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DATA EVALUATION RECORD

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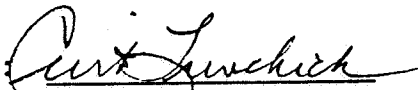
Prenatal/Postnatal (Reproduction) Toxicity Evaluation  
in the Pig of Trichlorfon Administered in the Feed

CITATION: Knox B, Askaa J, Basse A, Pitsch V, Eskildsen M, Mandrup M, Ottosen H, Overby E, Pedersen K, Rasmussen F. 1978. Congenital ataxia and tremor with cerebellar hypoplasia in piglets borne by sows treated with Neguvon<sup>R</sup> (Metrifonate, Trichlorfon) during pregnancy. Nord. Vet-Med. 30:538-545 [In English].

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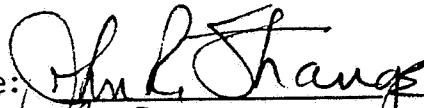


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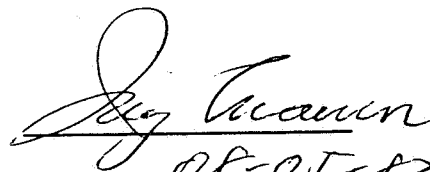
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2 August 1983

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## DATA EVALUATION RECORD

STUDY TYPE: Prenatal/postnatal (reproduction) toxicity evaluation in the pig of trichlorfon administered in the feed.

CITATION: Knox B, Askaa J, Basse A, Pitsch V, Eskildsen M, Mandrup M, Ottosen H, Overby E, Pedersen K, Rasmussen F. 1978. Congenital ataxia and tremor with cerebellar hypoplasia in piglets borne by sows treated with Neguvon<sup>R</sup> (Metrifonate, Trichlorfon) during pregnancy. Nord. Vet-Med. 30:538-545 [In English].

ACCESSION NUMBER: Not available.

MRID NUMBER: Not available.

LABORATORY: Royal Veterinary and Agricultural University, Copenhagen, Denmark.

TEST MATERIAL: Neguvon<sup>R</sup> vet. (trichlorfon, metrifonate). Purity, source, and description not stated.

### PROTOCOL:

1. Trichlorfon was studied for its effects on piglets exposed in utero. The trichlorfon was referred to as Neguvon<sup>R</sup> vet. Purity, source, and further description of the test material were not stated.
2. Two experiments were performed. The first experiment utilized 80 specific pathogen-free Landrace sows and gilts. Three sows and one gilt were treated with trichlorfon and the remaining 76 swine were assigned to the control group. Thirty-two "conventional" [strain not specified] sows were utilized in the second experiment. Four were treated with trichlorfon and 28 were assigned to the control group.
3. In the first experiment, the three sows and one gilt were given feed mixed with trichlorfon at 60 mg/kg on day 55 and day 70 of gestation. Two of the four sows in the second experiment were fed feed containing 50 mg/kg trichlorfon on day 66 of gestation, while the remaining two sows received feed containing 50 mg/kg trichlorfon on each of days 56 and 70 of gestation.

4. Blood samples from the treated animals in the first experiment were drawn before administration of the test material and every two weeks thereafter. Control samples were obtained from 50 of the control swine. Sera from the samples were examined for content of several complement fixing antibodies. The colostrum deprived piglets were bled and their sera examined for the presence of IgM.

Blood samples from the sows in the second experiment were drawn at 2, 6, and 24 hours and 5, 14, and 45 days after treatment. The blood was analyzed for plasma and RBC cholinesterase activity. Body weights were obtained on these pigs on the day of dosing.

Two of the treated sows from the first experiment were allowed to deliver naturally, while the remaining sow and gilt had their litters delivered by Cesarean section to avoid colostrum antibody uptake. All sows in the second experiment were allowed to deliver naturally. The piglets were observed for signs of toxicity after birth and mortality was recorded. At an unspecified time the piglets were weighed and sacrificed. The weight of the whole brain, cerebellum, and weight and length of the spinal cord were recorded on all piglets. Histological examination of the central nervous system was performed on the treated piglets from the first experiment. A virological examination was performed on brain, lung, and tonsil samples from the piglets.

5. A Student's t-test was performed on the data obtained from the neurological examination of the piglets. The report does not specify if statistical analyses were performed on other parameters.

#### RESULTS:

No data were provided on maternal body weight, food consumption, and observations with the exception of the body weights on the four sows bled for cholinesterase levels. Ataxia and tremors were observed in all piglets born to the trichlorfon-treated Landrace animals. The authors did not state at which time(s) after parturition these clinical signs were observed or their duration. The four litters from the trichlorfon sows and gilt consisted of 9, 10, 14 (plus one mummy), and 7 piglets. The control Landrace animals delivered 832 live piglets from 97 litters. [This reviewer questions how 97 litters could be delivered from 76 animals unless animals were used to produce more than one litter.] No "nervous signs" were reported among the control piglets. Ataxia and tremors were observed in 12 of 13 liveborn piglets from one "conventional" trichlorfon-treated litter. This sow also had three stillbirths. No piglets from the three remaining "conventional" trichlorfon litters (10, 12, and 10 piglets per litter) displayed ataxia or tremors. No tremors or ataxia were observed in the "conventional" control litters.

Effects on the central nervous system of the Landrace piglets are presented in Table 1. Significant decreases in the cerebellum to brain weight and cerebellum to body weight ratios were observed in the trichlorfon piglets. The spinal cord weight to spinal cord length ratios were significantly reduced among the trichlorfon piglets when compared to the controls. The authors did not state if the data presented used the piglet or the litter as the unit for statistical analysis. The authors reported that all piglets displaying ataxia and tremors from both experiments showed "marked hypoplasia of the cerebellum." Histopathologic examination of piglets from the four trichlorfon-treated Landrace litters indicated that the hypoplasia involved "all the structural elements of the cerebellum. Dysgenesis [defective development] of the lamina germinativa and dysplasia of the cerebellar cortex were found, especially in lobules I-II-III, VII-VIII-IX, and X. A diminished amount of myelin was present in the parts of the medulla that were related to the affected areas of the cortex." The serological and tissue examinations for viral infections were negative.

The results of plasma and RBC cholinesterase activities in the second experiment are presented in Table 2. It was observed that plasma cholinesterase activity dropped immediately after exposure and continued to decrease or remain stable until 24 hours post-treatment. The levels then slowly increased beginning at the 5-day post-treatment measurement. RBC cholinesterase activity remained relatively stable until 24 hours after treatment when it reached its greatest reduction (except sow 28) and then increased. Both cholinesterase activities among the two sows treated twice with trichlorfon tended to show a greater reduction in activity after the second treatment when compared to the first. The cholinesterase activities of sow 28 were more severely reduced than the remaining three sows. Sow 28 was the only "conventional" trichlorfon treated sow to deliver piglets displaying ataxia and tremors.

#### CONCLUSIONS:

Specific pathogen-free Landrace sows and gilts were treated with 60 mg/kg trichlorfon in the feed on day 55 and day 70 of gestation. "Conventional" sows were treated with 50 mg/kg trichlorfon in the feed on either day 66 of gestation or on days 56 and 70 of gestation. The piglets from the sows and gilts were examined for indications of trichlorfon toxicity.

Because there were only four sows per trichlorfon group, no specific conclusions with LEL's and NOEL's could be reached; however, general conclusions are possible. In utero exposure to trichlorfon produced postnatal toxicity in the Landrace piglets. All trichlorfon Landrace piglets displayed ataxia and tremors. Piglets from one of four "conventional" trichlorfon litters displayed ataxia and tremors. It is unclear, because of the small sample size, whether this effect resulted from unusual susceptibility to trichlorfon in the affected litter or is a representative toxic response among "conventional" piglets.

TABLE 1. Central Nervous System Effects of Prenatal Exposure to Trichlorfon in Landrace Piglets

Ratios	Trichlorfon Treated Piglets		
	Control Piglets	Natural Delivery	Cesarean Section
Cerebellum/Total Brain Weight (percentage)	9.8 ± 0.8	4.1 ± 0.5 <sup>a</sup>	5.3 ± 1.3 <sup>a</sup>
Cerebellum/Total Body Weight (percentage)	0.24 ± 0.05	0.08 ± 0.02 <sup>a</sup>	0.12 ± 0.03 <sup>a</sup>
Spinal Cord Weight/Spinal Cord Length (g/cm)	0.19 ± 0.01	0.16 ± 0.03 <sup>a</sup>	0.15 ± 0.02 <sup>a</sup>

<sup>a</sup>p<0.0001.

TABLE 2. The Effects of Trichlorfon on RBC and Plasma Cholinesterase Activity in Pregnant Sows

Sow No.	Body Weight (kg)	Dose Level (mg/kg)	Dosed on Day(s) of Gestation	Cholinesterase Activity (percent of Initial Activity)											
				Plasma						RBC					
				2 hrs	6 hrs	24 hrs	5 days	14 days	45 days	2 hrs	6 hrs	24 hrs	5 days	14 days	45 days
32	190	50	66	34	15	4	25	48	48	86	80	21	40	82	69
46	210	50	66	11	17	13	41	43	69	70	76	44	54	54	84
5	220	50	56	30	22	29	48	81	--	83	76	43	61	62	--
		50	70	40	16	10	37	67	84	69	52	26	47	49	68
28	230	50	56	14	6	10	51	80	--	30	26	58	55	67	--
		50	70	8	9	8	44	66	125	25	21	21	28	40	50

All the piglets displaying ataxia and tremors were observed to have cerebellar hypoplasia. Although not the intent of the authors, the occurrence of the ataxia, tremors, and hypoplasia of the cerebellum suggests a teratogenic action by trichlorfon in the Landrace pigs. The period of gestation when trichlorfon was fed to the sows (days 55 to 70 of gestation) encompasses the organogenic and growth phase of brain development. The data suggest that in utero exposure to trichlorfon in the Landrace pig is toxic and possibly teratogenic. The occurrence of possibly trichlorfon-related toxicity in one of four "conventional" litters is equivocal due to the small sample size.

CORE CLASSIFICATION: Supplementary data.

The following deficiencies were noted:

- o The the number of animals in the trichlorfon-treated groups was small.
- o No food consumption data were reported for the days trichlorfon was administered in the feed. Therefore, the actual intake of trichlorfon is unknown.
- o In the first experiment both sows and gilts were bred. The reproductive capacities of a sow are not comparable to a gilt.
- o More control Landrace litters existed than there were sows and gilts. This suggests some animals produced more than one litter.
- o The strain for "conventional" sows is unknown.