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Review Article

Teratogenic potential of pyrethroids: a review

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Abstract
Pyrethroids are modern synthetic insecticides commonly used for house hold and agriculture purposes and are extracted from the flowers of pyrethrums (*Chrysanthemum cinerariaefolium* and *C. coccineum*) in late 1900s. An extensive data on multiple aspects of genotoxicity, carcinogenicity, mutagenicity, reproductive toxicology and neurotoxicology is available except teratogenicity. This review concludes the teratogenic potential of sublethal doses of different types of pyrethroids in various groups of animals in systematic way. On line available data interpretation through Pubmed Central NCBI, Google Scholar and Google was done to achieve the target and 122 references were found the most relevant in this perspective.
Keywords: Pyrethroids, teratogenicity, malformations, Deltamethrin, Cypermethrin, Permethrin, Lambda-Cyhalothrin, β-Cyfluthrin, Esfenvalerate, Fenvalerate, Tefluthrin, Bifenthrin, Alethrin, Flumethrin

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INTRODUCTION

Pyrethroid insecticides are commonly applied in homes and on some agricultural crops (Walters *et al.,* 2009; Soderlund, 2015). They are broadly classified into two types: Type I such as permethrin, usually deficient for cyano group, while most Type II, such as cypermethrin and fenvalerate, always do (Ray and Forshaw, 2000). Among the most common pyrethroids are: allethrin, fenpropathrin, lambda-cyhalothrin, barthrin, bioresmethrin, bioallethrin, cyfluthrin, deltamethrin, dimethrin, fenothrin, flucythrinate, furethrin, phthalthrin, resmethrin, metofluthrin, tetramethrin, tralomethrin, biopermethrin, allethrin, silafluofen, fluvalinate, bifenthrin, transfluthrin, fenpropanate, cypertmethrin, fenvalerate, cyphenothrin, permethrin, resmethrin, esfenvalerate, cismethrin, etofenprox, tau-fulvalenate, fenpropathrin, flumethrin, imiprothrin, prallethrin, sumithrin, tefluthrin, tralomethrin, (Roberts and Reigart, 2013; https://en.wikipedia.org/wiki/ Pyrethroid # Types). The classic signs of pyrethroids induced toxicity are tremors and choreoathetosis with salivation. However, some may cause developmental neurotoxicity (Tsuji *et al*., 2012). They are axonicexcitoxins with known mechanism of causing failure of closure of the voltage gated sodium channels (Soderlund *et al*., 2002).Reduced birth weights have been recorded in response to prenatal exposure to pyrethroids (Ding *et al*., 2015). Susceptibility of an individual to teratogenesis depends upon genetic makeup, diet, lifestyle, and their environmental exposure (O'Brien *et al*., 1996). Prenatal exposure among prepubescent boys to pesticides had reduced the volume of testes and penile length (Wohlfahrt-Veje *et al*., 2012). Pyrethroids have been found to produce developmental anomalies of various intensities even at sublethal doses in different groups of animals (Table I).

I. Deltamethrin

Sea Urchin

Embryonic exposure of the sea urchin (*Paracentrotus lividus*) to increased strength of deltamethrin (6.10^{-5} and 6.10^{-2} µg/L) is known to affect spermiogenesis. In addition to dose-related toxicity on early cleavage, accelerated kinetics of early divisions, decreased average size of pluteus larvae, several developmental anomalies like fused and thin arms, and changed larval shape were observed (Gharred *et al*., 2015).

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Table I: Summary of teratogenicity of some pyrethroids

Compound Name	IUPAC/ Formula/Common Name	Experimental Animal	LC50	Experimental Dose	Affected organ/Disease	References
Deltamethrin ($C_{22}H_{19}Br_2NO_3$)	[(S)-cyano-(3-phenoxyphenyl)methyl] (1R,3R)-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane-1-carboxylate	Sea Urchin		6.10^{-5},6. 10^{-2} µg/L	Abnormal spermiogenesis, early development, fused and thin forelimbs	Gharred *et al*., 2015
		Common carp(Cyprinuscarpio)	24h: 0.17 µg/L 96h: 0.86- 210.0 ppb (Morolli *et al.,* 2006)	0.005, 0.05, 0.5, 5, 25, and 50 µg/L	decrease in hatching success	Koprucu and Aydin, 2004
		*Oreochromisniloticus*L.		5 µg/L	fused lamellae, telangiectasis, and hydropic degenerations	Yildirim et al., 2006
		Zebrafish	0.027ppm (Tarkhani *et al.,* 2012)	0.8 µg /L	Reduced hatching	Gorge and Nagel, 1990
				LC50	craniofacial deformities	DeMicco *et al*., 2010
				0.25-0.50 µg/L	locomotor deficits with	Kung *et al*., 2015
		Japanese quail		-	reduced birth weight	Martin, 1990
		Chick		12.5, 25, 50 µg/ml	mortality, abnormal survivors, and decreased body weight, hematomas, reduced growth, microphthalmia, subcutaneous hemorrhage, ectopic viscera, anophthalmia, microcephaly, anencephaly, exencephaly, poor ossification, ectopic viscera , scoliosis	Bhaskar *et al*., 2013; 2014
		Mice		5µg /g	malformed sperms	Ben *et al.,* 2012
				1 and 3 µg /g	Disrupted Lipid & Glucose metabolism	Armstrong *et al*., 2013
				19.36, 9.7, and 4.8µg/g	Sacral hygromae, microcephally, micromelia, open eyelids, microphthalmia, exophthalmia, cryptophthalmia, anophthalmia, droopingwrist, kyphosis, short tail, increased resorption, reduced bodyweight, crown rump length, brain and eyes circumferences, lengths of hind and forelimbs, tail size. Among histopathological malformations, defective nasal pouch, nasal septum with atrophied inferior cochlea, cleft palate, missed eye ball, pericranial hydrocephaly, degenerate jaw muscles, and necrotic brain, liver and intestinal tissue	Khan and Asmatullah, 2013
		Rat	Intraperitoneal: 58.8 µg/g(Panisha and Sasinovich,1983)	0.08 µg /g	latency to float and striatal activity	Lazarini *et al*., 2001
				0.25, 0.5,1.0 µg /g	alterations in the ontogeny of xenobiotic metabolizing cytochrome P450 isoforms in brain and liver	Johri *et al*., 2006
				0.75 µg /g	neurotoxic effects	Kumar *et al*., 2013
				2.0 µg/g	changes in reproductive behavior	Andrade *et al*., 2002
			67µg /L (Wolansky and Harrill, 2008)	3.35 and 6.70 µg /g	decreased the birth weight and neurobehavioral development	Li *et al*., 2006
				4.0 µg /g	Gonadotoxic	Andrade *et al*., 2002
					Sensitive Na channels	Meacham *et al*., 2008

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Cypermethrin $C_{22}H_{19}Cl_2NO_3$	[Cyano-(3-phenoxyphenyl)methyl]3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate]	*Odontesthesbonariensis* (a teleost)		0.1 µg/L	decreased survival rate	Carriquiriborde *et al*., 2009
		Medaka (*Oryziaslatipes*)		3.1 to 100.0 µg /L	gall bladder and pericardial edemas, spastic movements, spinal curvatures, altered swim bladder inflation	Gonz+ílez-Doncel *et al*., 2004
				40 µg /L	larval deformity	Kim *et al.,* 2008
		Zebrafish	0.05 µg /L(Sathya-¦ *et al*., 2014)	Dose dependent	pericardial edema	DeMicco *et al*. (2010).
				10, 20, 30µg /L	oxidative stress	Yang *et al.,* 2014
				0, 25, 50, 100, 200 and 400 µg /L	oxidative stress through apoptosis	Shi *et al*., 2011
				100µg/L	pericardial and yolk sac edema, crooked body, strong developmental toxicities	Xu *et al*., 2010
		Physalaemusbiligonigerus tadpoles		Sublethal and acute doses	apoptosis in the telencephalon	Izaguirre *et al*., 2000
		larvae of *Ranaarvalis*		Exposure time and dose depenent	twisting, writhing, abnormal swimming, behavioral abnormalities, mortality	Greulich and Pflugmacher, 2003
		larvae of *Bombinavariegata*		Exposure time and dose depenent	increased activity of glutathione S-transferase systems	Greulich and Pflugmacher, 2004
		Bufomelanostictus		0.01, 0.05, 0.1, 0.5, 1.0µg/L	delayed hatching, metamorphosis and limb development	Ghodageri and Pancharatna, 2011
		Pseudacrisregilla, Ranacascadae, and Rana aurora		0.5 and 5.0 µg /L	behavioral abnormalities and increased mortality	Biga and Blaustein, 2013
		Hypsiboaspulchellus		0.34, 0.83,4.18, 8.36 and 34.4 µg /L	lower growth and body length and malformations	Agostini *et al.,* 2010
		Duttaphrynusmelanostictus		0.33 µg/L	catastrophic effect on tadpoles	David *et al*., 2012
		Odontophrynusamericanus		5, 10, 20 or 40µg/L	significant increase in single small micronuclei	Cabagna *et al.,* 2006
		Fejervaryalimnocharis cricket frog)		25 and 50 µg /L	reduced survival, early metamorphosis among the surviving tadpoles, delayed metamorphosis	Nataraj and Krishnamurthy, 2012; Nataraj and Krishnamurthy, 2013
		Xenopuslaevis		sublethal doses	retarded growth and neurotoxicity	Yu *et al.,* 2013; Yu *et al*., 2014
				2.5 and 5.0 µg/L	synthesis of DNA-adducts	Yu *et al*., 2015
		Rhode Island Red Eggs		50 µL/egg	skeletal malformations	Uggini *et al*., 2012
		Chick embryo	676ppm(Anwar and Shakoori, 2010)	50,100,200 and 400 ppm	Decreased content of glycogen, lipid, cholesterol, free amino acid, DNA and reduced crown-rump length, size of brain, eye ball along with under developed eyes, beak and wing buds, micromelia, excardiogenesis, increased sinusoidal spaces in hepatic parenchyma, cytoplasmic vacuolations in hepatocytes, hepatocytic nuclear condensation, fatty degeneration, hydropic degeneration and necrosis of hepatocytes.	Anwar, 2003;(Anwar and Shakoori, 2010)
		Mice	Oral: 485 µg /g (Dahamna *et al*., 2010) Oral: 64 µg /g (Raees *et al.,* 2010)	2.5, 5, and 10 µg /g	delayed development of pinna detachment, eye opening, reduced body weight	Farag *et al*., 2007

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				0.12, 1.2, and 12 µg /g	decreased body and organ weight, dose-dependent decrease in sex ratio, a thinning of epithelium of seminiferous, interstitial hyperplasia, vacuolization of germ cells with increased apoptosis, serum testosterone level, expression of T production-related, mitosis-related and meiosis-related genes and increased estradiol level	Huang and Li, 2014
				3.2, 6.4 and 12.8 µg /g	dose and exposure dependent decrease in fetal density, head circumference and crown rump length, increase in gestational losses, developmental deformities like microcephaly, meromelia, hydrocephaly, drooping wrist, attached pinnae, epinnate ears, skewed neck, extradactyly, round back, hemoregia, forked paws, flipper limbs, torted hid limbs, and kinky tail were observed	Raees *et al*., 2010
		Rat	Oral: 4123 µg /g (Spencer, 1982); Male(Oral):187-326µg/g Female(Oral): 150-500µg /g Oral 250 µg /g (in corn oil) or 4123 µg/g (in water)(Nair *et al*., 2010) 250µg /L(Wolansky and Harril,2008)		immunomodulation of cytotoxic activity	Santoni *et al*., 1997
				1.25, 2.5, or 5 µg /g	decrease in the spontaneous locomotor activity	Singh *et al*., 2014
				25, 50 and 75 µg /g	DNA damage	Murkunde *et al*., 2012
				-	growth hormone and cognitive functions	Singh *et al*., 2015
				50 µg /g	impaired thymocyte differentiation and functioning, increased amounts of adrenaline, noradrenaline, plasma , and T cells	Santoni *et al*., 1998;1999
				55.1 µg /g	cerebral, nasal, ophthalmic, pulmonary, cardiac, and renal deformities, increased number of post-implantation deaths, dwarfness and subcutaneous oedema	Assayed *et al.,* 2010
				75 µg /g	Affected ovarian structure and functions	Molavi *et al*., 2014
				100/µg /g	decrease in glycogen, sialic acid, alkaline phosphatase, testosterone, leutinizing hormone, and follicle stimulating hormone along with increase in protein and cholesterol levels, acid phosphatase activity of testes	Joshi *et al*., 2011
Permethrin ($C_{21}H_{20}Cl_2O_3$)	(±)-3-Phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate	Sea Urchin (*Paracentrotuslividus)*	0.346 µg/L (Erkmen, 2015)	Dose dependent	neural and mental development	Erkmen, 2015
		Medaka (*Oryziaslatipes*)	24h: 0.024µg /ml 48h: 0.011µg /ml (Rice *et al*., 1997)	25, 50, 100, 200 or 300 µg /L	swim bladder with delayed inflation, unable to respond to stimulus; uncoordinated movements, myoskeletal malformations and momentary expansion of gall bladder	Gonzalez-Doncel *et al*., 2003
		Zebrafish	300µg /L (DeMicco et al., 2010)	100, 200, 300µg /L	morphological defects and more oxidative stress	Yang *et al*., 2014
				lethal concentrations	Craniofacial abnormalities	DeMicco *et al*., 2010
		Chick		50, 100 and 200 ppm	Structure & Function of kidney, decreased DNA & RNA content,	Khurshid, 2003

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				25, 50, 100 and 200 ppm	Altered enzyme activity and DNA and RNA content in muscles	Anwar *et al.,* 2004
					Altered enzyme activity, enlarged sinusoidal spaces, hepatocytic necrosis, nuclear condensation and cytoplasmic vacuolations, and hydropic and degeneration	Anwar *et al.,* 2004
				0.3125, 0.625, 1.25 and 2.5µg	spina bifida, gastroschisis, exencephaly, micrognathia, hydrocephaly, micromelia, meningocephalocoel, ectopiacordis, and microphthalmia, decreased body weight and crown- rump length	Andleeb *et al*., 2014
		Mice		2 and 75 µg /g	affected reflexes, swimming and standing ability, locomotor and open field activity	Farag *et al*., 2006; Imanishi *et al*., 2013
Lambda-cyhalothrin ($C_{25}H_{19}ClF_3NO_3$)	1:1 mixture of (S)-α-cyano-3-phenoxybenzyl -(Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl) -2,2-dimethylcyclopropane carboxylate and(R)-α-cyano-3-phenoxybenzyl (Z)-(1S,3S)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl) -2,2-dimethylcyclopropane carboxylate	Zebrafish	110µg /L (DeMicco et al., 2010)	Dose dependent manner	mortality and pericardial edema	DeMicco *et al*., 2010
		Common Carp		0.3, 1.5, 3, 6, and 15 µg/L	impaired growth and imbalanced defensive enzymes	Richterova *et al*., 2014
		Xenopuslaevis		-	enzymatic toxicity	Aydin-Sinan *et al.,* 2012
		Rat	56µg /L (Wolansky and Harrill *et al.,*2008)	0.018% and 0.02% (w/v)	delayed the age of testicle descent, development of fur, ear and eye openings	Gomes *et al*., 1991
				8µg /g	Hormonal imbalance	Tukhtaev *et al.,* 2012
Beta cyfluthrin ($C_{22}H_{18}C_{l2}FNO_3$)	3-(2,2-dichloro-vinyl)-2,2-dimethyl-cyclopropane-carboxylic acid cyano-(4-fluoro-3-phenoxy-phenyl)-methyl ester,	Carp (*Cyprinuscarpio* L.),	24h:0.22µg/L (Morolli et al.,2006)	10 µg/L	blocking sodium channel	Sepici-Dincel *et al*.,2009
		Mice		16 and 32 µg /g	poor ossification, short ribs	Soni *et al*., 2011
					increased mortality, reduced litter size and skull ossification, widened cranial sutures, short or absent ribs, microphthalmia, ventricular hydrocephaly , anophthalmia, and pulmonary as well as subcutaneous edema	Syed *et al*., 2010
				1.25, 2.50 and 5.00 µg/g	microcephaly, anophthalmia, micromelia, dysmorphogenesis, dysplasia and short tail along with other morphometric abnormalities	Ahmad *et al*., 2012
Esfenvalerate ($C_{25}H_{22}ClNO_3$)	(*S*)-α-cyano-3-phenoxybenzyl (*S*)-2-(4-chlorophenyl)-3-methylbutyrate ,	Medaka (*Oryziaslatipes*)		4, 21, 148 µg /g	fertilization and hatching	Werner *et al*., 2002
		Salmon (*Oncorhynchustshawytscha*)		10 and 100 ppb	myoskeletal abnormality	Viant *et al*., 2006
		feathead minnow (*Pimephalespromelas*)		0.072, 0.455, and 1.142 µg/L	delayed mortality, impaired feeding and swimming ability	Floyd *et al*., 2008

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		Zebrafish		LC50	Neurotoxic	Kluver *et al*., 2015
		Ranatemporaria		Higher conc.	growth	Johansson *et al.,* 2006
		Clawed frog, *Xenopuslaevis* and fire-bellied toads *Bombinabombina*		Sublethal	twisting and apparent partial paralysis	County *et al*., 2004
		Zebra fish		131.95, 107.18, 21.76, and 6.25 µg/L	weakened oxidative-DNA repair system, morphological abnormalities, apoptosis	Gu *et al.,* 2010
		Mice		30 µg /g	Gonadotoxic	Zhang *et al.,* 2010
				40 and 80 µg /g	increased mortality, violent behavior, hyperexcitability, and decreased ovarian weight, pre-antral follicles, corpora lutea, fecundity and ovulation number leading to weak reproductive development	Nassr *et al*., 2010; Guerra *et al*., 2011
Tefluthrin ($C_{17}H_{14}ClF_7O_2$)	(1*S*,3*S*)-*rel*-2,3,5,6-Tetrafluoro-4-methylbenzyl 3-((*Z*)-2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropanecarboxylate	Snapping turtle (*Chelydraserpentina*)		-	Deformities	de Solla *et al.,* 2011
		Rat		Dose dependent	hyperpolarization of channel activation	He and Soderlund, 2011
Bifenthrin ($C_{23}H_{22}ClF_3O_2$)	2-Methyl-3-phenylphenyl)methyl (1*S*,3*S*)-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]- 2,2-dimethylcyclopropane-1-carboxylate	Zebra fish	190µg / L(DeMicco et al., 2010)	20, 50, 100,109, 150, 145, 200, 226, 256µg/L	increased spontaneous movement, pericardial edema, curved body axis, impaired swimming behavior, disrupted endocrine level , oxidative stress, apoptosis and immunotoxicity	Jin *et al*., 2009; Jin *et al*., 2010, Jin *et al*., 2013
		Mice	48.00µg/g(Zafar and Asmatullah, 2013)		endocrine disruption	Jin *et al*., 2013
				6.00, 12.00 and 24.00 µg /g	necrotic liver and lung, impaired choroid plexus, renal and limb dysplasia, hypoplasia in ventricular walls of heart and non-glandular stomach, decreased ossification of cranio-facial, caudal and sacro-limbic regions, body weight, crown rump length, brain and eye circumference, size of pinna, snout, tail, fore and hind limb, bulging eye, micromelia, hemorrhage spot on head and abdomen, hind limb low arm set, kyphosis, anencephaly, hydrocephaly, macrocephaly, open eye lid, rough skin, and spina bifida	Zafar and Asmatullah, 2013; Zafar and Asmatullah, 2014
Allethrin ($C_{19}H_{26}O_3$)	(2-methyl-4-oxo-3-prop-2-enylcyclopent-2-en-1-yl) 2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-1-carboxylate	Rat	Male: 1,100 µg /g Female: 685 µg /g	3.6% w/v	abnormalities and oxidative stress	Sinha *et al.,* 2004; Sinha *et al*., 2006
Flumethrin ($C_{28}H_{22}Cl_2FNO_3$)	Cyano(4-fluoro-3-phenoxyphenyl) methyl 3-[2-chloro-2-(4-chlorophenyl)vinyl]-2,2-dimethylcyclopropanecarboxylate	Zebra fish		0.02 µg /ml	decreased time to hatching, and caused an increase in heart rate	Carlsson *et al*., 2013

Fish

Dose dependent decrease in hatching success has been recorded in embryos and larvae of common carp, *Cyprinus carpio* as 75.2, 64.6, 47.4, 26.0, 14.4, and 9.0% in response to 0.005, 0.05, 0.5, 5, 25, and 50 µg of deltamethrin L^{-1}respectively (Koprucu and Aydin, 2004). An exposure of 5 µg/L deltamethrin to fish fingerlings *Oreochromis niloticus* L., induced severe behavioral, histopathological, and morphological changes in gills and liver like hyperemia, fused lamellae, telangiectasis, and hydropic degenerations (Yildirim *et al.,* 2006). Reduced hatching rate has been recorded in fertilized eggs of zebra fish when exposed to several concentrations of deltamethrin 0.8 µg /L (Gorge and Nagel, 1990). While, embryonic exposure to LC (50) of deltamethrin resulted into craniofacial deformities (DeMicco *et al*., 2010) and locomotor deficits with 0.25-0.50 µg/L of deltamethrin, supposed to be mediated by dopaminergic dysfunction (Kung *et al*., 2015).

Birds

Among birds, eggs of Japanese quail (*Coturnix japonica*) showed increased incubation periods and reduced birth weight in exposure to deltamethrin (Martin, 1990). It exerts teratogenic effects in the developing chick when exposed to concentrations of 12.5, 25 and 50 µg/ml in form of mortality, abnormal survivors, and decreased body weight in dose dependent manner (Bhaskar *et al*., 2013). Regarding morphological and skeletal anomalies, hematomas, reduced growth, microphthalmia, subcutaneous hemorrhage, ectopic viscera, anophthalmia, microcephaly, anencephaly, exencephaly, poor ossification, ectopic viscera, scoliosis have been documented by Bhaskar (2014).

Mammals

Oral administration of 5 µg/g day of deltamethrin to female mice from 3rd to 21st day of pregnancy, produced the off spring with underweight testes affecting fertility in terms of reduced mobility, density, and increased count of malformed sperms (Ben *et al.,* 2012). Even lower doses like 1 and 3 µg /gto C57BL/6 pregnant mice given orally for every 3 days throughout the period of gestation and lactation, has decreased the expression of specific genes like adipogenesis-related transcription factors which ultimately disrupts normal adipogenesis as well as metabolism of lipid and glucose in the offspring(Armstrong *et al*., 2013). Sublethal concentrations (19.36, 9.7, and 4.8 µg/g BW) induced sacral hygromae, microcephally, micromelia, open eyelids, microphthalmia, exophthalmia, cryptophthalmia, anophthalmia, droopingwrist, kyphosis, short tail, increased resorption, reduced bodyweight, crown rump length, brain and eyes circumferences, lengths of hind and forelimbs , tail size. Among histopathological malformations, defective nasal pouch, nasal septum with atrophied inferior cochlea, cleft palate, missed eye ball, pericranial hydrocephaly, degenerate jaw muscles, and necrotic brain, liver and intestinal tissue were also observed (Khan and Asmatullah, 2013).

Prenatal exposure to the lowest dose 0.08 µg/g deltamethrin changes the latency to float and the general as well as striatal activity in male rats(Lazarini *et al*., 2001).Dose-dependent alterations in the ontogeny of xenobiotic metabolizing cytochrome P450 isoforms in brain and liver when exposed to low doses 0.25, 0.5,1.0 µg/g (Johri *et al*., 2006), neurotoxic effects when exposed to 0.75 µg/g (Kumar *et al*., 2013),while changes in reproductive behavior and physiology have been recorded in the off spring when exposed to dose 2.0 µg/g of body weight (Andrade *et al*., 2002). Another oral dose administration of 3.35 and 6.70 µg/g of body weight appeared to not only decrease the birth weight, but it is found responsible to retard activity of nitric oxide synthase of brain and the neurobehavioral development of their filial rats too (Li *et al*., 2006). A higher dose(4.0 µg/g) is found gonadotoxic, hence exerting adverse effects on weights of testes and epididymis, and the diameter of seminiferous tubules in adult male offspring of mothers exposed during pregnancy (Andrade *et al*., 2002). Juvenile rats are also found to be highly sensitive for Na channels to deltamethrin(Meacham *et al*., 2008).

In case of human among mammlas, detection of various metabolites (cis-DBCA, cis and trans-DCCA, 4-F-3-PBA, and 3-PBA) in urine samples from 295 pregnant women in exposure to deltamethrin (Dewailly *et al*., 2014) indicates the possibility of causing toxicity to fetus.

II.Cypermethrin

Fish

Newly hatched larvae of *Odontesthes bonariensis* (a teleost) exposed to lower dose 0 or 0.1 µg/L of cypermethrin encountered decreased survival rate (Carriquiriborde *et al*.,

2009). Medaka (*Oryzias latipes*), in exposure to six concentrations of cypermethrin (3.1 to 100.0 µg /L) at different developmental stages showed gall bladder and pericardial edemas, spastic movements at concentration of 6.3 µg /L, spinal curvatures, and altered swim bladder inflation at exposure of 12.5 µg /L (Gonzalez-Doncel *et al*., 2004).Similar results in form of larval deformity for *Oryzias latipes* have been found for higher dose(40 µg /L of cypermethrin) exposure (Kim *et al.,* 2008).

Zebrafish now being extensively used as experimental model, has led to various findings which helped in understanding the teratogenic potential of pesticides. Dose-dependent decreased survival rate along with increased pericardial edema has been observed in a study by DeMicco *et al*. (2010). Lower doses (10, 20, 30 µg/L) of cypermethrin has been found safer as resulted in mild natured developmental defects. However, it had significant effect on the activity of superoxide dismutase, increased activity of catalase, hence, causing oxidative stress (Yang *et al.,* 2014). In another study, exposure of higher concentrations of cypermethrin (0, 25, 50, 100, 200 and 400 µg/L) was found to induce oxidative stress through apoptosis and down-regulating ogg1 and increased p53 gene expression as well as the caspase-3 activity (Shi *et al*., 2011), pericardial and yolk sac edema, crooked body, strong developmental toxicities at concentration of 100µg/L (Xu *et al*., 2010).

Amphibians

Sublethal and acute doses of cypermethrin induce apoptosis in the telencephalon of *Physalaemus biligonigerus* tadpoles (Izaguirre *et al*., 2000). Exposure of eggs and larvae of *Rana arvalis* and *Bombina variegata* to different concentrations of alpha-cypermethrin exhibited various embryonic abnormalities depending upon exposure time and dose like twisting, writhing, abnormal swimming, behavioral abnormalities, mortality, increased activity of glutathione S-transferase systems (Greulich and Pflugmacher, 2003; Greulich and Pflugmacher, 2004). Developing eggs of *Bufo melanostictus* exposed to lower concentrations, 0.01, 0.05, 0.1, 0.5, and 1/µg/L of cypermethrin exhibited a delayed hatching, metamorphosis and limb development (Ghodageri and Pancharatna, 2011).Embryos, newly hatched larvae, and larvae with limb buds of *Pseudacris regilla, Rana cascadae, and Rana aurora* following 48 hrs exposure to 0.5 and 5.0 µg /L appeared with behavioral abnormalities and increased mortality (Biga and Blaustein, 2013).Larvae of *Hypsiboas pulchellus* exposed to 0.34, 0.83,4.18, 8.36 and 34.4 µg /L were obtained with lower growth and body length and malformations (Agostini *et al.,* 2010). Larval exposure of *Duttaphrynus melanostictus* to a sublethal concentration (0.33 µg/L) had catastrophic effect on tadpoles (David *et al*., 2012). *Odontophrynus americanus* tadpoles exposed to 5, 10, 20 or 40/µg/L) showed a significant increase in single small micronuclei (Cabagna *et al.,* 2006). Larvae of common rice paddy field frog (cricket frog) *Fejervarya limnocharis* receiving 25 and 50 µg /L appeared with reduced survival, early metamorphosis among the surviving tadpoles, delayed metamorphosis in a concentration-dependent manner (Nataraj and Krishnamurthy, 2012; Nataraj and Krishnamurthy, 2013). Embryonic and larval exposure of *Xenopus laevis* to sublethal doses of pesticide brought about various developmental disorders with retarded growth and neurotoxicity (Yu *et al.,* 2013; Yu *et al*., 2014). Embryonic exposure of 2.5 and 5.0 µg/L of α-cypermethrin with UVB radiation during last 7 h of 96 h led to inhibition of cyclobutane pyrimidine dimers repair and synthesis of DNA-adducts by altering the NER gene expression (Yu *et al*., 2015).

Birds

Birds are declared at equal risk to cypermethrin. A single dose of 50 µL on zero day of incubation given to fertilized Rhode Island Red eggs has found to induce skeletal malformations (Uggini *et al*., 2012). Other doses (50,100,200 and 400ppm) given to chick embryo on '0' day of incubation resulted into increased activity of amylase and decreased activity of alkaline phosphatase. Decreased content of glycogen, lipid, cholesterol, free amino acid, DNA and reduced crown-rump length, size of brain, eye ball along with under developed eyes, beak and wing buds, micromelia, and excardiogenesis (Anwar, 2003a).

Mammals

The strength of toxicity of the pesticide among mice can be estimated from the offspring with delayed development of pinna detachment, eye opening, reduced body weight, when their parents were exposed orally to 2.5, 5, and 10 µg/g/day of cypermethrin for 4 weeks/5 days prior to mating (Farag *et al*., 2007). Maternal exposure alone to 0.12, 1.2, and 12 µg/g day of

cypermethrin induced decreased body and organ weight, dose-dependent decrease in sex ratio, a thinning of epithelium of seminiferous, interstitial hyperplasia, vacuolization of germ cells with increased apoptosis, serum testosterone level, expression of T production-related, mitosis-related and meiosis-related genes and increased estradiol level among the offspring(Huang and Li, 2014). In another high dose exposure (3.2, 6.4 and 12.8µg/g BW of LD50) of pregnant mice, a dose and exposure dependent decrease in fetal density, head circumference and crown rump length, increase in gestational losses, developmental deformities like microcephaly, meromelia, hydrocephaly, drooping wrist, attached pinnae, epinnate ears, skewed neck, extradactyly, round back, hemoregia, forked paws, flipper limbs, torted hid limbs, and kinky tail were observed (Raees *et al*., 2010).

Maternal exposure of rats to cypermethrin during gestation showed immunomodulation of cytotoxic activity (Santoni *et al*., 1997).Low dose (1.25, 2.5, or 5 µg/g) prenatal exposure led to dose-dependent decrease in the spontaneous locomotor activity in Wistar rats (Singh *et al*., 2014). The most drastic situation is the deposition of cypermethrin as well as its metabolites in brains leading to shifting in amount of growth hormone and cognitive functions of offspring (Singh *et al*., 2015). In another study of prenatal exposure of higher doses like 25, 50 and 75 µg/g BW in Wistar rats came up with increased DNA damage in blood and liver of pups which confirmed its transplacentalgeno toxic potential (Murkunde *et al*., 2012). In other similar study, 50 µg/g of cypermethrin BW, was found to affect thymocyte differentiation pathways coupled with impaired functioning (Santoni *et al*., 1998), a striking and continuing increase in amounts of adrenaline, noradrenaline, and plasma followed by enhanced count of T cells (Santoni *et al*., 1999). A little higher dose 55.1 µg/g body weight of cypermethrin resulted in cerebral, nasal, ophthalmic, pulmonary, cardiac, and renal deformities, increased number of post-implantation deaths, dwarfness and subcutaneous oedema in their offspring (Assayed *et al.,* 2010).

Even more higher dose (75 µg/g) administration affected the ovarian structure and functions as it elevated the follicular atresia and significantly lowered the estradiol level, reduced antioxidant capacity, gonadotropins, induced RNA damage in granulosa and theca cells and elevated the deranged angiogenesis, reduced micro and macro vessels distribution (Molavi *et al*., 2014). Highest dose administration (100µg/g in rat during gestation, caused a substantial decrease in glycogen, sialic acid, alkaline phosphatase, testosterone, leutinizing hormone, and follicle stimulating hormone along with increase in protein and cholesterol levels, acid phosphatase activity of testes (Joshi *et al*., 2011).

In case of human, the ultimate target of the study, various metabolites have been detected in urine samples from pregnant women (Dewailly *et al*., 2014) associated with impaired fetal growth (El-Baz *et al*., 2015). In a comparative study, meconium of the fetuses has been announced as the most sensitive (1.9% and 1.7%) against the toxicity of the insecticide (Ostrea, Jr. *et al.,* 2008; Ostrea, Jr. *et al*., 2009). It is also related to the neural and mental development of infants negatively (Xue *et al*., 2013). Pyrethroids are known to induce neurotoxicity through affecting sodium channels in mammals (Tan and Soderlund ,2009; Tan and Soderlund, 2010; Tan and Soderlund, 2011; Oliveira *et al*., 2013).

III.Permethrin

Sea Urchin

Permethrin has been reported as culprit of inhibiting fertilization and normal development in a dose dependent manner in sea urchin *Paracentrotus lividus* (Erkmen, 2015).

Fish

A range of lower to higher dose (25, 50, 100, 200 or 300 µg /L) exposure to medaka (*Oryzias latipes*) produced the hatchlings with swim bladder with delayed inflation, unable to respond to stimulus; uncoordinated movements, myoskeletal malformations and momentary expansion of gall bladder (Gonzalez-Doncel *et al*., 2003). Higher doses like, 100, 200, 300 µg/L, induced morphological defects and more oxidative stress both in embryonic as well as larval stage of zebra fish (Yang *et al*., 2014), while lethal concentrations caused even more toxic effects in form of craniofacial abnormalities (DeMicco *et al*., 2010).

Birds

In biochemical and molecular toxicity assay with the exposure of three concentrations of permethrin (50, 100 and 200 ppm), the activities of various enzymes like acid phosphatase, alkaline phosphatase, glutamate

pyruvate transaminase, and glutamate oxaloacetate transaminase were decreased in kidney of developing chick, while the activity of lactate dehydrogenase was increased. Total protein and lipid, glucose, glycogen, and uric acid contents were raised significantly with diminishing DNA and RNA content. In histological analysis, necrotic tubules, reduced and distorted glomeruli with blood cell infiltration were observed due to damaged endothelial layer of Bowmann's capsule and epithelial layer of glomeruli (Anwar , 2003b). In other study on muscles, a dose of 25ppm in addition to the similar doses, the activities of alkaline phosphatase reduced whereas the activity of lactate dehydrogenase was elevated. Glucose content decreased at 50 ppm and increased at 200 ppm whereas glycogen showed increase at all the doses. Total protein content decreased at 200 ppm. Free amino acid contents were increased at 25, 50 and 100 ppm but decreased at 200 ppm. Uric acid content was reduced at 100 ppm but it increased at 200 ppm. Significant drop in DNA content was observed at 50 and 100 ppm, while RNA content improved at 200 ppm (Anwar *et al.,* 2004a).

Another study of similar dose administration in developing chick was achieved with declined activities of acid phosphatase, alkaline phosphatase, acid phosphatase, alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase along with reduced liver content of glucose, glycogen, total protein, soluble protein, urea and RNA. While total lipids and FAA content were significantly elevated along with enlarged sinusoidal spaces, hepatocytic necrosis, nuclear condensation and cytoplasmic vacuolations, and hydropic and degeneration (Anwar *et al.,* 2004b). Morphological and morphometric studies showed different abnormalities such as spina bifida, gastroschisis, exencephaly, micrognathia, hydrocephaly, micromelia, meningocephalocoel, ectopiacordis, and microphthalmia, decreased body weight and crown- rump length in developing chick in exposure to 0.3125, 0.625, 1.25 and 2.5µg of permethrin/0.1ml/egg (Andleeb *et al*., 2014).

Mammals

Brain has come forward as the main target in maternal exposure of various doses ranging between 2 and 75 µg/g /d of permethrin in mice. The toxicity appeared in the form of affected reflexes, swimming and standing ability, locomotor and open field activity (Farag *et al*., 2006; Imanishi *et al*., 2013).The toxic potential of permethrin in human is required to be taken very seriously with alarming news of a case study of congenital leukaemia in a preterm female newborn on account of heavily abused aerosolisedpermethrin(Borkhardt *et al*., 2003). Extent of fetal exposures to pesticides and their matbolies depends on maternal race, age, and smoking status (Dewailly *et al*., 2014). A negative association of the insecticide with the anti-inflammatory cytokine IL-10 is earned in new borns of exposed mothers (Neta *et al*., 2011).

IV. Lambda- cyhalothrin

Fish

High capacity for Lambda-cyhalothrin bioconcentration in Zebra fish embryos (Tu *et al*., 2014) leads to increased cases of mortality and pericardial edema in dose related manner (DeMicco *et al*., 2010). Newly fertilized eggs of common carp in exposure to 0.3, 1.5, 3, 6, and 15 µg/L, developed with impaired growth and disbalanced defensive enzymes (Richterova *et al*., 2014).

Amphibians

Such enzymatic toxicity has been seen in *Xenopus laevis* tadpoles too, in the form of inhibition of glutathione-S-transferase, carboxylesterase, acid phosphatase, aspartate aminotransferase and lactate dehydrogenase (Aydin-Sinan *et al.,* 2012).

Mammals

It is quite terrifying of finding that even dermal exposure of female rats with very low doses (0.018% and 0.02% (w/v)) throughout pregnancy delayed the age of testicle descent, development of fur, ear and eye openings (Gomes *et al*., 1991). In addition to this, pre-conceiving exposure of female rats to 8µg/g of (the drug) BW for 30 days led to a marked reduction and increase in thyroid and thyroid stimulating hormone levels in pups respectively, which was ultimately reflected in growth and development of the offspring (Tukhtaev *et al.,* 2012).

V. Beta cyfluthrin

Fish

Fingerlings of carp (*Cyprinus carpio* L.), in an exposure to sublethal concentration of 10 µg/L cyfluthrin encountered environmental stress through lipid peroxidation and blocking sodium channel (Sepici-Dincel *et al*.,2009).

Mammals

Pregnant female mice gave rise to the off spring with poor ossification, short ribs, affected surface righting and pivoting when exposed to 16 and 32µg/g of body weight (Soni *et al*., 2011).Similar doses in pregnant Swiss albino mice induced burrowing behaviour, increased mortality, reduced litter size and skull ossification, widened cranial sutures, short or absent ribs, microphthalmia, ventricular hydrocephaly, anophthalmia, and pulmonary as well as subcutaneous edema (Syed *et al*., 2010). Lower dose of β-cyfluthrin (1.25, 2.50 and 5.00 µg/g body weight) given orally on Day 6 of gestation induced microcephaly, anophthalmia, micromelia, dysmorphogenesis, dysplasia and short tail along with other morphometric abnormalities (Ahmad *et al*., 2012). Agricultural pregnant workers exposed to cyfluthrin have been reported to produce abnormal fetuses (El-Baz *et al.,* 2015).

VI. Esfenvalerate

Fish

Medaka (*Oryzias latipes*) when fed for 7 days on diets containing three variable concentrations (4, 21, 148µg/g BW) of esfenvalerate, affected fertilization and hatching success (Werner *et al.*, 2002). While it has been known to induce some degree of lordosis or myoskeletal abnormality in Salmon (*Oncorhynchus tshawytscha*) embryos at doses 10 and 100 ppb. ATP and phosphocreatine concentrations decreased significantly in eyed eggs (Viant *et al*., 2006).Larvae of the feathead minnow (*Pimephales promelas*) exposed to 0.072, 0.455, and 1.142 µg /L for 4 h resulted into delayed mortality, impaired feeding and swimming ability, leading to reduced growth and increased susceptibility to predation (Floyd *et al*., 2008). It has been announced as neurotoxic for Zebra fish embryos hence inducing changes in embryonic locomotion (Kluver *et al*., 2015).

Amphibians

An exposure of Tadpoles of *Rana temporaria* relatively high concentrations exerted negative effects on the growth (Johansson *et al.,* 2006). In another study embryos of clawed frog, *Xenopus laevis* and fire-bellied toads *Bombina bombina* were obtained with malformations like twisting and apparent partial paralysis (County *et al*., 2004).

VII. Fenvalerate

Fish

Larvae of Zebra fish exposed to with LC50 concentrations of various doses 131.95, 107.18, 21.76, and 6.25 µg /L of fenvalerate displayed morphological abnormalities, apoptosis, altered SOD activity, dose-related down-regulation of the expression of two genes: ogg1 and dlx2 genes, and weakened oxidative-DNA repair system (Gu *et al.,* 2010).

Mammals

Fenvalerate has confessed to be gonadotoxic established by decrease in testicular and epididymidal weight, number of mature seminiferous tubules, number of epididymal spermatozoa, level of serum testosterone and mRNA and protein of P450 (17alpha) among male offspring of pregnant mice in response to fenvalerate (30µg/g) during gestation (Zhang *et al.,* 2010). In such other studies, 40 and 80µg/g of fenvalerate resulted in increased mortality, violent behavior, hyperexcitability and decreased ovarian weight, pre-antral follicles, corpora lutea, fecundity and ovulation number leading to weak reproductive development (Nassr *et al*., 2010; Guerra *et al*., 2011).

VIII. Tefluthrin

Amphibians

Snapping turtle (*Chelydra serpentina*) eggs exposed to tefluthrin showed elevated frequency of deformities of hatchlings (de Solla *et al.,* 2011).

Mammals

In a study conducted in rat, sodium channels (Na (v) 1.6) were allowed to express in combination with the beta1 and beta2 auxiliary subunits in human embryonic kidney (HEK293) cells. It was found to produce dose-dependent shift in hyperpolarization of channel activation (He and Soderlund, 2011).

IX. Bifenthrin

Fish

Embryo-larval zebra fish exposed to bifenthrin at dose 20, 50, 100,109, 150, 145, 200, 226, 256µg/L accelerated the hatching process in a dose-dependent way, coupled with increased spontaneous movement, pericardial edema, curved body axis, impaired swimming behavior, and disrupted endocrine level(Jin *et al*., 2009; Jin *et al*., 2010). While, embryonic exposed led to oxidative stress, apoptosis and immunotoxicity (Jin *et al*., 2013a).

Mammals

Maternal exposure of mice is found to induce endocrine disruption in male offspring (Jin *et al*., 2013b). Prenatal exposure of three doses 6.00, 12.00 and 24.00 µg/g body produced necrotic liver and lung, impaired choroid plexus, renal and limb dysplasia, hypoplasia in ventricular walls of heart and non-glandular stomach, decreased ossification of cranio-facial, caudal and sacro-limbic regions, body weight, crown rump length, brain and eye circumference, size of pinna, snout, tail, fore and hind limb, bulging eye, micromelia, hemorrhage spot on head and abdomen, hind limb low arm set, kyphosis, anencephaly, hydrocephaly, macrocephaly, open eye lid, rough skin, and spina bifida (Zafar and Asmatullah, 2013; Zafar and Asmatullah, 2014).

X. Allethrin

Mammals

Inhalation of mosquito repellents composed of allethrin (3.6% w/v) during prenatal life may have key role in inducing abnormalities and oxidative stress by decreasing antioxidants in central nervous system among rat pups (Sinha *et al.,* 2004; Sinha *et al*., 2006). Human is equally targeted by the insecticide exposure, associated with impaired fetal growth (El-Baz *et al*., 2015).

XI. Flumethrin

Fish

Flumethrin exposure in Zebra fish embryos at dose of 0.02 µg/ml resulted in decreased time to hatching, and caused an increase in heart rate at 48 hpf (Carlsson *et al*., 2013).

CONCLUSIONS AND RECOMMENDATIONS

Conclusively pyrethroids are declared as embryo toxic at even very low dose independent of route of exposure for every group of animal, which recommends that:

1. Highly commendable achievements by the workers strongly condemn the exploitation of pyrethroids for various recommended targets to ultimately save the world from becoming abnormal.
2. Being found to be allied even with mortality among developing fetuses of different groups of animals under experimentation. Such findings are alarming signs which drives to establish certain legislations, strategic plans and campaigning by government, public health department and other national organizations to educate and guide the workers involved in formulation of pesticides, farmers (using on large scale), and house hold users, mainly women before conceiving or during pregnancy.
3. The recommendations must reflect the concentration, dosage, time as well as areas of application especially for indoor uses.

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