Emergency ban for pesticide deltamethrin needed

Brussels, 26-2-2025

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To: DG SANTE. Ms. Gallina and to the members ScoPAFF.

Concerning: Neuroendocrine effects of the pesticide deltamethrin.

Dear Ms.Gallani, dear pesticide experts, with this letter, we would like to draw your attention to several key new scientific evidence studies on neurotoxicity caused by Deltamethrin insecticide. Despite EU's obligation to review the new available scientific data every 10-15 years, the last review of this substance dates back in 2003. Considering the importance of the new scientific findings on brain development, we kindly urge you to take action and ban this substance.

New research reveals that the pesticide deltamethrin at the current EU regulatory 'No Observed Adverse Effect Level' (NOAEL) of 1 ppm and below causes brain damage in the offspring of exposed pregnant mice that is associated with learning and memory[1]. A related study with exposure of pregnant mice at NOAEL demonstrated damage to a brain region (hippocampus) that could lead, according to its authors, to loss of memory and to autism[2]. These two studies are the culmination of articles in the past few years that show that deltamethrin is extremely harmful for the (human) brain, especially at the developing stage. And at very low doses, below the NOAEL. In the Annex you will find close to 30 independent scientific studies that demonstrate the neuroendocrine effects of Deltamethrin in a range of test animals. These effects have been observed at the current NOAEL (1 ppm) but also far lower, i.e. 0,7 ppm, 0,15 ppm, 0,08 ppm. A safe level has not been not demonstrated and can certainly not be assumed given the serious irreversible adverse effects observed. Authors even conclude that adverse impacts of pyrethroid exposure on neurodevelopment are likely at exposure levels occurring currently in the general population[3].

It is a similar story as with chlorpyrifos which had to be banned with urgency back in 2020[4]. This happened based on a study[5] on brain anomalies and dysfunctions of

[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.
[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.

prenatally exposed children to chlorpyrifos, also after a range of animal studies demonstrated this type of harm. In the present case of deltamethrin and related pyrethroids, epidemiology research has also confirmed the link of pyrethroids to developmental disabilities such as autism[6],[7],[8]. Given the extreme low doses of deltamethrin at which the brain damage is observed, we urge you to immediately start an Art.21 procedure and ban the pesticide to avoid any further damage to the future of our children.

This case again points at the failure of current application dossiers to identify serious neurotoxic effects. Even for an insecticide like deltamethrin. We kindly ask you to include the obligation for all pesticide substances to perform sensitive developmental neurotoxicity animal testing that contains anatomical and behavioural/cognitive endpoints in the data requirements without delay.

Deltamethrin has multiple harmful effects on humans and the environment. A 'Pubmed' search with the search terms 'deltamethrin' and 'toxicity' generated 1270 studies, an astonishing number that cannot be disregarded any longer. Art. 4 of Regulation 1107/2009 obliges the Commission to take decisions based on current scientific insights. And it is remarkable to note that one of the most toxic pesticides used by farmers is not re-evaluated since 2003, 22 years ago! A very serious failure to grant the public and its environment the legally required 'high level of protection'.

Pyrethroids such as deltamethrin target the nervous system of insects primarily by inhibiting voltage-gated sodium channels and other ion channels. Due to similarities in neural function, pyrethroids also have neurotoxic properties in non-target organisms including humans[9]. Since the brain is particularly vulnerable to neurotoxicants during development, exposure in foetal and early life stages may have long-lasting impacts on brain function[10]. Although pyrethroids have rather low acute mammalian toxicity for humans, long-lasting brain dysfunction after prenatal or early postnatal exposure has been demonstrated in animal models. The effects include neurochemical (e.g., alterations in dopamine function) and neurobehavioral alterations (e.g., hyperactivity, and deficits in learning and memory) sometimes with more pronounced effects in males.

Pyrethroids may cross the placenta and have been detected in umbilical cord blood. Pyrethroids and some metabolites, including 3-PBA, have structural resemblance to thyroid hormones, i.e., thyroxine (T4) and triiodothyronine (T3), and they have been suggested to be thyroid hormone disruptors based on experimental studies, both in vivo

[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.

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

[10] Grandjean et al., Neurobehavioral effects of developmental toxicity, The Lancet Neurology, Volume 13, Issue 3, March 2014, Pages 330-338.

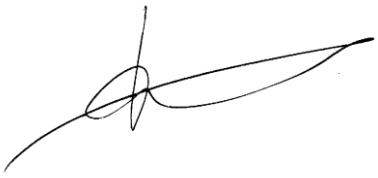
and in vitro[11],[12]. Maintenance of normal thyroid hormone levels is important for numerous physiological processes, including brain development, but pregnancy is an exceptionally vulnerable period, as both the mother and foetus are sensitive to even minor disturbances. Since the human foetus is unable to synthesize thyroid hormones during the first 12 weeks of pregnancy, placental transfer of maternal thyroid hormones plays a pivotal role in early fetal development. Even subtle changes in maternal thyroid hormone function in early pregnancy can affect fetal neural development and maturation.

Neurodevelopment toxicity may affect different aspects of human biology. Indeed, exposure to pyrethroids is also linked to alterations in sexual organ development in adolescents, through alterations in brain regulation of reproduction[13].

Finally, please also note the extreme toxicity of deltamethrin to non-target organisms. Exposure of 1/10 of the deltamethrin dose applied in the fields resulted in 100% mortality of all ants queens and even at 1/1000 of the deltamethrin dose level, mortality of queens was observed[14].

We urge you to act and immediately start a fast track Art. 21 procedure to ensure that the public and its environment get the protection they are granted legally. Deltamethrin should also be prohibited as a biocide, considering the important amounts that are sprayed through aerial spraying for mosquito control in some Member States

We are looking forward to your reaction to this letter.
Sincerely yours,



Hans Muilerman,
Pesticide Action Network Europe,
Brussels.

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[11] 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.

[12] [12] Freire C, Suárez B, Vela-Soria F, Castiello F, Reina-Pérez I, Andersen HR, Olea N, Fernández MF. Urinary metabolites of non-persistent pesticides and serum hormones in Spanish adolescent males. Environ Res. 2021 Jun;197:111016. doi: 10.1016/j.envres.2021.111016. Epub 2021 Mar 23. PMID: 33771511.

[13] 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.

[14] 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 parameters[15].

- 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, circuital, and behavioural vulnerabilities, indicating it is a potential driver in the exposome of autism[16].

- 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 offspring[17].

- 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,

[15] 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.
[16] 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.
[17] 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.

motor and dopaminergic activity systems and might reflect a persistent effect induced by the prenatal exposure to the pyrethroid[18].

- 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 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 offspring[19].

- 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 deficits[20].

- 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 warranted[21].

- 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 neurotoxin[22].

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[18] 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.
[19] 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.
[20] 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.
[21] Andersen et al., Pyrethroids and developmental neurotoxicity - A critical review of epidemiological studies and supporting mechanistic evidence, Environmental Research 214 (2022) 113935.
[22] Pitzer et al., Effects of pyrethroids on brain development and behaviour: Deltamethrin, Neurotoxicology and Teratology 87 (2021) 106983.

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 xenobiotics[23].

- 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 recorded[24].

- 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 cerebellum[25].

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 insecticide[26].

- 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 mice[27].

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[23] 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.
[24] 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.
[25] Patra et al., Neurotoxicological effects of deltamethrin on the postnatal development of cerebellum of rat, J. Biosci., Vol. 22, Number 2, March 1997.
[26] De Boer et al., CHANGES IN PLASMA CORTICOSTERONE AND CATECHOLAMINE CONTENTS INDUCED BY LOW DOSES OF D E L T A M E T H R I N IN RATS, Toxicology, 49 (1988) 263-270.
[27] Koff et al., Early life exposure to deltamethrin impairs synaptic function by altering the brain derived extracellular vesicle proteome, Molecular & Cellular Proteomics (2025).

- 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 plasticity[28].

- 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 larvae[29]. 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 zebrafish[30].

- 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 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' nests[31].

- In a critical review[32], 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. <u>Neuroendocrine effects</u>.

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

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[28] 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.
[29] 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.
[30] Lei et al., New evidence for neurobehavioral toxicity of deltamethrin at environmentally relevant levels in zebrafish, Science of the Total Environment 822 (2022) 153623.
[31] 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.
[32] 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.

- 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 maturation[33].

- 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 mice[34].

- 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 pathway[35].

- 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 pyrethroids[36].

3. Reprotoxic effects.

E. Effects on testis and reproduction:

[33] 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.
[34] Zhang et al., Exposure to deltamethrin in adolescent mice induced thyroid dysfunction and behavioural disorders, Chemosphere 241 (2020) 125118.
[35] Wu et al., Effect of chronic deltamethrin exposure on brain transcriptome and metabolome of juvenile crucian carp, Environmental Toxicology. 2024;39:1544–1555..
[36] Du et al., Assessing Hormone Receptor Activities of Pyrethroid Insecticides and Their Metabolites in Reporter Gene Assays, TOXICOLOGICAL SCIENCES 116(1), 58–66 (2010).

- 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 humans[37].

- 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 toxicity[38].

- Exposure of male Swiss al bino 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 spermatozoa[39].

- 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 rat[40].

- 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 exposure[41].

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[37] 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.

[38] 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.

[39] 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.

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

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

- 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 rats[42].

- 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 pyrethroids[43].

4. Immunotoxicity and other harmful effects.

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-c, IL-2, and IL-4 . Deltamethrin induces brain-derived neurotrophic factor (BDNF) expression by elevating calcium +2 (Ca +2) 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 deltamethrin[44].

- 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 tissues[45].

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[42] 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.
[43] Sheikh et al., Androgen receptor signalling and pyrethroids: Potential male infertility consequences, Front. Cell Dev. Biol. 11:1173575, 2023.
[44] 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.
[45] 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.

- 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 nephrotoxic[46].

[46] Chargui et al., Oxidative Stress, Biochemical and Histopathological Alterations in the Liver and Kidney of Female Rats Exposed to Low Doses of Deltamethrin: A Molecular Assessment, Biomed Environ Sci, 2012; 25(6): 672-683.