Evolution of Pesticide Resistance: Interactions Between Generation Time and Genetic, Ecological, and Operational Factors

JAY A. ROSENHEIM[1] AND BRUCE E. TABASHNIK

Department of Entomology, University of Hawaii, Honolulu, Hawaii 96822

J. Econ. Entomol. 83(4): 1184–1193 (1990)

ABSTRACT We used computer simulation modeling to clarify the relationship between generation time and the rate of evolution of pesticide resistance. We examined the influence of generation time under various assumptions about genetics, population dynamics, and selection pressures. The simplest model demonstrated that the time required for resistance to evolve can be independent of generation time. However, interactions of generation time with genetic, biological, and operational factors resulted in positive, negative, and U-shaped relationships between the number of generations per year and the time required for resistance to evolve. These results preclude any generalizations concerning the influence of generation time on resistance evolution. Some ability to predict the influence of generation time may still exist on a case-by-case basis if the context of the resistance episode can be specified.

KEY WORDS Insecta, pesticide resistance, generation time, resistance risk assessment

EVOLUTION OF PESTICIDE RESISTANCE in arthropod pests is an obstacle to chemical suppression of pest populations, with serious repercussions for world agriculture and human health (National Research Council 1986). Pesticide resistance can also provide insights into basic evolutionary processes. However, resistance evolution is extremely complex. Empirical and theoretical analyses have yielded few broadly applicable insights into resistance evolution. Instead, many factors may influence resistance evolution in important ways, and the effect of a given factor may vary dramatically in different contexts (e.g., Tabashnik & Croft 1982). The ability to quantify the future risk of resistance development has been suggested as a crucial component of successful pesticide resistance management (Brattsten et al. 1986, Dover & Croft 1986, Keiding 1986, National Research Council 1986); yet, this ability remains elusive (Delp 1986, Leeper et al. 1986, Rosenheim et al. in press).

One of the few factors that was thought to influence resistance evolution in a strong and consistent manner is the number of generations per year (GPY). Previous empirical and theoretical analyses uniformly supported a positive linear relationship between GPY and the rate of resistance evolution (Comins 1979; Georghiou 1980; Tabashnik & Croft 1982, 1985; May & Dobson 1986). However, in a recent survey of resistance evolution in 682 North American arthropod pests, we found no significant linear relationship between GPY and the documented development of resistance (Rosenheim & Tabashnik in press; one possible exception was noted for pests of pome fruits). Furthermore, a reappraisal of analytical and computer simulation models of resistance evolution suggested no theoretical foundation for a linear relationship between GPY and resistance evolution. Instead, an extension of May & Dobson's (1986) simplest-case analytical model suggested that the rate of resistance evolution was independent of generation time (Rosenheim & Tabashnik in press).

This simplest-case model, however, represents only a crude abstraction of the process of resistance evolution; details of the genetics of resistance, the population dynamics of the pest, and the pesticide-induced mortality were ignored. Furthermore, our empirical analysis revealed a highly variable but significant curvilinear relationship between GPY and resistance evolution; species with intermediate GPY values (3.5–10.5; n = 111 species) showed maximal abilities to evolve resistance. Therefore, GPY did appear to exert some influence on resistance evolution (Rosenheim & Tabashnik in press).

Here we used computer simulation modeling to investigate the influence of generation time on the rate of resistance evolution in more detail. As did Tabashnik & Croft (1982), we examined resistance evolution under a variety of assumptions concerning pest biology and pesticide selection pressures. We also used basic genetic theory to explore influences of GPY not amenable to testing with the simulation model.

Materials and Methods

We used the resistance simulation model developed by Tabashnik (1986a,b; see also Tabashnik & Croft 1982, 1985; Mason et al. 1989). This model includes population age structure, with daily tran-

[1] Current address: Department of Entomology, The Hebrew University of Jerusalem, P.O. Box 12, Rehovot 76-100, Israel.

0022-0493/90/1184–1193$02.00/0 © 1990 Entomological Society of America

sition probabilities between successive developmental substages determined by species development rate and natural and pesticide mortalities. We sought to demonstrate clearly the functional relationships between generation time and resistance evolution, rather than to mimic the details of resistance evolution for any specific insect. We therefore selected parameters for our simplest-case model to simplify the dynamics of the simulation. In the remaining simulations, we examined the effects of varying the values of key parameters.

Basic Biology. Time was measured using a 365-d calendar year. Insect development and pesticide applications were halted during a 125-d winter, leaving a 240-d active season.

The life cycle of our hypothetical insect was divided into 20 developmental substages, with five substages each for eggs, larvae, pupae, and adults. We altered GPY by changing the duration of each substage. We examined six values for the duration of each substage: 12, 6, 3, 1.5, 0.75, and 0.375 d. These development rates produced six values for GPY: 1.1, 2.2, 4.5, 9, 18, and 36, respectively. Values for GPY were calculated by dividing the 240-d active season by the cohort generation time, defined as the time from the egg stage (birth) to the mean age of reproduction. Because we assumed a 240-d active season for all species, the duration of a single generation was exactly inversely related to GPY.

Survival of each substage in the absence of pesticides was 0.90 for egg, pupal, and adult substages. Larval survival (LSURV) was density dependent. If the total number of larvae (TLARV) was $<10^5$, LSURV = 0.90; if TLARV $\geq 10^5$, LSURV = $0.90[1 - (TLARV/10^6)]$, with LSURV constrained to be ≥ 0.10. No adults survived past substage 20. Overwintering survivorship was 0.5 for all substages (Tabashnik & Croft 1985).

A 1:1 sex ratio was assumed at adult emergence. Random mating occurred during the first adult substage, and females produced 10 eggs per adult substage.

Resistance Genetics and Pesticide Mortality. Resistance was assumed to be controlled by one locus with a resistant allele, R, and a susceptible allele, S. To simplify the model, we assumed that SS individuals died at doses ≥ 0.001, RS individuals at doses ≥ 0.01, and RR individuals at doses ≥ 0.1 (units arbitrary). Two doses were tested: a low dose (0.004), which killed SS individuals only (resistance functionally dominant), and a high dose (0.04), which killed SS and RS individuals (resistance functionally recessive). Unless noted otherwise, simulations assumed low pesticide doses. We tested two kinds of pesticide applications, those killing larvae only and those killing individuals in all life stages. Unless noted otherwise, pesticide applications killed all life stages. To reflect incomplete field coverage, 10% of individuals in treated life stages escaped contact with pesticides on each day. We tested four calendar-based pesticide application schedules: 1 spray per year (day 120), 3 sprays per year (days 60, 120, and 180), 7 sprays per year (days 30, 60, 90, 120, 150, 180, and 210), and 14 sprays per year (every 15 d, day 15–210). We also investigated the effect of basing the decision to spray on an economic threshold. Sprays were applied on any of days 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, and 200 if there were $\geq 10^5$ larvae present. Pesticide residues decayed either immediately, such that mortality occurred only on the day of application, or decayed exponentially with half-lives of 3.5 or 7.0 d. Unless noted otherwise, simulations assumed immediate residue degradation.

Gene Flow. We examined the effects of immigration from an untreated population whose R allele frequency remained fixed at 0.0001. Immigrants arrived after daily pesticide mortality was computed, and therefore had at least one day to mate and reproduce before pesticide exposure. Two types of immigration were examined. In the first, the rate of immigration was independent of generation time; immigration rates of 1 and 10 adults per day were tested. In the second, a mandatory dispersal phase was assumed to be associated with adult eclosion. We therefore tested the effect of 2,400 migrants per generation. Unless noted otherwise, we assumed no immigration.

Fitnesses in the Absence of Pesticides. We tested three levels of reproductive disadvantage for resistant females in the absence of pesticides: none, moderate, and severe. For a moderate disadvantage, the relative fitnesses of SS, RS, and RR females were 1.00, 0.90, and 0.81, respectively. The number of eggs produced by each female was calculated as the female's fitness value times the oviposition rate of SS females (10 eggs per adult substage). Under a severe reproductive disadvantage, the relative fitness values of SS, RS, and RR females were 1.0, 0.7, and 0.49, respectively. We assumed that genotype had no effect on development rate. We also used the untested assumption that the costs of resistance are constant across species with different generation times. Unless noted otherwise, there were no reproductive disadvantages for resistance genotypes.

Initial Conditions and Criteria for Resistance. For all simulations the initial population consisted of 10^5 individuals with an R allele frequency of 0.0001. The initial age structure of the population (65% eggs, 25% larvae, 6% pupae, and 4% adults) approximated a stable age distribution. The simulation was run until one of two criteria for resistance was reached. The genetic criterion for resistance was met when the frequency of the R allele exceeded 0.5. The operational criterion was met when the genetic criterion was met and the larval population density exceeded the economic threshold of 10^5; these are conditions under which control failures would be expected in the field. Unless noted otherwise, we used the genetic criterion for resistance.

List 1. Key assumptions of the simplest-case simulation model of resistance evolution, which predicts that the time to resistance is independent of generation time

1. Frequency of sprays is ≤ frequency of genotype reconstitution.
2. Low pesticide dose (only SS individuals are killed).
3. No fitness costs of resistance in the absence of pesticides.
4. Population closed to immigration.
5. All life stages exposed and susceptible to pesticides.
6. Immediate breakdown of pesticide residues.
7. Genetic criterion for resistance.

Results and Discussion

Simplest-Case Model. The simplest-case simulation model, the assumptions of which are summarized in List 1, predicts that the time to evolve resistance is independent of generation time (Fig. 1). This result agrees with the prediction of our previous analytical model of resistance evolution (Rosenheim & Tabashnik in press). Below we consider how generation time can interact with genetic and population dynamical processes when assumptions of our simplest-case model (List 1) are relaxed.

Genetic Factors: Frequency of Genotype Reconstitution. Most insects reproduce sexually. Each generation, diploid parental genotypes are broken down by meiosis into haploid gametes and then, assuming random mating, are randomly reassembled by fertilization into new diploid genotypes following the Hardy-Weinberg law. Barring the occurrence of natural selection, this process will not alter allelic frequencies but can alter genotypic frequencies. Because selection acts on phenotypes produced by alleles in diploid genotypes, and not on allelic frequencies themselves, the frequency with which diploid genotypes are reconstituted from haploid gametes can affect the rate of resistance evolution. The frequency of genotype reconstitution in a given evolutionary lineage is equal to the frequency of generation turnover.

The effect of genotype reconstitution on the rate of resistance evolution is very slight when low pesticide doses are applied (Fig. 2). Low doses do not kill RS individuals; S alleles in heterozygotes are therefore shielded from the effects of selection. Genotype reconstitution can, however, move the shielded S allele into a SS homozygote, reestablishing selection pressures. If the frequency of sprays exceeds the frequency of genotype reconstitution, a given RS individual will experience more than one spray, decreasing the intensity of selection against S alleles compared with the case where genotypes are reconstituted at least once following each spray. Thus, resistance evolves less rapidly when generation turnover is slow relative to the frequency of sprays (Fig. 2). This effect is very subtle. Time to resistance is still nearly independent of GPY (Fig. 2), because until the R allele frequency increases substantially, virtually all S alleles are present in SS homozygotes rather than in RS heterozygotes.

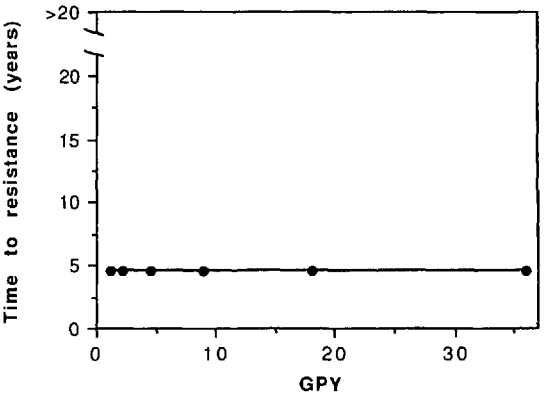

Fig. 1. Simplest-case simulation model of the relationship between GPY and the time to pesticide resistance evolution. Simulation assumes one spray per year and a low pesticide dose. See List 1 for a more detailed listing of assumptions.

If, however, we apply a high pesticide dose, the influence of the frequency of genotype reconstitution becomes important (Fig. 3). Under certain restrictive conditions, high pesticide doses can retard the evolution of resistance by removing R alleles present in RS heterozygotes from the population (Curtis et al. 1978, Taylor & Georghiou 1979, Tabashnik & Croft 1982). RR homozygotes are not killed by high doses; however, if RR individuals mate with SS individuals that survived a spray in refugia, they regenerate a class of RS individuals that can be killed by a subsequent application at a high dose. However, if the frequency of pesticide applications exceeds the frequency of genotype reconstitution, RR individuals remain inviolate over the course of multiple sprays, whereas the SS and RS populations are rapidly removed.

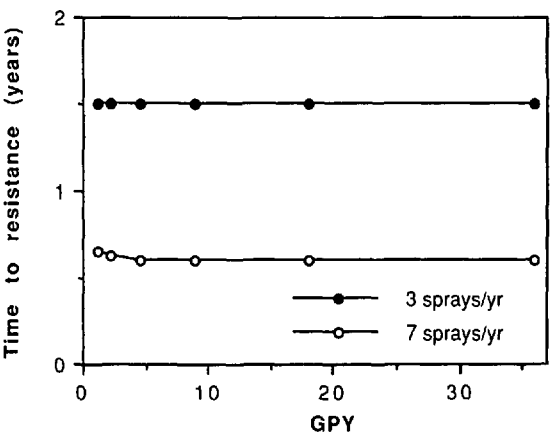

Fig. 2. Influence of the frequency of genotype reconstitution from haploid gametes on the relationship between GPY and the time to resistance evolution. Simulation assumes low pesticide dose and three or seven sprays per year. Note that the y-axis scale is different from that of all other figures.

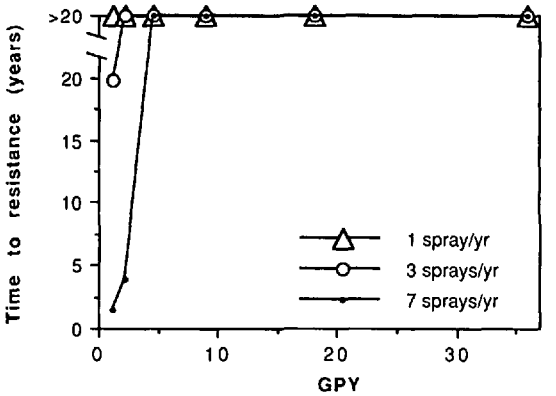

Fig. 3. Influence of the frequency of genotype reconstitution from haploid gametes on the relationship between GPY and the time to resistance evolution. Simulation assumes high pesticide dose and one, three, or seven sprays per year.

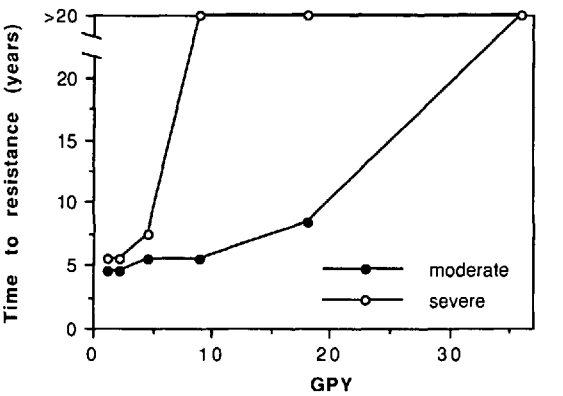

Fig. 4. Influence of fitness costs in the absence of pesticides on the relationship between GPY and the time to resistance evolution. Simulation assumes one spray per year and moderate or severe fitness costs.

The result is that the time to resistance is greatly shortened for species with lower GPY (Fig. 3). The high-dose strategy, like other resistance management strategies sensitive to the presence of multiple resistance factors in a single individual, fails when sprays are not spread over many generations (Comins 1977a, 1979).

Genetic Factors: Fitness Costs in the Absence of Pesticides. Significant pleiotropic costs of resistance traits are sometimes observed in the absence of pesticides (Roush & McKenzie 1987, Roush & Daly in press). Thus, during generations not treated with pesticides, the frequency of the R allele may be decreased by natural selection. If (as we have assumed) the per-generation fitness cost of resistance is independent of generation time, species with many unsprayed generations will exhibit retarded rates of resistance evolution (Fig. 4). This effect may be especially important in explaining the slowed resistance evolution observed in species with the highest GPY (Fig. 4; Rosenheim & Tabashnik in press).

Genetic Factors: Mutation Rate. Evolution involves two basic processes: (1) the production of genetic variability through mutation and recombination, and (2) the change in frequency of different genetic forms. Thus far we have discussed the influence of generation time only on the second process, the rate of increase of resistance allele frequency in a population under pesticide pressure. Although some authors have recognized the potential importance of the rate with which resistance genotypes are generated by mutation (Comins 1979, Whitten & McKenzie 1982, Brattsten et al. 1986), it is not generally feasible to measure directly the extent to which resistance evolution is limited by lack of genetic variation. Key resistance alleles may exist at frequencies too low to be sampled (Whitten & McKenzie 1982). Because no one has documented the absence of resistance alleles from field populations, most models of resistance evolution, like the one used in this study, have assumed that resistance alleles are present before the advent of pesticide-induced selection at some low equilibrium frequency (reviewed by Tabashnik in press; see also Comins 1979).

In a survey of resistance evolution in North American arthropod pests, Rosenheim et al. (unpublished data) found, however, that introduced species were significantly less likely to evolve resistance than native species, suggesting that introduced species had lost resistance alleles during the genetic bottleneck accompanying the colonization event. This result suggests that, at least for introduced species, the rate of resistance evolution may be constrained by the rate with which new resistance alleles are generated by mutation. How might GPY influence the rate of resistance allele production?

Resistance by Point Mutation. Resistance alleles may commonly be generated by point mutations (base substitutions or small deletions or insertions) that alter the kind or amount of protein produced (Soderlund & Bloomquist in press). If evolutionarily important point mutations occur predominantly during DNA replication in germline cells, and if the number of such replications per unit time is related to organismal generation time, then we would expect to see a relationship between GPY and mutation rate (Britten 1986). Under the neutral theory of molecular evolution, the evolutionary rate of nucleotide substitution is determined solely by the rate of mutation (Nei 1987). Thus, for neutral traits the dependence of mutation rate on generation time may be tested by examining the rate of molecular evolution in lineages with different generation times. Despite the apparent simplicity of this test, the interpretation of several studies attempting to measure the influence of generation time remains controversial. Some authors support a positive relationship between GPY and mutation

rate (e.g., Wu & Li 1985, Graur et al. 1989), and others argue against any role for GPY (e.g., Sarich & Wilson 1973, Ochman & Wilson 1987, Easteal 1988). Thus, evidence for accelerated mutation rates in species with high GPY is suggestive but not conclusive.

Resistance by Gene Amplification. Molecular evidence exists for a second basis for resistance: an increase in the number of copies of structural genes coding for key detoxification enzymes (Mouchès et al. 1986, Field et al. 1988). In theory, gene amplification may occur by several different mechanisms, which may be directly tied to DNA replication (i.e., sister chromatid exchange, disproportionate DNA replication) or meiosis (unequal homologous recombination), or be uncoupled from specific events in the cell cycle (i.e., RNA-mediated transposition) (Stark & Wahl 1984, Maeda & Smithies 1986). Gene amplification linked to DNA replication or meiosis should be accelerated in species with high GPY; especially important may be the accelerated pace of unequal homologous recombination, which appears to play a key role in the evolution of multigene families (Maeda & Smithies 1986). Thus, species with high GPY may have improved capacities to evolve resistance via gene amplification.

In summary, species with elevated GPY may have increased abilities to generate resistance genotypes by accelerated mutation and gene amplification. In addition, because the number of mutations per locus per generation is proportional to the mutation rate and the population size, the influence of GPY on population dynamics (discussed below) may also affect the probability of generating key mutations. However, additional work is required to quantify the importance of these effects.

Population Dynamics: Spray Frequency. Generation time has a strong influence on a population's intrinsic growth rate, r. Although r is only logarithmically related to species fecundity, it is linearly related to the rate of generation turnover (Price 1984).

In the field, however, many factors may cause the realized population growth rate to fall below that predicted by r. Host plant condition, the farmer's agronomic practices, weather conditions, and natural enemies can all restrain population growth. Thus, the relationship between GPY and realized population growth rates may be variable.

In some instances, realized population growth rate may influence the frequency of pesticide applications directed at key pests. Note that, by definition, nontarget pests do not determine spray frequencies regardless of their generation time. However, even for key pests, the link between realized population growth rate and spray frequency may be weak. Temporal variability in crop susceptibility, variation in the type of crop damage induced, and variation in the value of the crop may all influence spray frequency independently of pest population growth rate. Because of the variable

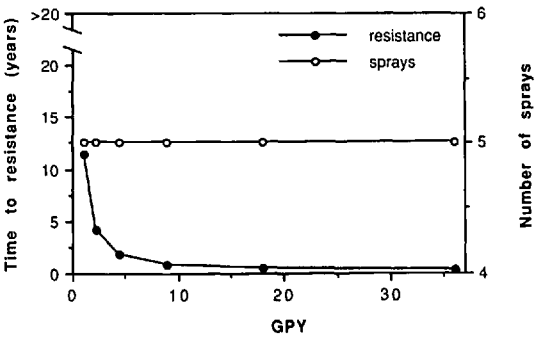

Fig. 5. Influence of threshold-based sprays on the relationship between GPY and the time to resistance evolution. Sprays applied when there are $>10^5$ larvae. Also shown are the number of sprays applied before the resistance criterion was met.

relationships between GPY and realized population growth rate and between realized population growth rate and spray frequency, the overall link between GPY and spray frequency is tenuous (Rosenheim & Tabashnik in press). Nevertheless, GPY will influence spray frequency for some key pests (e.g., *Sitophilus oryzae* L., Longstaff [1988]). For these species, resistance evolution will be strongly influenced by GPY. In simulations that base the decision to spray on an economic threshold, increasing GPY decreases the time to resistance (Fig. 5). That this effect is due solely to the influence of GPY on the number of sprays per year can be inferred from the observation that five sprays were required to generate resistance for all GPY values (Fig. 5).

Population Dynamics: Gene Flow. Gene flow into a sprayed population from unsprayed neighboring populations may retard the evolution of pesticide resistance (Comins 1977b, Georghiou & Taylor 1977, Tabashnik & Croft 1982, May & Dobson 1986). The magnitude of this effect depends in part on the proportional contribution of the immigrants to the new population. Generation time can modulate the importance of immigration by influencing the rate of population growth following a pesticide application, thereby determining the size of the population receiving the immigrants. As discussed previously, however, the relationship between GPY and realized population growth rate need not be precise; nevertheless, our model assumes such a precise relationship. With this caveat in mind, what is the relationship between GPY and resistance evolution in the presence of immigration?

First, if we assume that the immigration rate is constant per day (i.e., is independent of GPY), resistance evolves faster as GPY increases (Fig. 6). Increasing GPY increases population growth rate following pesticide applications; therefore, immigrants make a smaller contribution to the population and slow resistance evolution to a lesser degree. With one spray per year, immigration slowed resistance evolution only for the lowest GPY value (compare Fig. 1 and 6); at higher GPY values, the

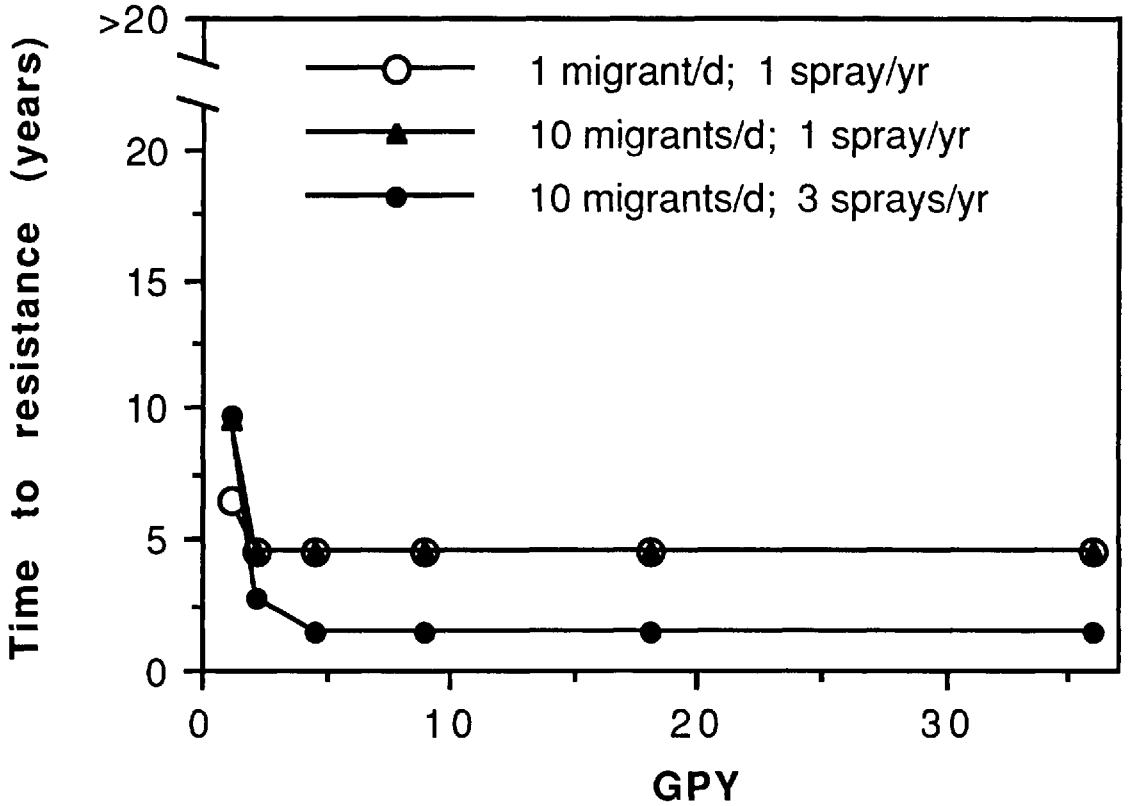

Fig. 6. Influence of a constant rate of immigration per day on the relationship between GPY and the time to resistance evolution. Simulation assumes one or three sprays per year and one or ten migrants per day.

population was too large to be influenced by either 1 or 10 immigrants per day. Increased fecundity and increased daily survivorship have been shown to generate analogous increases in the rate of resistance evolution in the face of immigration (Tabashnik & Croft 1982).

If, however, we assume that the rate of immigration is constant per generation (i.e., is directly proportional to GPY), we observe a more complex relationship (Fig. 7). As observed in Fig. 6, the time to resistance decreases as GPY increases for low values of GPY. At higher GPY values the trend is reversed. At these higher GPY values, the intrinsic rate of population growth is very high, but the maximum population size obtainable is restrained by density-dependent larval mortality. The number of immigrants continues to increase with increasing GPY, however, resulting in a greater proportional contribution of susceptible immigrants to the population experiencing selection. Resistance is therefore delayed.

Population Dynamics: Refuges. Several types of refuges from pesticide applications may have important influences on the evolution of pesticide resistance, including spatial refuges due to uneven spray coverage and refuges due to the nonsusceptibility of specific life stages. Refuges for particular life stages may be created when that stage inhabits portions of the environment not treated by pesticides, or when life stages are exposed but not susceptible to pesticides (e.g., eggs and pupae of many pest species [e.g., Ruscoe 1977]). Life stage refuges, generation time, and pesticide residue degradation rates interact strongly in their influence on the rate of resistance evolution (Rosenheim & Hoy 1988). There are two sorts of interactions depending on the spray frequency, "within-spray" and "between-spray" effects. We investigated these effects by simulating resistance evolution for a pest species in which only the larval stage is exposed and susceptible to pesticides.

Consider first the within-spray effect. If pesticide residues decay immediately following application, time to resistance is not strongly influenced by GPY (Fig. 8). The slight decline in time to resistance observed with increasing GPY is due in part to complex interactions of population age structure, density-dependent survivorship, and stage-specific pesticide-induced mortality. If pesticide residues decay more gradually, with a half-life of 7 d, the effect of GPY becomes much stronger (Fig. 8); species with high GPY exhibit greatly accelerated resistance evolution. Why do we observe this effect?

Species with high GPY values develop rapidly; therefore, the duration of residence within a life

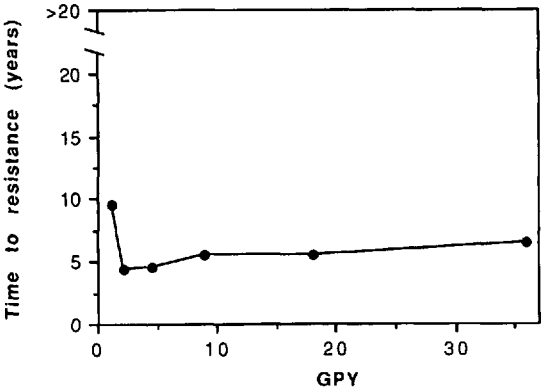

Fig. 7. Influence of a constant rate of immigration per generation on the relationship between GPY and the time to resistance evolution. Simulation assumes 2,400 migrants per generation and three sprays per year.

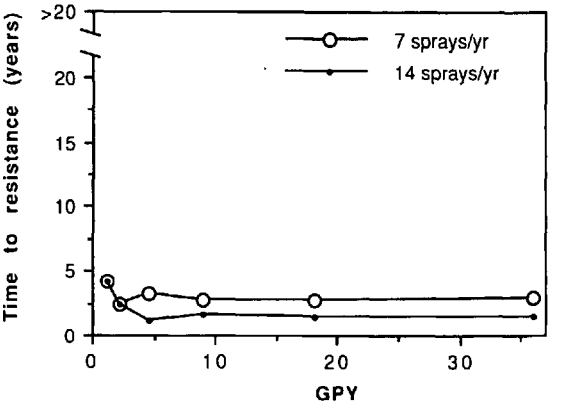

Fig. 9. Influence of life stage refuges on the relationship between GPY and the time to resistance evolution: the between-spray effect. Simulation assumes that only larvae are exposed to pesticides, no residue half-life, and 7 or 14 sprays per year.

stage refuge is short. In our example, only larvae were exposed, but the pesticide half-life (7 d) and dose (0.004) were such that 14 d elapsed before the residue decayed to levels not toxic to SS individuals (i.e., <0.001). Over this 14-d period, rapidly developing individuals (or their offspring) would at some point pass into the larval stage and be exposed to a lethal dose of pesticide. Selection pressure for rapidly developing species is therefore intense. For more slowly developing species, most individuals present as eggs, pupae, and adults at the time of pesticide application would remain in the same developmental stage during the 14 d of residue toxicity. Selection pressure acts, therefore, only on those individuals present as larvae at the time of pesticide application and is thus weak. Accordingly, resistance evolves slowly in slowly developing species and more rapidly in rapidly developing species (Fig. 8). Clearly, no such effect is to be expected in the absence of a persistent residue.

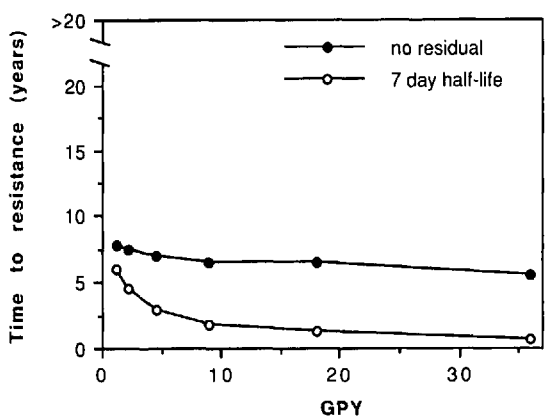

Fig. 8. Influence of life stage refuges on the relationship between GPY and the time to resistance evolution: the within-spray effect. Simulation assumes that only larvae are exposed to pesticides, three sprays per year, and an immediate pesticide breakdown or a half-life of 7 d.

The more subtle between-spray effect is most easily observed for sprays with no residue persistence. In this case, increasing spray frequency increases the extent to which species with high GPY exhibit accelerated resistance evolution (Fig. 9). This effect is due to the partial redundancy of successive sprays applied to slowly developing species. An initial spray kills most of the susceptible larvae; if a second spray is applied before additional individuals develop into the larval stage, there will be few susceptible larvae present in the population. Thus, the second spray fails to exert substantial additional selection pressure; it is redundant. Rapidly developing species, however, have ample time to regenerate a class of susceptible larvae, and therefore experience more intense selection. Accordingly, time to resistance is decreased for these species (Fig. 9).

Resistance Criteria. All simulations presented thus far have used the genetic criterion for resistance (i.e., R allele frequency >0.5). If instead we use an operational criterion for resistance, which adds the stipulation that population densities exceed an economic threshold, we observe an effect of GPY (Fig. 10). The longer times to resistance observed for species with low GPY reflect the inclusion of an additional period required for population density to build to an economic injury level after the R allele becomes common. Our model assumes that a positive relationship exists between realized population growth rate and GPY; as discussed previously, this assumption is probably valid, although the relationship may be somewhat variable. The effect of the operational criterion for resistance will have broad applicability to our perception of resistance evolution in the field, because resistance is rarely detected until control failures occur, and control failure is approximately equiv-

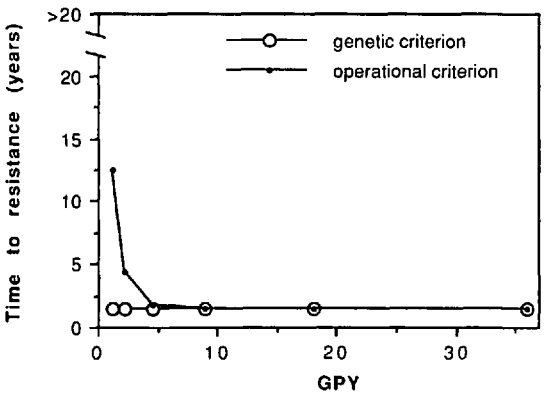

Fig. 10. Influence of an operational criterion for resistance on the relationship between GPY and the time to resistance evolution. Simulation assumes three sprays per year and either a genetic or an operational criterion for resistance.

alent to an operational criterion for resistance. In contrast to many of the influences of GPY on resistance evolution described above, the interaction of GPY and the operational criterion for resistance is a one-time effect, occurring only during the final phase of resistance evolution. Fecundity also interacts with the criterion for resistance evolution in the same way demonstrated here for GPY (Tabashnik 1986b, Mason et al. 1989).

GPY and Generation Time. We have presented a variety of potential influences of GPY on resistance evolution (summarized in Table 1). Throughout this paper we have equated the effects of GPY and generation time; however, the relationship between GPY and generation time will be exact only if all species have the same active season. In the field, some variation in active season duration will be observed; a species with a short active season may therefore have lower GPY than another species with a longer active season and still have a shorter generation time. Seven of the 12 effects presented in Table 1 (numbers 1, 4, 5, 6, 8, 9, and 12) are primarily effects of GPY. These are effects linked to per-generation fitness costs, the number of cell divisions per year, and the annual rate of population growth. For the remaining effects (numbers 2, 3, 7, 10, and 11), which involve the timing of genotype reconstitution, the rate of population growth during the period of crop susceptibility, and the duration of life stage refuges, the effects may be more closely linked to either GPY or generation time, depending on the case being considered. These distinctions are subtle, and are not critical to our study.

In Table 1, we have also presented an estimate of the relative commonness and strength of the various effects, based upon the results of our simulations and an admittedly subjective personal evaluation. Our estimates of the relative importance of different influences are offered only as possible guides to further research efforts.

Combinations of Factors. Although we identified factors creating strong positive or negative relationships between GPY and time to resistance, only one factor produced a relationship mirroring the empirically observed pattern of peak rates of resistance evolution for species with intermediate GPY values (Rosenheim & Tabashnik in press). Furthermore, this one factor, the influence of an immigration rate proportional to GPY, appeared to exert only a relatively weak effect (Fig. 7). We have, however, considered the operation of each factor in isolation; in the field, several influences may act in concert. By combining the effects of different factors, we can observe peak rates of resistance evolution at intermediate GPY values under a broader range of conditions. Some examples in Fig. 11 involve the combined influences of fitness costs in the absence of pesticides with various other factors. The total number of higher-order interactions between GPY and genetic, ecological, and operational factors is very large, with the interpretation of the resulting relationships between GPY and the rate of resistance evolution becoming increasingly difficult.

Table 1. Summary of the influences of the number of generations per year (GPY) on the time to evolve resistance

Effect	Relationship between GPY and time to resistance[a]	Fig. reference	Occurrence	Effect strength
1. Isolated effect of GPY	0	1	common	—
2. Frequency of genotype reconstitution: low dose	−	2	common	very weak
3. Frequency of genotype reconstitution: high dose	+	3	common	very strong
4. Fitness costs in the absence of pesticides	+	4	common	strong
5. Production of resistance genotypes: point mutations	0 or −	—	?	weak
6. Production of resistance genotypes: gene amplification	−	—	?	?
7. Spray frequency based on population threshold	−	5	rare	strong
8. Gene flow: immigration independent of GPY	−	6	rare to common	moderate
9. Gene flow: immigration proportional to GPY	U-shaped	7	rare to common	weak
10. Life stage refuges: within-spray effect	−	8	common	moderate
11. Life stage refuges: between-spray effect	−	9	common	very weak
12. Operational resistance criterion	−	10	common	moderate

[a] 0, time to resistance is independent of GPY; −, negative relationship, time to resistance decreases as GPY increases; +, positive relationship, time to resistance increases as GPY increases.

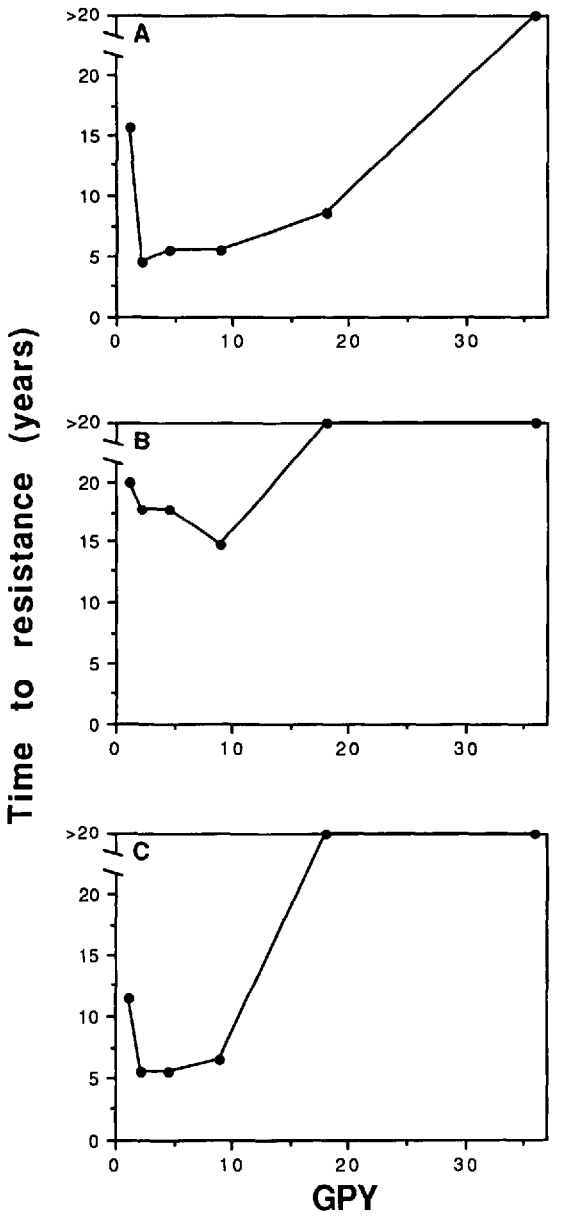

Fig. 11. Examples of some multiple-factor interactions that result in U-shaped relationships between GPY and the time to resistance evolution. Assumptions of the simulations are as described in List 1 except as noted. (A) Combined influences of fitness costs in the absence of pesticides and an operational criterion for resistance. Simulation assumes a moderate fitness cost and one spray per year. (B) Combined influences of fitness costs in the absence of pesticides and life stage refuges. Simulation assumes a moderate fitness cost in the absence of pesticides, only larvae are exposed to pesticides, one spray per year, and a residue half-life of 3.5 d. (C) Combined influences of fitness costs in the absence of pesticides and a constant rate of migration per generation. Simulation assumes a moderate fitness cost in the absence of pesticides, 2,400 immigrants per generation, and one spray per year.

Conclusions. In this study, we have not attempted to provide an exhaustive analysis of the possible influences of GPY. Rather, we demonstrated the diversity of relationships between GPY and the rate of resistance evolution with some representative examples. The goal of our study was to investigate the theoretical relationship between GPY and resistance evolution based on our previous empirical finding that there is no linear relationship between the two (Rosenheim & Tabashnik in press). A simplest-case simulation model (Fig. 1) confirmed the results of our previous analytical model, which suggested that the rate of resistance evolution can be independent of generation time (Rosenheim & Tabashnik in press). However, as the more complex simulations demonstrated, the influence of GPY on resistance evolution depends on the genetics of resistance, the population dynamics of the pest, and the nature of the pesticide-induced mortality. Interactions between GPY and these variables generated positive, negative, and U-shaped relationships between GPY and time to resistance (Table 1). Thus, our primary conclusion is that interactions between GPY and other variables preclude simple predictions regarding the influence of generation time on resistance evolution. The empirical data indicate that the sum of all the influences of GPY is the approximate independence of GPY and the ability to evolve resistance (Rosenheim & Tabashnik in press). However, for any specific case of resistance evolution, some predictive ability regarding the role of GPY may exist if the genetic, ecological, and operational context of the resistance episode can be defined.

Acknowledgment

We thank M. A. Caprio and two anonymous reviewers for critical review of the manuscript. This work was supported by USDA grants HAW00947H, Western Regional IPM grant 8902553, USDA/CSRS Special Grants in Tropical and Subtropical Agriculture 8902558, and a Fujio Matsuda Scholar Award to B.E.T. from the University of Hawaii Foundation. This is Paper No. 3398 in the Hawaii Institute of Tropical Agriculture and Human Resources Journal Series, University of Hawaii.

References Cited

Brattsten, L. B., C. W. Holyoke, Jr., J. R. Leeper & K. F. Raffa. 1986. Insecticide resistance: challenge to pest management and basic research. Science 231: 1255–1260.

Britten, R. J. 1986. Rates of DNA sequence evolution differ between taxonomic groups. Science 231: 1393–1398.

Comins, H. N. 1977a. The management of pesticide resistance. J. Theor. Biol. 65: 399–420.

1977b. The development of insecticide resistance in the presence of migration. J. Theor. Biol. 64: 177–197.

1979. The management of pesticide resistance: models, pp. 55–69. *In* M. A. Hoy & J. J. McKelvey, Jr. [eds.], Genetics in relation to insect management. Rockefeller Foundation, New York.

Curtis, C. F., L. M. Cook & R. J. Wood. 1978. Selection for and against insecticide resistance and possible methods of inhibiting the evolution of resistance in mosquitos. Ecol. Entomol. 3: 273–287.

Delp, C. J. 1986. Pesticide resistance management is a key to effective pest control. Bioscience 36: 101–102.

Dover, M. J. & B. A. Croft. 1986. Pesticide resistance and public policy. Bioscience 36: 78–85.

Easteal, S. 1988. Rate constancy of globin gene evolution in placental mammals. Proc. Natl. Acad. Sci. USA 85: 7622–7626.

Field, L. M., A. L. Devonshire & B. G. Forde. 1988. Molecular evidence that insecticide resistance in peach-potato aphids (*Myzus persicae* Sulz.) results from amplification of an esterase gene. Biochem. J. 251: 309–312.

Georghiou, G. P. 1980. Insecticide resistance and prospects for its management. Residue Rev. 76: 131–145.

Georghiou, G. P. & C. E. Taylor. 1977. Genetic and biological influences in the evolution of insecticide resistance. J. Econ. Entomol. 70: 319–323.

Graur, D., Y. Shuali & W.-H. Li. 1989. Deletions in processed pseudogenes accumulate faster in rodents than in humans. J. Mol. Evol. 28: 279–285.

Keiding, J. 1986. Prediction or resistance risk assessment, pp. 279–297. *In* National Research Council, Pesticide resistance. National Academy of Sciences, Washington.

Leeper, J. R., R. T. Roush & H. T. Reynolds. 1986. Preventing or managing resistance in arthropods, pp. 335–346. *In* National Research Council, Pesticide resistance. National Academy of Sciences, Washington.

Longstaff, B. C. 1988. Temperature manipulation and the management of insecticide resistance in stored grain pests: a simulation study for the rice weevil, *Sitophilus oryzae*. Ecol. Modell. 43: 303–313.

Maeda, N. & O. Smithies. 1986. The evolution of multigene families: human haptoglobin genes. Annu. Rev. Genet. 20: 81–108.

Mason, G. A., B. E. Tabashnik & M. W. Johnson. 1989. Effects of biological and operational factors on evolution of insecticide resistance in *Liriomyza* (Diptera: Agromyzidae). J. Econ. Entomol. 82: 369–373.

May, R. M. & A. P. Dobson. 1986. Population dynamics and the rate of evolution of pesticide resistance, pp. 170–193. *In* National Research Council, Pesticide resistance. National Academy of Sciences, Washington.

Mouchès, C., N. Pasteur, J. B. Bergé, O. Hyrien, M. Raymond, B. R. de Saint Vincent, M. de Silvestri & G. P. Georghiou. 1986. Amplification of an esterase gene is responsible for insecticide resistance in a California *Culex* mosquito. Science 233: 778–780.

National Research Council. 1986. Pesticide resistance. National Academy of Sciences, Washington.

Nei, M. 1987. Molecular evolutionary genetics. Columbia University Press, New York.

Ochman, H. & A. C. Wilson. 1987. Evolution in bacteria: evidence for a universal substitution rate in cellular genomes. J. Mol. Evol. 26: 74–86.

Price, P. W. 1984. Insect ecology, 2nd ed. Wiley, New York.

Rosenheim, J. A. & M. A. Hoy. 1988. Genetic improvement of a parasitoid biological control agent: artificial selection for insecticide resistance in *Aphytis melinus* (Hymenoptera: Aphelinidae). J. Econ. Entomol. 81: 1539–1550.

Rosenheim, J. A. & B. E. Tabashnik. In press. Influence of generation time on the rate of response to selection. Am. Nat.

Roush, R. T. & J. C. Daly. In press. The role of population genetics in resistance research and management. *In* R. T. Roush & B. E. Tabashnik [eds.], Pesticide resistance in arthropods. Chapman and Hall, New York.

Roush, R. T. & J. A. McKenzie. 1987. Ecological genetics of insecticide and acaricide resistance. Annu. Rev. Entomol. 32: 361–380.

Ruscoe, C. N. E. 1977. The new NRDC pyrethroids as agricultural insecticides. Pestic. Sci. 8: 236–242.

Sarich, V. M. & A. C. Wilson. 1973. Generation time and genomic evolution in primates. Science 179: 1144–1147.

Soderlund, D. M. & J. R. Bloomquist. In press. Molecular and biochemical mechanisms of insecticide resistance. *In* R. T. Roush & B. E. Tabashnik [eds.], Pesticide resistance in arthropods. Chapman and Hall, New York.

Stark, G. R. & G. M. Wahl. 1984. Gene amplification. Annu. Rev. Biochem. 53: 447–491.

Tabashnik, B. E. 1986a. Evolution of pesticide resistance in predator/prey systems. Bull. Entomol. Soc. Am. 32: 156–161.

1986b. Model for managing resistance to fenvalerate in the diamondback moth (Lepidoptera: Plutellidae). J. Econ. Entomol. 79: 1447–1451.

In press. Modeling and evaluation of resistance management tactics. *In* R. T. Roush & B. E. Tabashnik [eds.], Pesticide resistance in arthropods. Chapman and Hall, New York.

Tabashnik, B. E. & B. A. Croft. 1982. Managing pesticide resistance in crop-arthropod complexes: interactions between biological and operational factors. Environ. Entomol. 11: 1137–1144.

1985. Evolution of pesticide resistance in apple pests and their natural enemies. Entomophaga 30: 37–49.

Taylor, C. E. & G. P. Georghiou. 1979. Suppression of insecticide resistance by alternation of gene dominance and migration. J. Econ. Entomol. 72: 105–109.

Whitten, M. J. & J. A. McKenzie. 1982. The genetic basis for pesticide resistance, pp. 1–16. *In* Proceedings, third Australasian conference on grassland invertebrate ecology. S.A. Government Printer, Adelaide.

Wu, C.-I. & W.-H. Li. 1985. Evidence for higher rates of nucleotide substitution in rodents than in man. Proc. Natl. Acad. Sci. USA 82: 1741–1745.

Received for publication 6 September 1989; accepted 1 December 1989.