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Factors which Influence the Stability of Resistance to Insecticides

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In an Annual Review of Entomology article (Casida and Quistad 1998), the authors traced several "Golden Ages" of insecticide research and noted that insects were "conquered for the first time about 50 years ago" with the introduction of synthetic organic nerve poisons. The synthesis by Muller of the first modern insecticide in 1939, DDT, was widely heralded and led to his Nobel Prize in 1948. While DDT was being widely used to combat medical and agricultural pests, toxicologists continued discovering and synthesizing new insecticides in the "Golden Age of Insecticide Discovery". Based on the success of DDT, over the next 50 years chemists followed with eras of "chloronate everything" and "phosphorylate and methylcarbamylate everything" (Casida and Quistad 1998). These were the main insecticide categories until the synthesis of pyrethroids which achieved widespread use in the 1980s.

As Casida and Quistad (1998) note, the last few years have been difficult for the insecticide industry and "the optimism and development incentives of the 1940s to 1970s are a dream of the past" and only few new insecticides have been developed in the past few years. Such a perspective is understandable because of the high costs, perhaps $200 M, which may be incurred before a new insecticide even enters the marketplace. Additionally, we must ask ourselves how long can we rely on a new product before it loses its effectiveness against the pests which attack our food and fibre?

During the last 50 years, the prevailing philosophy of insect pest control has been to use insecticides to keep pest populations at extremely low levels (Metcalf 1989). Under this intense selection pressure, the insect species has two options: to become extinct or to develop the inherited ability to live and reproduce in an environment treated with insecticides (Brattsten 1989). While there are no documented cases of species extinction caused by the use of insecticides, there are plenty of cases of insecticide resistance. By 1960 there were > 50 cases of arthropods which had become resistant to DDT and in the latest survey there are over 500 species of arthropods that have developed strains resistant, under field conditions, to one or more of the five principal classes of insecticides (Georghiou and Lagunes-Tejeda, 1991). Interestingly, the survey did not include insect pathogens as one of the principal classes, but there are now cases of insects which have developed resistance to bacteria (especially strains of *Bacillus thuringiensis*), viruses and fungi (Shelton and Roush 2000).

Considerable research has been devoted to understanding the factors that directly or

indirectly influence the evolution of insecticide resistance (Georghiou and Taylor 1977 a, b, Taylor and Georghiou 1982, Georghiou 1983, Georghiou and Taylor 1986, Roush and Tabashnik 1990). This knowledge is of paramount importance for devising tactics to avoid, delay or manage resistance. On the other hand, however, when resistance to a particular insecticide occurs, it is important to consider whether it can be utilized sometime in the future. The factors that influence the rate at which insecticide resistance can be reversed in the absence of selection pressure are poorly understood despite their tremendous importance in managing resistance.

The objectives of this paper are to identify, classify and discuss the factors that directly or indirectly influence the stability or reversion of insecticide resistance in the absence of selection pressure. It is most appropriate to do this now in an era in which some new classes of insecticides (e.g. spinosyns) are being introduced into the market place. Already there are reports of strains of two species, *Spodoptera exigua* and *Plutella xylostella*, which have developed resistance to spinosad in the field (Moulton et al. 2000, Mau and Gusukuma-Minuto 2001). While certainly more cases will follow, does this mean this insecticide can no longer be used on these resistant strains? To answer these questions we present the following description of the factors that influence the stability or reversion of insecticide resistance. We choose not to emphasize information on Bt transgenic plants, although some of the same principles will apply, but to focus on the use of foliar and soil insecticides since we believe they will continue to play an important role in pest management for the foreseeable future.

Factors That Influence the Stability or Reversion of Insecticide Resistance

The available literature on insecticide resistance was reviewed to identify and classify those factors that affect the stability or reversion of resistance in the absence of selection pressure (Table 1).

Genetic factors

Before an insect pest population is targeted by an insecticide, the genes for resistance are at a very low frequency, ranging from 10^{-13} (Whitten and McKenzie 1982) to 10^{-2} (Georghiou and Taylor 1977a, b) and resistant individuals usually have fitness disadvantages relative to their

susceptible counterparts (Roush and Croft 1986). Otherwise insecticide resistance would be a common phenomenon regardless of the use of insecticides.

In general, the relative fitness of homozygous resistant individuals ranges from 0.5 to 1.0, and the relative fitness of heterozygous individuals is between 0.75 and 1.0 (Roush and Croft 1986). However further studies are needed to determine what these laboratory-based values mean in terms of the stability of insecticide resistance under field conditions. The relative fitness of cyhalothrin-resistant and the F_1 heterozygous individuals of *Helicoverpa armigera* in a field cage trial was 0.46 and 1.46, respectively, compared with a susceptible strain (Rui et al. 1999).

Several cases of stability or reversion of resistance in the absence of selection pressure have been documented (Keiding 1967, Georghiou 1972, Rodríguez 1994, Kristensen et al. 2000). Once the selecting agent is removed, the reversion of resistance may proceed at various rates (Lagunes 1980, Georghiou et al. 1982, Rodríguez 1994). For example, the intense use of DDT to control Danish house flies led to a highly stable resistance. However, once the selection pressure of DDT was removed, the resistant genes persisted at detectable frequencies in the population for more than 20 years. However, in another case with the same population, resistance to chlordane and dieldrin declined to almost undetectable levels 7 to 13 years after removing the selection pressure by these organochlorine insecticides (Keiding 1977). In a laboratory strain of *Culex quinquefasciatus* Say (Diptera: Culicidae) resistant to temephos, propoxur and permethrin, the stability or reversion of insecticide resistance varied by the individual insecticide. Resistance to temephos (due to esterases A2 and B2) was fairly unstable, resistance to temephos (due to esterases B1) became highly unstable, while resistance to permethrin (due to mixed function oxidases and sodium channel insensitivity) and propoxur (due to oxidases) became fairly stable (Ranasinghe 1976, Lagunes 1980, Rodríguez 1994). More recently, selection and reversion of azinphos-resistance in the housefly in Denmark has indicated that, despite the number of mechanisms involved in resistance, most of the resistance was highly labile and disappeared within 1-2 years (Kristensen et al. 2000). These findings indicate that periodic removal of azinphos may allow the product to become once again effective.

The diamondback moth, *P. xylostella*, is perhaps the agricultural insect pest which has shown the most propensity to develop resistance to insecticides, beginning with its development of resistance to DDT in 1953 (Talekar and Shelton 1993). Populations of this insect have now

developed resistance to all classes of insecticides, including growth regulators and insecticidal proteins from *B. thuringiensis*. Sun (1992) provides an overview of what is known about the stability of resistance in *P. xylostella* and notes that it tends to be stable for carbamates, "unstable in some cases" for organophosphates, and stable for pyrethroids. While these are general guidelines derived from a diversity of studies, they may provide some general guidelines for a resistance management program. Reversal of resistance to *B. thuringiensis* in *P. xylostella* occurred when selection pressure was removed for many generations (Tabashnik et al. 1994). Reversal of resistance was associated with restoration of binding of *B. thuringiensis* toxin to the brush-border membrane vesicles and with increased biotic fitness.

In an insect population of various resistant genotypes, the percentage of mortality caused by a given insecticide depends to a large extent on the dose, exposure time, frequency of resistant individuals and degree of expression of the resistant genes (Crow 1957, Crow and Kimura 1970, Rodríguez 1994). During the early stages of resistance, a population will be composed mainly of homozygous susceptible individuals. As insecticide selection proceeds, heterozygous individuals will arise and then increase in frequency. As random mating within the population continues, homozygous resistant individuals emerge. If selection pressure continues and the population is closed, the entire population may become homozygous resistant. If this occurs, the existing level of resistance will not decrease even if this resistance is associated with a fitness disadvantage as the role of backward mutation will be of negligible importance (Falconer 1989).

A key factor in the rate of decline in resistance is the initial frequency of resistant individuals within the population, rather than the percentage reduction of decline in each generation. For example, if the frequency of resistant individuals in a population is 0.90 and half of this frequency is eliminated in the next generation, insecticide resistance will decline significantly and be noticed under field conditions. On the other hand, if the frequency of resistant individuals is 0.005, a similar percent reduction in one generation will not lead to a significant decline in resistance and probably not be noticed under field conditions. Thus, the rate of resistance decline depends, among other factors, on the initial frequency of resistant individuals.

Once the population becomes resistant, the frequency of resistance genes never declines to the mutation frequency (Wood and Bishop 1981). Metcalf (1989) states that "the persistence of

the changed background of residual inheritance in the genome causes the strain to regain its resistance as soon as the insecticide is reapplied", indicating that the frequency of genes for resistance can remain well above the mutation rate for a long time.

Organophosphorous resistance due to gene amplification has been demonstrated in *Cx. quinquefasciatus* (Mouchès et al. 1986) and in *Myzus persicae* (Sulzer) (Field et al. 1988). This mechanism of resistance is characterized by the existence of many identical copies of the gene, each one encoding the same amount of enzyme that is associated with resistance. According to Devonshire and Field (1991) insecticide resistance due to gene amplification is usually unstable in the absence of selection pressure due to the lower relative fitness of resistant individuals.

Resistance to temephos in the Tem-R and Selax strains of *Cx. quinquefasciatus* is due to the overproduction of esterases B1 and A2B2, respectively (Mouchès et al. 1986, Raymond et al. 1987, Raymond et al. 1989, Wirth et al. 1990). In both strains, the B esterases are amplified (Mouchès et al. 1986, Raymond et al. 1989) and resistance is unstable (Rodríguez 1994).

Organophosphorous resistance in *M. persicae* is usually unstable, but in some strains it shows a remarkable stability (Beranek 1974, Sawicki et al. 1980) However, gene amplification has always been associated with unstable insecticide resistance.

According to Fisher (1930) "the rate of increase [or decrease] in fitness of any species is equal to the genetic variance for fitness". Variance for fitness can be increased as a result of insecticidal selection pressure if the substitution of a susceptible allele by a resistant one entails pleiotropic effects, thus resulting in the appearance of resistant individuals displaying, on average, lower relative fitness (Uyenoyama 1986). However, it is reasonable to assume that not all resistant individuals show the same relative fitness among them or relative to their susceptible counterparts. Those resistant individuals that possess a relative fitness similar to susceptible individuals will not be eliminated by natural selection and, since this is the most favored genotype combination during insecticidal selection pressure, the evolution of resistance and fitness could take place even before the selecting agent is removed.

Devonshire and Field (1991) observed that in some strains of *M. persicae*, resistance to organophosphate insecticides was fairly stable. However some individuals lost their phenotypic resistance in a single generation in the absence of selection pressure. Since this population developed resistance when subjected to selection pressure, it is thought that the genes for

resistance remained in the population but for some reason they were not expressed (Ffrench-Constant et al 1988). There is not sufficient information available concerning the fitness advantages of "turning off" the gene for resistance; however, it is reasonable to assume that the ability to suppress the phenotypic expression of the gene for resistance and hence avoid wasteful overproduction of enzymes associated with resistance could facilitate the process of ecological adaptation in the absence of selection pressure, relative to those individuals unable to control the expression of resistance.

Fitness disadvantages may strongly be associated with the type of mechanism of resistance (Georghiou, et al. 1982, Roush and McKenzie 1987, Roush and Daly 1990). Resistance due to overproduced esterases is usually unstable (Lagunes 1980, Rowland 1988, Roush and Daly 1990, Rodríguez 1994). In contrast, resistance tends to be stable if it is due to mixed function oxidases (MFO) (Vázquez-García 1983, Rodríguez 1994), altered acetylcholinesterase (Smissaert 1964), malathion specific carboxylesterase (Hemingway et al. 1984), and kdr-like mechanisms (Bogglid and Keiding 1958, Lagunes 1980).

In *M. persicae*, an esterase that confers resistance to OP-compounds amounts to as much as 3% of the total body protein (Devonshire and Moores 1982). Temephos resistance in the Tem-R strain of *Cx. quinquefasciatus* that is associated with the amplified B1 esterase represents from 6 to 12% of the total soluble protein of the resistant individuals (Fournier et al. 1987). Undoubtedly this overproduction of esterase-protein provides considerable protection against organophosphate insecticides (up to 800 fold in *Cx. quinquefasciatus* (Rodríguez 1994). However, in the absence of selection pressure, such overproduction of esterase may be wasteful. The natural role of esterases associated with insecticide resistance is unknown and if they do not serve a useful function in the absence of selection pressure they can be viewed as a fitness disadvantage. Mechanisms of resistance that interfere with the normal physiology of the resistant organism or show little or no natural role in the metabolism tend to be unstable in the absence of selection pressure. In contrast, mechanisms that play an important natural role, such as MFO, tend to be stable, and the metabolism of insecticides is considered as a secondary function (Georghiou 1972, Wilkinson 1983). However, Plapp (1976) indicates that MFO-resistant strains usually produce a type of microsomal oxidase that differs from the wild type in substrate specificity and other biochemical properties.

Some insect populations can evolve the ability to survive insecticide treatment and also regain their original fitness. These two processes can proceed at different rates (McEnroe and Naegele 1968). Abedi and Brown (1960) studied the development and reversion of resistance to DDT in *Aedes aegypti*. During the early stages of selection, the population suffered from fitness depression, thus DDT resistance was unstable. After three cycles of alternating DDT selection and relaxation of selection pressure, resistant individuals displayed a relative fitness similar to their susceptible counterparts.

McEnroe and Naegele (1968) selected a population of *Tetranychus urticae* with oxydemeton methyl at 0.05% during 30 generations. Resistance was unstable during the 13 generations of rearing *T. urticae* free of selection pressure. Then, they selected this population with the same acaricide and dose during 150 generations. After that, they removed the selection pressure and observed that resistance was stable, and that there were no significant differences in fitness between the selected population and control reference.

According to Mortlock (1982) if a population repeatedly encounters periods of selection and relaxation, it could develop the ability to live and reproduce successfully in both regimes. However, McKenzie et al. (1982) showed that coevolution between resistance and fitness does not necessarily require these alternate cycles of selection and relaxation. They observed that a field population of *Lucilia cuprina* was able to develop resistance without suffering from fitness disadvantages in only ten years of continuous selection by diazinon. This study warns against the risk of using the same insecticide for too long. However, further studies with *Lucilia cuprina* by McKenzie (1994) have indicated >70% mortality of the overwintering stage and that phenotypes resistant to diazinon overwinter less successfully in the absence of a fitness modifier. However, in the presence of the modifier, there is no such difference. Thus, the influence of the modifier has significant consequences on the maintenance of the resistant gene in natural populations and will affect the potential for reversion to susceptibility. How widespread such a modifier is in other populations is unknown, but its consequences could be profound.

One of the greatest mistakes in dealing with insecticide resistance is to consider the genes for resistance as separate and independent entities, rather than a part of a well assembled complex of genes that respond together, as a unit, to any environmental stressing agent (Uyenoyama 1986). Consideration of resistance genes as separate and independent entities denies

the potential coevolution between fitness and insecticide resistance.

A theoretical model that explains this coevolutive process was developed by Lerner (1958). Lerner reasoned that if the genes for a given trait are at low frequency, the population may not respond immediately to selection. Once that gene increases to a certain level, the response to selection could be of significant magnitude. During this stage, the respective trait is usually unstable because of the decrease in fitness among the selected individuals. If selection pressures continues, the increasing response will gradually level off as the population approaches homozygosity. The population fitness could decline to depletion of the existing variance for fitness. After that, the relative fitness remains constant until new variants with higher fitness show up in the population and the evolution of fitness begins. If some selected individuals retain a fitness similar to their non-selected counterparts, the coevolution between fitness and the selected trait can take place even before the selecting agent is removed. Perhaps not all insect populations have the ability to undergo coevolution between insecticide resistance and fitness. However, we do not know how much time should be allowed for the population to interact with a given insecticide before stating that it is unable to regain its original fitness.

Fournier et al. (1988) determined the relative fitness of a laboratory strain of *Phytoseiulus persimilis* highly resistant to methidathion. There were no significant differences between the susceptible reference strain and the methidathion-resistant strain relative to life history, vigor and resistance to starvation and drought. They concluded that methidathion resistance does not affect the fitness of this population, as was previously demonstrated by its successful release and establishment in commercial glasshouses (Fournier et al. 1987).

The available literature reveals that, in the absence of immigration, the stability of resistance depends to a large extent on the magnitude of the pleiotropic effects caused by the expression of the gene(s) for resistance. If the selected population suffers severe fitness disadvantages, it could take a longer time to regain its original fitness. If the gene for resistance is successfully integrated into the genome, resistance will be stable in the absence of selection pressure. More research is needed to clarify the factors that favor, or disfavor, this coevolutive process.

Ecological factors

The duration of the generation defines the required time for resistance to decline to a

certain level. If we compare two populations displaying significant differences in generation time, but similar rates of resistance decline on a per generation basis, the population with a shorter generation time will experience a faster decline in resistance during the same period relative to a population with a longer generation time.

If a target population is reared or lives under optimal conditions, a relaxed natural selection will allow individuals with poor fitness to survive, reproduce, and eventually increase in number due to genetic drift. Under this circumstance, the individuals possessing genes for resistance would probably display low natural survival and reproduction (Crow 1957). Insecticide resistance will thus be highly unstable in the absence of selection pressure, unless the population is closed and homozygous.

The size and geographic distribution of the selected population determine to a considerable extent the effectiveness of selection either in favor or against the genes for resistance (Crow 1957, Wood and Bishop 1981). If the population is small enough, and contains the genes for resistance, it may rapidly become homozygous resistant; thus a decline in the existing resistance will not occur with the removal of the selecting agent, unless the population is exposed to susceptible individuals. On the other hand, if the population is large enough, the probability of coevolution between resistance and fitness is greater. Species with a wide geographic distribution and significant gene flow are more likely to revert toward susceptibility if some areas remain untreated (Georghiou 1972).

The immigration of susceptible individuals is the major factor responsible of resistance reversion in field populations (Georghiou 1972). A fundamental key to resistance management is the use of a refuge to conserve susceptible alleles within the population. Such a refuge consists of plants which are left untreated, either in time or space, by the insecticide on which the resistance management program is focused. Such refuges are the basis for the resistance management program for Bt plants required by the Environmental Protection Agency in the US, and perhaps should be mandated for other insecticides as well, despite the problems outlines by Thompson and Head (2001). If a refuge is placed within an area, it is critical that the insects on the refuge and non-refuge plants can freely mate as adults. In field studies with *P. xylostella* in which a population with a known resistance allele frequency was introduced onto a planting, the population became more susceptible due to immigration of susceptible adults (Shelton et al.

1999).

The change in the frequency of genes for resistance due to immigration of susceptible individuals can be described by the following equation (Falconer 1989):

$$\Delta q = m(q_m - q_0)$$

Where:

Δq = change in frequency of the gene for resistance

m = relative proportion of new immigrants

q_m = frequency of the resistant gene among the immigrants

q_0 = frequency of the resistant gene among native individuals

The fate of the genes for resistance also depends on the relative fitness of resistance individuals as well as on the frequency of invasion of genes for susceptibility. Generally, there is not a unidirectional flow of genes. It is reasonable to assume that during the early stages of resistance, immigrants represent a valuable source of genes for susceptibility. As resistance evolves and spreads over the range of distribution of the targeted population, refugia could be contaminated with genes for resistance. Sooner or later these genes will go back to the treated population, thus changing their role in the dynamics of resistance.

Besides refuges, another way to ensure a steady supply of susceptible individuals consists of releasing laboratory-reared individuals. This practice, unfortunately, may pose several important problems. For instance, not all species of insects are suitable for rearing in adequate numbers (Benson 1971), the economic cost of rearing is usually high, and laboratory-reared individuals usually suffer fitness disadvantages (Wallace 1985), among other problems.

Baker (1984) studied the feasibility of releasing laboratory-reared male mosquitoes bearing a DDT-resistant gene translocated onto the Y chromosome. These males were expected to survive in environments contaminated by DDT and mate with native females but be unable to transfer the DDT-resistant gene to them. Therefore, it was expected that the released males would survive in the environment contaminated by DDT long enough to accelerate the rate of decline in resistance. Unfortunately, these males showed a poor field performance to compete with native males.

Operational factors

In general, susceptible individuals are at a selective disadvantage in the presence of an insecticide; however, the studies of Roush and Hoy (1981) and Daly and Fitt (1990) suggest that selection against resistant individuals is minor. However, the situation may be more complicated. The number of generations over which field populations are subjected to selection pressure, "age of resistance", influences the stability of resistance by allowing the needed time of selection of modifier genes to reduce the negative impact of resistance on fitness (Keiding 1967, Georghiou 1972, Wood and Bishop 1981). This hypothesis is supported by a number of studies. For example, Abedi and Brown (1960) noted that resistance to DDT in *Aedes aegypti* (L) was highly unstable during the early stages of selection but later on it was stable. There was a positive correlation between the number of selected generations and the degree of stability of insecticide resistance.

A population of *Lucilia cuprina* from Australia was documented as resistant to diazinon in 1967 (Shanahan 1967). Two years later, Arnold and Whitten (unpublished data, cited in McKenzie et al. 1982) showed that diazinon-resistant individuals of this population displayed lower relative fitness relative to diazinon-susceptible ones. Nine years later, McKenzie et al. (1982) showed that diazinon-resistant individuals of this population had, on average, a fitness similar to a susceptible reference strain. In all cases the field population was compared to the same susceptible strain. These studies indicate that the "age of resistance" may provide the necessary conditions to this coevolutive process.

Summary

The discovery, development and registration of new insecticides are costly and may take up to a decade from discovery to widespread use in the field. History has shown us that for some new products, insects may develop resistance in only a few years. If companies cannot recoup their expenses because of such resistance, they will be less likely to develop newer insecticides and the list of available materials that growers can use will decline. This is not only unhealthy for the economics of the agricultural industry but will result in problems in the field since different insecticides with different modes of action are needed if resistance management strategies are to be followed.

Research for insecticide resistance management has focused on documentation of resistance in the field and on the factors which influence the development of resistance. Since it is likely that insects will continue to develop resistance faster than new insecticides can be developed, it is important to implement preventive rather than curative measures to manage resistance. If and when we fail to do this, however, we must learn if and how we can recoup the usefulness of an insecticide. More research is needed to determine in a more precise way how we can manipulate the factors discussed above to accelerate the decline of resistance, and hence restore the performance of formerly effective insecticides.

The list of factors that influence the rate of stability and reversion of resistance discussed herein may not be complete, but is intended to challenge the reader to improve it by arguing in favor or against it.

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Table 1. Factors that directly or indirectly affect the stability or reversion of insecticide resistance in the absence of selection pressure.

GENETIC

1. Frequency of alleles for resistance
2. Gene amplification
3. Inheritable variance for fitness
4. Ability to "turn off" the genes for resistance
5. Type of mechanism of resistance
    - 5.1. Energetic cost of being resistant
    - 5.2. Natural role of the selected mechanism of resistance
    - 5.3. Interference of the evolved mechanism of resistance with the physiology of the insect
6. Coevolution between resistance and fitness
8. Pleiotropic effects of the gene for resistance

ECOLOGICAL

9. Generation time
10. Degree of natural competition before selection
11. Size and geographic distribution of the selected population
12. Immigration
    - 12.1. Relative proportion of susceptible immigrants
    - 12.2. Relative fitness of susceptible immigrants
    - 12.3. Frequency of immigration

OPERATIONAL FACTORS

13. "Age of resistance"