BIORATIONALS AND BIOTECHNOLOGY—THEIR FUTURE ROLE IN THE CONTROL OF INSECT PESTS IN THE URBAN ENVIRONMENT

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Abstract: This paper reviews the need for change in the techniques and materials that, until recently, have been the mainstays for dealing with insect infestation in homes, hospitals, food premises and other public buildings. Recent years have already seen the introduction of substantial changes including the increased use of so-called biorational molecules like juvenile hormone analogues and chitin synthesis inhibitors. These insect growth regulators (IGRs) are becoming increasingly important weapons in the battle to control urban insect pests and, their role may become even more prominent in the future. In addition to the introduction of a range of IGRs for public health pest control, we are beginning to see the first real efforts to use biological control (including predators and parasites), but this subject is covered by another paper in this symposium and therefore will receive only passing mention in this presentation. Finally, the novel technologies made available through developments in molecular biology and genetic engineering offer intriguing opportunities for use in future urban pest control strategies. In this paper, I hope to explore some of these possibilities and the potential problems that will influence just how much these new techniques will become a part of future urban pest control techniques.

INTRODUCTION

Why change what we do now to control urban insect pests?

Technology marches inexorably, hand in hand with time; new products are developed, new techniques adopted, and new problems (sometimes even "new" pests) appear on the horizon to challenge our ingenuity. Is the driving force behind this continual change simply a desire to accomodate the inevitable results of technological discoveries, so that, by providing "new lamps for old", industry can continue to be profitable? Certainly, it is not. The impetus for change in our industry comes not from the profit-driven motives of the industrialist, nor for that matter, from a feeling that stagnation must be avoided at all costs. It comes because only alternative technologies can help our industry to overcome some of the problems (often self-created) that it faces today. These problems include the development of resistance in insect pests to the chemicals we currently use to kill them; increasing requirements for detailed toxicological and efficacy data by registration authorities; and, perhaps most important of all, the public perception (eagerly spurred-on by the strong environmentalist lobby) that pesticides are environmentally damaging. Whilst this (arguably) may have been true of some molecules (e.g. DDT) in the past, it does not hold true today. In this paper, I shall try to demonstrate that just because a chemical can be used to eliminate a population of pests, it does not automatically follow that the substance is bound to be harmful to humans or to the environment.

The belief that "if it's a pesticide, it must be bad" is idealogically the irrational offspring of the marriage between ignorance and illogicality. As a result, simply dismissing all pesticidal chemicals as potentially harmful, is neither accurate nor sensible. Of course, where it is possible to use less hazardous pesticides, they should be used. Where it is possible to use lower amounts of insecticide, or to limit their widespread dispersal, by utilising targetted application techniques (e.g. baits, crack and crevice treatments etc.) they should be used. Furthermore, where non-chemical methods like improved hygiene, better proofing and biological control are appropriate, they too should be incorporated in an integrated control programme. All these ways of reducing the current reliance on the repeated application of conventional insecticides in the domestic environment are both sensible and laudable. Indeed, this objective is an integral part of the U.K. Government's policies on reducing the quantities of pesticides used, and on protecting the environment. It goes without saying, that any method used to alleviate the problems caused by insect infestations should be genuinely effective as well as offering increased margins of safety. Some of these technologies are already available, as we shall see later, and many of the most efficacious have been developed by using a biorational approach. In addition, newer technologies based on genetic engineering and

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molecular biology are now being extensively investigated for use in mainstream agricultural crop protection. These techniques are innately rather difficult to utilise in urban pest control, for reasons that will be explored later. Moreover, we will undoubtedly have a great barrier of bias or predudice against genetic engineering to overcome before the general public fully accepts the potential benefits of permitting, say, a genetically transformed virus to be sprayed in their homes to eliminate cockroaches.

Pesticides based on a rational biological approach.

Biorational pesticides are, as their name implies, developed on the basis of an understanding of the detailed aspects of the biology of pest organisms, and the utilisation of this knowledge to interfere with a specific life process of a pest in a way that is confined only to an individual target pest or pest group (e.g. insects). Insects are animals, and share many life processes with all other living creatures. However, there are several ways in which insects differ significantly from most other animal types. In this paper, I will discuss just two of these important differences in an attempt to illustrate the biorational approach to pesticide design. The two systems that I shall use to illustrate the biorational approach are a) the hard exoskeleton (cuticle) which is more or less confined to insects and some related arthropods, and b) the insect juvenile hormone system that controls development and reproduction only in insects. Because these biological phenomena occur only in target species, the disruption of these aspects of the insect's life systems can have serious consequences for the pests without affecting the physiology and survival of other living creatures. It is this attempt to achieve specificity of action that is the underlying rationale behind the development of these novel approaches to insect pest management. Thus, chitin synthesis inhibitors are an attempt to disrupt the processes that form the insect exoskeleton, whereas juvenile hormones (and their analogues) aim to interfere with the hormone-based control of metamorphosis and reproduction. These two types of biorational molecules are often referred to as insect growth regulators to distinguish them from conventional insecticides with neurotoxic action.

Insect juvenile hormone analogues.

In insects, the vital processes of metamorphosis and reproduction are under the control of a hormone that, as far as is known, does not have any biological function in any other group of living organisms. This hormone is produced by a pair of endocrine glands (the corpora allata) which are themselves controlled by neurohormones produced by the brain. From the time when a larva hatches from the egg, through to the point when the larva is almost fully grown, the corpora allata are active and produce a hormone which circulates in the blood. The function of this hormone is to prevent the larva metamorphosing to the adult stage. Because the hormone keeps the insect in a larval or juvenile state, it is called the juvenile hormone (JH). During the final larval instar, the corpora allata become inactive, the levels of juvenile hormone in the haemolymph rapidly disappear and the subsequent absence of JH in the blood triggers the process of metamorphosis. In holometabolous urban insect pests (e.g. ants, moths and beetles) the change from larval to adult insect proceeds via an intermediate pupal stage. In hemimetabolous urban pests (e.g. cockroaches, crickets and bed bugs) the metamorphosis is gradual, and the last stage larva (or nymph) is very similar (at least externally) to the adult insect. However, irrespective of the mode of development, the mechanism signalling that it is time for metamorphosis is the low JH level in the mature larva. In most insects, when metamorphosis has taken place and the adult state is reached, the corpora allata become active again and JH levels once more increase in the blood. The reappearance of JH in the adult insect has, of course, nothing to do with the control of metamorphosis—since this has already occurred. Instead, the hormone in adults acts as a gonadotropin, stimulating egg production and other aspects of reproductive physiology, especially in females. Thus, the juvenile hormone is controlling two critically important aspects of insect physiology *viz* reproduction and metamorphosis. Soon after the discovery of the chemical structure of naturally occurring JH (Roller *et al.*, 1967) it became apparent that artificial manipulation of JH levels in insects could have great potential as a way of controlling pest species by disrupting the processes of metamorphosis and/or reproduction. In addition, it became clear that synthetic chemical analogues of natural JHs were more active and more stable than the naturally-occurring homologues. As a result, several thousand juvenile hormone analogues (JHAs) were made and tested in a number of laboratories worldwide.

Of these, about half a dozen showed sufficient promise to be further developed for practical use, and the majority of these have been found to have particular application for the control of a range of urban insect pests. One of the reasons for this is that several urban insect pests are pests (or are perceived as pests) only in the adult stage (e.g. mosquitoes, fleas and ants). Early larval stages of these pests, which are generally unnoticed, are not affected by JHAs but adult stages fail to emerge because metamorphosis is prevented. Moreover, even in the case of urban insect pests where larvae as well as adults have significant pest status (e.g. cockroaches) JHAs can be such effective inhibitors of reproduction that they are extremely effective against even large and well established cockroach populations (Edwards and Short, 1993; Short and Edwards, 1993)).

It is beyond the scope of this paper to list all of the many practical applications of JHAs against urban pests that have been developed in recent years. Such information exists in several reviews (Edwards and Menn 1981; Menn *et al.*, 1989). In terms of the use of JHAs against pests of public health importance, it is significant to note that methoprene (the first commercially-developed JHA) was actually developed initially for mosquito control in the early 1970s (Schaefer and Wilder, 1972). Subsequently, the same molecule was registered in the U.K. for the control of the the Pharaoh's ant *Monomorium pharaonis* (Edwards and Clark, 1978). Since then, methoprene has been joined by hydroprene, fenoxycarb and pyriproxyfen, and these JHAs have been successfully developed for the control of cockroaches, ants, flies and fleas in and around the urban environment. Indeed, several papers presented at this conference amply illustrate the continuing development of JHAs for the control of urban insect pests. Methoprene is well established as an effective control agent for Pharaoh's ants and fleas, as is hydroprene for cockroaches. Fenoxycarb and pyriproxyfen have greater ultra-violet stability than the alkyl-2,4,-dodecadienoates (methoprene and hydroprene) and have therefore been developed for use against fleas and flies outdoors as well as inside buildings, and are equally effective against mainly indoor pests like cockroaches. The greater stability of these second generation JHAs has also led to the development of fenoxycarb for the control of peridomestic insect pests like the red imported fire ant, *Solenopsis invicta*, and pyriproxyfen for the control of urban mosquitoes.

The major advantages of the JHA-based insecticides over their broad-spectrum neurotoxic predecessors are their specificity of action (which is limited to insects and a few closely-related groups e.g. some crustaceans) coupled with their remarkably low acute and chronic toxicity to vertebrates. For example, the acute (oral) LD_{50} of methoprene and hydroprene in the rat is in excess of 30,000 mg/kg. Other JHAs have similarly negligible toxicity to non-target groups. Indeed, it is likely that, as a group, JHAs represent the safest type of insect control agent yet discovered. In support of this last statement, let me refer to a recent practical example in which the JHAs methoprene and hydroprene were used to control domestic ants and cockroaches in an urban environment which also supported the last remaining world population of an endangered vertebrate species—namely the last 23 individuals of the Seychelles magpie robin, *Copsychus seychellarum* (Edwards, 1992).

Despite the obvious advantages of JHAs (in terms of their safety to humans and to the environment), these molecules do have a major drawback. Fundamentally, this drawback is associated with the fact that they are active only at certain times during the insect's life cycle (i.e. at the end of larval development) and do not cause significant mortality in adults. They frequently disrupt metamorphosis, and often prevent reproduction in adults, but these actions, however effective, mean that effects on pest populations are considerably slower than can be achieved with chemicals that have direct toxic activity. As a result, JHAs are most effective when combined with other pesticides that give rapid mortality in pest populations. Such combinations can be extraordinarily effective. At first sight, it may be suprising to be seen to advocate the use of two pesticides where previously only one was deemed necessary. However, because JHAs have a highly effective but slow effect on pest poulations (e.g. cockroaches), their combination with an initial treatment involving fast-acting adulticides may actually reduce the need for the repeated application of conventional pesticides in order to achieve elimination of the pest population. Needless to say, the conventional insecticides chosen for such combination treatments should themselves, ideally, have negligible environmental impact.

It is clear that JHAs have already had a significant impact as environmentally acceptable control agents for a number of important urban insect pests, and future developments in formulations, combinations and application techniques may well increase the effectiveness and use of these molecules against a wider range of urban pest species. The juvenile hormone analogues are a classic example of the success of the biorational approach in pesticide design, and the significance, safety and efficacy of these molecules as control agents for urban insect pests should not be underestimated.

Chitin synthesis inhibitors.

Chitin forms the bulk of the exoskeleton that is characteristic of insects and other arthropods. It is a crosslinked proteinaceous material mostly comprised of poly-N-acetylglucosamine, and occurs only very rarely outside the insects (e.g. in some fungi and other lower organisms, and in molluscs). As larval insects grow, they need to shed their hard outer covering at intervals in order to grow in size. This process of moulting or ecdysis (also under hormonal control) involves the enzymatic degradation and resorption of a substantial proportion of the old cuticle, and the synthesis and deposition of the new one. Subsequently, the new cuticle (often soft and untanned) hardens and darkens as the polymer cross-links and the proteins become tanned.

The discovery that certain synthetic molecules (mostly acyl-ureas) were capable of interfering with the synthesis or deposition of chitin in the new cuticle during the moulting process, has led to the development of several such compounds for the control of urban insect pests, especially cockroaches and fleas. Because of their reported mode of action, these molecules have been termed chitin synthesis inhibitors (CSIs). However, despite the fact that accepted wisdom and some scientific evidence has led us to regard these molecules as inhibitors of chitin synthesis or deposition, my own experience with a number of these compounds leads me to suggest that this may not be the main (and certainly not the only) mode of action of some CSIs in several insect species. I say this not to denigrate the research that has been done previously, but to stimulate further studies on this interesting class of biorational molecules.

In Europe, two such molecules—triflumuron (Bayer) and lufenuron (Ciba) are currently registered and sold for cockroach control. In the U.K., one of the lead molecules, diflubenzuron (Dimilin) has been used against urban populations of the housefly (*Musca domestica*) breeding in housed livestock units, and could well be used for the control of the same species on urban rubbish tips. At this meeting we have seen that triflumuron and another CSI (flufenoxuron) are being developed for use against the German cockroach, *Blattella germanica*. No doubt, several other chitin synthesis inhibitors are currently being developed for use against a number of urban insect pests.

Like JHAs, chitin synthesis inhibitors are highly specific and they also exibit very low levels of acute and chronic toxicity to vertebrates. As an example, lufenuron is currently available as a control agent for fleas (e.g. *Ctenocephalides felis*) infesting cats and dogs, and is administered orally to the infested pet.

Because CSIs act on the moulting process, they are (at least theoretically) effective against all developing stages. In fact many CSIs may even act to prevent the hatching or emergence of the first instar larva from the egg. For this reason, CSIs may act more rapidly against insect pest populations than JHAs.

Another significant difference between CSIs and JHAs is that the former group of biorational pesticides tend to be much more (chemically) stable, and therefore persistent in the environments in which they are used. Whereas this could be seen as disadvantageous in some situations, the increased stability of CSIs is a definite advantge in situations where prevailing microclimatic conditions are harsh and tend to degrade other pesticides very rapidly. Such conditions are often found in situations where control of urban insect pests is required. For example, some years ago in a U.K. hospital, we recorded the air temperature in an underground service duct as 45°C, and estimated the relative humidity to be around 95%. Such conditions are highly conducive to the proliferation of pests, but degrade pesticides alarmingly rapidly.

Overall, chitin synthesis inhibitors have lagged some way behind JHAs in terms of their current use against urban insect pests. However, there has been a recent resurgence in interest in CHIs as public health pesticides, and I am confident that this group of biorational insecticides will, in future, play a prominent role in the battle against urban insect pests.

Biotechnology.

In recent years there have been significant developments in molecular biology, which have enabled breakthroughs to be made in gene tansfer technology. This is popularly known as "genetic engineering". The major advances have, of course, been made in agricultural pest control. For example we have seen the incorporation of a number of genes conferring resistance to insect pest attack into a variety of plant species (Vaeck *et al.*, 1987; Hilder *et al.*,1987). In a similar way, a number of insect-specific baculoviruses (NPVs) have been modified to contain genes which, when expressed in the host insect, produce insecticidal effects (Bishop, 1989). The most well known examples of these technologies in both plants and viruses is the insertion into a plant or virus of the gene coding for the production of the delta endotoxin of *Bacillus thuringiensis* (Merryweather *et al.*, 1990). However, experiments have been conducted with transformed baculoviruses containing genes coding for insect hormones (Eldridge *et al.*,1991), and, in some instances, other manipulations that impinge on the insect endocrine system (O'Reilly and Miller, 1989; Hammock *et al.*, 1990). At CSL we are currently investigating similar technologies for the utilisation of genes coding for highly-specific and highly-active insect allatostatic neuropeptides (Weaver *et al.*, 1993), and other insecticidal factors for the control of a variety of insect pests including several species of public health significance.

These advances in biotechnology will undoubtedly have a significant impact on the control of insect pests in agriculture. However, in the field of public health it is, as yet, not easy to predict exactly how similar technology will impact on our ability to control urban insect pests. For example, most urban insect pests do not eat plants, therefore, it is unlikely that transgenic plant technology will be applicable to public health pest control. Similarly, the viruses that are being modified for use against agricultural pests do not appear to be present in the major urban insect pest groups (i.e. in cockroaches, fleas or ants). In fact, the absence of suitable vectors is probably the most difficult technical problem which we will have to overcome if we are to see the fruits of genetic engineering applied to the control of urban insect pests. However, I am sufficiently confident that this technical problem will be overcome, and CSL in collaboration with a number or other institutes, is currently researching into a number of potential transgenic vectors that will be effective against the major groups of urban insect pests.

Notwithstanding our ability to overcome the technical problems in producing genetically modified urban pest control techniques, there is a far greater hurdle which will have to be surmounted before such technology finds full use and acceptance in the public health pest control industry. There is a perhaps understandable concern in the minds of the general public about the potential danger of utilising genetically modified organisms. In simple terms, this can be translated into a fear of having, in the first case, a virus or bacterium sprayed into their living environment, and this is likely to be even more unacceptable if that microbe has been genetically modified. This public perception of the possible dangers of genetic engineering is, of course, as ill-founded as their concern about the proper use of modern biorational insecticides. In fact if the principles that have been used in the development of biorational pesticides are applied to a new generation of genetically modified organisms for public health pest control, these new techniques should provide equally effective and environmentally and toxicologically acceptable. Thus, providing that specificity of action combined with negligible hazard to non-target organisms and the environment, remain the overiding guidelines for the development of biotechnological pest control techniques, they should prove to be as effective and as environmentally acceptable as the synthetic biorational chemicals. Indeed, it could well be argued that the JHAs and CSIs are early examples of the use of biotechnology in the development of insect pest control techniques. Thus, the use of similar principles in conjunction with modern molecular biological techniques can be seen as being merely an extension of the biorational approach.

Although genetic engineering and the creation of genetically modified organisms are perhaps the most obvious and dramatic examples of the use of biotechnology in pest control, they are by no means the only way in which molecular biological techniques can be used to improve our ability to control insect pests. Modern immunological techniques such as ELISA, gene probes, and DNA fingerprinting can undoubtedly help us to identify insect species (even from fragments or secretions) and to detect the presence of insecticide resistance in pest populations (sometimes by sampling a single individual). Many of these techniques need further refinement and development towards the point when they are truly practical, before they become an everyday part of the PCO's toolbox. Nevertheless, biotechnology offers great opportunities for the future of urban insect pest control and we must explore every new avenue in order to fullfil our role as guardians of a pest and disease free urban environment.

CONCLUSIONS

In summary, we have seen in recent years an increased public concern about the use of pesticides in our environment. This same concern is being more frequently expressed in relation to the use of pesticides in urban dwellings. In response to this concern our industry has made significant progress in developing and using new techniques and new technologies to improve the safety and efficacy of urban pest control techniques. Perhaps the best example of these improvements is the introduction of insect growth regulators and chitin synthesis inhibitors which are highly specific and therefore represent negligible hazard to both the pest control operator and his customer. Other ways of reducing hazard to the operator and to the environment are also being rapidly introduced in our industry. For example, we have seen techniques such as microencapsulation, water soluble sachets and crack and crevice treatments becoming more and more a normal part of the pest control armoury. We have already made significant advances in improving both the safety and efficacy of control techniques against urban insect pests. Indeed, the public health pest control industry is probably further advanced with many of these techniques than its agrochemical counterpart. Despite these advances, we have not yet reached our ultimate goal and, rather than shying away from the challenges presented by new technologies, we should take every opportunity to use and develop them to improve pest control techniques against urban insect pests both for our own purposes and for the benefit of the environment and those who need our services.

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