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Betreft: Intrekking pesticiden op basis van het insecticide deltamethrin.

Assen, 2 maart 2025.

Geachte Minister,

Met deze brief willen we uw aandacht vestigen op verschillende belangrijke nieuwe wetenschappelijke bewijsstudies over neurotoxiciteit veroorzaakt door het insecticide Deltamethrin. Ondanks de verplichting van de EU om de nieuwe beschikbare wetenschappelijke gegevens elke 10-15 jaar te beoordelen, dateert de laatste beoordeling van deze stof uit 2003. Gezien het belang van de nieuwe wetenschappelijke bevindingen voor de ontwikkeling van de hersenen, vragen wij u vriendelijk actie te ondernemen en in Brussel (ScoPAFF 11/12 maart) erop aan te dringen dat deze stof wordt verboden en een Art. 21 procedure in gang wordt gezet.

Nieuw onderzoek toont aan dat het pesticide deltamethrin bij de huidige Europese 'veilige waarde', het 'No Observed Adverse Effect Level' (NOAEL) van 1 ppm en lager hersenschade veroorzaakt bij de nakomelingen van blootgestelde drachtige muizen die verband houdt met leren en geheugen¹. Een verwant onderzoek met blootstelling van drachtige muizen bij NOAEL toonde schade aan een hersengebied (hippocampus) die volgens de auteurs kan leiden tot geheugenverlies en autisme². Deze twee onderzoeken zijn het hoogtepunt van een lange reeks aan artikelen in de afgelopen jaren die aantonen dat deltamethrin extreem schadelijk is voor de (menselijke) hersenen, vooral in de ontwikkelingsfase. En bij zeer lage doses, onder de NOAEL. In de bijlage vindt u bijna 30 onafhankelijke wetenschappelijke onderzoeken die de neuro-endocriene effecten van deltamethrin aantonen bij een reeks proefdieren. Deze effecten zijn waargenomen bij de huidige NOAEL (1 ppm), maar ook veel lager, d.w.z. 0,7 ppm, 0,15 ppm, en 0,08 ppm. Een veilig niveau is niet aangetoond en kan zeker niet worden aangenomen gezien de ernstige onomkeerbare bijwerkingen die zijn waargenomen. Auteurs concluderen zelfs dat nadelige effecten van blootstelling aan pyrethroïde op de neurologische ontwikkeling waarschijnlijk zijn bij blootstellingsniveaus die momenteel voorkomen in de algemene bevolking³.

¹ Koff et al., Early life exposure to deltamethrin impairs synaptic function by altering the brain derived extracellular vesicle proteome, *Molecular & Cellular Proteomics* (2025).

² Di Re et al., Environmental exposure to common pesticide induces synaptic deficit and social memory impairment driven by neurodevelopmental vulnerability of hippocampal parvalbumin interneurons, *Journal of Hazardous Materials*, Volume 485, 5 March 2025, 136893.

³ Andersen et al., Pyrethroids and developmental neurotoxicity - A critical review of epidemiological studies and supporting mechanistic evidence, *Environmental Research* 214 (2022) 113935

Het is een soortgelijk verhaal als met chloorpyrifos, dat in 2020 met spoed verboden moest worden⁴. Dit gebeurde op basis van een onderzoek naar hersenafwijkingen en disfuncties van prenataal blootgestelde kinderen aan chloorpyrifos⁵, ook nadat een reeks dierstudies dit type schade aantoonde. In het huidige geval van deltamethrin en verwante pyrethroïden heeft epidemiologisch onderzoek ook het verband tussen pyrethroïden en ontwikkelings-stoornissen zoals autisme bevestigd^{6,7,8}. Gezien de extreem lage doses deltamethrin waarbij hersenschade wordt waargenomen, dringen wij er bij u op aan ervoor te pleiten om onmiddellijk een Art.21-procedure te starten en het pesticide te verbieden om verdere schade aan de toekomst van onze kinderen te voorkomen.

Deze zaak wijst opnieuw op het falen van huidige aanvraagdossiers om ernstige neurotoxische effecten te identificeren. Zelfs voor een insecticide als deltamethrin. Wij verzoeken u vriendelijk er in Brussel voor te pleiten de verplichting voor alle pesticiden om gevoelige ontwikkelingsneurotoxiciteits dierproeven uit te voeren die anatomische en gedragsmatige/cognitieve eindpunten bevatten, onverwijld op te nemen in de gegevensvereisten.

Deltamethrin heeft meerdere schadelijke effecten op mens en milieu. Een 'Pubmed'-zoekopdracht met de zoektermen 'deltamethrin' en 'toxiciteit' leverde 1270 onderzoeken op, een verbazingwekkend aantal dat niet langer genegeerd kan worden. Art. 4 van Verordening 1107/2009 verplicht de Commissie om beslissingen te nemen op basis van de huidige wetenschappelijke inzichten. En het is opmerkelijk om op te zien dat een van de meest giftige pesticiden die door boeren wordt gebruikt, sinds 2003, 22 jaar geleden, niet opnieuw is geëvalueerd! Een zeer ernstig falen om het publiek en zijn omgeving het wettelijk vereiste 'hoge niveau van bescherming' te bieden.

Pyrethroïden zoals deltamethrin richten zich primair op het zenuwstelsel van insecten door het remmen van spanningsafhankelijke natriumkanalen en andere ionkanalen. Vanwege overeenkomsten in neurale functie hebben pyrethroïden ook neurotoxische eigenschappen bij niet-doelorganismen, waaronder mensen. Omdat de hersenen tijdens de ontwikkeling bijzonder kwetsbaar zijn voor neurotoxische stoffen, kan blootstelling in de foetale en vroege levensfase langdurige gevolgen hebben voor de hersenfunctie. Hoewel pyrethroïden een vrij lage acute zoogdiertoxiciteit voor mensen hebben, is langdurige hersendisfunctie na prenatale of vroege postnatale blootstelling aangetoond in diermodellen. De effecten omvatten neurochemische (bijv. veranderingen in dopaminefunctie) en neurogedrags-veranderingen (bijv. hyperactiviteit en tekorten in leren en geheugen), soms met meer uitgesproken effecten bij mannen.

Pyrethroïden kunnen de placenta passeren en zijn aangetroffen in navelstrengbloed. Pyrethroïden en sommige metabolieten, waaronder 3-PBA, lijken structureel op schildklierhormonen, d.w.z. thyroxine (T4) en triiodothyronine (T3), en op basis van experimentele studies, zowel in vivo als in vitro, is gesuggereerd dat ze schildklierhormoonverstoorders zijn. Het handhaven van normale schildklier-hormoonspiegels is belangrijk voor talrijke fysiologische processen, waaronder de ontwikkeling van de hersenen, maar zwangerschap is een buitengewoon kwetsbare periode, aangezien zowel de moeder als de foetus gevoelig zijn voor zelfs kleine verstoringen. Aangezien de menselijke foetus tijdens de eerste 12 weken van de zwangerschap geen schildklierhormonen kan synthetiseren, speelt placentaire overdracht van maternale schildklierhormonen een cruciale rol in de vroege ontwikkeling van de foetus. Zelfs subtiele

⁴ <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1578929027090&uri=CELEX:32020R0018>

⁵ Rauh et al., Brain anomalies in children exposed prenatally to a common organophosphate pesticide, PNAS, May 15, 2012, vol. 109, no. 20, 7871–7876.

⁶ Viel, J.-F., Rouget, F., Warembourg, C., Monfort, C., Limon, G., Cordier, S., et al., 2017. Behavioural disorders in 6-year-old children and pyrethroid insecticide exposure: the PELAGIE mother-child cohort. *Occup Environ Med* 74, 275–281

⁷ Viel, J.-F., Warembourg, C., Le Maner-Idrissi, G., Lacroix, A., Limon, G., Rouget, F., et al., 2015. Pyrethroid insecticide exposure and cognitive developmental disabilities in children: the PELAGIE mother-child cohort. *Environ Int* 82, 69–75.

⁸ Richardson, J.R., Taylor, M.M., Shalat, S.L., Guillot, T.S., Caudle, W.M., Hossain, M.M., et al., 2015. Developmental pesticide exposure reproduces features of attention deficit hyperactivity disorder. *FASEB J* 29, 1960–1972.

veranderingen in de functie van maternale schildklierhormonen in de vroege zwangerschap kunnen de ontwikkeling en rijping van de foetus beïnvloeden.

Neurologische ontwikkelingstoxiciteit kan verschillende aspecten van de menselijke biologie beïnvloeden. Blootstelling aan pyrethroiden is namelijk ook gekoppeld aan veranderingen in de ontwikkeling van geslachtsorganen bij adolescenten, via veranderingen in de hersen-regulatie van de voortplanting⁹.

Wij wijzen u tenslotte op de extreme toxiciteit van deltamethrin voor niet-doelorganismen. Blootstelling aan 1/10 van de deltamethrin-dosis die in het veld werd toegepast, resulteerde in 100% sterfte van alle mierenkoninginnen en zelfs bij 1/1000 van het deltamethrin-dosisniveau werd sterfte van koninginnen waargenomen¹⁰.

Wij dringen er bij u op aan om actie te ondernemen en in ScoPAFF te pleiten voor een snelle Art. 21-procedure om ervoor te zorgen dat het publiek en het milieu de bescherming krijgen die ze wettelijk gegarandeerd zijn.

Wij zijn benieuwd naar uw reactie,

Hoogachtend,

namens PAN-NL



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⁹ Castiello F, Suárez B, Beneito A, Lopez-Espinosa MJ, Santa-Marina L, Lertxundi A, Tardón A, Riaño-Galán I, Casas M, Vrijheid M, Olea N, Fernández MF, Freire C. Childhood exposure to non-persistent pesticides and pubertal development in Spanish girls and boys: Evidence from the INMA (Environment and Childhood) cohort. *Environ Pollut.* 2023 Jan 1;316(Pt 2):120571. doi: 10.1016/j.envpol.2022.120571. Epub 2022 Nov 7. PMID: 36356884.

¹⁰ Svoboda et al., Low concentrations of acetamiprid, deltamethrin, and sulfoxaflor, three commonly used insecticides, adversely affect ant queen survival and egg laying, *Nature Scientific Reports*, (2023), 13:14893.

ANNEX.
Deltamethrin toxicity

1. Developmental neurotoxicity

An abundant number of studies report on developmental neurotoxicity of deltamethrin.

We summarise the most important ones:

A. Exposure of pregnant animals and effects on offspring:

- Exposure of rats during gestation day 14-30 with low dose of deltamethrin (1 ppm) in utero during brain growth spurt period adversely affects the developing brain and the changes persist even up to 12 weeks in the postnatal period in rats. There is no significant recovery at 12 weeks assessment and significant impairment persists on biochemical and behavioural parameters¹¹.
- Exposure of pregnant mice to deltamethrin (1 ppm up to weaning) disrupts long-term potentiation (LTP) in the hippocampus of adult male offspring three months after exposure, a phenotype absent in female offspring. The authors conclude that they established a novel mechanistic link between maternal exposure to Deltamethrin at the NOEL and known cellular, circuitual, and behavioural vulnerabilities, indicating it is a potential driver in the exposome of autism¹².
- Exposure of pregnant Wistar rats to deltamethrin (1 ppm) from gestation to weaning. The authors conclude that maternal deltamethrin exposure impaired hippocampal development and learning and memory function in male offspring. Deltamethrin activated the PL-C/IP3R signalling pathway and increased the intracellular Ca²⁺ and CaN by ferroptosis, leading to learning and memory dysfunction in male offspring¹³.
- Prenatal exposure of deltamethrin (0,08 ppm) in rat alters latency to float and the activity of striatal dopaminergic system might reflect a persistent effect of the pesticide on animal motor activity, mainly in males. A decreased immobility latency to float and in general activity after the swimming test in male offspring was observed at adult age; higher striatal 3,4-dihydroxyphenylacetic acid (DOPAC) levels without modification in dopamine (DA) levels and an increased DOPAC/DA ratio were observed as well. These data indicate a higher activity of the dopaminergic system in these animals, The present trial showed that the prenatal exposure to a low dose of Deltamethrin alters offspring emotionality, motor and dopaminergic activity systems and might reflect a persistent effect induced by the prenatal exposure to the pyrethroid¹⁴.
- Exposure of deltamethrin of pregnant Wistar rat (0,5 ppm) has the potential to produce long lasting effects on the expression of xenobiotic metabolizing cytochrome P450s in brain and liver of the offspring. Dose-dependent alterations in the parameters of spontaneous locomotor activity in the offspring postnatally at 3 weeks have indicated that increase in cytochrome P450

¹¹ Aziz et al., Neurodevelopmental consequences of gestational exposure (GD14–GD20) to low dose deltamethrin in rats, *Neuroscience Letters*, Volume 300, Issue 3, 16 March 2001, Pages 161-165.

¹² Di Re et al., Environmental exposure to common pesticide induces synaptic deficit and social memory impairment driven by neurodevelopmental vulnerability of hippocampal parvalbumin interneurons, *Journal of Hazardous Materials*, Volume 485, 5 March 2025, 136893.

¹³ Huang et al., Maternal exposure to deltamethrin during pregnancy and lactation impairs hippocampal learning and memory function of male offspring by ferroptosis, *Ecotoxicology and Environmental Safety*, Volume 290., 15 January 2025, 117729.

¹⁴ Lazarini et al., Effects of prenatal exposure to deltamethrin on forced swimming behaviour, motor activity, and striatal dopamine levels in male and female rats, *Neurotoxicology and Teratology* 23 (2001) 665 – 673.

activity may lead to the accumulation of deltamethrin and its metabolites to the levels that may be sufficient to alter the behavioural activity of the offspring¹⁵.

- Exposure of deltamethrin (0,75 ppm) of rat intraperitoneally, close to the environmental exposure to the pregnant women due to their occupational or residential proximity to such insecticide treated farmlands, causes the defects in neuronal migration and subsequent lamina formation through reelin by its overexpression and/or blockade of its release and signalling, Deltamethrin exerts its neurotoxic effects possibly via the intracellular accumulation and low release of reelin leading to an impaired granule cell and Purkinje cell migration inhibition of neurite outgrowth and reduced spine density. Such impaired cerebellar development leads to motor coordination deficits¹⁶.
- The review of Andersen found sufficient evidence for an association between pyrethroid exposure during pregnancy and adverse neurodevelopment. The authors conclude that pyrethroids are probably human developmental neurotoxicants and adverse impacts of pyrethroid exposure on neurodevelopment are likely at exposure levels occurring in the general population. Preventive measures to reduce exposure among pregnant women and children are warranted¹⁷.
- Pitzer and colleagues conclude that existing data clearly show there are lasting effects of deltamethrin exposure on locomotor activity, acoustic startle, learning and memory, apoptosis, and dopamine in mice and rats after early exposure. The most consistent neurochemical findings are reductions in the dopamine transporter and the dopamine D1 receptor. The data show that deltamethrin is developmentally neurotoxin¹⁸.

B. Exposure of young animals to deltamethrin:

- Ten days old mice were given 1,2 ppm deltamethrin for 7 days. This dose revealed typical symptoms of pyrethroid poisoning, such as choreoathetosis for deltamethrin. The symptoms declined gradually during each successive day of administration and had disappeared by Day 4. At this dose deltamethrin affected the muscarinic receptors in the hippocampus and the nicotinic receptors in the cerebral cortex. This study further supports that the cholinergic system under rapid development in the neonatal mouse is sensitive to xenobiotics¹⁹.
- Postnatal exposure to deltamethrin (0,7 ppm) has been observed to delay the cytogenesis and morphogenesis of these neurons. In addition to this, damage to the developing vasculature has also been recorded in the form of thrombus and haemorrhage. Focal degeneration and spongy appearance of the tissue in the vicinity of the damaged blood vessels have also been recorded²⁰.

¹⁵ Johri et al., Long lasting effects of prenatal exposure to deltamethrin on cerebral and hepatic cytochrome P450s and behavioural activity in rat offspring, *European Journal of Pharmacology* 544 (2006) 58 – 68.

¹⁶ Kumar et al., Impaired Structural and Functional Development of Cerebellum Following Gestational Exposure of Deltamethrin in Rats: Role of Reelin, *Cell Mol Neurobiol* (2013) 33:731–746.

¹⁷ Andersen et al., Pyrethroids and developmental neurotoxicity - A critical review of epidemiological studies and supporting mechanistic evidence, *Environmental Research* 214 (2022) 113935.

¹⁸ Pitzer et al., Effects of pyrethroids on brain development and behaviour: Deltamethrin, *Neurotoxicology and Teratology* 87 (2021) 106983.

¹⁹ Eriksson et al., Effects of two pyrethroids, bioallethrin and deltamethrin, on subpopulations of muscarinic and nicotinic receptors in the neonatal mouse brain, *Toxicology and Applied Pharmacology* Volume 102, Issue 3, 1 March 1990, Pages 456-463.

²⁰ Patro et al., Neurotoxicological effects of deltamethrin on the postnatal development of cerebellum of rat, *Biosci.*, Vol. 22, Number 2, March 1997, pp 117–130.

- On exposure of Wistar rat pups by deltamethrin (0,7 ppm, postnatal day 9-13) the authors recorded a delay in the cytogenesis and morphogenesis of neurons. And, additionally, damage to the developing vasculature in the form of thrombus and haemorrhage. As well as focal degeneration and spongy appearance of the tissue in the vicinity of the damaged blood vessels. Deltamethrin delays and/or restricts differentiation of micro-neurons in the cerebellum²¹.

C. Exposure of adult animals to deltamethrin:

- Deltamethrin exposure of rats (intravenous) suggest that rather low doses (0,15 ppm) elicit vigorous autonomic and neuro-endocrine responses that indicate high levels of stress, presumably caused by the neurotoxic effect of the insecticide²².
- Deltamethrin exposure of mice at NOEL (1 ppm) causes an altered content of brain-derived extracellular vesicles that is sufficient to cause dysregulation of multiple signalling pathways within the brain. Strikingly, long-term potentiation at CA3-CA1 hippocampal synapses, a functional correlate of learning and memory, was intact in the control vesicles, but absent in naïve mice receiving vesicles from exposed mice²³.
- Exposure of Wistar rats (9–10-month-old) to inhalation of deltamethrin (2mg deltamethrin in nebuliser - exposure 10 minutes; 9 to 15 times the other day). The authors conclude that the deltamethrin inhalation at different periods induce motor and cognitive impairments in rats. Such alterations were accompanied by dopaminergic system damage and a possible dysfunction on synaptic plasticity²⁴.
- Exposure of zebrafish to deltamethrin (0,05 ug/L) caused an increase in coiling movement, heart rate, and apoptosis in the brain in early zebrafish embryos or larvae²⁵. The results of the transcriptome data also showed that low concentration deltamethrin induced the ACh-related genes and smooth muscle signalling pathways. Notably, deltamethrin induced apoptosis in the zebrafish brain. This indicates that deltamethrin exposure may have the potential risk of inducing neurodegeneration, and more attention should be paid to its effects in the future.
- Exposure of deltamethrin at environmental relevant concentration (30 ng/L) to zebrafish increased the glutamate level and promoted the release of such an excitatory neurotransmitter between the glutamatergic synapses in the brain, which eventually led to hyperactivity of social behaviours in adult zebrafish²⁶.
- Exposure of ant queens to deltamethrin (0,875 mg/L, 1/10, 1/100 and 1/1000 times lower than what is sprayed in the fields). The survival of the queens and the number of eggs laid was monitored. The insecticide caused severe lethal and sublethal concentration-dependent effects. At 1/10 of the dose applied in the field all queens died. Even at concentrations three orders of

²¹ Patra et al., Neurotoxicological effects of deltamethrin on the postnatal development of cerebellum of rat, *J. Biosci.*, Vol. 22, Number 2, March 1997.

²² De Boer et al., CHANGES IN PLASMA CORTICOSTERONE AND CATECHOLAMINE CONTENTS INDUCED BY LOW DOSES OF DELTAMETHRIN IN RATS, *Toxicology*, 49 (1988) 263-270.

²³ Koff et al., Early life exposure to deltamethrin impairs synaptic function by altering the brain derived extracellular vesicle proteome, *Molecular & Cellular Proteomics* (2025).

²⁴ Souza et al., Motor, memory, and anxiety-like behavioral impairments associated with brain-derived neurotrophic factor and dopaminergic imbalance after inhalational exposure to deltamethrin, *Brain Research Bulletin* 181 (2022) 55–64.

²⁵ Liu et al., The relationship between deltamethrin-induced behavioural changes and acetylcholinesterase activity in zebrafish embryos or larvae based on transcriptome, *Front. Vet. Sci.* 11:1526705, 2025.

²⁶ Lei et al., New evidence for neurobehavioral toxicity of deltamethrin at environmentally relevant levels in zebrafish, *Science of the Total Environment* 822 (2022) 153623.

magnitudes lower than recommended for field applications, deltamethrin caused 30% mortality of the queens while also significantly lower numbers of eggs were found in the queens' nests²⁷.

- In a critical review²⁸, authors conclude that acute and chronic exposure of deltamethrin leads to pathophysiology of a broad spectrum of cerebrovascular and neurodegenerative disorders like Parkinson disease, Lou Gehrig's disease, Alzheimer disease, developmental deficits, birth defects, low IQ, pervasive developmental disorder, attention problems and learning disabilities.

2. Neuroendocrine effects.

D. Neuroendocrine effects (thyroid) of animals exposed to deltamethrin:

- An in vitro study on binding of pyrethroids and their common metabolite 3-PBA to thyroid hormones (given their structural similarity). The authors conclude that the generic pyrethroid metabolite, 3-PBA, was able to competitively bind to TTR at low concentrations comparable to human exposure levels, and urinary 3-PBA concentrations were associated with higher fT3 among pregnant women. Thus, displacement of thyroid hormones from TTR by pyrethroids in early pregnancy may disturb the transplacental transport of thyroid hormones to the fetus during a very vulnerable window of development, including neural maturation²⁹.
- Exposure of mice to deltamethrin (6 ppm) for 26 days showed expanded thyroid follicles, scanty colloid and hyperplastic thyroid cells. Western blot results showed that the expression level of tyrosine hydroxylase (TH) protein decreased, and the content of dopamine transporter (DAT) protein increased in DM treated mice striatum. Collectively, the results indicated that deltamethrin exposure could induce thyroid dysfunction and behavioural disorders in adolescent mice³⁰.
- Chronic exposure of crucian carp to deltamethrin (0,6 ug/L) caused lipid metabolism disorder, endocrine disruption, and proinflammatory immune response by upregulating the pla2g4, cox2, log5, ptgis, lcn, and cbr expression. Importantly, the integrative analysis of transcriptomics and metabolomics indicated that the arachidonic acid metabolism pathway and steroid hormone biosynthesis were decisive processes in the brain tissue of crucian carp after Deltamethrin exposure. Furthermore, deltamethrin exposure perturbed the tight junction, HIF-1 signalling pathway, and thyroid hormone signalling pathway³¹.
- For a range of in vitro studies on endocrine disruption with deltamethrin, evidence is provided that a variety of pyrethroids and their metabolites have multiple effects on the endocrine system through interfering with ER, AR, and TR and might disrupt the function of multiple nuclear hormone receptors. This potentially affects the endocrine and the reproductive systems in humans. In the present study, both pyrethroid metabolites, 3-PBA and DCCA, showed antiestrogenic effects with potencies of approximately 100-fold and 1000-fold greater than that of their parent pyrethroids³².

²⁷ Svoboda et al., Low concentrations of acetamiprid, deltamethrin, and sulfoxaflor, three commonly used insecticides, adversely affect ant queen survival and egg laying, Nature Scientific Reports, (2023), 13:14893.

²⁸ Mani et al., Molecular Mechanism of Neurodevelopmental Toxicity Risks of Occupational Exposure of Pyrethroid Pesticide with Reference to Deltamethrin - A Critical Review, BAOJ Pathol 2017, 1: 2.

²⁹ Normann et al., Pyrethroid exposure biomarker 3-phenoxybenzoic acid (3-PBA) binds to transthyretin and is positively associated with free T3 in pregnant women, International Journal of Hygiene and Environmental health, Volume 264, March 2025, 114495.

³⁰ Zhang et al., Exposure to deltamethrin in adolescent mice induced thyroid dysfunction and behavioural disorders, Chemosphere 241 (2020) 125118.

³¹ Wu et al., Effect of chronic deltamethrin exposure on brain transcriptome and metabolome of juvenile crucian carp, Environmental Toxicology. 2024;39:1544–1555.

³² Du et al., Assessing Hormone Receptor Activities of Pyrethroid Insecticides and Their Metabolites in Reporter Gene Assays, TOXICOLOGICAL SCIENCES 116(1), 58–66 (2010).

3. Reprotoxic effects.

E. Effects on testis and reproduction:

- Deltamethrin exposure to pregnant albino rats caused lesions in the kidneys, liver and lungs and reduced the fertility of rats when administered at sub-lethal doses (1 ppm) with no clinical signs of intoxication. Thus, this study suggests that sublethal doses of both insecticides can provide chronic toxicity in humans³³.
- Exposure of rats to deltamethrin (2 ppm, subcutaneous, 1 month) produces an arrest of spermatogenesis, a significant disharmony in sex hormones and MDA levels in rats that is related to dose, length of treatment and to the lipid peroxidation which may be one of the molecular mechanisms involved in Deltamethrin-induced gonads toxicity³⁴.
- Exposure of male Swiss albino mice with deltamethrin (5 ppm) significantly decreased their testosterone and inhibin B levels and affected reproductive performance. The mice showed severe alterations of the seminiferous tubules, sloughing of the germ cells, the vacuolization of germ cell cytoplasm, and the disruption of spermatogenic cells. And conclude that deltamethrin affected the reproductive system of male mice explored by altered total sperm density, motility, and morphology in mice spermatozoa³⁵.
- Exposure of adult Wistar rat by deltamethrin (1 ppm, intraperitoneally, 1 month) caused a significant decrease in the diameter and the epithelium thickness (height) of the seminiferous tubules, associated collapse and distortion at sites of the tubules predominantly in the central region. The data obtained suggest that gonadal (testis) changes could seriously affect the reproductive potential of the rat³⁶.
- Exposure of rats to deltamethrin (5 ppm, 4 weeks) resulted in decreased serum testosterone, luteinizing and follicle-stimulating hormone levels. Testicular total oxidant capacity (TOC), poly (ADP-ribose) polymerase (PARP), lactate dehydrogenase (LDH) and DNA damage were significantly increased. Significant increase in bone marrow chromosomal aberrations, induced by deltamethrin, including chromatid breaks, deletions, fragments and gaps was also observed. RT-PCR demonstrated significant up-regulation in testicular mRNA for glutathione- S -transferase and heat-shockprotein-70 (HSP-70) whereas steroidogenic acute regulatory (StAR) mRNA was down-regulated after deltamethrin exposure³⁷.
- The present meta-analysis indicates that pyrethroid pesticides such as cypermethrin and deltamethrin decrease rat sperm count, sperm motility, and testosterone level and cause abnormal rat sperm morphology. Therefore, pyrethroid pesticides can damage the testis of male rats³⁸.

³³ Ana Janaina J.M. Lemos et al., Effect of sub-lethal doses of *Bacillus thuringiensis* subsp. *Aizawai* and deltamethrin with regard to fertility and organ toxicity in pregnant albino rats, *Experimental and Toxicologic Pathology* 65 (2013) 489–495.

³⁴ Issam et al., Toxic responses to deltamethrin (DM) low doses on gonads, sex hormones and lipoperoxidation in male rats following subcutaneous treatments, *The Journal of Toxicological Sciences (J. Toxicol. Sci.)*, Vol.34, No.6, 663-670, 2009.

³⁵ Ben Slima et al., Endocrine disrupting potential and reproductive dysfunction in male mice exposed to deltamethrin, *Human and Experimental Toxicology* 2017, Vol. 36(3) 218–226.

³⁶ Kumar et al., Histomorphometric study of testis in deltamethrin treated albino rats, *Toxicology Reports* 1 (2014) 401–410

³⁷ Ismael et al., Deltamethrin-induced genotoxicity and testicular injury in rats: Comparison with biopesticide, *Food and Chemical Toxicology* 50 (2012) 3421–3425.

³⁸ Zhong et al., Effect of pyrethroid pesticides on the testis of male rats: A meta-analysis, *Toxicology and Industrial Health* 2021, Vol. 37(4) 229–239.

- Reviews of available epidemiological studies indicated an association between pyrethroid exposure and male infertility. For example, pyrethroid exposure was associated with male reproductive toxicity, and concerns regarding semen quality, sperm DNA, reproductive hormones, pregnancy outcomes, and developmental problems were raised. Other studies also reported poor semen quality, such as low sperm count and abnormal sperm morphology in men exposed to pyrethroids³⁹.

4. Immunotoxicity and other harmful effects⁴⁰

F. Immune dysregulation and other effects on organs.

- Deltamethrin is an immune dysregulator as it has a strong affinity for cluster of differentiation (CD) 4 and CD8 receptors. Deltamethrin exposures decrease splenic T-cell and B-cell populations and suppress cytokines such as IFN- γ , IL-2, and IL-4. Deltamethrin induces brain-derived neurotrophic factor (BDNF) expression by elevating calcium +2 (Ca²⁺) influx in neurons and by phosphorylating extracellular signal-regulated kinases that affect neuronal activity in culture and in the rat brain, indicating the possibility of neuronal hyperexcitation if deltamethrin enters the brain.
- Exposure of Swiss Albino mice to deltamethrin (2,5 ppm) showed that deltamethrin exposure induces lung damage and immune dysregulation via dysregulating the NFAT signalling pathway. The mRNA expression of TCR, IL-4, and IL-13 showed upregulation, while the expression of NFAT and FOS was downregulated following a low dose of deltamethrin⁴⁰.
- Long term exposure of mice by deltamethrin (0,2 ppm) causes damage to the colon tissue. This had two main causes. Deltamethrin promotes oxidative stress in colon epithelial cells by inhibiting PRDX1, leading to apoptosis. In contrast, deltamethrin exerted toxic effects on the colon by affecting the balance of the intestinal flora. These results suggest that the long-term ingestion of agricultural products with deltamethrin residues is likely to have toxic effects on intestinal tissues⁴¹.
- Deltamethrin exposure by subcutaneous injections of female Wistar rats (0,003 ppm) displays harmful effects by disrupting hepatic and renal function and causing DNA damages in pubescent female rats. Low doses of deltamethrin are hepatotoxic and nephrotoxic⁴².

³⁹ Sheikh et al., Androgen receptor signalling and pyrethroids: Potential male infertility consequences, *Front. Cell Dev. Biol.* 11:1173575, 2023.

⁴⁰ Sharma et al., In Vivo Exposure of Deltamethrin Dysregulates the NFAT Signalling Pathway and Induces Lung Damage, *Journal of Toxicology*, Volume 2024, Article ID 5261994, 18 page.

⁴¹ Ma et al., Chronic exposure to low-dose deltamethrin can lead to colon tissue injury through PRDX1 inactivation-induced mitochondrial oxidative stress injury and gut microbial dysbiosis, *Ecotoxicology and Environmental Safety* 264 (2023) 115475.

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