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Toxicidade do imidacloprido sobre o desenvolvimento embriológico de roedores

Embryonic developmental toxicity of imidacloprid in rodents

Toxicidad del imidacloprid en el desarrollo embrionario de roedores

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RESUMO
Objetivo: compreender como o uso do neonicotinoide imidacloprido promove efeitos transgeracionais em modelos animais. **Método:** trata-se de uma revisão narrativa da literatura, fundamentada na análise de estudos experimentais que investigaram a exposição ao imidacloprido, com ênfase em períodos críticos do desenvolvimento, especialmente a fase embrionária, e seus desfechos ao longo do ciclo vital e em gerações subsequentes. **Resultados:** embora o imidacloprido tenha sido desenvolvido e comercializado como seguro para humanos devido à sua maior afinidade por neurorreceptores nicotínicos de insetos, os estudos analisados evidenciam preocupações relevantes quanto à exposição e aos danos em organismos não alvo. Os dados indicam que a exposição embrionária ao imidacloprido pode induzir comprometimentos à saúde na idade adulta e efeitos transgeracionais, abrangendo alterações metabólicas, reprodutivas, imunológicas, comportamentais e teratogênicas, observadas tanto nas gerações parentais quanto nas descendentes. **Considerações finais:** a revisão evidencia riscos potenciais à saúde associados à exposição a neonicotinoides, especialmente durante janelas críticas do desenvolvimento, reforçando a necessidade de métodos de avaliação mais padronizados e de regulamentações de segurança mais rigorosas, com vistas à mitigação dos riscos para humanos e para espécies não alvo.

DESCRITORES: Educação permanente em saúde; Profissionais de saúde; Hospitais.

ABSTRACT
Objective: to understand how the use of the neonicotinoid imidacloprid promotes transgenerational effects in animal models. **Method:** this is a narrative literature review based on the analysis of experimental studies that investigated exposure to imidacloprid, with emphasis on critical periods of development, especially the embryonic stage, and their outcomes throughout the life cycle and in subsequent generations. **Results:** although imidacloprid was developed and marketed as safe for humans due to its greater affinity for nicotinic receptors in insects, the studies analyzed reveal relevant concerns regarding exposure and damage to non-target organisms. The data indicate that embryonic exposure to imidacloprid may induce health impairments in adulthood and transgenerational effects, including metabolic, reproductive, immunological, behavioral, and teratogenic alterations, observed in both parental and descendant generations. **Final considerations:** this review highlights potential health risks associated with exposure to neonicotinoids, particularly during critical windows of development, reinforcing the need for more standardized assessment methods and stricter safety regulations to mitigate risks to humans and non-target species.
DESCRIPTORS: Neonicotinoids; Transgenerational effects; Environmental exposure; Metabolic alterations; Reproductive changes; Mammalia.

RESUMEN
Objetivo: comprender cómo el uso del neonicotinoide imidacloprid promueve efectos transgeneracionales en modelos animales. **Método:** se trata de una revisión narrativa de la literatura, basada en el análisis de estudios experimentales que investigaron la exposición al imidacloprid, con énfasis en períodos críticos del desarrollo, especialmente la etapa embrionaria, y sus desenlaces a lo largo del ciclo vital y en generaciones posteriores. **Resultados:** aunque el imidacloprid fue desarrollado y comercializado como seguro para los seres humanos debido a su mayor afinidad por los receptores nicotínicos de los insectos, los estudios analizados evidencian preocupaciones relevantes respecto a la exposición y a los daños en organismos no objetivo. Los datos indican que la exposición embrionaria al imidacloprid puede inducir deterioros en la salud en la edad adulta y efectos transgeneracionales, que incluyen alteraciones metabólicas, reproductivas, inmunológicas, conductuales y teratogénicas, observadas tanto en las generaciones parentales como en las descendientes. **Consideraciones finales:** la revisión pone de manifiesto riesgos potenciales para la salud asociados a la exposición a neonicotinoides, especialmente durante ventanas críticas del desarrollo, y refuerza la necesidad de métodos de evaluación más estandarizados y de regulaciones de seguridad más estrictas para mitigar los riesgos para los seres humanos y las especies no objetivo.
DESCRIPTORES: Neonicotinoides; Efectos transgeneracionales; Exposición ambiental; Alteraciones metabólicas; Cambios reproductivos; Mamíferos.

INTRODUCTION

The global expansion of agricultural practices has led to a substantial increase in the use of pesticides, including neonicotinoid compounds, which are used to control insects deemed pests in agriculture and domestic animals (Shattuck 2021). Due to their chemical structure resembling nicotine and interaction with nicotinic acetylcholine receptors (nAChRs), these pesticides primarily target the insect's nervous system causing paralysis and eventual death (Casida 2018).

Due to differences in the structures of nAChRs of vertebrates and insects, neonicotinoids were introduced to the commercial market promising to be less toxic to vertebrates (Sheets 2005). However, recent studies showed adverse effects in mammals - and even in humans, like metabolic (Yan et al. 2020), gastrointestinal (Nedzvetsky et al. 2021), and respiratory disorders (Kaur et al. 2024), skin diseases (Shi et al. 2016), memory loss (Tasman et al. 2021), and kidney failure (Zhang et al. 2024). These compounds are broadly marketed (Hladik et al. 2018) resulting in high exposure to humans through the ingestion of contaminated fruits, vegetables, and water (Wood and Goulson 2017; Han et al. 2018).

Imidacloprid (IMI) was the first neonicotinoid insecticide and has been exponentially used worldwide since 1991 (Elbert et al. 1991), even though it is restricted in some countries (EFSA 2013a, 2018). Due to its intense use, IMI residues have been found in the environment (Han et al. 2018; Borsuah et al. 2020; Mörtl et al. 2020) and can be biomagnified through the food chain to primary and secondary consumers (Tison et al. 2024), and even in human biological samples (Zhang and Lu 2022; Ottenbros et al. 2023). The implications for human health vary according to the way of exposure, with potentially greater severity during fetal development and lactation. Excessive contact with neonicotinoids, particularly during these periods, may induce epigenetic effects that persist throughout life and can be transmitted to subsequent generations (Grilo et al. 2021).

The European Food Safety Authority (EFSA 2019) established a list of potentially safe maximum limits for consumers, crops, and animals exposed to IMI, ranging depending on the product type. Although there are safety limits for IMI, it's important to note that these limits vary among countries (EFSA 2019; ANVISA 2023; EPA 2024). For instance, the permissible levels for IMI residues in surface water differ significantly among Canada, the European Union (EU), and the United States (US), highlighting considerable uncertainty and regulatory challenges, and hindering the establishment of consistent safety limits to effectively mitigate the risks associated with IMI exposure (Stehle et al. 2023). Scientific literature provides substantial information on IMI safe use and regulated risk assessments regarding acute and chronic toxicity tests in various species, including LOAEL (lowest observable adverse effect level), NOAEL (no observable adverse effect level), and LD (lethal doses) (EFSA 2013b). The lack of standardization in assessment methods can lead to a greater environmental contamination, the potential omission of sensitive species, and elevated regulatory thresholds that are not sufficiently protective (Stehle et al. 2023).

A concept that has been the focus of numerous contemporary studies since Barker's (1998) description of intrauterine events and postnatal diseases, now termed Developmental Origins of Health and Disease (DOHaD) (Lacagnina 2020), IMI can also cause toxicity in tissues of non-target organisms (Han et al. 2018; Thompson et al. 2020; Hassanen et al. 2022).

We aim to review the scientific literature on the use of the neonicotinoid IMI in animal models and to synthesize the evidence regarding its transgenerational effects and damages. We hypothesized that early exposure to IMI could induce health impairments in experimental animal models during adulthood and potentially be transmitted to subsequent generations.

METHODOLOGY

An extensive literature search was conducted across three indexed article databases (PubMed, Scopus, and Web of Science) and a gray literature database (Google Scholar) from May 7 to May 27, 2024. We systematically searched for terms tailored to the standards of each database ensuring coverage of relevant studies on the effects of IMI exposure during critical developmental stages in rodents. The searched terms were:

Fetus OR fetal OR offspring OR neonatal OR uterus OR gestation OR lactation OR pregnancy OR pregnant OR newborn AND imidacloprid AND rat OR Fetus OR fetal OR offspring OR neonatal OR uterus OR gestation OR lactation OR pregnancy OR pregnant OR newborn AND imidacloprid AND mice OR Fetus OR fetal OR offspring OR neonatal OR uterus OR gestation OR lactation OR pregnancy OR pregnant OR newborn AND imidacloprid AND mouse

Results were exported and compiled with the bibliometrix(Aria and Cuccurullo 2017) package at software R (R Core Team 2024). Articles were included regardless of their Qualis classification (CAPES Evaluation, Brazil) and their impact factor (JBR), also duplicates were excluded. Original articles that experimented in rodents (rat or mice) were selected to meet the following criteria: include at least one isolated group exposed to IMI; exposure occurred during mating, gestation, and/or lactation periods; results evaluated in at least one F1 generation and published in the last 20 years.

RESULTS AND DISCUSSION

The current revision evaluated and supplemented the articles as illustrated in Fig. 1 and the findings are presented in Table 1. This review selected 14 studies that used rats and mice as research animals, exposed to varying doses.

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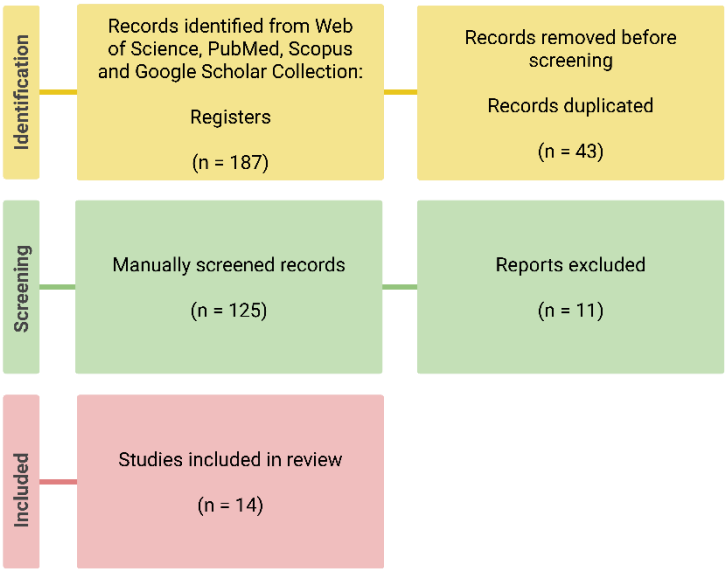

Fig. 1 Representative flowchart depicting the article selection process for the review on the effects of IMI exposure during embryonic development in rodents. Created by the authors with Biorender.

When animals were exposed during gestation it ranged from 0.118 to 44 mg/kg/day (Table 1). For those exposed during both gestation and lactation, doses ranged from 0.01 to 90 mg/kg/day (Table 1). One study used a single dose of 337 mg/kg (Abou-Donia et al. 2008), while two other studies used doses of 0.165 (Bhaskar and Mohanty 2014) and 0.65 mg/kg postnatally (Bhaskar et al. 2017) (Table 1). Animals were exposed with different vehicles and methods: via gavage, gastroesophageal intubation, miniosmotic pump, oral administration with vegetable oil, inclusion in food, administration via tail vein, drinking water, and intraperitoneal injection (Table 1).

There is a noticeable scarcity of data on the chosen topic. The methodology also varied greatly, with parameters studied including metabolic, reproductive, immunological, behavioral, and teratogenic effects despite the limited number of publications.

We provide a theoretical foundation on the IMI (sections "General characteristics of the neonicotinoid imidacloprid" and "Mode of action of imidacloprid"); a brief introduction and justification on its effects during critical periods of development (section "In utero and lactational exposure to imidacloprid"); and lastly, we present the results based on the effects of parental exposure to IMI on: maternal and offspring metabolism; the reproductive system of parents and offspring; the immune system of parents and offspring; behavior and neurotoxicity in parents and offspring; and on fetal development of offspring (Table 1).

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Table 1. Design characteristics of studies of imidacloprid exposure and transgenerational effects. "-" means not informed.

Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
Wistar rats	Gastroesophageal probe, entire gestation, 44 mg/kg/day	**Serum and plasma:** ↑glucose; ↑total cholesterol; ↓HDL; ↑LDL; ↑insulin; **Skeletal muscle:** ↓GLUT4 and ↑NFKβ	**4 and 12 weeks, serum and plasma:** ↑glucose; ↑total cholesterol; ↓HDL; ↑LDL; ↑insulin; **Skeletal muscle:** ↓GLUT4 and ↑NFKβ	**4 and 12 weeks, serum and plasma:** ↑glucose, ↑total cholesterol; ↓HDL; ↑LDL; ↑insulin; **Skeletal muscle:** ↓GLUT4 and ↑NFKβ	(Ndonwi et al. 2020)
Mice	Mini-osmotic pump, GD4 - PND21, 0.5 mg/kg/day	↓Fertility; Detection of IMI in the liver and brain	↓Body weight; Detection of IMI in liver and brain; ↓triglycerides; ↓depression; ↓aggression; ↑motor activity; ↑social dominance	Detection of IMI in liver and brain; ↓triglycerides; ↓depression; ↓aggression; ↑motor activity; ↑social dominance	(Burke et al. 2018)

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Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
Wistar rats	Oral with corn oil, two months before mating and again during mating, gestation, and lactation, 1/45 LD50 (10 mg/kg/day) and 1/22 LD50 (20 mg/kg/day)	**20 mg/kg/day:** ↓estrous cycle duration		Aggression; hyperactivity; ↓body weight; ↑ALT; ↑AKP; ↑G6PD; ↓AChE activity in brain and plasma; **Tissue morphology: Liver:** central vein dilation, leukocytic inflammatory cell infiltration, pyknotic nuclei; **Brain: perivascular** hemorrhage and neuronal nuclear migration; **Kidney:** ↑Bowman's capsule parietal layer, tubule degeneration, glomerular lobulation	(Vohra and Khera 2015)
Swiss albino mice	Oral with olive oil, PND1-PND28, 0.165 mg/kg		**PND28 and PND63:** IMI may compete with T3 in binding to thyroid receptors, but has no affinity with PPARγ	**PND28 and PND63:** IMI may compete with T3 in binding to thyroid receptors, but has no affinity with PPARγ	(Bhaskar and Mohanty 2014)

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Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
Wistar rats	Paste with 2-3 drops of Tween-80 and suspended in 0.5% carboxymethylcellulose for oral administration at a volume of 10 ml/kg body weight, DG6 - DG21 - PND21 - PND42 10, 30 and 90 mg/kg/day	↑hematocrit	**DG20 (30 and 90 mg/kg): Fetal malformations:** external and skeletal, anasarca, maceration; **PND21 and PND42:** alterations in humoral immunity development; ↑AST and ALP; ↓liver weight; ↓immunoglobulins and antibodies; adverse effect on cellular immunity; ↓phagocytic index; **PND21:** ↑platelets; ↑lymphocytes; ↓hemoglobin; **PND42:** ↓platelets; ↓lymphocytes; ↓leukocytes	**DG20 (30 and 90 mg/kg): Fetal malformations:** external and skeletal, anasarca, maceration; **PND21 and PND42:** alterations in humoral immunity development; ↑AST and ALP; ↓liver weight; ↓immunoglobulins and antibodies; adverse effect on cellular immunity; ↓phagocytic index; **PND21**: ↑platelets; ↑lymphocytes; ↓hemoglobin; **PND42:** ↓platelets; ↓lymphocytes; ↓leukocytes	(Gawade et al. 2013)
Mice	Gavage, GD6 - GD9, 0.118 mg/kg/day; 1.18 mg/kg/day; 4.1 mg/kg/day; 11.8 mg/kg/day; 41 mg/kg/day	Presence of IMI and metabolites in brain and plasma 1h after exposure	**Day 9 embryo:** Presence of IMI and metabolites in brain and plasma suggesting placental passage; **PND0:** IMI absent, indicating no bioaccumulation	**Day 9 embryo:** Presence of IMI and metabolites in brain and plasma suggesting placental passage; **PND0:** IMI absent, indicating no bioaccumulation	(Passoni et al. 2021)
Swiss albino mice	Mixed with food using olive oil as a vehicle, PND1 - PND28, 0.65 mg/kg/day		**PND29:** ↑corticosterone; ↓testosterone; hippocampal neuron degeneration **PND63:** ↑corticosterone; hippocampal neuron degeneration		(Bhaskar et al. 2017)

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Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
Sprague-Dawley rats	Intraperitoneal injection, GD9, 337 mg/kg in corn oil (75% of LD50)	No mortality or signs of toxicity	Sensory-motor deficits; ↑ChE in mesencephalon	Sensory-motor deficits; ↑ChE in cortex and brainstem	(Abou-Donia et al. 2008)
Wistar rats	Gastroesophageal probe, entire gestation (22 days), 44 mg/kg/day	**Liver:** ↑AST; ↑ALT; ↓SOD; ↓CAT; ↓GSH; ↑GPx; **Kidney:** ↑SOD; ↑GSH; ↑MDA	**Weaning:** **Liver:** ↑CAT **Kidney:** ↑SOD; ↑GSH; ↑GR; ↑MDA **Adults:** **Liver:** ↓SOD; ↑CAT; ↓GPx; ↓GSH; ↑MDA **Kidney:** ↑GPx; ↑MDA	**Weaning:** **Liver:** ↑CAT **Kidney:** ↑SOD; ↑GSH; ↑GR; ↑MDA **Adults:** **Liver:** ↓SOD; ↑CAT; ↓GPx; ↓GSH; ↑MDA **Kidney:** ↑GPx; ↑MDA	(Ndonwi et al. 2019)

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Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
Albino mice Mus musculus	Oral, mixed with feed and diluted with vegetable oil and water, GD0-GD18, 1.5 mg/g; 2.3 mg/g		**1.5 mg/g:** minor developmental alterations; **Liver:** cytoplasmic vacuolization, peripheral nucleus; **Kidney:** chronic inflammation and tubule degeneration; **2.3 mg/g:** alterations in hindlimb length, head circumference, tail, and body; **Liver:** congested sinusoid with red blood cells and degenerated hepatocytes; **Kidney:** tubule degeneration and inflammation	**1.5 mg/g:** minor developmental alterations; **Liver:** cytoplasmic vacuolization, peripheral nucleus; **Kidney:** chronic inflammation and tubule degeneration; **2.3 mg/g:** alterations in hindlimb length, head circumference, tail, and body; **Liver:** congested sinusoid with red blood cells and degenerated hepatocytes; **Kidney:** tubule degeneration and inflammation	(Javed et al. 2023)

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Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
Wistar rats	Tail vein, diluted in DMSO, GD7-GD21, 10 mg/kg			**PND1:** ↓Dax1 expression in ovary; **PND55:** ↓progesterone; ↓estradiol; =testosterone; ↓ovary weight; ↓ovary diameter; ↓number and diameter of primary primordial follicles, Graafian follicles, and corpora lutea; large atretic follicles observed; **F1 x F1** **PND55:** ↓pregnancy rate; ↓number of fetuses	(Nabiuni et al. 2015)

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Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
Albino rats	Oral, diluted in corn oil, F0= 10 weeks (8 + mating, gestation, and lactation) F1= 8 weeks (6 + mating, gestation, and lactation), 10 mg/kg/day; 20 mg/kg/day	**F0, 10 mg/kg/day:** ↓food consumption first week of treatment; ↑body weight after birth; **20 mg/kg/day:** ↓consumption first week of treatment; ↓estrous cycle; ↑body weight during gestation and lactation; ↑food consumption during gestation and lactation; ↓ovary weight **F1, 10 mg/kg/day:** ↑consumption compared to F0; ↑ALT; **20 mg/kg/day:** ↑final body weight; ↑food consumption during gestation and lactation; ↑ALT; ↓ovary weight	**20 mg/kg/day:** ↓body weight on PND21; ↑ALT	**20 mg/kg/day:** ↓body weight on PND21; ↑ALT	(Vohra and Khera 2016)

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Model	Mode, period, and exposure dose	Maternal assessment	Male offspring assessment	Female offspring assessment	Reference
C57BL/6 N mice	In drinking water from gestation (embryonic day 11.5) to maternal weaning when pups were 4 weeks old, 0.01 mg/kg/day		**13 weeks old:** ↓freezing rate in signaled fear test; ↑total central time in elevated plus maze test; ↓SOX2 (neural stem cell marker); ↓GFAP (astrocyte marker); i.e., ↓number of neural stem cells and stem cells eventually differentiating into astrocytes and dysfunctions in neural circuits related to memory and learning		(Saito et al. 2023)
Wistar rat	corn oil 1.2 mg/kg administered orally from day 1 of gestation to day 21 of lactation		***Did not differentiate males from females:** **F1 and F2:** ↓weight gain; =eye opening; ↓ability to turn (surface righting); ↓reflex capacity in negative geotaxis test; ↓time to move away from cliff edge; ↑time hanging by forelimbs. **Striatum and hippocampus (mitochondria):** ↓AChE activity; ↓CAT; ↓SOD; ↓GST; ↓GPx; ↓GSH; ↑LPO		(Haddad et al. 2023)

Abbreviations: HDL (High-Density Lipoprotein), LDL (Low-Density Lipoprotein), GLUT4 (Glucose Transporter Type 4), NFKß (Nuclear Factor Kappa Beta), GD (Gestational Day), PND (Postnatal Day), IMI (Imidacloprid), LD50 (Median Lethal Dose, lethal dose for 50% of the population), ALT (Alanine Aminotransferase), AKP (Alkaline Phosphatase), G6PD (Glucose-6-Phosphate Dehydrogenase), AChE (Acetylcholinesterase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase), T3 (Triiodothyronine), PPARγ (Peroxisome Proliferator-Activated Receptor Gamma), GR (Glutathione Reductase), MDA (Malondialdehyde), GPx (Glutathione Peroxidase), SOD (Superoxide Dismutase), CAT (Catalase), GSH (Glutathione), ChE (Cholinesterase), DMSO (Dimethyl Sulfoxide), Dax 1 (Regulator of gene expression during ovarian-related stages of development), (SOX2 (SRY-Box Transcription Factor 2, neural stem cell marker), GFAP (Glial Fibrillary Acidic Protein, astrocyte marker), LPO (Lipid Peroxidation), GST (Glutathione S-Transferase), F0 (Parental Generation), F1 (Offspring first Generation), F2 (Offspring second Generation).

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General characteristics of the neonicotinoid imidacloprid

Imidacloprid (IMI) was introduced to the consumer market in 1991 by Bayer AG and Nihon Tokushu Noyaku Seizo KK (Elbert et al. 1991). Since that, it has become one of the most widely used neonicotinoid insecticides worldwide (Casida and Durkin 2016; Casida 2018). Comprising chloropyridinyl, imidazolyl, and nitroimine moieties (Fig. 2), this pesticide is classified as a neonicotinoid (Casida and Durkin 2016).

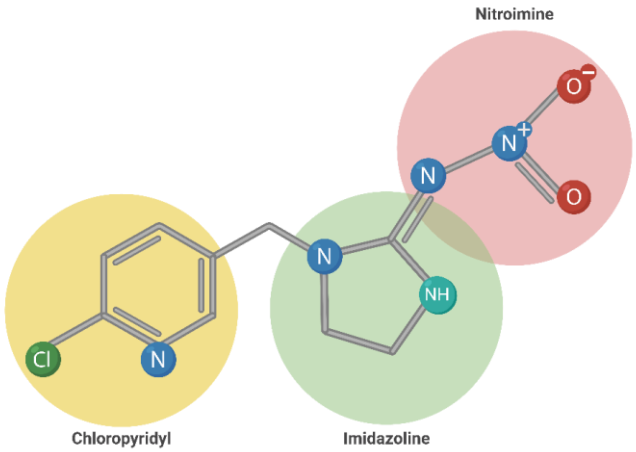

Fig. 2 Composition of IMI. 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine. Circles represent chloropyridinyl (yellow), imidazolyl (green), and nitroimine (red) portions. Created by the authors with Biorender.

The intensive commercialization and application of IMI increases the likelihood of exposure to non-target species. Neonicotinoid insecticides, such as IMI, can be applied through spraying, drip irrigation, or seed treatment. They can thereby disperse by water and soil, persisting in these environments for months to years (Han et al. 2018; Borsuah et al. 2020; Mörtl et al. 2020). This persistence is due to its high solubility in water and an environmental half-life that can range from weeks to months, depending on the composition of different matrices. For this reason, IMI is one of the most frequently detected neonicotinoids in water bodies in the world, present in both rural and urban areas (Nowell et al. 2018; Silvanima et al. 2018; Thompson et al. 2020; Deus et al. 2021). Moreover, standard wastewater treatment does not fully remove IMI, and it has been detected in drinking water in the Midwest United States (Klarich et al. 2017; Deus et al. 2021).

As a systemic insecticide, IMI can be translocated through plant tissues and is used prophylactically in seed treatments. It can also be found in the nectar and pollen of treated crops, providing a significant exposure route for pollinators (Hladik et al. 2018). Since plants absorb the chemical from their roots and distribute it through their vascular system, neonicotinoids are present in fruits and vegetables, with IMI being the most detected pesticide

(Craddock et al. 2019). In India, IMI was found in 24% of vegetable samples, 33% of cereals, and 22% of fruits (Kapoor et al. 2013); in Brazil, IMI was found in 713 samples of fruits and vegetables analyzed between 2017 and 2018 (ANVISA 2019); and in USA and China, IMI was present in over 50% of fruit and vegetable samples, with children aged 8 to 10 in China consuming neonicotinoids daily (Zhang et al. 2018).

The ingestion of contaminated food is just one way of animal exposure to IMI, as it may also occur through inhalation of contaminated pollen, residues in dust, and the insecticide itself during spraying (Zhang et al. 2018). IMI has been detected in various human biological materials, including hair, blood, breast milk, and, most frequently, urine (Zhang and Lu 2022). Indeed, Zhang and Lu (2022) showed that concentrations in human urine samples vary from 0.38 to 5.6 ng/mL for neonicotinoids and from 2.68 to 11.4 ng/mL for neonicotinoid metabolites, depending on the region of collection.

Mode of action of Imidacloprid

Neonicotinoids are designed to mimic nicotine structure, thus acting on the cholinergic system of insects. IMI mechanism action activates nicotinic acetylcholine receptors (nAChRs), depolarizing the postsynaptic membrane, leading to an excitation, paralysis, and eventually death of the exposed insect (Matsuda et al. 2005, 2020; Casida and Durkin 2016). Neonicotinoids are more toxic to insects than mammals due to differences in the conformation and amino acids of nAChR binding site (Casida and Durkin 2016). However, their metabolites can be toxic to mammals, such as desnitro-imidacloprid and imidacloprid-urea (Klarich Wong et al. 2019).

Imidacloprid is absorbed by the intestine and then distributed to all tissues, primarily the liver and kidneys, and excreted via urine (EFSA 2013b). IMI is metabolized in the liver by cytochrome P450 (CYP) enzymes and aldehyde oxidases (AOX) (Fig. 3). The primary steps include hydroxylation of the imidazolidine ring by CYP enzymes, reduction of the nitroimine substituent by AOX, and oxidative cleavage of the chloropyridinyl from the imidazolidine portion. Consequently, IMI is oxidized to the metabolites 5-hydroxy (IMI-5-OH) and olefin (IMI-ole), and reduced to the metabolites nitrosoguanidine (IMI-NNO), aminoguanidine (IMI-NNH2), desnitro-IMI (IMI-NH), and IMI-urea (Schulz-Jander and Casida 2002; Casida 2011; Swenson and Casida 2013; Casida and Durkin 2016). In mice, the accumulation of IMI in tissues follows a descending order: testicles > blood > brain > lung > kidney > inguinal white adipose tissue > gonadal white adipose tissue > mesenteric white adipose tissue > pancreas > liver (Nimako et al. 2021).

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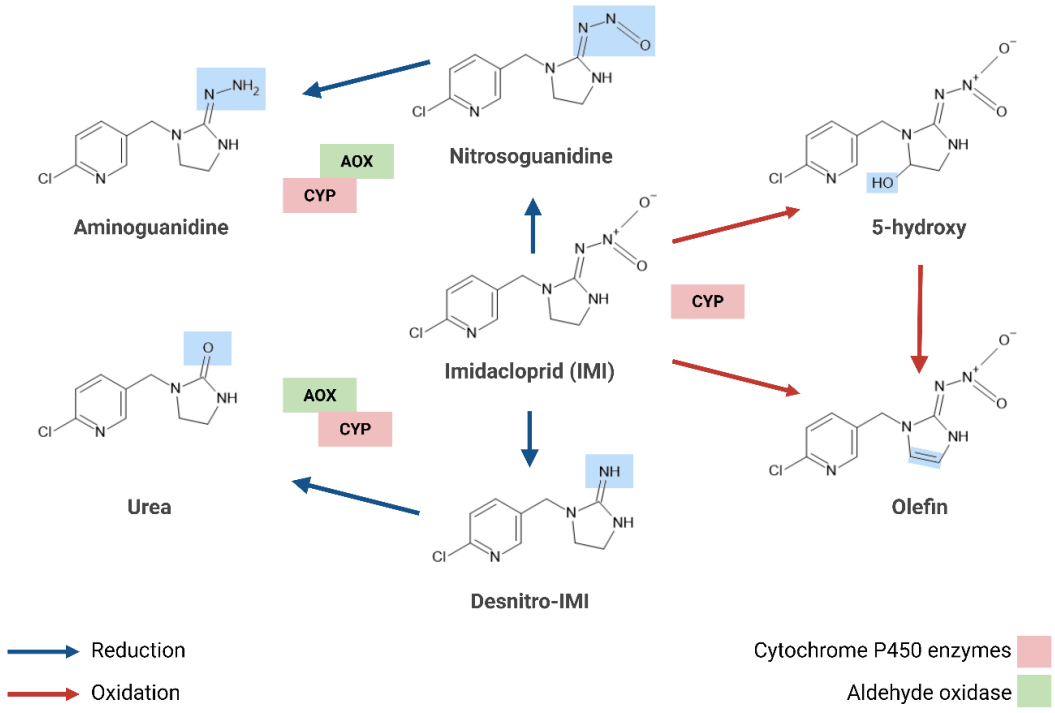

Fig. 3 Metabolism of IMI in mammalian liver. The reactions start with hydroxylation (highlighted in blue OH) of carbon 5 of the imidazolidine ring, shown on the right, forming the 5-hydroxy compound. The imidazolidine portion also undergoes desaturation (highlighted in blue double bond), resulting in the olefin compound. Both processes are catalyzed by cytochrome P450 enzymes (CYPs). On the left side of the figure, the reduction and cleavage (highlighted in blue structures) of the nitroimine substituent forming nitrosoguanidine, aminoguanidine, desnitro-IMI, and urea derivatives. These processes are catalyzed by CYP isoenzymes and aldehyde oxidase (AOX). Created by the authors with Biorender and adapted from Swenson and Casida (2013).

Although Neonicotinoids were early classified as low toxic to humans, these pesticides can cause hepatotoxic, genotoxic, neurotoxic, fertility, and embryonic developmental effects (Han et al. 2018). In the following sections, we will present the effects on different tissues and on different metabolic windows assessed in experiments with rats and mice.

Effects of parental exposure to Imidacloprid on offspring fetal development

Developmental defects in animals reflect xenobiotic toxicity after exposure during critical periods (prenatal, perinatal, or postnatal). So far, there is limited evidence of developmental anomalies in rodents due to maternal IMI exposure. Administration of 90 mg/kg of IMI during fetal development in Wistar rats showed skeletal alterations as the absence of thoracic ribs, fused ribs, wavy ribs, bifid vertebral centers, and incomplete ossification of phalangeal cartilage. Parental exposure to 30 mg/kg caused fused ribs in a single fetus (Gawade et al. 2013). Wavy ribs are transient in rodents and can be considered variations. However, this

variation and incomplete ossification of phalangeal cartilage, although transient, may represent significant delays in the ossification process due to IMI exposure. Bifid vertebral centers and the absence of thoracic ribs, on the other hand, are permanent malformations (Hofmann et al. 2016; DeSesso and Scialli 2018).

Ossification of bones in rodents and rabbits occurs near birth and is used as an indicator of fetal maturity in developmental toxicity studies. Even though fetuses with less ossification compared to controls indicate reduced development, it is not a malformation since it is temporary and occurs mainly during lactation, when there is a rapid increase in body mass and bone size. Evaluating the stage of ossification is crucial in teratogenic studies (DeSesso and Scialli 2018) (Fig. 4).

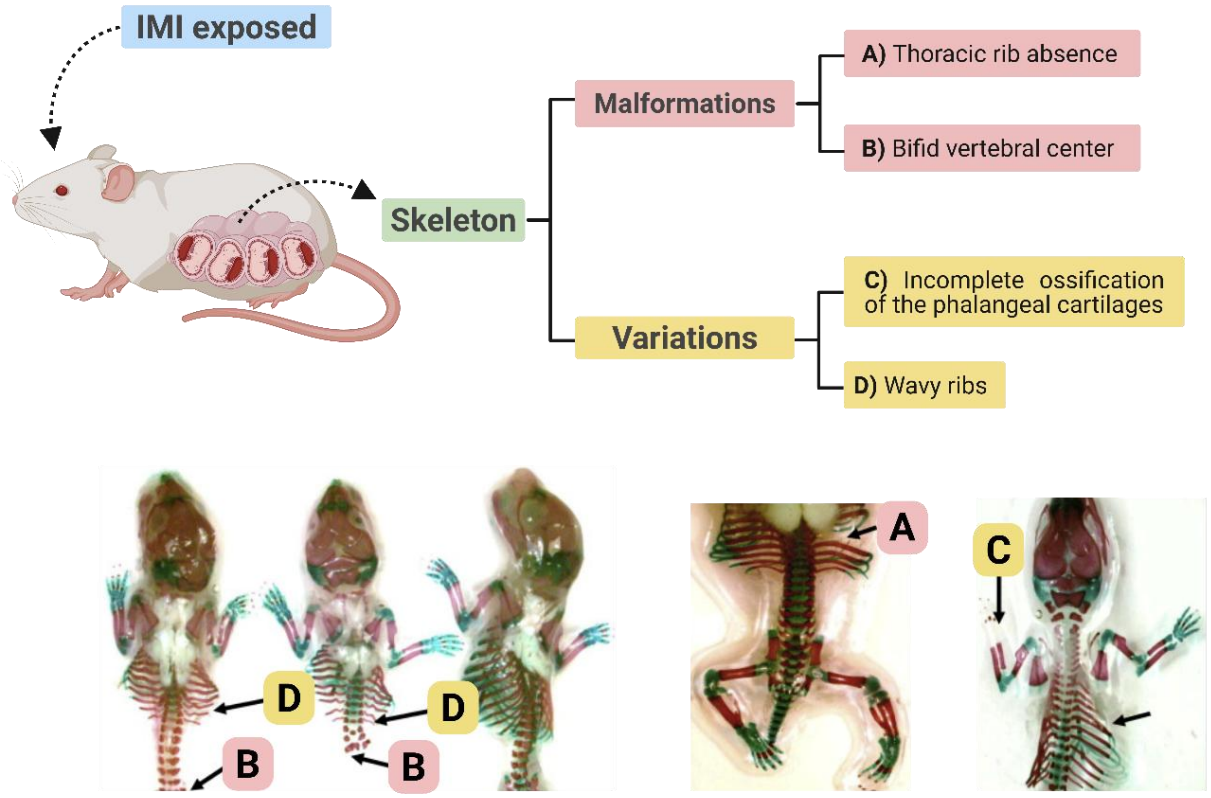

Fig. 4 Teratogenic malformations caused by IMI. Created by the authors with Biorender, based on Gawade et al. (2013).

Effects of parental exposure to Imidacloprid on maternal and offspring metabolism

The transfer of neonicotinoid pesticides, as clothianidin, and their metabolites from mother to fetus in animal models has already been proved (Ohno et al. 2020). Pregnant and lactating women are therefore considered high-risk groups for potential exposure (Mahai et

al. 2022). IMI can also affect the embryonic development of exposed mouse offspring by transport via placenta to the fetus (Passoni et al. 2021) and, the fetal exposure to pesticides is thereby a significant concern, as chemicals deemed safe for adults may not be safe for fetuses. There is also evidence of IMI presence (41.0 ± 24.3 ng/L) in human breast milk (Chen et al. 2020), raising concerns about food safety for infants during lactation. A study conducted in California found that 61% of 79 breast milk samples contained IMI, with an average concentration of 0.02 µg/L (Pedersen et al. 2021).

The exposure to IMI during fertilization, gestation, and lactation can significantly impact the metabolism of female parental generation. Classic metabolic alterations were observed in organisms exposed to IMI including increased glucose, total cholesterol, LDL cholesterol, and insulin levels, with decreased HDL cholesterol levels (Fig. 5). As shown by Wistar rats exposed to 44 mg/kg/day of IMI during gestation, with impaired glucose metabolism evidenced by decreased GLUT4 expression in skeletal muscle, responsible for insulin-mediated glucose uptake (Ndonwi et al. 2020). This exposure level during gestation also elevates liver damage markers, such as AST and ALT enzymes (Vohra and Khera 2016; Ndonwi et al. 2019), and reduces activities of hepatic antioxidant enzymes SOD, CAT, and GSH. Despite increased GPx enzyme activity, these findings indicate liver damage and insufficient antioxidant defense (Ndonwi et al. 2019).

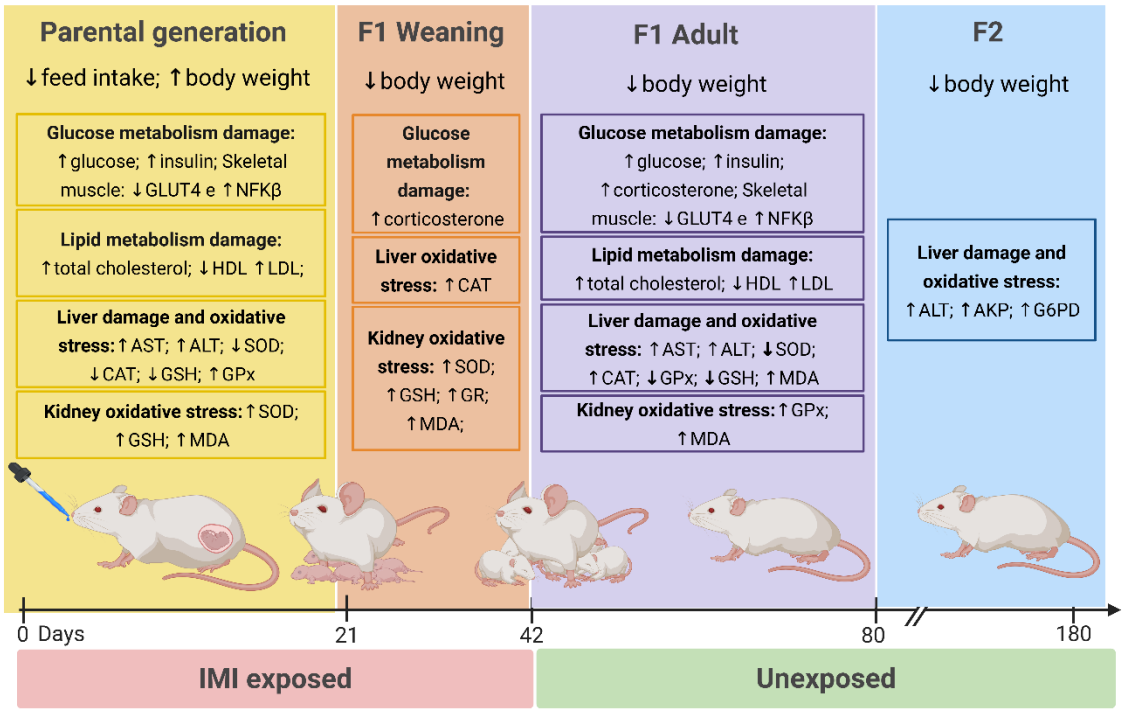

Fig. 5 Metabolic alteration evidence in parental, F1, and F2 generations after parental exposure to IMI. **Abbreviations:** HDL (High-Density Lipoprotein), LDL (Low-Density Lipoprotein), GLUT4 (Glucose Transporter Type 4), NFKB (Nuclear Factor Kappa Beta), IMI (Imidacloprid), ALT (Alanine Aminotransferase), AKP (Alkaline Phosphatase), G6PD (Glucose-6-Phosphate Dehydrogenase), AST (Aspartate Aminotransferase), GR (Glutathione Reductase), MDA (Malondialdehyde), GPx (Glutathione Peroxidase), SOD (Superoxide Dismutase), CAT (Catalase), GSH (Glutathione), LPO (Lipid Peroxidation), F1 (Offspring first Generation), F2 (Offspring second Generation). Created by the authors with Biorender.

Rats exposed to 10 and 20 mg/kg/day during mating, gestation, and lactation had increased renal antioxidant system activity, potentially counteracting excessive reactive oxygen species (ROS) due to IMI presence and oxidative metabolism alterations. Chronic oxidative stress induces stress-sensitive signaling pathways and increases NF-κB protein, as observed in pregnant rats exposed to IMI (Lingappan 2018; Ndonwi et al. 2020). Females also showed increased food consumption and body weight, suggesting metabolic changes (Vohra and Khera 2016). Mice exposed to 1.5 and 2.3 mg IMI/g feed had morphological changes in liver and kidneys related to inflammatory processes, likely from altered metabolism (Javed et al. 2023). Metabolic changes manifest in the parental generation during direct IMI exposure and in the F1 generation of both sexes (Burke et al. 2018).

IMI may disrupt metabolic regulation by competing with hormone T3, contributing to body weight gain (Bhaskar and Mohanty 2014). F1 offspring of mothers exposed to 30 and 90 mg/kg showed hepatic dysfunction at weaning and adulthood, with increased AST and ALP enzymes and reduced liver weight (Gawade et al. 2013). Mice male F1 offspring of mothers exposed to 0.65 mg/kg/day displayed increased corticosterone, influencing general metabolism and potentially leading to insulin resistance, glucose intolerance, hyperglycemia, fat accumulation, and weight gain (Beaupere et al. 2021).

In the parental generation, altered antioxidant systems may result from IMI presence and/or metabolic changes. These effects persist in the F1 generation even without continued pesticide exposure. Rats born to mothers exposed to 44 mg/kg/day during gestation had increased hepatic CAT and renal SOD, GSH, GR, and lipoperoxidation at weaning, showing the antioxidant system's attempt to neutralize oxidative damage. As adults, these animals kept high antioxidant activity but reduced SOD, GPx enzyme activity, and GSH substrate, with continuous and increased lipoperoxidation (Ndonwi et al. 2019).

When the parental generation of Wistar rats received 20 mg/kg/day of IMI during gestation, there were transgenerational effects, especially in F2 generation with increased ALT, ALP, and G6PD enzymes, indicating hepatic metabolic dysfunction (Vohra and Khera 2015). These changes manifested in the liver morphology, like central vein dilation, leukocyte

infiltration, and pyknotic nuclei, suggesting inflammatory processes (Vohra and Khera 2015). Recent studies confirmed both intergenerational and transgenerational effects. F1 and F2 offspring of Wistar rats exposed during gestation and lactation to 1.2 mg/kg of IMI showed reduced weight gain and decreased antioxidant system activity in the striatum and hippocampus (Haddad et al. 2023).

IMI metabolites may be antagonists of postsynaptic nicotinic acetylcholine receptors (nAChRs) (Loser et al. 2021), similarly to nicotine (Calarco and Picciotto 2020), affecting food intake and reducing body weight, explaining the reduced weight gain in F1 and F2 offspring. This impaired growth suggests the vulnerability of developing rats to pesticides, possibly due to placental transfer of the compound from mother to fetus. These findings imply that energy regulation and consequently food intake and body weight control are related to hippocampal alterations. In summary, metabolic alteration evidence in parental, F1, and F2 generations after parental exposure to IMI is illustrated on Fig. 5.

Effects of parental exposure to Imidacloprid on reproductive system of parents and offspring

IMI induces reproductive changes, as female mice had reduced fecundity with exposure to 0.5 mg/kg/day of IMI during gestation and lactation (Burke et al. 2018). There are also decreased estrous cycle days in rats exposed to 20 mg/kg/day of IMI (Vohra and Khera 2015, 2016) and reduced ovarian weight, persisting in the F1 generation (Vohra and Khera 2016).

Regarding hormonal alterations related to reproduction, the exposure of parental generation females to 10 mg/kg/day of IMI had reduced estradiol and progesterone levels in the offspring of IMI-treated mothers, with additional decrease in ovary size, number and diameter of primary follicles, Graafian follicles, and corpus luteum, and large atretic follicles present (Nabiuni et al. 2015). These conditions lead to reduced pregnancy rates and fewer fetuses, along with a decreased Dax1 protein levels, possibly due to oxidative alterations, a protein that plays a crucial role in ovarian and female reproductive organ development, highlighting the observed reproductive changes (Nabiuni et al. 2015). Pesticide-induced changes in female reproductive organs affecting reproductive success may result from two main pathways (Sharma et al. 2020). First, the excess reactive oxygen species (ROS) affect various physiological processes, from egg maturation to fertilization, embryo development, and gestation (Kapoor et al. 2011). Second, IMI may disrupt endocrine homeostasis by acting on the hypothalamus, inhibiting gonadotropins (GnRH) and consequently altering LH and FSH levels (Kapoor et al. 2011) (Fig. 6).

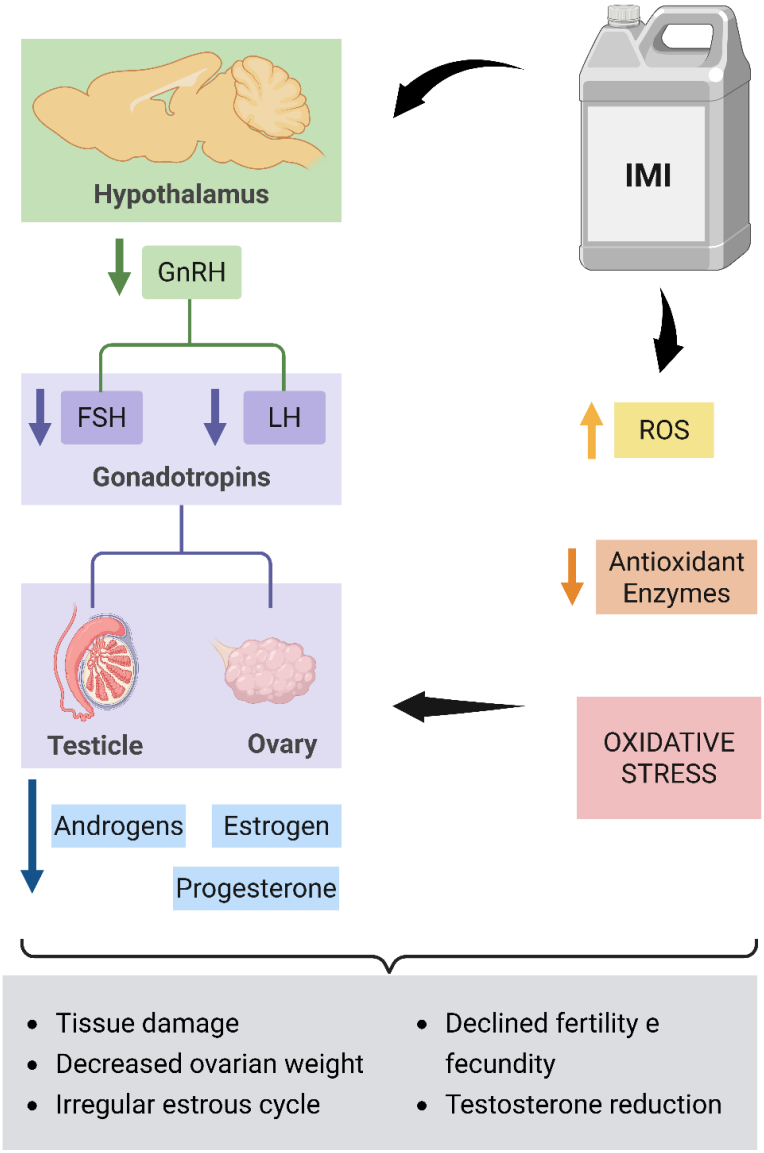

Fig. 6 IMI disrupts endocrine homeostasis. Colored arrows indicate changes: downward arrows for reductions and upward arrows for increases. Black arrows illustrate the cycle of changes caused by IMI. Pesticides can impact female reproductive success by increasing reactive oxygen species (ROS) that disrupt reproductive processes, by disrupting endocrine homeostasis (inhibiting gonadotropins such as GnRH and altering LH and FSH levels), and by directly affecting gonads through oxidative stress. Created by the authors with Biorender, based on Sharma et al. (2020).

IMI also causes reproductive changes in males when administered to the parental generation. Male offspring of mice exposed to 0.65 mg/kg/day of IMI through lactation (PND1 to PND28) showed reduced testosterone levels on the 29th day of life (Bhaskar et al. 2017). Testosterone is crucial for spermatogenesis, and its reduction leads to low sperm count, impaired fertility, decreased muscle mass, bone density, and cognitive function, as well as metabolic disorders significantly increasing cardiovascular disease risk. One discussed

mechanism involves oxidative stress, damaging Leydig cell mitochondria and reducing testosterone synthesis via cyclic adenosine monophosphate (cAMP) inhibition (Mendy and Pinney 2022) (Fig. 6).

Effects of parental exposure to Imidacloprid on the immune system of parents and offspring

The immune system is a defense against infectious agents and harmful substances, playing a vital role in maintaining body homeostasis (Rankin and Artis 2018). There is limited knowledge about the effects of IMI on immune system development, representing thereby a significant knowledge gap. Gawade et al. (2013) investigated developmental immunotoxicity by evaluating critical windows of immune system development. They exposed pregnant females to IMI during fetal organogenesis, as well as lactating females and weaned offspring until maturity (via gavage). Exposure to 30 mg/kg until postnatal day 21 (PND21) and 30 and 90 mg/kg until PND42 produced alterations in humoral immunity, with reduced total circulating immunoglobulins (Gawade et al. 2013), potentially affecting antigen neutralization, complement activation, and microorganism destruction dependent on leukocytes (Carroll 2004). Delayed hypersensitivity testing showed that the exposure at both ages resulted in less hypersensitivity effects, suggesting cellular immunity suppression. Reduced T lymphocyte circulation directly affects efficacy against cell-associated microorganisms, including phagocytosed and other intracellular microorganisms. Which increases susceptibility to infections by viruses, intracellular bacteria, some extracellular bacteria, and fungi (Carroll 2004; Fig. 7).

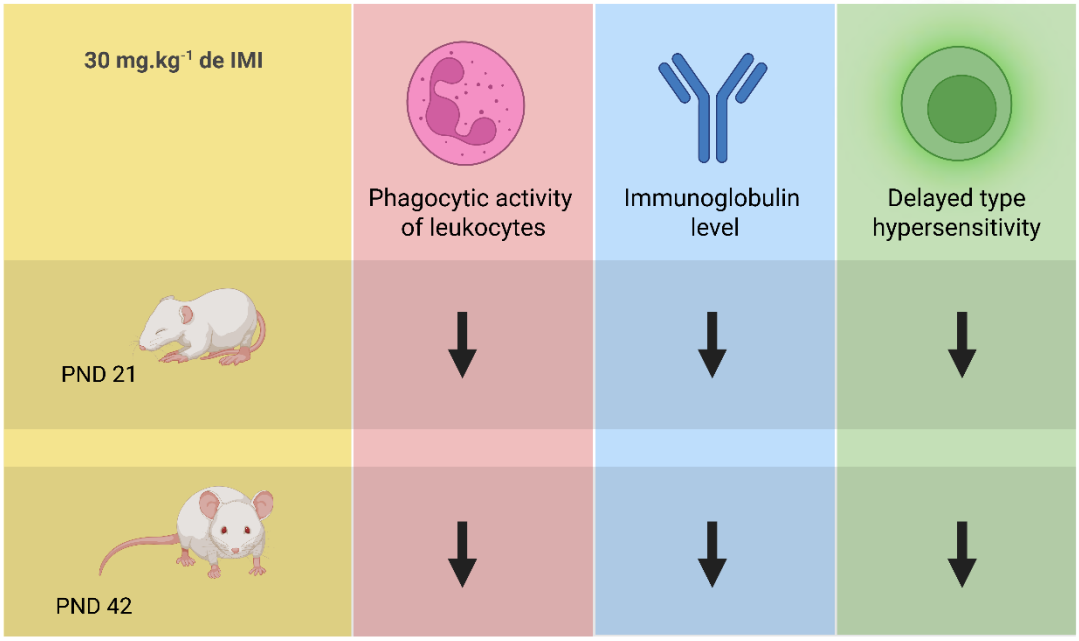

Fig. 7 Immune responses caused by exposure to IMI during lactating rats. Legend: PND (Postnatal Day). Downward black arrows indicate reductions in immune types. Created by the authors with Biorender.

There are also effects on innate immunity such as reduced leukocyte numbers and phagocytic index. Leukocytes recognize, ingest, and destroy many pathogens without adaptive immune response aid (Rankin and Artis 2018). The parental generation exposed to 10 mg/kg of IMI had less platelet numbers than the PND42 group exposed to 30 mg/kg of IMI (Gawade et al. 2013). While platelets are known as primary hemostasis mediators, there is growing recognition of their significant role in inflammation and microbial infection defense (Leslie 2010; Stokes and Granger 2012). Reduced platelet numbers can increase bleeding risk and affect immune responses because they are the second most numerous cells in the bloodstream and one of the most important pathogen detectors in the body (Leslie 2010).

Another alteration observed in the hematological parameters of the parental generation was increased hematocrit (Hct) (Gawade et al. 2013), which represents the volumetric content of red blood cells in the blood. Increased Hct levels may relate to the increased production of erythropoietin, which is produced by the kidneys and released in greater amounts under toxic conditions, resulting in increased red blood cell production (Akhtar et al. 2014).

In adulthood (PND42), there was a reduction in leukocytes. As the authors suggest, this can eventually have an immunosuppressive effect through adverse effects on normal bone marrow function, stress, or other factors responsible for maintaining normal leukocyte balance (Gawade et al. 2013).

Effects of parental exposure to Imidacloprid on offspring behavior and neurotoxicity

For mammals, IMI is classified as "moderately toxic" because their nAChRs exhibit lower binding affinity than those of insects. However, behavioral deficits have been observed in the offspring of animals exposed to IMI in acute and chronic exposures (Abou-Donia et al. 2008; Burke et al. 2018). A single dose (337 mg/kg) applied to the parental generation on gestational day 9 resulted in sensorimotor deficits that affected walking time and the offspring performance (Abou-Donia et al. 2008). Behavior integratively has been assessed by demanding relevant levels of consciousness, memory, and sensorimotor function. Biochemical and pathological alterations suggest that abnormalities in multiple brain regions may be involved in sensorimotor deficits in offspring due to maternal exposure to IMI (Fig. 8) (Abou-Donia et al. 2008).

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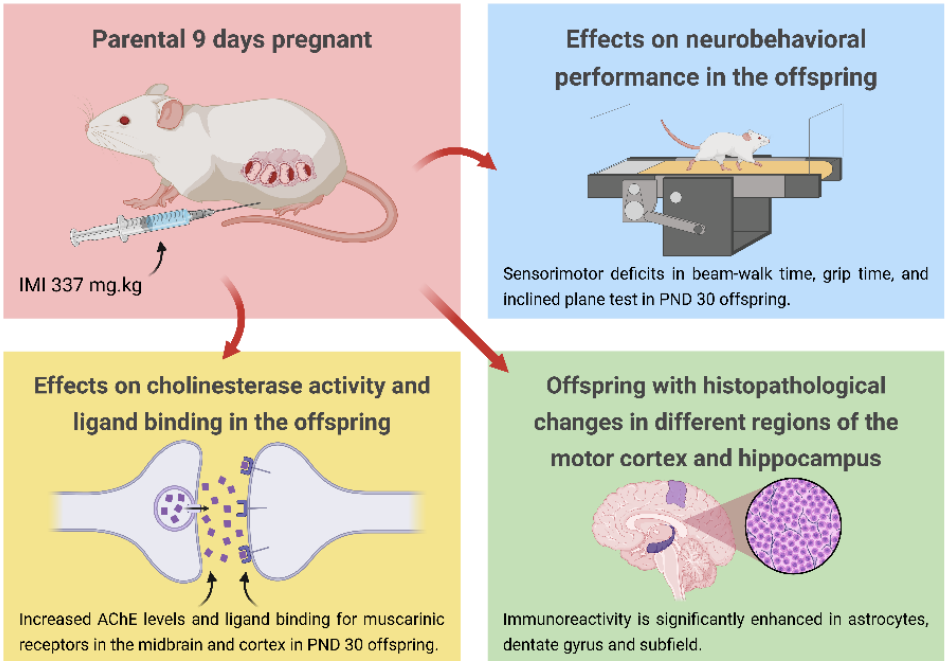

Fig. 8 Neurobehavioral deficits in rat pups caused after intrauterine exposure to IMI. Created by the authors with Biorender, based on Abou-Donia et al. (2008).

Like the findings for nicotine, those for IMI exposure remain controversial. No significant changes were observed in efficiency and duration in the T-maze test for male offspring of Swiss mice exposed to 0.65 mg IMI (mg/kg/day). However, female offspring of mice exposed to 0.5 mg/kg/day had less aggressive and depressive behaviors, more motor activity, and social dominance, suggesting elevated nAChR signaling after chronic neonatal IMI exposure (Burke et al. 2018). In another study, different neonicotinoids (thiamethoxam and clothianidin) presented dose-dependent effects on dopamine axon release in the rat striatum (de Oliveira et al. 2010). Neuronal nAChRs modulate neurotransmitter release such as dopamine, which is altered when exposed to agonists like nicotine (Zhang and Sulzer 2004).

Conversely, F2 offspring of rats whose parental generation was exposed to 20 mg/kg/day of IMI exhibited signs of aggression and hyperactivity along with reduced AChE activity in plasma and brain (Vohra and Khera 2015). Low nicotine concentrations initially result in nAChR desensitization, and with prolonged exposure, these receptors move to an inactive state. To restore homeostasis, the number of receptors increases. This could result from exposure during gestation and a consequent increase in nAChRs. Additionally, increased receptors may remain desensitized longer, necessitating higher ACh or agonist levels for channel opening and possible dopaminergic activation (Wittenberg et al. 2020).

The exposure to 0.01 mg/kg/day of IMI during gestation and lactation resulted in reduced neural stem cell markers in adult male mice. Which is supported by decreased freezing rates

in the fear-conditioning test and increased time spent in the center of the open field maze. Suggesting that low-level neonicotinoid exposure early in life disrupted nAChR-mediated neurotransmission may lead to long-term effects on brain structure and function, with reduced neural stem cells and differentiated astrocytes linked to impaired behaviors crucial for memory and learning (Saito et al. 2023).

Finally, cognitive learning and memory are also intergenerationally and transgenerationally altered. F1 and F2 offspring of Wistar rats, with direct exposure in the parental generation during gestation and lactation at 1.2 mg/kg of IMI, showed reduced antioxidant system activity in the striatum and hippocampus. These animals experienced negative impacts on neuromotor development such as delayed righting reflex (surface righting), coordinated movement development disturbances, and balance sense issues (Haddad et al. 2023). In complementary studies, exposure of parental generation females to 20 mg/kg/day resulted in perivascular hemorrhage and nuclear migration of neurons in F2 offspring (Vohra and Khera 2015), while doses of 0.65 mg/kg/day caused hippocampal neuron degeneration in male mice, with these changes observed in the male progeny of exposed mothers (Bhaskar et al. 2017).

FINAL CONSIDERATIONS

The present review summarized the effects of parental exposure to Imidacloprid on the parents, fetal development, offspring metabolism, reproductive damage, changes in the immune system and in behavior.

The main effect reported among parents and subsequent generations (F1 and F2) refer to the metabolic change expressed in weight gain. There are also reports of malformations in the fetal skeleton, which can affect the development and behavior of the offspring. The potential indicators of the risk that living beings face when exposed to different concentrations present in the environment are expressed in damage to the immune system and changes in the response of the antioxidant system of other tissues, especially in the reproductive system of generations following parents exposed to imidacloprid.

It is noteworthy that, in this review, there is a wide variation in concentrations of imidacloprid used in the studies. This variation represents a bias to be explored in future studies to clarify the effects related to each exposure concentration.

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Statements & Declarations

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Competing Interests

The authors declare no conflict of interest.

Author Contributions

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