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Imidacloprid as reproductive toxicant and endocrine disruptor: investigations in laboratory animals

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Imidacloprid, a neonicotinoid insecticide, has been used worldwide due to its selective toxicity for insects. Its residues may enter the food chain, which is why it is important to investigate the potential adverse effects of imidacloprid exposure. This review summarises current knowledge of the reproductive toxicity and disruptive endocrine effects of imidacloprid in laboratory animals. Investigations, conducted mostly on laboratory rats, have shown adverse effects of imidacloprid on the reproductive ability in both parental and offspring generation as well as on the development of the offspring. Like many pesticides, imidacloprid may also act as endocrine disrupting chemical (EDC). It may disrupt the metabolic homeostasis, contribute to obesity, and disrupt steroidogenesis by inhibiting cytochrome P450 (CYP) enzyme activities. All these adverse effects of imidacloprid may pose a serious risk for reproduction and development with long-term consequences in adulthood.

KEY WORDS: *endocrine disruption; insecticide; laboratory rats; neonicotinoids; reproductive toxicity*

Neonicotinoid insecticides, the most important class of synthetic neuroactive insecticides, are widely used to treat crops and livestock against a broad range of pests (1, 2). Imidacloprid (IMI) [1-(6-chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine] is a chlorinated analogue of nicotine and the first neonicotinoid registered for use as pesticide by the United States Environmental Protection Agency (US EPA). Since its introduction to the insecticide market in 1992, imidacloprid's use has been growing every year due to its selective toxicity and apparent safety for humans. Today, it accounts for 41.5 % of neonicotinoid use (2, 3). Imidacloprid is classified as a "Group E" carcinogen, which means that there is no evidence of carcinogenicity in humans (4). Neonicotinoid insecticides act as agonists of insect nicotinic acetylcholine receptors (nAChRs), which play an important role in synaptic transmission in the central nervous system (5). Due to structural differences between mammal and insect nAChRs and the higher binding affinity for insect nAChR, imidacloprid is considered a selective toxicant (6-8). Its oral LD_{50} in rats and mice is 450 and 131 mg kg^{-1} of body weight (bw), respectively (9). Even though imidacloprid is mildly toxic to mammals, it may still affect their heart, kidney, and other organs and cause gastrointestinal irritation and neurological symptoms or even death. There are many reports indicating adverse effects of imidacloprid in mammals, such as teratogenic (10, 11), mutagenic (12), neurotoxic (13-15), and immunotoxic effects (16, 17). The toxicity of imidacloprid is dose-dependent, as reported by a study that evaluated effects of 30 days oral administration of 1/85 LD_{50} and 1/120 LD_{50} of imidacloprid on thyroid toxicity in female rats (18) and a study of haematological and biochemical parameters in male rats after oral administration of 0.125 LD_{50} and 0.1 LD_{50} of imidacloprid, which correspond to the levels found in and on treated cucumbers one hour and one day after the application of imidacloprid, respectively (19).

In this mini-review, however, we focus on the current knowledge of adverse effects of imidacloprid on the reproductive and endocrine function as evidenced by recent animal studies.

REPRODUCTIVE TOXICITY

Studies conducted in male and female laboratory animals, mostly rats, have established that oral administration of imidacloprid could affect reproductive function, as summarised in Table 1 (20-28). Subchronic and chronic exposure to different doses of imidacloprid can cause histological damage of the testicular tissue, changes in sperm morphology, increased sperm mortality and abnormality, decreased sperm count and motility, inhibited spermatogenesis, and reduced testosterone levels in male rats, all of which could lead to infertility (20-24).

More specifically, studies in male rats by Bal et al. (20, 21) showed that a three-month exposure to imidacloprid doses lower than the no-observable-effect-level (NOEL), which is 5-10 mg kg^{-1} for rats, adversely affected their testicular function during early postnatal development and in adulthood. The elevated fatty acids and lipid peroxidation

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Table 1 *Summary of studies of imidacloprid (IMI) effect on reproduction in laboratory rats*

Reference, year of publication	Sex/age	Exposure conditions (duration and route of administration)	Dose(s)	Effects
Bal et al. (20) 2012	male developing	90 days oral (gavage)	0.5, 2 and 8 mg kg^{-1}	↓ weights of epididymis, right cauda epididymis and seminal vesicle ↓ epididymal sperm concentration at IMI – 8 mg kg^{-1} ↑ abnormal sperm rates (head, tale and total values) at IMI – 8 mg kg^{-1} ↑ apoptosis and seminal DNA fragmentation at IMI – 2 and 8 mg kg^{-1} ↓ serum T ↑ serum total cholesterol at IMI – 2 and 8 mg kg^{-1} ↑ testicular fatty acids ↑ MDA; ↓ GSH in testis at IMI – 8 mg kg^{-1}
Bal et al. (21) 2012	male adult	90 days oral (gavage)	0.5, 2 and 8 mg kg^{-1}	↓ weight of epididymis, right cauda epididymis and seminal vesicle ↓ epididymal sperm concentration at IMI – 2 and 8 mg kg^{-1} ↓ sperm motility at IMI – 8 mg kg^{-1} ↑ abnormal sperm rates (head, tale and total values) at IMI – 8 mg kg^{-1} ↑ apoptosis and seminal DNA fragmentation at IMI – 8 mg kg^{-1} ↓ serum T at IMI – 8 mg kg^{-1} ↓ GSH in testis at IMI – 8 mg kg^{-1} ↑ testicular fatty acids change in disturbance of fatty acid composition
Najafi et al. (22) 2010	male adult	60 days oral (gavage)	112 and 225 mg kg^{-1}	adverse histological changes on testicular tissue sperm mortality ↑ abnormal sperm velocity ↓ sperm viability ↓ motile sperm velocity ↓ T serum levels
Hafez et al. (23) 2016	male adult	15 days oral (gavage)	45, 90 and 450 mg kg^{-1}	↓ LH, FSH, T, E2 and prolactin in testis ↓ sperm count at 90 mg kg^{-1} ↓ motility and vitality affected sperm morphology at 45 and 90 mg kg^{-1} ↓ spermatogenesis
Lonare et al. (24) 2015	male adult	28 days oral (gavage)	45 and 90 mg kg^{-1}	↓ total epididymal sperm count ↓ sperm motility ↓ live sperm count ↑ sperm abnormalities (head and tail) ↑ γ-GT, LDH-x, SDH in testis ↓ T in plasma and testis ↓ 3ß-HSD, 17ß-HSD in testis ↑ LPO; ↓ GSH in testis ↓ CAT, SOD at 90 mg kg^{-1} in testis ↓ GPx and GST in testis histopathological alterations in testis and epididymis

Reference, year of publication	Sex/age	Exposure conditions (duration and route of administration)	Dose(s)	Effects
Kapoor et al. (25) 2011	female adult	90 days oral	5, 10 and 20 mg kg^{-1} day^{-1}	↓ ovarian weight at 20 mg kg^{-1} significant pathomorphological changes in follicles, antral follicles and atretic follicles at 20 mg kg^{-1} ↑ FSH; ↓ LH and P4 in serum at 20 mg kg^{-1} ↑ LPO in ovary at 20 mg kg^{-1} ↓ GSH, SOD, CAT and GPX in ovary at 20 mg kg^{-1}
Nabiuni et al. (26) 2015	pregnant female	from gestation day 7 to 21, *via* tail vein	10 mg kg^{-1} bw	↓ E2 and P in serum of 55-day-old offspring of IMI-treated mothers ↓ ovarian weight, ovary diameter, number and diameter of follicles and corpus luteum in the offspring of IMI-treated mothers ↓ rate of successful mating and number of fetus in the offspring of IMI-treated mothers down regulation of DAX1 gene in ovary of the offspring of IMI-treated mothers
Suter et al. (27) 1990	female adult	P1/P2: 84 days/105 days before mating, through mating, gestation and lactation oral	100, 250 and 700 ppm	↔ no reproductive effects ↓ body weight gain in P1 at 700 ppm ↓ food consumption in P1 at 700 ppm ↓ body weight gain in P1 – offspring until weaning at 700 ppm ↓ premating body weights in P1-F1 males at 700 ppm
Vohra et Khera (28) 2016	female adult	F0 females: 10 weeks or more F1 parents: 8 weeks or more oral	10 and 20 mg kg^{-1} bw day^{-1}	↓ ovarian weight in F0 and F1 generation at 20 mg kg^{-1} bw day^{-1} ↑ body weight of F0 pups (day 0) ↓ body weight of F1 pups (day 21) histopathology of ovary revealed different stages of follicles ↑ ALT in F1 and F2 females ↑ body weight of F1 pups on day 0 at 20 mg kg^{-1} bw day^{-1} ↓ body weight in F2 pups on day 21 at 20 mg kg^{-1} bw day^{-1} ↓ food consumption in IMI treated females of F0 and F1 generation

Abbreviations: ↑=increase; ↓= decrease; ↔ = no effect; ALT=alanine aminotransferase; bw=body weight; CAT=catalase; E2=oestradiol; F1/2=first/second generation of offspring; FSH=follicular stimulating hormone; GPx=glutathione peroxidase; γ-GSH=reduced glutathione; GST= glutathione-S-transferase; GT= gamma-glutamyl transpeptidase; 3ß-HSD= 3ß-hydroxysteroid dehydrogenase; 17ß-HSD= 17ß-hydroxysteroid dehydrogenase; IMI = imidacloprid; LDH-x= lactate dehydrogenase-x; LH=luteinizing hormone; LPO=lipid peroxidation; P4=progesterone; P/F0=parental generation; SDH=sorbitol dehydrogenase; SOD=superoxide dismutase; T=testosterone

(LPO) accompanied by lower glutathione (GSH) levels in the testes of the exposed rats resulted in impaired fertility, as evidenced by increased germ cell apoptosis and fragmentation of seminal DNA, lower serum testosterone level and higher rate of sperm abnormalities. The authors associated these adverse effects with the induction of oxidative stress in the testes, which are particularly sensitive to oxidative damage due to the presence of polyunsaturated fatty acids.

In female rats, Kapoor et al. (25) reported that exposure to imidacloprid (20 mg kg^{-1} day^{-1}) for 90 days caused changes in the ovarian morphology, reduced its weight, and adversely affected serum follicle stimulating hormone (FSH), luteinizing hormone (LH), and progesterone levels. The authors also reported induced oxidative stress, evidenced by lower activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and GSH and increased LPO level.

These studies were the first to suggest the mechanisms of adverse imidacloprid effects on male and female reproduction. Later research reported higher LPO and lower GSH levels, as well as lower CAT, SOD, GPx, and

glutathione *S*-transferase (GST) activities in male rats exposed to higher doses of imidacloprid (45 and 90 mg kg^{-1} bw, corresponding to 1/10 and 1/5 of LD_{50}) for 28 days and confirmed that oxidative stress is the mechanism that leads to reproductive toxicity of imidacloprid (24).

Reproductive toxicity of imidacloprid was also studied following *in utero* exposure of the female offspring of pregnant rats receiving 10 mg kg^{-1} bw of imidacloprid through the tail vein from gestation day 7 to 21 (26). The offspring showed disrupted follicular development, lower oestradiol and progesterone levels, lower ovarian weight and diameter as well as decrease in the rate of successful mating and reduction in foetal number due to down-regulation of ovarian *DAX1* gene compared to controls.

In a two-generation, two-litter study in rats Suter et al. (27) reported no adverse effects on the reproductive function or birth defects of imidacloprid exposure before and during mating, gestation, and lactation. However, the authors found decreased body weight in mother rats and male and female offspring that was associated with reduced food consumption at dietary imidacloprid dose of 700 ppm (corresponding to 47 mg kg^{-1} bw day^{-1}). In a three-generation reproductive study (28) oral administration of 20 mg kg^{-1} bw day^{-1} of imidacloprid affected body weight and food consumption and caused only minimal effects on the reproductive performance such as reduction in fertility index in the second and third generation.

Neurotoxicity as the consequence of imidacloprid exposure *in utero* has been investigated in rat offspring by Abou-Donia et al. (29). Gestational exposure to a single large dose (0.75 of the LD_{50}) of imidacloprid caused developmental neurobehavioral deficits and increased the expression of glial fibrillary acidic protein (GFAP) in the brain regions of 30-day-old offspring with possible long-term adverse health effects. An *in vitro* investigation by Gu et al. (30) has shown adverse effects of direct exposure to imidacloprid on the sperm function and embryonic development that may also present a risk for human reproductive health.

Investigations in other laboratory animals showed no adverse effects of imidacloprid exposure on the early development of the zebrafish (*Danio rerio*) (31), but in male rabbits (*Oryctolagus cuniculus*) it was associated with testicular damage that can lead to infertility and reproductive disorders (32).

ENDOCRINE DISRUPTION

Many pesticides, including imidacloprid, can affect the normal functioning of animal endocrine systems by interfering with natural hormones. Due to their strong affinity for oestrogen and androgen receptors, they can activate these receptors and mimic hormonal action or block the receptors and inhibit their action. In addition, endocrine disrupting pesticides can interfere with the synthesis, secretion, transport, metabolism, binding, or elimination of natural hormones (32).

Some investigations imply that exposure to environmental endocrine disruptors could be the generative cause of obesity (34, 35). This may also be true for endocrine disrupting pesticides. Imidacloprid's role in obesity was investigated in a study in which mice were exposed to low doses (0.5 % of the LD_{50}) of dithiocarbamate mancozeb and imidacloprid from postnatal day 1 to weaning (postnatal day 28) through lactating mother. The exposure to individual pesticides did not disrupt hormonal/metabolic homeostasis or affect body weight gain, but exposure to their combination did (36). An *in silico* study by the same authors showed that imidacloprid and mancozeb disrupted steroid hormone biosynthesis by impairing the activities of the cytochrome P450 (CYP) enzymes that have a key role in the synthesis and breakdown of various steroid hormones (37). Several studies have shown that imidacloprid potentiates adipogenesis in 3T3-L1 adipocytes and induces insulin resistance in C2C12 myotubes (38, 39). The same group of authors reported that oral exposure to low doses (0.6 and 6 mg kg^{-1} bw day^{-1}) of imidacloprid for 12 weeks in male and female C57BL/6J mice enhanced high fat-diet adiposity by mechanisms that still need to be clarified. Insulin resistance observed in male mice was not confirmed in females, which was explained by potential sex differences (40, 41).

CONCLUSION

Animal study evidence is pretty clear about the risks involved in imidacloprid exposure for male and female reproduction. It may alter essential reproductive functions by affecting hormone levels and cause reproductive organ disruption and suppression of their function, which may lead to infertility. *In utero* exposure to imidacloprid can significantly affect offspring development with lasting adverse consequences in adulthood. The European Commission has restricted the use of imidacloprid and two other neonicotinoids since 2013 due to their potential role in the collapse of the bee population (42). The updated risk assessment report regarding neonicotinoids was issued by the European Food Safety Authority in February 2018 (43). Although it points to risks for honeybees, the decision regarding a possible EU-wide ban of neonicotinoids was not made and remains the responsibility of the European Commission and Member state authorities. Nevertheless, since imidacloprid is still widely used, more measures should be taken to minimise its adverse effects.

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Conflicts of interest

The authors declare no conflict of interest.

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Imidakloprid kao reprodukcijski toksikant i endokrini disruptor: istraživanja na laboratorijskim životinjama

Imidakloprid, neonikotinoidni insekticid, koristi se diljem svijeta zbog svoje selektivne toksičnosti za insekte. S obzirom na to da njegovi ostaci mogu ući u hranidbeni lanac, važno je istražiti potencijalno štetne učinke izloženosti imidaklopridu. U ovom preglednom radu prikazani su podaci o reprodukcijskoj toksičnosti imidakloprida i njegovim učincima kao hormonskog otrova u laboratorijskih životinja. Istraživanja koja su provedena uglavnom na laboratorijskim štakorima pokazala su štetne učinke imidakloprida na reprodukciju roditelja i potomstva, kao i na razvoj potomstva. Poput mnogih pesticida, imidakloprid može djelovati i kao hormonski otrov te poremetiti ne samo metaboličku ravnotežu i pridonijeti povećanju pretilosti nego i steroidogenezu inhibicijom aktivnosti sustava enzima citokrom P-450 (CYP). Svi ti štetni učinci imidakloprida mogu predstavljati ozbiljan rizik za reprodukciju i razvoj s dugoročnim štetnim posljedicama u odrasloj dobi.

KLJUČNE RIJEČI: *endokrina disrupcija; insekticid; laboratorijski štakori; neonikotinoidi; reproduktivna toksičnost*