Review Paper

Toxic Mechanisms of Aryloxyphenoxypropionates in Target and Non-target Organisms

ABSTRACT

Herbicides are substances used to control unwanted plants-weeds. They can be classified into several classes: by mechanism of action. This review describes the members of aryloxyphenoxypropionate herbicides, their pharmacokinetic properties, metabolism and their mechanism of phytotoxicity in target and non-target organisms. Two major mechanisms are described. The first is by inhibition of lipid synthesis. This is achieved by inhibiting the rate limiting step of lipid biosynthesis catalyzed by acetyl CoA carboxylase. The second is by causing oxidative stress. This is achieved by generation of reactive oxygen species which in excess can cause oxidative damage to macromolecules and cellular structures especially the membrane lipids. Loss of vital membrane lipids alters the fluidity of membrane, loss of cellular contents and eventually cell death and death of the entire plant.

Keywords: Herbicides, aryloxyphenoxypropionates, phytotoxicity mechanisms, acetyl CoA carboxylase, free radicals, oxidative stress, membrane lipid peroxidation, antioxidants.

1. INTRODUCTION

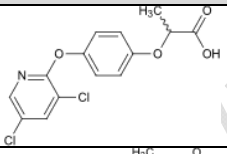
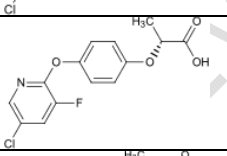
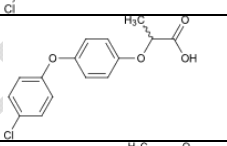
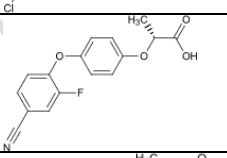
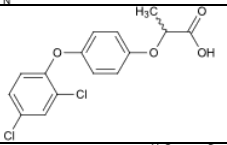
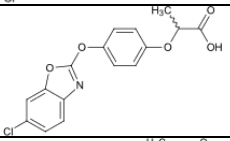
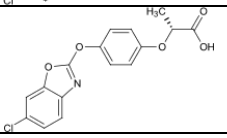
Herbicides (also known as weedkillers), are chemical substances used to control unwanted plants (weeds) [1]. Herbicides are described as either selective or non-selective. Selective herbicides are used to control specific weed species, while leaving the desired crop unharmed. The non-selective herbicides (total weedkillers) are applied to kill all plant species and therefore can be used to clear waste ground, construction sites, industrial sites etc. Apart from classification as selective/ non-selective, other classifications include persistence (by residual action), mechanism of uptake (whether they are absorbed through foliage, or through the roots, or by other means), and mechanism of phytotoxic action (how they kill succeptible plants). Herbicides may also be distinguised by application as pre-emergence or post- emergence. Pre-emergent herbicides are applied to the soil before the crop emerges and prevent germination of weed seeds and early growth of weeds. Post-emergent herbicides are applied after the crop and weeds have emerged [2].

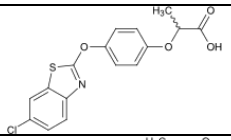
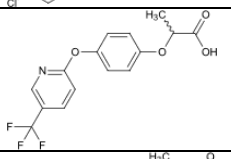
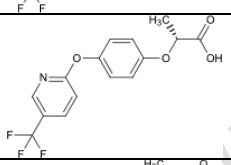
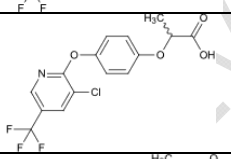
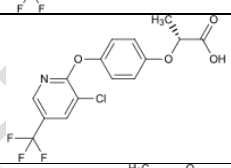
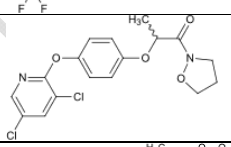
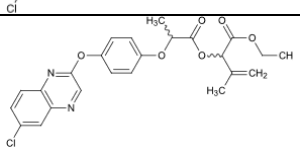
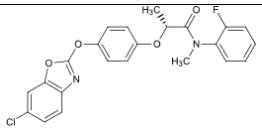
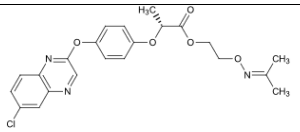
Aryloxyphenoxypropionic herbicides or aryloxyphenoxypropionates (ArOPPs) belongs to the class of phenoxy herbicides and the sub-class of phenoxypropionic herbicides [3]. ArOPPs are relatively new class of selective herbicides prepared from heterocyclic oxyphenoxypropionic acid derivatives for the control of graminaceous weeds in broad-leaved crops and tolerant cereal crops [4]. They are applied mainly on cotton, soybeans and sugar beet as well as in the wheat, corn, barley, rye, legumes, sunflowers, sesame, alfalfa, peanuts, lettuce, spinach, potatoes, cucumber, peas, tomatoes, fennel, and strawberries [5-8]. ArOPPs **They** are post – emergence (PoEm) herbicides composed of about fifteen members. Esters of ArOPPs are newer forms of PoEm herbicides with higher selectivity. In spite of a wide range of chemical structures, they display similar herbicidal action. The

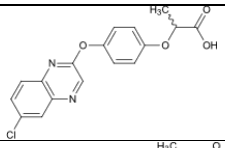
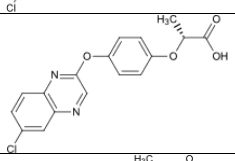
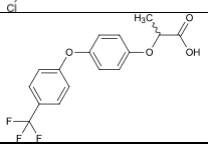
Common names, IUPAC names, Chemical structures and Chemical Abstracts Service registry numbers of AOPP herbicides are shown in Table 1.

ArOPPs control grassy weeds, and are applied mainly on cotton, soybeans and sugar beet as well as in the wheat, corn, barley, rye, legumes, sunflowers, sesame, alfalfa, peanuts, lettuce, spinach, potatoes, cucumber, peas, tomatoes, fennel, and strawberries [5-8].

Table 1. Common names, IUPAC names, Chemical structures and Chemical Abstracts Service (CAS) registry numbers of AOPP herbicides

S/N	Common Names	IUPAC Nomenclature	Chemical Structures	CAS No
1	Chlorazifop	(*RS*)-2-[4-(3,5-dichloro-2-pyridyloxy)phenoxy]propionic acid		60074-25-1
2	Clodinafop	*(R)*-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)phenoxy]propionic acid		114420-56-3
3	Clofop	*(RS)*-2-[4-(4-chlorophenoxy)phe noxy]propionic acid		26129-32-8
4	Cyhalofop	*(R)*-2-[4-(4-cyano-2-fluorophenoxy)phe noxy]propionic acid		122008-78-0
5	Diclofop	*(RS)*-2-[4-(2,4-dichlorophenoxy)ph enoxy]propionic acid		40843-25-2
6(a)	Fenoxaprop	(RS)-2-[4-(6-chloro-1,3-benzoxazol-2-yloxy)phenoxy]prop ionic acid		95617-09-7
(b)	Fenoxaprop-P	(R)-2-[4-(6-chloro-1,3-benzoxazol-2-yloxy)phenoxy]prop ionic acid		113158-40-0

7	Fenthiaprop	(RS)-2-[4-(6-chloro-1,3-benzothiazol-2-yloxy)phenoxy]propionic acid		66441-11-0
8(a)	Fluazifop	(RS)-2-{4-[5-(trifluoromethyl)-2-pyridyloxy]phenoxy}propionic acid		69806-34-4
(b)	Fluazifop-P	(R)-2-{4-[5-(trifluoromethyl)-2-pyridyloxy]phenoxy}propionic acid		83066-88-0
9(a)	Haloxyfop	(RS)-2-{4-[3-chloro-5-(trifluoromethyl)-2-pyridyloxy]phenoxy}propionic acid		69806-34-4
(b)	Haloxyfop-P	(R)-2-{4-[3-chloro-5-(trifluoromethyl)-2-pyridyloxy]phenoxy}propionic acid		95977-29-0
10	Isoxapyrifop	(RS)-2-[2-[4-(3,5-dichloro-2-pyridyloxy)phenoxy]propionyl]isoxazolidine		87757-18-4
11	Kuicaoxi	ethyl(2RS)-2-{(2RS)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionyloxy}-3-methylbut-3-enoate		3724-55-8
12	Metamifop	(R)-2-[4-(6-chloro-1,3-benzoxazol-2-yloxy)phenoxy]-2′-fluoro-N-methylpropionanilide		256412-89-2
13	Propaquizafop	2-isopropylideneaminooxyethyl(R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate		111479-05-1

14	Quizalofop	(RS)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionic acid		76578-12-6
	Quizalofop-P	(R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionic acid		94051-08-8
15	Trifop	(RS)-2-[4-(α,α,α-trifluoro-p-tolyloxy)phenoxy]propionic acid		58594-74-4

2. ABSORPTION, TRANSLOCATION AND METABOLISM OF ArOPPs

Following application to fields, herbicides (their active ingredients) must be absorbed significantly for effective herbicidal actions. In phytotoxicity studies, absorption refers to the quantity of applied active ingredient that has been absorbed by the leaves or roots of the treated plants. Distribution is the fractionation of accumulated herbicides in parts of the treated plant including treated leaf (or root) [9].

2.1 Absorption, translocation and Metabolism in Target Plant Species

In plants, AOPPs are absorbed mainly through the leaves. In few cases, they may be absorbed through the roots. Studies on the absorption of fluazifop-butyl (FB) through the leaves, for instance, was found to be about 75 % after 8 hours of application [10]. Translocation of FB from **leafs** leaves to root is also very rapid with up to 10 fold higher in the leaves compared to the root [11]. Similar absorption and translocation rates are also observed with other ArOPPs. A study carried out on cyhalofop-butyl showed an absorption of up to 73% in *Echinochloa* spp. (a major weed in rice) twenty-four hours after application [12]. Absorption/ translocation studies conducted by Aguero-Alvarado et al. [13] in soybean also revealed a significantly high absorption/ translocation of haloxyfop. Following absorption and translocation, they are metabolised into the acidic forms. The esters of ArOPPs undergo a more rapid decomposition, yielding the corresponding free acids as the main metabolites [14]. Fluazifop-p butyl (FPB), one of the most extensively studied ArOPPs, has been shown to be metabolized mainly to fluazifop-p (also known as fluazifop acid) and other minor metabolites (Figure 1). The major metabolites of **Haloxifop**haloxifop-p butyl and cyhalofop-butyl have also been found to be haloxyfop-p and cyhalofop-butyl acid respectively [13, 15]. These acidic metabolites are then translocated to the entire plant through the phloem and xylem systems, accumulating in the meristematic tissues of the plant [16].

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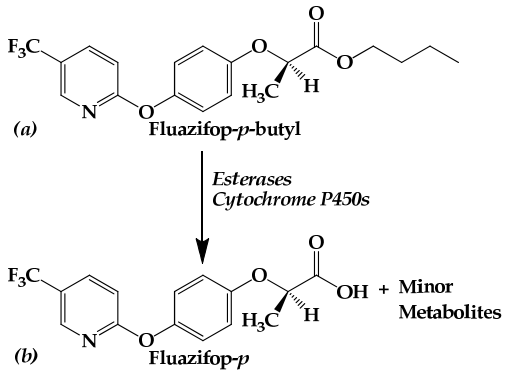

Figure 1. Metabolism of fluazifop-p-butyl (a) to fluazifop-p (b) and other minor metabolites [17].

2.2 Absorption, Pharmacokinetics and Metabolism in Human and Animals

Absorption of ArOPPs are also very rapid in animals by oral route. In a study on rats, cyhalofop-butyl was rapidly absorbed following oral dosing with maximum plasma levels attained within a few hours. The major metabolite in plasma, liver, bile, kidney, urine and **faeces**faces, was found to be cyhalofop-butyl acid (66-78%) and a minor metabolite, 4-(4-cyano-2-fluorophenoxy) phenol. Absorption of ArOPPs through the skin have also been reported in human and animal studies [18,19]. FPB is absorbed orally and through the skin, although at a slower rate through the skin [19, 20].

3. PHYTOTOXICITY MECHANISMS OF ArOPPs

Considerable efforts have been made towards understanding the mechanism of phytotoxic action of the ArOPP herbicides. These involved studies cutting across a wide range of plant species. Major phytotoxicity mechanisms identified include inhibition of lipid metabolism and oxidative stress.

3.1 Inhibition of lipid metabolism

3.1.1 Acetyl CoA carboxylase

All the known aryloxyphenoxypropionates show similar species specificity and similar symptoms in susceptible plants. Based on these similarities, it has been suggested that they have similar targets in susceptible plant species. Studies have postulated that ArOPPs acts by disabling the *de novo* fatty acid biosynthesis, but no specific site of action was identified [21, 22]. Studies have however demonstrated that they specifically inhibit acetyl-CoA carboxylase (ACCase) in target plants. ACCase (E.C. 6.4.1.2) is the rate-limiting enzyme in the *de novo* fatty acid biosynthetic pathway [23]. This plastid located enzyme catalyzes the adenosine triphosphate (ATP)-dependent formation of malonyl-CoA from acetyl-CoA and bicarbonate (Figure 2). Despite differences in regulation and protein structure across various species, ACCase is known to plays the same role in fatty acid synthesis [24].

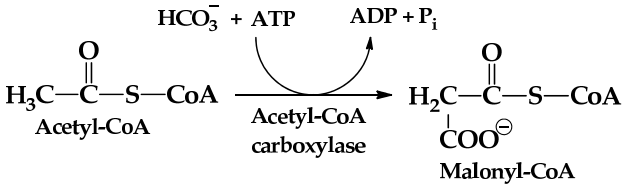

Figure 2. Acetyl CoA carboxylase catalyzed reaction; the first step in the sequence of reactions for the biosynthesis of fatty acids [25].

Fatty acids are the major components of the cell membrane. It is viewed that the inhibition of *de novo* fatty acid biosynthesis may lead to low production of relevant fatty acids. This leads to impaired membrane biosynthesis and loss of cellular components [26]. Other studies suggest that inhibition of ACCase results in an alteration of the fatty acids incorporated into the membrane resulting in altered electrochemical properties of membranes. Several esters of ArOPP such as diclofop, fenoxaprop, fluazifop, haloxyfop, quizalofop etc were found to cause similar effects in most plant species [26].

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3.1.2 Fatty acid synthase

Fatty acid synthase (FAS) has been implicated as another site of action for the graminicides [27]. Fatty acid synthase is the enzyme system that catalyzes the synthesis of saturated long-chain fatty acids from acetyl CoA, malonyl CoA, and NADPH. Inhibition of fatty acid synthase results in a decrease in the incorporation of malonyl-coenzyme A into fatty acids, but does not affect the incorporation of acetate into malonyl-coenzyme A.

3.2 Oxidative stress

Generation of oxidative stress has also been identified as one of the mechanism used by ArOPPs to kill susceptible plant species. This is achieved by generation of reactive species (RS), depletion of antioxidant defenses, and generation of oxidative stress. Oxidative stress can be defined as a serious imbalance between the production of reactive species and antioxidant defenses [28]. Reactive species are chemically reactive chemical species containing oxygen (reactive oxygen species, ROS), nitrogen (reactive nitrogen species, RNS) etc. ROSs (which are the most extensively studied RS) are oxygen-containing molecules exhibiting higher chemical reactivity than O_2. ROS is constantly generated in the chloroplasts due to partial reduction of O_2 or as a result of transfer of energy to O_2.

Table 2. Major reactive oxygen species, antioxidants and biomarkers of oxidative damage in plants [32, 33]

Major Reactive Oxygen Species (ROS)	
Free Radicals	Hydroxyl radical ($^{\bullet}OH$); Superoxide radical ($O_2^{\bullet-}$)
Non-radicals	Singlet oxygen ($^1O_2$); Hydrogen peroxide (H_2O_2)
Major Cellular Antioxidants and their protective functions	
Enzymic	Superoxide dismutase (SOD): converts $O_2^{\bullet-}$ to H_2O_2 and O_2 Catalase (CAT): converts H_2O_2 to $2H_2O$ and O_2 Ascorbate peroxidase (APX): converts H_2O_2 to $2H_2O$

	Glutathione peroxidase: detoxifies H_2O_2 using reduced glutathione (GSH) producing the oxidised form GSSG Glutathione reductase (GR): reduces GSSG to GSH
Non enzymic	Ascorbic Acid (AA): Detoxifies H_2O_2 via action of APX Reduced Glutathione (GSH): co-substrate for glutathione peroxidases α-Tocopherol: protects against membrane lipid peroxidation (LPO) Flavonoids: scavenges H_2O_2 and $^1O_2$ and $OH^{\bullet}$
Oxidative Damages to macromolecules and their cellular implications	
Lipids	Oxidation of membrane lipids to products like Malondialdehyde (MDA), lipid peroxide, 4-hydroxynonenal etc) Increase in membrane fluidity and permeability
Proteins	Site-specific amino acid, modification, Fragmentation of the peptide chain, Aggregation of crosslinked, reaction products, Altered electric charge, Enzyme inactivation, Increased susceptibility, of proteins to proteolysis
DNA	Deoxyribose oxidation, Strand breakage, Removal of nucleotides, Modification of bases, DNA-protein crosslinks

ROS may play two different roles in plant physiology; low levels can be used in adaptive signalling whereas, high concentrations of ROS can result in phytotoxicity [29]. The role of ROS in plant physiology has been extensively described [30]. Oxidative stres can also be defined as a disturbance in the pro-oxidant–antioxidant balance in favour of the pro-oxidants, leading to cell damage. An antioxidant is any substance that can inhibit the oxidation of the cell components such as DNA, proteins and lipids.

Damages resulting from oxidative stress are often called 'oxidative damages'. Oxidative damage to macromolecules (lipids, proteins, DNA etc) results in formation of oxidative damage products (lipid, protein, DNA oxidation products) which are usually considered biomarkers of oxidative stress [31]. Several levels of antioxidative defense mechanism are used by plants to prevent oxidative damages [32]. Table 2 shows the major reactive species, antioxidants and biomarkers of oxidative damage. Several studies have shown ArOPPs to cause oxidative stress or oxidative damage as a phytotoxicity mechanism in plant species. Studies on ArOPPs across a wide variety of plants are summarized in Table 3.

Table 3. Reports suggesting oxidative stress play a role in the phytotoxicity mechanism used by ArOPPs

ArOPP	Plant under study	Oxidative stress/ damage markers observed	Reference(s)
Clodinafop-propargyl	Winter wheat (*Triticum aestivum L.*); winter rye (*Secale cereale* L., and maize (*Zea mays L.)*	Increases in superoxide anion radical generation, LPO Increase in total antioxidant activity, catalase, and ascorbate peroxidase activity	[34]
Diclofop acid	*Arabidopsis thaliana*	High level of MDA High CAT, SOD and POD	[35]

		activity	
Diclofop-Methyl	Rice	Increase in MDA, SOD and peroxidase activity	[36]
	Oat (*Avena sativa* L.) and leafy spurge (E*uphorbia esula* L.).	Increase in MDA, SOD and peroxidase activity	[37]
Fenoxaprop-ethyl	wheat	Induction of GST	[38]
Fluazifop-p (Fluazifop acid)	Sea grass (*Zostera nigricaulis)*	Lipid peroxidation	[39]
Fluazifop-p-butyl	Bristly starbur (*Acanthospermum hispidum*)	Increase in MDA, membrane peroxidation	[40]
	bristly starbur (*Acanthospermum hispidum*) seedlings	Involvement of H_2O_2	[41]
	Acanthospermum hispidum	Membrane lipid peroxidation caused by increasing levels of reactive oxygen species (ROS)	[42]
Quizalofop-P-ethyl	*Radix isatidis*	Reduction in SOD activity Increase in Malondialdehyde (MDA)	[43]
	Lemna minor and *Lemna gibba*	Increase in MDA; SOD, and POD activities	[44]

4. TOXICITY MECHANISMS OF ArOPPs IN NON-TARGET ANIMAL SPECIES

Studies evaluating the toxicity of ArOPPs in non-plants has described similar toxicity mechanisms as those found in plant models. Studies in human and animal including bacterial models show inhibition of lipid metabolism and or generation of oxidative stress.

4.1 Inhibition of lipid metabolism

Metabolic studies indicate that ArOPPs are metabolized to the acidic metabolites similar to plant. Fluazifop-p butyl for instance is metabolised to fluazifop acid in human and animals models [18, 19]. These metabolites also appear to produce similar symptoms in mammals.

Also, weight loss observed in mammalian studies have been linked to inhibition of mammalian ACCase by fluazifop compounds [45].

4.2 Oxidative stress

Oxidative stress has also been linked to the toxicity mechanism elicited by ArOPPs in animal studies. A study carried out by Ye et al. [46] in which cyanobacteria was exposed to diclofop and its R-enantiomer reported an increase in MDA concentration and SOD activity. They suggested that diclofop and its R-enantiomer may cause a collapse in the transmembrane proton gradient and damage the cell membrane through lipid peroxidation and free radical attack. Exposure of rat to fluazifop-p butyl and haloxyfop-p methyl ester caused depletion in hepatic and testicular antioxidant defence system, resulting in lipid peroxidation and organ damage [17, 47]. Table 4 summarizes the studies carried out on non-plant species linking ArOPPs to oxidative stress.

Table 4: Some reports on induction of oxidative stress by ArOPPs in animal studies

ArOPP	Animal species under study	Oxidative stress marker/ Oxidative damage observed	Reference(s)
Diclofop acid	Cyanobacteria (*Microcystis aeruginosa*)	increase in MDA concentration and SOD activity	[46]
Fenoxaprop-ethyl	Rat	Increase in MDA and, SOD activity, decrease in GST activity, decrease in SH proteins	[48]
Fenoxaprop-*p*-ethyl	Cyanobacteria *Microcystis aeruginosa and Microcystis viridis*	generation of MDA and increase in activities of SOD, POD, CAT	[49]
Fluazifop-*p*-butyl	Rat	Increase in MDA level, decrease in GSH level and activities of GST, CAT, SOD	[17]
Haloxyfop-*P*-methyl ester	Rat	Increase in MDA level, decrease in GSH level and activities of GST, CAT, SOD	[47]

5. CONCLUSION

Aryloxyphenoxypropionates are a group of very effective selective post-emergence herbicides. Their mechanism of action in target plants (inhibition of lipid synthesis and generation of oxidative stress) is unique. Presentation of similar symptoms in non-target plant and animal species will help in understanding potential development of resistance to these chemicals. These mechanisms will also contribute to effective management of clinical cases of accidental exposure to these substances.

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