Teratogenicity and Embryotoxicity in Aquatic Organisms After Pesticide Exposure and the Role of Oxidative Stress

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Contents

1 Introduction

Complex factors have contributed to the decline of aquatic populations worldwide. Among these factors are intensification of agriculture, including the application of fertilizers and agents of crop protection, and loss of habitat. Various developmental abnormalities in natural populations of aquatic vertebrates have been documented, and agricultural pesticides are considered by many to be one of the important factors that cause such abnormalities. Amphibians may potentially be a target of environmental stressors and toxicants as a result of their biphasic life cycles and skin permeability. In this chapter, the role of oxidative stress in the teratogenic action of pesticides is reviewed and addressed, with special attention given to non-target aquatic organisms such as amphibians, fish, and invertebrates. The review of

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available literature indicates that many pesticides enhance oxidative stress in aquatic organisms, and such stress may be linked to developmental alterations, including reproductive effects, embryotoxicity, and/or teratogenicity.

Any external factor affecting cellular proliferation, differentiation, or apoptosis can produce embryotoxic or teratogenic effects, and such factors include chemical exposures at high concentrations; such effects may result in permanent congenital malformations, functional abnormalities, or even embryo death (Gilbert 2006). Several external factors may result in embryotoxicity and teratogenicity in the aquatic environment. These factors include ultraviolet radiation, extremes in pH, thermal and ionic conditions, infections, parasites, as well as chemicals such as pharmaceuticals, retinoid and aromatic compounds, and pesticides (Ankley et al. 2004; Bilski et al. 2003; Blaustein and Johnson 2003; Finn 2007; Hayes et al. 2006).

One mechanism by which chemicals induce toxicity is through oxidative stress, and it has been shown that several widely used pesticides are capable of producing pro-oxidants in cells (Tellez-Bańuelos et al. 2009; Vismara et al. 2001a). Furthermore, oxidative stress is the major mechanism by which some pesticides exert their effects; a prime example is the bipyridyl herbicides (Ruiz-Leal and George 2004; Sewalk et al. 2000).

Pesticides are regularly applied onto agricultural land worldwide, and the resultant timing of exposure often parallels the appearance of the early developmental stages of aquatic organisms (Greulich and Pflugmacher 2003). Although the various side effects that pesticides have on biota have been documented in many studies, to our knowledge, no consistent overview of pesticide embryotoxicity in aquatic invertebrates and vertebrates is available. Hence, in this review, we summarize the existing knowledge on this topic. Moreover, we present an overview of available information on the general teratogenic and embryotoxic effects of pesticides in aquatic biota such as fish, amphibia, and invertebrates. In this review we emphasize toxic effects that are related to oxidative stress and draw lines of evidence to support the view that it is a possible toxicity mechanism behind the induction of teratogenicity.

2 Pesticides and Teratogenicity in Fish

In fish, developmental malformations have been linked to the presence of several environmental pollutants such as persistent organochlorines, pesticides, or heavy metals (Westernhagen von 1988). In several studies, direct embryotoxicity has resulted from the presence of complex matrices such as oil (Heintz et al. 1999), and recently, tests for embryonic malformations in fish have been used as general water quality indicators (Klumpp et al. 2002).

The array of effects that pesticides have had on embryonic development in fish is summarized in Table 1.

Zebra fish (*Danio rerio*; family Cyprinidae) constitutes the most common model of test fish species, and it has been used in many pesticide studies; the results from Strmac and Braunbeck (1999) and Osterauer and Köhler (2008) are examples. Other species used in pesticide testing schemes include the Japanese medaka (*Oryzias latipes*; family Adrianichthyidae; Villalobos et al. 2000) and various salmonids

Table 1 The effects of selected pesticides on development and reproduction in fish

Pesticide	Organism	Toxic effect	References
Carbamates			
Thiobencarb	*O. latipes*	Bradycardia, pericardial edema, hemostasis, poor yolk resorption, cephalic and spinal deformities, abnormal hatching	Villalobos et al. (2000)
Dithiocarbamate	*D. rerio*	Twisted notochord, reduced hatching notochord distortions	Haendel et al. (2004), Tilton et al. (2006, 2008)
		Distorted notochord development and shortened anterior to posterior axis	van Boxtel et al. (2010)
Thiuram	*D. rerio*	Wavy notochords, disorganized somites, shortened yolk sac extension	Teraoka et al. (2006)
Carbaryl	*D. rerio*	Red blood cell accumulation, delayed hatching and pericardial edema, bradycardia	Lin et al. (2007)
Synthetic pyrethroids			
Esfenvalerate	*O. latipes*	Deleterious reproductive effects, reduced hatching success, and larval viability	Werner et al. (2002)
	Oncorhynchus tshawytscha	Myoskeletal abnormality, lordosis	Viant et al. (2006b)
Deltamethrin	*Cyprinus carpio*	Deleterious reproductive effects, decreased hatching success, larvae lethality, altered development	Köprücü and Aydin (2004)
	O. mykiss *Brachydanio rerio*	Fry lethality, loss of equilibrium enhanced larvae mortality, reduced hatching rate	Ural and Saglam (2005),
	D. rerio	Embryolethality, neurobehavioral effects – spastic movements, pericardial edema, craniofacial abnormalities	Görge and Nagel (1990), and DeMicco et al. (2010)
Cypermethrin	*C. carpio*	Embryolethality, reduced hatching success	Aydin et al. (2005)
	D. rerio	Embryolethality, neurobehavioral effects – spastic movements, pericardial edema	DeMicco et al. (2010)
Bifenthrin	*D. rerio*	Embryolethality, curvature of the body axis, neurobehavioral effects – spastic movements	DeMicco et al. (2010)
Λ-Cyhalothrin	*D. rerio*	Embryolethality, neurobehavioral effects – spastic movements, pericardial edema	DeMicco et al. (2010)

Table 1 (continued)

Pesticide	Organism	Toxic effect	References
Resmethrin	*D. rerio*	Neurobehavioral effects – spastic movements	DeMicco et al. (2010)
Permethrin	*O. latipes*	Delayed swim bladder inflation, inability of hatchling to respond to stimulus; uncoordinated movements, myoskeletal defects, and transient enlargement of gall bladder of larvae	González-Doncel et al. (2003)
	D. rerio	Embryolethality, curvature of the body axis, neurobehavioral effects – spastic movements, craniofacial abnormalities	DeMicco et al. (2010)
Organophosphates			
Malathion	*D. rerio*	Reduced growth, survival, and eye diameters	Cook et al. (2005)
	Clarias gariepinus	Deformed notochord and pericardial edema, larvae with bent body, and swollen yolk sac	Lien et al. (1997)
	Sciaenops ocellatus	Decreases in growth in weight of larvae, increased protein synthesis	McCarthy and Fuiman (2008)
	Melanotaenia fluviatilis	Moderate larval lethality	Reid et al. (1995)
Diazinon	*C. carpio*	Deleterious reproductive effects, reduced hatching success, and larval viability	Aydin and Köprücü (2005)
	O. latipes	Edemas both along vitelline veins and within the pericardial sac, delay in hatching, decrease in swim bladder inflation, decreased length	Hamm and Hinton (2000)
	D. rerio	Embryolethality, decreased heart rate, yolk sac and heart sac edema, spine deformations, altered hatching date	Osterauer and Köhler (2008)
Chlorpyrifos	*D. rerio*	Increased locomotor activity, paused jerky movements, heart edema, spinal deformity	Kienle et al. (2009)

Table 1 (continued)

Pesticide	Organism	Toxic effect	References
Organochlorines			
Endosulfan	*O. latipes*	Delayed hatching, smaller fry, altered mobility	Gormley and Teather (2003)
	D. rerio	Mild trunk curvature, abnormal behavior, edema, microcephaly, and impaired movement, along with increased death rate	Willey and Krone (2001)
Lindane	*S. aurata*	Myoskeletal defects, skin opacity, exophthalmia, weak swimming, depigmentation, behavioral changes	Oliva et al. (2008)
	O. mykiss	Hepatocytic alterations (glycogenic depletion, RER and dictyosome changes, secondary lysosome accumulation)	Sylvie et al. (1996)
	B. rerio	Enhanced larvae mortality, decreased growth	Görge and Nagel (1990)
Thiacloprid	*D. rerio*	Heart rate affection	Osterauer and Köhler (2008)
Organosulfurs			
Methyl isothiocyanate	*D. rerio*	Notochord distortions	Tilton et al. (2006)
Terbutryn (a triazine) + triasulfuron	*S. aurata*	Curvatures of the vertebral column, the hepatocytes forming slackly arranged cords, loss of cellular shape of hepatocytes, lipid inclusions, nuclear pyknosis	Arufe et al. (2004b)
Phenylpyrazole			
Fipronil	*D. rerio*	Notochord degeneration, shortening along the rostral–caudal body axis, ineffective tail flips	Stehr et al. (2006)
Triazines			
Atrazine	*S. ocellatus*	Altered growth, hyperactivity, and faster active swimming speed (elevated rate of energy utilization)	del Carmen Alvarez and Fuiman (2005), McCarthy and Fuiman (2008)
		Declines in growth in wet weight and protein content in larvae, increase in rates of protein degradation	
	B. rerio	Enhanced larvae mortality, increased number of deformations and edema	Görge and Nagel (1990)
Simazine	*S. aurata*	Reduced larvae survival, hepatic lesions, loss of cellular shape in hepatocytes, lipid inclusions, focal necrosis, abundant nuclear pyknosis	Arufe et al. (2004a)

Table 1 (continued)

Pesticide	Organism	Toxic effect	References
Cyanazine	*M. fluviatilis*	Moderate mortality with decreasing trend from the day of hatching	Reid et al. (1995)
Organotins			
Triphenyltin acetate	*D. rerio*	Larval mortality, delayed hatching, skeletal malformation, retarded yolk sac resorption, and edema in the heart and yolk sac regions, histo- and cyto-pathological alterations of larval liver including changes in nuclei and mitochondria as well as glycogen depletion	Strmac and Braunbeck (1999)
Dinitrophenol			
Dinoseb	*O. latipes*	Larval mortality, reduced eye growth, diminished heart rate, failed hatching, developmental retardation, pericardial edema, and reduced growth, reductions of eye area and width	Viant et al. (2006a, b)

RER, rough endoplasmic reticulum

such as *Oncorhynchus* sp. (family Salmonidae; Sylvie et al. 1996). The testing that has utilized these species has involved a wide array of pesticides and pesticide classes. For example, the toxicity of the following classes has been tested in these fish species: organophosphates, triazines, synthetic pyrethroids, carbamates, organochlorines, some studies with organosulfur pesticides (Arufe et al. 2004b; Tilton et al. 2006), phenylpyrazoles (Stehr et al. 2006), organotins (Strmac and Braunbeck 1999), and dinitrophenols (Viant et al. 2006a, b).

The array of pesticide effects that have been observed on fish embryonic development has included malformations in myoskeletal development (such as notochord abnormalities of degeneration), defects along the rostral–caudal body axis, curvature of the vertebral column, and reduced growth (McCarthy and Fuiman 2008; DeMicco et al. 2010; van Boxtel et al. 2010). In other studies, pesticides affected various visceral organs in ways that led to defects in the hepatic, cephalic, and eye region, and various edemas in pericardial area or yolk sac (Strmac and Braunbeck 1999; Hamm and Hinton 2000; Willey and Krone 2001). Besides these morphological alterations, embryonic and larval exposures to pesticides have also resulted in decreased hatching success and larval mortality (Görge and Nagel 1990; Aydin and Köprücü 2005; Viant et al. 2006a, b) or behavioral alterations such as uncoordinated movements and loss of balance (Ural and Saglam 2005; González-Doncel et al. 2003; Kienle et al. 2009).

As is clearly shown in Table 1, various pesticides have produced significant detrimental effects on developmental processes in different fish species. We address these effects and the role of oxidative stress in developmental toxicity in more detail below (Sections 5 and 6).

3 Pesticides and Teratogenicity in Amphibians

Amphibians are known to be highly sensitive organisms and can be affected by chemical, physical, and habitat factors; moreover, it is believed that pesticides are one of the causes of the worldwide decline in amphibian populations (Muths et al. 2006). Most amphibian species breed during the spring when pesticides are being applied onto the land for weed, fungal, insect, or other pest control, which makes amphibians highly vulnerable to pesticide toxicity (Greulich and Pflugmacher 2003).

In natural frog populations, morphologically malformed individuals usually constitute a small fraction of less than 2% (Ouellet 2000). However, a much higher incidence (up to 60%) of malformed specimens was documented to occur in contaminated ponds (Meteyer 2000). In agricultural ecosystems, developmental malformations resulting from pesticide exposure were documented to have occurred in several amphibian species in India (Gurushankara et al. 2007) or in Canada (Ouellet et al. 1997).

Embryotoxicity and teratogenicity of various pesticide classes have been documented to have occurred in amphibians in laboratory studies and in field observation studies (Table 2). Most of the studies used the prototypical model organism *Xenopus laevis* from the Pipidae family, but species from other families that included Ranidae, Bufonidae, Microhylidae, and others were also used.

Table 2 The effects of selected pesticides on development and reproduction in amphibians

Pesticide	Organism	Toxic effect	References
Mixture of pesticides	*Rana pipiens*	Altered development and growth, sex differentiation, behavior, timing of initiation, and completion of metamorphosis	Hayes et al. (2006)
Carbamates			
Carbofuran	*Microhyla ornata*	Blistering, distention of body cavities, curvature of the body axis, poor blood circulation, retarded growth, abnormal behavior, poor pigmentation	Pawar and Katdare (1984)
Carbamate ZZ-Aphox	*Rana perezi*	Histological damage of gill, liver, gall bladder, heart, and notochord	Honrubia et al. (1993)
Carbaryl	*Ambystoma barbouri*	Delayed hatching, reduced larval survival, lower growth rates, respiratory distress, limb deformities	Rohr et al. (2003)
	X. laevis	Abnormal tail flexure, skeletal muscle lesions, wavy or bent notochord	Bacchetta et al. (2008)
	Rana sphenocephala	Increased length of tadpoles, larger mass of metamorphosis	Bridges and Boone (2003)
Organophosphates			
Fenitrothion	*M. ornata*	Blistering, distention of body cavities, curvature of the body axis, poor blood circulation, retarded growth, abnormal behavior, poor pigmentation	Pawar and Katdare (1984)
	R. pipiens, Rana clamitans, Rana catesbeiana	Embryotoxicity, behavior alterations, paralysis	Berrill et al. (1994)
Guthion and guthion 2S	*X. laevis*	Embryolethality, decreased body length, developmental alterations	Schuytema et al. (1994)
Malathion	*X. laevis*	Defects of neuromuscular activity such as spasms, tremors, and affected swimming, abnormal tail flexure, distorted myocytes	Bonfanti et al. (2004)
	Ambystoma mexicanum	Embryonic mortality, delayed or stopped development, not completed neurulation, thin notochord, not fused neural folds, embryos without notochord and neural canal and located edema, erratic swimming	Robles-Mendoza et al. (2009)

Table 2 (continued)

Pesticide	Organism	Toxic effect	References
Chlorpyrifos	*X. laevis* *Hyla chrysoscelis* *Rana sphenocephala*, *Acris crepitans*	Reduced myotome size and hypertrophies; defects of neuromuscular activity such as spasms, tremors, and affected swimming, notochord flexure, distorted myocytes tadpole mortality, swim speed affection, lower mass of tadpoles	Colombo et al. (2005) Bonfanti et al. (2004) Widder and Bidwell (2008)
	Gastrophryne olivacea *Bufo bufo gargarizans* *A. mexicanum* *Rana boylii*	Shrunken fins, tail deformities, and head edema, behavioral changes, micronucleus induction, tadpole lethality thin notochord and neural canal, lateral tail flexure, convulsions, spasms and tremors, larval mortality	Yin et al. (2009) Robles-Mendoza et al. (2009) Sparling and Fellers (2007)
Diazinon	*Bufo melanostictus* *Polypedates cruciger*	Larval mortality, altered activity, growth retardation	Sumanadasa et al. (2008)
	R. boylii	Larval mortality	Sparling and Fellers (2007)
Organochlorines			
Dieldrin	*Limnodynastes tasmaniensis*	Abnormal otolith, otic capsule, and cephalic pigmentation	Brooks (1981)
Benzene hexachloride	*M. ornata*	Blistering, distention of body cavities, curvature of the body axis, poor blood circulation, retarded growth, abnormal behavior, poor pigmentation	Pawar and Katdare (1984)
Methoxychlor	*X. laevis*	Altered hind limb differentiation and tail resorption, interference with normal reproductive processes	Fort et al. (2004a, b)
	Xenopus tropicana	Altered rate of larval development, delayed development, chronic reproductive effects	
	Ambystoma macrodactylum	Altered startle responses and a shorter distance of travel following application of the startle stimulus, increased predation, mortality of larvae	Eroschenko et al. (2002)
Endosulfan	*Litoria citropa*	Reduced tadpole survival, increased vulnerability to predation	Broomhall (2002)

Table 2 (continued)

Pesticide	Organism	Toxic effect	References
Endosulfan and octylphenol	*A. barbouri*	Delayed hatching, reduced larval survival, lower growth rates, respiratory distress, limb deformities	Rohr et al. (2003)
Heptachlor	*Rana kl. Esculenta*	Decreased survival rate in tadpoles, alterations in the epidermis of tadpoles containing dilated and irregular vesicles, damaged mitochondria showing altered cristae	Fenoglio et al. (2009)
Pyridine			
Triclopyr	*R. pipiens*, *R. clamitans, R. catesbeiana*	Embryotoxicity, behavior alterations, paralysis	Berrill et al. (1994)
	R. pipiens	Reduced survival of tadpoles	Chen et al. (2008)
Bipyridyl			
Paraquat	*X. laevis*	Embryolethality, growth retardation, ventral tail flexure, abnormal somites; mitose alterations, necrotic myocytes, malformed intersomitic boundaries, altered swimming activity, embryolethality or embryos unable to swim, general reduction of length, medial flexures of the notochord and stunting	Vismara et al. (2000, 2001a, b), Mantecca et al. (2006), Osano et al. (2002)
Phenoxy carboxylic acid			
4-Chloro-2-methylphenoxyacetic acid	*X. laevis*	Growth retardation	Bernardini et al. (1996)
Chloroacetanilide			
Alachlor	*Bufo americanus* *R. pipiens*	Embryolethality, developmental alterations	Howe et al. (1998)

Table 2 (continued)

Pesticide	Organism	Toxic effect	References
Triazine			
Atrazine	*B. americanus*	Embryolethality, edemas	Howe et al. (1998)
	R. pipiens	Induced intersex animals	Carr et al. (2003)
	X. laevis	No effect on mortality, growth, time to metamorphosis, gonad and laryngeal development, or aromatase activity, sexual differentiation affection – increases in female ratios, no effects on reproduction, hatching success, or development	Coady et al. (2005), Oka et al. (2008), Du Preez et al. (2008)
	Rhinella arenarum	Embryolethality, greater mortality of larvae, alterations in the timing of metamorphosis	Brodeur et al. (2009)
Terpenoids			
Methoprene	*R. pipiens*	Severe developmental effects, dysmorphogenesis, high mortality	Ankley et al. (1998)
Methoprene degradation products	*X. laevis*	Eye, cranial, facial defects, spinal curvature and heart and gut malformations, dysmorphogenesis of craniofacial region, edemas, microphthalmia, reductions in the prosencephalon and mesencephalon, developmental delay	La Clair et al. (1998), and Degitz et al. (2003)
Amidine			
Amitraz	*X. laevis*	Growth retardation, edemas of the face, heart, and/or abdomen and axial flexures (curvature of the notochord or bending of the tail)	Osano et al. (2002)
2,4-Dimethylaniline	*X. laevis*	Subtoxic stimulation of growth, loss of pigment together with encephalomegaly, welling of the brain	Osano et al. (2002)

Similar to what occurs in fish, amphibians are known to be highly sensitive to several developmental effects; myoskeletal system, abnormal tail formation, and limb differentiation are among the most often reported effects caused by pesticide exposure (Fort et al. 2004a, b; Bacchetta et al. 2008). Further alterations include incomplete neurulation, edemas, epidermal defects, or gut malformations (Degitz et al. 2003; Robles-Mendoza et al. 2009), as well as severe dysmorphogenesis, embryonic and larval lethalities, delayed hatching, growth retardations, or altered metamorphosis (Vismara et al. 2000, 2001a, b; Brodeur et al. 2009).

In addition to investigations that have been performed with frogs and toads, a few studies were also performed with salamanders (family Ambystomatidae) exposed to pesticides; effects observed included larval mortality, limb deformities, and behavioral changes (Eroschenko et al. 2002; Robles-Mendoza et al. 2009; Rohr et al. 2003).

Similar to observations that have been made in fish studies (Table 1), testing results with amphibians (Table 2) indicate that significant embryotoxicity/teratogenicity and developmental toxicity result from pesticide exposure, and evidence suggests that oxidative stress may play a role in producing such effects.

4 Pesticides as Possible Teratogens in Invertebrates

Pesticides may not only alter development and reproduction in vertebrates but also affect various aquatic invertebrates. Data from studies that have documented developmental effects in invertebrates are presented in Table 3. Most invertebrate reproduction or developmental studies were performed with organophosphate and organochlorine insecticides (Key et al. 2007; Lee and Oshima 1998), although the effects of other pesticide classes (e.g., synthetic pyrethroids, chloroacetanilides and terpenoids; triazines, carbamates, azoles, and phenylpyrazoles) were also studied.

Among the effects found in gastropods, bivalve mollusks, echinoids, and decapod crustaceans were embryonic and larval lethality (Key et al. 2007; Harper et al. 2008), decreased hatching success or delayed hatching times (Lee and Oshima 1998; Sawasdee and Köhler 2009), as well as alterations in embryolarval development, and larval deformities (Bhide et al. 2006; Buznikov et al. 2007).

Model aquatic invertebrate organisms such as the cladoceran *Daphnia* were also investigated (Palma et al. 2009), but in this species, embryolethality was often masked by changes in other parameters, such as adult immobilization or number of offspring (Abe et al. 2001). Embryos and larvae of ascidian *Phallusia mammillata* were found to be a sensitive model, and the azole pesticides imazalil and triadimefon inhibited sperm viability and fertilization rate, and deregulated organogenesis of the nervous system in this species (Pennati et al. 2006).

Although oxidative stress possibly plays a role in the toxicity of pesticides to invertebrates as described in Table 3, to our knowledge no specific studies exist that link embryotoxicity directly to oxidative stress.

Table 3 The effects of selected pesticides on development and reproduction in aquatic invertebrates

Pesticide	Organism	Toxic effect	Reference
Carbamate			
Propoxur	*Lymnaea stagnalis*	Increased mortality, decreased hatchability, and larval deformities linked with deviation in protein fractions	Bhide et al. (2006)
Organophosphates			
Chlorpyrifos	*Strongylocentrotus droebachiensis*	Neurotoxicity, specific malformation – “mushroom”-shaped larva formation	Buznikov et al. (2007)
	M. galloprovincialis	Reduction of embryogenesis success	Beiras and Bellas (2008)
	Palaemonetes pugio	Lethality of newly hatched larvae and postlarvae	Key et al. (2007); Lee and Oshima (1998)
	Callinectes sapidus	Inhibited hatching	Palma et al. (2009)
	Daphnia magna	Underdeveloped second antennae, curved and incurved shell spine, arrested eggs, reduced number of offspring per female, embryos remaining at certain stage	
		Early larvae lethality, hatching time	
Dichlorvos	*L. stagnalis*	Increased mortality, decreased hatchability, and larval deformities	Bhide et al. (2006)
Diazinon	*Paracentrotus lividus*	Decreased length of primary mesenchymal branches and plutei, altered speed of development	Morale et al. (1998)
Malathion	*P. pugio*	Lethality of larvae, lower number of instars to post-larvae, lethality of newly hatched larvae	Key et al. (1998, 2007)
Azinphos methyl	*P. pugio*	Lethality of newly hatched larvae	Key et al. (2007)
Organochlorines			
Methoxychlor	*Strongylocentrotus purpuratus*	Disruption of gastrulation, abnormal cleavage, and gut development	Green et al. (1997)
Methoxychlor, dieldrin, lindane	*P. lividus*	Decreased rate of fertilization, increased polyspermy, mitotic alterations, altered development, intracellular Ca homeostasis	Pesando et al. (2004)

Table 3 (continued)

Pesticide	Organism	Toxic effect	Reference
Lindane	*M. galloprovincialis*	Reduction of embryogenesis success	Beiras and Bellas (2008)
Endosulfan	*C. sapidus*	Inhibited hatching in higher tested concentrations	Lee and Oshima (1998)
	Crassostrea gigas	Increased abnormal D-larvae and the level of DNA strand breaks	Wessel et al. (2007)
	P. pugio	Increased hatching time	Wirth et al. (2001)
Synthetic pyrethroids			
Fenvalerate, cypermethrin	*C. sapidus*	Inhibited hatching	Lee and Oshima (1998)
Bifenthrin	*P. pugio*	Larval lethality	Harper et al. (2008)
Azoles			
Imazalil, triadimefon	*P. mammillata*	Decreased rate of fertilization, alterations of the anterior structures, incorrectly differentiated papillary nerves and nervous system	Pennati et al. (2006)
Phenylpyrazoles			
Fipronil	*P. pugio*	High larvae lethality	Key et al. (2007)
Triazines			
Atrazine	*P. pugio*	Non-toxic to larvae at tested concentrations	Key et al. (2007)
	Mercenaria mercenaria	Increased dry mass, higher condition index, dose-dependent mortality, higher shell major axis length	Lawton et al. (2006)
	Marisa cornuarietis	Delay in hatching	Sawasdee and Köhler (2009)
Benzoylphenylureas			
Diflubenzuron	*C. sapidus*	Inhibited hatching	Lee and Oshima (1998)
Terpenoids			
Methoprene	*C. sapidus*	Inhibited hatching in higher tested concentrations	Lee and Oshima (1998),
	P. pugio	No embryonic mortality at tested concentrations	Wirth et al. (2001)
Nitroguanidine nicotinoids			
Imidacloprid	*P. pugio*	Larvae lethality	Key et al. (2007)
	M. cornuarietis	Decreased heart rate	Sawasdee and Köhler (2009)

5 Role of Oxygen and Antioxidant Defenses in Embryogenesis

Despite intensive research, the mechanisms involved in teratogenesis are still not sufficiently understood, but it is known that they differ among various compounds. The following mechanisms by which xenobiotics may induce developmental effects, however, are known and include alterations of DNA (i.e., mutations, chromosomal aberrations, or nucleic acid metabolism effects), inhibition of specific enzymes, membrane alterations, modulation of cellular energy supplies, as well as disruption of retinoic acid signaling or oxidative stress (Beckman and Brent 1984; Wells et al. 2005). Most often, a complex set of factors and/or the accumulation of errors produces morphological malformations or embryo lethality (Meteyer 2000).

Oxygen plays a key role in metabolism and is critical to the early developmental stages of organisms. Several oxygen derivatives, known as reactive oxygen species (ROS), are known to have signaling functions and may affect several physiological and pathological processes in an organism (Covarrubias et al. 2008; de Lamirande and Gagnon 1995). At the level of embryogenesis, sensitive regulation of ROS has been linked to control of oocyte cleavage (Allen and Balin 1989), as well as oocyte maturation, ovarian steroidogenesis, ovulation, implantation, and formation of blastocysts (Guerin et al. 2001).

However, ROS levels must be continuously controlled to prevent them from becoming highly toxic to biological macromolecules (e.g., proteins, DNA, and membrane lipids) (Agarwal et al. 2003). The teratogenic potential of xenobiotics thus depends on embryoprotective pathways and on detoxification and macromolecule repair (Wells et al. 2005). General antioxidant defenses were recently shown to play an important role in protecting both early aquatic larval stages (Maria et al. 2009; Tilton et al. 2008) and later developmental phases, as well as the metamorphosis process (Dandapat et al. 2003).

To protect against ROS, cells contain both non-enzymatic antioxidant molecules (the ubiquitous thiol-containing tripeptide glutathione, vitamin E, and metallothioneins) (Tilton et al. 2008; Wiegand et al. 2001) and enzymes that can detoxify ROS. These enzymes include the following: superoxide dismutase (SOD; EC 1.15.1.1) that exists in mitochondria and cytosol, catalase (CAT; EC 1.11.1.6) that catalyzes removal of hydrogen peroxide in peroxisomes, and glutathione peroxidase (GPx, EC 1.11.1.9) present in the nucleus, mitochondria, and cytosol (Wang et al. 2002). Other important enzymes that are known to protect the embryo against reactive molecules are glutathione-*S*-transferase (GST; EC 2.5.1.18) (Anguiano et al. 2001; Peńa-Llopis et al. 2003) and glucose-6-phosphate dehydrogenase (G6PD; EC 1.1.1.49) (Wells et al. 1997).

Antioxidants play an important role in protecting early larval stages against the effects of ambient oxygen levels in water (Arun and Subramanian 1998; Dandapat et al. 2003). Dandapat et al. (2003) showed that glutathione content increased during the metamorphic progression of the giant prawn larvae *Macrobrachium rosenbergii*. A similar increase was also observed in developing grass shrimp, *Palaemonetes pugio* (Winston et al. 2004), as well as in embryos of a toad, *Bufo arenarum* (Anguiano et al. 2001). In the trout, *Salmo iridaeus*, high CAT activities were observed during early development (in contrast to relatively lower levels of GPx), thus documenting the prime role of CAT over GPx in the removal of toxic hydrogen peroxide (Aceto et al. 1994). A gradual increase in CAT and GPx activities was observed during the progressive growth of the marine fish *Dentex dentex* from egg to larva (Mourente et al. 1999). On the other hand, in the same study, Mourente et al. (1999) showed that the titers of two other detoxification enzymes (GST and SOD) reached their highest levels in eggs, compared to later developmental stages. A gradual increase of antioxidant enzyme activities during embryogenesis, followed by a sudden rise in freshly hatched larvae, was also observed for the prawn *Macrobrachium malcolmsonii* (Arun and Subramanian 1998).

As is apparent, the results of available studies confirm that temporal changes of antioxidant agents are carefully regulated during the early development of aquatic organisms. Hence, such antioxidants play an important role. Notwithstanding, more research is needed to fully elucidate the physiological roles of ROS and antioxidant enzymes in maintaining homeostasis during early development.

6 Oxidative Stress in Embryotoxicity and Teratogenicity

While the previous section briefly described some physiological functions of ROS and the associated antioxidant defenses, the following paragraphs focus on the embryotoxicity that results from oxidative stress. Most research that has been conducted on this topic has included studies with model compounds such as hydrogen peroxide and has employed laboratory rodents or human embryos. In these studies, pro-oxidants induced severe oxidative stress damage to oocytes, mitochondrial alterations, ATP depletion, DNA damage and lipid peroxidation, apoptosis, or delays in whole embryo development (Aitken and Krausz 2001; Duru et al. 2000; Nasr-Esfahani et al. 1990; Ozolins and Hales 1999). The importance of oxidative stress in causing embryotoxicity or teratogenicity was also indirectly confirmed in mammalian and human studies, in which external additions of antioxidants prevented damage to embryos (Feugang et al. 2004; Fraga et al. 1991).

Similar to what occurs in mammals, studies with model pro-oxidants have also demonstrated detrimental effects in fish embryos and larvae (Westernhagen von 1988; Dietrich et al. 2005; Regoli et al. 2005), as well as in the larvae of the giant prawn *M. rosenbergii* (Dandapat et al. 2003). Moreover, the addition of antioxidants protected fish embryonal development against the effects of oxidative stress (Ciereszko et al. 1999; Toyokuni and Sagripanti 1992; Tilton et al. 2008).

7 Pesticides and Oxidative Damage During Early Development in Aquatic Organisms

Although pesticides may disrupt reproduction and development in many aquatic organisms (see Tables 1, 2, and 3), our search of the literature disclosed only a few studies that experimentally documented the role of oxidative stress in pesticide-induced teratogenicity (see Table 4).

Table 4 Teratogenic effects of some pesticides that are linked to effects on detoxification, antioxidative parameters, oxidative stress, or modulation of antioxidative processes in the early life stages of various fish species, amphibians, and invertebrates

Pesticide	Organism	Biochemical effect	Developmental effect	References
Fish				
Atrazine	*D. rerio*	Breakdown of the GST isoenzymes, altered microsomal and soluble GST activity, abnormal development, atrazine–GSH conjugate formation	Delay in embryonic development, unfinished epiboly or edema, decrease of heart rate and dysfunction of circulatory system, reduced development, reduced genesis of eyes, somites, otolithes, and melanophores	Wiegand et al. (2000, 2001)
Aldicarb, aldicarb sulfoxide	*D.rerio*	Inhibited carboxylesterase heart rate affection (embryo)		Küster and Altenburger (2007)
Paraquat	*O. mykiss*	Elevated G6PD and GR activity (juvenile)		Ĺkerman et al. (2003)
Azinphos methyl	*O. mykiss*	Reduced GSH level, CAT, and carboxylesterase activity (juvenile)		Ferrari et al. (2007)
Carbaryl	*O. mykiss*	Inhibited carboxylesterase and GSH level, altered CAT, induced GST activity and CYP1A level (juvenile)		Ferrari et al. (2007)
Dichlorvos	*S. aurata*	Increased LP level, decreased RNA/DNA ratio (juveniles)		Varó et al. (2007)
Endosulfan	*O. niloticus*	ROS production, lipid peroxidation (juveniles)		Tellez-Bańuelos et al. (2009)
Hexachlorobenzene	*C. carpio*	Altered GSH content and SOD and GPx, GR, GSSG activity, ROS generation, lipid peroxidation (juveniles)		Song et al. (2006)

Table 4 (continued)

Pesticide	Organism	Biochemical effect	Developmental effect	References
Amphibia				
Carbaryl	*B. arenarum*	Altered GSH content, SOD, GST, and GR activity, increased CAT and GPX activity	Progressive dropsy, body bending, and paralysis	Ferrari et al. (2009)
Azinphos methyl	*B. arenarum*	Decreased GSH level, altered GR, GPX, GST, and CAT, decreased SOD activity	Gill atrophy, notochord curvature, folded tail fin, generalized delay in the development, hyperactivity	Ferrari et al. (2009)
Parathion	*B. arenarum*	Alteration of GST activity	Decreased rate of gastrulas, curvature of the antero-posterior axis, tail folding, circle-swimming movement, frequent dropsy, and edema	Anguiano et al. (2001)
Malathion	*B. arenarum*	Reduced GSH content in both embryos and larvae, increased GST activity	Decreased rate of gastrulas, curvature of the antero-posterior axis, tail folding, circle-swimming movement, frequent dropsy, and edema	Anguiano et al. (2001)
	R. boylii	Decreased GR and CAT activities and the GSH pool (embryolarval)		Ferrari et al. (2008)
		Inhibited carboxylesterase activity, induced mixed function oxidase (larvae)		Venturino et al. (2001a, b)
		Depleted acid-soluble thiols (larvae) Larval mortality		Sparling and Fellers (2007)
Lindane	*B. arenarum*	Decreased GSH in embryo, increased GST activity	Decreased rate of gastrulas, irregular blastomeres, axis curvature, tail folding, edema, organ displacement, hemorrhage, hyperactivity, profuse scaling, dropsy, organ displacement, and bent tail	Anguiano et al. (2001)

Table 4 (continued)

Pesticide	Organism	Biochemical effect	Developmental effect	References
Dieldrin	*B. arenarum*	Increased GST activity	Exogastrulation, hyperactivity, hemorrhagia	Anguiano et al. (2001)
Acetochlor	*Bufo raddei*	Enhanced LP level and DNA single-strand break in liver (juvenile)		Liu et al. (2006)
Invertebrates				
Malathion	*C. gigas*	Increased CAT activity (larvae)		Damiens et al. (2004)
Heptachlor	*Homarus americanus*	Elevated CYP45 and HSP70 levels	Larvae mortality, delays in ecdysis	Snyder and Mulder (2001)
Carbofuran	*C. gigas*	Increased LP level, modulation of CAT activity (larvae)		Damiens et al. (2004)
Permethrin	*P. pugio*	Increased time to hatch, lethargy of larvae, altered GSH and LP levels (larvae)		DeLorenzo et al. (2006)

CAT, catalase; CoA, coenzyme A; CYP1A, cytochrome P 450 1A isozyme; EROD, ethoxyresorufin-*O*-deethylase; G6PD, glucose-6-phosphate dehydrogenase; GSH, glutathione; GSSG, oxidized glutathione; GR, glutathione reductase; GST, glutathione-*S*-transferase; GPx, glutathione peroxidase; HSP, heat-shock protein; LP, lipid peroxidation; ROS, reactive oxygen species; SOD, superoxide dismutase

Among the few pesticides on which oxidative stress effects were studied were the following: the triazine herbicide atrazine, the organophosphate insecticides parathion and azinphos methyl, and the organochlorine insecticides dieldrin and lindane.

Exposures of *D. rerio* embryos to atrazine lead to retardation of organogenesis (especially eyes, somites, otolithes, and melanophores), dysfunctions of the circulatory system, edemas, and a delay in embryonic development; in addition, these effects occurred in parallel with alterations of GST activities (Wiegand et al. 2000, 2001).

Mortality in embryos and developmental abnormalities, along with oxidative stress markers, were also observed in two studies with embryos of the toad *B. arenarum*. Anguiano et al. (2001) discovered that the organochlorine insecticide lindane caused abnormal segmentation of furrows, along with irregular blastomeres, profuse scaling, dropsy, organ displacements, and bent tail. Interestingly, only moderate alterations of embryonic morphology and hemorrhagia were observed after exposure to another organochlorine insecticide – dieldrin (Anguiano et al. 2001). In the same study, Anguiano et al. (2001) also showed that the organophosphate insecticides malathion and parathion were highly embryotoxic and caused a pathological curvature of the antero-posterior axis, tail folding edema, frequent dropsy, and also induced circle-swimming movements. Ferrari et al. (2009) studied the effects of carbaryl and azinphos methyl on the embryos of *B. arenarum* and demonstrated progressive dropsy, notochord malformations, gill atrophy, paralysis, and delayed development. The above-described effects were also correlated with modulations of glutathione levels and elevated activities of GST, SOD, CAT, and glutathione reductase (GR; EC 1.8.1.7) (Anguiano et al. 2001; Ferrari et al. 2009).

In studies with invertebrates, Snyder and Mulder (2001) demonstrated oxidative stress and pesticide toxicity after exposure to heptachlor or disruption of grass shrimp development by permethrin (DeLorenzo et al. 2006). Damiens et al. (2004) also showed larval toxicity and modulation of antioxidant and detoxification parameters after exposures to complex media contaminated with pesticides.

Direct toxic effects of pesticides on developing fish embryos were not found in other studies, but signs of oxidative stress and variable modulation of the antioxidative system were observed (Ĺkerman et al. 2003; Song et al. 2006; Ferrari et al. 2007; Varó et al. 2007; Küster and Altenburger 2007; Tellez-Bańuelos et al. 2009).

The bipyridyl herbicides paraquat and diquat are of special interest. The major mechanism by which they produce their toxic action in target organisms, whether animals or plants, is through lipid peroxidation. Disturbances of normal early developmental processes, after exposure to paraquat, were clearly documented to have occurred in *X. laevis* embryos (Vismara et al. 2000, 2001a; see Table 2). These toxic effects were prevented after the addition of the water-soluble antioxidant ascorbic acid to the test medium (Vismara et al. 2001b, 2006). Antioxidant protection by ascorbic acid was also confirmed in our studies (unpublished results), in which we compared the embryotoxicity of diquat and paraquat to *X. laevis*.

Few studies exist in which the oxidative stress damage caused by pesticides (herbicides atrazine, paraquat, and diquat; the organophosphate insecticides parathion and azinphos methyl; organochlorines dieldrin and lindane) to developing aquatic organisms has been described. Therefore, further research is needed in this area to better understand the levels of embryotoxicity that may result from other, less-explored pesticides.

8 Further Evidence – Pesticides and Antioxidative Defense in Adult Aquatic Biota

Although there are only a limited number of studies that link oxidative stress caused by pesticides with embryotoxicity, other evidence with adult aquatic organisms exists that supports the importance of this mechanism. Any comprehensive treatment of the topic of pesticide-induced oxidative stress in adults is beyond the scope of this chapter, and there are several credible recent reviews that address this topic (Valavanidis et al. 2006; Monserrat et al. 2006; Slaninova et al. 2009; Debenest et al. 2010). Nevertheless, to provide supporting data, representative studies that address selected pesticides (e.g., organophosphates, organochlorines, and bipyridyl herbicides) are presented in Tables 5, 6, and 7 (these tables address studies with fish, amphibians, and invertebrates, respectively).

In general, exposures of adult specimens to different pesticides induced antioxidative defenses, such as increases in titers of ethoxyresorufin *O*-deethylase (EROD), SOD, GST, and GR or G6PD, along with declines in glutathione concentrations and oxidative damage to lipids, DNA, proteins, and tissues (hepatic alterations, necrosis, etc.). For example, diazinon and glyphosate induced tissue-specific alterations of CAT and GPx activities, together with enhanced SOD activity and lipid peroxidation, in fish species (*Oreochromis niloticus* and *Prochilodus lineatus*; Durmaz et al. 2006; Langiano et al. 2008). Similarly, lipid peroxidation and detoxification responses were induced in methyl parathion-exposed *Brycon cephalus* (Monteiro et al. 2006), as well as in the mosquito fish *Gambusia affinis* that was exposed to the organophosphorus insecticides monocrotophos and chlorpyrifos (Kavitha and Rao 2008; Kavitha and Rao 2007, 2008). Glutathione redox cycle and CAT were shown to protect against endosulfan-induced toxicity in trout *Oncorhynchus mykiss* cells (Dorval et al. 2003; Dorval and Hontela 2003). Endosulfan also induced lipid peroxidation and altered various enzymatic activities in *Jenynsia multidentata* (Ballesteros et al. 2009). Paraquat, a herbicide that acts via ROS production, induced lipid peroxides and modulated SOD, GR, and GST in various fish, such as *Sparus aurata* (Pedrajas et al. 1995; Rodríguez-Ariza et al. 1999) or Nile tilapia *O. niloticus* (Figueiredo-Fernandes et al. 2006a, b). Paraquat also induced protein carbonylation in liver, kidney, and gills and modulated glutathione and ascorbic acid levels in *Channa punctata* (Parvez and Raisuddin 2005, 2006).

Comparable results were obtained in experiments with the amphibian (frog) *Rana ridibunda* (Table 6). Herein, mixtures of propamocarb and mancozeb caused elevated lipid and protein peroxidation and suppressed SOD activity (Falfushinska et al. 2008). Oxidative stress caused by pesticides, pyrethroid insecticides for example, was also observed in several experiments performed with invertebrates

Table 5 The effects of selected pesticides on detoxification, antioxidative, and other important biochemical parameters in fish

Pesticide	Organism	Biochemical effect	References
Carbamates			
Molinate	*Anguilla anguilla*	Increased hepatic GSH, GR and GSH:GSSG ratio, decreased muscular GSH	Peńa-Llopis et al. (2001)
Carbaryl	*O. niloticus*	Decreased SOD, GR, GST, and CAT activity, hepatocellular basophilia, necrotic foci	Matos et al. (2007)
Organophosphates			
Monocrotophos	*G. affinis*	SOD, CAT, GR, and lipid peroxidation induction, recovery response of antioxidant enzymes	Kavitha and Rao (2007)
Chlorpyrifos	*G. affinis*	SOD, CAT, and GR inhibition, recovery response of antioxidant enzymes, lipid peroxidation	Kavitha and Rao (2008)
Azinphos methyl	*O. niloticus*	Increased activity of G6PD, GPx, and GR, SOD decrease	Oruçand Üner (2000)
	C. carpio	Increase of SOD and GST activities, elevation in CAT and GPx activities in carp decrease of GPx in tilapia	Oruç et al. (2004)
Glyphosate	*P. lineatus*	Plasma glucose and CAT activity increase, histological alterations impairing normal organ functions	Langiano and Martinez (2008), Modesto and Martinez (2010)
		Reduced SOD and GPx activities, increased GST activity and GSH level, lipid peroxidation	
	Carassius auratus	Decreased GSH content and SOD, GR, G6PHD activity and hepatic GST, increased CAT activity	Lushchak et al. (2009)
Diazinon	*O. niloticus*	SOD increase, CAT and GPx alteration, lipid peroxidation	Durmaz et al. (2006)
	O. mykiss	Increased LP level, GSH depletion, modulation of SOD, GR, GST, GPX activities	Isik and Celik (2008)
	C. carpio	Increased SOD, decreased CAT, and altered GPx activity and protein carbonyl level, lipid peroxidation	Oruçand Usta (2007)

Table 5 (continued)

Pesticide	Organism	Biochemical effect	References
Methyl parathion	*Brycon cephalus*	SOD, CAT, GST induction, GPx alteration, lipid peroxidation	Monteiro et al. (2006)
	O. mykiss	Increased LP level, GSH depletion, modulation of SOD, GR, GST, GPx activities	Isik and Celik (2008)
Malathion	*S. aurata*	Increased LP and GST	Pedrajas et al. (1995)
Fenthion	*O. niloticus*	Increased GSH and GSSG content and GPx activity	Piner et al. (2007)
Organochlorines			
Endosulfan	*O. mykiss*	CAT, GPx, GSH alterations, lipid peroxidation	Dorval and Hontela (2003)
	J. multidentata	Reduced GSH and GPx, induced GST and CAT, lipid peroxidation	Dorval et al. (2003)
	C. punctata	GST, GR, GPx, and CAT alterations, lipid peroxidation	Ballesteros et al. (2009)
		Increased protein carbonyls in liver, kidney, and gills	Parvez and Raisuddin (2005)
Dieldrin	*S. aurata*	CAT, SOD, and palmitoyl-CoA-oxidase induction, increased protein concentration in peroxisomal fraction; increased LP and GST;increased 8-oxoG marker	Pedrajas et al. (1995, 1996), Rodríguez-Ariza et al. (1999)
Chlorothalonil	*Morone saxatilis*	ROS production, altered GSH level	Baier-Anderson and Anderson (2000)
DDT	*Hoplias malabaricus*	Increased intracellular ROS, increased CAT and G6PDH activities, GSH content, lipid peroxidation and protein carbonyl level, decreased SOD, GST, and GR activities; decreased cell viability	Filipak Neto et al. (2008)
Triazines			
Atrazine	*D. rerio*	Induced cytochrome P450 content, increased NADPH-P450 reductase, erythromycin *N*-demethylase, and aminopyrine *N*-demethylase	Dong et al. (2009)
	Lepomis macrochirus	Increased hepatic GSH and GSSG levels and GST, SOD activities, lipid peroxidation, altered GPx and GR activities	Elia et al. (2002)

Table 5 (continued)

Pesticide	Organism	Biochemical effect	References
Mixture of atrazine, simazine, diuron, isoproturon	*C. auratus*	Enhanced production of superoxide, induced SOD activity in liver, reduced CAT activity	Fatima et al. (2007)
Simazine	*C. carpio*	Lipid peroxidation, increased GSH level	Oropesa et al. (2009)
Bipyridyls			
Paraquat	*O. niloticus*	High hepato-somatic and gonado-somatic index, increased EROD activity, hepatic alterations of parenchyma, like vacuolization, necrosis, and an increase of macrophage aggregates and eosinophilic granular cells; higher SOD, GST activity, gender-dependent increase of GR	Figueiredo-Fernandes et al. (2006a, b)
	C. punctata	Increased protein carbonyls in liver, kidney, and gills, reduced GSH in liver and gills, increased ascorbic acid level	Parvez and Raisuddin (2005, 2006)
	S. aurata	Increased LP, GST, and SOD Decreased GPX, higher G-6PDH activity, increased GR	Pedrajas et al. (1995), Rodríguez-Ariza et al. (1999)
2,4-D-Phenoxy carboxylic acid			
2,4-Dichlorophenoxy acetic acid dimethyl amine	*O. niloticus*	Increased activity of G6PD, GPx, and GR	Oruç and Üner (2000)
	C. carpio	Increase of SOD and GST activity, elevation in CAT and GPx activities in carp decrease of GPx in tilapia	Oruç et al. (2004)
Synthetic pyrethroids			
Deltamethrin	*C. punctata*	Lipid peroxidation and GSH level increase, alterations in CAT, SOD, and GST activity and ascorbic acid level Increased protein carbonyls in liver, kidney, and gills	Sayeed et al. (2003), Parvez and Raisuddin (2005)
Cypermethrin	*C. carpio*	Increased hepatic SOD and CAT activities, decreased GPx, lipid peroxidation	Uner et al. (2001)
	O. niloticus	Increased hepatic SOD, GPx, and CAT activities, lipid peroxidation	

Table 5 (continued)

Pesticide	Organism	Biochemical effect	References
Bifenthrin	*Cyprinodon variegatus*	Increasing trend in GSH level and CAT activity with toxicant dose	Harper et al. (2008)
Chloroacetanilides			
Butachlor	*C. gariepinus*	Lipid peroxidation, altered SOD, GST, and CAT activities and GSH level	Farombi et al. (2008)
Organofluorine			
Etoxazole	*O. niloticus*	Lipid peroxidation	Sevgiler et al. (2004)
Pyrazoles			
Fenpyroximate	*Paralichthys olivaceus*	Altered SOD, CAT, GST, GPx, and EROD activities	Na et al. (2009)
Dichlorobenzenes			
3,4-Dichloroaniline	*C. auratus*	Enhanced SOD activity and LP, decreased NO synthase and GSH level in liver	Li et al. (2003)

CAT, catalase; EROD, ethoxyresorufin-*O*-deethylase; G6PD, glucose-6-phosphate dehydrogenase; GSH, glutathione; GSSG, oxidized glutathione; GR, glutathione reductase; GST, glutathione-*S*-transferase; GPx, glutathione peroxidase; NADPH P450, NADPH–cytochrome P450 reductase; NO, nitric oxide; LP, lipid peroxidation; SOD, superoxide

Table 6 Effects of carbamates on detoxification, antioxidative, and other important biochemical parameters in amphibians

Pesticide	Organism	Biochemical effect	Reference
Amphibians			
Carbamate			
Mixture of propamocarb and mancozeb	*R. ridibunda*	Decreased SOD; lipid and protein peroxidation, neurotoxicity and endocrine disruption	Falfushinska et al. (2008)

SOD, superoxide dismutase

(Table 7). Several studies were conducted with mollusks on the pyrethroid insecticides, for example, cypermethrin and alphamethrin; these insecticides inhibited reproduction and induced oxidative stress in the freshwater snail *Lymnaea acuminata* (Tripathi and Singh 2004). In addition, lindane, an organochlorine insecticide, induced oxidative damage and stress responses in the mussel *Mytilus galloprovincialis* (Khessiba et al. 2005).

Table 7 The effects of selected pesticides on detoxification, antioxidative, and other important biochemical parameters in aquatic invertebrates

Pesticide	Organism	Biochemical effect	References
Organophosphates			
Fenitrothion	*M. galloprovincialis* *Flexopecten flexuosus*	GSH and GSSG depletion, reduction of GSH/GSSG ratio, decreased survival	Peña-Llopis et al. (2002)
Organochlorines			
Lindane	*M. galloprovincialis*	CAT activity induction	Khessiba et al. (2005)
Endosulfan	*Penaeus monodon*	Increased HSP level in muscles	Dorts et al. (2009)
Tetradifon	*D. magna*	Decreased protein, lipid, glycogen, and caloric content, decreased mean body dry weight	Villarroel et al. (2009)
Synthetic pyrethroids			
Cypermethrin alphamethrin	*L. acuminata*	Altered oxidative metabolism in hepatopancreas and ovotestis tissues, reduced survival	Tripathi and Singh (2004)
Deltamethrin	*P. monodon*	Increased LP level and protein carbonyls in gills	Dorts et al. (2009)
Bipyridyls			
Paraquat	*Biomphalaria glabrata*	Increased LP, decreased SOD	Cochón et al. (2007)

CAT, catalase; GSH, glutathione; GSSG, oxidized glutathione; HSP, heat-shock protein; LP, lipid peroxidation; SOD, superoxide dismutase

9 Summary

Many pesticides have been documented to induce embryotoxicity and teratogenicity in non-target aquatic biota such as fish, amphibians, and invertebrates. Our review of the existing literature shows that a broad range of pesticides, representing several different chemical classes, induce variable toxic effects in aquatic species. The effects observed include diverse morphological malformations as well as physiological and behavioral effects. When developmental malformations occur, the myoskeletal system is among the most highly sensitive of targets. Myoskeletal effects that have been documented to result from pesticide exposures include common notochord and vertebrate column degeneration and related abnormalities. Pesticides were also shown to interfere with the development of organ systems including the eyes or the heart and are also known to often cause lethal or sublethal edema in exposed organisms. The physiological, behavioral, and population endpoints affected by pesticides include low or delayed hatching, growth suppression, as well as embryonal or larval mortality. The risks associated with pesticide exposure increase particularly during the spring. This is the period of time in which major pesticide applications take place, and this period unfortunately also coincides with many sensitive reproductive events such as spawning, egg laying, and early development of many aquatic organisms.

Only few experimental studies with pesticides have directly linked developmental toxicity with key oxidative stress endpoints, such as lipid peroxidation, oxidative DNA damage, or modulation of antioxidant mechanisms. On the other hand, it has been documented in many reports that pesticide-related oxidative damage occurs in exposed adult fish, amphibians, and invertebrates. Moreover, the contribution of oxidative stress to the toxicity of pesticides has been emphasized in several recent review papers that have treated this topic.

In conclusion, the available experimental data, augmented by several indirect lines of evidence, provide support to the concept that oxidative stress is a highly important mechanism in pesticide-induced reproductive or developmental toxicity. Other stressors may also act by oxidative mechanisms. This notwithstanding, there is much yet to learn about the details of this phenomenon and further research is needed to more fully elucidate the effects that pesticides have and the environmental risks they pose in the early development of aquatic organisms.

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