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Toxic Effects of Deltamethrin exposure on Health: special emphasis on CNS

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Abstract: Background: Deltamethrin (DEL) is a synthetic pyrethroid insecticide and acaricide with a wide range of applications in agriculture and veterinary field. It is regarded as the most dominant of the synthetic pyrethroids. When compared to certain pyrethroids, it is up to three times more active. It has become the preferred pesticide in most countries due to its rapid metabolism, low toxicity to humans and other non-target animals, and high efficacy against a wide range of pests. DEL is a type II pyrethroid that is considered the most potent neurotoxic pyrethroid. It was the first to be prescribed for pyrethroid type II poisoning syndrome. Sign words for products with DEL can range from caution to danger. The sign word reflects the common toxicity of the active ingredient and other ingredients in the produce. In the CNS, DEL modifies potassium channels. This modulation may cause a rise in the excitability and possibly even the death of hippocampus neurons since it involves changes in peak amplitude, activation, steady-state inactivation, and the time constant of recovery of transient outward K channels. Additionally, it works on voltage-sensitive calcium independent chloride channels, gaminobutyric acid-mediated chloride ionophores, and inhibits Ca2 and Mg2-ATPase. DEL cause choreoathetosis and salivation (CS Syndrom). In rats, this behavior manifests as touching and digging, followed by salivation and tremors, and finally choreoathetosis. Clonic convulsions may occur in the later stages. When rats were given DEL orally, they developed motor incoordination, salivation, respiratory abnormalities, limb and tail spasms, and clonic convulsions.

Keywords: *Deltamethrin, Toxic Effects, CNS*

Introduction

Deltamethrin (DEL) is a synthetic pyrethroid insecticide and acaricide with a wide range of applications in agriculture and veterinary field. It is regarded as the most dominant of the synthetic pyrethroids. When

compared to certain pyrethroids, it is up to three times more active. It has become the preferred pesticide in most countries due to its rapid metabolism, low toxicity to humans and other non-target animals, and high efficacy against a wide range of pests **(1).**

DEL is widely used to protect vegetables,fruits and agricultural crops from pests like ants, mites,weevils and beetles. Additionally,It is used for nurseries, urban structural ,golf courses, residential home,landscaping sites and garden pestcontrol.Furthermore, it is used topically in farm animals as an ectoparasiticide against mites ,ticks, fleas and flies to control vector-borne diseases **(2).**

DEL is (S) a-cyano3 phenoxybenzyl, (1R, 3R)-3-(2, 2dibromovinyl) -2, 2 dimethylcyclopropane carboxylate in addition to the previous,disallowed term decamethrin. The empirical formula is $C_2HBr2NO$, and its Molecular weight is about 505.2 g/mol. Technical grade DEL (≥98% pure) is composed of colorless to light beige, odorless, and non-corrosive crystals **(3).**

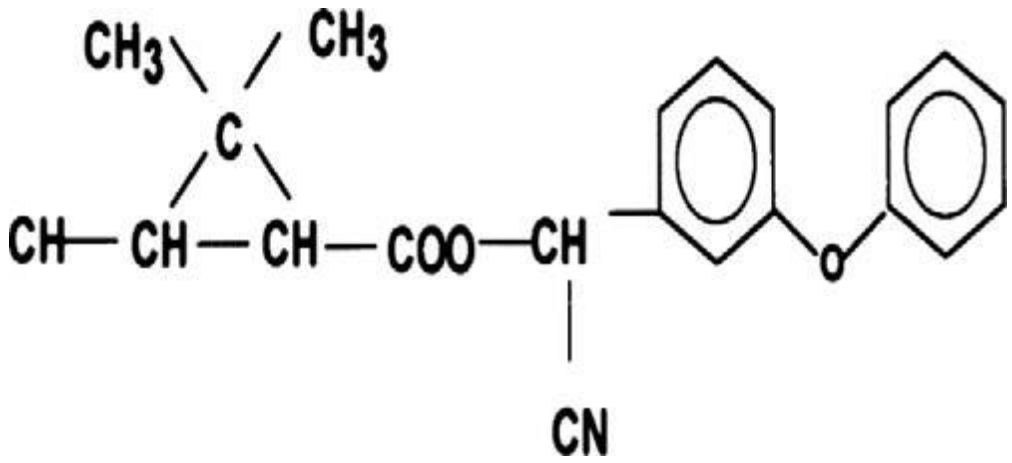

Fig. (1) : Chemical structure of DEL **(4).**

DEL breaks down by microbial action, hydrolysis, and photolysis. It is not susceptible to oxidation by light. It is especially insistent in soils that have a lot of clay or biological matter. For DEL in sandy or silt loam, half-lives have been reported in aerobic laboratory conditions ranging from 11 to 72 days, and in anaerobic soil conditions ranging from 31 to 36 days **(4).**

DEL is easily absorbed orally ; however, the hauler or solvent may interfere with the degree of absorption, only about half of a swallowed dose of DEL is absorbed.The absorption through the respiratory and digestive systems is higher than that through the skin. Because human skin is less permeable than rat skin, human skin is expected to absorb DEL at a relatively weak rate of 2%. Rats absorbed 3.6% of the DEL applied to their skin **(5).**

following absorption, DEL rapidly dispersed throughout the body due to its high lipophilicity and lack of exclusion by the multi-drug transporter glycoprotein, allowing for easy entry into the brain.it freely traverses cell membranes and the blood-brain barrier without the need for any specific or active transport **(6).**

DEL plasma concentrations peaked in rats at 2.1 hours after a single oral dose. DEL spread to nervous tissues as well as all tested brain regions .There is a slight tendency for DEL to accumulate in tissues. In rats, DEL had a blood half-life of 5.5 hours **(3).**

Studies on human metabolism using pyrethroids have demonstrated that these substances are quickly metabolized by hydrolytic cleavage of the ester bond, then by oxidation of methyl groups and aromatic rings, breakdown of the ester linkage, and conjugation reactions, resulting in a wide variety of metabolites that are mainly eliminated in urine after oral, inhalation, or dermal exposure **(5).**

The metabolic processes took place in the kidneys, liver, and other organs, as well as (very slightly) in nerve tissue. The presence of the alpha-cyanogroup in type II pyrethroids will slow down the ester bond's hydrolysis and cause the cyano group to change into thiocyanate. The prolonged elimination half-lives and high absorptions in various brain regions and peripheral nervous system tissues were revealed by the toxicokinetic behavior of these pyrethroids **(7).**

Following intraperitoneal or oral administration of DEL to rats, thiocyanate remained the predominant metabolite. PBA (3-phenoxybenzoic acid), 4'-OH-PB acid sulfate (4-hydroxy-3-phenoxybenzoic acid sulfate), and Br_2CA (3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylic acid) along with its glucuronide conjugate are the other metabolites. It is determined that DEL, the parent compound, alone, has significant toxicological implications **(3).**

In mammals, almost all of an oral dose of pyrethroids is excreted as metabolites in the urine and feces in a few days. Metabolites typically conjugate and are eliminated through first-order kinetics **(7).**

Anadón et al. (7) reported that in 48 hours, the removal of DEL fed to rats was almost complete. The practical dose (36–59%) was found in about equal amounts in the urine and feces. The elimination half-life of DEL given intravenously was 33.0 hours, whereas that of DEL given orally was 38.5 hours.

Following a single oral dose, DEL was excreted in milk in small amounts (0.42-1.60%). In a separate investigation, DEL concentrations in cow drains peaked 7 days after cutaneous treatment. Another study found that Leghorn hen eggs contained minimal quantities of DEL residues after the chickens were fed 7.5 mg per day for three days. Remains in the eggs were found during the first 24 hours of treatment **(3).**

The highest residues were observed 48 hours after the previous treatment. Within 12 hours of occupational contact and up to 48 hours after application, DEL and its metabolites were found in the urine of laborers **(8).**

DEL is a type II pyrethroid that is considered the most potent neurotoxic pyrethroid. It was the first to be prescribed for pyrethroid type II poisoning syndrome. Sign words for products with DEL can range from caution to danger. The sign word reflects the common toxicity of the active ingredient and other ingredients in the produce **(9).**

Pyrethroids' exposure, including DEL, results in neurotoxicity which can be manifested as locomotion disturbance, anxiety-like behavior, oxidative stress, and DNA damage **(10).**

Acute DEL exposure can result in neurotoxicity manifested by ataxia,loss of coordination, hyperexcitation, , convulsions, and paralysis. DEL neurotoxicity may be caused by a variety of cellular, biochemical, or molecular

mechanisms. Numerous studies point to DEL's apoptotic role as a key factor in neurodegenerative diseases. DEL affects neuron survival in the rat brain by inducing mitochondria-mediated apoptosis **(11).**

DEL exposure during pregnancy can also have an impact on rat offsprings' development and behavior **(12).** Furthermore, neonatal exposure to pyrethroids, even at relatively low doses, can affect the normal neurogenesis of the brain **(13).**

The key mechanism of DEL's acaricidal and insecticidal effects is thought to be its binding to a separate receptor site on voltage-gated sodium channels, elongating the open state by inhibiting channel deactivation and inactivation. However, due to its high hydrophobicity, DEL may have other effects on biological membranes besides the voltage-dependent sodium channel **(14).**

In the CNS, DEL modifies potassium channels. This modulation may cause a rise in the excitability and possibly even the death of hippocampus neurons since it involves changes in peak amplitude, activation, steady-state inactivation, and the time constant of recovery of transient outward K channels. Additionally, it works on voltage-sensitive calcium independent chloride channels, gaminobutyric acid-mediated chloride ionophores, and inhibits Ca2 and Mg2-ATPase **(6).**

The neurotransmitter acetyicholine binds to both the esteratic and anionic sites of AChE. Aromatic amino acids in the enzyme's active site also form a hydrophobic area. Pyrethroids, such as DEL, are thought to bind with this hydrophobic area and suppress AChE activity **(15).**

Acute toxicity:

DEL cause choreoathetosis and salivation (CS Syndrom). In rats, this behavior manifests as touching and digging, followed by salivation and tremors, and finally choreoathetosis. Clonic convulsions may occur in the later stages. When rats were given DEL orally, they developed motor incoordination, salivation, respiratory abnormalities, limb and tail spasms, and clonic convulsions **(5).**

After one hour of DEL dermal exposure, rats exhibited increased indications of biting, itching, and defeat. Rats that inhaled DEL showed grooming symptoms, hypersensitivity to touch and noise, clumsiness in movement, and hyperactivity **(8).**

When humans are exposed to it directly to the skin, it can temporarily cause paresthesia (stinging, burning, tingling) and numbness. Following ingestion, symptoms can include diarrhea, tenesmus, nausea, vomiting, unconsciousness, and respiratory failure that results in mortality **(16).**

Chronic toxicity:

<u>Effects on the heart:</u>

DEL has a cardiotoxic impact on the heart, causing increased lipid peroxidation, decreased antioxidant enzyme activity, increased heart rate, p decreased QRS complex amplitude , duration and decreased p wave duration. Ultrastructurally, DEL-treated rats showed dilatation in sarcoplasmic reticulum cisternae and disorganization in myofibrils. **(17).** Chronic exposure to DEL can cause oxidative stress linked to the Nrf2/HO-1 signaling pathway, which in turn can cause quail cardiomyocyte inflammation and apoptosis **(18)**

<u>Effects on liver&kidney:</u>

Küçükler et al. (19) Reported that DEL has hepatotoxic and nephrotoxic effect on male rats exposed to 1.28 of DEL for 30 days as it significantly increased serum ALT, AST, ALP, urea, and creatinine levels in rats, while decreasing nephrine. Furthermore, it enhanced the activation of apoptotic and inflammatory pathways by upregulating TNF-α, NF-κB, IL-1β, p38α MAPK, COX-2, iNOS, beclin-1, Bax, and caspase-3 protein levels and/or activity, while lowering Bcl-2. It also increases immunohistochemical expression of C-fos in the tissues and enhanced the mRNA expression levels of PARP-1, VEGF.

Effects on lung:

In a 45-day study, 30 adult male Wistar rats were given doses of 6.0 and 12.0 mg/m3 of a 1:10 dilution of DEL aerosol spray for 30 minutes every day. Under a light microscope, the following conditions were seen: emphysema, peribronchial lymphoid tissue hyperplasia, focal hemorrhage, focal nonspecific interstitial pneumonia, heavy congestion, marked perivascular edema, and lymphoplasmocytic infiltration **(20).**

Effects on pancreas:

In rats, long-term exposure to DEL resulted in elevated blood glucose and glycosylated haemoglobin levels, along with a discernible decline in insulin and total haemoglobin levels. Hexokinase activity and the amount of glycogen in the liver also declined. Furthermore, due to DEL toxicity, oxidative stress biomarkers (SOD, CAT, GPx, and GSH) changed and pancreatic lipid peroxidation increased **(21) .**

Effects on blood:

According to **Abdul-Daim et al. (2)**, DEL intoxication caused leucocytosis in rats while lowering hemoglobin concentration, platelet and red blood cell counts, and hematocrit values. there may have been a notable decline in these parameters because of the suppression of hemosynthesis and erythropoiesis as well as an increase in the rate of erythrocyte destruction in hemopoictic organs.

Effect on the immune system:

Being a strong immunotoxicant, DEL influences both cell-mediated immunity and humoral immunity. The B cell marker CD45 and CD28 receptors' active sites exhibited a strong binding affinity for DEL. DEL reduces the number of B and T cells in the spleen in a concentration-dependent way. The immune system is altered as a result of DEL-induced apoptotic pathways. ROS could function as an intracellular signal in the immunotoxicity caused by DLM **(22).**

Prethroids have the ability to cross placental barriers and cause cardiolesioning in rat offspring. Rats treated with DEL had a higher incidence of early embryonic deaths. Growth retardation, lung hypoplasia, renal pelvis dilatation, and an increase in placental weight were all brought on by DEL **(23).**

In rodents, DLM has multiple developmental effects, with long-lasting influences on cognition and behavior. The mechanism by which these behaviors are changed is not yet known, but there is mounting evidence that dopaminergic and glutamatergic pathways are involved. Recent studies in rats and mice show that DLM has lasting effects after early exposure, however, differences between studies in experimental conditions make only limited generalizations possible. Once the mechanisms are elucidated there will remain the task of determining the best way to extrapolate animal findings to children. Nevertheless, recent experiments provide leads worth pursuing, including the reduced release of DA in the n. accumbens, reduced *Drd1* mRNA expression in striatum, increased CA1 LTP, changes in NMDA-NR2 subunits, cell death, and possibly changes in cytokines. These effects are region specific, showing the need to avoid studies in whole brain. If pyrethroids adversely affect children's neurodevelopment, finding out how this occurs and at what exposure levels is required. Experiments reviewed here represent the beginning of the process of finding the developmental mechanism, but more studies are needed and are important given the widespread use of DLM. **(23).**

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