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THE ROYAL SOCIETY

Myths, models and mitigation of resistance to pesticides

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Resistance to pesticides in arthropod pests is a significant economic, ecological and public health problem. Although extensive research has been conducted on diverse aspects of pesticide resistance and we have learned a great deal during the past 50 years, to some degree the discussion about 'resistance management' has been based on 'myths'. One myth involves the belief that we can manage resistance. I will maintain that we can only attempt to mitigate resistance because resistance is a natural evolutionary response to environmental stresses. As such, resistance will remain an ongoing dilemma in pest management and we can only delay the onset of resistance to pesticides.

'Resistance management' models and tactics have been much discussed but have been tested and deployed in practical pest management programmes with only limited success. Yet the myth persists that better models will provide a 'solution' to the problem. The reality is that success in using mitigation models is limited because these models are applied to inappropriate situations in which the critical genetic, ecological, biological or logistic assumptions cannot be met. It is difficult to predict in advance which model is appropriate to a particular situation; if the model assumptions cannot be met, applying the model sometimes can increase the rate of resistance development rather than slow it down.

Are there any solutions? I believe we already have one. Unfortunately, it is not a simple or easy one to deploy. It involves employing effective agronomic practices to develop and maintain a healthy crop, monitoring pest densities, evaluating economic injury levels so that pesticides are applied only when necessary, deploying and conserving biological control agents, using host-plant resistance, cultural controls of the pest, biorational pest controls, and genetic control methods. As a part of a truly multi-tactic strategy, it is crucial to evaluate the effect of pesticides on natural enemies in order to preserve them in the cropping system. Sometimes, pesticide-resistant natural enemies are effective components of this resistance mitigation programme. Another name for this resistance mitigation model is integrated pest management (IPM). This complex model was outlined in some detail nearly 40 years ago by V. M. Stern and colleagues.

To deploy the IPM resistance mitigation model, we must admit that pest management and resistance mitigation programmes are not sustainable if based on a single-tactic strategy. Delaying resistance, whether to traditional pesticides or to transgenic plants containing toxin genes from *Bacillus thuringiensis*, will require that we develop multi-tactic pest management programmes that incorporate all appropriate pest management approaches. Because pesticides are limited resources, and their loss can result in significant social and economic costs, they should be reserved for situations where they are truly needed—as tools to subdue an unexpected pest population outbreak. Effective multi-tactic IPM programmes delay resistance (=mitigation) because the number and rates of pesticide applications will be reduced.

Keywords: evolution; resistance models; resistance management; pesticide resistance; integrated pest management; pesticide selectivity

1. INTRODUCTION

Resistance to pesticides in arthropod pests is a significant economic, ecological and public health problem (Georghiou & Saito 1983; Georghiou 1986; National Academy of Sciences 1986; Roush & Tabashnik 1990; Denholm *et al*. 1992; McKenzie 1996). More than 500 arthropod species have become resistant to insecticides and acaricides, with many species having become resistant to the major classes of such products.

In this essay I will address three myths that must be dispelled before we can adopt a more effective paradigm for reducing the effects of pesticide resistance. One myth involves terminology that affects how we think about the problem, another involves the effectiveness and appropriateness of 'management' models, and a third myth involves our reluctance to recognize that resistance to pesticides and other xenobiotics is an evolutionary response to stress that will remain a persistent problem.

2. TERMINOLOGY MYTHS

'Managing' resistance is, in my opinion, an inappropriate term for what we can achieve and distorts our

perception of our true objective. According to Webster's dictionary (2nd college edition, 1982), 'managing' is defined as 'to control the movement or behavior of; handle; manipulate; to have charge of'. I think that 'having charge of, or controlling' resistance is a myth. At best we can delay the onset of resistance. A better term might be 'mitigate', which is defined as 'to make or become milder, less severe, less rigorous or less painful; to moderate'. I will argue that our more realistic goal is to mitigate resistance.

3. MODELS AND MYTHS

Scientists have attempted to model pesticide resistance in a variety of ways and the models have been extremely helpful in clarifying issues and concepts (Tabashnik 1990). The models can be classified by the basic assumptions employed, the modelling approach taken, the variables considered, and the problem addressed. Analytical, simulation, optimization and empirical models have been developed, but each has limitations and/or assumptions that are not always recognized. These limitations and assumptions severely restrict the generality and applicability of the models to resolving real-world problems.

(a) *Analytical models*

Analytical models, which attempt to analyse general trends using a simple mathematical description without providing realistic details, are relatively simple and '... seek to define fundamental principles' (Tabashnik 1990). Analytical models usually '... assume simple population dynamics with discrete generations and no age structure. Population growth is usually determined by some form of the logistic equation' (Tabashnik 1990).

How realistic are these assumptions and what effect would violation of these assumptions have on the outcome of the model? We know that relatively few arthropods have discrete generations; most of those that are prone to developing resistance (spider mites, aphids and whiteflies) are multivoltine, and have overlapping generations.

(b) *Simulation models*

Simulation models are more complex and realistic than analytical models because they attempt to incorporate details of the biology, behaviour and ecology of the population and often contain complex population dynamics, including age structure, overlapping generations and temporal and spatial variation in pesticide dose (Tabashnik 1990). Simulation models can be used to evaluate different options for mitigating resistance by including empirical data in the parameters included in the model. These parameters also can be varied in a systematic way to determine how important each is. Yet simulation models have serious limitations, as well.

Collaborations with Michael Caprio and Bruce Tabashnik allowed me to recognize additional issues important to resistance development (Caprio & Hoy 1994, 1995; Caprio *et al*. 1991). Our goal was to increase frequencies of pesticide resistance alleles in natural enemy populations. The development of simulation models was useful and intellectually stimulating, but it became very clear that the details of the population biology and ecology of species sometimes had a pronounced influence on the rate of resistance development. For example, premating isolation and metapopulation structure can influence rate of resistance development in unexpected ways.

Premating isolation in diplodiploid and in haplodiploid species affected the rate of resistance development in sometimes counterintuitive ways (Caprio & Hoy 1995). The amount of mating bias (preference of females to mate with males of the same genotype) determined the rate of establishment when resistant individuals comprised 10% of the population. Interactions between mating bias, degree of dominance and diploidy state also were significant.

Population structure also may influence the rate of resistance development (Caprio & Hoy 1994). A stochastic metapopulation model investigating the establishment of a pesticide-resistant strain of predatory mite found that metapopulation dynamics increased local homozygosity within predator patches, and thus accelerated resistance development most when the resistance mechanism was recessive. Metapopulation dynamics also were important in inducing genetic bottlenecks by high rates of overwintering mortality, which synchronized loss of rare alleles in small populations. We concluded that the mitigation tactics that '... reduce the pest species' population size at critical periods such as overwintering may limit the potential of those populations to maintain resistance alleles' (Caprio & Hoy 1994).

What happens if we make simulation models more complex and more like the real world? Can we really capture all the essential biological, ecological and behavioural aspects of a particular pest species? Do we know enough about these details for many species? Is each species or population unique? Jaffee *et al*. (1997) pointed out that 'One of the most important criticisms to the use of models in biology, and in explaining genetic resistance in particular, is that biological and ecological systems are rather complex, and that simple models ignore that many relevant biological phenomena are emergent properties from complex interactions.' The concept of emergent properties suggests that we are unlikely to know enough to adequately model real species in sufficient detail. Jaffee *et al*. (1997) concluded 'This criticism is difficult to refute as evidence of the emergence of unexpected properties from complex system simulations is mounting.'

Despite the concerns of Jaffee *et al*. (1997) about complexity and emergent properties, they developed a complex model incorporating the effect of various selection pressures on 17 different genes evolving simultaneously in a population. Their results confirmed previous findings that the likelihood of emergence of genetic resistance in a given population is related to many factors, including the size of the initial population, length of the treatment with pesticides, mutation rate, sexual strategy (sexual or asexual), application methods (rotations versus mixtures), timing of the pesticide applications, and residue length. They concluded that '... evolution under a complex assemblage of selection pressures is different from evolution driven by a single environmental factor such as a pesticide.' They further concluded that 'Emergence of genetic resistance is an irreversible process.' This implies that reversion is unlikely to provide

Table 1. *Important assumptions of resistance mitigation tactics investigated by models*
(Based on a review by Tabashnik (1990).)

model type	assumptions
mixtures	resistance to each product is monogenic no cross-resistance occurs between products in mixture resistant individuals are rare in the population products have equal persistence some of the population remain untreated (refuge) resistance is functionally recessive (only homozygotes survive exposure)
mosaics	susceptible individuals are maintained and able to move into surrounding patches may require negative cross-resistance or fitness costs associated with resistance
rotations	the frequency of individuals resistant to one product will decline during application of the alternative product, which is true if there is negative cross-resistance (rare), a substantial fitness cost associated with resistance, or immigration of susceptible individuals occurs
natural-enemy/pest system	food limitations are sufficient to constrain the ability of natural enemies to develop resistance in the field
high-dose strategy	assumes complete coverage, effective kill of all individuals, ignores negative effects on secondary pests, natural enemies, or the environment

an opportunity to reuse a product once resistance has developed.

(c) *Optimization models*

Optimization models evaluate, using dynamic programming techniques, which management strategy will maximize profit when pest susceptibility to a pesticide is considered a non-renewable natural resource. The goal is to balance the future cost of reduction in pest susceptibility with the present losses in crop yield due to the effects of the target pest. The details of the biology of the target species are usually simplified and considered a constraint to the model, which focuses on an economic analysis (Tabashnik 1990).

Because details of biology, ecology and behaviour of the pest are critically important to the development of resistance, as are the characteristics of the specific pesticide product, the rate at which resistance develops in specific situations may vary widely. Thus, optimization models may over- or underestimate the longevity of any product and lead to inaccurate predictions of the costs of losing a specific product.

(d) *Empirical models*

Empirical models are based on actual relationships among variables, with no assumptions made about the causal mechanisms. The models are derived from data and probably are appropriate only to the specific conditions of the observed populations (Tabashnik 1990). Thus, empirical models are least useful for developing a strategy for delaying resistance in an unknown situation if we assume that the important variables can vary between populations (mode of inheritance, cross-resistances, fitness costs, allele frequency and selection intensity).

(e) *Mitigation myths*

In my opinion, resistance mitigation investigated by models remains limited both by the objectives considered and the basic assumptions made (table 1). Even if we limit the discussion to the evolution of resistance by one pest, and the models include situations in which pesticides are applied in mixtures, rotations or mosaics, we remain uncertain whether to recommend alternation of different pesticides or to recommend mixtures as the best method for slowing the development of resistance.

(i) *Mixtures*

Mixtures of products are applied so that individuals are exposed simultaneously to more than one toxicant. Most models involving mixtures require a remarkable array of assumptions: that resistance to each product is monogenic, no cross-resistance occurs between the products used in the mixture, that resistant individuals are rare, the products have equal persistence, and that some of the population remains untreated (Tabashnik 1990). Another assumption is that resistance for each insecticide is functionally recessive so that only homozygous individuals survive. If resistance is not completely recessive, the rate of resistance development is increased. If the products are applied in the field in such a way as to vary the dosage each arthropod experiences, then some heterozygous individuals experiencing lower doses could survive, again speeding the rate of resistance development (Tabashnik 1990).

Few field experiments have been conducted with mixtures. How often can all these assumptions be met and what is the penalty if one or more is violated? I think the situations in which we know that cross-resistance will not occur are rare; we certainly would not expect there to be any degree of cross-resistance between products in different pesticide classes. However, cross-resistance between abamectin and pyrethroids has been reported (Lasota & Dybas 1991), and other examples of cross-resistances between different pesticide classes could be cited. Furthermore, how often is it appropriate to assume resistance is monogenic? When the genetics of resistance

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can be analysed carefully, as with *Drosophila melanogaster*, resistance often is found to be determined by genes located on more than one chromosome. Although a 'major' gene may determine the bulk of the resistance, several other loci also may contribute to the resistance. As geneticists, we should expect that resistance can develop in a variety of ways (either at different points in the biochemical pathway or through totally different mechanisms) (Scott 1990, 1995; Soderlund & Blomquist 1990). We know that different mutations (alleles) will vary in their effect, that different alleles will vary in their mode of inheritance (in a continuum from fully dominant to fully recessive), and that different populations may contain different resistance alleles or loci. 'Modifier genes' may affect the degree of resistance and the fitness of the organism.

(ii) *Rotations*

The hypothesis is that if two or more pesticides are alternated in time, each individual is exposed to only one material but the population experiences more than one product over time. The assumptions include: the frequency of individuals that are resistant to one product will decline during the application of the other product (which can occur if there is negative cross-resistance), a fitness cost associated with the resistance, or movement of susceptible individuals into the population.

The assumption that reduced fitness could be used in resistance mitigation programmes continues to be controversial and may have limited application. Resistance alleles do not always produce detectable levels of lowered fitness over a long period of time (e.g. Hoy & Conley 1989; Hoy 1990; Roush & Daly 1990). It is likely that natural selection will increase the number of 'modifying genes' that restore fitness to individuals carrying resistance alleles.

(iii) *Mosaics*

Mosaics are a spatial patchwork of pesticide applications so that different sites are treated with different pesticide products. Mosaic mitigation models require that susceptible individuals migrate into the treated area, or that negative cross-resistance occurs (which is rare), and that fitness costs are high. The size of the patches required will vary with the biology and ecology of the pest arthropod. Unfortunately, details of dispersal rate and distance vary by species, but often are unknown even for key pests.

(f) *Experimental validation of models*

Relatively few resistance 'mitigation' experiments have been conducted under realistic field conditions. Such experiments are expensive to conduct and require long time periods. Yet, without validation of mitigation models, we are left with little justification for recommending specific actions.

One experiment, in which resistance in the two-spotted spider mite, *Tetranychus urticae* Koch, was measured during seven years in southern Oregon pear orchards (Flexner *et al*. 1995), is particularly interesting because it illustrates some of the problems associated with the theoretical models and their limited application to specific field situations and pest populations. During the experiment, five treatments were applied in replicated field plots twice a season: consecutive organotin use, consecutive hexythiazox use, alternation of both within year, between-year rotations of both organotins and hexythiazox, and a combination at half rates of both types of compound.

Flexner *et al*. (1995) concluded that 'Overall, use in the field was not extended by rotations or half-rate combinations compared with consecutive uses, but benefits from these programs may occur because of slow registration of new acaricides.' Thus, the rotations did not allow increased numbers of applications of a specific product to be made but, because the applications were made in different years, the products lasted longer, which could be useful if this time interval allowed for registration of new products. This might not provide a benefit if the pest population was already resistant to the new product, for they went on to state that 'Resistance to organotins conferred cross-resistance to hexythiazox.' Again, there was no reason, *a priori*, to assume cross-resistances between these two very different products. Flexner *et al*. (1995) also noted that 'cautions are needed before extending [our results] to other situations.' They were concerned that their relatively small plot sizes and the relatively high rate of immigration of susceptible individuals into the plots could have led them to overestimate the potential for resistance management. They were also concerned that although the population of *T. urticae* they worked with readily reverted to susceptibility when left unselected, such reversion does not occur in all populations of this mite. Third, they noted that the parameters used to define resistance (field failure and elevated LC_{50} values) are quite specific to the crop and cultivar.

Some of our most fundamental assumptions about resistance are being questioned. The assumption that resistance is preadaptive may be wrong in some cases. Devonshire & Field (1991) reviewed gene amplification and insecticide resistance in aphids and mosquitoes and speculated that insecticides might act to increase mutation rates, especially with regard to amplified resistance genes, although there are no data to support this at present. Another controversial issue is the possibility that resistance alleles are extremely rare and that resistant individuals may migrate much greater distances than expected, leading to the spread of resistance alleles around the world in a surprisingly short time (Guillemaud *et al*. 1996; Pasteur & Raymond 1996).

Tabashnik (1990) concluded that '... theoretical models and available data suggest that the effectiveness of mixtures, rotations, and mosaics requires special conditions that are not generally met in the field.' He further concluded that '... reducing pesticide use through integrated pest management may be more productive than attempts to optimize pesticide combinations.'

The resistance mitigation models developed to date generally rely on a single tactic (rotation of products or mixture of products or providing a patchwork of treated and untreated sites so that susceptible individuals persist). We have already learned that single-tactic mitigation models are unlikely to be sustainable over long periods of time. The proposed methods of mitigating resistance to *Bacillus thuringiensis* (Bt) toxins in transgenic crops (seed

mixtures or pyramiding or refugia for susceptible individuals) are fundamentally single-tactic approaches (Roush 1996) and also are unlikely to be sustainable.

What do we know about mitigating resistance? I think we know a lot about what does not work. An evaluation of pest management programmes since the 1940s indicates that when pesticides are applied in a manner designed to achieve the elimination of a target pest, serious environmental and other problems usually ensue (National Academy of Sciences 1986; National Research Council 1989; Office of Technology Assessment 1992; Pimentel & Lehman 1993). The intensive and extensive use of pesticides to increase food production and improve human and animal health has failed to be sustainable. It seems likely that relying on transgenic crops that express high levels of a single toxin (a high-dose strategy) also will be a doomed strategy.

Although we can learn from studying pesticide resistance in ubiquitous pests in other geographic regions and thus be alerted to a potential problem, this is an inefficient and often inappropriate method for mitigating resistance in arthropods, especially if different species or different geographic populations develop resistance by different mechanisms. Geneticists know that resistance mechanisms may vary, their mode of inheritance may vary, and the degree of reduction in fitness associated with different alleles or loci may vary. Monitoring programmes are unlikely to be cost effective because it is difficult to sample rare individuals in natural populations (Brent 1986) and therefore they are best employed to document a problem once it has developed (Hoy 1992, 1995).

What is wrong with past resistance mitigation research? In my opinion, the problem is that resistance mitigation research and IPM research programmes usually have been considered different topics (Hoy 1992, 1995). As a result, an effective paradigm for resistance mitigation has not been adopted.

We have tried the simple approaches, in models and in experimental and operational programmes. The simple solutions and models fail owing to our lack of data on the true fitness costs, true selection intensity, mode of inheritance, dispersal rates and distance, and cross-resistance patterns of the resistance gene(s) in the target pest in the specific environment. Often, if one or more essential assumption is violated, the models (and the programmes) fail. Because it is nearly impossible to anticipate all key factors *a priori*, and it is difficult to obtain data in sufficient time, we need to adopt a different approach.

4. MULTI-TACTIC APPROACHES TO MITIGATING RESISTANCE

Multi-tactic approaches to mitigation of resistance are more robust and sustainable than single-tactic approaches. One multi-tactic resistance mitigation model was developed in 1959 and it continues to provide a sustainable solution to resistance if the principles developed then are adopted today. Stern *et al*. (1959) recognized that 'All organisms are subjected to the physical and biotic pressures of the environments in which they live, and these factors, together with the genetic make-up of the species, determine their abundance and existence in any given area.' Stern *et al*. (1959) conducted their research to mitigate the problem of pesticide resistance in the spotted alfalfa aphid in California. They noted that 'Without question, the rapid and widespread adoption of organic insecticides brought incalculable benefits to mankind, but it has now become apparent that this was not an unmixed blessing.' The problems of resistance, secondary outbreaks of arthropods, resurgence of pest arthropods, toxic residues on food and forage crops, and hazards to insecticide handlers and persons, livestock and wildlife from contamination by pesticide drift '... have arisen from our limited knowledge of biological science; others are the result of a narrow approach to insect control' (Stern *et al*. 1959).

The integrated pest management programme developed by Stern *et al*. (1959) for alfalfa in California included a variety of tactics, including monitoring, assessing economic injury levels, using selective pesticide products, and integrating chemical and biological control. 'Chemical control of an arthropod pest is employed to reduce populations of pest species which rise to dangerous levels when the environmental pressures are inadequate. When chemicals are used, the damage from the pest species must be sufficiently great to cover not only the cost of the insecticidal treatment but also the possible deleterious effects ...' (Stern *et al*. 1959). They went on to state that 'Chemical control should be used only when the economic threshold is reached and when the natural mortality factors present in the environment are not capable of preventing the pest population from reaching the economic-injury level.' Stern & van den Bosch (1959) recognized that there was '... an imperative need for an insecticide that would give adequate aphid control and also allow the native predators to survive treatment' and concluded that 'The desirability of attaining a pest-control program in which chemical and biological control are as well integrated as possible is indisputable.'

A multi-tactic resistance mitigation model developed by Barclay (1996) compared the effects of combining methods of insect pest control on the rate of selection for resistance. He found that when two control methods are used in combination, selection for resistance against the two is a linear function if the two do not interact. If the two interact, the function may be sublinear or supralinear. He concluded that the '... control methods that appear least likely to encounter resistance are natural enemies and the use of pheromone traps for male annihilation. These should be integrated into a control program where possible to minimize the development of resistance to other control methods being used.'

Tabashnik & Croft (1985) demonstrated that evolution of resistance in pests was slowed when pesticide applications could be reduced because predators were maintained in the system (Tabashnik & Croft 1985; Tabashnik 1990). There is general agreement that reduced pesticide use is an essential element of any resistance mitigation programme (Croft 1990*b*; Tabashnik 1990; Metcalf 1994). Thus, the compatibility of pesticides and biological control agents is a crucial issue in pesticide resistance mitigation as well as effective IPM programmes.

Pesticide-resistant natural enemies are a special category of pesticide selectivity that can help to delay

resistance in a multi-tactic IPM programme. Relatively few natural enemies have developed resistance to pesticides through natural selection, but several have been deployed in IPM programmes (Croft 1990*a*; Hoy 1990). Artificial selection of phytoseiid predators for pesticide resistance can be a practical and cost-effective tactic for the biological control of spider mites (Hoy 1990). However, development of pesticide-resistant natural enemies should not be considered before exploring other, less expensive options for IPM and pesticide resistance mitigation.

Multi-tactic resistance programmes have been suggested for managing resistance to crops containing Bt genes that include consideration of natural enemies. Hokkanen & Wearing (1995) suggested five tactics for Bt resistance mitigation in oilseed *Brassica*: (i) provide refugia for susceptible individuals; (ii) do not use pesticides that kill susceptible individuals of pests that are targets for control by the Bt gene; (iii) do not use pesticides that kill natural enemies of any of the pests in the crop; (iv) enhance natural control of pests by crop rotation or tillage practices; and (v) rotate between susceptible and resistant crop genotypes synchronously over large areas, while observing points (i–iv). Wearing & Hokkanen (1994) evaluated the potential for development of resistance to Bt genes inserted into apples and kiwi fruit in New Zealand. They suggested that '... the ecological characteristics of the pest provide strong natural mechanisms for retention of susceptibility.' The natural host range of the target species, the natural availability of refugia and the mobility and likely gene flow in the populations should promote susceptibility. 'Even in these circumstances, it is essential that Bt-apple and Bt-kiwi fruit in New Zealand are released into carefully managed IPM programmes, particularly avoiding pesticides toxic to [insects in] refugia, immigrants and natural enemies, and including mating disruption where required.'

5. LEGISLATIVE ISSUES

Nearly everyone will agree that reducing pesticide use is an effective resistance mitigation tactic (Croft 1990*a*; Tabashnik 1990). What has not been widely acknowledged is that resistance mitigation programmes also should include altering the way pesticides are developed and registered. Decisions on application rates and the numbers of applications per growing season should be made with the understanding that they affect the speed with which resistance will develop. In some cases, new products should not be registered for a specific crop because they are toxic to natural enemies and thus could disrupt effective IPM programmes already in place, which will speed the development of resistance in specific pests.

Adoption of new legislation requires that we admit that nearly all major insect and mite pests can develop resistances to all classes of pesticides given sufficient selection pressure over sufficient time. This important assumption may have exceptions, but the generalization is reasonable given the documented record of resistance development in arthropod pests during the past 50 years. Resistance to stress is a fundamental evolutionary response by living organisms and has been achieved by diverse molecular methods (Scott 1995). On an evolutionary time-scale, we should expect insects to have evolved mechanisms to survive extreme temperatures, allelochemicals and other environmental stresses. Although new pesticide classes have been proclaimed to be a potential 'silver bullet', and not subject to resistance development, these hopes have been misplaced to date. It seems appropriate to assume that the development of resistance is nearly inevitable and the issue is not whether resistance will develop, but when.

There are increasing social, economic and ecological pressures to reduce pesticide use through legislative measures in the USA and to increase the use of non-chemical control tactics such as host-plant resistance, biorational methods, cultural controls and biological controls (National Research Council 1989; Office of Technology Assessment 1992; Lewis *et al*. 1997). There is an increasing interest on the part of research scientists, regulatory agencies, legislators and the public in using pesticides that are non-toxic to biological control agents and that have minimal impacts on the environment and human health. The issue of compatibility of pesticides with natural enemies and other non-chemical tactics is critical for improving pest management and environmental quality, and for mitigating resistance to pesticides in pest arthropods. Enhancing the compatibility of pesticides and biological control agents is complex and sometimes difficult (Croft 1990*a*; Hoy 1985, 1990; Hull & Beers 1985), but can pay handsome dividends in improved pest control (Metcalf 1994) and pesticide resistance mitigation (Tabashnik & Croft 1985).

If the pesticide registration process in the USA is changed, we can delay resistance as well as achieve improved IPM programmes (Hoy 1992, 1995). For example, some pesticides are relatively non-toxic to important natural enemies in cropping systems at low rates, but the recommended application rates are too high (Hoy 1985). Use at the high rates disrupts effective biological control, leading to additional pesticide applications, which exerts unnecessary selection for resistance in the pest. Under these circumstances, it may be appropriate for the label to contain two different directions for use; one rate could be recommended for the traditional strategy of relying solely on pesticides to provide control (although this is becoming a less viable option). A lower rate could be recommended for use in an IPM programme that employs effective natural enemies. This dual approach to labelling could reduce selection for resistance in both target and non-target pests in the cropping system.

Another innovation in pesticide registration in the USA would require that the toxicity of the pesticide be determined for a selected list of biological control agents in each cropping system. This information should be provided, either on the label or in readily available computerized databases, perhaps via the Internet. Without such information, pesticides are used that disrupt effective biological control agents, which often results in unnecessary use of pesticides. Enhancing biological control not only leads to improved pest management, but also is an essential tool in mitigating pesticide resistance.

How could information about the toxicity of pesticides to biological control agents best be made available? How

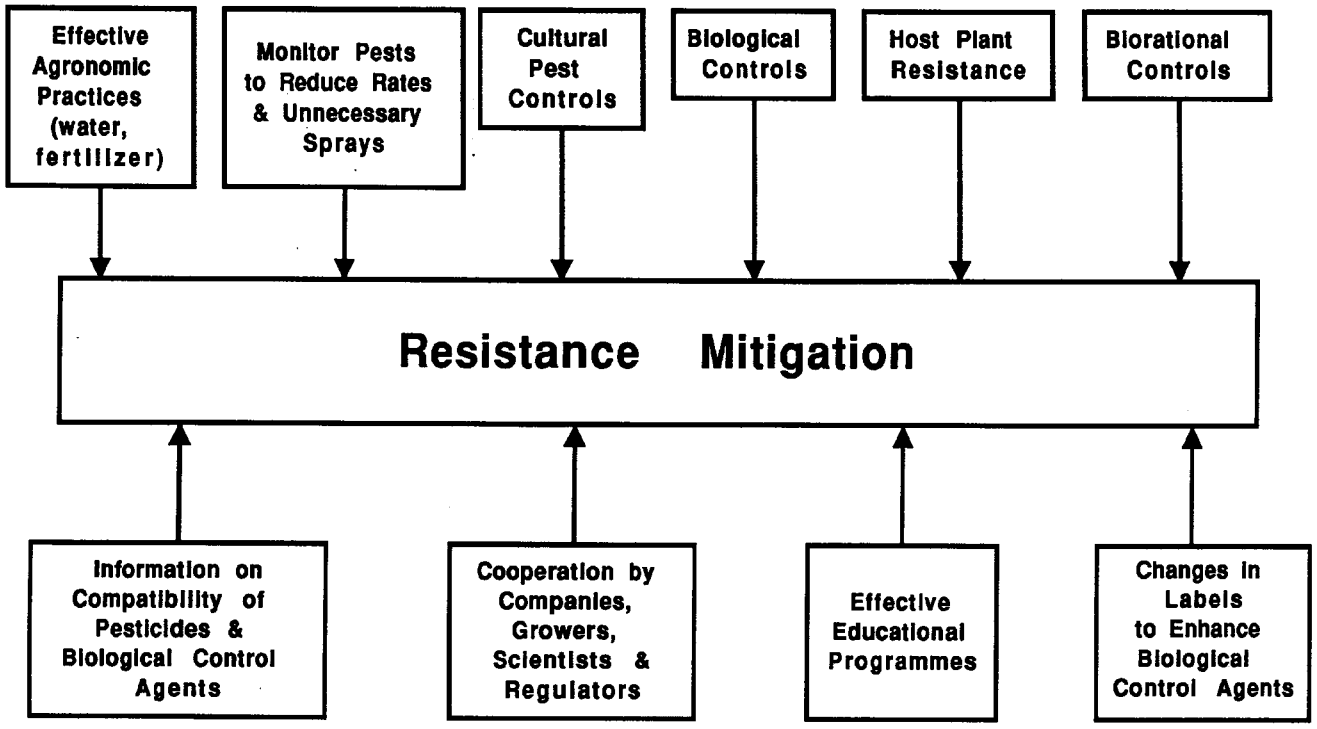

Figure 1. Effective resistance mitigation and integrated pest management: one and the same?

should bioassays be conducted to evaluate pesticide selectivity? There are no simple answers. Theiling & Croft (1988) and Croft (1990*b*) compiled an extensive set of data on the impact of pesticides on natural enemies, but additional data also are buried in publications or reports that are difficult to find. Unfortunately, even if the data can be found, it is not always easy to interpret bioassay data obtained by different scientists using different assay methods. Different bioassays can produce different conclusions about the toxicity of pesticides to natural enemies, and it is often difficult to predict the impact of pesticides under field conditions based on laboratory assays (Hoy 1990; Hassan *et al*. 1991; Robertson & Preisler 1992). Thus, the recommendation that labels or databases be developed with information on the impact of pesticides on natural enemies requires considerable discussion and additional research. Should pesticide companies conduct the research using standard bioassay methods? Should a consortium of pest management scientists conduct the assays? Who should pay for the research? What species of natural enemies should be tested? However, the concept is not new, and in Europe standardized bioassays already are being conducted on selected natural enemy species (e.g. Hassan *et al*. 1991; Oomen *et al*. 1994). Increased international consultation and cooperation between scientists, regulatory agencies and pesticide companies could resolve many of the questions raised above.

6. CONCLUSIONS

The mitigation of resistance in pest arthropods is a difficult and complicated business and is unlikely to be resolved by simple solutions. Mitigation of resistance to Bt toxins in plants also is unlikely to be easy or simple. It is doubtful that resistance to Bt-toxin genes can be prevented by stacking or pyramiding them in transgenic plants; in at least some arthropods a single gene confers resistances to multiple Bt toxins (Tabashnik *et al*. 1997). The deployment of crop plants with toxin genes that exert continuous selection pressure on both target and non-target arthropod populations, whether or not the target pest exceeds an economic injury level, is an unusually effective selection method. If the toxin genes are expressed at a sufficiently high level that arthropod populations are eliminated at least temporarily, both host-specific and generalist natural enemies will be unable to sustain themselves in the cropping system without their food, and this is a familiar scenario for inducing secondary pest outbreaks. Effective IPM programmes require that we use a holistic and multi-tactic strategy that includes enhancing the compatibility of pesticides and biological control agents (Hoy 1992; figure 1).

We should preserve sprayed Bt products because they have limited negative effects on the environment, non-target organisms and humans. Sprayed Bt products are especially useful for certain arthropod pests in minor crops, which are increasingly ignored by pesticide companies because they are a small market. Registration of new pesticides for these crops is likely to be more difficult and expensive in the future, which could leave us with extremely limited options for mitigating certain recalcitrant pests. If resistant pests develop in crops containing Bt-toxin genes and they are able to move over to 'minor' crops, then the repercussions of resistance to Bt toxins would be amplified. Sprayed Bt products are limited resources.

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An effective paradigm for resistance mitigation has not yet been widely deployed. This is because we have failed to accept that satisfactory resistance mitigation is based on the development of effective, fully integrated multi-tactic IPM programmes. Such programmes ideally will consider the entire agroecosystem and acknowledge the role of monitoring, economic injury levels, biological controls, genetic controls, cultural controls, and bio-rational controls such as mating disruption, insect growth regulators and mass trapping (figure 1). A key issue in such programmes should always be whether pesticides can be used in a precise and selective manner without disrupting natural enemies. Disruption of natural enemies is not limited to acute toxicity, but can occur if pesticides are applied over a sufficiently large area so that natural enemies are limited in abundance by available food resources. It is time we recognize, as Stern *et al*. (1959) did, that true resistance mitigation requires a holistic approach to pest management.

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