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Quantitative Genetic Tools for Insecticide Resistance Risk Assessment: Estimating the Heritability of Resistance

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ABSTRACT Quantitative genetic studies of resistance can provide estimates of genetic parameters not available with other types of genetic analyses. Three methods are discussed for estimating the amount of additive genetic variation in resistance to individual insecticides and subsequent estimation of the heritability (h^2) of resistance. Sibling analysis and offspring–parent regression permit direct estimates of h^2 by comparing the resistance phenotypes of individuals of known relatedness. Threshold trait analyses, performed on data from selection experiments, provide estimates of realized heritability. Procedures are outlined for predicting changes in resistance to insecticides based on h^2 estimates. Quantitative genetic theory is examined as it relates to resistance and resistance as a quantitative trait; quantitative genetic methods also are unique in providing estimates of genetic correlations between traits. Comments are included on estimates of genetic correlation between resistance and phenotypic traits (e.g., development time) and how they may be used to predict changes in the genetic aspects of phenology that result from insecticide applications (i.e., to predict how the reproductive capacity of future generations will differ from that of the treated generation).

KEY WORDS Insecta, sibling analysis, offspring–parent regression, threshold trait analysis

RESISTANCE OF INSECTS to insecticides is an urgent problem. Various species of pests are developing resistance to new pyrethroids (Martinez-Carrillo & Reynolds 1983, Jensen et al. 1984, Luttrell et al. 1987, Payne et al. 1988, Schouest & Miller 1988). Efforts to manage pest populations and our ability to predict changes caused by resistance have been limited by our understanding of the genetics of insecticide resistance (Plapp 1976, Taylor 1983, Roush & McKenzie 1987). Accurate prediction of the dynamics of change as susceptible populations become resistant has been especially difficult. Recent efforts by Taylor (1983), Georghiou & Taylor (1986), May & Dobson (1986), Tabashnik (1986, 1987), Roush & Croft (1986), and others (reviewed by Roush & McKenzie [1987]) have increased the accuracy of resistance predictions by the application of population genetic models. However, the resolution of these models is limited by the assumption that resistance is a single-gene trait; many resistance systems cannot be modeled adequately under this assumption. Even when the action of a single major gene has been demonstrated, unexplained genetic variation that is assumed to result from the action of modifier loci is usually present (i.e., the system is polygenic).

Here, we outline a quantitative genetic approach that makes no assumptions regarding the number of genes involved. The expression of quantitative traits depends on environmental factors as well as the actions of one or more genes, each with one or more alleles. These methods are, therefore, appropriate regardless of inheritance mechanism. In particular, resistance systems that depend on the action of a single major gene acting under the influence of minor factors are amenable to quantitative genetic analysis.

Estimation of heritability and genetic correlation with quantitative genetic methods provides the means to predict the direction and extent of genetic change in selected traits and traits that are correlated genetically with the selected trait. In resistance studies, quantitative genetics provides the means to predict the speed and potential amount of genetic change involved in resistance and the direction, speed, and extent of genetic change in correlated fitness traits. Certain theoretical implications of quantitative genetic models for resistance management have been noted recently (Holloway 1986, Via 1986), but only a few studies have estimated heritability of resistance in experimental populations (Ferrari et al. 1982, Wolfenbarger et

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al. 1982, Holloway 1986, Tabashnik & Cushing 1989).

Theoretical Background. Quantitative genetic methods are used to partition phenotypic variation into environmental and genetic components; these methods are appropriate for studies of various traits that deviate from Mendelian inheritance patterns, including monogenic traits that are affected by environmental factors. The analyses are most powerful, however, when performed on quantitative traits whose phenotypic expression is not limited to one or two classes but which can assume several values. Quantitative variables can be analyzed using offspring–parent regression or sibling analysis to estimate the contribution of genetic factors to phenotypic expression; these methods also provide direct estimates of genetic correlations between pairs of traits. For threshold traits, which vary in a discontinuous manner but are not inherited in a simple Mendelian manner (Hartl 1988, Falconer 1989), realized heritability can be estimated from selection experiments, but genetic correlations cannot be estimated directly. Thus, quantitative genetic methods provide the means to estimate the proportion of resistance variation within a population that is genetically based and to make informed predictions about changes in resistance and associated traits.

Insecticide applications impose selection, and continued effectiveness of an insecticide depends not only on the strength of that selection but also on the pest population's genetic ability to respond to the selection pressures. Ability of the population to respond across generations is critically dependent upon the amount of additive genetic variation (V_A) in resistance within the population (Hartl 1988, Falconer 1989). Defined by the equation $V_P = V_A + V_D + V_I + V_E$, V_A is the heritable portion of the total phenotypic variation (V_P) in a population. V_A excludes environmentally induced variation (V_E), including behavioral variation and maternal effects, and the nonadditive genetic effects of dominance (V_D) and epistasis (V_I) (Falconer 1989). Because expression of resistance is affected by all of these factors, separating V_A from the other components of variation is critical to predictions of the proportion of the next generation that is likely to be resistant.

A susceptible population cannot become resistant to a particular insecticide unless its resistance to that insecticide includes an additive genetic component. The insecticide itself, acting as selective agent, promotes development of population resistance (Roush & McKenzie 1987). Quantitative genetic theory provides an explanation for certain observed patterns of resistance development (Holloway 1986). Before exposure to a particular insecticide, or early in the selection process, genotypes conveying some level of resistance may be so rare that they are difficult to detect. When applications begin, insecticide concentrations are relatively low, selection for resistant genotypes is relatively weak, and the magnitude of V_A changes slowly from one generation to the next while resistant genotypes are still rare. The process by which population resistance develops consists largely of a reduction in V_A as insecticide applications increase in frequency and concentration, and only the most resistant genotypes survive. This pattern of initially slow increase in frequency of resistance, followed by rapid attainment of population resistance, has been observed in both field and laboratory studies (Brown & Payne 1988). Monitoring changes in the amount of V_A in resistance within a population provides a unique and powerful predictive tool: knowledge of future evolutionary potential.

Estimates of V_A are usually reported as the heritability (h^2) of the trait in a narrow sense; i.e., a population parameter defined as that proportion of the total phenotypic variation in a trait that is additive genetic variation (Falconer 1989):

$$h^2 = V_A/V_P \qquad (1)$$

Heritability estimates refer specifically to the degree to which a trait is passed from one generation to the next. Heritability (H^2) of a trait in a broad sense represents that portion of the total phenotypic variation in a trait that is genetically based and includes additive, dominance, and epistatic variance. The usefulness of H^2 is limited because nonadditive forms of genetic variation are included (Falconer 1989). Hereafter, we use heritability to refer to h^2.

When two traits are genetically correlated, selection on either will cause genetic change in both (Lande 1982). For example, if the genetic correlation between fecundity and resistance is negative, insects that survive insecticide application will have reproductively inferior genotypes. If the correlation is positive, insecticide applications will select for individuals that are genetically both resistant and fecund (e.g., Holloway 1986). Genetic correlations between traits of juveniles (e.g., developmental rate) and adult resistance level can also be estimated.

Resistance as a Quantitative Trait: Tolerance. Individuals or populations have been classified as either susceptible or resistant to a particular insecticide. However, actual responses of individuals grouped in this manner vary considerably (e.g., Whitten 1978, Roush & Wolfenbarger 1985, Payne et al. 1988, Tabashnik & Cushing 1989). Treating resistance as a quantitative variable allows differentiation among degrees of response rather than imposition of simplistic categories (i.e., dead or alive). Simple binomial classification of response is a major feature of simple probit analysis, which was designed specifically to allow the use of parametric statistics (regression) on a quantitative variable that is recorded as though it were categorical (Finney 1971, Sokal & Rohlf 1981).

To differentiate between categorical and quantitative measures of resistance, we use the term tolerance (in the sense of Finney [1971]) to refer

to a quantitative measure of resistance that is normally distributed among individuals within a population. The range of tolerance values, therefore, includes the most susceptible and the most tolerant individuals, the latter of which may be considered resistant. We use "resistant" to refer to individuals or populations that are apparently unaffected by the insecticide in question, to be consistent with authors of cited works, or when discussing resistance as a threshold trait.

When dose–mortality relationships are presented as frequency distributions of tolerance phenotypes, the result is a continuous, bell-shaped curve (Finney 1971, Via 1986, Tabashnik & Cushing 1989). For example, we converted probit data from empirically derived dose–mortality curves (Payne et al. 1988, Fig. 2A) into a frequency histogram of tolerance phenotypes (Fig. 1). The published probit lines were used to estimate percentage of kill in each dose interval. Data from the probit lines intended to represent three distinct genotypes (RR, RS, SS) were pooled to represent the range of tolerance values within the population (the backcross data were not included because they represent assortative mating of only one of six types). We used each of the three groups included in our analysis (S, R, and F_1) to represent one third of the population. Had the probit lines not overlapped, three distinct distributions would have resulted (Via 1986). However, Fig. 1 shows that tolerance variation in this population is continuous and normally distributed. This pattern is characteristic of a quantitative trait.

Although most dose–response data are truncated (i.e., the distribution stops at the highest dose tested), the curve can be assumed to continue as the most tolerant individuals are killed by doses above the highest dose tested. In general, a small proportion of most populations is either very tolerant or very susceptible, whereas the tolerance of most individuals is intermediate (e.g., Meyer et al. 1987). Although some tolerance variation is environmentally induced, some also results from the variety of genetically distinct physiological and behavioral mechanisms that contribute to an individual's tolerance phenotype (Crow 1957; Plapp 1976, 1986; Strickberger 1976; Plapp et al. 1979; Liu et al. 1981; Plapp & Wang 1983; Tsukamoto 1983; Georghiou & Taylor 1986; Raymond et al. 1987; Wilson & Thurston 1988).

Most attempts to describe the transmission genetics of resistance in simple terms have proven unsatisfactory: resistance is seldom inherited in simple Mendelian fashion. Even when the action of a single major gene is observed, additional variation that cannot adequately be attributed to environmental factors usually exists. Although inheritance patterns for resistance seldom fit a Mendelian model, they are often ascribed simple Mendelian inheritance mechanisms with qualifiers such as "incompletely recessive" (Roush & Luttrell 1987, Payne et al. 1988), "incompletely dominant"

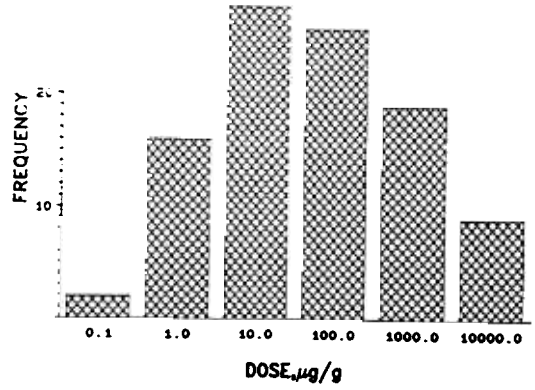

Fig. 1. Frequency distribution of tolerance phenotypes showing frequency of individuals that died in each dosage interval. See text for plotting criteria.

(Whitten 1978, Roush & Wolfenbarger 1985), or "nearly completely dominant" (Roush & Plapp 1982). The frequency with which these qualifying descriptions are used to describe inheritance patterns of resistance is inconsistent with genetic theory (Holloway 1986). Lack of fit to Mendelian inheritance patterns usually implies the existence of underlying genetic factors (e.g., modifier loci). By interpreting these types of data as evidence for monogenic resistance, much of the observed resistance variation is left unexplained. In laboratory studies in which environmentally induced variation is minimized, variation over two or three orders of magnitude suggests the presence of genetic variation within "genotypes." If observed genetic variation in resistance cannot be explained by the action of a single gene, such as when a major gene acts under the influence of one or more minor genes (e.g., Halliday & Georghiou 1985, Roush et al. 1986), resistance is, by definition, polygenic. Such systems may be modeled more accurately with quantitative measures of resistance (i.e., tolerance).

Roush & McKenzie (1987) argued that the common finding of polygenic resistance is largely a laboratory phenomenon resulting from selection regimes peculiar to laboratory experiments. Although this may help explain some forms of laboratory-generated resistance such as gene amplification (Mouches et al. 1986), the argument assumes that laboratory selection precedes genetic analysis. Such an assumption is not valid when polygenic resistance is found in field-collected insects (e.g., Liu et al. 1981). When polygenic resistance is evident in a wild population, genetic models that incorporate polygenic effects will predict genetic change most accurately.

Regardless of whether resistance to an insecticide results primarily from the action of a single major gene or from many interacting genes, the system is amenable to quantitative genetic analysis. Although the genetic basis of resistance is pertinent to any examination of the evolution of resistance,

quantitative genetic analyses are advantageous because they require no assumptions concerning the number of loci affecting the expression of resistance.

Roush & McKenzie's (1987) caution concerning inferences drawn from laboratory assessments of resistance also pertains to quantitative genetic estimates. Resistance levels measured in the laboratory are specific to laboratory conditions and may suffer from a lack of correspondence with field resistance. High levels of environmental variation in field situations affect the predictive power of h^2 estimates because some insects that are genotypically of low resistance will survive as a result of environmental factors (e.g., large size, avoidance), leading to an overestimation of V_A in the laboratory. However, Roush & Luttrell (1987) note that such problems can be minimized with appropriate experimental design.

Quantifying Resistance. In most resistance studies, individuals are classified as either alive or dead at a specified time following treatment. However, resistance is a continuous variable that interacts with the environment and is quantifiable. Finney (1971) noted the difficulty of measuring the exact dose needed to kill different individuals in a population, but alternative methods of quantification exist. Cohan & Graf (1985) and Holloway (1986) quantified time to knockdown allowing differentiation between individuals that died immediately and those that were more tolerant, survived for a period of time, then died. Wolfenbarger et al. (1982) and Tabashnik & Cushing (1989) quantified resistance variation by comparing percentage mortality among families.

No standard criterion for death is used in resistance studies; usually, some portion of the insects that are classified as dead are actually still alive at the time of observation. A variety of adverse responses to treatment with insecticide can be distinguished (e.g., Roush & Wolfenbarger 1985, Luttrell et al. 1987, Hoy et al. 1988) and can be used as indicators of the tolerance level of individuals (unpublished data). Other quantifiable parameters include sublethal effects such as reduced fecundity (Roush & Plapp 1982, Haynes 1988, Rosenheim & Hoy 1988) or impaired host-finding and feeding behavior (Haynes 1988).

When resistance is quantified, the choices of dose, type of observation, and observation schedules are critical because they determine the shape of the frequency distribution of tolerance phenotypes. The parametric statistics of quantitative genetic analyses (e.g., regression, analysis of variance [ANOVA]) assume that groups of data are normally distributed, can be normalized with transformations, or are assumed to have an underlying normal distribution. Doses that are too high could result in clumping at the bottom of the distribution, whereas low doses could result in many individuals being classified as unaffected and clumping at the upper portion of the distribution.

Methods

Breeding Design and Calculation of Heritability. The complete theoretical background and exact formulas needed to estimate genetic parameters are too lengthy to be given here and can be found in Becker (1984) and Falconer (1989). Other helpful sources include Kempthorne (1973), Mather & Jinks (1977), Bulmer (1980), and Hartl (1988). Quantitative genetic methods and analyses are constantly being refined and becoming more sophisticated. While the three basic methods of estimating genetic parameters described here are well established, current literature offers a variety of refinements and caveats which are not given in detail here (Via 1984a,b, 1988; Via & Lande 1985; Shaw 1987; Groeters 1988).

Quantitative genetic methods are the only means to obtain estimates of V_A, h^2, and genetic correlations between traits; they suffer, however, from two shortcomings. First, estimates of genetic parameters are specific to the conditions under which they were made (Falconer 1989). More advanced quantitative genetic models that consider gene–environment interactions (Via & Lande 1985, Via 1986) may be helpful in this regard. Via (1986) considered theoretical implications to resistance changes in populations that experience simultaneous selection from multiple insecticides. The second shortcoming is that estimates of quantitative genetic parameters usually have large standard errors associated with them and require large sample sizes to be meaningful.

Offspring–Parent Regression. In offspring–parent regression, estimation of heritability of tolerance is based on the degree of similarity between parents and their offspring. Data are grouped into pairs with tolerance of one offspring (or average of several offspring) serving as the dependent variable, and tolerance of one parent (or average of two parents, the midparent) serving as the independent variable. The assumptions of linear regression require that both variables be quantitative (Sokal & Rohlf 1981). Results from techniques that violate this assumption (e.g., Im & Gianola 1988) should be interpreted cautiously. When resistance is treated as a quantitative trait, estimates of covariation between parents and offspring are precise.

Virgin animals of any stage are collected from the natural population and mated to produce the parent generation that is reared and mated in single pairs. To obtain an unbiased sample of genotypes and to ensure that susceptible genotypes are represented, parents should be mated before their tolerance phenotypes are determined. Following oviposition, parental tolerance is measured (from which the mean tolerance level of the population is determined) and used as the independent variable in the offspring–parent regression. Offspring are reared, and offspring tolerance levels are used as the dependent variable in the regression. When the

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Sibling Analysis. In sibling analysis, variation within and between families of offspring resulting from single-pair matings is compared (Holloway 1986). Phenotypic variation is partitioned into its environmental and genetic components with ANOVA and is based on phenotypic covariation among individuals of known relatedness (Falconer 1989). Typically, a single male (sire) is used to inseminate one or more females (dams). If each sire mates with a single dam, only full-sib females are produced, and the genetic information obtained is limited because dams may affect the quality of their offspring in ways that are nonheritable. Full sibs may resemble each other because they experienced a common environment, maternal effects, or dominance effects (Falconer 1989).

Multiple matings by each sire are desirable so that both full- and half-sib families are produced. Families are compared by nested ANOVA (dams within sires). The sire component of variation, which results from comparisons among half-sib families, includes only V_A effects because nonadditive variation is removed with the dam component. Tests for significance of the sire component are made using the mean square of the dam effect as the error term in the F ratio.

Parental phenotypes need not be determined because estimates of h^2 and genetic correlation are based on degree of similarity among siblings. Virgin animals of any stage can be collected and mated to produce the experimental cohort. Heritability of tolerance for any life stage can be estimated. Estimates of genetic correlation between tolerance and reproductive traits are limited to adult tolerance; toxicity tests on earlier stages would kill some individuals, would violate the assumption of no selection during the experiment (Becker 1984), and would bias further genetic estimates.

Production of half-sibs presents problems for species whose mating behavior makes it difficult or impossible to obtain successful matings from multiply mated sires. In species that allow only the production of full-sib families, genetic parameters can be estimated, but they are less precise because nonadditive effects are included in family means.

Threshold Trait Analysis. When individuals are classified as either resistant or susceptible (or as dead or alive following treatment with insecticide), resistance is being treated as a threshold trait. With the appropriate experimental design, quantitative genetic analysis can be performed. Threshold trait analysis provides an estimate of realized heritability which is based on actual response to selection from one generation to the next and describes effectiveness of a selection experiment (Hartl 1988).

Various techniques can be used for threshold trait analysis. Ferrari et al. (1982) and Wolfenbarger et al. (1982) estimated realized heritability of resistance, and Ferrari et al. (1982) indirectly estimated genetic correlations between resistance to various insecticides (genetic cross resistance) by comparing correlated and direct responses to selection. Cohan & Graf (1985) used a form of Equation 3 (see below) to estimate realized heritabilities following selection for knockdown resistance to ethanol fumes in *Drosophila melanogaster* L. Tabashnik & Cushing (1989) described an innovative technique using full-sibling analysis to investigate threshold resistance to fenvalerate in *Plutella xylostella* (L.); they estimated H^2 by comparing percentage mortality among full-sib families.

When threshold trait analysis follows selection experiments, the proportion of resistant individuals in the population before mating (and before insecticide is applied) is compared with the proportion of resistant individuals in the generation after insecticide application. Here, estimates of realized heritability are made with Equation 2:

$$h^2 = 2\mu'/\mu, \qquad (2)$$

where μ, represents the mean tolerance level of the parents that survived the insecticide application and reproduced, and μ' represents the mean tolerance in the next generation (Hartl 1988). Because resistance levels are not actually quantified, μ' and μ, are derived variables. Hartl (1988) provides formulas needed to derive μ' (based on the assumption that tolerance phenotypes are normally distributed) and μ, by providing their numerical relationship with a measurable variable; i.e., the proportion of the population that is resistant to the experimental dose.

Regardless of whether threshold trait analysis is based on field applications or on laboratory selection, an unbiased estimate of population tolerance levels in the parent generation must be made before selection. Then, resistance selection is applied before mating begins to ensure premating selection of the reproductive cohort.

Strength of selection in the experiment is determined by choice of insecticide dose, for which no strict guidelines exist. Doses should be high enough to ensure that only the more tolerant individuals survive to reproduce but weak enough to ensure a reproductive cohort of reasonable size. Once the proportion of the population that is resistant to the experimental dose is determined, insecticide is applied, and mass mating is allowed to proceed. The actual proportion that survive to reproduce is measured and used to estimate μ, and strength of selection (see below). When the next generation is produced, the proportion of individuals resistant to the original experimental dose is determined and used to estimate μ'. As with sibling analysis, threshold trait analysis is not limited to analysis of adult

resistance because any life stage can be tested, but selection must occur before mating.

Choice of Method. Threshold trait analysis (as a laboratory method) is the easiest to do, requires no single-pair matings, and can be conducted on any life stage. Although genetic correlations between resistance and other traits cannot be estimated directly, threshold trait analysis coupled with selection experiments has two distinct advantages: it is the only method of the three that can be based on field experiments, and genetic correlations between resistance to different insecticides can be estimated (Ferrari et al. 1982).

The single-pair matings in offspring–parent regression (and threshold trait analysis as performed by Tabashnik & Cushing [1989]) add complexity to the experimental design, but families of known parentage provide more precise estimates of heritability. With offspring–parent regression, the increased effort provides estimates of genetic correlations. Breeding design and statistical analyses are less complex than in sibling analysis, but offspring–parent regression requires that two generations be analyzed, and estimates could be biased by variation between generations. Although offspring–parent regression is limited to analysis of adult tolerance, Tabashnik et al. (1988) investigated the relationship between larval and adult resistance and found strong correlations. Similar findings could be used to support inferences about heritability of larval tolerance based on toxicity tests on adults.

Sibling analysis requires the most complex breeding design and statistical analyses. Resulting estimates of h^2 and genetic correlations are direct and are not confounded by variation between generations. Heritability of tolerance at any life stage can be estimated; the limiting factor is the necessity to produce half-sib families, which may preclude sibling analysis for some species.

Risk Predictions Using Heritability Estimates. Various prediction equations, each specific to a particular type of selection (Hartl 1988, Falconer 1989), can be used in quantitative genetics. Insecticide application acts as individual selection, also known as truncation selection. The corresponding prediction equation is

$$R = (h^2)S. \quad (3)$$

Here, R (response to selection) is the predicted change from one generation to the next in the population mean as a result of selection. S (selection differential) is the mean deviation of the breeding population from the population mean. S is defined by

$$S = \mu_s - \mu, \quad (4)$$

where μ is the population mean before selection. A form of Equation 3 was given by Via (1986) as

$$\text{change in } LD_{50} = (V_A/V_P)S. \quad (5)$$

Because it is specific to the mean tolerance level of individuals in a population, we propose use of Equation 6

$$\text{change in } T = h^2S \quad (6)$$

with

$$S = T_s - T \quad (7)$$

where T is the mean tolerance level in the population before insecticide application, and T_s is the mean tolerance of individuals that survive the insecticide to produce the next generation.

With an estimate of h^2 made in the laboratory, various values of T_s can be substituted in Equation 6 to predict the mean tolerance level in the generation following insecticide application. R is then added to T to predict T', the population mean in the next generation (Equation 8):

$$T' = R + T \quad (8)$$

For either offspring–parent regression or sibling analysis, Equations 6 and 8 can be used in at least two ways. First, predicted responses of the population (in terms of future tolerance levels) treated with insecticide applications of various strengths can be compared. Combined with information about expected control levels (an estimate of S), this approach could be used to optimize degree of control and genetic change in population tolerance levels. Insecticide applications of reduced strength reduce selection pressure (Taylor & Georghiou 1982, Tabashnik & Croft 1982, Roush & McKenzie 1987) and may delay the establishment of completely resistant populations. Comparison of the effects of various levels of selection is made by choosing groups of parents from the data set to represent survivors of insecticide applications of various strengths and juxtaposing the predicted changes in population tolerance. Second, Equation 6 can be used to predict tolerance levels in the next generation, after the effectiveness of an insecticide application has been determined.

Population genetic parameters change with time. Changes caused by natural processes usually are small enough from one generation to the next that estimates of h^2 and genetic correlation are reliable for several generations (Falconer 1989, Hartl 1980). However, insecticide applications that kill a large proportion of a pest population may alter population genetic structure more quickly. To maximize accuracy, regardless of the method used, h^2 of tolerance and genetic correlations should be reestimated after major selection events.

Conclusions

Quantitative genetic methods provide a means to estimate the amount of tolerance variation within a population that is heritable. With this knowledge, predictions concerning the evolution of resistance within pest populations can be refined. These methods are unique because they provide

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estimates of genetic correlations between tolerance and other traits. These estimates allow predictions to be made about the direction and speed of changes in population dynamics following selection imposed by insecticide applications.

Quantification of resistance to insecticides has several advantages. When resistance is treated as a quantitative variable (tolerance), its relationship with other quantitative traits (e.g., weight, age) can be analyzed with a variety of statistics not applicable when individuals are scored as either dead or alive. For example, relationships between weight and tolerance can be analyzed by regression techniques (unpublished data), ANOVA can be used to test for interactions between dose and weight, and temporal toxicity patterns can be investigated by quantifying resistance at time intervals.

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ABSTRACT
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