orally at the LD_{50} rate, compared to TOCP administered at 500 mg/kg/bw did not produce clinical observable delayed paralysis in hens.

Before this study can be accepted it will be necessary for the laboratory to provide the correct information about Merphos dosing rate, was it 11 ml/kg bw or 11 mg/kg bw? If it was 11 ml/kg please ask the laboratory to convert the dose to mg/kg of active chemical. Also please ask the laboratory to correct the TOCP Table 8 wherein it appears these hens received a second dose but the text states they did not.

For reference purposes please ask the laboratory to provide Protocol No. 76156.

Merphos - Dermal exposure - hens - FDRL #5297, 4/24/77

Exposure Scheme - single dose

	No. Hens	
Merphos	40	)
TOCP	10	) - 1 ml/kg bw - single dose
Corn oil	10	)

Observation period - Post treatment - 21 days

Delayed neurotoxicity grading

0 - no signs
2 - ? or minor signs
8 - positive signs
12 - advanced signs
16 - death

Results:

Corn oil

All exposed birds negative.

Merphos

Bird No.	Time, degree of severity and duration of signs — Weeks 0-7	9	12	14	16	19	21	Histopatho. Nerve
32021	-	-	-	-	-	2	2	+ Spinal Cord
32024	-	2	2	12	12	12	12	Normal
32031	-	-	2	-	-	-	-	Not examined
32034	-	-	-	-	2	8	8	Normal
32035	-	2	2	8	8	12	8	+ Spinal Cord
32037	-	2	2	12	16	X	X	Normal
32038	-	2	2	8	12	16	X	+ Brain
32041	-	-	-	2	2	-	-	+ Sp.C.,Brain
32055	-	-	-	-	2	2	2	+ Sp.C.,Brain
32057	-	-	-	-	2	2	2	+ Sp.C.,Brain
32060	-	-	-	2	8	8	8	+ Sp.C.,Brain

Sp.C. = Spinal Cord
\- = Signs absent
X = Absent - prior death

TOCP

Bird No.	Time, degree of severity and duration of signs — Weeks							Histopath.
	0-7	9	12	14	16	19	21	Nerve
32011	-	-	-	8	12	12	12	+ S.N.,Sp.C.
32012	-	-	-	2	8	12	16	+ S.N.,Sp.C.
32013	-	-	-	8	12	12	12	+ B,S.N.,Sp.C.
32014	-	-	-	2	8	12	12	+ S.N.,Sp.C.
32015	-	-	-	8	8	12	12	+ S.N.,Sp.C.
32016	-	-	-	2	8	12	12	+ B,S.N.,Sp.C.
32017	-	-	-	12	12	12	12	+ Sp.C.,S.N.
32018	-	-	-	2	2	8	8	+ Sp.C.
32019	-	-	2	12	12	12	12	+ Sp.C.
32020	-	-	2	8	8	12	12	+ Sp.C.

B = Brain
Sp.C. = Spinal cord
S.N. - Sciatic Nerve
- = Signs absent

Discussion

Clinically and microscopically, it was clearly demonstrated that Merphos produced delayed paralysis with associated cellular nerve tissue reactions, similar to TOCP produced delayed paralysis and nerve tissue reactions.

At exposed levels, TOCP was demonstrated to be a more potent agent for nerve tissue effects since all 10 exposed birds reacted severely. Of 40 birds exposed to Merphos, 11 were clinically affected but generally less severely than the TOCP hens. All the 10 TOCP hens exhibited cellular changes in brain, spinal cord or sciatic nerve, whereas only 7 of 10 Merphos hens examined exhibited cellular changes.

Before final acceptance of thisdreport the 1 ml/kg bw exposure level for both TOCP and Merphos needs to be converted to actual chemical as mg/kg bw and the protocol, No. 76168, needs to be provided as a supplement to this study.

George E. Whitmore, D.V.M.

cc:
Bipin Gandhi

GEWhitmore/ccw 9/16/77