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Neonicotinoid Exposure and Reproductive Dysfunction: Mechanisms and Evidence

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Abstract:

Background: Neonicotinoids are a widely used class of insecticides introduced in the 1990s, primarily valued for their selective toxicity to insect nervous systems. However, mounting evidence suggests that these compounds are not as innocuous to non-target species, including humans, as once thought. Concerns about their persistence in the environment and their detection in human tissues have spurred investigation into their potential systemic health impacts, particularly reproductive toxicity.

Objective: This review synthesizes current evidence on the reproductive effects of neonicotinoid pesticide exposure and elucidates the underlying toxicological mechanisms responsible for reproductive dysfunction across genders and species.

Methods: A comprehensive analysis of published literature from 2000 to 2024 was conducted using electronic databases such as PubMed, Scopus, and Web of Science. Studies were selected based on relevance to neonicotinoid exposure, reproductive endpoints, and mechanistic insights. Animal model, in vitro, and limited human epidemiological studies were included.

Results: Neonicotinoids exert reproductive toxicity through several mechanisms, including endocrine disruption, oxidative stress, apoptosis, and hormonal imbalance. In males, exposure is associated with decreased sperm count, motility, and testosterone levels, along with histopathological changes in testicular tissue. In females, alterations in estrous cycles, folliculogenesis, and hormonal profiles have been observed, often resulting in reduced fertility. Developmental and transgenerational effects—such as fetal growth retardation and epigenetic modifications—further exacerbate concerns. Comparative studies show that imidacloprid and clothianidin are particularly potent in disrupting reproductive function. While mechanistic data in animal models are robust, human studies are sparse but indicate possible associations with adverse reproductive outcomes in high-exposure populations.

Conclusion: The evidence implicates neonicotinoids as potential reproductive toxicants with multisystemic effects. There is an urgent need for longitudinal human studies, regulatory reassessment, and mitigation strategies to minimize exposure, particularly in vulnerable populations such as pregnant women and agricultural workers.

Keywords: Neonicotinoids, reproductive toxicity, endocrine disruption, sperm quality, ovarian dysfunction, imidacloprid, clothianidin, oxidative stress, developmental toxicity.

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Introduction

The exponential growth of agricultural productivity in the modern era has been largely supported by the widespread application of synthetic pesticides. Among these, neonicotinoids—a class of neuro-active insecticides chemically similar to nicotine—have garnered global usage due to their systemic properties and relative selectivity for insect nicotinic acetylcholine receptors (nAChRs) over mammalian ones. Introduced in the early 1990s, neonicotinoids such as imidacloprid, clothianidin, thiamethoxam, and acetamiprid are now among the most frequently applied insecticides worldwide, used in crop production, seed treatments, veterinary medicine, and household pest control [1–3].

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Although initially considered safer alternatives to older pesticide classes like organophosphates and carbamates, recent evidence challenges the benign profile of neonicotinoids. Increasing reports suggest that these compounds persist in the environment, bioaccumulate, and exert sub-lethal effects on non-target organisms, including humans. Their detection in food items, water sources, and even human biological fluids has raised concerns about chronic exposure and associated health risks [4–6].

Of growing concern is the potential impact of neonicotinoids on reproductive health. Several studies in animal models and in vitro systems indicate that these compounds may act as endocrine disruptors, interfere with steroidogenesis, induce oxidative stress, and impair gametogenesis [7–9]. Furthermore, prenatal and early-life exposures have been linked to developmental toxicity and transgenerational effects [27–31]. Despite the accumulating preclinical evidence, epidemiological data in humans remain limited and inconclusive, warranting further investigation [35–37].

The aim of this review is to critically examine the available evidence on the reproductive toxicity of neonicotinoid pesticides and to explore the underlying biological mechanisms of action. Specifically, this review seeks to summarize the current knowledge on the exposure pathways of neonicotinoids in both humans and animals, providing insight into how these compounds enter biological systems. It further aims to review mechanistic evidence detailing how neonicotinoid exposure leads to reproductive dysfunction, including endocrine disruption, oxidative stress, and hormonal alterations. Additionally, the review compares the toxicological profiles of commonly used neonicotinoids, such as imidacloprid, clothianidin, and acetamiprid, to identify differences in their reproductive impact. Finally, it highlights existing research gaps and offers recommendations for future investigations and public health policy, emphasizing the need for improved risk assessment and regulatory oversight.

1. Neonicotinoids: Classification and Global Use:

Neonicotinoids are classified into several generations based on their chemical structure and target receptor binding affinity. The major compounds include imidacloprid, thiamethoxam, clothianidin, acetamiprid, and dinotefuran. These substances act on insect nAChRs, causing persistent activation that leads to paralysis and death. Their systemic action allows them to be absorbed by plants and distributed throughout tissues, including pollen and nectar [1].

Their widespread use in agriculture and other settings has resulted in substantial environmental distribution. Imidacloprid and thiamethoxam are among the top insecticides used globally, especially in crops such as corn, soybeans, and fruits [2]. Despite partial restrictions in regions like the European Union, their usage continues in other parts of the world [3].

Table 1. Classification of Neonicotinoid Insecticides and Their Key Characteristics

Chemical Class	Generation	Representative Compounds	Mode of Action	Systemic Properties	Primary Usage
Nitroguanidines	1st Generation	Imidacloprid, Thiamethoxam, Clothianidin	Bind strongly to insect nicotinic acetylcholine receptors (nAChRs), leading to persistent activation and neural overstimulation [1]	Highly systemic, translocated throughout plant tissues including nectar and pollen	Widely used in agriculture (e.g., corn, soybean, cotton, fruits) [2]
Cyanoamidines	2nd Generation	Acetamiprid, Thiacloprid	Similar action on nAChRs, but lower binding affinity; considered moderately toxic to mammals	Systemic, though less persistent than nitroguanidines	Used in vegetables, fruits, ornamentals; also applied in veterinary and household products [1,3]
Tetrahydrofuryl Compounds	Newer	Dinotefuran	Rapidly absorbed and fast-acting; lower mammalian toxicity profile	Highly water-soluble, quickly translocated	Applied in both agricultural and urban pest control settings [3]

2. Human and Environmental Exposure Pathways:

Humans are exposed to neonicotinoid insecticides through multiple routes, including dietary intake, contaminated drinking water, occupational contact, and residential or domestic use. Among these, dietary exposure is the most common and significant pathway for the general population. Due to the systemic nature of neonicotinoids, these compounds are absorbed by plants and distributed throughout all parts of the plant—including leaves, stems, flowers, pollen, nectar, and fruits—leading to their presence in raw agricultural commodities and processed food products [4]. Residues of neonicotinoids such as imidacloprid and acetamiprid have been frequently detected in fruits, vegetables, cereals, honey, and tea, even after washing or cooking, indicating their persistence through food processing.

Drinking water contamination is another concern, particularly in areas of intensive agricultural activity. Neonicotinoids are highly water-soluble, enabling them to leach from treated fields into nearby groundwater and surface water systems. Once in aquatic environments, they are resistant to degradation and can persist for weeks to months, posing risks to both aquatic organisms and human populations relying on these water sources [6]. Routine monitoring studies in countries like the United States, Canada, and parts of the European Union have confirmed the presence of neonicotinoids in tap and well water at levels that sometimes exceed regulatory safety thresholds.

Occupational exposure occurs in agricultural workers, pesticide applicators, and greenhouse laborers who handle neonicotinoid formulations directly. Exposure can take place via inhalation of aerosols, dermal absorption through the skin, or accidental ingestion. Individuals working in pesticide manufacturing or seed treatment facilities may also be at elevated risk due to chronic, low-level exposure[5]. Protective measures are often inconsistent across regions, especially in low- and middle-income countries.

Residential exposure, while typically lower than occupational exposure, can still contribute to overall body burden. Neonicotinoid-based insecticides are commonly used in household pest control products, flea and tick treatments for pets, and garden sprays. Indoor use can result in prolonged contact through contaminated surfaces, air, and dust, particularly affecting children and other vulnerable groups.

Biomonitoring studies have provided direct evidence of human exposure. For instance, population-based studies in Japan and the United States have detected neonicotinoid metabolites such as N-desmethyl-acetamiprid and 6-chloronicotinic acid in the urine of both adults and children [6]. These findings suggest not only widespread exposure but also the possibility of continuous, low-dose accumulation in the body. Importantly, some studies have correlated urinary metabolite levels with neurological symptoms and hormonal changes, highlighting potential health risks that warrant further investigation[7].

3. Mechanisms of Reproductive Toxicity:

3.1 Endocrine Disruption

Neonicotinoids have shown the potential to interfere with the endocrine system, particularly the hypothalamic-pituitary-gonadal (HPG) axis. They can mimic or block natural hormones, leading to disrupted feedback mechanisms. In animal studies, clothianidin and imidacloprid exposure resulted in altered levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), disrupting spermatogenesis and ovulation [8].

3.2 Oxidative Stress and Apoptosis

Oxidative stress is a well-documented mechanism of toxicity for many pesticides. Neonicotinoids induce the generation of reactive oxygen species (ROS) that damage cellular components, including lipids, proteins, and DNA. This can lead to apoptosis in reproductive cells, impairing testicular and ovarian function [11].

3.3 Hormonal Alterations

Chronic exposure has been associated with decreased testosterone and estrogen levels in rodents. Imidacloprid and thiamethoxam interfere with steroid biosynthesis, likely through downregulation of key enzymes involved in hormone production [14].

4. Effects on Male Reproductive System

4.1 Sperm Morphology and Function

Neonicotinoid exposure in male rats and mice has led to significant reductions in sperm count, motility, and viability. Morphological abnormalities, such as head and tail defects, have also been observed [15].

4.2 Testicular Histopathology

Histological evaluations reveal degeneration of seminiferous tubules, reduction in germ cell layers, and increased interstitial space in testicular tissue following exposure to imidacloprid and acetamiprid [18].

4.3 Steroidogenesis Disruption

Studies confirm that neonicotinoids impair Leydig cell function and testosterone production. This is primarily attributed to downregulation of steroidogenic acute regulatory (StAR) protein and other key enzymes [20].

5. Effects on Female Reproductive System

5.1 Ovarian Function and Follicular Development

Female rodents exposed to imidacloprid and other neonicotinoids show disrupted estrous cycles, decreased

follicle counts, and abnormal folliculogenesis. There is also evidence of increased follicular atresia [22].

5.2 Fertility Outcomes and Menstrual Irregularities

Exposure has been linked to reduced mating success, lower implantation rates, and altered menstrual cycle parameters. Hormonal profiling indicates suppression of estrogen and progesterone [25].

5.3 Embryonic and Fetal Development

Prenatal exposure to neonicotinoids in animal models has resulted in fetal growth retardation, congenital anomalies, and postnatal neurodevelopmental impairments [27].

6. Transgenerational and Developmental Toxicity:

Emerging research highlights the potential for neonicotinoids to induce epigenetic modifications that may have lasting consequences across generations. Unlike direct toxicity, which affects only the exposed individual, epigenetic changes can alter gene expression without changing the DNA sequence and may be heritable through germline transmission. These modifications include DNA methylation, histone modification, and alterations in non-coding RNA expression—mechanisms that regulate critical developmental and reproductive pathways[28].

In experimental studies using zebrafish and rodent models, exposure to neonicotinoids such as imidacloprid and clothianidin has been linked to persistent reproductive dysfunction not only in the directly exposed animals but also in their offspring and subsequent generations [30]. In zebrafish, early-life exposure to low doses of neonicotinoids led to reduced sperm motility, impaired oocyte development, and abnormal sex hormone levels in progeny. Rodent studies have reported similar outcomes, including reduced fertility indices, increased rates of embryonic resorption, and disrupted spermatogenesis in F1 and F2 generations[29].

These effects suggest that neonicotinoids may interfere with the epigenetic reprogramming that normally occurs during gametogenesis and early embryonic development. For example, male offspring of exposed rodents often exhibit altered expression of genes involved in steroidogenesis, oxidative stress response, and cell cycle regulation—changes that may result from modifications in promoter methylation patterns[30].

The implications of these findings are profound. If such heritable effects also occur in humans, populations exposed to neonicotinoids could face reproductive challenges that extend beyond the current generation. Moreover, these epigenetic disruptions could interact with other environmental and lifestyle factors, compounding their impact on public health[31].

Thus, transgenerational toxicity represents a critical dimension of neonicotinoid risk assessment. It calls for more comprehensive studies using multigenerational animal models and advanced molecular tools to elucidate epigenetic mechanisms. Regulatory frameworks should also consider long-term reproductive risks in addition to immediate toxicity, especially when setting safety thresholds for chronic low-dose exposure.

7. Comparative Toxicology of Neonicotinoids:

Comparative studies show that imidacloprid and clothianidin are among the most toxic to reproductive endpoints. Acetamiprid, although considered milder, still exhibits significant effects at higher doses. Toxicity appears dose-dependent and varies with route and duration of exposure [32].

Table 2. Comparative Toxicology of Neonicotinoids on Reproductive Health Parameters

Compound	Relative Toxicity	Key Reproductive Effects	Dose-Dependency	Notable Studies
Imidacloprid	High	↓ Sperm count and motility, ↓ Testosterone, testicular degeneration, altered estrous cycle	Strong dose-response relationship observed	[30], [32], [33]
Clothianidin	High	Testicular apoptosis, hormonal imbalance, ↓ fertility rate, ovarian follicle atresia	Toxic effects intensified with dose/time	[30], [34]
Acetamiprid	Moderate	Endocrine disruption, ↓ sperm viability, delayed sexual maturity at high doses	Significant effects at higher exposures	[32], [35]
Thiamethoxam	Moderate	Leydig cell damage, ↓ estradiol and LH, testicular weight loss	Less toxic than imidacloprid, still dose-dependent	[33], [36]
Dinotefuran	Low to Moderate	Mild hormonal alterations, ↓ oocyte quality in long-term exposures	Relatively safer; mild effects at high doses	[32], [37]

8. Epidemiological Evidence in Human Populations:

Despite extensive experimental data on the reproductive toxicity of neonicotinoids in animal models, epidemiological studies directly investigating these effects in human populations remain limited. This scarcity is partly due to challenges in accurately assessing long-term exposure, the complexity of mixed chemical environments, and variability in individual susceptibility[33]. However, emerging research from agricultural and pesticide-exposed communities suggests possible links between neonicotinoid exposure and adverse reproductive outcomes.

Several biomonitoring studies have measured urinary metabolites of neonicotinoids, such as N-desmethyl-acetamiprid and 6-chloronicotinic acid, as biomarkers of exposure in both adults and children [34]. These studies demonstrate widespread and chronic exposure even in non-occupational populations, highlighting the pervasive presence of these chemicals in the environment.

More specifically, a few observational studies conducted in farming regions with intensive pesticide use have reported correlations between elevated urinary neonicotinoid metabolite levels and alterations in reproductive hormone profiles. For example, changes in circulating testosterone, luteinizing hormone (LH), and estradiol levels have been documented, suggesting endocrine disruption that could impair fertility and sexual development[35].

Furthermore, epidemiological data have indicated an association between maternal neonicotinoid exposure and adverse birth outcomes. In some agricultural communities, higher exposure levels were linked to increased risks of low birth weight, preterm delivery, and congenital anomalies. Although causality cannot be firmly established due to confounding factors, these findings raise concern about the potential impact of neonicotinoids on reproductive health at the population level[36].

Occupational studies of agricultural workers exposed to neonicotinoid pesticides have also reported increased incidences of fertility issues, including reduced sperm quality and irregular menstrual cycles, though these results are often complicated by concurrent exposure to other pesticides[37].

9. Regulatory Status and Risk Assessment:

Several regulatory agencies have evaluated neonicotinoid risks. The European Union has banned or restricted key compounds like imidacloprid, citing environmental and potential human health risks [38]. In contrast, the United States maintains conditional registrations pending further data [39]. The WHO emphasizes the need for updated risk assessments considering chronic exposure and vulnerable populations [40].

10. Conclusion and Research Perspectives:

Neonicotinoids, while instrumental in pest control, pose significant risks to reproductive health across species. Their mechanisms of toxicity include endocrine disruption, oxidative stress, and hormonal imbalance. While animal studies provide robust evidence, human data remain limited. Future research should prioritize longitudinal cohort studies and biomonitoring programs. Policymakers must consider this growing body of evidence to ensure appropriate regulations and protect vulnerable populations.

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