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DATA EVALUATION RECORD

TRICHLORFON

1. Acute Toxicity in Rats, Mice, and Guinea Pigs
2. Subchronic Toxicity in Rats
3. In vitro and in vivo Cholinesterase Determinations in Rats
4. Metabolism in Rats

CITATION: DuBois KP, Cotter GJ. 1955. Studies on the toxicity and mechanism of action of dipterex. AMA Arch Ind. Health. 11:53-60.

REVIEWED BY:

Nicolas P. Hajjar, Ph.D.
Senior Scientist
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: Nicolas P. Hajjar

Date: Aug 5, 1983

John R. Strange, Ph.D.
Department Director
Dynamac Corporation
11140 Rockville Pike
Rockville, MD 20852
301-468-2500

Signature: John R. Strange

Date: 5 August 1983

APPROVED BY:

Irving Mauer, Ph.D.
EPA Scientist

Signature:

Date: 08-05-83

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ACCESSION NUMBER: Not available.

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LABORATORY: Department of Pharmacology, University of Chicago, Chicago, Illinois.

> (Jm. 08.05.83)

TEST MATERIAL: Trichlorfon (≥99 percent purity). Supplied by Dr. G. Schrader, Farbenfabriken-Bayer, Leverkusen, Germany.

PROTOCOL:

1. Dipterex (trichlorfon) of greater than 99 percent purity was used. For the acute, subchronic, and metabolism studies Dipterex was dissolved in aqueous solutions and the animals were injected intraperitoneally. For the in vitro study, it was dissolved in Ringer-bicarbonate buffer and added to the test system.

2. Animal species used included the following: male and female Sprague-Dawley rats weighing 200-250 g; male and female Carworth mice weighing about 20 g; male and female Guinea pigs reported as being "of mixed sexes." (weights not specified). For cholinesterase activity, "various concentrations" of Dipterex were added to homogenates of brain, submaxillary gland, or serum from rats. [Numbers of animals per group, dose levels, and individual data were not presented].

3. Cholinesterase activities were performed manometrically by the method of DuBois and Mangun (Proc. Soc. Exp. Biol. Med. 64:137, 1947).

RESULTS:

Acute Toxicity: The following acute LD_{50} values ("estimated from the mortality by the log probability method") were reported:

Rat, ip, 225 mg/kg (sex not specified)
Rat, po, 450 mg/kg (sex not specified)
Mice, ip, 500 mg/kg (sex not specified)
Guinea pigs, ip, 300 mg/kg (sex not specified).

All deaths occurred within one day of dosing. Signs of toxicity, such as body twitching, salivation, and urination, appeared within 10 minutes and recovery or death due to respiratory failure and cardiac arrest occurred within a few hours. Mice pretreated with a single ip dose of atropine sulfate at 100 mg/kg were protected from Dipterex doses up to 1,500 mg/kg but not doses of 2,000 mg/kg.

Subchronic Toxicity: Groups of 5 rats (sex not specified) were administered intraperitoneally 50, 100, or 150 mg/kg/day of Dipterex for 60 days. Symptoms that preceded death were identical to those in acutely poisoned animals. The toxic mechanism was described as being "the same as that of other insecticidal organic phosphates and was explainable on the basis of anticholinesterase action." All animals survived the 50 mg/kg dose level. All animals died in the 150 mg/kg/day group (4 between days 5-10, and one between days 30-60). In the intermediate group (100 mg/kg/day) 2/5 died, one between days 5-10 and one between days 30-60.

In vitro Cholinesterase Activity: The in vitro I_{50} value for brain cholinesterase was reported to be 2.0×10^{-6} M Dipterex. Cholinesterase inhibition of serum, submaxillary gland, and brain were reported to be "equally susceptible" to Dipterex; but no data were presented.

In vivo Cholinesterase Activity: Groups of 21 rats (sex not specified) were administered 25, 50, or 125 mg/kg of Dipterex intraperitoneally. Three rats from each test group were killed after 15, 30, and 60 minutes and at hourly intervals thereafter. Inhibition of brain acetylcholinesterase activity was noted at all 3 dose levels after 15 minutes, with about 85-90 percent inhibition noted at the highest dose. However, activity increased gradually with time, and returned to about 80 percent of normal at 5 hours in animals receiving the two higher doses. Animals receiving the low dose recovered after 1 hour. Results were presented only in graphic form, without ranges or standard deviations.

To obtain information on the cholinesterase activity in rats following repeated (daily) administration, doses of 50 or 100 mg/kg/day were injected intraperitoneally. Groups of 3 rats (sex not specified) were killed at "frequent intervals" (24 hours after the last dose), and brain and serum cholinesterase activity determined. Results indicated a progressive decrease (50-75 percent) in activity in rats receiving the low dose during the first 5 days. The enzyme activity remained at this level throughout the 60-day treatment. At the high dose, activity decreased progressively throughout the 14-day treatment. Results were presented only in graphic form, without ranges or standard deviation.

Metabolism: The rate of disappearance of Dipterex from blood in rats (sex and number per group not specified) receiving a single intraperitoneal dose of 75, 100, or 150 mg/kg was studied. The concentrations of Dipterex in blood were measured by cholinesterase inhibition and comparing the results with a standard curve obtained in the in vitro portion of this study. Dipterex was found to disappear rapidly from the blood. Within 15 minutes, animals receiving 75 mg/kg had returned to normal levels; and within 30 minutes, animals receiving 100 and 150 mg/kg were within 30 percent of normal; and all groups were normal within 60 minutes of dosing. Additional experiments were performed to determine if the compound was excreted unchanged or transformed rapidly into inactive products. Groups of 3 rats were administered a single intraperitoneal dose of 25, 50, 75, 100, or 150 mg/kg Dipterex, and their urine samples collected daily. Of these dosages, about 1 to 3 percent of the Dipterex was excreted unchanged during the subsequent 24 hr period, with no measurable quantity excreted thereafter. Another group of rats (sex and number unspecified) given daily doses of 100 mg/kg daily for 21 days also excreted only 1 to 3 percent unchanged Dipterex daily for the duration of the test. The authors also state that no Dipterex was detected in the liver "15 minutes after administration of 75 mg/kg." [Species, sex, route of administration, method of sacrifice and method of analysis not specified]. Results were presented only in graphic form, without ranges or standard deviations.

CONCLUSIONS:

Dipterex appeared to behave similarly to other organophosphorus insecticides as it caused excessive stimulaton of the central nervous system, the parasympathetic nervous system, and the somatic motor nerves. Its action was brief, and there was complete recovery in rats and mice within a few hours after acute exposure (assuming the dosage was not lethal). The cholinesterase inhibition was readily reversible following a single dose, and it appeared that the low toxicity to mammals was due to rapid detoxification in animal tissues. The compound disappeared rapidly from the tissues and was not excreted in the urine, leading the authors to conclude that the low toxicity and short duration of action of Dipterex was due to its rapid detoxification.

In the opinion of this reviewer insufficient data are present to establish NOEL for the acute and subchronic studies. Acute parameters seem to indicate that the compound has an LD_{50} from 300 to 500 mg/kg in mice, rats, and guinea pigs. The subchronic study extended for 60 days with only 5 animals (sex unspecified) per dose, and no food consumption or body weights were determined. All animals survived the 50 mg/kg/day dosage. Cholinesterase inhibition occurs following exposure to Dipterex. However, the data are presented only in graphic form for both the in vitro and in vivo studies; and again the numbers of animals are not specified.

CORE CLASSIFICATION: Acute--Supplementary data.
Subchronic--Supplementary data.
In vitroand In vivo cholinesterase determinations--
Supplementary data.
Metabolism--Invalid.

The primary deficiencies in all of these studies were the lack of information on the number of animals per group, the dosage levels per group, and the failure to present the data in a numerical format. The metabolism study was conducted with a nonradioactive compound and was not designed to determine all possible routes of release of the compound, with only urine determinations made. Furthermore, the procedures used in this 1955 study would provide qualitative rather than quantative data.