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Reproductive Toxicity of Organophosphate Pesticides

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Abstract

In recent years, second generation of Organophosphate Pesticides (OP), due to their target specific actions and low bioaccumulation properties, have replaced the most persistent organochlorines. However, subsequent studies revealed acute toxicity of organophosphates in non-target animals. Besides causing mortality, some OPs even at very low doses are known to affect the physiology of reproduction in higher vertebrates. Chronic sub-lethal exposure of birds to OPs may lead to reduced fertility, suppression of egg formation, eggshell thinning and impaired incubation and chick rearing behaviors. Likewise, OP-induced changes in sexual behavior and performance, adverse effects on onset of puberty, gamete production and transport, abnormal reproductive cycle, premature reproductive senescence and infertility are reported in several mammalian studies. Due to their ability to cross the placental barrier, different OPs may affect the fetal brain, growth, and survivability in rats. The mechanisms by which OPs induce reproductive toxicity in animals include altered release of neurotransmitters leading to impaired functions of Hypothalamo-Pituitary-Gonadal (HPG) regulatory axis, and/or suppressed steroidogenesis in the gonads. This review essentially summarizes existing information on the adverse effects of organophosphates on the reproductive functions in higher vertebrates and underlines the potential mechanism of reproductive toxicity induced by them.

Keywords: Organophosphate pesticides; Reproductive toxicity; Birds; Mammals

Introduction

Environmental contamination is a threat to living system in every corner of world and thus a wide range of animals as well as humans are progressively confronted with a large number of hazardous chemicals. Over the past two decades, the release of synthetic chemicals by industry, agriculture and other activities has increased by 20%. Miscellaneous anthropogenic sources of xenobiotics essentially include manufacturers of chemicals and drugs, domestic sewage, polymer and petrochemical-based industries, oil refineries, mining sites, glass blowing factories, and many others. However, pesticides and heavy metals are the most prevalent xenobiotics arising out of agricultural and industrial activities. A wide variety of chemicals like insecticides, pesticides, and herbicides are used to enhance the agriculture production. Globally 4.6 million tons of chemical pesticides are sprayed annually into the environment [1].

Acute as well as lethal poisoning of wild life due to toxic chemicals in the environment are reported extensively in the literature [2,3]. The major classes of agricultural stressors are the pesticides. Rachel Carson in his book 'Silent Spring' elucidated publicly that indiscriminate application of pesticides and other chemicals are polluting water bodies, impairing lives of different free-living animals and causing health problems in humans [4]. Neurotoxic nature of organochlorine, organophosphate, carbamate, pyrethroid, neonicotinoid insecticides is generally implicated to behavioural disturbances in animals, and thereby directly or indirectly leads to adverse changes in their population. High concentrations of such compounds persist in the areas like fruit orchards, where organochlorine (OC) pesticides particularly DDT related compounds were intensively used in the past decades [5]. Higher animals (birds and mammals) are unable to excrete easily the metabolites of OC due to their lipophilic nature and high Octanol-Water (Kow) and Octanol-Air partition (Koa) coefficients, resulting in their accumulation in adipose tissues and biological magnification at the end [6]. Residues of P,P′-DDE are reported as high as 105 μg/g in the eggs of Eastern blue bird (Sialis sialis) from Ontario orchards [7] and 302 μg/g in the eggs of American robins in Okanagan orchards (British Columbia) [8]. Thus search for substitutes of persistent chlorinated hydrocarbon compounds having acute biocidal effects has been globally a greatest challenge. As an obvious outcome, organophosphate chemicals, being simple derivatives of

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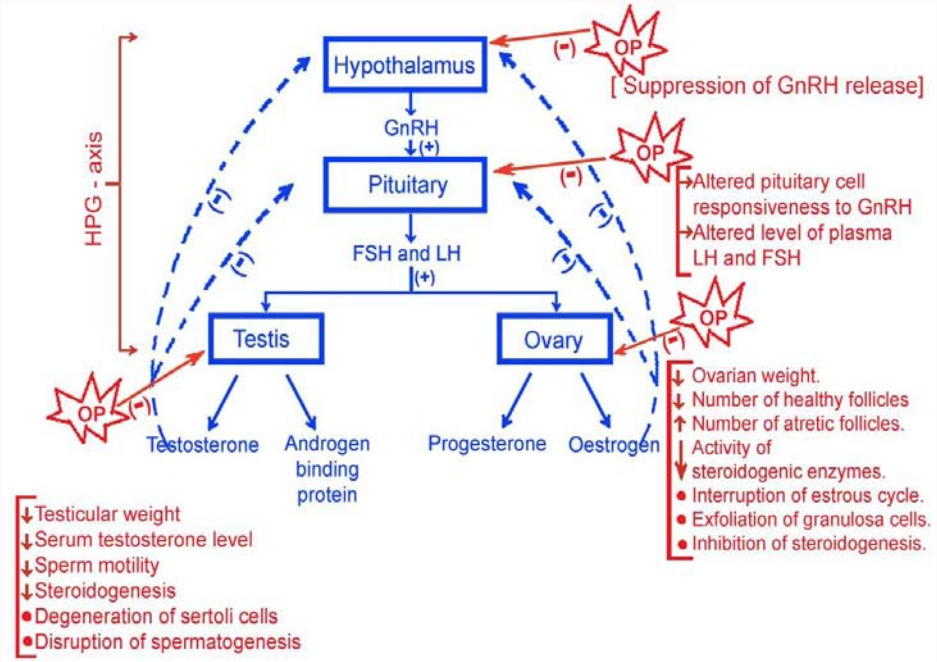

Figure 1: Schematic presentation of the potential target sites of action of Organophosphate (OP) pesticides in the regulation of reproductive functions in male and female vertebrates through HPG (Hypothalamo-Pituitary-Gonadal) axis.

phosphoric and thiophosphoric acids, find easy access to modern life for the control of agricultural pests and disease vectors.

Since 1980s, the second-generation broad-spectrum pesticide Organophosphates (OPs) and Carbamates (CBs), due to their low persistence and low bioaccumulation properties, have gradually replaced the persistent DDT and cyclodienes, and are used as most common pesticides. According to available report, approximately 60 million pounds of OPs are applied to about 60 million acres of U.S. agricultural crops annually, while nonagricultural uses accounted for about 17 million pounds per year [9]. However, the amount of OP insecticides used in the U.S. has declined more than 70% from an estimated 70 million pounds to 20 million pounds in 2012 due to their hitherto unknown acute toxicity on non-target animals [10].

There are manifold reasons for preference of OP pesticides over the organochlorine compounds: (a) Fast degradation in soil and biota [11], low potential to accumulate in the environment [12] and in the tissues of homoeothermic animals [13], (b) Least possibility of movement in ecosystem through food webs [14], and (c) selectivity in causing toxicity to a great extent among insects than among higher vertebrates [15]. Though ecotoxicological effects of organophosphate compounds were less pronounced, adverse effects appeared alarming in non-target animals [16]. Unfortunately, greater acute toxicity of OP than OC compounds leading to male reproductive failure resulted after repeated exposure [17]. In the current scenario, more than 200 OPs are used for a variety of purposes, such as protection of crops, grains, gardens, homes and public health [18] and most of them cause acute and sub- acute toxicity. Besides acute toxicity, OP pesticides may induce several clinical effects like, immunotoxicity, impaired reproduction, endocrine disruption, cellular damage, oxidative stress, and teratogenicity [19].

Different OPs exert adverse effects by irreversible inhibition of Acetylcholinesterase (AChE) at the cholinergic synapses in the central and peripheral nervous systems [20], leading to accumulation of the neurotransmitter acetylcholine at the nerve terminals and neuromuscular junctions which have severe consequences like seizures, respiratory failure, and eventually, death [21,22]. Although OPs were considered safe to non-target organisms, a number of studies reported an alarming decline of bird population (namely sparrow-hawk, mallard, brown pelicans) from the past to recent due to OP poisoning [3,23-26]. Population level impacts are known for several avian species [27]. Large scale monitoring of wading birds in the northeast revealed multiple pathologies linked to water quality loss across a range of urban, suburban and rural estuaries [28,29]. Worldwide, over 100,000 bird deaths appear to cause by the worst organophosphate, monocrotophos [30]. During the last two decades in the past century, about 335 separate mortality events of nearly 9,000 birds due to OP intoxication were reported in the U.S. [31]. Besides large-scale mortality, some OPs cause altered reproductive physiology including direct effects on breeding adults, developmental effects on embryo, reduced fertility, suppression of egg formation, eggshell thinning, impaired incubation and chick rearing behaviors [32]. Direct effects on avian populations may be due to disturbances in reproduction, feeding, or avoidance of predation [19]. Since birds are highly potential for rapid detection of environmental damages [33], healthy avian populations are used as indicators of ecological integrity and declining avian population as alarming indication of collapsing ecosystem [34,35].

Organophosphate-induced reproductive toxicity in mammals is generally manifested by alterations in sexual behavior and performance, onset of puberty, production and transport of gametes, abnormal reproductive cycle, and premature reproductive senescence, infertility, loss of the fetus during pregnancy, or modifications in other functions, which are dependent on the integrity of the reproductive systems in both female and male individuals [36-38]. Animal as well as human studies revealed that OP pesticides have the potential to act as endocrine disruptors. Workers in a Chinese pesticide factory exposed to ethylparathion and methamidophos was

associated with increased serum levels of LH and FSH, and decreased testosterone levels, as assessed by urinary p-nitrophenol levels [39]. In rats, anti-androgenic activity of chlorpyriphos-methyl resulted from binding to androgen receptors [40]. Exposure to dimethoate showed decreased LH serum levels in sheep [41]. In Mexican agricultural workers, a negative association between urinary levels of Dialkyl Phosphates (DAP), a metabolite of OP pesticides and serum levels of FSH and LH was found without significant changes in the levels of estradiol, prolactin, and testosterone [42]. Toxicity of xenobiotics among animals is known to vary in relation to the animal species, route of administration, dose and duration of treatment, diversity of metabolism, tissue penetrating ability and speed of elimination [43]. Any dysfunction in reproductive system ought to initiate gradual decline in the population size of concerned species. Thus, investigation on reproductive ability of the species that survives even after the exposure to xenobiotics necessarily demands special consideration. This review is essentially an attempt to provide basic information on the sub-lethal effects of organophosphates on the reproductive system in higher animals, i.e. birds and mammals, with an additional note on underlying physiological mechanism of reproductive toxicity induced by different organophosphates of common occurrence.

Toxico-dynamics of OP pesticides

The pesticides are used primarily for controlling the population of insects and other hazardous animals. Following restriction on the use of DDT in the 1970s, organophosphates have been the choice of insecticides. The OPs potentially act on nervous system specifically at cholinergic nerves. However, the insects are not the only animals which have cholinergic nerves, rather all the vertebrates have the same. Therefore, application of OPs not only reduces the insect pest population, but undergoes vertical migration to reach the non-target higher animals [44,45].

The mechanism of neurotoxicity induced by OP pesticides has been well studied by a number of workers [2,46-49]. These pesticides are competitive inhibitors of Acetylcholinesterase (AChE), the key enzyme in the transmission of nerve impulses. Some OP compounds have a direct effect on the inhibition of acetylcholinesterase, while others such as parathion is converted in liver to its metabolites paraoxon that inhibits acetylcholinesterase [50]. About 75% of the registered pesticides metabolize to the dialkyl phosphate metabolites [9]. AChE is readily phosphorylated by the OPs at the active site serine [51] and results in an accumulation of acetylcholine (ACh) in the synapse [52] and thereby causes overstimulation of postsynaptic cells [21]. Synaptic acetylcholine may increase to abnormally high concentrations in the presence of an irreversible inhibitor of AChE, which precipitates a cholinergic crisis having a multitude of fatal consequences [53-55]. In the event of acute poisoning, nicotinic and muscarinic cholinergic receptors are affected. In mammals, acute OP poisoning is manifested clinically as hypothermia, lethargy, tremors, depression, convulsions, sweating, blurred vision, coma, paralysis, ataxia, bronchial constrictions, incontinence, nausea, vomiting, and diarrhea [56]. Clinical signs in birds include goose stepping, ataxia, wing spasm, wing droop, dyspnea (difficulty in breathing), tenesmus (spasm of anal sphincter), diarrhea, salivation, lacrimation, ptosis (drooping) of the eyelids and wing beat convulsions. Loss of AChE activity may cause numerous physiological problems for non-target wild as animals, which are unable to thermoregulate [57]. A primary mechanism of tolerance to AChE inhibition depends on the down regulation of postsynaptic cholinergic receptors [21]. The rate of irreversible inhibition by OPs may exceed the rate of 10^5-$10^6 \times M^{-1} \times min^{-1}$ [58].

The phosphorylated enzyme is extremely stable and the spontaneous regeneration of the active cholinesterase enzyme is a slow process that sometimes requires several hours. The degree of inhibition of AChE by OPs varies in relation to the chemicals [59], animal species, age, sexes, sexual status of the affected animals [60-64], environmental temperature [65] and also to the level of exposure [49,61,66-69]. A quantitative study reveals that mean plasma cholinesterase inhibition considering both generation and all test compounds may be of about 74% for females, whereas 51% inhibition may occur in males [70] denoting greater sensitivity in females than in males. The birds appear more sensitive to cholinesterase inhibitors than mammals (predicted LD50 values in sensitive birds is below 1 mg kg^{-1} body weight, whereas in rat this value is <10 mg kg^{-1} body weight) [71,72]. Due to high activity of AChE in the brain of birds, the rate of binding of cholinesterase inhibitors to AChE is more rapid in birds than in other animals [73,74]. Greater susceptibility of avian species to the toxic effects of this compound may also be due to relatively low levels of anti-cholinesterase detoxifying enzyme activity in birds [75]. Complete recovery of AChE activity in animals, which survive after OP exposure, occurs primarily by dephosphorylation (spontaneous reactivation) of inhibited AChE and by synthesis of new AChE [15]. The rate of recovery of AChE activity depends upon the chemical nature of OP [2], the degree of inhibition [76], and the ambient temperature [77]. A rapid initial recovery of AChE from 50% to 60% of normal, followed by a slower rate of recovery until the normal levels attained, is observed in all the studied animals [78,79]. An inhibition of Cholinesterase (ChE) activity occurs more rapidly in plasma than in brain [80]. AChE activity in the brain requires less than 30 days to reach the normal levels [81]. Analysis of brain cholinesterase activity is routinely used as biomarker for monitoring the exposure to anti cholinesterase agents which help to assess the exposure and effects of OPs on non-target animals [82,83]. However, plasma AChE activity may also be considered indicative of the central nervous cholinergic status [84].

Poisoning of some OPs (chlorpyrifos, dichlorvos, isofenphos, methamidophos, mipafox, trichlorfon, trichlornat and phosphamidon) may lead to development of secondary symptoms called OP-induced delayed neuropathy (OPIDN), in which phosphorylation occurs in brain Neuropathy Target Esterase (NTE) that affects limb immobility in exposed individuals [85]. OPIDN is characterized by demyelination of nerve fibers and paralysis, which can be observed 2-3 weeks after single or repeated exposure(s) [57]. Laboratory and controlled field studies reveals that influences of OP exposure on wild animals are diverse and often diligent in nature.

Impact of organophosphates on the reproductive functions

In wild birds: Consumption of pesticide contaminated foods is one of the naturally occurring phenomena in wildlife especially birds. Critical assessments of the effects of pesticides on avian systems clearly reveals that adult mortality, reduced fecundity, and partial sterility induced by pesticides could differentially reduce reproductive potential according to the rate of population turnover [86]. Since most of the wild birds attain sexual maturity only once in a year [87], the latter two effects may cause significant changes in the population size of such wild birds. OP insecticides exclusively affect almost all body functions [88] that may provide an insight to the population and ecological consequences of long-term exposures [89].

The OP induced behavioral changes in avifauna include interference in thermoregulation, food consumption, sexual behavior, clutch size, embryonic development, mobility, migratory behavior, territorial behavior and parental care [57,90]. Such effects have the potential to reduce the survival and reproductive fitness, which ultimately affects the population up to local extinction of several bird species [57].

Exposure of adult female bobwhite quail (Colinus virginianus) to parathion for 10 days is known to cause decreased egg production (>50 ppm parathion) and impaired follicular development (>100 ppm parathion) [13]. Significant reductions in plasma progesterone, corticosterone and luteinizing hormone are also observed in female quail following ingestion of 100 ppm parathion for 10 days in comparison to 0 or 25 ppm parathion ingested birds [91]. The reproductive disorders following short-term ingestion of parathion are attributed to imbalance of steroid hormones. Cholinergic component of the hypothalamus might be responsible for the OP-induced reduction in plasma LH levels in quail [92].

Existing information on the influences of very low doses of OP pesticides on gonadal functions in wild birds is limited mostly to the studies on parakeets and munias. An experimental study on adult male rose-ringed parakeets (Psittacula krameri) demonstrated for the first time that oral administration of phosphamidon at a dose of 70 µg/kg body weight/day for 10 days leads to impaired testicular functions [93]. Another study using the same pesticide at graded but relatively low doses (i.e. 5 µg -or 10µg-, or 20 µg/100 g body wt/day) for durations varying from 1 day to 10 days reveals a dose and duration dependent degenerative changes, including exfoliation and vacuolation of germ cells leading to gradual loss of healthy germ cells in the seminiferous tubules, but no remarkable changes in the Leydig cells, of testes [94,95]. When the birds are treated separately with quinalphos or methyl parathion for 1 day or 5 days or 10 days, gradual decrease in paired testicular weight and seminiferous tubular diameters along with progressive degenerative changes in seminiferous epithelial cells are pronounced, and the response varies in relation to the dose and duration of the ingested pesticides [96,97].

The effects of oral administration of phosphamidon, quinalphos and methyl parathion have also been studied in munia (Lonchura malabarica), a wild passerine bird [95,98,99]. Notably, several degenerative changes in the testicular germ cells are observed in the quinalphos ingested birds, but none of these features could be ascribed as the marker for the level of exposure [95]. However, the study depicting a significant negative correlation between testicular AChE activity and the percentage of tubules with degenerated germ cells suggests that the anti-gonadal action of given pesticide may be pharmacological in origin. Likewise, phosphamidon-induced anti-gametogenic effects in munias is attributed to compromised cholinergic functions in the brain and/or the testis of concerned birds [98]. Though methyl parathion ingestion is found harmful to gametogenic functions in both parakeets and munias, significant variations are noted among the males at the level of minimum effective dose of the pesticide. Disorganized seminiferous epithelium with partial loss of sperm and appearance of vacuoles are noted in the parakeets after treatment with methyl parathion at a dose of 10 µg - for 5 days [97]. Even single administration of pesticide at the lowest employed dose i.e. 5µg/100 g body wt. induces reproductive disorders by decreasing the number of seminiferous tubules with healthy germ cells [99]. Short-term ingestion of parathion leads to significant decrease in plasma tires of LH, progesterone, and corticosterone in female bobwhite quail [13]. Exposure of parakeets to graded dose of methyl parathion also results in impaired testicular functions along with parallel decrease in circulating milieu of LH and testosterone [48].

Sub-lethal exposure of female white-throated munia (Lonchura malabarica) to different OPs (methyl parathion/phosphamidon/quinalphos) also result in marked degenerative changes in the ovary and significant reductions in the activity of two important steroidogenic enzymes, Δ^5-3β-hydroxysteroid dehydrogenase (3βHSD) and 17β-hydroxysteroid dehydrogenase (17βHSD), in the growing ovarian follicles in a dose-dependent manner [100]. These two steroidogenic enzymes (3βHSD and 17βHSD) in the ovary play regulatory role in the production of oestrogen and progesterone respectively [101]. The degenerative changes in the ovary of OP-treated birds include reduced thickness of membrana granulosa layer, vacuolation and exfoliation of granulosa cells of mature follicles [100]. Taken together, the findings on both male and female birds clearly suggest that OP pesticides even at very low concentrations impair gametogenic as well as steroidogenic functions of the gonads. It is also evident that the nature and extent of damage in the reproductive organs essentially depends on the chemical nature of the pesticide, dose, and duration of the treatment, as well as the species of studied bird.

In mammals: The effects of OP on reproduction have been extensively investigated in rats. Dimethyl Methyl Phosphonate (DMMP) and Trimethyl Phosphate (TMP) are the OP compounds, which evoke sterility in rodents, e.g. treatment with DMMP for 5 weeks results in occasional multinucleated giant cells composed of late spermatids in stage X, XI, XII a cytoplasmic vacuolation of Sertoli cells [102]. Chronic exposure of wister rats to methyl parathion causes decrease in the weight of seminal vesicle, epididymis and prostate gland [103,104]. Other OPs like pirimiphos-methyl, profenofos, malathion, and chloropyrifos also have similar effects [105-109]. Significant changes in the testicular histology, testosterone level, testicular sperm counts, and morphology of sperm result from chlorpyrifos toxicity [109]. A negative correlation is found between dialkyl phosphate metabolites with serum FSH and LH levels in men who are occupationally exposed to a variety of chemical pesticide [38].

Administration of methyl parathion at a daily dose of 5 mg/kg body wt to hemicastrated virgin rats for 10 or 15 days results in significant decrease in ovarian weight gain with 21.36% and 31.98% hypertrophy respectively, as well as a significant decrease in the number of healthy follicles but no changes in the number of atretic follicles. Moreover, the number of estrous cycles and the duration of each phase of the estrous cycle are significantly affected in pesticide treated rats [110]. Monocrotophos treatment at the dose of 1.2 mg/kg/day for 10 days results in reduced ovarian weight [111]. Another OP, Diethylumbelliferyl Phosphate (DEUP), was shown to block the cAMP stimulated mitochondrial accumulation of 30 Kda mitochondrial StAR protein to cause impaired steroidogenesis [112]. Several OP pesticides interrupt the estrous cycle and decrease the number of healthy follicles with increased atretic follicles [113,114]. Exposure of adult female wister rats to diazinon (60 mg/kg for 2 weeks) induced apoptosis in the ovarian follicles [115]. Acute exposure of female wister rats to malathion also induced oxidative stress and increased number of apoptotic follicles [116]. Treatment of quinalphosphos for 30 days in rats leads to reduced number of

healthy follicles, frequent atretic follicles in the ovary and decreased thickness of myometrium of uterus [117].

Potential mechanisms of organophosphate-induced reproductive toxicity

Alteration in the reproductive behavior following ingestion of sub-lethal concentrations of OP compounds may be endocrinological and/or pharmacological in origin. Several studies suggest that OPs may influence reproductive functions in vertebrates by altering neurotransmitter levels and thereto impair Hypothalamo-Pituitary-Gonadal (HPG) regulation of reproduction [114,118] (Figure 1). Another possibility is disturbance in hormonal homeostasis by suppressing the release of hypothalamic GnRH that may directly impair gonadotropin synthesis and secretion or, indirectly alter the pituitary cell responsiveness to GnRH through the actions of gonadal steroids resulting from reduced levels of FSH and LH by feedback mechanism [119]. OPs may cause endocrine disruption either by direct interaction with receptors or alteration of the enzymes involved in the synthesis and metabolism of steroid hormones [120] to result adverse effects on reproduction and development [121,122]. OPs can affect the endocrine system at any stage of hormonal regulation from synthesis to hormone receptor binding [123].

The anti-gonadal effects of OPs may be due to their inhibitory effects on the synthesis of steroid hormones. Abnormality in the estrous cycle, like prolonged diestrus, decreased number of healthy follicles, and increased number of atretic follicles in the mice ovary due to exposure of carbofuran may result from reduced synthesis of steroids in the ovary and an imbalance in the estrogen and progesterone ratio [114]. Repeated exposure to dimethoate leads to decreased serum testosterone levels, testicular weight, sperm motility and increased the percentage of dead and abnormal sperm in both rats and rabbits [124]. Since adequate levels of testosterone critically regulate spermatogenesis and fertility, the ability of dimethoate to reduce testosterone levels in serum may contribute to the reduction in spermatogenesis and fertility in pesticide exposed animals. Although OPs reduce serum steroid hormone levels by enhancing steroid catabolism and elimination, several studies suggest that these compounds directly inhibit the process of steroidogenesis. OP pesticides are potent inhibitors of the production of primary metabolites of CYP3A4 and major testosterone metabolites noncompetitively and irreversibly [125]. Dimethoate exposure leads to inhibited steroidogenesis in a dose and time-dependent manner by blocking transcription of the Steroidogenic Acute Regulatory (StAR) gene [126], the product of which (StAR protein) mediates the rate limiting step in steroidogenesis - the transfer of cholesterol from the outer to the inner mitochondrial membrane. Sub-lethal chronic treatment of quinalphos results in elevated levels of serum LH, FSH, prolactin, and testosterone, and severe disruption in spermatogenesis in adult rats [68]. An increased serum prolactin influences the population of LH receptors in the Leydig cells to augment testosterone release [127].

Conclusion

Organophosphate compounds have been increasingly popular for agricultural, industrial, as well as domestic uses. They are less persistent in nature, but a large number of studies unequivocally demonstrate that OP compounds are not safe for not only non-target animals but humans as well, even when they are exposed to very low concentrations for long duration. Now it is well established that an indiscriminate and excessive use of these compounds may exert serious impact on reproductive system by acting on the endocrine system in vertebrates. The anti-gonadal effects of OPs may primarily be due to their potent anti-acetylcholine esterase actions in the cholinergic nervous system, which may lead to impaired functions at any levels of the hypothalamo-pituitary-gonadal axis or a direct inhibitory action on the testis/ovary. There are several recommendations for pharmacological use of atropine (an antagonist to muscarinic receptors of acetylcholine) and pralidoxime (reactivates AChE) for treating acute poisoning of OPs. However, monitoring and prevention of OP-induced reproductive dysfunctions remain as a major concern and thus warrant serious attention for management of pesticides in the regulation of insect pests as well as for protection of human health. Pesticide authorization body aims to limit the harm of pesticides on non-target species, though measures for reducing risks from pesticides are far from being reached. Nonetheless, regulatory controls alone are not sufficient to reduce the impact on non-target species, additional initiatives are required to mitigate the effects of pesticides on biodiversity and protection of reproductive health of human beings.

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