FORUM

Insecticide Resistance and Dominance Levels

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ABSTRACT Dominance has been assessed in different ways in insecticide resistance studies, based on three phenotypic traits: the insecticide concentration required to give a particular mortality (D_{LC}), mortality at a particular insecticide dose (D_{ML}), and fitness in treated areas (D_{WT}). We propose a general formula for estimating dominance on a scale of 0 to 1 (0 = complete recessivity and 1 = complete dominance). D_{LC}, D_{ML}, and D_{WT} are not directly related and their values depend on genetic background and environmental conditions. We also show that pest management strategies can have the consequence to increase D_{WT} via the selection of dominance modifiers. Studies on resistance to *Bacillus thuringiensis* toxins provide the ultimate example of the complexity of the definition of the concept of dominance. Almost all studies have focused on calculation of D_{LC}, which provides little information about the efficiency of pest management programs. For instance, one assumption of the high dose/refuge strategy is that *Bacillus thuringiensis* resistance must be effectively recessive (i.e., D_{ML} must be close to zero). However, D_{WT}, rather than D_{ML}, is relevant to the resistance management strategy. Therefore, we strongly suggest that the time has come to focus on fitness dominance levels in the presence and absence of insecticide.

KEY WORDS *Bacillus thuringiensis*, effective dominance, fitness cost, balanced polymorphism, resistance management, transgenic crops

THE LEVEL OF dominance is a measure of the relative position of the phenotype of the heterozygote relative to the phenotype of the two corresponding homozygotes. Can dominance level be predicted? If a wild-type gene (A) mutates to a deleterious allele (a), the Aa heterozygote usually displays a wild-type phenotype: the deleterious effects of mutations are generally recessive. For almost a century the explanation of this phenomenon has been the subject of a long and passionate debate in evolutionary biology (Porteous 1996). It is now thought that the typical recessivity of deleterious alleles is a by-product of the kinetic structure of simple enzymatic pathways, as initially proposed by Wright (1934) and subsequently developed by Kacser and Burns (1981). However, simple enzymatic pathways are somewhat special cases and previous conclusions are not general (Bourguet 1999). Insecticide resistance seems to be a good model for investigating dominance relationships (Bourguet et al. 1996, Bourguet et al. 1997) because most of the genes and mutations responsible for resistance have been identified, and the physiological processes in which they are involved are known (McKenzie 1996). In addition, there is a large variation of the level of dominance of resistance. For example, the insecticide resistance conferred by mutations decreasing the affinity of insecticide target sites varies from complete recessivity to complete dominance (Bourguet and Raymond 1998).

Dominance is not an intrinsic property of an allele (Sved and Mayo 1970, Nanjundiah 1993, Mayo and Bürger 1997, Bourguet 1999). A resistance allele may be dominant (over a susceptible allele) for one insecticide, and recessive for another (for an example, see Bourguet et al. 1996). It is therefore inappropriate to talk about the dominance of a resistance allele in the way used in many papers (e.g., for resistance to *Bacillus thuringiensis* toxins [Hama et al. 1992; Alstad and Andow 1995, Ferré et al. 1995; Martinez-Ramirez et al. 1995, Rahardja and Whalon 1995; Tabashnik et al. 1997a, 1997b; Tabashnik et al. 1998; Frutos et al. 1999; Huang et al. 1999a]) without specifying the environmental parameters. This is because dominance describes the relationship between the phenotypes of the three genotypes, which may vary between traits and environments. In addition, the definition of dominance is rather confused, because of the use of several characters and three concepts.

The four goals of this study were as follows: (1) to clarify the various concepts of dominance that have been used, sometimes confusedly, in insecticide resistance studies; (2) to give a general formula for assessing dominance level; (3) to emphasize that dominance is not a fixed parameter but varies as a function of environment and genetic background; and (4) to investigate the use of dominance levels in recent studies of resistance to *Bacillus thuringiensis* toxins.

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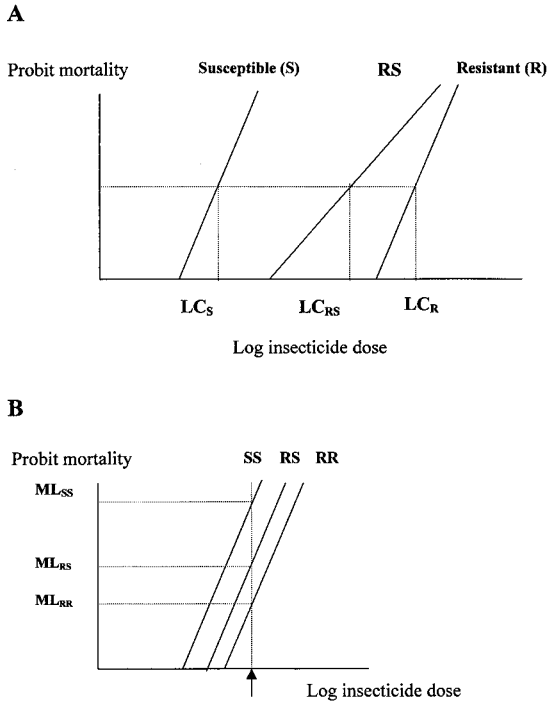

Fig. 1. (A) Level of dominance of insecticide resistance. For each mortality level (ML), an insecticide concentration can be calculated for the susceptible (LC_S) and resistant (LC_R) strains and for heterozygotes (LC_{RS}). The level of dominance of insecticide resistance is defined as $D_{LC} = (\log LC_{RS} - \log LC_S)/(\log LC_R - \log LC_S)$ and varies between 0 and 1. In the example, $D_{LC} = 0.7$ at a ML of 50% (dotted line). (B) Dominance level of survival at a given insecticide dose (*effective dominance*). For any insecticide dose, an ML can be calculated for the three genotypes. Dominance level is calculated as $D_{ML} = (ML_{RS} - ML_{SS})/(ML_{RR} - ML_{SS})$. For the insecticide dose indicated by the arrow, $D_{ML} = 0.6$.

Defining and Measuring Dominance

Three different ways of assessing dominance level have been used in studies of insecticide resistance. First, dominance may be based on the position of the mortality curve for heterozygous individuals relative to those for both homozygotes, at a given mortality level (Fig. 1A). This is the dominance level of insecticide resistance. Second, the mortality of heterozygous individuals relative to that of both homozygotes, at a given insecticide concentration (Fig. 1B), has been used. This is the dominance level of survival at a given insecticide dose, often called *effective dominance*, closely related to dominance with respect to fitness. The third way of assessing dominance compares the fitness of the heterozygotes to that of the two homozygotes at a given insecticide dose.

The Dominance of Insecticide Resistance. In toxicology, dominance level was initially determined by comparing the mortality curves of susceptible, resistant, and hybrid individuals (Milani 1963). Resistance was qualitatively (and arbitrarily) classed as recessive or dominant according to whether the hybrid mortality curve was closer to the susceptible or resistant mortality curve, respectively. Resistance was considered codominant (sometimes referred to as an absence of dominance) if hybrid mortality curves were equidistant from those of homozygotes. A quantitative measure of dominance level was then introduced by Stone (1968), using Falconer's formula (1964):

$$D = (2\log LC_{RS} - \log LC_R - \log LC_S)/(\log LC_R - \log LC_S), \quad [1]$$

where LC_R, LC_{RS}, and LC_S are the lethal concentrations for the resistant, hybrid and susceptible individuals, respectively. D varies from -1 to 1 (-1 = complete recessivity and 1 = complete dominance). D is usually calculated for a mortality level (ML) = 50% (Liu and Tabashnik 1997), set arbitrarily (Stone 1968), but may also be calculated as a function of ML, as shown by Bourguet et al. (1996, 1997). Stone's formula remains the most widely used method for determining the dominance of insecticide resistance. However, to obtain a more classical 0–1 range, Bourguet et al. (1996, 1997), Bourguet and Raymond (1998) and Charlesworth (1998) have proposed the calculation of D_{LC} as follows:

$$D_{LC} = (\log LC_{RS} - \log LC_S)/(\log LC_R - \log LC_S). \quad [2]$$

Thus, following Liu and Tabashnik (1997).

$$D_{LC} = (D + 1)/2. \quad [3]$$

Effective Dominance. Curtis et al. (1978) were the first to point out that D_{LC} is of little value for pest resistance management. This is because strategies for delaying insecticide resistance mostly involve determining whether it is technically feasible to use doses such that all heterozygotes are killed (assuming monogenic resistance). Independently of the value of D_{LC}, and depending on the doses applied "in practical conditions, either full dominance or full recessivity would effectively exist" (Curtis et al. 1978, p. 284). This led to the concept of *effective dominance*, which was further developed by Roush and McKenzie (1987). Hence, whereas D_{LC} assesses the relative insecticide concentrations required to give a similar ML, effective dominance assesses the relative ML for a given insecticide concentration. We therefore refer to this dominance parameter as D_{ML}, which may be quantified as follows:

$$D_{ML} = (ML_{RS} - ML_{SS})/(ML_{RR} - ML_{SS}). \quad [4]$$

D_{ML} varies between 0 and 1 (0 = survival is recessive and 1 = survival is dominant).

The Dominance of Relative Fitness in the Treated Area. We can define the dominance of the advantage conferred by an insecticide resistance allele in the treated area (D_{WT}) according to the following formula:

$$D_{WT} = (W_{TRS} - W_{TSS})/(W_{TRR} - W_{TSS}), \quad [5]$$

where W_{TSS}, W_{TRS}, and W_{TRR} are the relative fitness in a treated area at a particular insecticide concen-

tration for susceptible homozygotes, heterozygotes, and resistant homozygotes, respectively. Values of D_{WT} range from 0 to 1 (0 = recessive fitness and 1 = dominant fitness). As pointed out by a number of authors (e.g., Mallet and Porter 1992, Tabashnik 1994), D_{WT} is related to h, the dominance level of fitness or fitness components defined in population genetics, with either $D_{WT} = h$ or $D_{WT} = 1- h$, depending on whether homozygous resistant or susceptible individuals are used as the fitness reference. Unfortunately, D_{WT} has often been referred to as effective dominance (Mallet and Porter 1992) or as the genetic dominance coefficient (Mallet and Porter 1992, Tabashnik 1994), making unclear and confusing the distinction between the various dominance levels notably between D_{ML} and D_{WT}.

There is no obvious correlation between D_{WT} and D_{ML}. Three cases must still be distinguished. The first case is when insecticide concentrations give a $ML_{RS} \leq ML_{SS} < 100\%$. In this situation, no predictions can be done. Although insecticide treatments certainly decrease the fitness of the survivors we cannot predict how this fitness will be modified for each genotype. This can be illustrated with the following example where $D_{ML} = 0.75$:

	Genotypes	SS	RS	RR
Mortality level (ML)		80	20	0
	D_{ML}	0.75		
Scenario 1				
Relative fitness of the survivor in the treated area		0.5	1	1
Relative fitness in the treated area (W_T)		0.1	0.8	1
	D_{WT}	0.77		
Scenario 2				
Relative fitness of the survivor in the treated area		0.5	0.75	1
Relative fitness in the treated area (W_T)		0.1	0.6	1
	D_{WT}	0.55		

In this example, RR and RS survivors may not differ in fitness, whereas SS survivors have a relative fitness of 0.5 (scenario 1). In this case, $D_{WT} = 0.77$, which is a higher value than those calculated from the observed mortality level. However, if the relative fitness of SS, RS, and RR that survive the insecticide treatment are 0.5, 0.75, and 1, respectively (scenario 2), then $D_{WT} = 0.55$, which is less than D_{ML}. Interestingly, when $D_{LC} = 0$ for all range of LC then $D_{ML} = 0$ whatever the mortality level induced by the insecticide concentration. As a consequence, when $ML_{RS} \leq ML_{SS} < 100\%$, D_{WT} does not necessarily equal D_{ML} if $D_{ML} = 0$.

The second case correspond to the situation where $ML_{RS} < ML_{SS} = 100\%$. In this situation we can predict D_{ML} to have a higher value than D_{WT}. This is because heterozygous individuals that survive to the insecticide treatment may have a lower contribution to the gene pool than RR individuals. Unlike D_{WT}, D_{ML} does not take into account all reductions in the fitness components that may occur after survival of exposure to the insecticide. Other fitness components that may be affected include mating success, larval development, the fertility and fecundity of females, and the survival of their offspring. If these components are more affected in RS than in RR individuals then $D_{WT} < D_{ML}$.

The last situation is when the insecticide concentration is lethal to all RS and SS individuals ($ML_{RS} = ML_{SS} = 100\%$). In such a case D_{ML} and D_{WT} are equivalent and equal to 0.

A General Formula for Dominance Levels in Relation to Insecticide Resistance. As dominance depends on the character affected by the resistance gene, we can propose a general formula for calculating the dominance level for a phenotypic trait, X:

$$D_X = (X_{RS} - X_{SS}) / (X_{RR} - X_{SS}) \quad [6]$$

where X_{SS}, X_{RS}, and X_{RR} are the quantitative values calculated for a trait X for susceptible homozygotes, heterozygotes, and resistant homozygotes, respectively. We have seen above that X may correspond to the log of the LC required to obtain a certain ML (for estimating D_{LC}), the ML at a particular insecticide concentration (for estimating D_{ML}) or the relative fitness in an insecticide-treated area (for estimating D_{WT}). Hence a dominance level can be calculated for other traits, such as fitness in an untreated area, or D_{WNT}, corresponding to the dominance level of the fitness cost:

$$D_{WNT} = (W_{NTRS} - W_{NTSS}) / (W_{NTRR} - W_{NTSS}) \quad [7]$$

where W_{NTSS}, W_{NTRS}, and W_{NTRR} are relative fitness in the absence of insecticide for susceptible homozygotes, heterozygotes, and resistant homozygotes, respectively.

Similarly, a dominance level may be calculated for each fitness component affected by the resistance allele in the absence or in presence of an insecticide. D_X will always lie between 0 (trait recessive) and one (trait dominant).

Variation, Plasticity, and Evolution of Dominance

It is generally believed that the dominance level for a particular character (e.g., D_{LC}, D_{ML}, D_{WT}, D_{WNT}) is a fixed parameter. However, it may be influenced by environmental conditions and genetic background. Moreover, the selection of an insecticide resistance allele may be accompanied by an evolution of its dominance levels. In addition, selection may favor insecticide resistance alleles conferring more dominant phenotypes (e.g., fitness) through allele replacement.

Plasticity of Dominance. For a given insecticide D_{LC} varies with certain environmental variables. This phenomenon is referred to as plasticity. Bourguet et al. (1996) studied the D_{LC} of insecticide resistance conferred by an insensitive acetylcholinesterase in the mosquito *Culex pipiens* L. in two different environments, defined mainly by the water depth in the cup used for larval bioassays. D_{LC} differed greatly between the two environments. For example, for ML = 50%, propoxur resistance varied from partial dominance ($D_{LC} = 0.7$) to partial recessivity ($D_{LC} = 0.35$), de-

pending on water depth. For some of the insecticide concentrations considered, D_{ML} (and probably D_{WT}) was also affected by such environmental differences.

Dominance Modifiers. Changes in dominance may also arise because of alleles at linked or unlinked loci, which may be viewed as modifiers of dominance. Modifiers may be generalist, affecting the values of several dominance levels simultaneously, or more specific, affecting the dominance level of one trait only.

A dominance modifier has been reported for insecticide resistance by Grigolo and Oppenoorth (1966). They showed that in houseflies a DDT-ase, a detoxifying enzyme conferring a very low level of resistance level by itself, increased the DDT resistance conferred by sodium channel modification (*kdr*). The RS and RR mortality curves were modified differently such that D_{LC} was higher in the presence of the DTT-ase. Depending on the dose of DDT considered D_{ML}, and hence D_{WT}, were also increased.

The existence of dominance modifiers for insecticide resistance is further suggested by data reported by Bourguet et al. (1997). They found that four resistant strains with a modified acetylcholinesterase, originating from different geographical areas, differed in D_{LC}. A correlation between greater acetylcholinesterase activity and higher D_{LC} was found. Biochemical studies suggested that the strains did not differ in the amino acid sequence of the catalytically active regions of the acetylcholinesterase. Therefore, Bourguet et al. (1997) concluded that acetylcholinesterase synthesis was regulated by either neighboring or distant sites, thereby altering at least the D_{LC}.

Evolution of D_{WT} and D_{WNT}. The occurrence of modifiers in natural populations raises the question as to whether selection for such modifiers is possible. This is a key question because the selection of a resistance allele is favored by high values of D_{WT} and low values of D_{WNT}. According to the theoretical argument of Fisher (1931) and Sheppard (1958) and the analysis performed by Otto and Bourguet (1999), modifiers increasing D_{WT} and decreasing D_{WNT} may be strongly selected if there is a balanced polymorphism, because heterozygotes are maintained at high frequencies for extended periods. Balanced polymorphism may be maintained either by overdominant selection or by migration in a patchy environment (Otto and Bourguet 1999). Overdominance occurs, rarely if at all, in insecticide resistance (but see Wool et al. 1982). Conversely, pest-managed areas are often heterogeneous environments with treated and untreated patches leading to the following fitness matrix:

Genotype	RR	RS	SS
Fitness in treated area (W_T)	1	$1 - (1 - D_{WT})s$	$1 - s$
Fitness in nontreated area (W_{NT})	$1 - c$	$1 - D_{WNT}c$	1

where s and c are the selection coefficients in the presence and absence of insecticide, respectively. If a stable polymorphism is maintained, a modifier allele increasing the value of D_{WT} or decreasing the value of D_{WNT} is likely to invade the population (Otto and Bourguet 1999). Interestingly, even if the modifier increases heterozygote fitness in one patch and decreases it in the second patch, the modifier can invade so long as it increases the weighted average fitness over the two patches. In situations in which a balanced polymorphism is not maintained, modifiers of D_{WT} and D_{WNT} may still be partly selected during the spread of insecticide resistance alleles throughout the population. However, such modifiers are not necessarily present during this window of selection and, even if present, they may not increase in frequency before fixation of the resistance allele (Haldane 1956). Finally, dominance may be modified by the replacement of alleles conferring a recessive insecticide resistance by alleles conferring a more dominant resistance. Although cases of allele replacement have been described at insecticide resistance loci (e.g., Guillemaud et al. 1998, Lenormand et al. 1998), the extent to which dominance coefficients are affected is still unclear.

Dominance of *Bacillus thuringiensis* Resistance

Resistance to *B. thuringiensis* (*Bt*) toxins provides the ultimate example of confusion in the definition of dominance level. Several genetic studies have been undertaken and more than half these studies did not quantify dominance (Table 1). Most studied only D_{LC}, and none investigated D_{WT}, which is the relevant dominance measure for predicting the evolution of *Bt* resistance.

Dominance Levels of *Bt* Resistance. *Bt* resistance has often been defined as recessive according to mortality curves (Bourguet and Raymond 1998, Frutos et al. 1999). Here we report that D_{LC} varies between 0.00 and 0.88 and that no general pattern emerged (see Table 1). Major cases of resistance to *Bt* correspond to modification of the toxin receptors. *Bt* toxins create channels that disrupt ion regulation, and the loss of affinity of the toxin for the receptor may account for *Bt* resistance being recessive if the formation of only a few pores is sufficient to cause osmotic swelling, cell lysis, and death, then in heterozygotes (with 50% sensitive receptors) the phenotype is likely to be the same as for susceptible homozygotes. For incompletely dominant resistance ($0.5 < D_{LC} < 1$), it is possible that modification of midgut proteolytic activity rather than modification of the toxin receptor is responsible for resistance, as observed for a strain of *O. nubilalis* resistant to Dipel-ES (Huang et al. 1999b).

Implications for *Bt* Resistance Management. The high dose/refuge strategy proposed by Georghiou and Taylor (1977) and developed by Alstad and Andow (1995) is the most appropriate for managing transgenic crops and is currently used for *Bt* cotton and *Bt* corn in North America (Ostlie et al. 1997). This strategy was developed for *Bt* crops partly because resistance to *Bt* toxins was initially found to be recessive, and could therefore be expected to be effectively recessive (Alstad and Andow 1995, Gould 1998, Roush 1998). Based on the considerations given above, the high dose/refuge strategy requires D_{ML} to be close to 0, a situation expected because D_{LC} is sometimes low

Table 1. Review of the genetic studies on *Bt* resistance

Species	Toxins	Data	Dominance calculated by the author(s)				D_{LC}[a]	References
			Quantification	Formula	Symbol	Value[a]		
Plodia interpunctella	Dipel[b]	LC	No	—	—	—	0.05	McGaughey (1985)
	Dipel	LC	No	—	—	—	0.47	McGaughey and Beeman (1988)
	Dipel	LC	No	—	—	—	0.44	McGaughey and Beeman (1988)
	Dipel	LC	No	—	—	—	0.41	McGaughey and Beeman (1988)
	Dipel	LC	No	—	—	—	0.37	McGaughey and Beeman (1988)
	Dipel	LC	No	—	—	—	0.33	McGaughey and Beeman (1988)
Plutella xylostella	Dipel	LC	No	—	—	—	0.09	Tabashnik et al. (1992)
	Cry1Ab	LC	No	—	—	—	0.00	Martinez-Ramirez et al. (1995)
	Cry1C	ML	Yes	Hartl (1992)[c]	*h*	0.00	—	Liu and Tabashnik (1997)
	Cry1C	LC	Yes	Stone (1968)[d]	*D*	0.26	0.63	Liu and Tabashnik (1997)
	Cry1Ac, Cry1Ab	ML	Yes	Hartl (1992)	*h*	0.22	—	Tabashnik et al. (1997a)
	Javelin[b]	LC	Yes	Priesler et al. (1990)[d]	D	−0.67	0.16	Tang et al. (1997)
	Toarow CT[e]	LC	No	—	—	—	0.42	Imai and Mori (1999)
	Toarow CT	LC	Yes	Stone (1968)	D	−0.73	0.13	Hama et al. (1992)
Heliothis virescens	Cry1Ac, Cry1Ab	LC	No	—	—	—	0.16	Gould et al. (1995)
	Cry1Ac	LC	No	—	—	—	0.23	Gould et al. (1992)
	Not given	LC	No	—	—	—	0.71	Sims and Stone (1991)
Leptinotarsa decemlineata	Cry3A	LC	Yes	Stone (1968)	*D*	0.76	0.88	Rahardja and Whalon (1995)
Ostrinia nubilalis	Dipel	LC	Yes	Stone (1968)	*D*	0.72	0.86	Huang et al. (1999a)
Spodoptera littoralis	Cry1C	LC	Yes	Stone (1968)	*D*	−0.58	0.21	Chaufaux et al. (1997)

For each study we review the type of data that were collected (lethal concentration [LC] or mortality level [ML]) and whether a dominance level was calculated. Those for which a dominance level had been quantified we indicate the formula and the symbol used and the values that were obtained. Finally, for all studies which provided LC data, we give an estimation of the D_{LC}. D_{LC} was calculated as = $(\log LC_{RS} - \log LC_S)/(\log LC_R - \log LC_S)$ using the LC_{50} of susceptible homozygous (LC_s), resistant homozygous (LC_R) and heterozygous individuals (LC_{RS}). If not available LC_{50} was estimated directly from mortality curves.

[a] If LC_{50} for both crosses (RR females × SS males) and (SS females × RR males) were available only the lowest dominance level is given unless the pooled F_1 LC_{50} was available. Identically when several dominance levels were calculated for different toxins only the lowest dominance level is given.

[b] Dipel and Javelin are commercial formulations of *B. thuringiensis* subsp. *Kurstaki* that contains spores and the genes for Cry1Aa, Cry1Ab, Cry1Ac, Cry2A and Cry2B.

[c] Hartl's (1992) formula corresponds to equation (5) for calculating D_{WT}.

[d] Stone's (1968) and Priesler's et al. (1990) formulae correspond to equation (1) for calculating *D*.

[e] Toarow CT® is a commercial formulation containing 7.0% crystal toxin WP. The toxins contained in this formulation are not given.

(see above). However, the actual D_{ML} depends not only on D_{LC} but also on resistance ratio and the doses of toxin produced by transgenic *Bt* crops. Thus, even incomplete recessive *Bt* resistance (e.g., $D_{LC} \approx 0$) can be effectively dominant (i.e., $D_{ML} > 0.5$) at some *Bt* concentrations. Heterozygote survival and D_{ML} may also be affected by the location on the *Bt* crop, the amount of resources available and the density of larvae feeding on the host plants. Moreover, such environmental variation may be associated with variations in toxin production over space and time in *Bt* plants. All these considerations were taking into account by the FIFRA Scientific Panel to answer the questions posed by the U.S. Environmental Protection Agency on *Bt* plant-pesticide resistant management (EPA 1998a). Thus, in a meeting held in 1998, this Scientific Panel defined the high dose as 25 times the concentration needed to kill susceptible larvae (EPA 1998b). Following our considerations this can be formalized by saying that EPA can expect $D_{ML} = 0$ when *Bt* crops produced 25 times the LC given a $ML_{SS} = 100\%$.

However, the dominance measure relevant for predicting and managing *Bt* resistance is not effective dominance (D_{ML}), but the dominance level of fitness, D_{WT}. Therefore we must emphasize that the high dose/refuge strategy requires D_{WT}, not D_{ML}, to be close to 0. When *Bt* crops kill all RS individuals, then $D_{WT} = D_{ML} = 0$ so that measuring the dominance of the fitness in transgenic fields is no longer required. One of the best examples is the work by Metz et al. (1995) showing that hybrids (putative heterozygotes) of the diamondback moth, *Plutella xylostella* (L.), do not survive on transgenic *Bt* broccoli. Similar results have been found for *Heliothis virescens* (F.) (Gould et al. 1997) and for *Pectinophora gossipiela* (Saunders) (Liu et al. 1999). Although such cases may be common, there is no certitude that all *Bt* plants in heterogeneous environments will work as well as they should do as underlined by the FIFRA Scientific Panel (EPA 1998b). First, some *Bt* crops do not control all SS individuals. For example it is known that the *Bt* maize containing the transformation event #176 did not produce enough toxin to kill SS individuals during the second generation of infestation by the European corn borer, *O. nubilalis* (Hübner). Second, resistance to *Bt* crops may be a long story and we see no reason why *Bt* resistance alleles would never allow heterozygous individuals to survive on *Bt* crops. This has also been underlined by the FIFRA Scientific Panel who recognized that it is conceivable that a heterozygote may develop with higher than 25-fold resistance (EPA 1998b). Thus, EPA is aware that D_{ML} would not systematically equal 0.

When $D_{ML} > 0$, the actual D_{WT} could not be directly predicted as demonstrated in a previous section. However, we have seen that when $ML_{SS} = 100\%$, D_{ML} certainly overestimates D_{WT}. Thus, D_{WT} can still equal 0 whenever $D_{ML} > 0$, which is good news for pest management in general and for the high dose refuge strategy in particular.

Changes in the Dominance of *Bt* Resistance. The effect of the environment on the various measures of dominance for *Bt* resistance has not yet been investigated. Conversely, modifiers of D_{LC} and D_{ML}, and thus probably of D_{WT}, have been identified by Tabashnik et al. (1997b). It is therefore relevant to investigate whether the strategy implemented for managing *Bt* resistance may favor the selection of D_{WT} modifiers. The use of refuges to sustain the usefulness of transgenic *Bt* plants is leading to a fragmented landscape with two patch types. The *Bt* resistance allele is favored in a *Bt* patch, whereas it may confer a disadvantage in non-*Bt* patches, as suggested by Groeters et al. (1993, 1994). Therefore, a polymorphism at the resistance locus may be maintained by migration between transgenic and nontransgenic *Bt* plants, providing an ideal situation for the selection of modifiers of dominance level (Otto and Bourguet 1999). The high dose/refuge strategy proposed by Alstad and Andow (1995) corresponds to a small-scale patch model with complete mixing among reproductive adults from each patch at each generation (Otto and Bourguet 1999). Assuming that offspring settle randomly within one of the two habitats, the chance of encountering a patch depends on its area. If the treated and untreated patches are assumed to account for a proportion α and 1- α, respectively, of the total area, the fitness averaged over the two patch types is as follows:

W_{RR}	W_{RS}	W_{SS}
$1 - (1 - \alpha)c$	$1 - (1 - D_{WT})\alpha s - 1\ (1 - \alpha)D_{WNT}c$	$1 - \alpha s$

A balanced polymorphism will be maintained if $W_{RS} > W_{SS}$ and W_{RR} (Otto and Bourguet 1999). Concerning the high dose/refuge strategy, it is often recommended that s, D_{WT}, and α are initially equal to 1, 0, and 0.8, respectively (Roush 1997). If these conditions are met, then the condition $W_{RS} > W_{SS}$ and W_{RR} is never satisfied. Thus, this strategy cannot lead to a globally stable polymorphism and does not allow extensive modification of D_{WT} or D_{WNT} to occur.

Modifiers of the dominance measures D_{WT} and D_{WNT} may still be partly selected during the spread of *Bt* resistance alleles through the population. Dominance may also be modified by the replacement of alleles conferring a recessive *Bt* resistance by alleles conferring a more dominant resistance.

In conclusion, three dominance measures related to resistance have been used in insecticide resistance studies. These dominance measures reflect three different phenotypic traits: the insecticide concentration required to give a particular ML, the ML at a particular insecticide dose, and the fitness in treated areas. To distinguish clearly among these dominance measures we refer to them as D_{LC}, D_{ML}, and D_{WT}, respectively. All these dominance measures can be estimated by the same general formula given above. Other dominance measures related to an insecticide resistance allele, such as the dominance of fitness in untreated areas (D_{WNT}) can also be calculated with this simple formula. All these dominance measures vary between 0 (complete recessivity) to 1 (complete dominance).

Both D_{LC} and D_{ML} can be directly inferred from mortality curves and may be plotted as a function of toxin concentration and ML, respectively. Nevertheless, D_{ML} depends on three parameters: the resistance ratio, the dominance of resistance D_{LC}, and the dose of toxin. Models predicting changes in allele frequency compare the relative fitnesses of the three genotypes SS, RS, and RR. D_{WT} and D_{WNT}, the dominance levels of fitness in the presence and absence of insecticide, respectively, are therefore required for such models. It has been claimed that $s = LC_{RR} - LC_{SS}$ (Arpaia et al. 1998). We see no reason why s should be considered to be the difference between the LC of the two homozygotes. Actually, s depends on the insecticide concentration in the treated patch, which may vary spatially within the patch, so the coefficient of selection cannot be directly related to the position of the heterozygote mortality curve relative to those of the homozygote curves. More generally, none of the dominance measures described in this article (D_{LC}, D_{ML}, D_{WT}, D_{WNT}) are directly related to any of the others.

D_{WT} is a key parameter with a large impact on the implementation of resistance management strategies (Lenormand and Raymond 1998). Estimating D_{WT} in natural populations is difficult because insecticide concentration in the treated area (and the toxin concentration in transgenic *Bt* crops) and s are variable in time and space. In addition, D_{WT} may be affected by genetic background and environmental factors, as suggested by the variation of D_{LC} (Bourguet et al. 1996, 1997), and may change during selection of the insecticide resistance allele. No study of the genetics of insecticide resistance has yet focused on calculation of the dominance measure D_{WT}. We strongly suggest that the time has come to focus on the estimation of D_{WT} and D_{WNT}. We are aware that such estimations will be a difficult task notably in natural populations. However, some researchers have already measured components of the fitness in the field with and without insecticide applications (McKenzie and Whitten 1984, Follet et al. 1993 and Chevillon et al. 1998). When resistance is rare (notably and currently for *Bt* resistance), release of heterozygotes and resistant homozygotes would be unethical so that such estimation must only be done in the laboratory or in controlled field experiments.

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