



## Review

# Mode of action of pesticides and the novel trends – A critical review

Shaon Kumar Das

ICAR Research Complex for NEH Region, Sikkim Center, Gangtok-737102, India  
E-mail: [Shaon.iari@gmail.com](mailto:Shaon.iari@gmail.com); Tel: +91-9475680474

### ABSTRACT

The mode of action of pesticides is extremely fascinating because the subject covers so many fields of biology and chemistry and has many practical implications. To understand how pesticides work (their mode of action), it is necessary to understand how the pests' targeted systems normally function. It is also helpful to understand how human systems function in order to see similarities and differences between humans and the pests we try to control. Another reason, it is important to understand the modes of action of the pesticides we use, is to prevent development of pesticide resistance in the target pest(s). Using pesticides with the same modes of action contributes to this problem by killing the susceptible pests and leaving only those with resistance to the entire class of pesticides that work through similar mechanisms. Development of pest resistance can be avoided or delayed by rotating pest control chemicals that work through different modes of action. To be acceptable, pesticides must not have strong toxicity toward non-target organisms, especially humans. Yet, to be efficient, they must be highly toxic toward their intended targets. The mechanism of this type of selectivity is often the targeting of a molecular target site that is found only in the pest or, if in other organisms, is particularly vulnerable in the pest; e.g., an enzyme form that is significantly different from that of other organisms. Natural toxins are a source of new chemical classes of pesticides, as well as environmentally and toxicologically safer molecules than many of the currently used pesticides. Furthermore, they often have molecular target sites that are not exploited by currently marketed pesticides.

**Keywords:** Mode of action, pesticide, pest resistance, natural toxins, enzyme.

## INTRODUCTION

The mode of action of pesticides is extremely fascinating because the subject covers so many fields of biology and chemistry and has many practical implications. All disciplines of biology have developed greatly since 1,1,1-trichloro-di-(4-chlorophenyl)ethane better known as DDT and the other synthetic pesticides were introduced just after the Second World War. At that time, the knowledge of the normal biochemical and physiological processes in organisms was not sufficiently clarified to make it possible for us to understand properly either the mode of action of the pesticides at the target site or their uptake, distribution, and degradation in the ambient environment. The development of resistance of various pests to pesticides should have been possible to predict at that time, even before the use of these pesticides had expanded so much, but how rapidly or to what degree resistance would develop and what biochemical

mechanisms where behind the development had to be a matter of experience and research. We now know how nerve impulses are transmitted, how plants synthesize amino acids, and how fungi invade plant tissue. To understand the toxicology of pesticides, it is first necessary to learn organic chemistry, biochemistry, almost all disciplines of plant and animal physiology at the cellular or organismic level, and ecology, as well as the applied sciences within agriculture.

### Pesticides and Opinion

From 1962 to about 1975, there was hot debate about pesticides. Everyone had an opinion about them. Knowledge of chemistry, agriculture, toxicology, and so on, was not necessary. The debate was a precursor to

the conflicts in the 1970s about environmental issues. In those days words like pollutants, environmental contamination, biocides, pesticides, DDT, mercury, etc., were synonymous. People were putting together all negative properties of synthetic compounds: they were all called biocides, were persistent with a tendency to bioaccumulate, and were all regarded as carcinogens. Toxicology was, and still is, a much less developed science than, for instance, the science of making bridges, or other fields where hazard and risk assessments must play an essential role. Pesticides are toxic substances applied on plants that are going to be food. It is therefore not difficult to understand the great focus from the public on these substances. The legislation and control of their use were not very much developed, and at the same time, the need for pest control agents was very high, but the growing urban population was a little removed from this reality. We must, of course, not forget the very high and unchallenged optimism of the first decade after the Second World War. DDT and the newer persistent pesticides should solve all problems of controlling insect-borne diseases as well as preventing food loss due to insect pests. Rachel Carson's (1962) book *Silent Spring* was an important warning and should be read (with caution) today.

### Why is a toxicant poisonous?

Paracelsus' idea that all substances are poisons is, of course, correct; even water, air, and sugar are poisons in sufficient amounts, but by looking at the chemical structures of typical poisons, and trying to sort out the reactions they tend to be involved in, we can roughly put them into seven categories. By using the molecular theory, the law of mass action, and our knowledge of the nature of the chemical processes in organisms, we can condense biochemical toxicology to three sentences, and about seven types of reactions:

1. Toxic molecules react with biomolecules according to the common laws of chemistry and physics, so that normal processes are disturbed.
2. The symptoms increase in severity with increasing concentration of the toxicant at the site of reaction.
3. This concentration increases with increasing dose.

### Enzyme inhibitors

The toxicant may react with an enzyme or a transport protein and inhibit its normal function. Enzymes may be inhibited by a compound that has a similar, but not identical structure as the true substrate; instead of being processed, it blocks the enzyme. Typical toxicants of this kind are the Carbamates and the organophosphorus insecticides that inhibit the enzyme acetyl cholinesterase. Some extremely efficient herbicides that inhibit enzymes

important for amino acid synthesis in plants, e.g., glyphosate and glufosinate, are other good examples in this category. Enzyme inhibitors may or may not be very selective, and their effects depend on the importance of the enzyme in different organisms. Plants lack a nervous system and acetyl cholinesterase does not play an important role in other processes, whereas essential amino acids are not produced in animals. Glyphosate and other inhibitors of amino acid synthesis are therefore much less toxic in animals than in plants, and the opposite is true for the organophosphorus and carbamate insecticides. Sulfhydryl groups are often found in the active site of enzymes. Substances such as the  $Hg^{++}$  ion have a very strong affinity to sulfur and will therefore inhibit most enzymes with such groups, although the mercury ion does not resemble the substrate. In this case, the selectivity is low.

### Disturbance of chemical signal system

Organisms use chemicals to transmit messages at all levels of organization, and there are a variety of substances that interfere with the normal functioning of these systems. Toxicants, which disturb signal systems, are very often extremely potent, and often more selective than the other categories of poisons. These toxicants may act by imitating the true signal substances, and thus transmit a signal too strongly, too long lasting, or at a wrong time. Such poisons are called agonists. A typical agonist is nicotine, which gives signals similar to acetylcholine in the nervous system, but is not eliminated by acetyl cholinesterase after having given the signal. Other quite different agonists are the herbicide 2,4-D and other aryloxyalkanoic acids that mimic the plant hormone auxin. They are used as herbicides. An antagonist blocks the receptor site for the true signal substance. A typical antagonist is succinylcholin, which blocks the contact between the nerve and the muscle fibers by reacting with the acetylcholine receptor, preventing acetylcholine from transmitting the signal. Some agonists act at intracellular signal systems. One of the strongest man-made toxicants, 2,3,7,8-tetrachlorodibenzodioxin, or dioxin, is a good example. It activates the so called Ach receptor in vertebrates, inducing several enzymes such as CYP<sub>1A1</sub>. Organisms use a complicated chemical system for communication between individuals of the same species. These substances are called pheromones. Good examples are the complicated system of chemicals produced by bark beetles in order to attract other individuals to the same tree so that they can kill them and make them suitable as substrates. Man-made analogues of these pheromones placed in traps are examples of poisons of this category. The kairomons are chemical signals released by individuals of one species in order to attract or deter individuals of another. The plants' scents released to attract pollinators are good examples. Signals

given unintentionally by prey or a parasite host, which attract the praying or parasitizing animal, are important. A good example is  $\text{CO}_2$  released by humans, which attracts mosquitoes. The mosquito repellent blocks the receptors in the scent organ of mosquitoes.

### **Toxicants generating reactive molecules destroy cellular components**

Most redox reactions involve exchange of two electrons. However, quite a few substances can be oxidized or reduced by one-electron transfer, and reactive intermediates can be formed. Oxygen is very often involved in such reactions. The classical example of a free radical-producing poison is the herbicide paraquat, which steals an electron from the electron transport chain in mitochondria or chloroplasts and delivers it to molecular oxygen. The superoxide anion produced may react with hydrogen superoxide in a reaction called the Fenton reaction, producing hydroxyl radicals. This radical is extremely aggressive, attacking the first molecule it meets, no matter what it is. A chain reaction is started and many biomolecules can be destroyed by just one hydroxyl radical. Because one paraquat molecule can produce many superoxide anions, it is not difficult to understand that this substance is toxic. Copper acts in a similar way because the cupric ion ( $\text{Cu}^{++}$ ) can take up one electron to make the cuprous cation ( $\text{Cu}^+$ ) and give this electron to oxygen, producing the superoxide anion ( $\text{O}_2^{\cdot-}$ ). Free radical producers are seldom selective poisons. They work as an avalanche that destroys membranes, nucleic acids, and other cell structures. Fortunately, the organisms have a strong defense system developed during some billion years of aerobic life.

### **Weak organic base or acids degrade pH gradient across membrane**

Substances may be toxic because they dissolve in the mitochondrial membrane of the cell and are able to pick up an  $\text{H}^+$  ion at the more acid outside, before delivering it at the more alkaline inside. The pH difference is very important for the energy production in mitochondria and chloroplasts, and this can be seriously disturbed. Substances like ammonia, phenols, and acetic acid owe their toxicity to this mechanism. Selectivity is obtained through different protective mechanisms. In plants, ammonia is detoxified by glutamine formation, whereas mammals make urea in the ornithine cycle. Acetic acid is metabolized through the citric acid cycle, whereas phenols can be conjugated to sulfate or glucuronic acid. Phenols are usually very toxic to invertebrates, and many plants use phenols as defense substances.

### **Toxicants that dissolve in lipophilic membrane and disturb physical structure**

Lipophilic substances with low reactivity may dissolve in the cell membranes and change their physical characteristics. Alcohols, petrol, aromatics, chlorinated hydrocarbons, and many other substances show this kind of toxicity. Other, quite unrelated organic solvents like toluene give very similar toxic effects. Lipophilic substances may have additional mechanisms for their toxicity. Examples are hexane, which is metabolized to 2,5-hexandion, a nerve poison, and methanol, which is very toxic to primates.

### **Toxicants that disturb electrolytic or osmotic balance or pH**

Sodium chloride ( $\text{NaCl}$ ) and other salts are essential but may upset the ionic balance and osmotic pressure if consumed in too high doses. Babies, small birds, and small mammals are very sensitive. Too much or too little in the water will kill aquatic organisms.

### **Strong electrophiles, alkalis, acids, oxidants or reductants that destroy tissue, DNA or proteins**

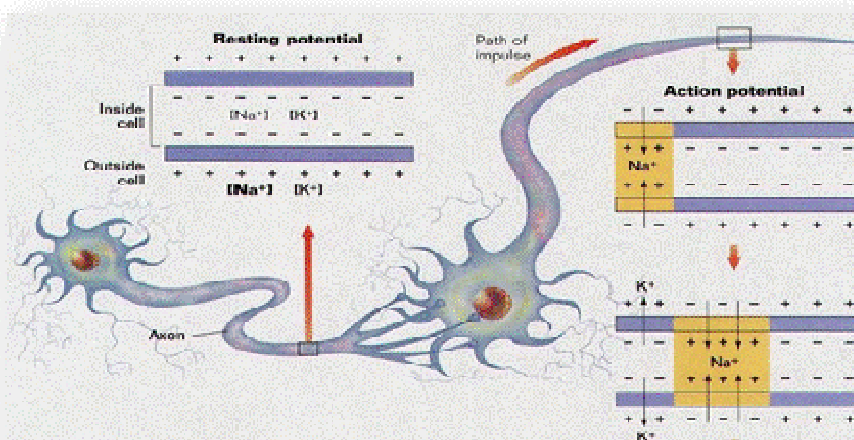
Caustic substances like strong acids, strong alkalis, bromine, chlorine gas, etc., are toxic because they dissolve and destroy tissue. Many accidents happen because of carelessness with such substances, but in ecotoxicology they are perhaps not so important. More interest is focused on electrophilic substances that may react with DNA and induce cancer. Such substances are very often formed by transformation of harmless substances within the body.

### **Why new pesticides?**

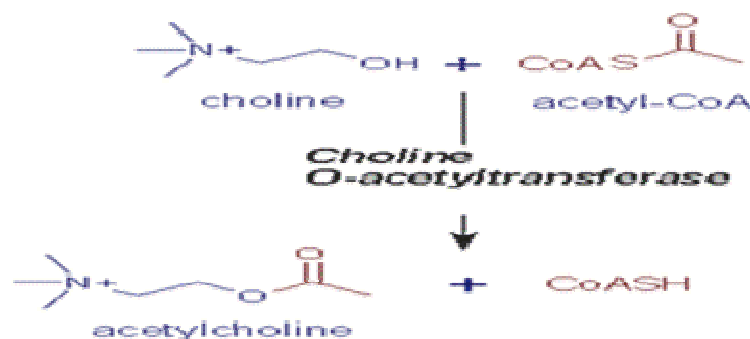
Due to various problems like insect pest resistance in existing pesticides we have to develop new pesticides having novel mode of action and also that is able to give higher productivity and sustainability, safety and phytosanitary measures, ecological and requires very little amount, biodegradable and very less residue problem, target specific and causes no harm to non target organism. Pesticide may be of four types like insecticide, fungicide, herbicide, nematicide

### **Organo chlorine insecticides**

These insecticides act as nerve poisons by altering the permeability of nerve axons to  $\text{Na}^+$  and  $\text{K}^+$  ions (Figure 1).



**Figure1.** Mode of action of organ chlorine insecticides



**Figure 2.** Mode of action of organophosphorus and organocarbamate insecticides

By disrupting the ionic balance in this way, nerve axons fire repetitively, producing tremors, convulsions, and eventually death. These group of insecticides are generally toxic to mammals, chemically stable (and therefore persistent in environment), Lipophilic, readily absorbed by fish, and therefore can enter the food chain and ultimately not safer.

### Organophosphorus and carbamate

The organophosphorus and the Carbamates work by tying up or inhibiting *cholinesterase* (ChE). The enzyme is said to be *phosphorylated* (organophosphorus) or *carbamoylated* (carbamates). When it becomes attached to the phosphorous moiety of the insecticide, binding is irreversible (Figure 2). This inhibition results in the accumulation of acetylcholine (ACh) at the neuron/neuron and neuron/muscle (neuromuscular) junctions or synapses, causing rapid twitching of voluntary muscles and finally paralysis.

### Disadvantages of OP and OC

The major disadvantages of OP and OC are that they have high mammalian toxicity and low LD<sub>50</sub> value, some OP's are of bad odours, carbamates require MIC gas to prepare and cause danger.

### Novel trends of new insecticides

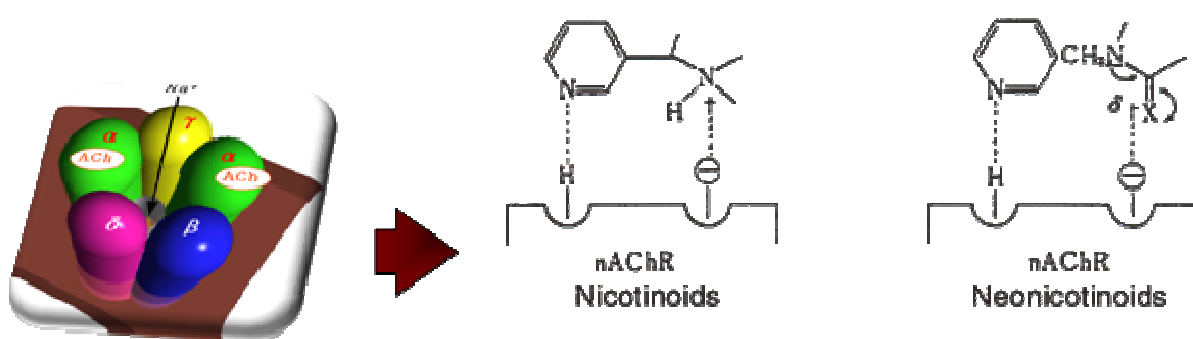
Recently some new pesticides has been introduced in market like neo nicotinoids, pyrroles, Pyrazoles, pyridzinone, phenyl Pyroazole, avermectins, J H Mimics, Spinosins, Chitin Synthesis Inhibitors etc.

### Neonicotinoids

Neonicotinoids displaces radiolabelled alpha bungraotoxin a special legend of the nicotinic acetylcholine receptors from its binding sites. Neonicotinoids acts directly on the nAChR causing

**Table1.** Example of OP and their LD<sub>50</sub> value

Compounds	LD <sub>50</sub> (mg/kg body wt.)
Aldicarb	0.93
Phorate	3.7
Phosphamidon	17.9
Propoxur	50
Methyl parathion	4.5-16
Methomyl	17

**Figure 3.** Mode of action of neonicotinoids

its toxic effect on insects ( Naveen et al. 1996). The presence of an electron donating groups which makes H-bonding to the receptor at 5.9 Å apart from the positively charged centre which interacts with the anionic site of the receptor (Figure 3). The partially positively centre in neonicotinoids must be the centre to interact with the anionic centre.

### Spinosad

Spinosyns are one of the new class of insecticides, represented by spinosad. Spinosad is a fermentation metabolite of the actinomycete *Saccharopolyspora spinosa*, a soil-inhabiting microorganism. It is a mixture of spinosyns A and D (thus its name, spinos AD). Spinosad acts by disrupting binding of acetylcholine in nicotinic acetylcholine receptors at the postsynaptic cell (Salgado VL, 1997). No phytotoxic activity yet reported, quick degradation by microbes, wide safety to mammals, birds and beneficial organisms.

### Fipronil

Fipronil is the only insecticide in Phenylpyrazoles, introduced in 1990. It is a systemic molecule with contact and stomach activity. Fipronil is used for the control of soil and foliar insects. Fipronil blocks the gamma-aminobutyric acid- (GABA) regulated chloride channel in neurons, thus antagonizing the "calming" effects of GABA, similar to the action of the Cyclodienes.

### Pyrroles

Chlorfenapyr is the first and only member of this unique chemical group, as both a contact and stomach insecticide-miticide.

### Pyrazoles

The pyrazoles consist of tebufenpyrad and fenpyroximate. These were designed as non-systemic contact and stomach miticides.

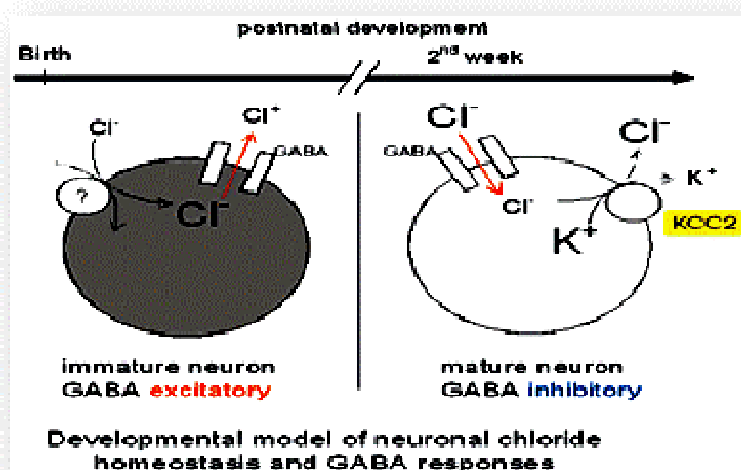


Figure 4. Mode of action of fipronil

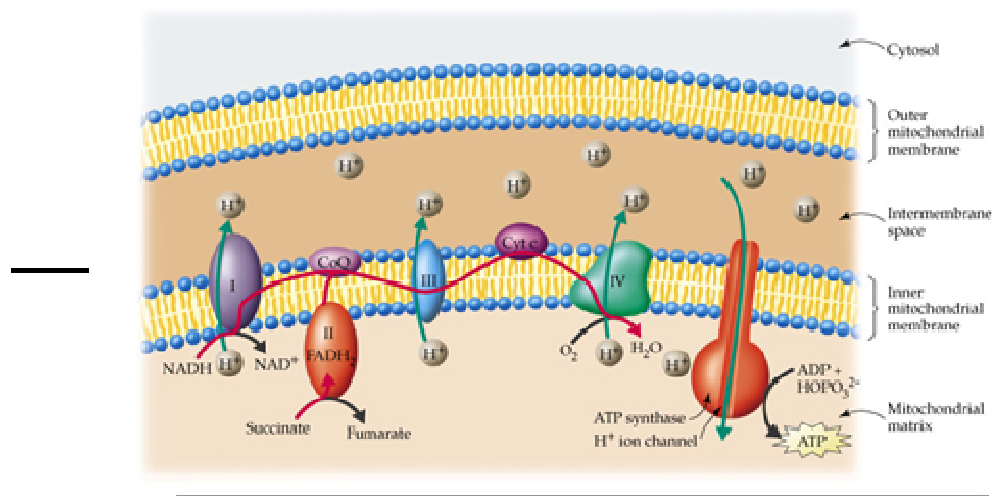
Table 2. Some common herbicides and their family they belong

Sl. No.	Herbicide name	Family
1		
2	Auxin mimic	Phenoxy acetic acid
3	ALS inhibitor	SU's, Imidazolinone
4	EPSP synthase inhibitor	Glyphosate
5	N metabolism inhibitor	Glufosinate
6	ACCase inhibitor	Fop's, Cyclohexanedione
7	Microtubule function inhibitor	Dinitroaniline
8	Seedling root inhibitor	Pyridazine
9	Seedling shoot inhibitor	Chloroacetamide
10	Lipid biosynthesis inhibitor	Thiocarbamate
11	Cell wall synthesis inhibitor	Benzamide
12	PS II inhibitor (mobile)	Triazine
13	PS II inhibitor (nonmobile)	Benzothiadiazole, Nitrile
14	PPO inhibitor	Diphenyl ether
15	PS I inhibitor	Bipyridilium
16	Carotenoid synthesis inhibitor	Isoxazolidinone
	HPPD inhibitor	Triketone

### Pyridazinones

It is a selective contact insecticide and miticide. Pyridaben provides exceptionally long residual control, and rapid knockdown at a broad range of temperature. The mode of action of pyrroles, pyrazoles and pyridazinones are that Inhibit mitochondrial electron

transport at the NADH-CoQ reductase site, leading to the disruption of adenosine triphosphate (ATP) formation, the crucial energy molecule (Figure 5). They disrupt the proton gradient across mitochondrial membranes and thus impair the ability of mitochondria to produce ATP, leading to cell destruction and ultimately death of the organism.



**Figure 5.** Mode of action of pyrazoles and pyridazinones

### Indoxacarb

Indoxacarb blocks the  $\text{Na}^+$  channel of neuron and they have high MSR and persistence in soil.

### JH mimics

For mature larvae to metamorphose into adult, the concentration of JH must decline; the application of JH or JH mimics at this stage kill the insect (Henrick, 1982). JH mimics affect the hormonal balance in insects and suppress embryogenesis, metamorphosis and adult emergence (Itaya et al, 1987; Kochler et al, 1991).

### Avermectins

Insecticidal, acaricidal, and antihelminthic agents that have been isolated from the fermentation products of *Streptomyces avermitilis*, a member of the actinomycete family. *Abamectin* is the common name assigned to the avermectins, a mixture of containing 80% avermectin B<sub>1a</sub> and 20% B<sub>1b</sub>, homologs that have about equal biological activity. It potentiates the ability of GABA and /or glutamate to stimulate an influx of chloride into nerve cells. Anthelmintic properties are due to the potentiation and/or direct opening of Chloride channels. In insects, avermectins binds into multiple sites of  $\text{Cl}^-$  channel resulting loss of cell function and nerve impulse. Insects are paralyzed and stops feeding.

### Chitin synthesis inhibitor

Poisoning symptoms are only seen around the time of moulting. As a result of chitin deficiency, the procuticle disrupts under the pressure of exuvial fluid and the insect becomes unable to moult. Immature stages are incapable of casting their exuvie and die in a typical moulting position accompanied by blackening and loss of moisture (Raynolds, 1987; De Cock et al, 1995).

### Fungicides

Homer in 1000 BC first reported Sulfur with pest controlling properties. They are H-acceptor in metabolic system and hinder hydrogenation & dehydrogenation. Then came bordeaux mixture for the control of *Plasmopara viticola*. They cause Precipitation and denaturation of protein/enzymes & their inactivation.

### Era of organometalics

The mode of action of organo Hg, Sn and As are inhibit the biochemical reactions of electron transport chain in photosynthesis, inhibit oxidative phosphorylation of Mitochondria and strongly inhibit the enzymes oxidizing  $\alpha$ -ketonic acid, respectively. But their main disadvantages are that they have long half life, so residual toxicity problem, undergo decomposition and the metals are exposed, which are very toxic, cause chronic toxicity to Human and animal beings-acute if applied in high doses, some of them has carcinogenic action, organo mercury caused minamata disease in Japan.

### **Anilinopyrimidins**

They inhibit secretion of hydrolyzing enzymes, inhibit fungal methionine biosynthesis.

### **Organophosphorus**

They have multiple mechanism which responsible for fungitoxicity. They inhibit melanin biosynthesis and chitin synthesis. The dehydrogenase inhibitory action effect glycolysis and citric acid cycle.

### **Benzimidazole**

Inhibition of fungal mitosis by binding the fungal tubulin or microtubules. At the site of action, they act by inhibiting biosynthesis of microtubules through polymerization of tubulin.

### **Melanin biosynthesis inhibitor**

They are mainly fused bicyclic structure. Their mode of action is that some intermediates of fungal melanin biosynthesis have fused bicyclic structures and compounds having similar structures, act as competitors. So the fungal activity disrupts within very short period.

### **Dicarboxamide**

Disorder of fungal cell structure when the cells are growing and multiplying. Morphological changes to hyphae and leakage of fungal cell content.

### **Antibiotics**

Among antibiotics major important are blasticidin S - *Streptomyces griseochromogenes* which inhibits incorporation of leucine and phenylalanine, polyoxins - *Streptomyces cacaoi* *Alternaria alternata*, *Rhizoctonia solanii* which inhibit synthesis of cell wall chitin and therefore nontoxic to livestock, fish and plants.

### **Pyrimethalin**

They inhibit secretion of extracellular proteins like fungal hydrolase. No cross resistance occur here. They control strains resistant to benzimidazoles, dicarboxamides, N-phenyl Carbamates. They have very low mammalian toxicity (Oral LD<sub>50</sub> = 5000 mg/Kg).

### **New products compounds from natural products**

Some new products recently released in market are sabadilla (*Schoeocaulon officianale*) seeds source of veracevine alkaloids, semisynthetic derivatives exhibit good fungicidal activity, fungicidal activity against *Ascomycetes Fusarium*, *Glomerellia cingulata*.

### **Herbicides**

Herbicides, also commonly known as weed killers, are pesticides used to kill unwanted plants. Selective herbicides kill specific targets, while leaving the desired crop relatively unharmed. Some of these act by interfering with the growth of the weed and are often synthetic mimics of natural plant hormones. Herbicides used to clear waste ground, industrial sites, railways and railway embankments are not selective and kill all plant material with which they come into contact. Smaller quantities are used in forestry, pasture systems, and management of areas set aside as wildlife habitat. Some plants produce natural herbicides, such as the genus *Juglans* (walnuts), or the tree of heaven; such action of natural herbicides, and other related chemical interactions, is called allelopathy. Herbicides are widely used in agriculture and landscape turf management. In the US, they account for about 70% of all agricultural pesticide use.

### **Als inhibitor**

For amino acid biosynthesis, firstly a pyruvate molecule binds to TPP at the active site and is decarboxylated to yield an enzyme-substrate complex and CO<sub>2</sub>. Second pyruvate then reacts with the complex and the acetoacetate is released. Herbicides bind tightly to this complex to prevent addition of second pyruvate molecule (La Rossa & Schloss, 1984).

### **ACC inhibitor**

Stimulate induction of 1-amino-cyclopropane-1-carboxylic acid (ACC) activity and promote ethylene biosynthesis. In susceptible dicots increased ethylene trigger accumulation of ABA causing growth inhibition, induction of epinasty and senescence.

### **HPPD inhibitor**

In plants, HPPD leads to increased tyrosin levels. HPPD inhibitors lead to the depletion of the plastoquinone



(critical cofactor of phytoene desaturase. Leads to reduction of carotenoids and bleaching symptoms.

## CONCLUSION

From that above discussion it can be conclude that For insecticides, the mode of actions are sought by the way so that it does not harm the mammals or non target organisms, like bees, soil microbes etc. For fungicides also, the novel mode of action are focused on the principle to kill only the fungus without harming the host plant. For herbicides, novel mode of action are to kill the weeds where the host plant gets the resistance towards the herbicide or it detoxifies the molecule. The overall LD<sub>50</sub> values of the compounds are tending to be increased. The pesticides have become more target specific and thus attacking a particular site.

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