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DATA EVALUATION RECORD

TRICHLORFON

Postnatal Evaluation of Orally Administered Trichlorfon in Rats Exposed In Utero

CITATION: Sulinski A, et. al. [Full translation not provided by translator.] 1979. Effect of intoxication of pregnant rats with trichlorfon on the activities of some brain enzymes in the progeny during postnatal development. Neuropatologia Polska. 17(1):135-143 [English translation].

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DATA EVALUATION RECORD

STUDY TYPE: Postnatal evaluation of orally administered trichlorfon in rats exposed in utero.

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ACCESSION NUMBER: Not available.

MRID NUMBER: Not available.

LABORATORY: Institute of Biopharmacy, Medical Academy of Warsaw, Warsaw, Poland.

TEST MATERIAL: Trichlorfon (Dipterex). Identified as "0,0-dimethyl-1-hydroxy-2,2,2-trichloroethylphosphate." The purity of the trichlorfon was 97.85 percent and it was prepared in the Institute of Physical Chemistry, Polish Academy of Sciences.

PROTOCOL:

1. Trichlorfon was studied for its postnatal effects following in utero exposure. The chemical identification was given at "0,0-dimethyl-1-hydroxy-2,2,2-trichlorethylphosphate." It was produced by the Institute of Physical Chemistry, Polish Academy of Sciences with a purity of 97.85 percent.

2. Pregnant female albino rats weighing 230-250 g were used in the study to produce the progeny. The strain was not stated. The number of adult rats in each of the three test groups was not specified.

3. Eleven or 56 mg/kg trichlorfon was "introduced orally" to the pregnant females during the last seven days of gestation. The dose levels were 2 and 10 percent respectively of an LD_{50} of 560 mg/kg (Rusiecki W. Toksykologia ochrony roslin, PZWL, Warszawa, 1973,77). The vehicle control received water. The dose volume was 2 ml per animal. [The specific days of gestation that the animals were dosed was not stated. Rats normally deliver between days 21 and 23 of gestation. It is unclear if the animals were dosed until parturition or until a given day of gestation, i.e., day 22. Either method would produce variability in the dosing regimen unless all animals delivered as scheduled.]

4. No data appear to have been recorded on the dams. Brain and plasma acetylcholinesterase (ACh) activities were determined in the rat pups at 1, 4, 8, 12, 16, 24, 32, 48, and 64 days of age. ACh activities were determined by spectrophotometric methods. Cytochrome oxidase and succinate dehydrogenase levels in the brain were determined at 1, 4, 8, 12, 16, 32, 42, and 56 days of age in the rat pups by spectrophotometric methods. The authors did not state the numbers of pups analyzed at each interval for each of the enzymes. The method of selecting pups for analysis was not stated and it is unknown if pups from all litters were analyzed at each interval or if all pups from one litter were utilized at one time.

5. Statistical significance was determined for the enzyme levels at $p<0.05$. The method of statistical analysis was not described.

RESULTS:

Specific activities of the enzymes were not presented. Bar graphs were provided that gave the approximate activities in nmoles/min/mg protein for ACh, K/sec/mg protein for cytochrome oxidase [the value of K is not defined in this translation], and μmoles/min/mg protein for succinate dehydrogenase.

In utero exposure to 56 mg/kg trichlorfon significantly reduced brain ACh activity at day 1 of age when compared to the vehicle control. This activity was significantly increased at day 4 and then became significantly reduced when compared to the controls from day 16 to day 64 of age. Brain ACh activity was comparable to the vehicle control levels at day 8 of age. The effect on brain ACh activity were less pronounced in the pups exposed to 11 mg/kg trichlorfon. Brain ACh activity was comparable to the vehicle controls from day 1 to day 24 of age. This activity was slightly reduced on days 32 and 64 of age and the reduction was significant at day 48 of age when compared to the vehicle controls.

Plasma ACh activity was affected by in utero exposure to trichlorfon from day 1 until day 16 of age. The ACh activities of both treatment groups were comparable to the controls at day 24 to day 64 of age. The activity of plasma ACh in the high dose was significantly reduced at days 1, 4, 8, and 16 of age compared to the controls. At the low-dose level, plasma ACh activity was significantly increased on days 1 and 4 of age. The activity was comparable to the controls on day 8 of age and then significantly reduced at day 16 of age. As previously stated, this parameter stabilized to levels comparable to the vehicle controls by day 24 of age.

The cytochrome oxidase activity was significantly reduced in the pups exposed at 56 mg/kg trichlorfon from day 1 to day 16 of age. Beginning at day 32 of age the activity was comparable to the vehicle controls. The cytochrome oxidase activity among the pups exposed to 11 mg/kg trichlorfon was unaffected with enzyme activity comparable to the vehicle controls throughout the study period.

The effect of trichlorfon on succinate dehydrogenase activity was similar to that observed for cytochrome oxidase. Among the rat pups exposed to 11 mg/kg trichlorfon, succinate dehydrogenase activity was comparable to the vehicles controls throughout the study. At 56 mg/kg significant reductions in activity was detected during the first 12 days of life and the enzyme activity was reduced at day 16 of age, but this reduction was not significant. At days 32, 42, and 56 of age, succinate dehydrogenase activity in the high-dose pups was comparable to the vehicle controls.

CONCLUSIONS:

Pregnant albino rats were orally administered trichlorfon at 11 and 56 mg/kg daily, during the last seven days of gestation. The progeny were analyzed for plasma and brain ACh activity at 1, 4, 8, 12, 18, 24, 32, 48, and 64 days of age. The progeny were also analyzed for brain cytochrome oxidase and succinate dehydrogenase activity at 1, 4, 8, 12, 16, 32, 52, and 56 days of age.

In utero exposure to trichlorfon produced fluctuations in brain ACh activity at 56 mg/kg throughout the study. At 11 mg/kg the effects were delayed and not evident until the latter half of the study. The in utero exposure to trichlorfon also affected plasma ACh activity. These effects were evident during the early portions of the study and were not evident after the 16th day of age.

Reductions in both cytochrome oxidase and succinate dehydrogenase activity were detected at 56 mg/kg during the first portion of the study. The effects of trichlorfon on the activities of these enzymes at 56 mg/kg were not evident after the 16th day of study or at any time at 11 mg/kg.

The authors did not discuss the conditions of the dams during or after trichlorfon administration. This prevents any comparison between the effects observed in the progeny and any possible toxicity in the maternal animals.

From the information presented, it appears to this reviewer that trichlorfon depresses brain ACh for at least 64 days post parturition in the high-dose pups (except at days 4 and 8). Likewise cytochrome oxidase and succinate dehydrogenase activities appeared depressed at the high dose for the first 16 days after birth.

CORE CLASSIFICATION: Supplementary Data.

The following deficiences were noted.

- Actual enzyme activities were not reported. The data were presented in bar graphs.
- The number of pups utilized at each interval for the enzyme activity analyses and the method of pup selection was not stated.

- No data on the maternal animals were provided. It is unknown if trichlorfon produced maternal toxicity.

- The actual days of gestation that trichlorfon was administered was not stated. Unless all dams delivered on the same day of gestation the dosing regimen would vary depending on what day of gestation parturition occurred.

- The strain of rat is not stated.

- The chemical description of trichlorfon is incorrect. This appears to be a translation error.