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Betreft: Verzoek intrekking alle bestrijdingsmiddelen op basis van de actieve stof deltamethrin.

Assen, 13 maart 2025.

Geacht College,

Hierbij verzoeken wij u te besluiten de 13 (gewasbeschermings)middelen die u hebt toegelaten met als werkzame stof deltamethrin[1] in te trekken. Wij hebben vastgesteld dat aan Art. 29.1.e van Verordening 1107/2009 niet wordt voldaan waardoor intrekking op grond van art. 44, derde lid van die Verordening geboden is.

Nieuw onderzoek toont aan dat het pesticide deltamethrin bij de huidige Europese/nationale '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 geheugen[2]. 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 autisme[3]. Deze twee onderzoeken zijn het voorlopige 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, ver onder de NOAEL. In de bijlage vindt u bijna 30 onafhankelijke wetenschappelijke studies 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, 0,08 en 0,014 ppm. Een veilig niveau is niet aangetoond en kan ook zeker niet worden aangenomen gezien de ernstige onomkeerbare bijwerkingen die zijn waargenomen. Auteurs concluderen zelfs dat nadelige effecten van blootstelling aan pyrethroïden op de neurologische ontwikkeling waarschijnlijk zijn bij blootstellingsniveaus die momenteel voorkomen in de algemene bevolking[4]. Andere auteurs[5] bevestigen de schadelijke neurocognitieve effecten van pyrethroïden bij werknemers in de landbouw.

[1] Van 'Decis' tot en met "Luxan Delete Spray", zie: https://toelatingen.ctgb.nl/nl/authorisations
[2] Koff et al., Early life exposure to deltamethrin impairs synaptic function by altering the brain derived extracellular vesicle proteome, Molecular & Cellular Proteomics (2025).
[3] 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.
[4] Andersen et al., Pyrethroids and developmental neurotoxicity - A critical review of epidemiological studies and supporting mechanistic evidence, Environmental Research 214 (2022) 113935
[5] Hansen et al., Neurological Deficits After Long-term Pyrethroid Exposure, Environmental Health Insights Volume 11: 1–11, 2017.

Art. 29.1.e van de Verordening stelt als voorwaarde voor een toelating dat voldaan is aan Art. 4(3) van de Verordening. Art. 4(3) vereist dat er geen onmiddellijk of vertraagd schadelijk effect op de menselijke gezondheid zal optreden, met inbegrip van die van kwetsbare groepen. En dat dit moet worden vastgesteld in het licht van de huidige wetenschappelijke en technische inzichten. De studies die wij aandragen vormen de meest recente wetenschappelijke inzichten en laten er geen twijfel over bestaan dat blootstelling aan deltamethrin bij de huidige door u gehanteerde 'veilige waarde', en zelfs ruim daaronder, schadelijke effecten (onder meer hersenschade) veroorzaakt bij het nageslacht. De toelatingen kunnen dus niet in stand blijven en dienen direct ingetrokken te worden.

De voortdurende stroom aan wetenschappelijke studies over de schadelijke neurotoxische effecten van deltamethrin geven ons een 'déjà vu'. Een soortgelijk verhaal is er te vertellen als over de stof chloorpyrifos die in 2020 met spoed verboden moest worden[6]. Dat gebeurde op basis van een onderzoek naar hersenafwijkingen en disfuncties van prenataal blootgestelde kinderen aan chloorpyrifos[7], en ook hier nadat een reeks dierstudies dit type schade al jarenlang aantoonde. In het huidige geval van deltamethrin en verwante pyrethroïden heeft (ten overvloede) epidemiologisch onderzoek het verband tussen pyrethroïden en ontwikkelingsstoornissen zoals autisme bevestigd[8],[9],[10]. Tot nu toe is er weggekeken door de verantwoordelijke overheden bij die effecten. Gezien de extreem lage doses deltamethrin waarbij hersenschade wordt waargenomen kan dit niet langer en dringen wij er bij u op aan de 13 middelen onmiddellijk in te trekken om verdere schade aan toekomstige generaties te voorkomen.

Deze zaak legt opnieuw het falen bloot van de huidige aanvraagdossiers bij de identificatie van ernstige neurotoxische effecten. Wij verzoeken u vriendelijk in Brussel ervoor te pleiten onverwijld een verplichting voor alle pesticiden op te nemen in de gegevensvereisten om gevoelige ontwikkelings-neurotoxiciteits dierproeven uit te voeren met anatomische en gedragsmatige/cognitieve eindpunten.

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 het Ctgb om beslissingen te nemen op basis van de huidige wetenschappelijke inzichten. En het is opmerkelijk om te zien dat een van de meest giftige pesticiden die door boeren wordt gebruikt, sinds 2003, 22 jaar geleden, niet opnieuw is beoordeeld! Een zeer ernstig falen om het publiek en zijn omgeving het wettelijk vereiste 'hoge niveau van bescherming' te bieden. In recente uitspraken van het Europese Hof[11],[12] wordt gesteld dat het beschouwen en beoordelen van de huidige wetenschappelijke en technische inzichten cruciaal is en er juist voor kan zorgen dat het doel van de Verordening, een hoog niveau van bescherming, wordt nagestreefd[13].

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.

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[6] https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1578929027090&uri=CELEX:32020R0018

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

[8] 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

[9] 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.

[10] 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.

[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A62022CJ0309&qid=1738576901784

[12] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A62022CA0308&qid=1738577102420

[13] Case C-308/22, paragraph 103: The possibility of submitting to the authorities and courts of the Member State concerned referred to in Article 36(2) of that Regulation all relevant, reliable and up-to-date scientific and technical knowledge for the purpose of authorizing a plant protection product in the territory of that Member State contesting contributes to the achievement of that goal, taking into account the precautionary principle.

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 neurogedragsveranderingen (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 schildklierhormoonspiegels 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 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 pyrethroïden is namelijk ook gekoppeld aan veranderingen in de ontwikkeling van geslachtsorganen bij adolescenten, via veranderingen in de hersenregulatie van de voortplanting[14].

Deltamethrin kan een scala aan negatieve gezondheidseffecten veroorzaken, niet alleen neurotoxiciteit. In de bijlage (hoofdstuk 2) treft u onderzoek aan dat aantoont dat deltamethrin en zijn metaboliet 3-PBA via binding aan schildklierhormonen neurotoxische effecten veroorzaken en dus als hormoonverstorende stof fungeren. Een hormoonverstorend pesticide kan niet toegelaten blijven vanwege het uitsluitingsprincipe in de Verordening.

Deltamethrin kan tegelijk schadelijke effecten veroorzaken op de voortplanting. In de bijlage (hoofdstuk 3) wordt aangetoond dat deltamethrin bij blootstelling van proefdieren vruchtbaarheidsproblemen kan veroorzaken bij subletale doses. Ook kan er hormoonverstoring optreden (testosteron) met als gevolg problemen met de spermatogenese.

Voor deltamethrin is in proefdierstudies ook aangetoond dat het immunotoxisch is (hoofdstuk 4 van de bijlage). Het aantal B- en T-cellen gaan achteruit met mogelijk een indirect effect op de neuronen in de hersens. Naast verstoring van het immuunsysteem zijn in proefdieren nog diverse andere schadelijke effecten aangetoond, op de longen, op de dikke darm, lever en nieren. Om al deze redenen dienen de middelen met onmiddellijke ingang te worden verboden.

Naast effecten op de menselijke gezondheid bepaalt de Verordening ook in Art. 4(3) dat er geen onaanvaardbare effecten mogen optreden voor niet-doelwit organismen. In verband hiermee wijzen u 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 waargenomen[15]. Schadelijke effecten op de hersenen zijn ook waargenomen in zebravis studies (bijlage,

[14] 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.

[15] 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.

hoofdstuk 1C), terwijl bij kevers bij zeer lage doses (0,014 ppm) hersenen, darmen en seksuele klieren zijn aangetast[16]. Ook om deze redenen moet deltamethrin ingetrokken worden.

Wij dringen er bij u op aan met spoed om actie te ondernemen. En te besluiten tot intrekking van de 13 gewasbeschermingsmiddelen met de werkzame stof deltamethrin om ervoor te zorgen dat het publiek en het milieu de bescherming krijgt die de Verordening hen heeft gegarandeerd.

Wij kijken uit naar uw reactie,

Hoogachtend,

Namens PAN-NL

M. Mantingh
06 12532813

[16] Pandya et al., Toxic effects of deltamethrin on oxidative stress, behavioural, organosomatic indices and histopathological changes in *Digitonthophagus gazella* (Coleoptera: Scarabaeinae), Environmental Toxicology and Pharmacology, Volume 114, March 2025, 104642.

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[17].

- 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[18].

- 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[19].

- 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 pyrethroid[20].

- 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

[17] 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.
[18] 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.
[19] 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.
[20] 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 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[21].

- 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[22].

- 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[23].

- 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[24].

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[25].

- 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[26].

- 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

[21] 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.
[22] 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.
[23] Andersen et al., Pyrethroids and developmental neurotoxicity - A critical review of epidemiological studies and supporting mechanistic evidence, Environmental Research 214 (2022) 113935.
[24] Pitzer et al., Effects of pyrethroids on brain development and behaviour: Deltamethrin, Neurotoxicology and Teratology 87 (2021) 106983.
[25] 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.
[26] 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.

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[27].

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[28].
- 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[29].
- 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[30].
- 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[31]. 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[32].
- 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[33].

[27] Patra et al., Neurotoxicological effects of deltamethrin on the postnatal development of cerebellum of rat, J. Biosci., Vol. 22, Number 2, March 1997.
[28] 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.
[29] Koff et al., Early life exposure to deltamethrin impairs synaptic function by altering the brain derived extracellular vesicle proteome, Molecular & Cellular Proteomics (2025).
[30] 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.
[31] 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.
[32] Lei et al., New evidence for neurobehavioral toxicity of deltamethrin at environmentally relevant levels in zebrafish, Science of the Total Environment 822 (2022) 153623.
[33] 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.

- In a critical review[34], 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 maturation[35].

- 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[36].

- 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[37].

- 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[38].

3. Reprotoxic effects.

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

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 humans[39].

- 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[40].

- 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[41].

- 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[42].

- 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[43].

- 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[44].

- 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

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reported poor semen quality, such as low sperm count and abnormal sperm morphology in men exposed to pyrethroids[45].

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[46].

- 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[47].

- 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[48].

- Deltamethrin exposure of the beetle *Digitonthophagus gazella* had profound and irreversible pathological consequences on various vital organs and systems in D. gazella, affecting reproduction and nesting[49]. Exposure at very low doses (0,014 ppm) caused significant down regulation of *cyp4g7*, *cyp6bq9*, and *cyp4q4* expression indicates enhanced oxidative stress. Additionally, a reduction in the organosomatic index, accompanied by histological changes in the brain, gut, and gonads, suggests potential functional disturbances.

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