Environmental Health Perspectives
Vol. 14, pp. 119–126, 1976

Insect Growth Regulators and Insect Control: A Critical Appraisal

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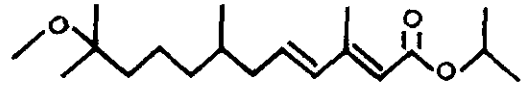
Insect growth regulators (IGRs) of the juvenile hormone type alter physiological processes essential to insect development and appear to act specifically on insects. Three natural juvenile hormones have been found in insects but not in other organisms. Future use of antagonists or inhibitors of hormone synthesis may be technically possible as an advantageous extension of pest control by IGRs.

A documented survey of the properties, metabolism, toxicology, and uses of the most commercially advanced chemical, methoprene, shows it to be environmentally acceptable and toxicologically innocuous. Derivation of its current use patterns is discussed and limitations on these are noted. Residue levels and their measurement in the ppb region have allowed exemption from the requirement of tolerances in the EPA registered use of methoprene for mosquito control. Tolerances for foods accompany its fully approved use for control of manure breeding flies through a cattle feed supplement. The human health effects of using this chemical appear to be purely beneficial, but further advances through new IGR chemicals appear unlikely without major changes in regulatory and legislative policy.

Objective

Since the purpose of this conference is to review current knowledge and to anticipate future human health effects of new approaches to insect pest control, it is particularly appropriate to review and discuss insect growth regulators. At this time they represent the newest of all approaches to operational and commercial insect control. Only one insect growth regulator (IGR) has so far achieved the status of full commercial registration by any government regulatory agency (in this case the Environmental Protection Agency) for its uses, and my discussion will therefore focus on this chemical (*1,2*), common name methoprene, trademark name Altosid IGR, for the main reason that a large body of information and knowledge is available for this substance. However, it is important to note that its first registered use pattern (*3*) is for the control of flood water mosquitoes, which are among the insect carriers of serious diseases. Thereby its human health effects are directly discernible through the prevention of human diseases, and these effects could even be estimated by NIEHS in terms of cases prevented.



Methoprene

Since the second registered use pattern (*4*) is the controlled feeding of Altosid IGR to cattle for the control of manure breeding flies, which results in increased yields of beef and milk, we may again anticipate beneficial human health effects in the form of greater availability of high value nutrition, the cost of which would be higher without such fly control.

In order to assess whether these beneficial human health effects have been achieved without other detrimental effects, it will be necessary to discuss some of the theories and practices which underlie the use of an IGR for pest control. However, it will be more important to discuss the chemical and toxicological properties, not as isolated facts

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with limited value, but rather in the specific context of the field use rates and of the use patterns which have been approved by the regulatory agency.

Introduction and Definition

An IGR may be defined in terms of its mechanism of action, as a substance which acts within an insect to accelerate or inhibit a physiological regulatory process essential to the normal development of the insect or its progeny, in such a way that the action of the substance is necessarily dependent on the life stage of the insect. Although there are numerous other physiological processes which are essential for the survival of an insect, chemicals such as organophosphates or carbamates which interfere with these other processes are not to be included, since they interfere with processes which accompany but do not regulate normal development.

It follows that an IGR need not necessarily be toxic to its target, but may instead lead to an abnormality which impairs the survival of the insect. However, it is important to note that those IGRs which have found practical uses cause the relatively rapid death of the insect through failure in the operation of a key process such as emergence of adults from pupae. From the definition above it follows that the life stage at which an insect can be affected by an IGR will usually be an immature stage or a reproductive stage of the adult. This information has often been incorrectly extrapolated to imply that an IGR can only be a preventative control agent, but I believe this is true only in the rare case of a highly synchronized insect population. In the much more common case of an evenly distributed population, where many life stages may be present together, an IGR which acts at only one specific life stage would have to be moderately persistent. A sufficient chemical residue would be required over the time span in which insects of the population could reach and pass through the sensitive stage, or sensitive window, in which they would be affected. For this reason we can expect that many uses of IGRs will center around insects which have a rapid developmental cycle and which pass through more than one generation per season.

Occurrence and Distribution of Juvenile Hormones

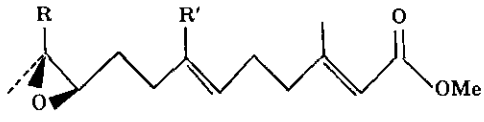
Although numerous natural substances regulate the growth and development of insects, the juvenile hormones (JH) have been singled out for refinement of their biological and chemical properties by synthesis of chemical analogs which are insect growth regulators. Historically, the major reasons for the selection of JH as a rational lead for pesticide design were the beliefs (*5*) that this hormone occurred in insects, that it had a specific function in insects, and that it did not occur in higher animals. The implication was that juvenile hormone would therefore be selectively active in insects. Although current knowledge strongly supports the beliefs, we have no formal proof that JH does not occur outside the class of insects. It may be philosophically impossible to obtain proof since we are only able to say that JH has not yet been identified in other organisms, within the detection limits of our instrumentation. The real problems are that very few species have been extracted and examined in chemical detail, and that numerous plants and animals are already known to contain sesquiterpenelike molecules which possess weak JH activity. To pursue this question, which bears on the environmental impact of JH analogs, new research would have to involve chemical identification rather than rely on bioassay, which formed the basis of reports (*6*) of JH activity in mammalian tissues in the late 1950's.

On phylogenetic grounds it could be anticipated that JH might occur in other classes of the phylum arthropoda, such as the crustaceans, which definitely contain the same molting hormones as insects (*7*). Even this is doubtful, because a large body of toxicological testing of IGRs on various crustacean species at several developmental stages has shown no effects which were even vaguely hormonal in nature. More extensive tests of the natural JH and several hundreds of their analogs revealed no hormonal activity on spider mites belonging to the class Acarina of the arthropod phylum, even though these phytophagous mites which are serious agricultural pests exhibit a complex metamorphosis comparable with that of insects (*8*). Although it is conceivable that crustacean and noninsect metamorphosis is regulated by known JH, perhaps so tightly protein-bound as to elude detection, it is more reasonable to presume that molecules other than the known JH may be responsible for the regulation of metamorphosis of arthropods other than insects. Though several workers have searched for effects of insect JH on nematodes, no clearly hormonal effects have been demonstrated (*9*). The widespread distribution of substances identical with insect molting hormones has been well documented and reviewed (*10*), but in contrast the insect JH appear to be quite restricted to the insects.

Despite the apparently very narrow distribution of JH, the abundance of natural JH in the environment can certainly not be described as limited. There are more species of insects than of all other living things combined (*11*), and it is estimated that a billion billion insects are alive at any given time. Relative to insect body weight, the natural hormones occur at levels between 0.1 and 5.0 ppb in the majority of species investigated (*12*), but at 300 ppb in giant silkmoths. If we use 10 mg as the average weight of an insect, it follows that about 10 tons of natural JH is present in the environment at any given time.

Despite this apparent bonanza, even the isolation of nanogram quantities of natural JH from insects is a truly difficult task (*13*). A considerable amount of research has been devoted both to the improvement of established classical methods (*12*) and more recently to the development of a fundamentally different approach. The newer approach is based on a combination of *in vitro* organ culture with high resolution liquid chromatography (*14*), and such an approach led in this laboratory to the discovery of the third natural JH (*15*).

At the present time there appear to be only three natural JH molecules, despite the variety of insects



JH I: R=R'=Et
JH II: R=Et, R'=Me
JH III: R=R'=Me

which has now been investigated in chemical detail. From the relatively primitive cockroaches and grasshoppers (*12*) to the more recently evolved moths, whose metamorphosis is considerably more complicated, the same three hormones appear to be the regulatory molecules.

Anti-Juvenile Hormones

Though the chemical structures of the JH represent relatively simple organic molecules, the effects of these hormones on immature insects are profound. In their total absence, a condition readily brought about by surgical removal of the corpora allata glands, precocious metamorphosis occurs leading larvae to molt prematurely into nonviable pupae. Though the results of this type of surgery have been known for several decades, the search for synthetic chemicals which induce premature metamorphosis has only recently been successful (G. B. Staal, personal communication), and a natural phytochemical antagonist of JH has been found (W. S. Bowers, personal communication).

Since the chemical induction of premature metamorphosis may have lethal effects on early larval insects, which are the major pests in crop agriculture, it is likely that the next decade will see considerable research and development in academic and industrial laboratories to this end. Small molecules which completely antagonize juvenile hormones, which are selectively cytotoxic to the endocrine organs, or which inhibit the unique biosynthetic pathway (*16*) to the JH could become very valuable in agriculture and pest control. Such chemicals would also be definable as IGRs, but their properties would show considerable advantages over the known JH-analog IGRs, since the latter have little if any practically useful effect on early-stage caterpillars. Nevertheless it appears that through the detailed study of the JH and of insect endocrinology will come the basic knowledge needed to design new chemicals for the selective control of early developing insects.

Properties of Methoprene

Chemical Properties

Chemical properties of methoprene have been reported (*1*), together with information on biological potency relative to natural JH and to several members of this class of chemicals. Chemical and physical properties are summarized in Table 1.

The properties of the stereoisomers of a related ethyl ester have been reported (*17*), and a general rule for this class is that the 2*E*,4*E* isomer (all *trans*) is the most biologically active of the four

Table 1. Properties of methoprene (Altosid IGR), isopropyl (2*E*,4*E*)-11 methoxy-3,7,11-trimethyl-2,4-dodecadienoate.

Property	
Empirical formula	$C_{19}H_{34}O_3$
Molecular weight	310
Physical state	Amber liquid (technical material)
Specific gravity (20°C)	0.9261 g/ml
Solubility	
Organic solvents	Soluble
Water	1.39 ppm
Vapor pressure	
At 25°C	2.37×10^{-5} mm Hg
At 40°C	1.60×10^{-4} mm Hg

isomers possible. Many approaches to the synthesis have been explored (*1,17,18*) but the method of choice is a stereoselective synthesis (*19,20*) involving the condensation of dialkyl 3-methylglutaconates with 7-methoxycitronellal, a key raw material for manufacture of methoprene. This raw material is in turn manufactured from the pinenes present in oil of turpentine. Curiosusly, 7-methoxycitronellal, used in the perfumery industry, is one of the earliest metabolites of methoprene in alfalfa.

Biological Properties

IGRs with JH activity have been reviewed in detail (*21*) from a biological viewpoint. Practical results are covered in this review and laboratory bioassay methods are detailed elsewhere (*22*). Perhaps more so than in other fields of pesticide research, large variations in insect biological activity are associated with small changes in chemical structure (*1*). High biological activity in one species of insect cannot be extrapolated to related families. This selectivity of action within the insects has been discussed (*21*) and appears to be a stumbling block to commercial development of IGRs.

Environmental Chemistry and Metabolism

A comprehensive study of the environmental fate of methoprene has been completed and reported in detail (*23–31*). Perhaps mainly as a consequence of the aquatic use pattern in the control of mosquito larvae, where many nontarget plants and organisms are also exposed, these studies have been unusually broad in scope. When methoprene first came to the attention of the EPA through petitions for registration of its use, it represented a completely novel active ingredient with a new mode of action relative to known insecticides, and understandably came under more than detailed scrutiny. One of the earliest indications that the study of metabolism of methoprene would be unusually complicated came from aerobic soil studies. Despite the placement of a carbon radiolabel in a central position at C-5 in methoprene, over 50% of the applied dose was converted to radiocarbon dioxide (*26*) at a surface treatment rate of 1 kg/ha. Although methoprene showed an initial half-life of about 10 days in soil, the only primary metabolite to be positively identified was the hydroxy ester resulting from *O*-demethylation of methoprene (0.7% of applied dose). Radioactivity also incorporated into humic acid, fulvic acid, and humin fractions of sandy loam, indicating rapid and extensive breakdown of methoprene in soils. These data were explained by catabolism of [5-^{14}C] methoprene to intermediary metabolites of normal biochemical pathways. In later studies of metabolism by a steer, it was shown (*28*) that C-5 of [5-^{14}C] methoprene is degraded to [2-^{14}C]acetate which incorporates into [$_{14}$C] cholesterol and other natural products. The formation of labeled acetate from methoprene by soil microorganisms may explain the incorporation of radioactivity into humic and fulvic acid fractions.

The serious complication referred to above is that multitudes of radiolabeled nonmetabolite products will in all likelihood be formed regardless of the position of radiolabel in methoprene. In these circumstances, study of the metabolism of the parent active ingredient and of its primary metabolites becomes exceedingly complicated, time consuming and expensive, because the molecule is highly biodegradable. Such biodegradability to natural products may be ideal for environmental acceptability and may significantly minimize human health effects, but may be a strong demotivating factor to the would-be developer of a regulated product. The problem centers around the regulatory agencies and the laboratories of the developers but no acceptable solution is in sight. Here is a clear need for a new approach to registration of biodegradable chemicals in general.

A partial solution could be for the metabolism chemist to focus attention in rat metabolism studies first on the isolation of natural intermediary metabolites such as acetate, amino acids, or Krebs cycle acids, and to assay these for radioactivity, having first placed a label in what would appear to be the least biologically accessible region of the IGR molecule. Such information, taken together with the usual balance of active ingredient in tissues and excreta, would give an early indication of the future complexity of a registration program. Similar studies rapidly carried out in cultures of primitive microorganisms for comparison would usefully add to this early profile of metabolic properties.

During studies on methoprene metabolism by alfalfa and rice (*23*), an unusual oxidative scission of the 4-ene double bond led to the principal nonpolar metabolite 7-methoxycitronellal, which was isolated from vapors evolved from the plants (13% of applied dose) when the equivalent of 1 lb/acre was applied. The major photochemical reaction (*25*) was the expected photoisomerization of 2-*trans* methoprene to the biologically inactive 2-*cis* isomer, reversibly. Surprisingly this

isomerization in the forward direction from 2-*trans* to 2-*cis* was found (*27*) to be an effective mode of insect detoxication in a study of metabolism of methoprene by houseflies and mosquitoes. Larvae of both mosquitoes and houseflies can effect biological isomerization but cannot rapidly isomerize the product 2-*cis* isomer back to the active 2-*trans*-methoprene. Since methoprene is an isopropyl ester, it appears unlikely that the isomerization in insects requires hydrolysis to the acid with later re-esterifications, but is more likely to be a direct isomerization. One possible mechanism could involve the reversible addition of a sulfhydryl residue on an enzyme, across the 2,3-double bond, with rotation about the 2,3-single bond of the intermediate.

Studies of methoprene metabolism in a lactating dairy cow (*30*) given a large single oral dose (465 mg) showed no detectable primary metabolites (<0.01 ppm) in milk, although 8% of the radioactivity appeared in milk. Since only 1% of this milk radioactivity was present in the trace of methoprene (0.015 ppm) an extensive analysis of the milk was completed (*30*) and revealed the now familiar array of radiolabeled natural products.

From numerous studies such as these it is clear that methoprene does not bioaccumulate and is nonpersistent; in fact, artificial prolongation of its persistence through microencapsulation formulation was necessary to achieve 4–7 days effectiveness in field use for mosquito control.

Residues

Predictably, residues of methoprene tend to be vanishingly small, and the development of comprehensive methods for determination of these residues posed considerable problems. These methods have been published in detail (*32*) and reviewed recently (*12*). Compounding the problem of low to nondetectable residues is the absence from methoprene of elements which would allow the use of selective element-sensitive detectors; further, its chromatographic properties are extremely similar to those of several natural products. The use of multiple ion detection programs in modern chromatography–mass spectrometry data-processing machinery (mass fragmentography) provided a partial solution to these problems (*33*).

Low residue levels (in the region of ppb) seem inevitable when the field use rate of 0.025 lb/acre for mosquito control is taken into account. This use rate corresponds to about 0.01 ppm in 1 acre-ft of water, and the LC_{95} for methoprene against yellow fever mosquitoes is approximately 0.001 ppm.

Use Patterns

Aspects of the mosquito use pattern have been discussed in detail by Staal (*21*), and the selectivity for target versus nontarget species has been reported by Miura and Takahashi to be excellent (*34*). Though the effects of methoprene are demonstrable on numerous insect species (*21*), the demonstration of such widespread effects requires remarkably high doses relative to the field use rate. Since the field use rate is mainly determined by economic considerations, the selectivity which methoprene exhibits in practical use reflects the fact that the molecule is basically much more active on dipteran insects than on several other orders of insects. At times this selectivity can be unfavorable, for example larvae of *Culex pipiens* are 10 times less sensitive than those of *Aedes aegypti* mosquitoes (*21*). This problem, added to the nonsynchronous nature of *Culex* populations, leads to a requirement for higher field use rates and more frequent applications which are economically unacceptable in present day mosquito abatement practice. The greater degree of synchronization in floodwater mosquitoes, their greater sensitivity to methoprene, the absence of larval damage by these species of insects and the urgent need for control of insecticide-resistant floodwater mosquitoes stimulated the selection of this use pattern for early registration, which was completed in 1975.

Toxicology

The toxicological properties of Altosid IGR technical, as summarized by the manufacturer, are listed in Table 2, and are discussed in more detail by Wright (*35*). Methoprene is a relatively nontoxic substance for which finite residue tolerances have been established (*3,4*).

Other IGRs

From several thousand candidate compounds a small number of IGRs have received considerable attention for possible development toward commercial use. Their field performance problems, and prospects in selective insect control have been reviewed recently (*36*). Though much has been written, only one IGR has been registered for use as of September 1975.

Table 2. Toxicological properties of methoprene (Altosid, technical).

Test	Effect
Acute oral toxicity	
Rat	LD_{50} > 34,500 mg/kg No deaths at highest single dose which could be administered.
Dog	LD_{50} = 5000–10,000 mg/kg
Subacute oral toxicity (dog and rat)	
500 ppm for 90 days	No toxic effect
5000 ppm for 90 days	No mortality, no irreversible deleterious effects
Primary skin and eye irritation (rabbit)	Nonirritating
Acute dermal toxicity (rabbit)	LD_{50} = 3000–10,000 mg/kg
Subacute dermal toxicity (rabbit)	
For 21 days at 400 mg/kg	No abnormal or toxic effects
Acute aerosol inhalation	
Rat and guinea pig	LC_{50} > 210 mg/1.
Subacute inhalation (rat)	
At 20 mg/1. for 21 days	No toxic effects
Three-generation reproduction	
Rats fed 2500 ppm	No toxic or reproductive effects, including mortality, pregnancy and fertility rates, food consumption values, length of gestation periods, offspring viability at parturition, offspring survival, litter survival, or sex ratios
Teratology studies (rat, rabbit)	
Rat, 1000 mg/kg to pregnant animals	No teratogenic effects
Rabbit, 500 mg/kg to pregnant animals	No teratogenic effects
Dominant lethal mutagenicity (rat)	
Single dose, 2000 mg/kg	No lethal mutagenic effects
Static fish toxicity studies	
Blue gill	TL_{50} = 4.62 ppm
Trout	TL_{50} = 4.39 ppm; TL_{50} (aerated water) = 106 ppm
Channel catfish	TL_{50} = 100 ppm
Coho salmon	TL_{50} = 32 ppm
Crustacean toxicity studies	
Crayfish, freshwater shrimp,	LC_{50} = 100 ppm
White and pink shrimp	LC_{50} = 100 ppm
Subacute oral feeding studies	
Mallard duck	LC_{50} >10,000 ppm
Bobwhite quail	LC_{50} = 10,000 ppm
Chicken	LC_{50} = 4640 ppm
Reproduction studies	
Bobwhite quail (30 ppm continuous feeding)	No effect
Mallard duck (30 ppm continuous feeding)	No effect
Mammalian hormone bioassay	
Mouse and rat	No estrogenic, androgenic, anabolic or glucocorticoid activity

Conclusion

Perhaps the only certain conclusion is that insects will continue to be devastating pests (*37*), but it is also clear that IGRs have devastating effects on their target insects (*21*). In contrast, the approved uses of methoprene appear to be environmentally harmless (*34*), and the fact that it is technically feasible to achieve this goal is encouraging. However, it has been pointed out emphatically (*38*) that unless major changes occur in regulatory and governmental policy, few if any improvements are likely. The multimillion dollar investment without which the discovery and development of significantly improved pesticides is impossible carries no guarantee of a return. Corbett (*39*) concluded that "there are no biochemical reasons to suggest that such improvement is impossible," and the ball appears to be in the legislative court.

Acknowledgement

I am deeply grateful to the people of Zoecon Corporation whose work and ideas made this contribution possible, and to Mrs. Carmen Schubert for help in typing the manuscript.

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