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Review Article

USE OF PESTICIDES IN AGRICULTURE AND EMERGENCE OF RESISTANT PESTS

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Crop protection chemicals known as pesticides are playing a significant role to ensure food security. Besides controlling pests in agriculture, they are also used in human and animal health programmes. Development of resistant pests poses a real challenge towards the effectiveness of these toxic pesticides leading to their increased application associated with residual toxicity in food and environment. An estimated 954 pest species which include arthropods, weeds and plant pathogens have developed resistance against various types of pesticides, viz. insecticides, herbicides and fungicides. Resistance development in pest populations is influenced by biological, genetic and operational factors. Various mechanisms involved in resistance development in insects, microbes and weeds are discussed. The extent of insecticide, fungicide and herbicide resistance in various pest species is also highlighted. Effective pest and resistance management practices require understanding the factors influencing its development. The important role of Insecticide Resistance Action Committee (IRAC), Fungicide Resistance Action Committee (FRAC) and Herbicide Resistance Action Committee (HRAC) for resistance management is indicated. Strategies to mitigate the resistance development in conventional pesticides, use of Plant Incorporated Protectants (PIPs) and biopesticides as alternative to chemical pesticides along with some general recommendations are suggested for adoption.

Key words: Fungicide, Herbicide, Insecticide, Pest resistance, Resistance mechanism and management

Introduction

General: The use of agrochemicals like fertilizers and pesticides have become an important component of modern agricultural systems during the last century to bring about a

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significant increase in crop yields (Alexandratos and Bruinsma, 2012). It has been estimated that about 35-45% crop production is lost due to inadequate crop protection measures against pest attack by insects, weeds and diseases. Global use of pesticides such as insecticides, acaricides, fungicides, rodenticides, herbicides and antibiotics for crop protection was approximately 2.72 million metric tons in 2012 (Atwood and Paisley-Jones, 2017). Europe is the major consumer of pesticides (about 45%) followed by USA (25%) and the rest of the world (30%) including India. Among the pesticide classes, consumption of herbicides is maximum (about 47.5%) followed by insecticides (29.5%), fungicides (17.5%) and only 5.5% is shared by other pesticide classes (Agarwal *et al*., 2015). Besides controlling pests in agriculture, pesticides are also used to control human and livestock disease vectors and also to prevent or control organisms affecting other human activities.

In India, the estimated losses in crop production due to pests attack are approximately US $ 43 million. The maximum consumption of pesticides has been reported in cotton followed by paddy, wheat and sugarcane (Subash *et al*., 2017). Unlike the world trend, the Indian crop protection market is dominated by insecticides covering almost 60% of domestic crop protection chemicals (Devi *et al.*, 2017). Fungicides and herbicides are the largest growing segments accounting for 18% and 16%, respectively of total crop protection chemicals market (Devi *et al.*, 2017). The rate of consumption of pesticides in India is amongst the lowest in the world (0.6 kg/ha) compared to 5-7 kg/ha in UK and almost 20-30 times (~ 13 kg/ha) in China (Yadav and Dutta, 2019). Erstwhile Andhra Pradesh (Seemandhra and Telangana), Maharashtra, Uttar Pradesh, Punjab and Haryana are the states that accounted for 70 per cent of total pesticide consumption in India (Devi *et al*., 2017).

Sustainable crop protection is an essential component of present and future food security. But the continuous and extensive use of these pesticides over the last few decades has led to serious pest resistance which also resulted in pest resurgence. Development of pest resistance against a particular pesticide makes the crop protection product ineffective and thereby reducing the pest management options. In addition, the evolution of pesticide resistance leads to increased application of chemicals for crop protection (Foster *et al*., 1998) and causes significant implications in both human health and the environment due to residual toxicity of pesticides (Mondal *et al*., 2018; Biswas *et al*., 2019). Compared to the effectiveness of antibiotics to control human diseases due to evolution of resistant bacteria or other microbial strains (WHO, 2014), the control of crop pests is also threatened by the evolution of resistance against insecticides, fungicides and herbicides (Powles and Yu, 2010; Bass *et al*., 2015; Lucas *et al*., 2015).

Pest resistance: Pest resistance toward pesticides is a serious and an urgent global problem limiting the use of pesticides in pest control. Development of pest resistance has been a major factor influencing pest management strategies for more than half a century. The first incidence of insecticide resistance was reported almost 100 years ago

(Melander, 1914). Thereafter, with the introduction of synthetic organic insecticides likeDDTs (dichlorodiphenyltrichloroethane), cyclodienes, etc. during 1940s, there was also a rapid increase in occurrence of insecticide resistance due to their extensive use. The increasing trend of insecticide resistance with the number of species and pesticidal products was increased over time. The resistance of weeds against herbicides and that of various disease causing organisms like fungi against fungicides have been reported during 1960s and 1970s. However, the cases of insecticide resistance were much more as compared to the cases of herbicide and fungicide resistance. The trend in resistance development in various pest organisms has been well reviewed by Sparks and Nauen (2015).

Resistance reported in mosquitoes in different countries made DDT ineffective in preventing malaria in those regions (Miller, 2004). Consequently, mosquito-borne diseases have become resurgent, largely because of the developed insecticide resistance in mosquito vectors and the drug resistance of pathogens (Nannan, 2015). The horn fly, *Haematobia irritans* L. (Diptera: Muscidae), an important parasites affecting cattle herds around the world exhibited widespread resistance against pyrethroid insecticides while resistance against organophosphate insecticides was not identified in any of the fly populations evaluated (Brito *et al*., 2019). Pest resistance to transgenic crops (which are genetically developed to defend themselves against some pests) have also been reported in Bt (*Bacillus thuringiensis*) maize (Gassmann *et al*., 2011). So far pest resistance to pesticides has been recorded in about 954 pest species worldwide which include arthropods (546 species), weeds (218 species) and plant pathogens (190 species) (Tabashnik *et al*., 2014).

Development of pest resistance

The evolution of resistance to pesticides, drugs and antibiotics by pests and pathogens is due to adaptation to changes in environmental conditions, especially to stress situations. The process of evolution of resistance in various pest organisms against pesticides is a major challenge for applied evolutionary biologists (Hendry *et al*., 2017; Gould *et al*., 2018). The process is rapid and widespread and difficult to counter in most cases once resistance is detectable. Therefore, resistance management practices advocate delaying the evolution of resistant traits before they become widespread. Such approaches can protect the effective period of a pesticide with long-term economic use (Edwards *et al*., 2014).

Resistance development in field populations is influenced by biological, genetic and operational factors. Amongst these, biological (like generation time, offspring number, and dispersal) and genetic (resistance gene, genotype and resistance alleles) factors are seldom influenced by human being. While the operational factors like chemistry and mode of action of the pesticide, method of treatment, time and dosage of application, etc. can be controlled (Sarwar and Salman, 2015).

Mechanism of insect resistance: The insects

can develop resistant through involvement of one or more mechanisms, viz., Metabolic resistance, Altered target-site resistance, Target site insensitivity, Penetration resistance and Behavioral resistance (Karaagac, 2012). Metabolic resistance is the most common mechanism which detoxifies the toxicant quickly by utilizing internal enzyme systems like mono-oxygenases, mixed function oxidases, cytochrome P-450 dependent oxidases, hydrolases (esterases) and glutathione-S-transferase, etc. Altered target-site resistance mediates change in the structure of the site of toxic action in the insect. By target site insensitivity the insecticide penetrates the insect cuticle, but the target site become insensitive. Penetration resistance can protect insects from a wide range of insecticides. It happens when insects such as the housefly, *Musca domestica* can slowly absorb the chemicals into their bodies because their outer cuticle has developed with the barriers against the products. Behavioral resistance occurs when insects are able to evade contact with insecticides through avoidance.

Example of target site insensitivity is the reduced sodium channel sensitivity in nerve cell membranes which was observed in *Musca domestica* and *P. xylostella* to DDT and pyrethroid insecticides. This mode of resistance was termed knockdown resistance (kdr) (Ying *et al*., 2019). The kdr sodium channel gene mutation was detected in horn fly populations, and the super kdr sodium channel gene mutation was found in homozygous resistant kdr individuals (Brito *et al*., 2019).

Although a number of studies focussed to understand the biochemical mechanism responsible for reduced sensitivity, but resistance development is an evolutionary process. Organisms are capable to evolve genetic mechanisms to overcome stress conditions such as pest infestation or pesticide selection. Therefore, greater understanding of the evolutionary mechanisms would be more useful for assessment and management of resistance (Maclean *et al.*, 2010; Neve *et al.*, 2014). The gene amplification process contributes to the evolutionary progression of many organisms. However, the precise mechanism(s) of gene duplication contributing to pesticide resistance is limited (Jugulam and Gill, 2018). Pesticide resistance may be monogenic, conferred by a single gene or it may evolve as a polygenic quantitative trait, especially when pesticide dose is low. Monogenic resistance is often associated with pests that are exposed to high doses of pesticides (Groeters and Tabashnik, 2000). Therefore, evolution of resistance could be inferred from the increase in dose or concentration required to cause a given level of mortality across generations (Haridas and Tenhumberg, 2018).

A comparison of the resistance development processes in the three major pesticide groups, viz., insecticides, herbicides and fungicides revealed the involvement of some common evolutionary forces along with some important differences (Hawkins *et al*., 2019). Fungicide resistance evolved by point mutations in the target-site encoding genes; herbicide resistance evolved through selection of polygenic metabolic resistance from standing variation; and insecticide

resistance evolves through a combination of standing variation and mutations in the target site or major metabolic resistance genes (Hawkins *et al*., 2019). For example, Ran has been reported as the deltamethrin resistance gene. Further studies indicated that Ran is also associated with the resistance to multiple pesticides including parathion, DDT, carbaryl, etc. Therefore, Ran may be considered as a potential molecular target gene for control of pesticide resistance (Bo *et al*., 2018).

Mechanism of disease resistance: Change in genetic makeup of a fungal pathogen is considered as the origin of fungicide resistance. The process of resistance development may be single-step or a discrete process including major gene resistance or it may be a multi-step or continuous process including minor gene resistance, positive and negative cross resistance and multiple resistance (Brent and Hollomon, 2007; Malandrakis *et al*., 2015).

Single step resistance is characterised by a sudden and marked loss of effectiveness of the fungicide as observed in several major groups of fungicides including benzimidazoles, phenylamides, dicarboximides, etc. A gradual recovery of sensitivity has been reported in *Phytophthora infestans,* the potato late blight pathogen, to phenylamide fungicides (Cooke *et al.,* 2006). In such cases, resistance tends to return quickly if unrestricted use of the fungicide is resumed. Multistep resistance is defined as gradual decline in disease control and decrease in sensitivity of pathogen populations as developed by azole and 2-amino-pyrimidine fungicides (Brent and Hollomon, 2007). A somewhat different 'polygenic' process of genetic change is thought to underlie the 'quantitative' or 'multi-step' pattern of resistance. The best known and most studied example is cereal powdery mildews, which are rather hard to study genetically and some of the data are conflicting (Hollomon *et al.,* 1984).

Positive cross resistance is a phenomenon where pathogen populations that develop resistance to one fungicide automatically and simultaneously become resistant to other chemically related fungicides with similar mechanism of fungi-toxicity. For example, pathogen strains that resist carbendazim are almost always highly resistant to other benzimidazole fungicides such as benomyl, thiophanate-methyl and thiabendazole (Chung *et al*., 2009). Negative cross resistance is the condition where a sensitive pathogen becomes resistant to a fungicide, automatically confers a change to sensitivity to other fungicides. This phenomenon is totally different from cross-resistance in its origin and mechanism, and is usually termed 'multiple resistance'. An example is the common occurrence of strains of *Botrytis cinerea* that have become resistant to benzimidazole, dicarboximide and many other fungicides (Chen *et al*., 2016). Resistance to multiple fungicides was observed in the field population of *Venturia inaequalis* (Chapman *et al*., 2011).

Many types of resistance mechanisms are known. These include alteration of the biochemical target; increased production of the target protein; developing an alternative metabolic pathway that bypasses the target site; metabolic breakdown of the fungicide; exclusion or expulsion of the fungicide through ATP-ase dependent transporter

proteins (Brent and Hollomon, 2007; Hawkins and Fraaije, 2018).

The fungi can alter the target site as has been observed in methyl benzimidazole carbamates (MBC), phenylperroles and dicarboximides (Hawkins and Fraaije, 2018). Increased production of the target protein, viz., overexpression of tubulin protein in MBC resistant strain and over-countenance of C14 demethylase during sterol biosynthesis resistant strain were documented to nullify the toxic effect of the fungicide (Cools *et al*., 2012). Tolerance to *Ustilago maydis* to the antibiotic actimycin A was due to developing an alternative metabolic pathway that bypasses the target site. Metabolic breakdown of a fungicide often leads to its detoxification, while exclusion or expulsion of fungicide through ATP-ase dependent transporter proteins leading to fungicide resistance was correlated with levels of fungicide accumulation within fungal cells (Omrane *et al.*, 2015).

Mechanism of weed resistance: Development of herbicide resistance in weeds may be genetic or it may be caused by herbicides from the selection of natural mutation or small pre-existing population of resistant plants (Duke *et al*., 1991). The selection pressure is the application of herbicides, which select for survival of members of the population that contain a mechanism imparting resistance to them. The term resistance should not be confused with tolerance. For example, wild oat (*Phalaris minor*) is described as tolerant to isoproturon because the species as a whole is naturally tolerant to this active ingredient (Powles and Yu, 2010). The herbicide resistance mechanisms may be grouped as: target site resistance, non target site resistance, cross resistance and multiple resistance (Heap and LeBaron, 2001; Sammons and Gaines, 2014; Yu and Powles, 2014).

Target site resistance (TSR) is generally due to a single or several mutations in the gene encoding the herbicide target enzyme which, in turn, decreases the affinity for herbicide binding to that enzyme. Most, but not all cases of resistance to herbicide Acetolactate synthase (ALS) inhibitors, Acetyl-CoA carboxylase (ACCase) inhibitors, triazine, dinitroaniline, etc. are due to modifications of the site of action of the herbicide. In addition, gene overproduction (amplification) is the most recently identified herbicide resistance mechanism. For example, EPSPS gene amplification correlates with glyphosate resistance in *Amaranthus palmeri* and *Kochia scoparia* and causes resistance by increasing the production of the target enzyme, effectively diluting the herbicide in relation to the target site (Gaines *et al.*, 2010; Vila-Aiub *et al.*, 2014; Godar *et al.*, 2015).

Non target site resistance (NTSR) is caused by mechanisms that reduce the amount of herbicidal active compound before it can attack the plant. Reduced absorption (penetration) or altered translocation, increased herbicide sequestration or enhanced herbicide metabolism (detoxification) can cause resistance due to the restriction of herbicide movement where the herbicide does not reach its site of action in sufficient concentration to cause plant mortality. Active vacuolar or cell walls sequestration can keep the herbicide from

the site of action leading to resistance. For example, vacuolar herbicide sequestration correlates with glyphosate resistance in *Conyza canadensis*, *Lolium* sp. etc. (Ge *et al.*, 2010; 2012). The biochemical reactions that detoxify herbicides can be grouped into four major categories: oxidation, reduction, hydrolysis and conjugation.

Cross resistance (CR) means that a single resistance mechanism causes resistance to several herbicides. CR can be conferred by a single gene or by two or more genes influencing a single mechanism. There are two types of CR: target site cross resistance (TS CR) and non target site cross resistance (NTS CR). The most common type of CR is TS CR where an altered target site confers resistance to many or all of the herbicides that inhibit the same enzyme. For example, Trp 574 Leu amino acid substitution within the ALS gene was found in two populations of *Cyperus iria* after exposition to the herbicides, viz., bispyribac sodium, halosulfuron, imazamox and penoxsulam (Riar *et al.*, 2015). On the other hand, NTS CR is the type of herbicide resistance in which a mechanism other than resistant enzyme target sites is involved (e.g. reduced absorption, translocation, or enhanced herbicide detoxification).

Multiple resistance is the phenomenon in which a weed is resistant to two or more herbicides having different mechanisms of action. Resistances of *Lolium* sp. populations to glyphosate and ACCase inhibitors, as well as resistance to glyphosate and ALS inhibitors were confirmed by multiple resistance (Sosnoskie *et al.*, 2011). Multiple resistance can happen if a herbicide is used until a weed population displays resistance and then another herbicide is used repeatedly and the same weed population also becomes resistant to the second herbicide, and so on. Multiple resistance can also occur through the transfer of pollen (cross-pollination) between sexually compatible individuals that are carrying different resistant genes.

Status on pest resistance

Insect resistance scenario: Resistance in insects towards insecticides is a major problem since dates back, not only in agricultural insect pests but also insects of medical and veterinary importance, which invited for introduction of new insect control tools. At present, insecticide resistance is increased and has become a concern in wide range of insects and the problem extended to all major groups of insecticides including the new insecticides (Karaagac, 2012). Moreover, the resistance increases faster in greenhouse situations where insects reproduce rapidly.

The Colorado potato beetle, *Leptinotarsa decemlineata*, has been reported for resistance development against more than 50 insecticides while some populations of diamondback moth, *Plutella xylostella* against practically all available insecticides (Alyokhin *et al*., 2008; Haridas and Tenhumberg, 2018). Resistance to a number of insecticides has also been reported in various kinds of thrips infesting citrus, flower, onion, etc. (Shelton *et al*. 2006; Bielza *et al*., 2007). Later on resistance in tobacco thrips, *Frankliniella fusca* was also reported against neonicotinoid insecticides like imidacloprid and thiamethoxam, respectively making the thrips management strategies critical for

sustainability of cotton production (Huseth *et al*., 2016; Darnell-Crumpton *et al*., 2018).

A number of sap-feeding insects, viz., Green Peach aphid, *Myzus persicae*; Cotton aphid, *Aphis gossypii*; Sweet potato whitefly, *Bemisia tabaci*; and Brown plant hopper, *Nilaparvata lugens* have a history of developing resistance to a number of insecticides. Later on many of these sap-feeding insect pests have also been reported to develop resistance against neonicotinoid insecticides (Sparks *et al*., 2013). Therefore, Sulfoxaflor, belonging to a new class of insecticides sulfoximines, has been introduced with high degree of efficacy against a number of sap-feeding insects, including those resistant to neonicotinoids and other insecticides (Sparks *et al*., 2013).

The status of physiological resistance and behavioural avoidance of mosquito vectors of human diseases to insecticides was reviewed (Chareonviriyaphap *et al*., 2013). Many mosquito populations have been reported in Thailand to develop resistance to all three classes of insecticidal active ingredients, viz., organochlorines, organophosphorus and pyrethroids. But, no pyrethroid resistance case was reported in Anopheles populations during 2000-2011. It was assumed that behavioral avoidance to insecticides might have played a significant role in reducing the selection pressure in developing and spreading of insecticide resistance (Chareonviriyaphap *et al*., 2013). Molecular basis for development of insecticide resistance is important for understanding the emerging problem of resistance development in mosquito vectors of human diseases and its management (Sweileh *et al*., 2016). A literature survey in Cameroon revealed the insecticide resistance was highly prevalent in both *Anopheles gambiae* and *A. funestus*. Bendiocarb, DDT, deltamethrin and permethrin appeared to be the most affected compounds by resistance and some genes including P450 monooxygenase was associated with resistance development process (Antonio-Nkondjio *et al*., 2017).

The arthropod pest species differed significantly in time required to develop resistance. The median duration between the introduction of an insecticide and the first report of resistance was reported to be 66 generations. It was also reported that the highly-resistant arthropods did not evolve resistance faster than their relatives. The resistance development did not differ by the mode of action or year of introduction of the insecticide (Brevik *et al*., 2018).

Disease resistance scenario: At present more than 105 chemical groups comprising non-systemic, systemic and antibiotic fungicides are used in disease control in agriculture (FRAC Code List, 2019). Even in the present day agricultural production system, they form one of the key components of integrated disease management. Systemic fungicides have a low toxicological profile for humans and other non-target organisms, become key components of disease management programmes, targeting to block a single biochemical step but prone to resistance development. Resistance of fungal pathogens to fungicides can be widespread and much worse or may be localized to a particular location or a few locations. The risk of resistance can vary greatly between regions where disease pressure and fungicide use are high and neighbouring areas where there is less disease or where yields are

too low to support widespread fungicide use. For example, in Northern Europe several key cereal pathogens had developed resistance to a number of fungicide groups whereas in Southern Europe the same pathogens remained sensitive (Kuck, 2005).

Penicillium sp. causing storage rot of citrus was the plant pathogen against which resistance of aromatic hydrocarbons was recorded in 1960, after 20 years of its commercial release. There were a few sporadic records of fungicide resistance up to 1970 when only the non- systemic fungicides were used for crop protection. The time required for development of resistance (from the date of commercial release) for those non-systemic fungicides [like organomercurials, dodine and triphenyltins] was 15-40 years, where it was 5-10 years in case of some systemic fungicides and antibiotics [like dicarboximide, sterol biosynthesis inhibitors, phosphorothiolates and kasugamycin] and within 2 years in some other systemic fungicides [like benzimidazoles, 2- amino-pyrimidines, phenylamides, quinone outside inhibitor and melanin bio-synthesis inhibitor] (Brent and Hollomon, 2007).

Most of the earlier fungicides such as copper, sulphur, dithiocarbamates, phthalimides, etc. have retained their full effectiveness in all their uses, despite their extensive and sometimes exclusive use over many years. The older generation fungicides rarely encounter resistance problems. Once they have penetrated the fungal cell, the older fungicides act as general enzyme inhibitors, affecting many target sites (hence they are sometimes called 'multi-site' inhibitors). They act selectively on fungi, rather than on plants and animals, because they penetrate and accumulate much more readily in fungi. Thus, just a single gene mutation can cause the target site to alter and become much less vulnerable to the fungicide (Steffens *et al.*, 1996; Carter *et al.*, 2014).

Biochemical evidence for polygenic resistance to azole fungicides indicated involvement of at least the five resistance mechanisms as discussed above; four mechanisms for quinone outside inhibitor and at least two mechanisms for methyl benzimidazole carbamate, anilinopyrimidine, phenyl pyrrole, dicarboximides, etc. (Hawkins and Fraaije, 2018). Among the different resistance mechanisms employed by fungi, an alteration to the biochemical target site is by far the most common mechanism.

Weed resistance scenario: The incidence of resistance against the herbicide 2, 4-D was observed in 1957, but the first confirmed report of herbicide resistance was recorded against triazine herbicide in common groundsel, *Senecio vulgaris* (Ryan, 1970). Worldwide herbicide resistance has been recorded in 259 weed species (151 dicots and 108 monocots) to 167 different herbicides in 93 crops distributed in 70 countries (Heap, 2019). The highest number of resistant weed biotypes has been observed against the herbicides belonging to ALS inhibitors, viz., imidazolinones, pyrimidinylthiobenzoates, sulfonylureas, triazolopyrimidines. The second most common group with resistant biotypes is the photosystem II inhibitors (primarily triazines). Dinitroaniline and triazine herbicides appear to have a medium level of inherent risk while chloroacetamides and

synthetic auxins have a low inherent risk. A low inherent risk for resistance combined with extensive use can result in a higher risk potential. For example, the herbicide glyphosate was generally considered to have a low inherent risk. However, extensive use of glyphosate in absence of other weed control methods greatly increased the incidence of resistance. Heritable variability in the herbicide glyphosate sensitivity has been detected in some weed populations. Adaptive potential for herbicide resistance was assessed and evidence of directional selection for glyphosate insensitivity was reported for field resistance (Comont *et al*., 2019).

Resistance management strategies

Effective pest and resistance management practices require understanding the factors influencing its development including the genetics of resistance as well as ecological and environmental factors that affect the life-history of the pest. A major goal of insect resistance management (IRM) is to delay the evolution of resistance in an insect population against the pesticides it is exposed to. Therefore, there is a need for clear knowledge on the process of pest resistance for different classes of pesticides like herbicide, insecticide and fungicide, etc. for adoption of appropriate resistance management strategies (Buhler, 2019). Tabashnik *et al*. (2014) has provided various terminologies and their definitions related to pesticide resistance to facilitate understanding and management of resistance.

Resistance action committees: The Insecticide Resistance Action Committee (IRAC), an international association of crop protection companies, was established in 1984. It is focused to ensure long term effectiveness of insecticides, acaricides and traits through adoption of effective resistance management strategies (IRM) for sustainable agriculture and improved public health (IRAC, 2019). The most important function of IRAC is to develop the Mode of Action (MoA) classification of insecticidal products to provide up-to-date information on their modes of action which can serve as the basis for developing appropriate IRM strategies for crop protection and vector control. The IRAC also advocated for MoA labeling with IRM recommendations which have been adopted by many countries and reflected on the container labels of insecticides (Sparks and Nauen, 2015).

Fungicide Resistance Action Committee (FRAC) is a Specialist Technical Group of Crop Life International with the purpose to provide guidelines for management of fungicide resistance to prolong the effectiveness of fungicides (FRAC, 2019). Based on the risk of resistance development, fungicides has been classified by FRAC as high, medium to high, medium, low to medium, low and no risk fungicides. The global Herbicide Resistance Action Committee (HRAC) founded by the agrochemical industry helps by supporting efforts in the fight against herbicide-resistant weeds (HRAC, 2019).

Resistance management in conventional pesticides: Sustainable pest management strategy should include resistance management programme in association with alternative pest management strategies and integrated pest management (IPM) programs. To combat or slow down

pesticide resistance in conventional pesticides, Environmental Protection Agency (EPA) of United States released two Pesticide Registration Notices (PRNs). The first one (PRN 2017-1) is the 'Guidance for Pesticide Registrants on Pesticide Resistance Management Labeling' applies to all conventional agricultural pesticides. The pesticide product labels should provide information for the users to minimize and manage pest resistance. The second one (PRN 2017-2) is the 'Guidance for Herbicide Resistance Management Labeling, Education, Training, and Stewardship' applies to herbicides only (US EPA, 2017).

Regulation of plant incorporated protectants: Application of plant genetic engineering technology in agriculture has developed some insect-resistant crops. Plant-incorporated protectants (PIPs) are pesticidal substances produced by plants possessing necessary genetic constituents to produce the substance. The developed PIP crops such as cotton resistant to lepidopteran insects and maize resistant to lepidopteran as well as coleopteran insects have become popular in global agriculture leading to reduction in pesticide use (Brookes and Barfoot, 2005). Gatehouse (2008) have updated some developments in Bt strategy and selected alternative methods for engineering insect resistance in plants.

The PIP crops have genes for the production of endotoxin derived from the bacterium *Bacillus thuringiensis* (Bt)). Regulatory aspects on PIP crops include resistance-management as well as risk evaluations on human health and environment. EPA's regulation of PIPs includes the strategy for IRM by reducing the selection pressure for Bt PIPs resistance through the use Non-PIP crops to serve as refuges (US EPA, 2017).

Biopesticides and resistance management: Biopesticides derived from biological sources, viz., bacteria, fungi, plants, etc. may be considered for resistance management programs in crop protection. Introduction of new pesticidal constituents including natural product-based pesticides are needed to combat the evolution of resistance to pesticides (Dayan *et al.*, 2009). The use of bio-pesticides in integrated pest management could reduce pesticide use by 66 per cent in cotton and by 45 per cent in cabbage. Thus, bio-pesticides can play an important role in shifting the focus from chemical pesticides to reliable, sustainable and environment friendly options (Subash *et al.*, 2017).

Bio-pesticides are becoming critical components of resistance management programs. Most of the bio-pesticides, especially the microbial products, have multiple modes of action and usually do not target a single site or gene. Therefore, a resistant pest with a single mode of action is unlikely to have cross resistance to a bio-pesticide with multiple modes of action or target sites. Thus, use of bio-pesticides may reduce or eliminate the development of resistance to pesticides (Dimock and Ockey, 2017).

Botanical pesticides are attractive alternatives to synthetic chemical insecticides for pest management derived from plants with insecticidal properties. They have several advantages over the synthetic pesticides due to the fact that they are cheap, easy to prepare, non-poisonous to human

due to short life span and in most cases readily available and have more than one active ingredient which work synergistically making it difficult for pests to develop resistance (Tello *et al*., 2013).

General recommendations: Adoption of IPM strategies will help to prevent the increase in resistant pest types. Some of the general steps are as follows (US EPA, 2017):

- **Apply recommended doses of pesticides:** Recommended doses must be maintained to check the development of resistance and to get desired levels of pest control efficacy. With regard to multi-step resistance, low dose can enhance resistance development by favouring the survival of low-level resistant forms which would be inhibited by the full dose. Selection for resistance to triazole fungicides in barley powdery mildew was slowed down by lowering the fungicide concentration (Porras *et al.,* 1990). Reducing the rate of triadimenol fungicide to its half level enhanced the development of resistance in grape powdery mildew in France.
- **Use of pesticides alternatively or in mixture with different chemistry and modes of action**: Laboratory studies showed that mixing of insecticides delays resistance mechanisms. The use of both mixtures and rotations of fungicides can delay the build-up of resistant variants. Application of mixtures of a phenylamide fungicide with mancozeb or mancozeb plus cymoxanil decreased the build-up of phenylamide resistance in *Phytophthora infestans* compared with phenylamide alone (Staub and Sozzi, 1984; Samoucha and Gisi, 1987).

  Ideally, there should be more than one site of action to decrease the risk of evolution of resistance to a new pesticide. However, the development of new, highly active members of an existing pesticide class, which retain the same primary mechanism of action, may also be of some use in resistance management. The introduction of triazole fungicide prothioconazole has to some extent decreased problems of triazole resistance in cereal powdery mildews (Kuck and Mehl, 2004).
- Crop rotation to avoid the use of same pesticides, and Rotation of insecticides so that not all generations of the species are exposed to the same kind of chemical.
- Apply pesticides only when the pest population exceeds the economic threshold limit.
- Time of pesticide application should match the most vulnerable stage of the pest. Some of the resistance mechanism is poorly expressed in particular life stage of the pest. For example, both pyrethroid resistant and susceptible *H. armigera* neonates killed by fresh deposits of pyrethroids.
- Use of synergists to suppress detoxification mechanisms - applicable when resistance is governed by a single mechanism.

Conclusion

Sustainable crop protection plays a pivotal role for current and future food security to feed the anticipated nine billion world population by 2050 (Godfray *et al*., 2010). However, the effectiveness of the plant

protection chemicals known as pesticides is threatened by the evolution of resistant pests and has become the major and alarming concern in the agrarian country. The evolution of pesticide resistance leads to increased application of chemicals for crop protection (Foster *et al*., 1998) and causes significant implications in both human health and the environment (Mondal *et al*., 2018; Biswas *et al*., 2019). Unfortunately, the specificity of the modern selective pesticides with the objective to reduce non-target effects makes them vulnerable to develop resistance to the intended target pests (Hawkins *et al*., 2019). In order to overcome this scenario, it will be necessary to understand the processes that mediate the development of resistance and there is a need for empirical research on the mechanisms conferring resistance to novel chemical groups to combat the future threat. The importance of integrated pest management need to be revisited along with alternatives to chemical pesticides, especially the use of bio-pesticides should be emphasized in combination with other approaches such as insect or disease resistant crop varieties. Regulatory measures in the use of conventional chemical pesticides may also be adopted for mitigating the pesticide resistance.

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