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# *The influence of deltamethrin on memory processes in mice*

Pyrethroid compounds are synthetic analogues of natural substances, pyrethrins, which are derived from Chrysanthemum flowers. They are divided into two groups: type I – non-cyano-compounds causing T syndrome with tremor, hyperexcitation and incoordination, and type II, cyano-compounds causing CS syndrome with choreoatetosis and salivation (3, 7, 13, 15, 16, 18). The major target site for pyrethroids is the axonal sodium channel (14). They also modulate acetylcholine (ACh) release in the hippocampus of rats (8).

DTM belongs to type II pyrethroids and is known to imapir movement activity in intoxicated animals (5, 6). Chronic administration of deltamethrin induces an increase in the activity of acetycholinesterase (AChE) in various brain regions of rats (8). There are also data indicating that prenatal exposure to DTM causes a higher activity of the dopaminergic system in these animals (11).

There are hypotheses that some neurodegenerative diseases, as Alzheimer's disease (AD) and Parkinson's disease (PD), development might result from exposure to pesticides (10). AD is clinically characterised with memory impairment and, eventually, progressive dementia. In AD, there is a dramatic loss of choline acetyltransferase (ChAT) in the brain resulting in reduction of ACh realease (4, 17). PD is a progressive human neurodegenerative disorder, affecting primarily the aged, that is defined by a resting tremor, stooped posture, poor balance, and dementia. The most prominent brain pathology in PD is neuronal loss in the nigrostriatal tract, in which dopaminergic neurons projecting from the substantia nigra to portions of the striatum are selectively destroyed during the disease process. Exposure to pesticides is one of the possible causative factors of PD. The majority of presently used pesticides are neurotoxic. Therefore the commonly used insecticide, DTM is a plausible suspect agent for neurodegenerative disorders such as PD (10).

The aim of the present study was to find out if single and prolonged (for 7 and 14 days) exposure to DTM caused any change in memory processes and movement activity in mice.

## METHODS

There were 4 groups of randomly selected animals, each of 8 female Albino-Swiss mice weighing 18 to 24 g, used in the experiment. All the animals were given a 7-day acclimation period and were maintained on a 12L: 12D photoperiod (0600 : 1800). Food and tap water were provided ad lib. Temperature was maintained at 21+/–2°C and relative humidity at 40%+/–20%.

Deltamethrin (technical grade 99%) as pulvis in violis á 0.25g was purchased from the Institute of Industrial Organic Chemistry, Annopol near Warsaw, Poland. DTM $LD_{50}$ was estimated with use of computer program based on Lichtfield and Wicoxon's method (12). Estimated DTM $LD_{50}$ was 83 mg/kg (79.2–87.0). 0,1 DTM $LD_{50}$ was suspended in bidistilled water with one drop of Tween 60 (purchased from Laboratoriums Reagenzien, Germany) and administered i. p. to three groups of mice: I – once, II – for 7 subsequent days and III – for 14 days. Controls were injected with respective volumes of bidistilled water i.p.

Memory retention was examined in passive avoidance task (PA). 30 min. after the last or the only, respectively, dose of DTM each animal was placed in a well lit part of a two chamber box. 30 sec. later a passage joining the well lit and dark part of the box was opened. After entering the dark chamber an animal was affected with an electric shock (2 mA for 2 sec). 24 h later each animal was placed in the same apparatus. Memory retention was measured as latency of entering the dark chamer within 180 sec. of observation. Fresh spatial memory was examined in a Y-maze immediately after PA. A Y- maze consists of three 10x10 cm boxes joined together with 4-cm long corridors at 120° in such a way that each corridor opens to one chamber only. Each animal was placed in one box and its spontaneous alternations were observed for 8 min. Spontaneous movement activity was estimated indirectly by counting the number of transfers from one box of Y-maze to another.

PA results were analysed with nonparametric ANOVA one-way analysis of variance (Kruskal-Wallis Test) and *post hoc* Dunn's Test. Results obtained in Y-maze were analysed with parametric ANOVA one-way analysis of variance and *post hoc* Student-Newman-Keuls multiple comparison test. P value $< 0.05$ was considered statistically significant.

## RESULTS

Memory retention after DTM examined in passive avoidance task was not significantly impaired in the examined groups compared to the control (Fig.1). Fresh spatial memory tested in Y-maze was impaired after a single dose of 0.1 $LD_{50}$ DTM, and to a lesser extent after 7-day-long exposure without statistical significance. It was slightly improved after 14-day-long exposure compared to the control without statistical significance (Fig. 2). Movement activity was significantly impaired after one and 14 injections of DTM (Fig. 3).

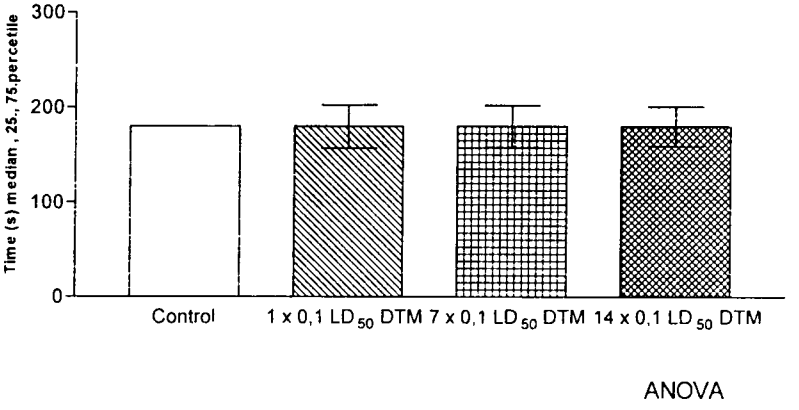


Fig. 1. Results obtained in passive avoidance task after single, 7-day long and 14-day long exposure to 0.1 $LD_{50}$ of deltamethrin (DTM). No statistical significance in comparison with control (n=8)

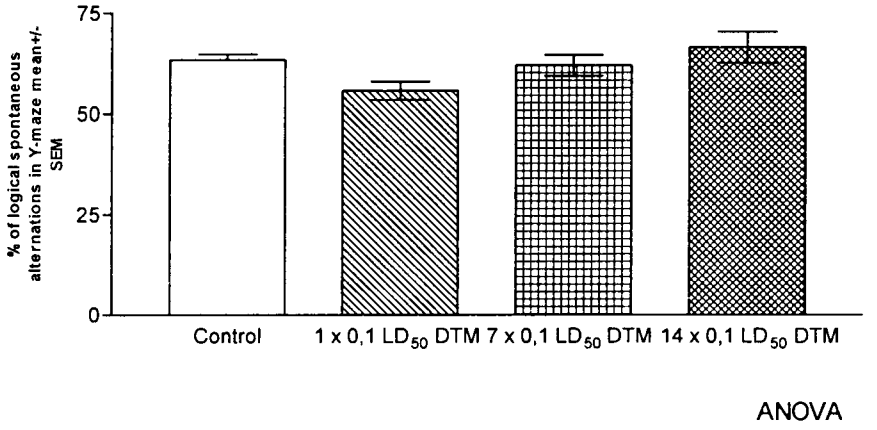


Fig. 2. Spontaneous alternations in Y maze after single, 7-day long and 14-day long exposure to 0.1 $LD_{50}$ of deltamethrin (DTM). No statistical significance in comparison with control (n=8)

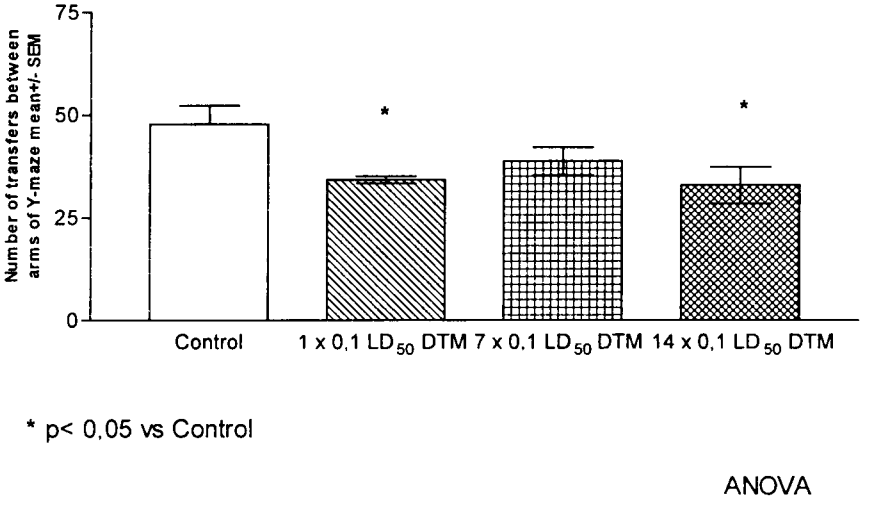


Fig. 3. Movement activity in Y-maze (counted as number of transfers from one arm of Y-maze to another) after single, 7-day long and 14-day long exposure to 0.1 $LD_{50}$ of deltamethrin (DTM). P<0.05 1 x 0.1 $LD_{50}$ vs control, P<0.05 14 x 0.1 $LD_{50}$ vs control (n=8)

## DISCUSSION

Deltamethrin is widely used for indoor and outdoor pest control. Attributes that favour the insecticidal use of DTM include its physical propertis: low volatility, lipophilicity, limited persistence due to numerous sites for metabolic degradation and relatively low inherent toxicity in mammals. Humans are able to tolerate higher doses of DTM than other insecticides. However, paresthesias and peripherial sensory phenomena are repeatedly experienced in man after exposure to DTM (1). Anadon et al. studied DTM's kinetic profile. DTM's major metabolite is 4'-HO-

deltamethrin. After a single oral dose of 26 mg/kg of DTM it was efficiently distributed to nervous tissues. High DTM and 4'-HO-deltamethrin concentrations were reached in all regions of brain and the highest was (in decreasing order) in hypothalamus, hippocampus, anococcygeus, cerebellum, vas deferens, frontal cortex, caudate putamen and medulla oblongata. Additionally the peak concentrations of DTM and its metabolite 4–8 h after administration were significantly higher than maximum plasma levels. The study of Anadon et al. supports the hypothesis that DTM-induced neurotoxicity results from the disposition of this chemical in CNS (1).

Hossain estimated oral DTM's $LD_{50}$ for rats as 135 mg/kg (9). Kirby et al. considered 12 mg/kg of DTM intravenous $LD_{50}$ for mice (10). 83 mg/kg that we consider DTM $LD_{50}$ is almost mean of these two doses. Although the main mechanism of DTM action is believed to be an effect on $Na^+$ channels of the nerve cell membrane, it may have other effects underlying the neurotoxicity (3, 16). It is known that the main humoral events of cholinergic synapses include ACh synthesis by ChAT activity, ACh hydrolysis by AChE activity and choline supply by high affinity choline uptake (HACU). Hossain et al. demonstrated that DTM modulates the hippocampal HACU (9). It was found that after 60 mg/kg of DTM administered i.p. to rats choline acetyltransferase (ChAT) concentration was elevated in hippocampus and cortex, and statistically significantly elevated in striatum. It had no effect on AChE. 60 mg/kg b.m. of DTM administered i.p. significantly affected HACU in synaptosomal preparations obtained from rat hippocampus 60 min. after treatment with DTM (9). A single dose of 20 and 60 mg/kg of DTM did not change the activity of AChE in any of the rat brain regions, apparently the enzyme activity change was not involved in the acute effects of DTM on central nervous system (CNS) (9).

DTM affects also the dopaminergic neurons. Lazarini et al. investigated neurobehavioural effects of prenatal exposure of rats to DTM. Swimming behaviour impairment was observed. Additionally, the animals presented higher striatal 3,4-dihydroxyphenylacetyc acid (DOPAC) levels without modification in dopamine (DA) levels and an increased DOPAC/DA ratio. These data indicate a higher activity of the dopaminergic system in animals exposed to DTM. Noradrenaline (NA) levels were increased, serotonin (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) levels as well as the homovanillic acid (HVA)/DA ratio were not modified. On the other hand, the observed animals showed decrease in general motor activity. The authors suspect high levels of emotionality induced by exposure to experimental procedures to affect the motor activity (11).

Kirby et al. have found out that DTM is a potent releaser of dopamine via its action on voltage-dependent sodium channels. They compared DTM's ability to release dopamine, serotonin, and glutamate from preloaded synaptosomes prepared from striatum (dopamine) and cortex (serotonin and glutamate). The studies revealed that DTM was able to release dopamine with greater potency than other transmitters. They concluded that DTM caused permanent alteration in the function and/or structure of the nigristriatum and thus played a possible role in PD pathogenesis (10). Calore et al. have found that 4-day long rat exposure to DTM caused sciatic and tibial nerves degeneration. 7 days after discontinuation of DTM treatment no lesion was found in the nerves. Since the histologic changes were found to be transitory and scarce an interesting question arouse: were they related to the changes in $Na^+$, $K^+$-ATPase activity or $Na^+$ channels caused DTM? (2).

## CONCLUSIONS

The results of the work are equivocal with those published by other authors when it comes to impairing influence of DTM on movement activity in animals. The influence of DTM on memory processes is not significant. However, many authors have proved a significant influence of DTM on dopaminergic, and especially cholinergic systems in animals. Therefore, it is still uncler if DTM and other pyrethroids play any role in pathogenesis of neurodegenerative diseases in humans.

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## SUMMARY


Deltamethrin (DTM) is a type II pyrethroid widely used as an insecticide. Literature reports of its neurobehavioural effects varying depending on the dose and route of administration. However, little is known about the influence of DTM on memory processes in mammals. Therefore, in the present study we examine the influence of 0.1 $LD_{50}$ of DTM on memory processes and movement activity in mice after single administration, after 7-day long and after 14-day long exposure. Memory retention after DTM examined in passive avoidance task was not significantly impaired in the examined groups compared to the control. Fresh spatial memory tested in Y-maze was impaired after a single dose of 0.1 $LD_{50}$ DTM, and to a lesser extent after 7-day long exposure without statistical significance. It was slightly improved after 14-day long exposure compared to

the control without statistical significance. Movement activity was significantly impaired after one and 14 injections of DTM. The results are equivocal with those published by other authors referring to movement activity impairment after DTM. However, they indicate that mammal exposure to DTM does not significantly affect memory processes.

Wpływ deltametryny na procesy pamięci u myszy

Deltametryna (DTM) należy do pyretroidów typu II i jest powszechnie stosowana jako środek owadobójczy. W piśmiennictwie opisywane są różne neurobehawioralne skutki działania DTM w zależności od dawki i drogi podania. Jednak wciąż niewiele wiadomo na temat wpływu DTM na procesy pamięci u zwierząt. W pracy zbadano wpływ 0,1 $LD_{50}$ DTM na procesy pamięci po jednokrotnym podaniu, po 7-dniowej i 14-dniowej ekspozycji. Retencję pamięci badano w teście biernego unikania, a świeżą pamięć przestrzenną w labiryncie Y. Aktywność ruchową badano pośrednio poprzez zliczanie liczby przejść między ramionami labiryntu Y. Retencja pamięci po DTM nie była istotnie statystycznie upośledzona w żadnej z badanych grup w porównaniu z kontrolą. Pamięć przestrzenna była najbardziej upośledzona po jednokrotnym podaniu 0,1 $LD_{50}$ DTM, zaś nieco mniej po 7-krotnym podaniu. Po 14-krotnym podaniu DTM obserwowano nieznaczną poprawę pamięci przestrzennej w porównaniu z grupą kontrolną. Aktywność ruchowa była istotnie statystycznie upośledzona po jednokrotnym i 14-krotnym podaniu DTM w porównaniu z kontrolą. Wyniki pracy są zgodne z pracami innych autorów co do upośledzającego wpływu DTM na aktywność ruchową myszy. W pracy wykazano, że DTM nie wpływa istotnie na procesy pamięci.