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Strategy for Insecticide Resistance Management Approach to IPM

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ABSTRACT Insecticide resistance is a serious threat to IPM, resulting in various adverse effects not to mention the loss of yield in agriculture. One approach to counter the problem is the disruption of resistance mechanisms. This can be achieved by (1) compounds which show a negative correlation with resistance at the site of action, (2) specific metabolic inhibitors which serve as synergists, or (3) a certain combination of two insecticides producing a joint action. This approach, however, requires certain precautions for the side effects may cause an increase in toxicity to mammals. Owing to the recent advances in theoretical studies on resistance management employing computer simulation and mathematical models, a few principles to reduce the risk of development of resistance have been clarified. They are helpful in designing operational strategies with regard to, for instance, insecticide doses to be applied, mode of application, and choice and nature of the insecticide(s) to be used. For restoration of insecticide susceptibility of a resistant population, reintroduction of susceptible individuals to the resistant population is feasible when certain conditions are met. Natural enemies which developed resistance to insecticides can be an important component of IPM as has been shown in the pest management in apple orchards. After all, the implementation of a successful resistance management program depends upon cooperation between different sigments of the agricutural community. Although resistance is a preadaptive phenomenon, in some cases spontaneous loss of resistance does occur without contamination by susceptible individuals. The instability of resistance in these insects implies the possible existance of a switch machanism controlling the expression of resistance gene(s). Elucidation of such a mechanism may eventually provide us with a new technical approach with which we can combat the problem of insecticide resistance.

KEY WORDS Insecticide resistance, resistance management, disruption of resistance mechanism, synergism, joint action of insecticides, instability of resistance, operational strategy, current status of resistance, selectivity with synergists

INTRODUCTION

Insecticide resistance is a serious threat for insect pest management programs in which chemical control has been playing a central role and is expected to remain indispensible despite an extensive effort in finding alternative methods (Ruscoe 1987). The consequence of resistance is the loss of crop

both in quantity and quality due to a control failure. Another consequence is the increased applications of insecticides in dose and in frequency, resulting in higher costs of production, possible health hazards to the applicators, adverse effects on the environment, as well as residue problems in the subsequent food. A large number of insect species developing resistance were first observed in the early 1950s, the number reaching 504 by 1988(Georghiou 1986, 1990). Resistant species comprise several insect orders of agricultural and medical importance, and chemicals to which they have developed resistance include all the major insecticide groups. Misleading the expectations of many researchers in this field, insects have shown an astonishing ability to adapt to a toxic environment, developing resistance to such unconventional insecticides as fumigants, insect growth regulators including juvenile hormone analogs, and even microbial insecticides(Rie et al. 1990). Judging from history, it appears that no insect and no insecticide can be exempted from the resistance problem.

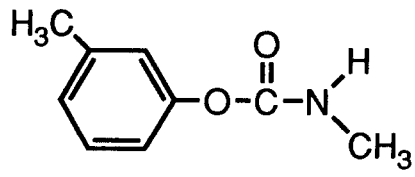
Resistance is defined as a "preadaptive phenomenon" in which an insecticide serves as a selecting agent for resistant individuals present at a small frequency in a natural population of insect species showing polymorphism (Oppenoorth & Welling 1976, Oppenoorth 1985). Resistance in recent years is charaterized by two factors, *i.e.* an extremely high degree of resistance and cross-resistance to a diverse group of insecticides. The former symptom makes it practically impossible to control the pest population by the chemical even when a many-fold increased concentration is applied. The latter symptom often leaves only a few or no effective insecticides available making the control of the pest population very difficult. For example, these have been the cases encountered with mites on fruit trees and the diamondback moth on cruceferous vegetables in Japan.

In most cases, both of these symptoms are the result of the accumulation of multiple mechanisms of resistance, or more precisely mutiple genes responsible for the mechanisms, in the population involved. The accumulation occurs as a result of the combination of intensive and extensive selections and interbreeding of resistant populations each carrying different genetic background. Thus, a 1,400-fold resistance to diazinon in the Yachiyo strain of the housefly originally collected from a landfill near Tokyo was found to be due to a multiplied effect of several factors(Oi et al. 1990). The factors involved were reduced cuticular penetration, reduced activation of diazinon to diazoxon, increased detoxication by three enzyme systems, *i.e.* the cytochrome P450-dependent monooxygenases, glutathione transferases and phosphorotriester hydrolase, and reduced sensitivity at the site of action, *i.e.* acetylcholinesterase(AChE). These factors, which bring about only a certain degree of diazinon resistance when present alone, produced a multiplied effect when combined to the extent that makes the control of the flies by diazinon impossible.

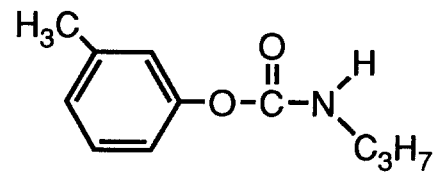
It is a challenge for us to develop tactics and strategies which enable us to manage the problem of resistance so that we can continue to control insect pests.

DISRUPTION OF RESISTANCE MECHANISM

One of the tactics to combat a pest population which has already developed resistance is to disrupt the mechanisms responsible for resistance. An alteration at the site of action of an insecticide often results in cross-resistance to various other insecticides acting on the same site of action. A factor

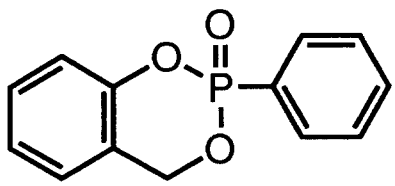


Metolcarb

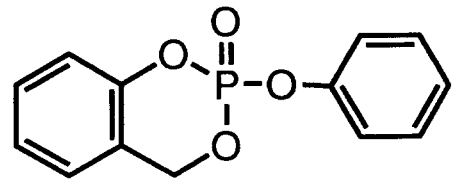


N-propyl analog of Metolcarb

Inset 1. metolcarb and N-propyl analog of metolcarb.

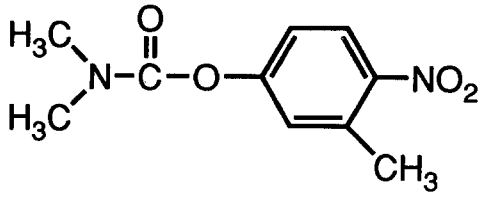


K-1

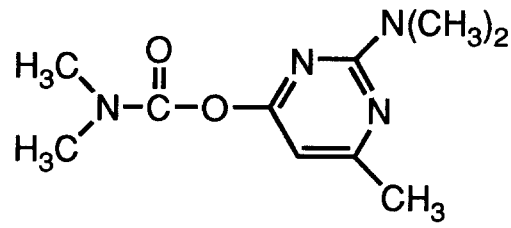


K-2

Inset 2. K-1 and K-2



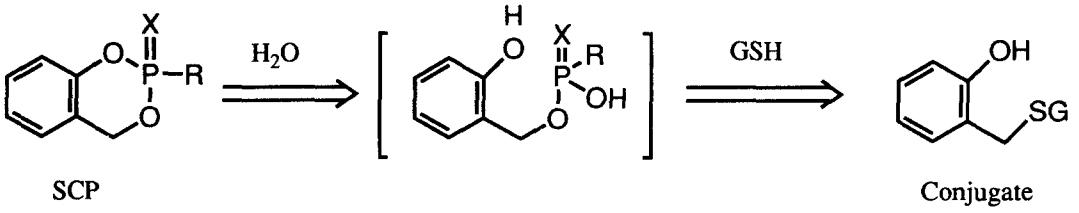
SK-2



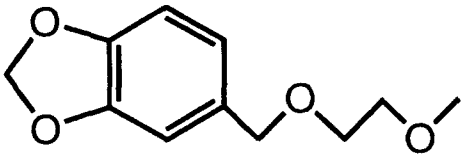
SK-102

Inset 3. SK-1 and SK-102.

called "KDR"(termed for the "knock down resistance" symptom) causes cross-resistance not only to various pyrethroids but also to DDT, both of which are known to act on the sodium channel of axonal membrane of the nervous system(Ahn et al. 1987, Farnham et al. 1987). Similarly, an altered AChE which exhibits reduced sensitivity to inhibition leads to cross-resistance to many organophosphate and carbamate insecticides, both of which act on the same target. Therefore, cross-resistance brought about by a change at the site of action is a serious problem which makes many insecticides ineffective.



Inset 4. SCP, intermediate and conjugate.



NO. 1

Inset 5. No. 1.

It is logical, however, to assume that an alteration of properties toward one compound at the site of action may also affects its affinity to other compounds in another way.

That proved to be the case with a carbamate resistant strain of the green rice leafhopper, *Nephotettix cincticeps*, which had an altered AChE insensitive to metolcarb(*m*-tolyl methlycarbamate) (Hama & Iwata 1971). The resistant strain had negatively correlated cross-resistance to the N-propyl analog of metolcarb(Takahashi et al. 1977, Yamamoto et al. 1983). Therefore, a mixture of these two compounds was effective in controlling both resistant and susceptible populations of the insect. This was an example that an reduction of sensitivity to one compound concommitantly produced an increase in sensitivity to another compound.

Another example of negative correlation at the site of action was recently reported with the tobacco budworm, *Heliothis virescens*, which was highly resistant to methyl parathion(Brown 1992). The altered AChE insensitive to the "type A" inhibitors such as methyl paraoxon, fenitrooxon, propxur and eserine was very sensitive to inhibition by the "type B" inhibitors such as monocrotophos and 4-nitrophenyl di-2-thienylphosphate. Finding compounds which show negative correlation with resistance at the site of action is an effective way to neutralize existing resistance, and this is an area which requires more research efforts.

When insecticide resistance is due to a mechanism associated with an increase in degradation of the insecticide, specific metabolic inhibitors can be used as synergists against the resistant populations. Actually, a number of chemicals are known to inhibit the enzymes responsible for insecticide degradation and thereby synergize the toxicity of these insecticides to resistant populations. To name a few,

Table 1. Joint action of diazinon (A) and carbofuran (b) against the Yachiyo strain of *Musca domestica*

Mixing Ratio (A) : (B)	LD_{50}[a] (μg/우)	Co-toxicity coefficient
1 : 0	62.2	–
0 : 1	14.7	–
1 : 0.05	3.75	1,438
1 : 0.236	1.86	2,067
1 : 1	1.70	1,399
1 : 10	6.32	250

Data modified from Oi & Motoyama, 1991c

[a] Expressed as the sum of two insecticides mixed

the fungicide iprofenfos(S-benzyl 0,0-diisopropyl phosphorothioate) and saligenin cyclic phosphorus esters K-1 and K-2 are carboxylesterase inhibitors which synergize malathion toxicity to malathion resistant strains in many insect species including the Kanzawa spider mite, *Tetranychus kanzawai*, and the green rice leafhopper(Kuwahara et al. 1981, Miyata et al. 1981). Malathion resistance in these insects is mainly due to increased degradation of malathion by carboxylesterases.

Some of the substituted phenyl esters, SK-2, and substituted heterocyclic esters, SK-102, of N,N-dimethylcarbamate strongly synergize fenitrothion and pirimiphosmethyl toxicities to the rice stem borer, *Chilo suppressalis*, resistant to these insecticides (Konno 1989).

The synergism is probably based upon the inhibition of phosphorotriester hydrolase which was the main factor responsible for resistance in this insect.

When resistance is the result of increased degradation of insecticides by the cytochrome P450-dependent monooxygenases, methylenedioxyphenyl compounds such as piperonyl butoxide(PBO), an oxidase inhibitor, synergize the toxicity of these insecticides in resistant populations(Motoyama et al. 1991a). Synergistic effects are also obtained by the join action of two insecticides. One serves as a substrate or inhibitor for the degradation reaction, while the other exerts its action on the target. The theoretical background for the joint action has been studied in detail(Oi & Motoyama 1991a, 1991b) and an example was actually demonstrated with a combination of diazinon and carbofuran (Oi & Motoyama 1991c). The mixture exhibited a profound potentiation effect against a housefly, *Musca domestica*, strain resistant to each of the two insecticides.

Another example of joint action was demonstrated with a combination of saligenin cyclic phosphates(SCPs) and fenitrothion against the 3rd Yumenoshima strain of the housefly resistant to organophosphates(Shiotsuki et al. 1989).

In this case, a glutathione conjugate of the former compound, S-(2-hydroxybenzyl) glutathione, produced *in vivo* inhibited the degradation of fenitrothion by a glutathione transferase, allowing the latter compound to exert its toxic action.

Thus, insecticide resistance can be overcome by disrupting resistance mechanisms either with a synergist or a combination of two insecticides. A pitfall of this approach, however, is that it often leads to the potentiation of insecticidal toxicity not only to pest insects but also to mammals, therefore increasing the toxic risk to humans significantly. In search of safer synergists to circumvent this side

effect, we recently found several methylenedioxyphenyl compounds which selectively inhibited the cytochrome P450-dependent monooxgenases of insects but not those of mammals(Motoyama et al. 1991a). One of the compounds, 3,4-methylenedioxybenzen-1-(2'-methoxyethoxymethyl ether)(NO. 1), exhibited synergistic action when applied in combination with pyrethroids against the diamondback moth and housefly strains resistant to these insecticides. The degree of resistance in these insects dramatically decreased with no significant increase in the toxicity to the rat. This study demonstrates that the selectivity that scientists have been finding for insecticides can be found for synergists as well.

OPERATIONAL STRATEGY

A conventional methods to prevent or delay the development of insecticides resistance is the rotational use of two or more insecticides with different modes of action(Graham-Bryce 1987). The practice is based upon the assumption that the frequency of resistanc gene(s) condensed by selection with a chemical would be diluted again when the population is selected with another chemical and would not reach a proportion high enough to make the population resistant as long as the rotational use of the selecting agent continues. The success of the method, however, depends upon various factors associated with the target pest population and chemical used. Basically there are three factors influencing the development of resistance in the field populations, *i.e.* genetic, biological/ecological, and operational(Georghiou & Taylor 1986). Owing to a number of theoretical studies employing computer simulation and mathematical models(for a list see Tabashnik 1986), one can now have general understanding of dynamics of the development of resistance. Although an over-simplification should be avoided, a few principles to reduce the resistance risk are:

(1) A dose of insecticides used should be large enough to make the resistance functionally recessive.

(2) The application of the insecticides should leave some susceptible individuals, or allow susceptible individuals to move into the previousely treated area from surrounding areas to dilute the frequency of resistance gene(s).

(3) Insecticides with non-persistent nature are desirable, or application methods allowing less residual activity should be employed. The latter two of these principles are likely to produce incomplete control of the pest population, which contradicts the purpose of the insecticide application. In practice, the damage from incomplete control should not exceed the economic threshold. There are some other operational factors which are important but still under debate and cannot be generalized yet. For instance, which of the two application method, rotations (in another word, a sequential application of two or more insecticides) or a combination(in another word, a simultaneous application of two or more insecticides as a mixture) is more advantageous in delaying the build up of resistance gene(s)? This all would depend upon various factors associated with the target pest population. However, either method is probably more effective than the repetitive use of a single insecticide.

In most Japanese hog farms, for example, repeated aerial application of an insecticide against the adult stage has been the dominant method to control the housefly. The practice was not only costly

Table 2. Relative toxicity of azinphosmethyl to organophosphorus-resistant orchard populations of the predaceous mite, *Amblyseius fallacis*, and its prey

Mite Species	Orchard	LC_{50} at 24 h (1b[a]/100 gal water)
A fallacis	Laboratory S[b]	0.07
	Fletcher	5.8
	Lowe	2.0
P. ulmi	Sandhill	4.2
	Fletcher	2.3
	Lowe	2.2
T. urticae	Sandhill	6.2

Data modified from Rock & Yeargan, 1971
[a] 50% WP
[b] susceptible strain

but it also resulted in the development of resistance to most insecticides, *i.e.* organophosphates, carbamates, and pyrethroids. These resistant flies were controlled very effectively by a combination of three application methods, each with different aim:

(1) An aerial spray of a mixture of fenitrothion, d-resmethrin, and PBO for an immediate control of existing resistant flies.

(2) A painting of the walls and posts with azamethiphos containing sugar bait for an extended control of flies continuously emerging from pupal pool.

(3) A treatment of the compost with pyriproxyfen, a juvenile hormone analog, for larval control.

The combination was so effective that it required only a few additional treatments to keep the fly population under control during the entire season. This in turn would give the flies less of chance of developing resistance.

As an alternative method in dealing with a pest population which has already developed resistance, reintroduction of susceptible males to dilute resistance gene(s) would be feasible if (a) the resistance is of a recessive nature, (b) the population size is limited such as in a green house, (c) a large population of susceptible individuals is available, and they are competitive with the resistant males in mating, and (d) the male adult is not the injurious stage. The effectiveness of the method would be enhanced if the resistant males in the pest population could be removed by sex pheromone traps prior to the reintroduction of susceptible males.

Under certain circumstances, natural enemies which have developed insecticide resistance can play a key role in IPM. Azinphosmethyl has been used continuously for many years to control the codling moth, *Cydia pomonella*, on apples without resistance problems in North Carolina, U.S.A.

The practice resulted in the incidental development of azinphosmethyl resistance in an another important pest on apple, the European red mite, *Panonychus ulmi*(Rock & Yeargan 1971). The mite , however, required no specific treatment, because the continuous use of azinphosmethyl also resulted in the development of azinphosmethyl resistance in the predaceous mite, *Amblyseius fallacis*, which

controlled the European red mite. Introduction of new insecticides in this situation would be disastrous since the balance between the chemical control of the codling moth and the biological control of the European red mite on which the IPM relied could be lost easily by the new insecticides which may wipe out the predaceous mite.

Despite the long history of insecticides resistance, extensive studies on the subject, and the abundance of available information and tactics to combat with, there are only a few cases where the resistance problem was actually solved, not just delayed(Graham-Bryce 1987). It appears that the implementation of a successful resistance management program dependes upon cooperation between different segments of the agricultural community. The choice of the insecticides to be used is a political and economical issue as much as a technical isssue (Dover & Croft 1984). When pyrethroids failed to control the diamondback moth several years ago in Japan, which was already cross-resistant to various other insecticides, a resistance management program was implemented consisting of a monthly rotation of four groups of insecticides *i.e.* cartap and related compounds, a mixture of carbaryl and dioxabenzofos, BT, and chlorfluazuron and related compounds. The program worked very well providing excellent control of the diamondback moth in the area ever since. The success of the resistance management program was insured by the strict implementation of the program which was made possible through the full cooperation of four segments of the agricultural community involved , *i.e.* the university laboratory, the extension service of a prefectural government, the growers' association, and the local agricultural cooperative association which supplied insecticides to the growers.

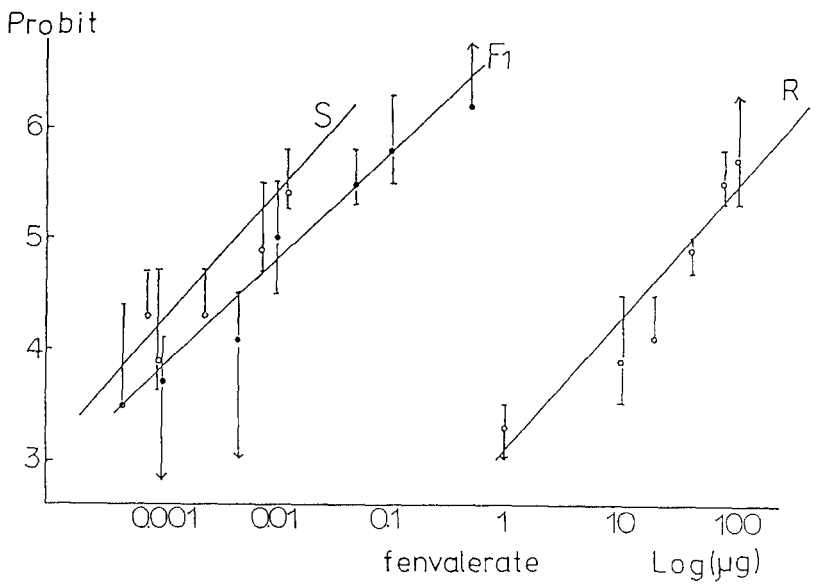


Fig. 1. LD-P line of F_1 progeny obtained by crossing S(female) × R(male) of *Plutella xylostella* (Data from Motoyama et al. 1991b).

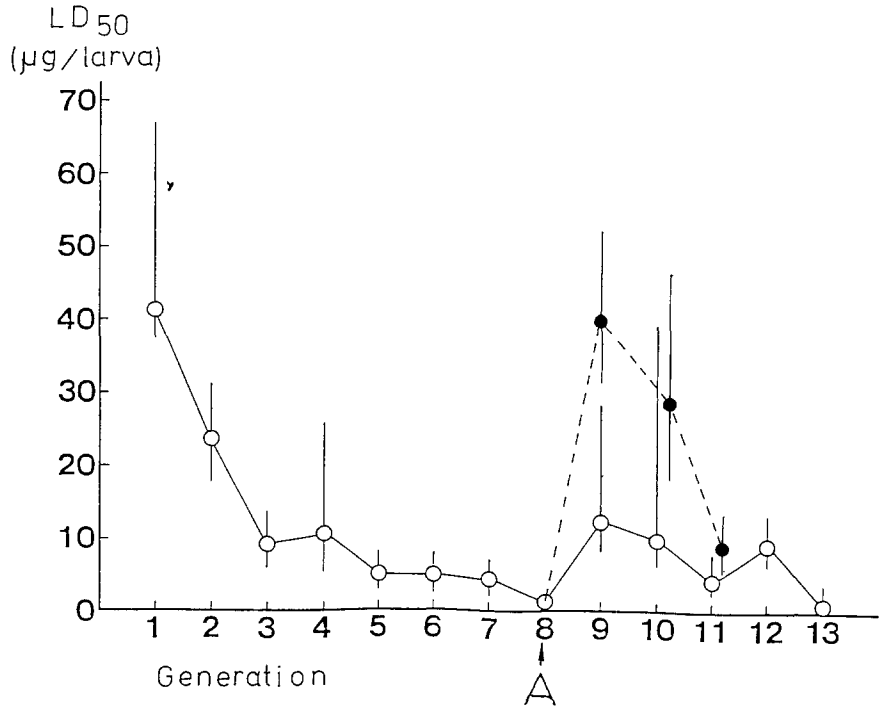


Fig. 2. Change in response to fenvalerate in the resistant strain of *Plutella xylostella* following the termination of selection(○) and the effect of resuming selection once(●) with 20 μg(A) of fenvalerate (Data modified from Motoyama et al. 1991b).

FUTURE PROSPECTS··· A POSSIBLE SWITCH TO TURN OFF THE EXPRESSION OF RESISTANCE GENE(S)

Most investigators working on insecticide resistance have experienced or suffered from an unintentional loss of resistance in the insects they are studying. When this happens whether in the laboratoy or in the field, contamination by susceptible individuals from somewhere is the most likely explanation for reversion. In some cases, however, spontaneous loss of resistance does occur without contamination.

A pyrethroid resistance strain of the diamondback moth originally collected in Thailand and subsequently selected repeatedly with fenvalerate in the laboratory had a LD_{50} value of 41 μg per 4th instar larva and was 8,200-fold resistant to the pyrethroid when compared with the susceptible strain (Motoyama et al. 1991b).

Judging from the LD-P lines of the resistant and susceptible strains and their F_1 hybrids, the resistance appears to be of a recessive nature and the resistant strain seems apparently homogeneous. Neverthless, the fenvalerate resistance of this strain could not be maintained without constant selection pressure with the insecticide. Once the selection was terminated, the LD_{50} decreased every gene-

ration, eventually reaching the level of the susceptible strain. Resumption of the selection at the 8th generation, however, restored the resistance immediately bring the LD_{50} back to the original level.

Since the experiment was carried out in a well isolated laboratory where no other strains or insects were maintained, a possibility of contamination is excluded. Furthermore, no significant difference was found between the resistant strain and its revertant with regard to biological fitness, excluding a possible inferiority in the reproductive rates for the resistant individuals. The phenomenon seems outside the context of the "preadaptation" theory and would probably be best explained by assuming the presence of a genetic switch which is turned-off spontaneously upon release from the selection pressure.

An analogous situation has been encountered more clearly with the green peach aphid, *Myzus persicae*. The insect usually reproduces parthenogenetically and therefore genetically defined nature such as insecticide resistance is expected to be inherited without change within a clone. This was not the case with the E_4 esterase responsible for insecticide resistance in the aphids(Sawicki et al. 1980).

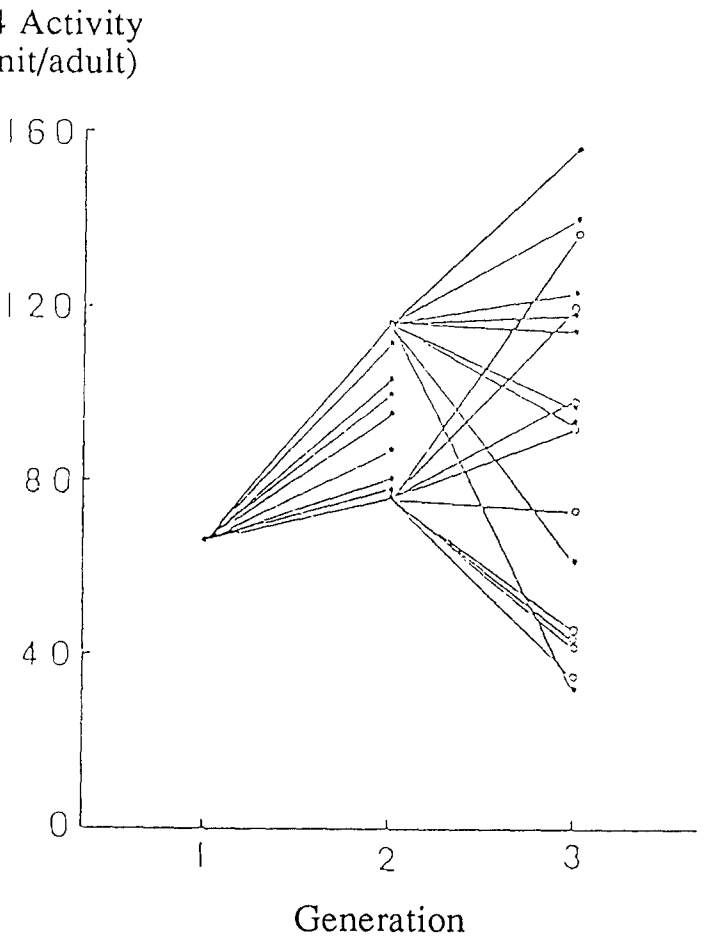


Fig. 3. Intraclonal fluctuation of the E_4 activity in Rt_6 clone of *Myzus persicae*(Data from Motoyama et al. 1992).

Table 3. Comparison of various properties between the two resistant clones, Rn and Rt_6, of *Myzus persicae*

Properties	Rn	Rt_6
Karyotype	Normal	Al.3 Translocated
Degree of resistance	Carbamate>OP	OP>Carbamate
Esterase activity	High(FE_4)	High(E_4)
Stability of esterase and resistance	Stable	Unstable
Effect of population density on E_4	?	Profound
Fecundity at 28℃	Normal	Low
JH Ⅲ degradation	High	High
Ester hydrolysis	Low	High
Epoxide hydration		

The E_4 activity of an equivalent clone in Japan also fluctuated drastically when titrated by immunoprecipitation method using its antibodies(Motoyama et al. 1992). The instability of the E_4 activity of this clone was erratic--while the activity fluctuated every generation under certain conditions, it remained elevated without fluctuation even for a few years under another condition.

Symbionts known to produce a 63 KDalton protein in the aphid were examined and shown not to be involved for the erratic behavior of the E_4 activity. Nor was the difference in host plant the cause of the erratic amount of the enzyme. It was the population density that gave a profound effect. The higher the population density, the less stable the enzyme activity become. At the highest population density examined, individuals with no detectible level of E_4 activity were produced even in one generation. Although it is not known how the high population density affected the accelerated production of "revertant", it seems possible that demethylation of the E_4 gene reported by Field et al.(1989) took place, turning off the expression of the gene and thereby terminating the synthesis of the E_4 protein.

There is another example of detrimental response to environmental stress leading to the instability of insecticide resistance in the green peach aphid (Motoyama et al. 1992). A field observation that the degree of insecticide resistance decreases in the summer prompted us to compare the effect of various temperatures on the reproductive rates between a resistant and susceptible clone. While both clones produced respective F_1 offsprings normally at 28℃, few of the larvae developed to the adult stage in the resistant clone thus failing to produce F_2 offsprings.

This was observed only in the resistant clone with A1,3 chromosomal translocation, and a detailed observation clarified that it was due to the inhibition of larval development. Based upon the assumption that the inhibiton of larval development at the high temperature could be due to a change in hormonal balance, comparison in the degradation of juvenile hormone(JH Ⅲ) by the soluble as well as microsomal enzymes was made among two resistant and one susceptible clone. The results showed that the resistant clone with A1,3 chromosomal translocation had higher epoxide hydrase activity which degraded the JH Ⅲ than the susceptible clone and the resistant clone with normal karyotype. Further studies are in progress to correlate the high epoxide hydrase activity and the inhibition of larval development at the high temperature.

An understanding of the mechanisms of instability of insecticide resistance may provide a key lead-

ing to the development of methods by which one day we may be able to manipulate the switch controllng the expression of resistance gene(s).

CONCLUSION

We have been abusing insecticides taking them for granted, using them carelessly and thereby allowing pest insects to develop resistance, which is causing various adverse consequences. Due to an increasing difficulty in finding alternative new insecticides on which control of the resistant populations has been dependent, we can no longer afford to continue this practice. Aside from efforts to develop new technical possibilities as discussed, the establishment of a cooperation between government agencies, academic experts, growers, and pesticide industries is vital and long due for the effective implementation of resistance management strategy.

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