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Pesticide- and sex steroid analogue-induced endocrine disruption differentially targets hypothalamo–hypophyseal–gonadal system during gametogenesis in teleosts – A review

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ABSTRACT

Pesticide-induced endocrine disruption often mimics sex steroidal action resulting in physiological functional disarray of hypothalamo–hypophyseal–gonadal (HHG) system at multiple levels. Among various group of pesticides, organochlorine and organophosphate family of pesticides are known to impart sex steroidal mimicking activity with slightly higher resemblance to estrogens when compared to androgenic action. This review will highlight the effects of organochlorine (for e.g. endosulfan) and organophosphate (for e.g. malathion) pesticides in comparison with sex-steroid analogue-induced changes on HHG axis during gametogenesis in few teleost fish models. Interestingly, the effects of these compounds have produced differential effects in juveniles and adults which also vary based on exposure dosage and duration. Further, the treatments had caused at times sexually dimorphic effects indicating that the action of these compounds bring out serious implications in sexual development. A comprehensive overview has been provided by considering all these aspects to recognize the adverse impacts of pesticide-induced endocrine disruption with special reference to endosulfan and malathion as those had been applied even today or used before for controlling agricultural pests in several Asian countries including India. This review also compares the effects of sex-steroid analogues where in sex reversal to reproductive dysfunction is evident, which may imply the extent of sexual plasticity in teleosts compared to other vertebrates.

1. Introduction

Pesticides can be categorized by target pests such as insecticides, nematicides, molluscicides, rodenticides, fungicides, herbicides, plant growth inhibitors and others. Among these, organochlorine and organophosphate family of pesticides were often used to control various insect pests which might have the possibility to end up in the aquatic ecosystem due to their extensive usage and run off from agricultural crop fields. Teleost fishes are excellent animal models due to their competency in showing sexual plasticity and sensitivity to sex steroids or xenobiotics which may also imply the non-target effects of these compounds (Nagahama, 2005; Dutta-Gupta, 2013). Interestingly, pesticides tend to mimic sex steroidal activity more like analogues and hence it is important to compare the potential effects of sex steroid analogues to understand the molecular mode of action of certain pesticides. Considering the ability of pesticides to mimic like sex steroids, molecular action of these compounds often target hypothalamo–hypophyseal–gonadal (HHG) axis at multiple levels resulting in disarrayed gametogenesis. This review specifically highlights the impact of organochlorine (for e.g. endosulfan) and organophosphate (for e.g. malathion) family of pesticides due to their broad usage in the past and/or present in the Asian sub-continent including India. Though endosulfan is banned or phased-out in several nations including India in Stockholm convention on persistent organic pollutants held at Geneva during April 2011 by the UN convention for production and use, it is important to analyze the serious effects caused by this compound in the past due to their persistence in the environment. After the ban of endosulfan, malathion belonging to organophosphate family is used extensively even today due to its short half-life and high selectivity to target insect pests. Molecular mode of action of these compounds mimics sex steroidal activity resulting in the modulation of gonadal development and growth by targeting HHG axis which is a serious point of concern for discussion. In addition to these, the effects of certain other organochlorine and organophosphate pesticides are discussed to understand their impact on aquatic environment using teleosts as animal models. Molecular chemical structure of pesticides and sex steroid analogues mentioned in this review is depicted in Fig. 1.

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1.1. Organochlorine family of pesticide-induced endocrine disruption at the level of HHG axis

The major organochlorine pesticides include dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenylethylene (DDE), aldrin, dieldrin and endosulfan. Among these, endosulfan was most abundantly used and banned recently for pesticidal use in several nations including India because of their acute toxicity at various levels. Interestingly, all those compounds mentioned earlier are referred as environmental estrogens (Narita et al., 2007). Endosulfan exposure had caused considerable damage at animal and human levels in several Asian subcontinent nations including India and alarmingly high levels of endosulfan were found in the aquatic ecosystems before being proposed for ban/phase-out (see Rajakumar et al., 2012). The effects of endosulfan when compared to other organochlorine pesticides at various levels emphasize the extent of toxicity of organochlorine pesticides for complete phase-out of this family of pesticides.

1.1.1. Endosulfan

Endosulfan (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3- benzodioxathiepin-3-oxide) is a broad spectrum insecticide and acaricide first registered for agricultural field use in the United States in 1954 to control agricultural insect and mite pests on agricultural crops, which was then utilized by several other nations for similar purpose. Technical-grade endosulfan is composed of two stereochemical isomers, namely α- and β-endosulfan, in concentrations of about 70% and 30%, respectively (Stanley et al., 2009). Extensive usage of the commercial formulations of endosulfan before might have reached the aquatic environment surrounding agricultural fields either through atmospheric transport or field runoff as concentrations ranging in the low part per billion measured in streams and rivers bordering these areas (Hose et al., 2003; Wan et al., 2005a,b). Evidence for the presence of endosulfan in fish from remote water bodies throughout the U.S., Canada, Europe and India were already demonstrated in the last two decades (Simonich and Hites, 1995; Ahmad et al., 1996; McConnell et al., 1998; LeNoir et al., 1999; Rao and Pillala, 2001; Vilanova et al., 2001; Carrera et al., 2002; Stern et al., 2005; Usenko et al., 2007; Ackerman et al., 2008; Begum et al., 2009; KSCSTE, 2011). Endosulfan I and II are primarily metabolized to diol form in water and sulfate form in soil and sediment after reaching the environment (Hose et al., 2003). The endosulfan sulfate and diol can further break down to ether, hydroxyl ether, lactone and alcohol forms (Hose et al., 2003). Among these by-products, endosulfan sulfate is potentially toxic and persistent (Berntssen et al., 2008). Though the half-lives of endosulfan I and II in water are on the order of days to months, endosulfan sulfate is on the order of weeks/months to years (Leonard et al., 2001; Wan et al., 2005a), which is a serious point to debate as there are nations which had inadvertently used endosulfan including aerial exposure before ban/phase-out (KSCSTE, 2011). It is also noteworthy to mention that both forms of endosulfan metabolites are more persistent in sediment (Leonard et al., 2001; Wan et al., 2005a). This is a stern point to ponder as this should pave way for previously sedimented endosulfan metabolites to reach aquatic environment where pond culturing of fish are practiced even today in several nations including India. Hence, it is highly appropriate to understand the detrimental effects of this compound to tackle those aquatic environment or terrestrial areas where alarmingly high level of exposure occurred in the past which might show some residual effects (KSCSTE, 2011).

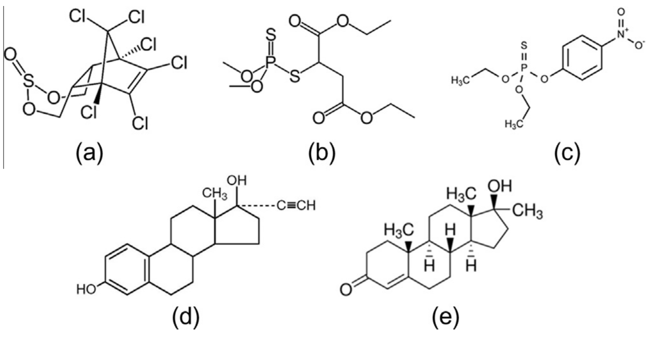

Fig. 1. Molecular chemical structure of pesticides and sex steroid analogues. (a) Endosulfan, (b) malathion, (c) parathion, (d) ethynylestradiol, and (e) methyltestosterone.

In general, endosulfan and its metabolites are toxic to majority of aquatic organisms including fish and the LC_{50} values ranges between 1 and 100 μg/L depending upon the fish species and stage of exposure, for example, 0.8 μg/L for rainbow trout (Hose et al., 2003), 1.6 μg/L for zebrafish (Jonsson and Toledo, 1993) and 60 μg/L for the Asian catfish (Tripathi and Verma, 2004). The values of LC_{50} for selected fish species are depicted along with duration of usage in Table 1 not only for endosulfan but also for other pesticides discussed in this review. Like many other organochlorine pesticides, endosulfan also exerts neurotoxicity by the blockade of gamma-aminobutyric acid (GABA)-gated chloride channels (ATSDR, 2000; Jia and Misra, 2007) in mammals. Though this mechanism is not demonstrated in pisces, yet juvenile zebrafish shows symptoms of neurotoxicity upon exposure to low levels of endosulfan (Stanley et al., 2009). Most of the earlier reports in a variety of teleosts demonstrated genotoxicity, embryotoxicity and impaired vitellogenesis process (Chakravorty et al., 1992; Willey and Krone, 2001; Palma et al., 2009) after exposing to high doses of endosulfan.

Being estrogenic, endosulfan is known to impart serious effects on reproductive system. Earlier studies using high dose exposure of endosulfan, both technical and commercial formulations revealed deleterious effects on ovarian recrudescence in freshwater fish, *Channa punctatus* (Haider and Inbaraj, 1986). In accordance to this, Pandey (1988) had also shown blockade of oocyte development upon exposure to endosulfan in *Colisa (Trichogaster) fasciatus*. In another study, it has been demonstrated that endosulfan acts in a dose-dependent manner to cause ovarian regression in *Lepomis macrochirus* (Dutta and Dalal, 2008). Most of the earlier studies often used adult fish or embryos exposed to high levels of endosulfan (Pandey, 1988; Stanley et al., 2009). Thus, many reports which had analyzed the effects of endosulfan earlier often had common deleterious effects due to usage of high doses. Further, earlier studies done in Indian laboratories often used wild caught laboratory acclimated fish instead of laboratory reared ones free of previous contamination. Considering this standpoint, more refined approaches are necessary to evaluate the effects of endosulfan in terms of eco-relevant dose and laboratory reared fishes with specific age to understand the potential and residual effects. In the first instance, use of wild caught fishes for pesticidal toxicological studies is not advisable as the age and previous pesticidal exposure history is lacking before the treatment. Next aspect is the dosage wherein the treatments performed in earlier reports considered LC_{50} values rather than exposing animals relevant to doses found in certain environment. In this regard, more recent reports from our laboratory (Chakrabarty et al., 2012; Rajakumar et al., 2012) revealed differential effect of endosulfan at eco-relevant low doses using the Asian catfish, *Clarias batrachus* as animal model with definite age groups. Such an attempt was not done in other annually breeding teleosts during early development. Exposure of endosulfan to 50 days post hatch (dph) catfish juveniles for fifty days resulted in the upregulation of ovarian aromatase activity and estradiol-17β (E_2) levels (Chakrabarty et al., 2012). In accordance