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Economic issues in resistance management

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Economic issues in resistance management

by

Silvia Secchi

A dissertation submitted to the graduate faculty

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Major: Economics

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For the Major Program

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For the Graduate College

To Steve.

TABLE OF CONTENTS

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CHAPTER I.
INTRODUCTION

Our well being and the productivity of the economy depend on nonrenewable natural resources, that is, resources which are in the class of non-produced goods, like land: their natural rate of growth is zero. Unlike land, however, exhaustible resources are depleted when used as inputs in production, because the amount of services that can be obtained from them is finite (Dasgupta and Heal, 1979).

In this dissertation, I analyze economic issues related to the use of one of these resources: susceptibility to a chemical compound. There are various types of compounds used to control susceptible targets. Here, the focus will be on two types: agricultural pesticides and antibiotics. Through natural selection, continuous utilization of the chemical compound increases the frequency of the genes resistant to the active ingredients of the pesticide or drug in the target population, and it decreases the available biological capital of genetic susceptibility[1].

Two issues are particularly important in the determination of the optimal use of these resources: the common property nature of susceptibility and technological change. The nonrenewable characteristic is partly a function of technological change. Probably the most visible example is given by oil. The stock of oil is a limited quantity, but the number of oil deposits available increases as extraction technology improves. Moreover,

[1] If the resistant target organism is less fit, that is, has higher mortality or lower reproductive rates than the average organism, the depletion of susceptibility may not only be slowed down or halted, but even reversed. In such a case, susceptibility is better seen as a renewable resource. Here we will focus on the resistant organisms' fitness being identical to that of susceptible ones.

technological change allows the substitution of a resource with another, that can be either exhaustible or renewable. For instance, natural gas and solar energy, which is in unlimited supply, can substitute for oil.

Clearly, if backstop technologies are discovered at a sustained pace and the returns to research are high, biological susceptibility to an existing substance is not a very valuable good. If, on the other hand, the outcomes of the innovative process are uncertain and research requires substantial investments, the pesticides and drugs we have should be used more sparingly to prolong their life span. Also, if all the active ingredients being discovered are similar to each other, in that they have a similar mode of action, it is likely that resistance to a chemical will result in reduced susceptibility to another one. Such cross-resistance is a problem for both antibiotics and pesticides, where the classical example of cross-resistance is the case of resistance to DDT. One of the genes conferring resistance to DDT, *kdr*, also gives resistance against pyrethroids (Georghiou). Multi-drug resistance is widespread because bacteria have various mechanisms to exchange the genetic material that makes them resistant (Levy 1992). For example, if the bacterium *Hemophilus influenzae*, which causes ear infections, meningitis and pneumonia, develops resistance to penicillin, it can transmit this resistance to *Escherichia coli*. Thus, bacteria never directly exposed to any antibiotic can still possess resistance genes.

Common property issues are key to understanding resistance because the individual contribution to the buildup of resistance is generally very low. Moreover, both pests and bacteria are mobile, so first-best behavior today does not guarantee successful

outcomes of the pesticide application or the drug therapy in the future. For both these reasons, decentralized solutions to the problem of optimal use of pesticides/drugs are likely to be suboptimal.

Genetic susceptibility to pesticides has been long been identified in the economic literature as an exhaustible resource (Taylor and Hadley, and Hueth and Regev). On the other hand, the problem of resistance to antibiotics has attracted less attention in economics until recently (see Brown and Layton, and Laxminarayan and Brown). Recent events have increased the importance of determining optimal use of existing substances in the case of both pesticides and antibiotics.

For pesticides, an important event that has brought the issue of resistance management to the forefront of the policy debate has been the successful introduction of plants genetically engineered to produce toxins which kill pests. The first generation of these products uses toxins produced by a bacterium, *Bacillus thuringiensis* (*Bt*). The rapid expansion of these products poses important policy questions on how to utilize these new resources so that resistance buildup is limited. For instance, according to the Third Biennial National Organic Farmers' Survey conducted by the Organic Farming Research Foundation (OFRF), *Bt* sprays are the most important external input used by organic farmers for pest management. Moreover, *Bt* sprays are used on over half of the US production of crops such as celery, cabbage and fresh tomatoes (USDA, 1999a). There is a concern that the heavy use of *Bt* toxins produced by the plant pesticides will cause resistance to develop, thereby depriving farmers of the possibility to use *Bt* sprays (EPA, 1998a). In order to preserve susceptibility, the EPA has mandated the use of

refuges, untreated portions of the field in which insects susceptible to *Bt* can survive, so that their mating with resistant pests can slow down the mining of susceptibility.

In the case of antibiotics, the problem of resistance is more dramatic for two reasons. The first is that the failure of a drug to treat an illness has more serious consequences than crop failure: The second reason is that antibiotic discoveries were concentrated in the 1940s and 1950s (Kingston). Only two new classes have been discovered since them, and the newest class, the oxazolidinones, is still not commercially available (Diekema and Jones).

Here is a brief synopsis of the chapters that follow. Chapter II consists of a general theoretical model of resistance development that explicitly incorporates a spatial dimension. When determining pesticide applications and their impact on the development of resistance, decision makers have two control variables at their disposal: one is how much chemical to use in a given portion of the region, and the other is the percentage of the total region over which to apply the chemical, or the refuge size. The use of refuges is not a novel idea (see for instance Georghiou and Taylor, 1977), but it is receiving more attention recently because of the EPA's policy towards *Bt* crops. The explicit presence of a spatial element in the model allows us to examine the impact of pest mobility on the common property nature of susceptibility and its effects on refuge. The inclusion of pest mobility is also instrumental in specifying the conditions in which eradication policies may be successful. Should eradication not be a feasible option, the model includes a salvage function for the pest population and the susceptibility to the pesticide. This allows us to discuss the role of cross-resistance in determining pest management policies.

Chapter III presents an empirical analysis of the consequences of pest mobility on the development of resistance in the context of *Bt* corn. The model takes into account the existence of mandatory (structured) refuges for farmers planting *Bt* crops and analyzes the impact of incomplete market penetration on resistance development and profits. If part of the crop production area is seeded with traditional, non-bioengineered seed, these fields act as an unstructured refuge. The current EPA policy is effectively based on a 100% market penetration. Given the reluctance of the European Union to accept agricultural products containing bio-engineered material, it is possible that market penetration could stagnate. In such an instance, the presence of a spatial component allows an explicit evaluation of the role of structured and unstructured refuges and their costs.

Chapter IV concentrates on the optimal use of existing antibiotics and on the optimal time path of investment in the development of new technologies. The intertemporal allocation of susceptibility and the development of alternative technologies are important social issues, particularly in the case of pharmaceutical products, because health can be considered a necessary good. The analysis focuses on three scenarios. In the first, no technological change is possible, so the existing antibiotic is the only one that will ever be available. In the next two scenarios, endogenous technological change is introduced. First, discovery is in the form of the certain (costly) introduction of another antibiotic that still depends on the presence of susceptible targets. In the second case, innovation produces a novel technology, based on a renewable resource. Since this

backstop is an entirely novel technology, however, there is uncertainty on when it will become available.

Finally, in Chapter V, I present some general conclusions and discuss the importance of externalities and of technological change in the optimal depletion of genetic susceptibility.

CHAPTER II.
A SPATIOTEMPORAL ANALYSIS OF PESTICIDE USE AND RESISTANCE DEVELOPMENT

Introduction

This chapter extends the literature on nonrenewable resources by analyzing the management of an agricultural pest population through a pesticide which promotes resistance when spatial refuges are used to prolong the pesticide's efficacy. Suppose that, in a given crop production region, a decision-maker has to choose the quantity of chemical input (pesticide) to use. The optimal amount of pesticide applied depends on two factors. The first is that a higher usage of the input, while it reduces today's pest population, also causes resistance to develop in the future, thereby reducing efficacy in the long run. The second factor is the mobility of the pest population. Weeds, fungi and insects are all mobile, so mobility is potentially important to many pests. The movement of pests from field to field may help counter the natural selection process that gives rise to the development of resistance because this movement affects the genetic make-up of the pest population and will affect the evolution of resistance. Therefore, a decision maker concerned with the long term efficacy of the pesticide has two control variables at her disposal: how much chemical to use in a given portion of the region, and the percentage of the total region in which the chemical is applied. Thus, the optimal exhaustion path of pesticide susceptibility has both temporal and spatial dimensions.

Previous studies (Hueth and Regev, Taylor and Hadley, Regev *et al.*, Lazarus and Dixon, Clark and Carlson and Gorddard *et al.*) have concentrated on the pesticide dose as

the only control variable, and have not considered how pest mobility over space affects the dynamic path of resistance. Specifically, Hueth and Regev analyze resistance development within one season, and do not include a spatial element[1]. Taylor and Hadley develop an explicit genetic model of resistance inheritance which produces a resistance path similar to the one used in this paper (see Hartl and Clark). Regev *et al.*, 1983, Lazarus and Dixon and Clark and Carlson illustrate the possible problems deriving from the common property nature of pests. Gorddard *et al.* focus on weeds, and on the integration of chemical and non-chemical control to slow down resistance development.

The value of susceptibility to a pesticide is higher if the pest causes considerable crop damage, or if backstop technologies are not discovered frequently. In addition, delaying resistance is valuable if cross resistance is a potential problem.

Cross resistance occurs if the active chemical element present in the pesticide has a mode of action that overlaps with that of another existing or yet to be invented pesticide. The presence of cross resistance means that susceptibility has a positive value even after the backstop technology is introduced. Clearly, it is not possible to attribute a general value to cross resistance, as each pesticide will have different levels of cross resistance with respect to other pesticides. However, as long as pesticides use a similar mode of action, cross-resistance is likely. Hammock and Soderlund, for example, note how most neurotoxins used as insecticides "act at only two sites in the nervous system. Thus, genetic modifications that change the sensitivity of these sites of action (altered

[1] This paper discusses the development of resistance in a multiseason setting, and it introduces the role of space explicitly. However, wherever applicable, Hueth and Regev's assumptions on the characteristics of the functions involved are considered.

acetylcholinesterase for carbamates and phosphates, nerve insensitivity resistance for DDT and pyrethroids) produce cross-resistance that renders entire classes of compounds ineffective against resistant populations" (p.120).

Given these possibilities, it might be optimal to preserve susceptibility by leaving a portion of the crop production region untreated, so that it can serve as a refuge for susceptible pests. Their mating with the resistant pests growing in the treated part of the region slows down resistance buildup. The use of untreated areas as refuges for susceptible pests is not a novel idea. It has been analyzed by entomologists at the theoretical level (see for instance Georghiou and Taylor, and Caprio), and it has been advocated in practice as a strategy to slow down the resistance to acaricides used to control the two spotted spider mite in pear orchards (Croft and Dunley), imidacloprid applied to suppress the Colorado potato beetle in potatoes (Dively *et al.*) and foliar applications of *Bacillus thuringiensis* (*Bt*) used to control the diamondback moth in cabbage cultivations (Perez *et al.*)[2].

Most importantly perhaps, the introduction of genetically modified crops that produce *Bt* toxins lethal to Lepidopteran insects has prompted the Environmental Protection Agency (EPA) to mandate the use of refuge to preserve the efficacy of the toxins (EPA, 1998a). Hurley *et al.* (1997) provide a clear economic analysis of various refuge scenarios in the case of *Bt* corn.

Consideration of the interaction of space and pest mobility is also important in

[2] In the case of weeds, the use of refuges as a resistance management strategy is more controversial. See Jasieniuk *et al.*

determining the degree to which private pest control decisions lead to the first best outcome. If the pest population is only mobile within a farm's perimeter, there are no externalities. However, if more farmers are involved, pest mobility may well create a spatial externality[3], as different levels of treatment will bring about different levels of pest population density. Farmers using more pesticide will eliminate a high percentage of the pest population, thereby lowering the number of pests moving to neighboring farms. Conversely, farmers who use low levels of treatment will have a higher pest population, and more pests will tend to move to adjacent farms. An externality is present as long as the net influx of pests from one farm to another is different from zero. The externality is positive for low-treatment farmers, and negative for the high-treating ones.

Mobility has implications on susceptibility as well, because pests in the areas treated less frequently will have lower resistance, so their movement into the zones treated more often will slow down resistance buildup. Thus, in terms of resistance, the signs of the externality are reversed: pests moving from low-treatment areas are more susceptible to the pesticide, so their mating with the more resistant pests in the high-treatment areas may help slow down resistance buildup. The effects of mobility illustrated above have considerable implications on the optimal pest management strategy. If there are many farmers in the crop production region, and each of them is optimizing chemical usage and treated area independently from the others, without considering the effect of his actions on the neighboring field's pest population and their

[3] The exception would be if all farmers behaved identically and had identical fields, in which case the externalities would be perfectly offset against each other.

dynamic consequences on the development of resistance, there might be the need of an institutional arrangement to coordinate the farmers' decisions, such as a pest management group. Miranowski and Carlson discuss how market structure and pest mobility affect management strategies, and they point out that "if the pest being considered is mobile, optimal management of pest susceptibility may require some form of organization or regulation, given the "common property" nature of pest susceptibility" (p. 446)[4].

To analyze these issues, this chapter develops a discrete time model of optimal usage of pesticide and refuge, and determines the shadow values of the pest population and of susceptibility to the pesticide. The effects of pest mobility on the first-best policy are also discussed. The model's framework is also used to discuss the common property aspect of susceptibility and how this can bring about myopic behavior towards the buildup of pesticide resistance. The model also allows us to examine the impact of cross-resistance in the determination of pest management strategies and the role of eradication policies. Eradication, if successful, eliminates the pest problem permanently: this justifies high one-time or short term expenditures. However, eradication is arduous for pests feeding on more than one crop[5] (polyphagous) or for very mobile pests, because it requires a high level of coordination. A continuous version of the model is also developed, in which the farmer only chooses the refuge level. This is the case for *Bt* crops, for which the level of chemical concentration is determined via genetic manipulation by the seed producers, and it is also applicable to farmers who follow the

[4] For an analysis of conditions of participation into pest management groups, see also Rook and Carlson.
[5] For instance, the corn borer is also a cotton pest.

recommended dosage instructions for spraying. This version is used to analyze the optimal time path of the refuge.

Susceptibility does not necessarily have to be viewed as non-renewable. If there are fitness costs, that is, resistant pests are less healthy than the susceptible ones, either in terms of reproductive potential or survival capacity, then a reduction in the use of the chemical will result in renewed susceptibility. Though circumstances will vary from species to species, and from pesticide to pesticide, there are clear instances of non-reversibility of resistance[6]. Here we assume that resistant pests behave identically to susceptible ones in all respects except in the response to the pesticide.

The chapter is organized as follows. First, a stylized spatiotemporal model is presented. Then, first-best management rules are found, and some second best scenarios are discussed. Third, we derive a continuous version of the model in which farmers have no control over the dose of pesticide to use and we analyze the time path of the refuge. Finally, some policy implications of the model are discussed in the conclusions.

The model

As noted above, the presence of an explicit spatial component in modeling pest management is crucial if we want to understand the impact of refuges in delaying pesticide resistance. Even without the introduction of refuges, the spatial dimension – both in terms of area treated and degree of mobility of the pest – plays an important role in determining the degree to which pest population and susceptibility to the pesticide are

[6] See for instance Andrews and Morrison, Croft and Whalon, Penrose, and Romero and Sutton.

treated as common property resources. Common property characteristics are exacerbated if the pest is very mobile and the area being considered is large.

When introducing a spatial element, care must be taken to insure that all the critical spatial effects of the specification chosen are included in the analysis. For example, if a square grid is specified, there is a two dimensional variable for τ, the fraction of the area in which the chemical is used, because for each level of τ there is a corresponding average distance between treated and untreated fields, and a variance.

For clarity and analytical tractability, the problem is modeled here using an approach inspired by Von Thünen's monocentric model[7]. We assume that the area of production is given and that it is represented by a circle, and that τ represents the fraction of area in which the chemical is used (Figure II.1).

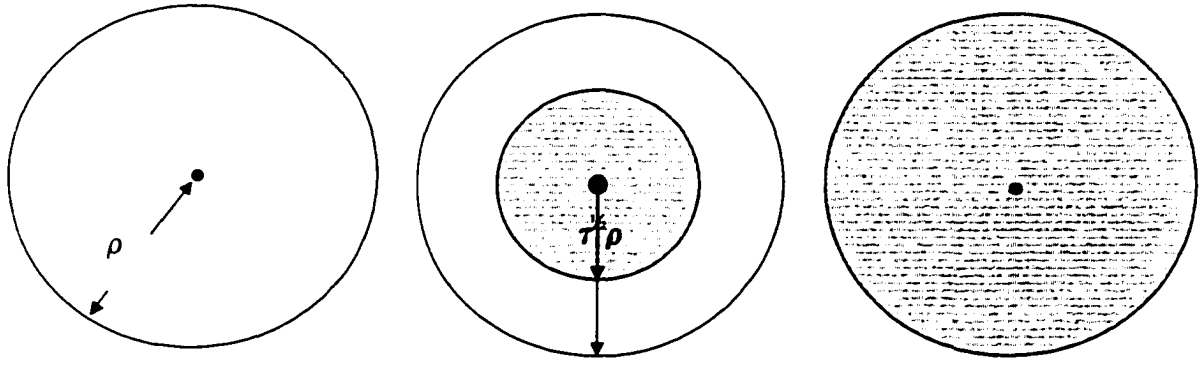

Figure II.1 – The region of production

[7] See Samuelson for an analytical version of the Von Thünen model.

The area of chemical usage can then be described with a one dimensional variable. Define ρ as the radius of the area under consideration, and remember that for a circle π = circumference/diameter, and that area A is $A = \pi \times (radius)^2$. Then for any share τ, such that $0 \leq \tau \leq 1$, the area of the share is $\pi\tau\rho^2$, versus the total area of the region, $\pi\rho^2$, and the circumference of the share is $2\pi\tau^{1/2}\rho$, versus the region's circumference, $2\pi\rho$. The circumference is proportional to the radius, so an increase in τ brings about a $2\pi\rho\Delta(\tau^{1/2})$ increase in the size of the circumference. Therefore, in this specification, the parameter τ suffices to completely characterize the spatial dimension of the model.

The area of production in this context is identified as being a habitat for the pest population, circumscribed by physical boundaries, such as natural barriers, or non-host crops for the pest in question. As we noted above, the single decision maker can represent one farmer or a group of farmers acting together via an institution such as pest management groups. Since we are dealing with ecosystems, the choice of the limits of the production region is not inconsequential. If the boundaries are administrative rather than real, the pests included in the area examined will not necessarily behave as a population. We would have to consider several pest populations or less than one population. As will be discussed later, dealing with one habitat does not necessarily imply that the pest population is a completely isolated system.

The model represents a single crop, single pest problem, and it uses the year as the time unit. The results are generalizable to a multi-pest, multi-crop situation. The sequence of events in each season is based on the behavior of univoltine (one generation

per year) European corn borers (*Ostrinia nubilalis*)[8]. We assume that each time period starts with the reproduction of the adult pests. Treatment is directed to the offspring, the larvae, which cause the crop damage. The larvae then overwinter, pupate and become adult moths. The adult moths move, and then reproduce, at which point the next season starts (Mason *et al.*). This model could also be used to describe the life cycle of the corn rootworm or other pests with minor alterations[9]. The three fundamental relations of the model are:

$$Z_t = P_t\,[1-u(S_t)k(C_t,\ \tau_t;\ \lambda_{t-1})], \tag{II.1}$$

$$P_{t+1} = Z_t + g(Z_t,\ A), \tag{II.2}$$

$$S_{t+1} = S_t - [h(S_t)r(C_t,\ \tau_t;\ \lambda_{t-1},\ A)], \tag{II.3}$$

where:

Z = pest population causing the damage,

P = size of pest population at the beginning of time period t (state variable),

$u(\cdot)$ = function characterizing susceptibility's impact on the pesticide action, $0 \leq u \leq 1$,

S = susceptibility level (state variable),

---

[8] See Mason *et al.* for a more detailed exposition of the European corn borer's life cycle.

[9] In the case of the corn rootworm, reproduction occurs at the end of the growing season. Thus, we would synchronize the beginning of each time period t with the end of the growing season. The corn rootworm overwinters in the egg stage. It hatches in the Spring, and the larva causes damage by feeding on the corn root system. Soil insecticides are applied to prevent larval damage. The corn rootworm then pupates and becomes an adult in late Summer. This pest causes damage in the adult form as well, so there may be different forms of treatment for the same generation of pests. However, the damage caused by the larvae is by far more significant (Willson).

$k(\cdot)$ = chemical efficacy function, $0 \leq k \leq 1$,

C = amount of chemical input applied per unit area (control variable),

τ = fraction of the area A in which the chemical is used(control variable), $0 \leq \tau \leq 1$,

λ = pest mobility parameter,

$g(\cdot)$ = pest population growth function,

t = time,

A = $\pi\rho^2$, total area under consideration,

$h(\cdot)$ = change in resistance as a function of the level of susceptibility, $0 \leq h \leq 1$,

$r(\cdot)$ = change in resistance as a function of chemical use and area treated, $0 \leq r \leq 1$.

Equation (II.1) characterizes the behavior of the pest population causing the damage within the course of one season, and it encapsulates the effects of chemical treatment and refuge. The pest population causing the damage to the crop, Z, is a linearly increasing function of the initial pest population that year, P: $Z_P = \{1-[u(S_t)k(C_t, \tau_t); \lambda_{t-1}]\} \geq 0$ and $Z_{PP} = 0$, where non-t subscripts denote a partial derivative. In this particular formulation, Z can be taken to represent the simple survival of a one-generation per year pest population. However, we could define Z more in general as $Z = z[P, S, C, \tau, \lambda]$ to accommodate the case of multiple generations per season. In this case, Z could be interpreted as a reduced form of more complex intra-seasonal dynamic behavior of the pest population.

An increase in the chemical dose increases the number of pests killed, $k_C > 0$, and decreases the surviving pest population: $Z_C = - P_t u(S_t) k_C < 0$. Note that by C we indicate the amount of chemical used per unit area, or the dose. The total amount of pesticide used will be given by $C\tau A$. We assume that there is diminishing marginal productivity on the chemical used: $k_{CC} < 0$, so that we have $Z_{CC} = - P_t u(S_t) k_{CC} > 0$. This parameterization is equivalent to the assumption made by Hueth and Regev that the pesticide action is not density dependent. In the case of the area treated τ, a decrease in refuge increases the number of pests killed, $k_\tau > 0$, so that $Z_\tau = - P_t u(S_t) k_\tau < 0$. Because of pest mobility we assume diminishing marginal productivity on the sprayed area as well, $k_{\tau\tau} < 0$, therefore we have that $Z_{\tau\tau} = - P_t u(S_t) k_{\tau\tau} > 0$. Since the dose and the area treated are complements, $k_{C\tau} > 0$. These relationships are depicted in Figure II.2.

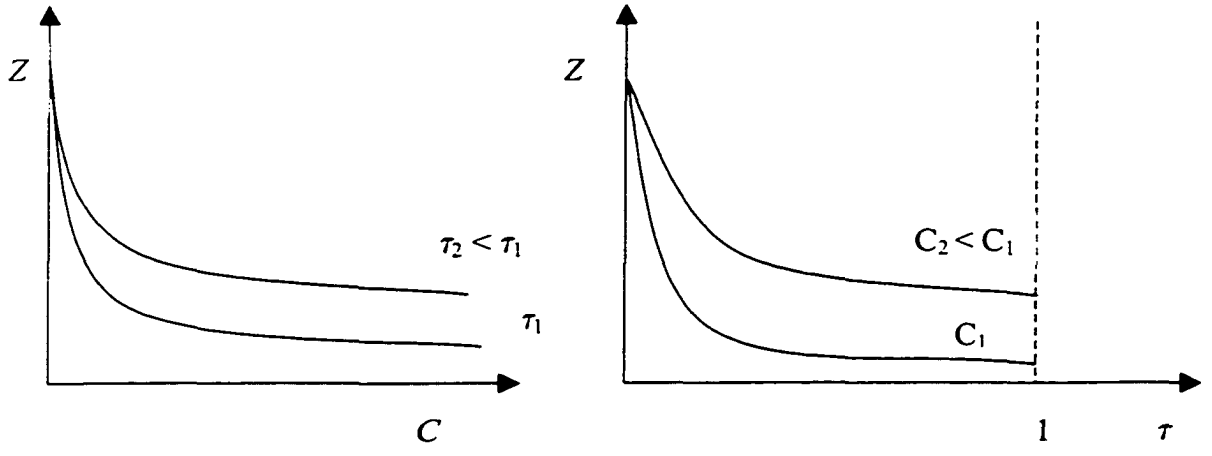

Figure II.2 – The relationship between Z, C and τ

Intuitively, the function $k(\cdot)$ is such that $k(C_t, 0) = k(0, \tau_t) = 0$. The function is bounded to the interval [0, 1]. In practice, the upper boundary is likely to be strictly smaller than one. Pesticides may not able to control the whole pest population, even if sprayed in high doses, because pests may live in parts of the plant, such as the roots, which are difficult to reach.

The function u is bounded between 0 and 1, with $u' > 0$ and $u'' > 0$. An increase in susceptibility to the pesticide decreases the number of surviving pests, $Z_S = - P_t u'k < 0$. The second order effect of susceptibility on the surviving pest population is positive: $Z_{SS} = - P_t u''k > 0$. Note that resistance Γ can be defined as the negative of susceptibility, so when $S = 0$, $\Gamma = \{\Gamma_{max}\}$ and, when $\Gamma = 0$, $S = \{S_{max}\}$ (Figure II.3).

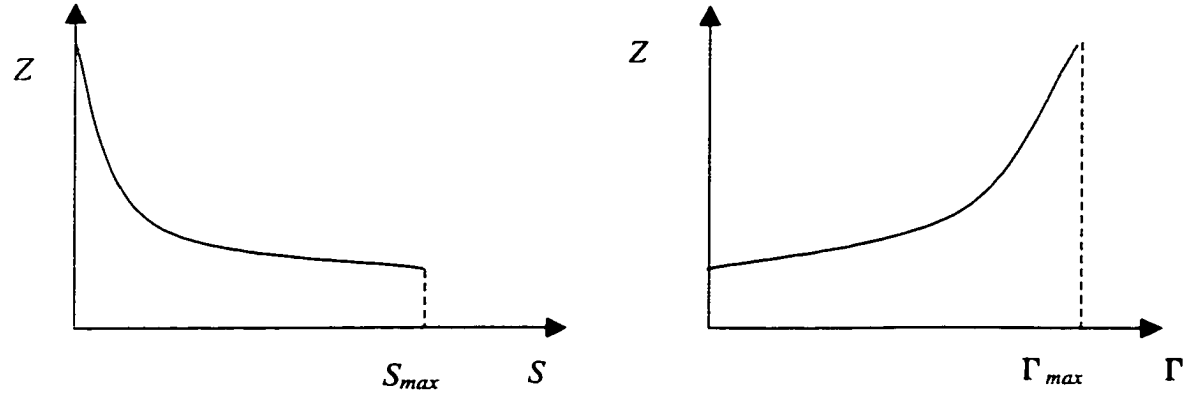

Figure II.3 – The relationship between Z, S and R

For simplicity, we will abstract from the effects of A, the area under consideration. Its inclusion in the function would indicate that there are scale and size effects involved, as the pest population dynamics may differ depending on the dimensions of the region of production.

The parameter λ represents a vector characterizing pest mobility. As this constitutes an important element of the model, and its specification has implications on the feasibility of eradication policies and on the transversality conditions of the problem, a brief digression on how pest mobility has been characterized in the literature follows.

The traditional distinction is between migration and local dispersal (see for instance Johnson). The former refers to inter-habitat movement, while the latter indicates intra-habitat dispersal. Both forms of dispersal may coexist (see Byrne *et al.* on the green peach aphid, for example). If that is the case, a 'partial equilibrium' approach, that treats the region of production as a closed system, is inappropriate. A better characterization would require the use of metapopulations, and of models of stratified dispersal, in which discontinuous long distance dispersal and short-distance continuous dispersal are both present (Hengeveld).

More simple, one-population models either impose equations of movement (Shigesada and Kawasaki), or start off with an empirical analysis, and then fit rules of dispersal from observation to obtain dispersal predictors (see Pacala and Silander for a weed example, and Stinner *et al.* for an insect one). In either case, the models require assumptions on the original pest density, and rules on the boundary conditions. Pests reaching the edge of the habitat will either turn back and not cross, or be lost to the

population. In the first instance, the boundary condition is called reflecting while in the second case, the boundary is absorbing. When dealing with an environment not completely isolated, and in the absence of a metapopulation model for the pest in question, the boundary rules would have to allow for some infiltration of pests from the outside. This is the most interesting possibility in economic terms, because in this case eradication policies within the region are not effective, and the susceptibility to the pesticide is a resource worth preserving.

To simplify the present analysis, we assume that the pests have no preferred direction of movement, and that the time/distance traveled ratio is inconsequential in terms of the choice of pest management strategy, so that a dispersal predictor can be approximated with the first two moments of a distribution, and the elements to be included in λ are simply the average distance traveled and its variance[10].

We also assume that the parameter λ, which is the result of biological characteristics of the pest population considered, is the same for the treated and untreated portions of the population. That is, the chemical treatment does not affect mobility of surviving pests. Note that, if $\lambda = 0$, there are effectively two separate populations in the area. This assumption is clearly not realistic, since some degree of mobility within each region of production is necessary for the pest population to reproduce[11]. If the chemical is effective enough to kill the whole population in the area when applied in sufficiently high doses, the population could be eliminated in the first period by setting $\tau_1 = 1$, and

[10] We also need to assume an initial spatial distribution such as a two-dimensional uniform.
[11] This is obvious for diploid pests that reproduce sexually as they need to move to find a partner, but it holds also for, say, the haploid phases of fungi, since the mitospores will have to move away in order to find a site where to germinate.

applying a high enough dose of the pesticide. In this case, resistance would not develop. However, in practice, it is likely that the chemical used will have efficacy rates of less that 100%, as noted when discussing the function $k(\cdot)$. Another possibility, as we discussed before, could be that the pest population in the region is not totally isolated, in which case eradication would not be feasible without substantial concerted efforts, since all the farmers operating in the connected habitats would have to be involved. In such an instance, we would define the immigrant pest population in the region as $P_{min} > 0$, and, for logical consistency, we would consider the boundaries as being absorbing[12].

In general, we can infer the behavior of the pest population with respect to the average level of mobility λ^1 included in $\boldsymbol{\lambda}$ for a given $C > 0$ and $\tau > 0$. The use of the pesticide at time t reduces the relative pest population density in the treated area, and it has no impact on the density of the pests in the untreated area. As the pests move, more of them will tend to redistribute from the higher density area (untreated) to the one of lower density (treated). The higher the level of mobility, the higher the redistribution of pests from the untreated to the treated portion of the region. In period t, this does not have any effect on survival: $\partial Z_t / \partial \lambda_t^1 = 0$. However, at time $t + 1$ the population in the treated area is higher[13] the greater the average distance traveled. Therefore the same dose of chemical and the same area treated will eliminate a higher absolute number of pests:

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[12] Note that, symmetrically, some of the pests lost to the local habitat would survive and emigrate to another one. The susceptibility of the immigrant pests could be different from that of the local ones. We assume, for simplicity, that they have the same genetic make-up, as if there were n regions of production of radius ρ, all optimizing profits.

[13] The population density in the area treated increases with mobility, but it will not necessarily be as high as the pest population in the untreated area. Very high levels of mobility are necessary to redistribute the pest population so that its distribution is homogeneous among the treated and untreated areas.

$k_{\lambda^1} > 0$, so that $\partial Z_{t+1} / \partial \lambda_t^1 = -P_t u(S_t) k_{\lambda^1} = Z_{\lambda^1} < 0$. Since $\boldsymbol{\lambda}_t = \boldsymbol{\lambda}\ \forall\, t$, $\partial Z_t / \partial \lambda^1 < 0$ for any $t > 0$[14]. A higher variance of the distance traveled (λ^2) will increase the chances that pests from the untreated area will be lost if the boundaries are absorbing, so that $\partial Z_t / \partial \lambda^2 < 0$ for $t > 0$[15]. Therefore, if the boundaries are absorbing, we can write $Z_{\boldsymbol{\lambda}} < 0$[16]. For consistency, we will also assume that $k_{C\lambda}$ and $k_{T\lambda}$ are positive.

Equation (II.2), reproduced below for convenience, denotes the dynamic behavior of the pest population:

$$P_{t+1} = Z_t + g(Z_t, A). \qquad \text{(II.2)}$$

Equation (II.2) illustrates how the initial population at time $t + 1$ is a function of the surviving population at t after movement has occurred, and possibly of the area of interest if there are scale effects. The structure of $g(\cdot)$ will depend on the growth function chosen. If we were to use a discrete time logistic growth function, for instance: $P_{t+1} = Z_t \exp(1 + r(1 - Z_t / K(A))$, where K represents the environmental carrying capacity ($K_A \geq 0$), then the sign of g_Z would be at first positive and then become negative. For simplicity, here we assume that growth occurs exponentially and we abstract from scale

[14] For this reason, we will eliminate subscripts for λ from now on.
[15] If the boundaries are reflecting it is not possible to sign $\partial Z_t / \partial \lambda^2$ a priori, because the net effect of a high λ^2 will depend on the average distance traveled in relation to the total area.
[16] Note that, if the refuge were to be rotated from the outside to the inside region every season, we would have the opposite sign for Z_{λ}, since a higher level of mobility would redistribute the pests into this year's treated region which will be, at least partly, next year's refuge area.

effects so that $P_{t+1} = Z_t + \phi Z_t = \theta Z_t$. Therefore, $g_Z = \phi > 0$ and $g_{ZZ} = 0$[17]. Note that this assumption is less restrictive that it may appear at first, since the logistic function behaves similarly to the exponential in its lower portion. As long as τ and C are strictly positive, so that there is some form of population control, it is reasonable to assume that we are in the lower part of the growth function, therefore the exponential provides a good approximation for the logistic. Since $Z_\lambda < 0$, we can see the effect of increased mobility on the dynamics of the pest population: $dP_{t+1}/d\lambda = \theta(\partial Z_t/\partial \lambda) < 0$

The rationale for the sign is that a higher level of mobility causes a higher redistribution of pests from the untreated to the treated area, so that in the next season, there are fewer pests living in the refuge and a higher number of pests that, having moved to the treated area, are killed by the pesticide application. High levels of mobility bring about higher levels of population redistribution from high to low density areas, so, over time, the refuge will retain a smaller part of the pest population.

Equation (II.3), shown below for convenience, establishes the path of resistance evolution. Susceptibility in year $t+1$ is equal to the stock of susceptibility in the previous year t minus the amount of resistance developed in t. For simplicity, we normalize the stock of susceptibility to be in the interval [0, 1], so that $S_0 = 1$:

$$S_{t+1} = S_t - [h(S_t)r(C_t, \tau_t; \lambda_{t-1}, A)]. \qquad \text{(II.3)}$$

[17] In the simplest case, $P_t = Z_t$, so $P_1 = P_0(1 + \phi)$ and $P_2 = P_1(1 + \phi) = P_0(1 + \phi)^2$. In general, $P_t = P_0(1 + \phi)^t$. We want $\phi > 0$ or else the population will either decrease or remain constant over time (Hastings). To introduce scale effects, we could have $P_{t+1} = \varphi(A)W_t(1 + \phi)$, for instance.

The function $0 \leq r \leq 1$ is such that: $r(0, \tau_t) = r(C_t, 0) = 0$. Resistance is an increasing function of chemical usage, and it is reasonable to assume that $r_{CC} > 0$ since this implies that natural selection increases resistance buildup at an increasing rate as chemical usage increases. The relationship between the buildup of resistance and the area treated is really a dynamic one, therefore a more accurate notation for r_τ would be $\partial r_{t-1}/\partial \tau_t$. As discussed above, for any given level of the chemical's dose, an increase in the area treated will reduce the number of surviving pests. Correspondingly, the selection pressure for resistance will increase, so $r_\tau > 0$ (Figure II.4).

As we assumed that $r_{CC} > 0$, for symmetry, we also assume that $r_{\pi\pi} > 0$. The reason is that increases in chemical usage, both in extensive and intensive terms, promote natural selection pressures at an increasing rate. Since C and τ both increase resistance, we assume that they are complements: $r_{C\tau} > 0$.

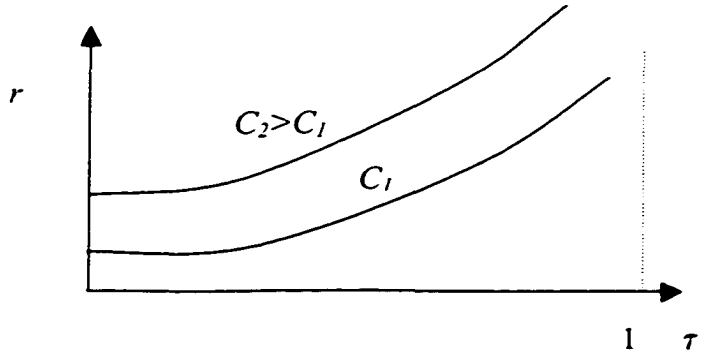


Figure II.4 – The relationship between r, τ and C

The function $0 \leq h \leq 1$ is such that: $h(0) = 0$. Resistance is commonly modeled as being conferred by a single not sex-linked allele, partially dominant (Taylor and Hadley) or recessive (Hurley *et al.*). In both cases, the time path of resistance follows a sigmoid curve similar to the one in Figure II.5 (Hartl and Clark). If resistance develops according to a sigmoid, as susceptibility decreases, at first $h' > 0$, and then $h' < 0$. For consistency, we will assume that $h'' < 0$.

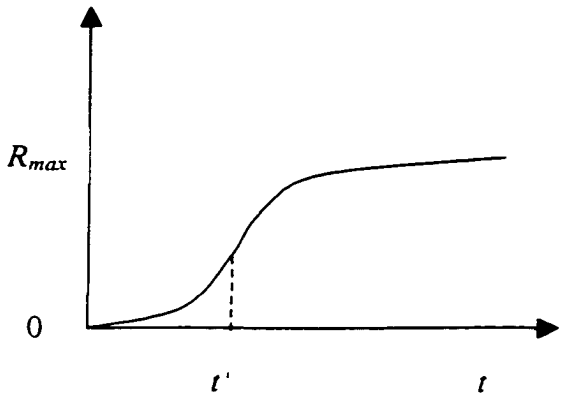


Figure II.5 – The time path of resistance

We have discussed above the effects of mobility on the pest population density. Higher mobility favors the redistribution of the pests, so that through time, a higher proportion of the pest population will reach the treated area and be exposed to the pesticide. In terms of the effects of mobility on the rate of development of resistance, entomological evidence (Peck *et al.*, 1999, Caprio, 1998) indicates that low rates of migration increase the rate of resistance development in the whole region of production.

The reason is that lower mobility isolates the treated area from the untreated one, thereby increasing the speed at which resistance develops locally. The low mobility also limits the dispersal of the resistant pests: in effect, the refuge is isolated from the treated area, so the resistant pests are less likely to mate with susceptible ones and dilute resistance. The mobility results of Peck *et al.* and Caprio appear to be robust to changes in their models' parameters. However, these results are not necessarily general. For instance, the scale of the region involved could alter the influence of mobility. Since both models agree on the effect mobility has on resistance, we will abstract from scale effects and assume that increases in the parameter λ shift the curve $r(\cdot)$ downwards. Figure II.6 illustrates the relationship in the r and C space.

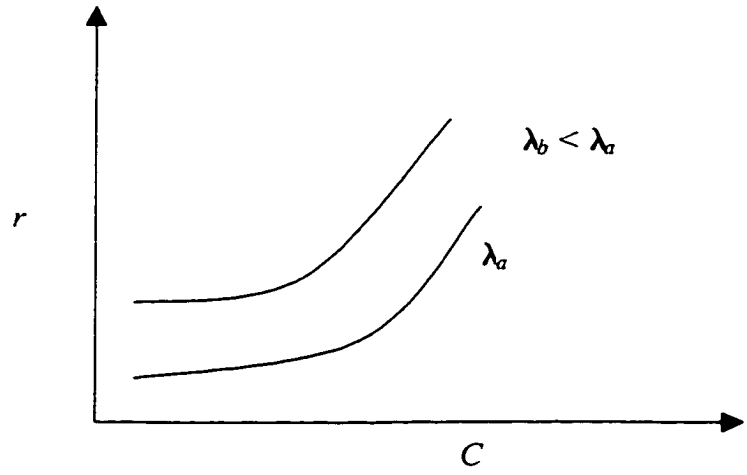


Figure II.6 – The relationship between mobility and resistance development

The optimal level of pest control

The objective function to be maximized by the decision maker with respect to the control variables C and τ is:

$$\sum_{t=0}^{T} \rho^t \Pi_t + \Omega(P_T, S_T) = \sum_{t=0}^{T} \rho^t [Y_t - D(Z_t) - q(C_t, \tau_t)] + \Omega(P_T, S_T), \qquad \text{(II.4)}$$

where:

T = time at which a backstop technology becomes available, assumed to be known,

$\rho = 1/(1 + \delta)$ discount factor, where δ is the discount rate,

Π = profit,

$\Omega(P_T, S_T)$ = salvage function,

Y = pest-free yield for area A,

$D(\cdot)$ = damage function,

$q(\cdot)$ = total cost of using the chemical, with $q_C > 0$, $q_{CC} \geq 0$ and $q_\tau > 0$, $q_{\tau\tau} \geq 0$.

We assume that a rise in the pest population increases the damage at an increasing rate, as in Hueth and Regev, since more dense pest populations cause damages to escalate. Therefore, $D_Z > 0$ and $D_{ZZ} > 0$. The function $q(\cdot)$ is increasing in both C and τ and convex in its arguments, and $q(0, \tau_t) = q(C_t, 0) = 0$. Without loss of generality, we normalize output price to one, so revenue for area A at time t is equal to pest-free yield

minus the damage of the pest. Total profit in year t then is equal to total revenue minus production costs, which depend on how much chemical is used and over how much area it is used.

The existence of the salvage function $\Omega(P_T, S_T)$ can be motivated in a number of ways. Here, the two that are considered are cross resistance and the potential development of alternative technologies based on the same toxin. The latter is in some sense a special case of cross resistance, in that resistance to the chemical in one form completely overlaps with resistance to the chemical in another form. Such is possibly the case of *Bt*, which is produced in a spray form and by genetically engineered plants.

Since we have assumed that we know the time when a new technology will become available, we have a classical optimal control problem, fixed time, free state:

$$\text{Max} \sum_{t=0}^{T} \rho^t [Y_t - D(Z_t) - q(C_t, \tau_t)] + \Omega(P_T, S_T), \qquad \text{(II.5)}$$

s.t. $P_{t+1} - P_t = \theta Z_t - P_t$ (multiplier μ_1),

$S_{t+1} = S_t - [h(S_t) r(C_t, \tau_t; \lambda_{t-1})]$ (multiplier μ_2),

$0 \leq \tau \leq 1$ (multipliers μ_3 and μ_4),

$C \geq 0$ (multiplier μ_5).

Note how this shows that Z_t is just a function of P_t, and thus is not real dynamic variable of the problem. The maximization can be rewritten as:

$$\sum_{t=0}^{T} \rho^t \left[Y_t - D\{P_t[1 - u(S_t)k(C_t, \tau_t; \lambda_{\tau-1})]\} - q(C_t, \tau_t) \right] + \Omega(P_T, S_T),$$

s.t. $P_{t+1} - P_t = \theta P_t\{1 - [u(S_t)k(C_t, \tau_t; \lambda_{\tau-1})]\} - P_t,$

$S_{t+1} = S_t - [h(S_t)r(C_t, \tau_t; \lambda_{\tau-1})],$

$0 \leq \tau \leq 1$, and $C \geq 0$.

The Lagrange multiplier for the first dynamic relationship, μ_1, is negative, because an increase in (future) pest populations decreases (future) profits. The current value function V is given by:

$$V(P_t, S_t, C_t, \tau_t, t) = Y_t - D\{P_t[1 - [u(S_t)k(C_t, \tau_t; \lambda_{\tau-1})]]\} - q(C_t, \tau_t). \quad \text{(II.6)}$$

We assume that the starting values for the state variables are: $S_0 = max\ S = \bar{S}$ and $P_0 = \bar{P}$. The first starting value indicates that no previous use was made of the resource susceptibility. In relation to the previous discussion on the salvage function, this means that the chemical in question is the first one to have an effect on the susceptibility, both directly and indirectly through cross-resistance.

Then we can write the current value Hamiltonian for the problem, H, as:

$$H = V(P_t, S_t, C_t, \tau_t, t)$$
$$+ \rho\, \mu_1^{t+1} P_t[\theta(1 - u(S_t)k(C_t, \tau_t; \lambda_{\tau-1})) - 1] + \rho\, \mu_2^{t+1}[-h(S_t)r(C_t, \tau_t; \lambda_{\tau-1})]. \quad \text{(II.7)}$$

This Hamiltonian is not necessarily concave with respect to the state and control variables. However, for reasonable parameterizations of the problem it is possible to

ensure concavity and therefore a unique solution. The Lagrangian for the problem is the Hamiltonian augmented by the constraints $0 \leq \tau \leq 1$ and $C \geq 0$:

$$L = H + \mu_3 (1 - \tau_t) + \mu_4 \tau_t + \mu_5 C.$$

We will assume interior solutions throughout, so that $\mu_3 = \mu_4 = \mu_5 = 0$, and $L = H$. We can now get first order conditions:

$$S_0 = \bar{S}, \tag{II.8}$$

$$P_0 = \bar{P}, \tag{II.9}$$

$$P_{t+1} - P_t = \partial H(t) / \partial(\rho \mu_1^{t+1}) = \theta Z_t - P_t, \tag{II.10}$$

$$S_{t+1} - S_t = \partial H(t) / \partial(\rho \mu_2^{t+1}) = - h(S_t) r(C_t, \tau_t; \lambda_{t-1}), \tag{II.11}$$

$$0 = \partial H(t) / \partial C_t, \tag{II.12}$$

$$0 = \partial H(t) / \partial \tau_t, \tag{II.13}$$

$$\mu_1^{t+1} - \mu_1^t = - \partial H(t) / \partial P_t, \tag{II.14}$$

$$\mu_2^{t+1} - \mu_2^t = - \partial H(t) / \partial S_t, \tag{II.15}$$

$$[\mu_1^T - \Omega_P(P_T, S_T)]^*[P_T - P_{min}] = 0, \tag{II.16}$$

$$\mu_1^T \geq \Omega_P(P_T, S_T),$$

$$P_T \geq P_{min},$$

$$[\mu_2^T - \Omega_S(P_T, S_T)]^*[S_T - S_{min}] = 0, \tag{II.17}$$

$$\mu_2^T \geq \Omega_S(P_T, S_T),$$

$$S_T \geq S_{min}.$$

Note that P_{min} represents the lowest possible pest population in the production area, while S_{min} denotes the minimum level of susceptibility needed for the new technology to be effective. As we discussed before, if eradication is possible, there is no reason to preserve susceptibility to the pesticide, and the salvage function equals zero, so the transversality conditions reduce to having $P_T = P_{min} = 0$ and $S_T = S_{min} = 0$. Therefore in the following analysis, we will focus on the case in which eradication of the pest population is not a feasible option.

The first order condition with respect to the chemical's use C is:

$$0 = \partial H(t) / \partial C_t = D_z P_t u(S_t) k_C - q_C - \rho \mu_1^{t+1} \theta P_t u(S_t) k_C - \rho \mu_2^{t+1} h(S_t) r_C. \qquad \text{(II.18)}$$

The first order condition rearranged below shows that, at the optimum, the marginal cost of the chemical must equal the effect of the marginal change in chemical dose on the damage caused by the pest population plus (remember that μ_1^{t+1} is negative) the discounted shadow value of the reduction in the future pest population minus the discounted shadow value of the increase in resistance buildup due to the usage of the chemical. These are the terms of the trade-off in the use of the pesticide. The marginal benefits in terms of present and future reduction in the pest populations must equal the sum of two types of marginal costs: direct production costs, and costs of resistance buildup:

$$q_C = D_z P_t u(S_t) k_C - \rho \mu_1^{t+1} \theta P_t u(S_t) k_C - \rho \mu_2^{t+1} h(S_t) r_C.$$

In the case of the area treated, τ:

$$0 = \partial H(t)/\partial \tau_t = D_z P_t u(S_t) k_\tau - q_\tau - \rho \mu_1^{t+1} \theta P_t u(S_t) k_\tau - \rho \mu_2^{t-1} h(S_t) r_\tau. \qquad \text{(II.19)}$$

This first order condition, as rewritten below, indicates that, at the optimum, the marginal cost of increasing the treated area equals the marginal impact of a change in area treated on the damage made by the present pest population plus the discounted shadow value of the effect of increasing the treated area on the future pest population minus the discounted shadow value of the change in resistance buildup due to the variation in the treated area. As in the case of the intensive application of the pesticide, in terms of extensive use, at the optimum, the marginal benefits in terms of present and future reduction in the pest population equals the sum of production cost and resistance cost:

$$q_\tau = D_z P_t u(S_t) k_\tau - \rho \mu_1^{t+1} \theta P_t u(S_t) k_\tau - \rho \mu_2^{t+1} h(S_t) r_\tau.$$

As for the transversality conditions, if the binding condition is $\mu_1^T = \Omega_P(P_T, S_T)$ then $P_T \geq P_{min} > 0$, and similarly, $\mu_2^T = \Omega_S(P_T, S_T)$, and $S_T \geq S_{min} > 0$, so that the value of susceptibility at time T is positive. Note that, in the case of the state variable susceptibility, the problem could be transformed into a fixed time, fixed state one as well. The rationale for that would be that the amount of susceptibility needed by the backstop technology is known. If the susceptibility is useless, then the desired final state for S is

$S_T = 0$. Alternatively, if there is cross resistance and/or the backstop technology operates on the same susceptibility (in a different way), then the requirement is a positive S_T. In the case of P, if a fixed state were desired, such as $P_T = 0$, it would be equivalent to saying that eradication of the pest is the objective at the end of the life span of the chemical (for logical cogency, then, it would have to be $S_T = 0$ also).

The determination of the transversality conditions will allow us to identify some characteristics of the path of the costate variables. First, we rewrite the first order condition (II.14) to get an explicit expression for the change in value of the multiplier through time:

$$\mu_1^{t+1} - \mu_1^t = -\partial H(t)/\partial P_t = -[\partial V(t)/\partial P_t + \rho\,\mu_1^{t+1}\theta(1 - [u(S_t)k(C_t, \tau_t; \lambda_{t-1})]) - 1], \text{ or} \quad \text{(II.20)}$$
$$\mu_1^{t+1} - \mu_1^t = D_Z(1 - uk) - \rho\,\mu_1^{t+1}[\theta(1 - uk) - 1].$$

Since, for positive levels of chemical controls, $(1 - uk) < 1$, the sign of $\mu_1^{t+1} - \mu_1^t$ will vary. If $\theta(1 - uk)$ is bigger than one, the pests are able to generate enough offspring to reach at least the previous year's population level. In such a case, since μ_1 is negative, this relationship shows that higher pest populations at the beginning of the time period are more costly, because they increase the size of the pest populations for the all remaining periods. Similarly, for μ_2 we have:

$$\mu_2^{t+1} - \mu_2^t = -\partial H / \partial S_t,$$
$$\mu_2^{t+1} - \mu_2^t = -\{\partial V / \partial S_t - \rho\mu_1^{t+1}\theta P_t u'(S_t)k(C_t, \tau_t; \lambda_{t-1}) - \rho\mu_2^{t+1}h'(S_t)r(C_t, \tau_t; \lambda_{t-1})\}, \quad \text{(II.21)}$$
$$\mu_2^{t+1} - \mu_2^t = -D_Z P_t u'k + \rho\mu_1^{t+1}\theta P_t u'k + \rho\mu_2^{t+1}h'r.$$

If resistance develops according to a sigmoid, as S decreases, at first $h_S > 0$ and then $h_S < 0$. However, if we assume that a change in susceptibility has a greater impact on the present and future effectiveness of the pesticide than on the development of resistance[18], so that $D_Z P_t u'k - \rho \mu_1^{t+1} \theta P_t u'k - \rho \mu_2^{t+1} h'r > 0$, then we can sign $\mu_2^{t+1} - \mu_2^t$ as globally negative. This implies that the additional marginal benefits of susceptibility are decreasing through time, because, as the stock of susceptibility is mined, the pesticide loses efficacy, both in the present and in the future. Even when resistance buildup is growing at a decreasing rate, so that decreases in susceptibility have less and less of an impact on the evolution of resistance, the effects of susceptibility on the present and future efficacy of the pesticide are still high enough to keep the shadow value of an increment in susceptibility starting at time $t+1$ lower than that of an increment in susceptibility starting at time t. To find the shadow values, we use the transversality conditions. If $\mu_1^T = \Omega_P(P_T, S_T)$ and $\mu_2^T = \Omega_S(P_T, S_T)$, we can write:

$$\mu_1^{T-1} = \mu_1^T + \partial H(t)/\partial P_{T-1} = \Omega_P(P_T, S_T) + \partial H(t)/\partial P_{T-1},$$

$$\mu_1^{T-1} = \Omega_P(P_T, S_T) - D_{ZT-1}(1 - u_{T-1}k_{T-1}) + \rho\, \Omega_P(P_T, S_T)[(\theta(1 - u_{T-1}k_{T-1}) - 1],$$

$$\mu_1^{T-1} = \Omega_P(P_T, S_T)[1 - \rho + \rho\, \theta(1 - u_{T-1}k_{T-1})] - D_{ZT-1}(1 - u_{T-1}k_{T-1}),$$

$$\mu_1^{T-2} = \mu_1^{T-1} + \partial H(t)/\partial P_{T-2},$$

$$\mu_1^{T-2} = \mu_1^{T-1} - D_{ZT-2}(1 - u_{T-2}k_{T-2}) + \rho\, \mu_1^{T-1}\, [\theta(1 - u_{T-2}k_{T-2}) - 1],$$

$$= \{\Omega_P(P_T, S_T)[1 - \rho + \rho\, \theta(1 - u_{T-1}k_{T-1})] - D_{ZT-1}(1 - u_{T-1}k_{T-1})\}[1 - \rho + \rho\theta(1 - u_{T-2}k_{T-2})]$$
$$- D_{ZT-2}(1 - u_{T-2}k_{T-2}).$$

[18] This is not a very strong assumption, since it is equivalent to saying that susceptibility is a global good: $\partial H(t) / \partial S_t > 0$.

Therefore, if we define $[1-\rho+\rho\theta(1-u_{T-i}k_{T-i})]= M_{T-i}$:

$$\mu_1^T = \Omega_P(P_T, S_T),$$

$$\mu_1^{T-1} = \Omega_P(P_T, S_T)\, M_{T-1} - D_{ZT-1}(1 - u_{T-1}k_{T-1}),$$

$$\mu_1^{T-2} = [\Omega_P(P_T, S_T)\, M_{T-1} - D_{ZT-1}(1 - u_{T-1}k_{T-1})]\, M_{T-2} - D_{ZT-2}(1 - u_{T-2}k_{T-2}),$$

....

$$\mu_1^{T-i} = \Omega_P(P_T, S_T)\, M_{T-1}\, M_{T-2} \ldots M_{T-i} - D_{ZT-1}(1-u_{T-1}k_{T-1}) M_{T-2} \ldots M_{T-i} \ldots$$
$$- D_{ZT-i+1}(1-u_{T-i+1}k_{T-i+1})\, M_{T-i} - D_{ZT-i}(1 - u_{T-i}\, k_{T-i}).$$

In general:

$$\mu_1^{T-i} = \left[\Omega_P(P_T, S_T)M_{T-1} - \sum_{k=1}^{i} D_{ZT-k}(1-u_{T-k}k_{T-k})\right]\prod_{h=k+1}^{i} M_{T-h} - D_{ZT-i}(1-u_{T-i}k_{T-i}). \quad \text{(II.22)}$$

As the expression below shows, an increase in the value (cost) of the pest population in the salvage function directly affects the shadow value of the pest population. As there is a link between the present and future levels of the pest population, when the cost of having a pest population at the final time T increases, the pest population's shadow value will increase for all the periods preceding T: $\frac{\partial \mu_1^{T-i}}{\partial \Omega_P} = \sum_{j=0}^{i} M_{T-j}$.

Similarly, for the second multiplier, we define $D_z P_t u'(S_t)k(C_t, \tau_t; \lambda_{t-1}) = Q_t$, $\theta P_t u'(S_t)k(C_t, \tau_t; \lambda_{t-1}) = J_t$, and $h'(S_t)r(C_t, \tau_t; \lambda_{t-1}) = X_t$. Then we have that $H(t)/\partial S_t = Q_t - \rho\, \mu_1^{t+1}\, J_t - \rho\, \mu_2^{t+1} X_t$, so we can rewrite (II.21) to get:

$$\mu_2^t = \mu_2^{t+1} + \partial H(t)/\partial S_t = \mu_2^{t+1} + Q_t - \rho\,\mu_1^{t+1} J_t - \rho\,\mu_2^{t+1} X_t = \mu_2^{t+1}(1-\rho\,X_t) + Q_t - \rho\,\mu_1^{t+1} J_t.$$

Note how the shadow value of susceptibility depends directly on that of the pest population. The higher the cost of the pest, in terms of present and future damage, the higher the value of preserving susceptibility. As in the previous case:

$$\mu_2^T = \Omega_S(P_T, S_T),$$

$$\mu_2^{T-1} = \mu_2^T(1-\rho X_{T-1}) + Q_{T-1} - \rho\,\mu_1^T J_{T-1} = \Omega_S(P_T, S_T)(1-\rho X_{T-1}) + Q_{T-1} - \rho\,\mu_1^T J_{T-1},$$

$$\mu_2^{T-2} = \mu_2^{T-1}(1-\rho X_{T-2}) + Q_{T-2} - \rho\,\mu_1^{T-1} J_{T-2},$$

$$\mu_2^{T-2} = [\Omega_S(P_T, S_T)(1-\rho X_{T-1}) + Q_{T-1} - \rho\,\mu_1^T J_{T-1}](1-\rho X_{T-2}) + Q_{T-2} - \rho\,\mu_1^{T-1} J_{T-2},$$

...

$$\mu_2^{T-i} = \Omega_S(P_T, S_T)(1-\rho X_{T-1}) \ldots (1-\rho X_{T-i}) + (Q_{T-1} - \rho\,\mu_1^T J_{T-1})(1-\rho X_{T-2}) \ldots (1-\rho X_{T-i}) + \ldots$$
$$\ldots (Q_{T-i+1} - \rho\,\mu_1^{T-i+2} J_{T-i+1})(1-\rho X_{T-i}) + (Q_{T-i} - \rho\,\mu_1^{T-i+1} J_{T-i}).$$

In general:

$$\mu_2^{T-i} = \Omega_S(P_T, S_T)\prod_{k=1}^{i}(1-\rho X_{T-k}) + \sum_{k=1}^{i-1}[(Q_{T-k} - \rho\mu_1^{T-k+1} J_{T-k})\prod_{k}^{i-1}(1-\rho X_{T-k-1})] + Q_{T-i} - \rho\mu_1^{T-i+1} J_{T-i}. \qquad \text{(II.23)}$$

This way we can substitute in the values of μ_1 calculated above to obtain explicit values for both the costate variables. As in the case of μ_1, an increase in the terminal

value of susceptibility, Ω_S, directly increases the shadow value of susceptibility: $\frac{\partial \mu_2^{T-i}}{\partial \Omega_S} = \prod_{k=1}^{i}(1-\rho X_{T-k})$.

In this model susceptibility does not possess any existence value, and it has social significance only because of its effect on the renewable resource via the pesticide's action. Since it does not add to biodiversity, susceptibility is worthless without the economic significance of the pest population it is coupled with. If the pest population does not cause any damage, $D(Z) = 0 \; \forall \; t$, and $\Omega_P(P_T, S_T) = \Omega_S(P_T, S_T) = 0$. Since there is no damage, there is no chemical usage, and we have that $\mu_1^{T-i} = 0$, and $Q_{T-i} = 0$, so that $\mu_2^{T-i} = 0$.

It is apparent that a permanent increase in mobility will cause a reduction in the (negative) shadow value of the pest population in each time period, since the same combination of dose and refuge is more effective in controlling the pest. However, it is not possible to say, *ceteris paribus*[19], whether the shadow value of susceptibility is reduced in every period. Therefore, it cannot be ascertained theoretically that lower refuges will be required in each time period for more mobile pests. The reason is twofold. The first is linked to the sigmoid shape of resistance development. In some periods, the marginal impact of the stock of susceptibility on its rate of change, h', may impact the path of resistance in such a way as increase the shadow value of susceptibility for a more mobile pest. The second reason is that, the pest population being less valuable, there is less of an economic incentive to spray the area: for instance, if the pest

[19] This is an important caveat, since a more mobile pest population might have a bigger habitat size.

population causes negligible damages, the field will not be sprayed at all, effectively becoming refuge. Therefore, it might be optimal to increase the refuge level, at least in some years, for more mobile pests. This is likely to have implications on resistance management strategies for the second generation of *Bt* crops, now in the experimental phase, which provide control against the corn rootworm, a more mobile pest than the European corn borer.

The effects of suboptimal management

There are many possible ways to characterize second best situations within this model's framework. For instance, if we assume that there is only one decision maker, she could exhibit myopic behavior. While myopic behavior with respect to the pest population's increases is less likely in a realistic setting, since changes in the pest population are more immediately visible to the farmer, lack of consideration of resistance development is a possibility, particularly if the time frame of reference is long. It could also be the case that the pest is extremely mobile, or feeds on more than one crop, so that its resistance development dynamics become unintelligible to the decision maker. In the context of the optimization set up above, the myopic optimum would be:

$$0 \leq \partial H(t)/\partial C_t = D_z P_t u(S_t) k_C - q_C - \rho\, \mu_1^{t+1}\, \theta P_t u(S_t) k_C, \qquad \text{(II.24)}$$

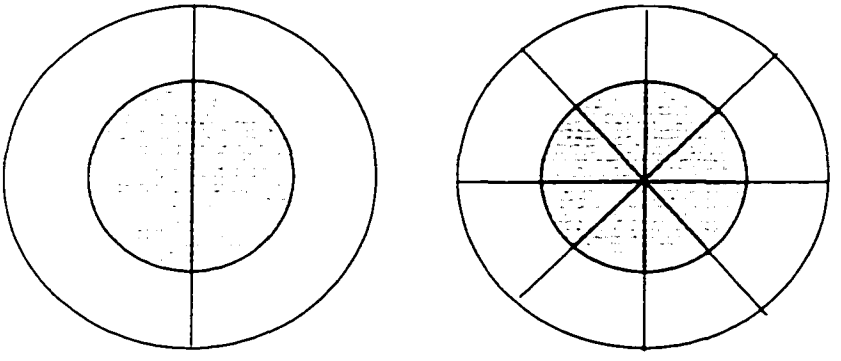
$$q_C \leq D_z P_t u(S_t) k_C - \rho\, \mu_1^{t+1}\, \theta P_t u(S_t) k_C,$$

$$0 \leq \partial H(t)/\partial \tau_t = D_z P_t u(S_t) k_\tau - q_\tau - \rho\, \mu_1^{t+1}\, \theta P_t u(S_t) k_\tau, \qquad \text{(II.25)}$$

$$q_\tau \leq D_z P_t u(S_t) k_\tau - \rho\, \mu_1^{t+1}\, \theta P_t u(S_t) k_\tau.$$

In this case, refuge serves no purpose in terms of preserving susceptibility. We will have $\tau < 1$ only if the marginal cost of increasing the area treated rises rapidly. For relatively flat cost functions, we are likely to have corner solutions: it will be optimal to plant no refuge at all.

The model can also be used to illustrate how having more than one decision maker might bring about second best outcomes, since the existence of externalities will create incentives for farmers not to comply with the refuge policy. Compliance is likely to be an issue for the *Bt* crops (Hurley *et al.*, 1999). Suppose we had n farmers in the region of production, each farming an area of $A/n = \pi\rho^2/n$ (Figure II.7).



Two farmers Eight farmers

Figure II.7 – More than one decision maker

If each farmer is rational and well informed, and takes into consideration the effects of his/her actions on susceptibility, given that each farmer's actions have identical effects, the optimal management strategy is still attainable. However, as n increases, and each farmer's marginal impact on resistance management goes to zero, there will be a tendency to free ride. Since each season the pests cause the crop damage and then move, farmers that do not treat will still suffer reductions in yield. Consequently, they will then tend not to plant the refuge but will still spray. In terms of the dose, the net impact of free riding is ambiguous, since it will depend on the size of two opposite effects. Farmers care less about future pest populations and damages, so they spray only to control present populations. At the same time, farmers also care less about resistance, which will cause them to spray more. This is consistent with the conclusions of Regev *et al.*, in which only the optimal dose issue was analyzed. In terms of the refuge, however, the results are not ambiguous, unless the cost function is very steep. If the cost of extending the area treated is not very high, since farmers see no benefits in the planting of refuge besides the reduction in cost, the presence of externalities will result in pesticide overapplication in spatial terms. We are then in the situation described in equations (II.26) and (II.27):

$$0 \leq \partial H(t)/\partial C_t = D_z P_t u(S_t) k_C - q_C, \qquad \text{(II.26)}$$

$$q_C \leq D_z P_t u(S_t) k_C,$$

$$0 \leq \partial H(t)/\partial \tau_t = D_z P_t u(S_t) k_\tau - q_\tau, \qquad \text{(II.27)}$$

$$q_\tau \leq D_z P_t u(S_t) k_\tau.$$

Farmers will equate the direct cost of increasing the chemical dose with the marginal benefit a higher dose has in reducing the current pest population. Similarly, the benefit in current pest reduction offsets the marginal cost of expanding the area treated. In this context, since planting refuge has no benefits besides the reduction in spraying costs, the whole area is likely to be treated.

Miranowski and Carlson note that the incentive to free ride is stronger for more mobile pests, because susceptibility becomes more of a common property resource. This implies that high levels of pest mobility may be a mixed blessing for pest control. On the one hand, as we saw before, high pest mobility has positive effects on the delaying of resistance buildup and on the number of surviving pests. On the other hand, the contribution of each farmer's action towards pest control is harder to observe for mobile pests, so that free riding is more likely.

Another possible second best instance is given by the underestimation of problems of cross-resistance. If the decision maker believes that the backstop technology will rely on a completely different mode of action[20], $\Omega_S = 0$. In such a case, $\mu_2^T = 0$, so the shadow value of susceptibility is lower in each time period, and equation (II.23) reduces to:

$$\mu_2^{T-i} = \sum_{k=1}^{i-1}[(Q_{T-k} - \rho\mu_1^{T-k+1}J_{T-k})\prod_{k}^{i-1}(1-\rho X_{T-k-1})] + Q_{T-i} - \rho\mu_1^{T-i+1}J_{T-i}. \qquad \text{(II.28)}$$

[20] Once again, we are assuming that eradication is not a feasible option.

Susceptibility will have a lower value, since it brings benefits to the farmer only within the period in which the pesticide is used, and this will imply a heavier use of the chemical. Note, however, that this will not necessarily mean that refuges will not be used. Intuitively, the longer the time frame for the usage of the chemical and the more economically significant the damage of the pest, the more important it is to preserve susceptibility.

Similarly, let us suppose that the decision-maker aims at eradicating the pest population. In this case, we could have a situation in which a corner solution for both the dose and refuge is optimal: farmers spray the highest consented dose over all of their fields, so as to eliminate the pest as quickly as possible. If the decision maker is wrong in thinking that eradication is feasible - say because he has underestimated the size of the immigrant pest population in the habitat - he might have to bear large long-term costs, because the pesticide has become less effective due to the intensive use that eradication requires, while the pest population has not been eliminated and still needs to be controlled.

The case of a fixed dose

We will now analyze a particular form of the problem discussed so far. We will assume that the only decision variable that the farmer has at his disposal is the amount of refuge to plant, and that the dose is exogenous to his choice set. The dose can be considered fixed if farmers follow literally the instructions on recommended dosage for traditional spraying pesticides, but, perhaps more importantly, this formulation reflects

the farmer's choice set in the case of *Bt* crops, since the dose is determined by the chemical company. So far, the literature on *Bt* crops has concentrated on static refuges, that is, refuges whose size is fixed throughout the period in which the pesticide is used (see for instance Hurley *et al.*, 1997 and 1999, Livingston *et al.* 2000). The rationale for this is that nowadays research on refuges has very strong policy implications, and the EPA has focused its attention on static refuges, since they are considered easier to implement[21]. The next pages provide a first insight on how a first best policy may differ from the static refuge case.

In order to analyze the time path of refuge, the problem is presented in continuous time form. The equations of motion become:

$$\dot{S} = -h(S)r(\tau), \text{ and}$$
$$\dot{P} = \theta P[1 - u(S)k(\tau)].$$

The present value Hamiltonian is:

$$H(t) = Y - D[P(1 - u(S)k(\tau))] - q(\tau) + \rho\mu_1(t)\theta P[1 - u(S)k(\tau)] - \rho\mu_2(t)h(S)r(\tau). \quad \text{(II.29)}$$

For realistic parameterizations, this Hamiltonian will be concave. Assuming once again interior solutions, the first order condition with respect to the control variable is:

[21] Note that, in practice, refuge recommendations have not been constant, since the EPA has been regularly updating the refuge management policy (see EPA 1999b, and 1998a).

$$0 = \frac{\partial H}{\partial \tau} = D'Pk'(\tau)u(S) - q_\tau - \rho\mu_1(t)\theta Pk'(\tau)u(S) - \rho\mu_2(t)h(S)r'(\tau). \quad \text{(II.30)}$$

The adjoint equations are:

$$\dot{\mu}_1 = -\frac{\partial H}{\partial P} = D'(1 - u(S)k(\tau)) - \rho\mu_1\theta[1 - u(S)k(\tau)], \text{ and} \quad \text{(II.31)}$$

$$\dot{\mu}_2 = -\frac{\partial H}{\partial S} = -D'Pu'(S)k(\tau) + \rho\mu_1\theta Pu'(S)k(\tau) + \rho\mu_2 h'(S)r(\tau). \quad \text{(II.32)}$$

We differentiate the first order condition to get:

$$\dot{\tau} = \frac{\left\{\begin{array}{l}\left[D''[1-uk]P + (1-\rho)\left(D' - \mu_1\theta\right)\right]k'u\theta P[1-uk] - \rho^2\mu_1\theta Pu'khr' \\ +\left[(D''Pku - D' + \rho\mu_1\theta)Pk'u' + \rho\mu_2 h'r'(1-\rho)\right]hr + \rho D'Pu'khr'\end{array}\right\}}{\left\{D''\left[Pk'u\right]^2 - D'Pk''u + q_{\tau\tau} + \rho\mu_1\theta Pk''u + \rho\mu_2 hr''\right\}}. \quad \text{(II.33)}$$

The optimal policy is to decrease the amount of refuge at first, when resistance increases at an increasing rate, that is, when $h' > 0$, if we assume that $\rho\frac{r'(\tau)}{r(\tau)} > \frac{k'(\tau)}{k(\tau)}$. This assumption forces the elasticity of the resistance function to be globally higher than the elasticity of the kill function. In essence, this implies that as the area treated changes, the development of resistance is more responsive to the changes than the percentage of pest population killed off (Details of the proof are given in the appendix). Farmers start off at time zero with a relative high level of refuge and then decrease it because the marginal benefits in terms of resistance decrease through time as the resistance increases at an increasing rate.

When resistance starts increasing at a decreasing rate, it is no longer possible to say *a priori* what should happen to the size of the refuge. Resistance increases more slowly, which implies that the marginal value of increasing refuge is lower. Of course, this marginal impact of refuge has to be counterbalanced by the fact that, in absolute terms, resistance is already relatively high so that the refuge is not as useful as it was before. This is an interesting result in terms of the current refuge policy debate for *Bt* crops. As we noted before, the EPA and the industry (EPA, 1999a) are thinking in terms of constant refuge recommendations, and so is the theoretical literature (for instance Hurley *et al.*, 1997 and 1999). The rationale for the policy is that it is believed that it might be problematic to inform farmers on the optimal refuge size each year. The last result shows that this approach is not economically optimal – at least if administration costs for the policy are excluded.

Conclusions

The model underscores how the success of a long term pest management strategy is going to depend on two classes of factors: biological and economical. The characteristics of the pest population, ranging from mobility to reproduction, and the dynamics of resistance development are crucial elements of the policy. Of no lesser importance are the attributes of the farmers planting the crop and of the pesticide they use, as Miranowski and Carlson point out. Market structure of the chemical industry, farm size and pest mobility are going to be key factors in the determination of the management strategies.

It is not possible to say explicitly how mobility affects the first best refuge policy. However, since higher mobility means that susceptibility becomes more of a common property resource, suboptimal refuges are more likely for highly mobile pests. If the farmers have control over the dose, the effect of the concentration of chemical used will be ambiguous: susceptibility is carried by pests, and as mobility increases, both future pest populations and their genetic makeup become common property resources.

The families of pesticides available are limited, and some of them share common modes of action. For instance, the four major classes of synthetic organic insecticides produced in the post-war period, chlorinated hydrocarbons, carbamates, organophosphates and pyrethroids, are all nerve poisons (Hammock and Soderlund). To the extent that cross-resistance is present, long term strategies that put a positive value on the preservation of susceptibility are needed. The need to preserve susceptibility, therefore, will not disappear even for the next generation of biotechnology products, which are likely to possess stacked toxins, as long as these toxins exhibit some degree of cross-resistance. The analysis presented in this chapter illustrates how the likelihood of cross-resistance in the future influences current management practices.

In the case of a fixed dose, the results point out that the use of static refuges is not a first best policy. It makes intuitive sense that refuge should be higher at the beginning of the time frame of analysis, since this means that susceptibility will preserved for a relatively long time. The main limitation of this analysis – common to all the existing literature – is that it takes the level of market penetration of the new technology as complete. In practice, market penetration is likely to be only partial. The next chapter

will examine the impact of market penetration on the dynamics of resistance development and the returns to the farmers.

In the choice of eradication versus pest management, attention must be paid to the biology of the pest population, and to its mobility in particular. If a pest is mobile over great distance and/or it is polyphagous, eradications are likely to fail. Policy makers should also take into account the existence and cost of alternative forms of control for the pest, should eradication fail.

The time in which a new technology becomes commercially available is at least partly endogenous. The longer the regulatory process takes for the approval of a new product, the longer existing technologies will have to be viable. If, as the historical evidence suggests, environmental and food safety are a luxury good, then richer countries might have to implement policies such as refuge to prolong the life-span of pesticides.

In more general terms, this model points to the importance of taking a systemic approach to pest management. Habitat size, crop systems, spatial and temporal behavior of the pest population are all important elements in the determination of a pest management strategy. Entomologists have long recognized the need to analyze the pest problem in the context of the whole production system in which they cause damage (Pedigo). Failure to do so may cause policies to be substantially ineffective or even backfire.

CHAPTER III.
IMPACT OF MARKET PENETRATION AND PEST MOBILITY ON *BT* CORN

Introduction

The use of agricultural biotechnologies has been increasing dramatically in the United States since the mid 1990s. Among the most successful crops are *Bt* plant-pesticides, engineered to express the *Bacillus Thuringiensis* (*Bt*) δ-endotoxins and targeting the European Corn Borer (ECB). *Bt* pesticides have long been used in spray form by organic and Integrated Pest Management (IPM) farmers, and their effectiveness and safety are well established. Because these farmers and environmental groups are concerned about the possible development of resistance to *Bt* by the targeted pests, the Environmental Protection Agency (EPA) requires farmers who want to grow *Bt* corn and cotton to plant refuges. Refuges are portions of the field in which non-*Bt* seed is sown, and *Bt* insecticides are not sprayed, so as to allow the interbreeding of pests susceptible to *Bt* with resistant pests. This interbreeding slows down resistance buildup. Refuge is coupled with high doses of the toxin throughout the season and throughout the corn plant, so that only the few resistant pests survive.

EPA's current refuge requirements are based on certain fundamental assumptions. At the market level, the conjecture is that market penetration will be complete, or equivalently, that no externalities will occur in the resistance management plan because of pest mobility. Mobility creates externalities in the management of susceptibility to a pesticide unless all farmers behave identically and their fields have identical characteristics. Otherwise, farmers spraying less have higher levels of susceptible

populations, so that pest movement into the fields of high-spraying farmers creates both a negative externality, the net influx of pests in their fields, and a positive one, since those very pests will be more susceptible to the pesticide.

Pest mobility can substantially alter the efficacy of resistance management plans, because when mobility is present resistance becomes a common property resource. The level of pest mobility determines the extent of the externality created and therefore influences the resistance management strategy (Miranowski and Carlson). Therefore, the issue of pest mobility goes hand in hand with that of market penetration. When different pest control practices are used in adjacent fields, the natural selection that gives rise to the development of resistance may be countered by the movement of pests from field to field. This movement affects the pest population genetic make-up and may dilute the evolution of resistance. The extent to which this alleviation will occur will depend on the market penetration of the resistance-inducing technology.

The EPA implicitly acknowledges that pest mobility is a crucial component of the resistance question, since the very rationale of the EPA's regulatory effort is based on the possibility that, because of pest mobility, resistance may spread, making the *Bt* used as a spray in organic farming ineffective (EPA, 1998a). The same population biology processes behind the in-field refuge strategy apply to the field to field case. The EPA and entomologists, in fact, call the fields planted with non-*Bt* hybrids unstructured or market-driven refuge (see for instance EPA 1998d).

Figures III.1 and III.2 show the level of *Bt* corn market penetration in 1999 by county for the US, and they suggests that market penetration is varied, ranging from less

than 10% to over 50% of the corn acreage. This entails the need to analyze in more detail the importance of market penetration in the development of resistance. On the one hand, the penetration of the *Bt* technology could remain limited, and the presence of unstructured refuge might be enough to guarantee that resistance never becomes a concern. This is a distinct eventuality, given the Japanese and European position on genetically modified organisms (GMOs). On the other hand, knowledge of the impact of market penetration on resistance could improve the effectiveness of resistance management policy. In particular, to identify the threshold market penetration for which the unstructured refuge becomes ineffective could prompt regulatory authorities to monitor refuge compliance more closely, or to increase the level of refuge recommended.

In is important to note that the issues analyzed here are likely to become more central to policy makers, because the industry is developing new genetically modified crops that will be active against both the corn rootworm and the ECB.

The problem of resistance development had been analyzed by economists since the 1970s (Taylor and Hadley, 1975; Hueth and Regev, 1974; Regev, Gutierrez and Feder, 1976; Regev, Shalit and Gutierrez, 1983). In line with these models, susceptibility to a pesticide will be considered a nonrenewable resource, that is, it will be assumed that there are no fitness costs: resistant pests have the same reproductive potential and survival capacity as susceptible ones.

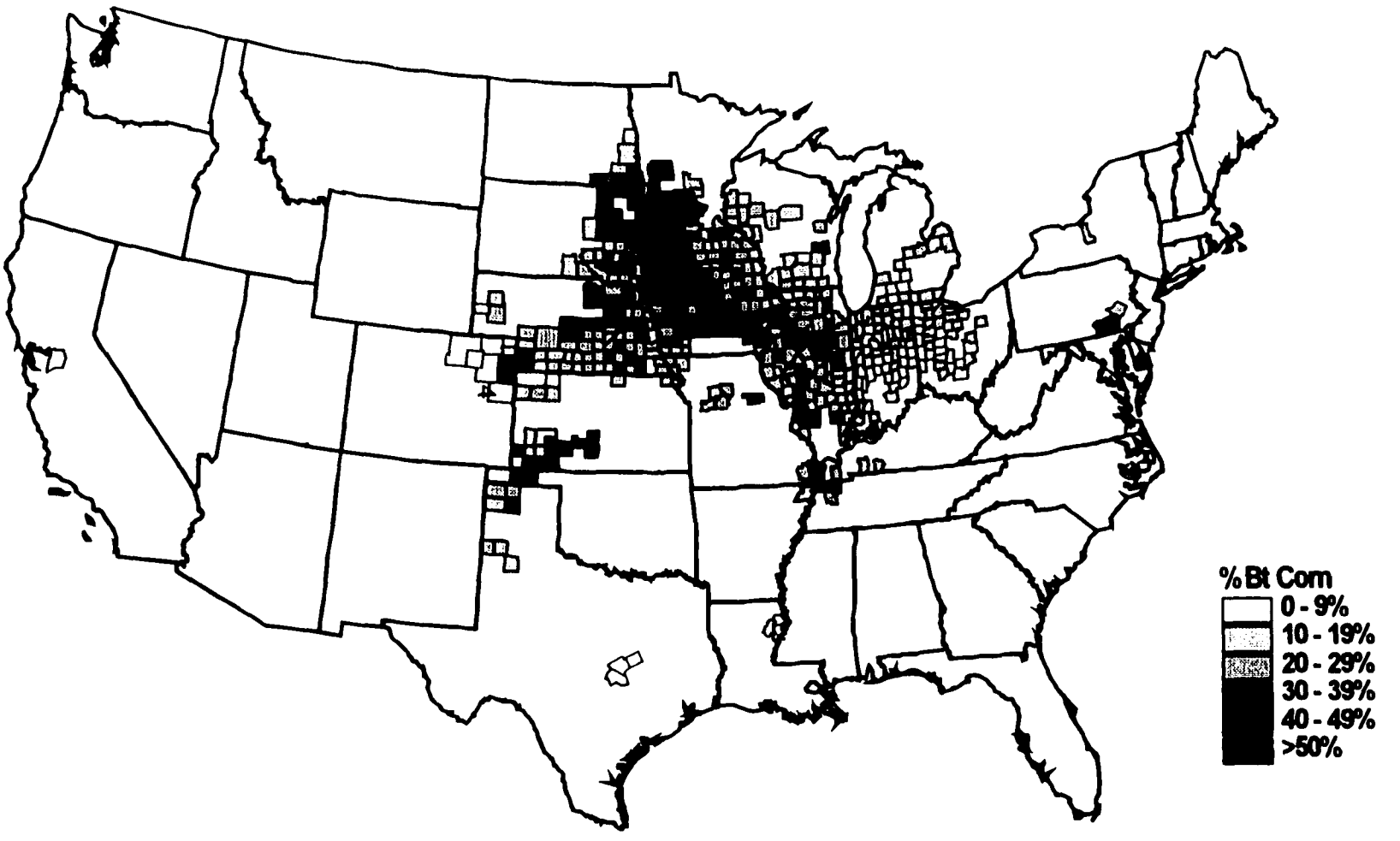


Figure III.1 - U.S. Distribution of *Bt* Corn

The figure represents the percentage of total corn acreage planted to Bt corn hybrids in counties in which > 50,000 total acres of corn were planted.
Source: Bt corn industry sales data as compiled by FSI, Inc., 1999.

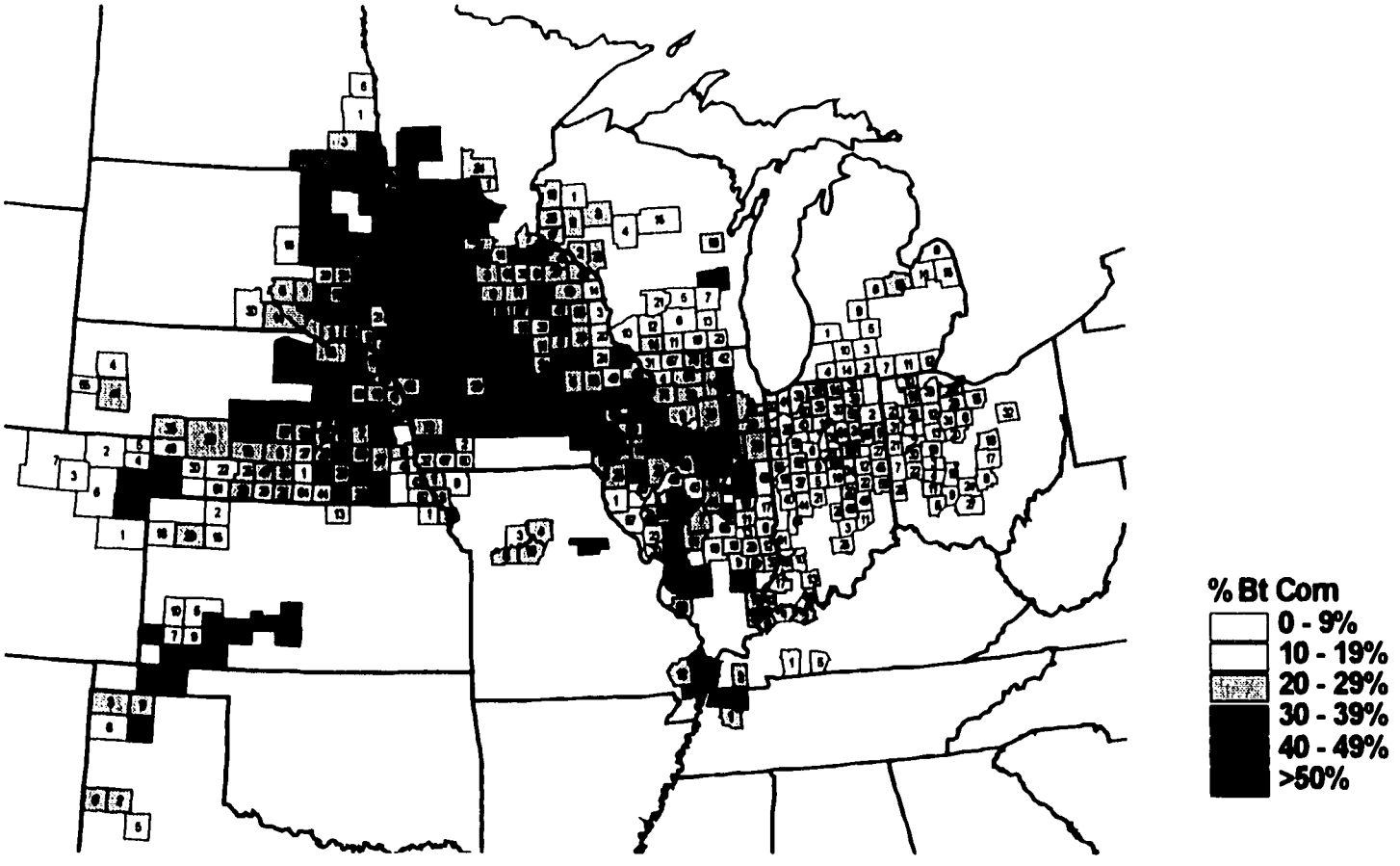


Figure III.2 - Distribution of *Bt* Corn - Central Corn Belt

The figure represents the percentage of total corn acreage planted to Bt corn hybrids in Central Corn Belt counties in which > 50,000 total acres of corn were planted.
The numbers represent county identifiers and not the level of market penetration.
Source: Bt corn industry sales data as compiled by FSI, Inc., 1999.

This chapter presents a dynamic farm production model and uses simulation results to analyze the interplay between the externalities created by pest mobility and the management of resistance at different levels of market penetration and pest mobility. The object is to determine the effect of pest mobility on the buildup of resistance. As noted above, there is evidence that the ECB mobility is limited. A recent study has suggested that mobility is higher than previously assumed (Showers *et al.*), but given the insufficient amount of evidence, the model presented below analyzes the problem at various levels of pest mobility. The model is applied to the case of corn production, and uses a grid of nine fields which can be sown with the *Bt* seed or with a traditional corn hybrid. The model is developed along the methodological lines of Lazarus and Dixon and Hurley *et al.* (1997). Lazarus and Dixon use a nonlinear programming model to combine both common property resource issues with explicit genetics for the corn rootworm, while Hurley *et al.* (1997) examines the economic value of mechanisms to slow down resistance build-up for *Bt* crops.

The model

The model builds on Hurley *et al.* (1997). It is based on pest population dynamics that allow the direct measurement of resistance development following the Hardy-Weinberg principle, with resistance being conferred by a single allele, so that the pest population is composed of homozygote susceptible (SS), heterozygote (RS) and homozygote resistant (RR) individuals. The only difference with the genetics of the pest population in the Hurley *et al.* (1997) model is that a random element is introduced to

mimic the real variability of the pest population from year to year, since European corn borers' populations are highly variable, and it is difficult to accurately predict corn borer pressure from the previous' year pest population size. Also, adding a stochastic element prevents a collapse in the ECB population in the field without suddenly increasing the population size beyond reason. Deterministic models tend to exhibit such a long-term collapse of the pest population, a phenomenon which most observers think is unrealistic.

Each year, the initial pest population size is drawn from a uniform random distribution. The stochastic shock does not affect the genetic make up of the pest population, because it represents environmental conditions such as weather and amount of rainfall. The random number is the same for all the fields considered, reflecting the fact that the atmospheric conditions are likely to be similar across adjacent fields, but the scale of the shock is proportional to the size of the previous' year surviving population. Scaling increases the realism of the simulation results in two ways. First, in general, the European corn borer populations in the *Bt* fields will be smaller than those in the non-*Bt* fields, so that resistance to *Bt* might actually occur[1]. Second, farmers treating with traditional sprays will be unable to drive the pest populations to extinction.

The pest population analyzed has two generations per year (bivoltine), but the model is generalizable to uni-or multi-voltine populations. More generally, this framework is easily applicable to all pests which exhibit some degree of mobility,

[1] It is essential that populations be fairly small for resistance to become prevalent, since the initial frequency of the resistance gene is very low to start with. As the pest population size declines, susceptible pests (and their genes) will all be killed by the pesticide and the resistant pests will take over.

ranging from insects to weeds and fungi, and to crops which suffer damage from a common pest population[2].

The model is based on nine corn fields, some of which--always the same[3]--are planted with *Bt* corn. Following Onstad and Guse and Mason *et al.*, the damage function of the ECB is linear, but differentiated across generations. First generation ECBs cause more damage to corn because they attack it at an earlier stage of development when the plant stalk can withstand less damage. The farmer planting the non-*Bt* corn has the choice of applying a non-*Bt* based pesticide for both the first and second generation of pests. The cost of applying the chemical input is fixed, and the pesticide has a maximum efficacy bound which is set at various levels, ranging from 70% to 90%. The reason for analyzing various levels of efficacy is that the level of efficacy of the sprayed pesticide determines the effective size of the unstructured refuge: for a given level of market penetration, the higher the efficacy of the spray, the lower the effective level of unstructured refuge. Also, the effectiveness of sprays has been increasing in the recent past, so that at this time efficacy can reach 90% in optimal conditions (Dr. Hellmich, personal communication). The decision to spray is based on economic thresholds which are described in Mason *et al.*; the thresholds depend on the level of damage of the pest, the costs of spraying, and, of course, the effectiveness of the pesticide. As we noted above, the pest population modeled are in the high range, since this is mostly the case in locations where significant acreage of *Bt* corn is planted.

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[2] For instance, the model could be applied to corn and cotton, which are both ECB hosts.
[3] This appears to be a non-trivial question when analyzing resistance development. See Peck *et al.*

The *Bt* farmers plant corn and refuge, which is left unsprayed. The refuge size considered is 20% of the field, which is consistent with current EPA regulation. Following Hurley *et al.* (1997), this proportion of the field is constant throughout the time horizon. The yearly profit per acre for the *Bt* farmer is given by:

$$\left\{(1-\theta)p_y Y\left[1-\left(E_{G1}N_{G1}+E_{G2}N_{G2}\right)\right]-P\right\}+\theta p_y Y\left[1-\left(E_{G1}N_{G1}+E_{G2}N_{G2}\right)\right]-C, \quad \text{(III.1)}$$

where[4]:

θ = proportion of refuge, here 20%,

p_y = real corn price per bushel at 1992 prices, $ 2.35,

Y = pest free average yield, 130 bushels per acre,

N_{G1} and N_{G2} = number of pests per plant, first and second generation,

E_{G1} and E_{G2} = damage per pest per plant, E_{G1} = 0.05 and E_{G2}= 0.024,

C = costs of production net of the spraying price, $185 per acre,

P = *Bt* premium, $10 per acre.

We assume there are no price nor yield differentials between the *Bt* corn and the hybrid planted in the refuge. Since the damage function is linear and mating is random, we can rewrite equation (III.1) as:

$$p_y Y\left[1-\left(E_{G1}N_{G1}+E_{G2}N_{G2}\right)\right]-C-\theta P. \quad \text{(III.2)}$$

[4] For the specific values see Mason *et al.*, Onstad and Guse, and Hurley *et al.* (1997).

The non-*Bt* farmer maximizes:

$$p_y Y\,[1 - E_{G1}N_{G1}(\alpha(1-S_1)) - E_{G2}N_{G2}(\alpha(1-S_2)] - C - p_s(S_1+S_2), \qquad \text{(III.3)}$$

$$\text{s.t. } \alpha \in [0.7, 0.90] \text{ and } S \in \{0,1\},$$

where:

p_s = cost of the spray application, $14 per acre,

S = non-*Bt* spray application,

α = maximum efficacy of the non-*Bt* spray.

The sizes of the initial pest population in the *Bt* and non *Bt* fields in each season are calibrated to ensure that spraying occurs regularly in the non-*Bt* fields throughout the 15 years considered, and that the pest population in the *Bt* fields can reach the small size necessary for resistance to develop in the absence of mobility but does not collapse and can increase again once resistance is established. The initial pest population in the non-*Bt* fields each year is given by:

$$N_{G1}(t) = \varepsilon, \text{ and}$$
$$\varepsilon \sim U[0, 0.1]. \qquad \text{(III.4)}$$

The initial pest population in the *Bt* fields each year is given by the surviving second generation pests, S_{G2}, plus the stochastic element ϵ scaled by a factor ϕ:

$$N_{G1}(t) = S_{G2}(t-1) + \phi\varepsilon,$$
$$\varphi = 0.000001, \text{ and} \qquad \text{(III.5)}$$
$$\varepsilon \sim U[0, 0.1].$$

The presence of the previous year survivors in the determination of the initial pest population for the next season guarantees that the pest population numbers in the *Bt* fields can increase once resistance is established. The shock, common to *Bt* and non *Bt* fields, guarantees that the population does not collapse, while the scaling factor ϕ ensures that, at first, the pest population numbers decrease enough for resistance to develop.

The intra-season population dynamics, that is, the relationship between first and second generation, is the same as in Hurley *et al.* 1997.

Equation (III.1) and (III.3) incorporate the effects of the population dynamics and the impact of changes in its genetic make-up. Changes in N_{G1} and N_{G2} can be the direct result of changes in the pest population's size or, indirectly, can be due to variations in the genetic frequency of resistant pests. As resistance increases, there is a decrease the effectiveness of the *Bt* toxins, so that a higher number of pests survives and damages the crop. Since our focus is resistance to *Bt*, we will assume that resistance to the spray pesticides used by the farmers planting conventional hybrids does not develop. This would be the case, for instance, if farmers rotated pesticides with different modes of action. The rate of interest used for the net present value of production is 4%. As noted above, the time horizon utilized is 15 years, which is a conservative estimate of the time in which backstop technologies will become available.

The mobility of the pest is parameterized by the percentage of the pest population on a field that moves to neighboring fields and then breeds with the local population. We will use here three levels of pest mobility: one pest out of ten thousand, one per one hundred thousand or one pest per million will leave the field. The mobility levels are very low because corn borers are not very mobile. Note that such low mobility will tend to give conservative results in terms of resistance development, as it will limit the influx of susceptible pests into the *Bt* fields.

Consistent with the field evidence (Dr. David Andow, personal communication), only first generation ECBs are modeled as moving outside the field[5]. This form of effective pest mobility is *de facto* a reduced form embodying two kinds of variables: the first is the pest mobility proper, as determined by biological and environmental factors, and the second is the farm size. The larger the field, the less likely pests are to create an externality by migrating from one farm to the next, as they tend to live and mate within the perimeter of the field.

We assume that pests will move only to adjacent fields. We will also assume that the grid of nine fields examined is representative of a larger production region that follows the same production practices. More specifically, we assume that the production characteristics of the nine fields examined are mirrored in the neighboring nine field groups. An example is given in Figure III.3, where the gray area in the center is the one actually analyzed in the simulations. This formulation has the advantage that the

[5] The reason for this appears to be that second generation pests have less of an incentive to leave their corn field, since the corn is at a later development stage and provides a better habitat.

positioning of fields in the grid becomes irrelevant, and the only variable that affects results is how many *Bt* fields there are in the grid, so as to allow us to concentrate on market penetration. The model is programmed in Matlab's simulation environment, Simulink. The averages for each scenario are calculated out of 100 replications of the 15 year time horizon runs. It is important to note that the cost of pesticide application per acre for the non-*Bt* fields represents just direct costs. It does not include the time that the farmer spends scouting for pests to determine the pest population levels. Therefore, the results presented below will generally underestimate the benefits of *Bt* corn.

Bt	Non *Bt*	*Bt*	*Bt*	Non *Bt*	*Bt*	*Bt*	Non *Bt*	*Bt*
Non *Bt*	*Bt*	Non *Bt*	Non *Bt*	*Bt*	Non *Bt*	Non *Bt*	*Bt*	Non *Bt*
Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*
Bt	Non *Bt*	*Bt*	**Bt**	**Non Bt**	**Bt**	*Bt*	Non *Bt*	*Bt*
Non *Bt*	*Bt*	Non *Bt*	**Non Bt**	**Bt**	**Non Bt**	Non *Bt*	*Bt*	Non *Bt*
Non *Bt*	Non *Bt*	Non *Bt*	**Non Bt**	**Non Bt**	**Non Bt**	Non *Bt*	Non *Bt*	Non *Bt*
Bt	Non *Bt*	*Bt*	*Bt*	Non *Bt*	*Bt*	*Bt*	Non *Bt*	*Bt*
Non *Bt*	*Bt*	Non *Bt*	Non *Bt*	*Bt*	Non *Bt*	Non *Bt*	*Bt*	Non *Bt*
Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*	Non *Bt*

The darker areas in the Bt fields represent refuges.

Figure III.3 – An example of the spatial grid used in the model

Results

The results of the baseline case of zero mobility will also correspond to the zero and full market penetration cases. If all farmers plant non-*Bt* hybrids, no resistance to *Bt* will occur and profits will be determined by the efficacy of the sprayed pesticides and the modalities of their applications. If, on the other hand, all farmers plant *Bt* corn, the evolution of resistance will follow the same path as if only one farmer were planting *Bt*, acting in an isolated environment.

In the baseline case of no pest mobility, the net present value per acre of planting *Bt* corn for 15 years is $1300.85. There is little variability in the returns across the simulation runs, because the *Bt* toxins are extremely effective in killing the pests, and the population does not have time to recover in the 15 year time horizon considered. The average final frequency of resistance is 0.76, with a standard deviation of 0.29. As for the farmers planting a non-*Bt* hybrid, their profits will depend on the effectiveness of the pesticide they have at their disposal, and on the pest population dynamics. Table III.1 shows how profits increase as the pesticide efficacy goes up. For any given pesticide efficacy, profits are always higher for the lower pest population, since the population causes less damage and requires fewer pesticide applications.

The effect of an increase in pesticide efficacy is twofold. First, the number of applications to control first generation corn borers increases, because the cost of application is the same but its productivity is higher. Second, the number of pesticide applications to control second generation corn borers goes down as the first application's level of control increases.

Table III.1 – Average net present value of non-*Bt* profits per acre with zero mobility

Pesticide efficacy (percentage of pest population killed)	Dollars
70%	1122.80 (27.96)
80%	1161.62 (24.04)
90%	1213.72 (13.37)

Standard deviations across simulation runs in parenthesis.

Table III.2 – Average number of pesticide applications for the non-*Bt* farmers

Pesticide efficacy (percentage of pest population killed)	1st generation	2nd generation
70%	6.7 (1.9)	12.5 (1.3)
80%	7.6 (1.8)	9.2 (1.8)
90%	8.6 (1.8)	4.5 (1.8)

Standard deviations across simulation runs in parenthesis.

Table III.2 reports the average numbers of times that spraying occurs for first and second generation borers, in the 15 year time frame. For instance, a farmer who has at his disposal a pesticide with a 80% efficacy will spray on average 7.6 years out of 15 for first generation borers and 9.2 years out of 15 for second generation borers. The results reported in Table III.2 illustrate that the average pest populations used in the simulations are high. The reason for this choice is twofold. First, *Bt* adoption rates are likely to be higher where corn borers pressure is intense, as the technology is more valuable to farmers: if the farmer had not adopted *Bt*, they would have had to spray very frequently, therefore their returns would have been substantially lower. Secondly, in terms of the

development of resistance, lower pest populations are not likely to exhibit a substantially different behavior, since the pest population will be lower in both the *Bt* and non *Bt* fields.

The introduction of mobility has little effect on the profits of the *Bt* farmers. The reason for this is that the corn borers moving into the *Bt* field from the non-*Bt* fields tend to be susceptible to the *Bt* toxin, so the pests are killed off and are not able to cause any damage. Similarly, for the non-*Bt* farmers, profits are inelastic to changes in the level of market penetration for all levels of mobility considered. Returns depend only on the efficacy of the pesticides that farmers have at their disposal. The reason resides in the much lower pest population densities that are found in the *Bt* fields, in the relatively low levels of mobility considered in the simulations, and in the fact that the spray pesticides have a mode of action different from *Bt*, so they can easily kill the few resistant pests moving out of the *Bt* fields.

As for resistance, with 20 % refuge in the *Bt* fields, there are no changes to the genetic make-up of the pest population in the non-*Bt* fields. This suggests that the spread of foci of resistance outside the *Bt* fields might become a concern only for very high levels of market penetration, and low compliance to the refuge recommendations. This does not imply that no resistance will develop in the *Bt* fields. As we will see next, this is not generally the case. It does however mean that resistance is probably going to be contained in the *Bt* fields, since very few resistant corn borers will move out of the field. The small number that move to the non-*Bt* areas will either mate with susceptible insects or be killed by the applications of spray pesticides.

In the *Bt* fields, resistance could very well develop, depending on the level of market penetration, the efficacy of the pesticide used in the non non-*Bt* areas, the level of mobility and of pest population pressures. Specifically, lower levels of mobility cause more resistance to develop, because of the isolation of resistant pests. Figure III.4 shows that resistance is not an issue for the two higher levels of pest mobility, since the higher levels of mobility introduce enough susceptible pests into the *Bt* fields to dilute the resistance genes. However, resistance could become a concern if mobility were very low. As Figure III.4 illustrates, for very low mobility, the final frequency of resistance would be higher than 0.1 for market penetration levels above 60%. It is important to note that neither market penetration nor pesticide efficacy play a role in the development of resistance for the higher levels of mobility: the absolute number of pests leaving the non-*Bt* fields is always high enough to guarantee that resistance does not take hold.

The proportion of resistant alleles stays low irrespective of the level of market penetration and pesticide efficacy for the highest levels of mobility. Figure III.5 shows how the proportion of resistant alleles stays low irrespective of the level of market penetration and pesticide efficacy when mobility is 0.01%. More interestingly even, standard deviations are very low, and the final frequency of resistance is well below 0.01 in all the simulation runs. Things are not substantially different if mobility decreases to 0.001%, with two exceptions. Standard deviations increase substantially for the highest level of market penetration, and there is a positive, if low, probability that the final frequency of resistance might be high. For instance, if pesticide efficacy is 70%, the probability that the final frequency of resistance exceeds 0.1 is 0.0025.

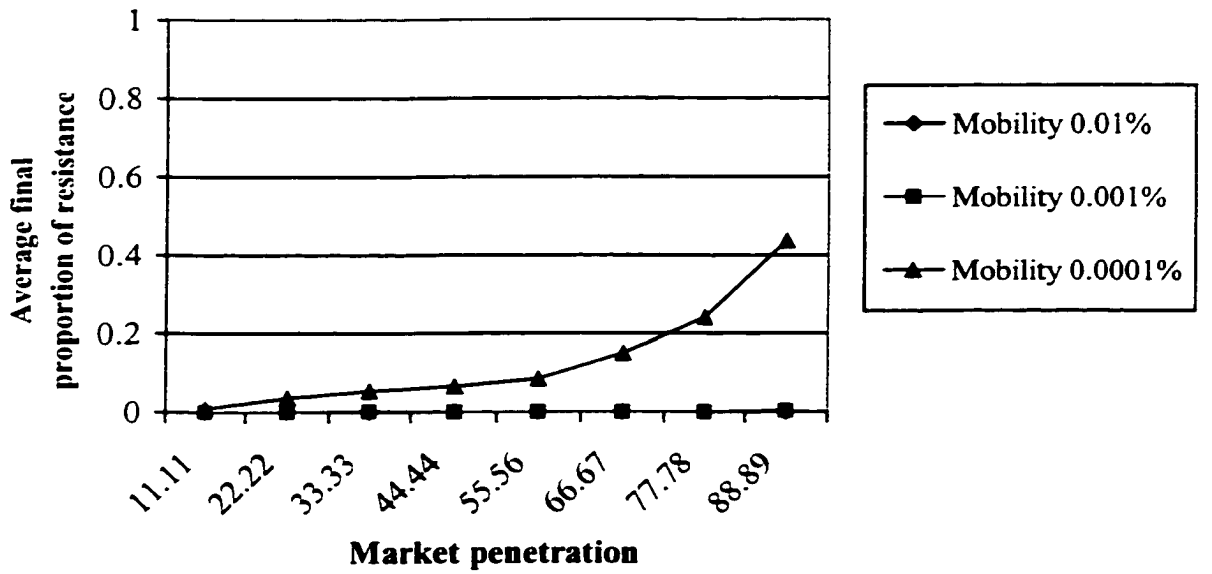

Figure III.4 – Average final proportion of resistant alleles in the *Bt* fields with 70% efficacy in the non-*Bt* fields

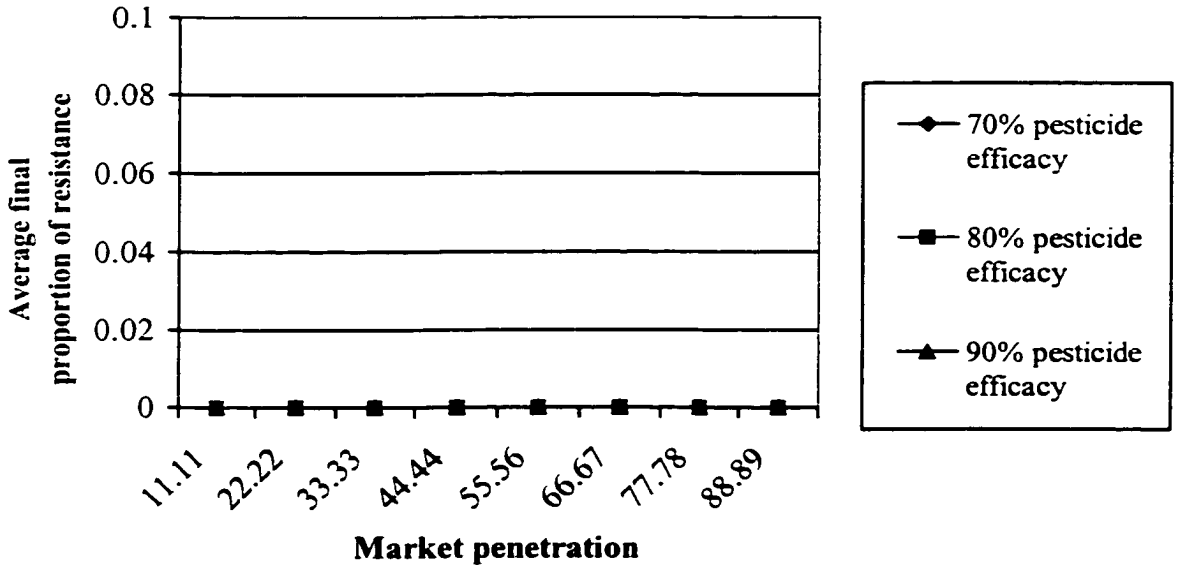

Figure III.5 – Average final proportion of resistant alleles in the *Bt* fields with 0.01% mobility

Both pesticide efficacy and market penetration play a role in the lowest level of mobility analyzed here. Figure III.6 indicates that, if the *Bt* technology is utilized in half of the fields or so, resistance will increase substantially. Variances are very high as well, and they tend to increase as market penetration increases. Also, at this very low level of mobility, lower pesticide efficacy will actually facilitate the development of resistance, at relatively low levels of market penetration. The reason is that the lower efficacy of the pesticide will bring about higher numbers of susceptible corn borers moving into the *Bt* fields. As they mate with resistant corn borers, the number of heterozygotes increases.

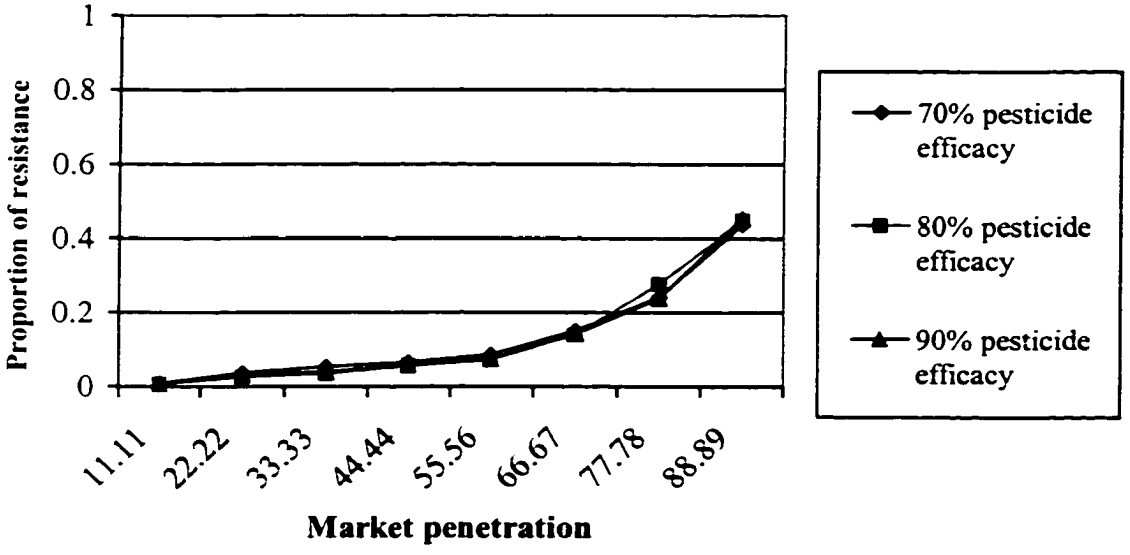

Figure III.6 – Average final proportion of resistant alleles in the *Bt* fields with 0.0001% mobility

As we discussed before, these results are much less worrisome than they might appear at first sight when we take into account that the very small population size will assure that the resistance is not transmitted to the non-*Bt* fields. The few resistant pests escaping from the *Bt* fields will either mate with susceptible pests or be killed off by the pesticides used by the non-*Bt* farmers, which have a mode of action different from *Bt*. This underscores the importance of the assumption we made that the farmers planting traditional hybrids do not use a *Bt*-based spray. If the non-*Bt* areas were sprayed with a *Bt*-based pesticide, resistance might well spread from the transgenic planted fields.

Conclusions

In general, in the case of *Bt* corn, the net outcome of the presence of externalities discussed in the previous chapter is clear. Farmers using traditional hybrids have a higher pest population which is highly susceptible to *Bt*. The negative externality produced by the net influx of these pests into the *Bt* fields is more than offset by the positive impact that the susceptible pests have on resistance buildup. On the other hand, the number of pests moving into the non-*Bt* fields is very low and does not cause significant damage.

The simulations' results in the various scenarios indicate some parameter levels at which the spread of resistance might become a concern. First off, the results are fairly robust in terms of the fact that resistance does not spread from the *Bt* to the non *Bt* fields, at least in the 15 year time horizon considered here. This is an important result, because it suggests that even if foci of resistance develop, they will be contained by the higher

population pressure in adjacent fields: the high dose concept does indeed work. Secondly, for the two higher levels of mobility considered – which are still very conservative in terms of how many corn borers will move from field to field, the *Bt* fields themselves do not become significantly resistant.

To put the mobility parameters into perspective, let us consider some of the results of the Showers *et al.* paper mentioned in the introduction. According to the USDA (1999b), the average farm size in the US in 1997 was 436 acres, or 1.744 square kilometers. If we simplistically assume that the farms are square, they will have a side of about 1321 meters. Showers and his co-authors, in 1986, released 283436 adult corn borers at the beginning of the growing season[6]. They set up traps at 200, 800 and 3200 meters from the release site. At the 3200 meter distance they retrieved 35 corn borers, or 0.012% of the insects that had been released. Of course, caution is necessary in the use of these data. For instance, the Showers experiment set up the traps to retrieve the corn borers in habitats different from corn: in the specific case mentioned here, they were three combinations of brome and alfalfa and giant foxtail and a creek. Showers reports that habitat was a significant factor in determining the number of corn borers retrieved. This indicates that corn-from-corn movements might have different characteristics from the ones Showers *et al.* report. The direction of flight also seems to be significant, and this could indicate that the dispersal is not as homogeneous as the simulations have assumed. Despite these caveats, however, the Showers results indicate that the levels of mobility

[6] Showers *et al.* also released – and recaptured – corn borers further into the growing season. However, the number of corn borers retrieved at a distance greater than 1 km was always lower in the second release, indicating that corn borers tend to move further away at the beginning of the season.

used in the scenarios discussed above are likely to be somewhat conservative.

Market penetration plays a role at the lowest level of mobility. In such a scenario, having over 50% of the fields planted with *Bt* corn might be problematic. In general, the results on the frequency of resistance in the *Bt* fields are highly dependent on the level of pest mobility. This suggests more information is needed on the characteristics of the movement of the European Corn Borer. The simulations presented here suggest other questions for future research. First of all, the grid size could be increased so as to analyze whether scale plays a role in the spread of resistance. In particular, in all the cases presented here the *Bt* fields were contiguous to at least one non-*Bt* fields. A finer grid could allow the exploration of the case of a less than complete market penetration with *Bt* fields being completely surrounded by *Bt* fields. Secondly, if mobility is very low, the assumption of random mating is likely to become less representative of the behavior of the pest population: the number of corn borers in the *Bt* fields is very low, so it might happen that the resistant borers surviving in the *Bt* portion of the fields will tend to mate among themselves, as will the susceptible borers living in the refuge. Therefore, the possibility of non-random mating in the *Bt* fields should be taken into account and its impact on resistance development examined. Thirdly, the simulations suggest that compliance to the refuge recommendations might be critical to the preservation of susceptibility. The introduction of a compliance function could increase the significance of the model's results.

CHAPTER IV.
OPTIMAL ANTIBIOTIC USAGE WITH RESISTANCE AND ENDOGENOUS TECHNOLOGICAL CHANGE

Introduction

A recent review article on the New England Journal of Medicine stated that "the prevalence of antimicrobial-resistant human pathogens is rapidly increasing, but the discovery and development of new antimicrobial drugs that are active against multidrug-resistant organisms have slowed dramatically" (Gold and Moellering, p. 1446). As Table IV.1 shows, most of the antibiotic families known today were discovered in the 1940s, during the " antibiotic revolution" (Kingston).

Table IV.1 – Main antibiotic families and some of their characteristics

FAMILY	TYPE	USAGE	DATE OF FIRST DISCOVERY	DATE OF FIRST USE
Aminoglycosides	Natural	Antitubercolosis agents	1944	1946
Cephalosporins	Natural	Broad spectrum	1945	1964
Chloranphenicol	Natural, synthetic	Broad spectrum	1947	1949
Macrolides	Natural	Pharyngitis, pneumonia	1952	1950s
Oxazolidinones	Synthetic	Broad spectrum	1987	Undergoing human trials
Penicillins	Natural, semi-synthetic	Broad spectrum	1929	1942
Quinolones	Synthetic	Broad spectrum	1962	1960s
Sulfonamides	Synthetic	Broad spectrum	1932	1935
Tetracyclines	Natural	Broad spectrum	1947	1966

Sources: Levy (1992), Encyclopædia Britannica Online (2000a, 2000b), Diekema and Jones, Kingston.

More recently, discoveries have substantially slowed down: only one class, the quinolones, was discovered in the 1960s. A new class, the oxazolidinones, is presently undergoing clinical trials (Diekema and Jones).

The problem of resistance is not limited to bacteria: it also affects the treatment of viruses such as the ones responsible for AIDS (Fauci), and disease carriers, such as the *Anopheles* mosquito which is a host for the malaria parasite. According to the World Health Organization and the World Bank, resistance is one of the main reasons why it has not been possible to eradicate malaria (World Health Organization/World Bank)[1].

The usage of these drugs[2] poses an impure public goods problem: utilization jointly generates a (positive) private characteristic, which depends exclusively on the individual's consumption of the chemical, and a (negative) public characteristic, that is, the reduction in susceptibility. The magnitude of the reduction depends on the sum of all the individuals' use, both in the present and in the past, as in the case of an accumulating form of pollution. Susceptibility has a common property nature because individual usage has a minimal impact on it, therefore individuals tend to ignore the effect that their actions have on resistance. Susceptibility is a scarce resource, and although resistance management plans that slow down resistance development are feasible, they can only reduce the impact of antibiotic usage on resistance development and not eliminate it.

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[1] Another instance of the importance of resistance is given by agricultural pesticides: according to the National Audubon Society, in 1993, 504 insect species were known to be resistant to at least one formulation of pesticide, while one hundred and fifty fungi and other plant pathogens had developed resistance to fungicides (Cate and Tinkle). As for weeds, 212 herbicide resistant weed biotypes were reported to be in existence in 1998 (Heap).

[2] We will use the terms drug, antimicrobial and antibiotic interchangeably.

In a first best world, resistance buildup should affect optimal usage: benefits of antibiotic use in terms of improved health must be weighed against the costs of lower susceptibility in the future. Society also faces the decision of how many resources to invest in the discovery of new agents effective against the pest/microbe. Therefore, there is the need to examine the issues of resource allocation and availability of substitutes.

The object of this paper is to explicitly identify the public nature characteristics of susceptibility in a dynamic setting and to characterize the optimal intertemporal usage problem from a social planner perspective. This allows us to discuss two essential social welfare issues. The first is the optimal number of people to treat while susceptibility to an existing drug lasts, that is, the trade-off between present and future use of a drug. The second issue is how many resources to allocate to the development of new drugs. The allocation of effort for the development of alternative technologies is an important social welfare issue, particularly in the case of pharmaceutical products, since we are dealing with human health. The decision of how many resources to devote to research efforts aimed at discovering new chemical compounds will depend on these activities' relative costs and benefits. These costs and benefits will in turn be a function of both stock and flow variables, such as the production costs of the chemicals, the level of susceptibility of the existing resource and the overall amount of effort already spent on research.

Similarly, the determination of the optimal number of people to whom to administer treatment is a significant issue, particularly because there is abundant anecdotal evidence of excessive and unnecessary usage of antimicrobials. According to the Centers for Disease Control and Prevention, for instance, around a third of the 150

million outpatient antibiotics prescribed each year are unneeded (as quoted in Levy, 1998). Table IV.2 shows how in some countries antibiotic usage is much higher than in others, and includes a higher amount of broad spectrum antibiotics, for which the development of resistance is a greater concern. In Australia in particular, the situation has spurred various government inquiries (Doessel)[3].

Table IV.2 – Non-public sector[1] antibiotic sales in 1983

COUNTRY	DEFINED DAILY DOSE[2] /1,000 POPULATION /DAY	BROAD/NARROW RATIO
Sweden	7.01	1.72
UK	9.36	4.03
Canada	11.64	2.74
USA	13.22	2.07
Australia	17.12	4.69

[1] Non-public sector sales excludes in-hospital use.
[2] The Defined Daily Dose is an aggregate measure of usage that allows comparisons.
Source: Doessel, 1998.

Research on substitute technologies can be subdivided into two types: research on compounds similar to those already known, and basic research on new alternative technologies. The objective of the first type of activity is to discover antibiotics (or pesticides) that use a similar mode of action to those already known. This type of

[3] In agriculture, there exists a corresponding problem. Because of the mobility of the pest population and the common property nature of susceptibility, farmers may exhibit myopic behavior towards the future development of resistance which results in overapplication of the pesticide. In case of overutilization of the chemicals, be they antimicrobials or pesticides, the first step is to determine optimal usage to help devise policies that reduce suboptimal utilization.

research is likely to involve a lower degree of uncertainty, since the existing drug provides a blueprint for scientists. Examples are the development of the semi-synthetic methicillin from penicillin, and the discovery of various pesticides all belonging to the same family, such as the chlorinated hydrocarbons, which includes DDT, dieldrin and endrin.

In most of these cases, there is likely to be cross-resistance between the old and new compounds. Cross-resistance occurs when the development of resistance to a compound also confers at least partial resistance to another chemical, so that the second chemical is less effective than it would have been if it had been used first. The likelihood of cross-resistance depends on the fact that the chemicals have a similar mode of action or a resembling structure (Levy, 1992).

In the case of antibiotics, cross-resistance causes multidrug resistance to occur. This is a particularly dangerous phenomenon, because it can become impossible to treat an illness. The present emergence of multidrug-resistant tuberculosis worldwide is a case in point (Cohn *et al.*). Cross-resistance is particularly worrisome in antibiotics because resistance is transmitted from one strain of bacteria to another[4], so that multidrug resistance in bacteria is the rule rather than the exception (Levy, 1992). Resistance has developed to all known antimicrobial drugs (Gold and Moellering), while, as we saw, the discovery of new classes of antibiotics has slowed down since the 1950s, so this problem is particularly important in terms of policy. According to the American Society for

[4] This occurs via mobile pieces of DNA, called plasmids or transposons, which move from a bacterium to another and become part of the new host's genetic material.

Microbiology (ASM), we are in an "incipient public health emergency, albeit one that is poorly appreciated and recognized"(ASM, p. 4)[5].

Resources can also be invested is the discovery of novel technologies, for which cross resistance is not likely to be an issue. For example, vaccines are a cost effective alternative to antibiotics. Other possible alternatives include both biospecific antibodies, which support the body's immune system in eliminating microbes by itself, and bacteria-attacking viruses (Nemecek)[6].

In broad terms, the discovery of novel active ingredients and treatments is likely to involve a higher degree of pure research than the discovery of new antibiotics or pesticides that use a similar mode of action to those already known. Nowadays most pharmaceutical and chemical companies maintain substantial in-house research facilities[7], and the traditional dichotomy of public sector/pure research and private sector/applied research is not clear-cut. However, the discovery of totally new compounds is likely to involve a high level of basic research, and this might have implications on both private and public research priorities and activities.

Both in the case of pests and in that of microorganisms, susceptibility could be modeled either as a non-renewable or as a renewable resource. The choice impinges on

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[5] In the case of pesticides, the transmission of resistance occurs only via reproduction, so the time path of resistance development is easier to predict, and multipesticide resistance is not the norm. However, cross-resistance is a concern at the core of the policy debate nowadays, as it is the rationale for the Environmental Protection Agency's (EPA) unprecedented policy of mandatory refuges for *Bacillus thuringiensis* (*Bt*) plant pesticides, genetically engineered to produce pesticides (EPA, 1998a).

[6] In the pesticide field, novel pesticides, which combine lower toxicity for humans and alternative modes of actions, range from chemical modifiers of development and behavior (pheromones, growth regulators) to artificial analogues of natural elements, such as the chloronicotinyls (from nicotine) to insect-tolerant plants and genetically modified crops (Pedigo).

[7] See Gambardella for the pharmaceutical industry and Hammock and Soderlund for the pesticide industry.

the relative fitness of the resistant individuals compared to the susceptible ones. Should there be a fitness cost for the resistant organisms, they would tend to disappear once the usage of the chemical selecting for them had been stopped. There appears to be evidence that resistant bacteria do not suffer from any fitness cost (Stewart *et al.*)[8].

Limited literature exists on the common property nature of susceptibility in the case of antibiotics. Tisdell provides a basic analysis, even though he frames the issue in terms of a prisoner's dilemma and not as a problem of the commons. Brown and Layton analyze the externalities involved in the use of antibiotics focussing on the trade-off involved in the usage of antibiotics as growth promoters for animals. Both farmers and sick individuals choose the optimal level of medication taking resistance as given, thereby overutilizing the antibiotic. Laxminarayan and Brown examine how to optimally utilize two antibiotics with different impacts on resistance, without incorporating the development of backstop technologies, in a problem similar that of the mining of various deposits of ore of different quality. Kile models the R&D expenditure in the private sector as a function of resistance. He finds some evidence that increases in the levels of resistance have a positive impact on the level of R&D expenditure, the rationale being that higher levels of resistance shorten the life span of existing drugs, so that their producers need to find alternative products.

Even though the economics literature has not focussed on antibiotics use in optimal planning models, there is a large body of work on issues of common property and

[8] As for pests, there are various instances of lack of fitness costs, see for instance Andrews and Morrison, Croft and Whalon, Penrose, and Romero and Sutton.

externalities in relation to exhaustible resources. Kamien and Schwartz (1982) provide an excellent literature review.

An extensive amount of economics literature, spurred by the energy crisis of the early '70s, has analyzed the issues related to the use of a nonrenewable resource when the discovery of backstops is uncertain. Dasgupta and Heal's seminal paper (1974) analyzes the problem when there is uncertainty on the date of discovery of the new, nonexhaustible technology (and not on its characteristics). The probability of the discovery date is exogenous, and there are no investment efforts. They prove that in certain circumstances the uncertainty is formally equivalent to an increase in the discount rate. Kamien and Schwartz (1978) and Dasgupta, Heal and Majumdar extend the model to endogenize the level of investment which accelerates the time of discovery of the new technology. Davison uses essentially the same framework for the case in which the probability of discovering a backstop is a function of the flow of R&D and not its stock.

In the next pages, we will develop an expected utility model with heterogeneous individuals and we will apply some of the approaches devcloped in the energy literature to determine the optimal time path for the depletion of susceptibility to an existing drug and to discuss the characteristics of the discovery process. We will assume that technological change is endogenous and analyze the dynamics of research in backstop technologies both in a certain and in an uncertain world.

The basic framework

For individuals taking an antibiotic, the dose is exogenously given by the doctor or the manufacturer. Therefore, we treat the choice of individual drug use as a discrete choice problem. Individuals are heterogeneous in their need for treatment, which allows analysis of the marginal impact of each treatment, the optimal number of individuals treated and the externalities created by the increase in resistance induced by usage.

We will use the expected utility framework (Evans and Viscusi) to examine the issue of optimal use of antibiotics. We will also show how the model can be easily utilized for the case of pesticides. Preferences are quasilinear. Utility derived from the consumption of good x is contingent on good health, while utility obtained from the numeraire good y is independent of health. Therefore, each agent's utility is of the form: $\alpha(x') + y'$, where $\alpha' > 0, \alpha'' < 0$, and $\lim_{\delta x \to 0} \alpha(x) = \infty$. We can think of good x as any good that requires good health to provide positive utility: in bad health, the utility derived from x is zero (Fuchs and Zeckhauser).

The economy is either based on endowments or is such that the supply of labor is fixed over time: each individual i is given an identical endowment/wage m at each time t. In each time period each individual also faces a lump sum tax τ to finance activities that prevent the buildup of resistance and the research in backstop technologies. We limit ourselves to the case in which τ is identical for everybody. This is consistent with the public nature of susceptibility, and with the fact that the level of infection is independent of agents' actions. Alternatively, we could think that taxes are set *ex ante*, before people get sick, and, *ex ante,* individuals are identical in every respect.

Individuals maximize instantaneous utility. As discussed in more detail below, individuals cannot use their past sickness as a predictor for the future and the development of resistance has a public good nature, thus each individual takes the existing stock of susceptibility E as given and his/her contribution to resistance development as negligible. There is no 'golden glow' effect on the part of untreated individuals with respect to the health levels of others in the economy, and susceptibility has no option value. We define treatment for individual i as $e^i = 1$ and the no treatment case as $e^i = 0$, with p as the price of the antibiotic. We assume that the marginal cost of production, χ, is constant, and the pharmaceutical industry is perfectly competitive[9], so that $p = \chi$[10].

The budget constraint for each agent is then $x^i + y^i + \tau + pe^i = m$. We can then rewrite the utility function as $\alpha(x^i) + m - x^i - pe^i - \tau$[11]. Agents maximize expected utility:

$$EU^i = \Pr(\text{healthy})\left[\alpha(x^i) + m - x^i - pe^i - \tau\right] + \Pr(\text{sick})\left[m - x^i - pe^i - \tau\right], \text{ and}$$
$$EU^i = \Pr(\text{healthy})\alpha(x^i) + m - x^i - pe^i - \tau.$$

More specifically, we assume that the probability of being healthy for untreated agents is determined by an exogenous parameter $\theta^i \in \mathbb{N}, \theta^i \in [0, n]$[12], which represents

[9] The pharmaceutical industry is also myopic in its behavior towards resistance, since E is a public good.
[10] This is a simplification in the case of patented drugs, but it reflects reality for older drugs.
[11] We will not concern ourselves with non-negativity constraints for y.
[12] It would be possible to choose a more complex distribution that puts some mass at θ^1. This would not change the quality of the results.

the severity of the infection. At 0, the agent is healthy, at n he is the sickest in the population, which has size n+1. We assume that the sicker a person is, the less likely he is to recover without treatment. Therefore, the probability is a function of θ: pr(no recovery) = p(θ), with p'(θ) > 0, and pr(recovery) = 1- p(θ). In particular, to calculate explicit results, we will assume that pr(no recovery) = $\frac{\theta^2}{n^2}$ and pr(recovery) = $1-\frac{\theta^2}{n^2}$. We will also assume that, in each period of time, the probability that a particular individual is assigned a certain θ^i is independent of the θ^i of the previous period, so that neither the government nor the agents can use past sickness as a predictor[13]. This formulation therefore implies that the level of resistance each individual faces at any point in time is the same and independent from each person's medical history. This is consistent with the fact that resistance spreads easily from one bacterium to another (Levy, 1992). Therefore, we can write:

$$EU^i(m,\theta^i)=\left(1-\frac{\theta^2}{n^2}\right)\alpha(x^i)+\frac{\theta^2}{n^2}0+m-x^i-\tau=\alpha(x^i)-\frac{\theta^2}{n^2}\alpha(x^i)+m-x^i-\tau. \quad \text{(IV.1)}$$

If agents receive treatment for their infection, their expected utility is no longer a function of the severity of the infection. Recovery depends on whether the infecting mechanism is susceptible to the treatment. The higher the level of susceptibility, the higher the probability of recovery. We normalize the stock of susceptibility E to the

[13] Alternatively, we could interpret this as having a stationary population of size n with individuals living only one time period.

[0, 2^n-1] interval, and assume that the probability of recovering is $\frac{\ln(1+E)}{n\ln(2)}$, and the probability of no recovery is $1-\frac{\ln(1+E)}{n\ln(2)}$. If the treatment is effective, once again $U^i = \alpha(x^i) + m - x^i - p - \tau$. If the treatment does not work, utility from x once again equals zero. Therefore:

$$EU^i(m,\theta^i) = \frac{\ln(1+E)}{n\ln(2)}\left[\alpha(x^i) + m - x^i - p - \tau\right] + \left[1 - \frac{\ln(1+E)}{n\ln(2)}\right]\left[0 + m - x^i - p - \tau\right],$$

$$\text{and } EU^i(m,\theta^i) = \frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) + m - x^i - p - \tau. \qquad \text{(IV.2)}$$

The agents' maximization then consists of a discrete choice problem:

$$EU^i(m,\theta^i,e^i=1) = \frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) + m - x^i - p - \tau,$$

versus

$$EU^i(m,\theta^i e^i=0) = \left(1-\frac{\theta^2}{n^2}\right)\alpha(x^i) + \frac{\theta^2}{n^2}0 + m - x^i = \alpha(x^i) - \frac{\theta^2}{n^2}\alpha(x^i) + m - x^i - \tau,$$

$$\text{if } \frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) - p > \alpha(x^i) - \frac{\theta^2}{n^2}\alpha(x^i) \Rightarrow e^i = 1, \text{ and}$$

$$\text{if } \frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) - p < \alpha(x^i) - \frac{\theta^2}{n^2}\alpha(x^i) \Rightarrow e^i = 0.$$

Therefore, for agents with a serious infection, for whom pr(sickness) = $\frac{\theta^2}{n} \to 1$, treatment will be worthwhile even if the efficacy of the treatment is low. More specifically, for the sickest individual in the population, for whom pr(sickness) = 1, it will always be worthwhile to undergo treatment as long as $\frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) > p$ [14]:

$$EU^i(m,n,e^i=1) = \frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) + m - x^i - p - \tau > EU^i(m,n,e^i=0) = m - x^i - \tau .$$

In a world of decentralized choices, the marginal individual (we assume the equality will hold for one person) is the one for whom:

$$\frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) - p = \alpha(x^i) - \frac{\theta_I^2}{n^2}\alpha(x^i), \text{ that is,}$$

$$\theta_I = n\sqrt{1 + \frac{p}{\alpha(x^i)} - \frac{\ln(1+E)}{n\ln(2)}}.$$

[14] In the case of pesticides, this basic framework could be used to analyze the behavior of risk-neutral farmers who receive an endowment m in each time period and whose crops are produced by a composite input x via a concave production function α. The application of pesticides can be considered a discrete problem, either because the farmers follow the recommended dosage instructions or because they do not have a choice over the dosage, as in the case of the recently introduced *Bt* crops, which are genetically engineered to produce a pesticide. We indicate the level of infestation by θ, the stock of susceptibility as $E \in [0, 2^n\text{-}1]$, the cost of the pesticide application as p and the efficacy of the pesticide, a function of susceptibility, as $\frac{\ln(1+E)}{n\ln(2)}$. Then the expected profits have the same form as the expected utilities specified above.

In this simple formulation, we are ignoring the fact that, at least in Western countries, antibiotics are not available over the counter, and a doctor is needed to prescribe the medicine. One simple way to accommodate this would be to introduce a floor on the level of θ^i below which doctors will not treat the patient, θ_D^i. Given the evidence of antibiotics over-prescription discussed in the introduction, however, it is reasonable to assume that in practice this constraint does not bind, $\theta_D^i > \theta_I^i$.

The stock of susceptibility to antibiotics or pesticides used until time t, denoted by E, is such that its behavior through time can be described by the following equation of motion:

$$\dot{E} = \frac{-\omega \sum_{i=0}^{n-1} e^i}{\mathrm{P}+1}. \qquad \text{(IV.3)}$$

Where ω is the marginal impact of individual usage on resistance development, and P is the amount spent in resistance management activities such as education on the risks of resistance. The preventive activity is financed by the lump sum taxes τ levied on each individual in the community, so that $(n + 1)\tau = \mathrm{P}$. In the medical literature, activities that could be included in P range from *ex ante* prevention to *ex post* containment of the infection (Murray). They include: education on the risks of resistance and on the appropriate use of the chemical; techniques through which the chemical is put to use such as 1,3, or 10 days antibiotic cycles (*ex ante*), and containment of the infection or of the resistant pest population (*ex post*).

This specification follows Brown and Layton in that the effect of antibiotic usage on the stock of susceptibility is linear. We will discuss some of the consequences of a nonlinear specification later. This characterization of the problem's dynamics indicates that the increase in resistance taking place in each period affects only the future effectiveness of the antibiotic. This lag is due to the fact that resistance takes some time to spread.

In this formulation, if there is no usage of the chemical, resistance management is ineffective. The reason is that resistance management is not independent from utilization of the drug, being essentially a way to minimize the impact of usage on the development of resistance. This will insure that the stock of susceptibility E is effectively a nonrenewable resource and that at each point in time, E is such that $E \leq E_0$, where E_0 is the initial stock of the resource. We are implicitly assuming that the level of preventive activity P is always as high as possible. The rationale for this is twofold. First, the effects of preventive activities are certain and immediate, and the benefits derived from a correct use of antibiotics are not limited to the slowing down of resistance, but include better health for the individuals treated. Taking a course of antibiotics correctly improves a patient's chances of recovery besides reducing resistance buildup. Secondly, P is in practice of limited effectiveness and cannot eliminate the development of resistance, so an analysis of its dynamics is of limited interest.

Increases in the antibiotic price p, will decrease the number of people taking the medicine, since if $p_0 > p_1$:

$$\theta_I^0 = n\sqrt{1 + \frac{p_0}{\alpha(x^i)} - \frac{\ln(1+E)}{n\ln(2)}}, \text{ and}$$

$$\theta_I^1 = n\sqrt{1 + \frac{p_1}{\alpha(x^i)} - \frac{\ln(1+E)}{n\ln(2)}}, \text{ so}$$

$$\theta_I^0 - \theta_1^1 - = n\sqrt{1 + \frac{p_0}{\alpha(x^i)} - \frac{\ln(1+E)}{n\ln(2)}} - n\sqrt{1 + \frac{p_1}{\alpha(x^i)} - \frac{\ln(1+E)}{n\ln(2)}} > 0.$$

This is an expected result. It indicates that the magnitude of the change in p that would be needed to bring down overuse depends on $\frac{p_0}{\alpha(x^i)}$, the real price of the medicine in utility terms. If income is large compared to the cost of the antibiotic, as is typically the case in Western countries, very large increases in price will be needed to substantially decrease overuse.

In a decentralized world, there is overuse of the antibiotic, but usage decreases with time as efficacy decreases. The socially optimal marginal individual (we assume the equality will hold for one person) is the one for whom:

$$\frac{\ln(1+E)}{n\ln(2)}\alpha(x^i) - p - \mu\frac{\omega}{\mathrm{P}+1} = \alpha(x^i) - \frac{\theta_S^2}{n^2}\alpha(x^i), \text{ that is,}$$

$$\theta_S = n\sqrt{1 + \frac{p}{\alpha(x^i)} - \frac{\ln(1+E)}{n\ln(2)} + \mu\frac{\omega}{\alpha(x^i)(\mathrm{P}+1)}}.$$

And it is evident that:

$$\theta_S > \theta_I = n\sqrt{1 + \frac{p}{\alpha(x')} - \frac{\ln(1+E)}{n\ln(2)}}.$$

This is similar to Brown and Layton's characterization. The difference between the social optimum and the decentralized case is given by the shadow value of susceptibility times the individual effective impact of usage on resistance, $\frac{\omega}{(P+1)}$, weighted by the utility of consuming good $x, \alpha(x')$. The higher the utility derived from the consumption of good x which might be foregone if the agent is sick, the closer θ_S is to θ_I, since the benefits of using the antibiotic in the present (the costs of delaying usage) are higher. As for the decrease in usage in the decentralized case, $\frac{\Delta\theta_I}{\Delta E} = -\frac{1}{2\ln(2)(1+E)}\left(1 + \frac{p}{\alpha(x')} - \frac{\ln(1+E)}{n\ln(2)}\right)^{-1/2} < 0.$

First scenario: no substitutes to the antibiotic

We start by discussing the simplest case. In this scenario, there are no alternatives to the antibiotic, and resistance management is the only activity that can slow down the mining of susceptibility. This is not necessarily a realistic scenario, since it assumes that no technological change is possible, but it is useful in setting the stage of the problem. The social planner seeks to maximize[15]:

[15] Note that this maximization indicates the lack of credit markets for both the government and individual agents.

$$\underset{e^{i\forall t}}{\text{Max}} \int_0^{\infty} \left[\sum_{i=0}^{\gamma} EU^i(\text{untreated}) + \sum_{i=\gamma+1}^{n+1} EU^i(\text{treated}) \right] e^{-rt},$$

$$\text{s.t.} \quad \dot{E} = \frac{-\omega(n-\gamma)}{\mathrm{P}+1}.$$

Assuming that n is large, so that the proportion of population not taking the drug, γ/n, can be treated as a continuous variable, and remembering that $\sum_{i=1}^{K} i^2 = \frac{1}{6}K(K+1)(2K+1)$, we can reformulate the problem as:

$$\underset{\frac{\gamma}{n}}{\text{Max}} \sum_{i=0}^{\gamma} EU^i(\text{untreated}) + \sum_{i=\gamma+1}^{n+1} EU^i(\text{treated}).$$

We can rearrange the maximand:

$$\sum_{i=0}^{\gamma}\left[\left(1-\frac{\theta^2}{n^2}\right)\alpha(x^i)+m-x^i-\tau\right]+\sum_{i=\gamma+1}^{n+1}\left[\frac{\ln(1+E)}{n\ln(2)}\alpha(x^i)+m-x^i-p-\tau\right]=$$

$$(\gamma+1)\alpha-\frac{\gamma(\gamma+1)(2\gamma+1)}{6n^2}\alpha+(\gamma+1)(m-x^i-\tau)+\frac{\ln(1+E)}{n\ln(2)}(n-\gamma)\alpha$$

$$+(n-\gamma)(m-x^i-p-\tau)=$$

$$(\gamma+1)\alpha-\frac{\gamma(\gamma+1)(2\gamma+1)}{6n^2}\alpha+\frac{\ln(1+E)}{n\ln(2)}(n-\gamma)\alpha+(n+1)(m-x^i)-p(n-\gamma)-(n+1)\tau=$$

$$(\gamma+1)\alpha-\frac{\gamma(\gamma+1)(2\gamma+1)}{6n^2}\alpha+\frac{\ln(1+E)}{n\ln(2)}(n-\gamma)\alpha+(n+1)(m-x^i)-p(n-\gamma)-\mathrm{P}.$$

It is worthwhile noting that in this problem the presence of a positive discount rate for the future, r, is a debatable assumption. As Ramsey wrote, the discounting of future generations is "ethically indefensible and [originating] merely from the weakness of the imagination" (Ramsey, p. 543). We can view this as a general formulation of the problem that allows for the particular case of $r = 0$[16]. The present value Hamiltonian is then:

$$H = \left[(\gamma+1)\alpha - \frac{\gamma(\gamma+1)(2\gamma+1)}{6n^2}\alpha + (n-\gamma)\frac{\ln(1+E)}{n\ln(2)}\alpha + (n+1)(m-x') - p(n-\gamma) - \mathrm{P} \right] e^{-rt} - \mu\frac{\omega(n-\gamma)}{\mathrm{P}+1}.$$

We rewrite the Hamiltonian in terms of the proportion of people treated:

$$H = \int_0^{\infty} \left[\left(\frac{\gamma}{n}n+1\right)\alpha - \frac{\left(\frac{\gamma}{n}n\right)\left(\frac{\gamma}{n}n+1\right)\left(2\frac{\gamma}{n}n+1\right)}{6n^2}\alpha + \left(n-\frac{\gamma}{n}n\right)\frac{\ln(1+E)}{n\ln(2)}\alpha + (n+1)(m-x') - p\left(n-\frac{\gamma}{n}n\right) - \mathrm{P} \right] e^{-rt} - \mu\frac{\omega\left(n-\frac{\gamma}{n}n\right)}{\mathrm{P}+1}.$$

We can simplify this to:

[16] Note that a negative discount rate could be advocated in this context, since the future generations will necessarily be poorer than the present ones, as the stock of susceptibility at their disposal is lower. See Goodin for arguments against the use of discounting, particularly when human health is concerned.

$$H = \int_0^{\pi} \left[\begin{array}{l} \left(\frac{\gamma}{n}n+1\right)\alpha - \left[\left(\frac{\gamma}{n}\right)^3\frac{n}{3}+\left(\frac{\gamma}{n}\right)^2\frac{1}{2}+\left(\frac{\gamma}{n}\right)\frac{1}{6n}\right]\alpha - \mathrm{P} \\ +\left(1-\frac{\gamma}{n}\right)\frac{\ln(1+E)}{\ln(2)}\alpha + (n+1)(m-x') - pn\left(1-\frac{\gamma}{n}\right) \end{array} \right] e^{-r t} \\ -\mu\frac{n\omega\left(1-\frac{\gamma}{n}\right)}{\mathrm{P}+1}. \qquad \text{(IV.4)}$$

The first order conditions are:

$$0 = \frac{\partial H}{\partial \gamma / n} = \left[n\alpha - \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\alpha - \frac{\ln(1+E)}{\ln(2)}\alpha + np \right] e^{-r t} + \mu n \frac{\omega}{\mathrm{P}+1}, \qquad \text{(IV.5)}$$

$$\mu = \frac{\mathrm{P}+1}{\omega}\left[-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p \right] e^{-r t}, \qquad \text{(IV.6)}$$

$$\dot{\mu} = -\frac{\partial H}{\partial E} = -\left(1-\frac{\gamma}{n}\right)\frac{\alpha}{(1+E)\ln(2)} e^{-r t}. \qquad \text{(IV.7)}$$

PROPOSITION 1 – The proportion of untreated people increases over time if the discount rate is positive.

PROOF:

We take the derivative of (IV.6) with respect to time, and equate it to (IV.7):

$$\dot{\mu} = \frac{\mathrm{P}+1}{\omega}\left\{\left[2\left(\frac{\gamma}{n}\right)n+1\right]\frac{\alpha}{n}\left(\frac{\dot{\gamma}}{n}\right) - \frac{\alpha}{n(1+E)\ln(2)}\frac{\omega(n-\gamma)}{\mathrm{P}+1}\right\}e^{-\pi}$$

$$-r\frac{\mathrm{P}+1}{\omega}\left\{-\alpha+\left[\left(\frac{\gamma}{n}\right)^2 n+\left(\frac{\gamma}{n}\right)+\frac{1}{6n}\right]\frac{\alpha}{n}+\frac{\ln(1+E)}{n\ln(2)}\alpha-p\right\}e^{-\pi},$$

and since $\dot{\mu} = -\frac{\partial H}{\partial E} = -\left(1-\frac{\gamma}{n}\right)\frac{\alpha}{(1+E)\ln(2)}e^{-\pi}$, we can write:

$$\left[2\left(\frac{\gamma}{n}\right)n+1\right]\frac{\alpha}{n}\left(\frac{\dot{\gamma}}{n}\right) = r\left\{-\alpha+\left[\left(\frac{\gamma}{n}\right)^2 n+\left(\frac{\gamma}{n}\right)+\frac{1}{6n}\right]\frac{\alpha}{n}+\frac{\ln(1+E)}{n\ln(2)}\alpha-p\right\}. \qquad \text{(IV.8)}$$

This result implies that, if the discount rate is zero, the optimal policy is to have a constant percentage of population receiving treatment through time. The level of social welfare will however decrease over time as the efficacy of the antimicrobial declines. If, on the other hand, $r > 0$, $\left(\frac{\dot{\gamma}}{n}\right) \geq 0$, as the term in brackets is positive.

Note that the result that $\dot{\gamma} = 0$ for $r = 0$ is independent from the specification of the dynamics of resistance, but it does depend on resistance development being linear. We could see resistance buildup as exponential, since resistance in bacteria is not transferred only via reproduction, but also through gene exchange. Therefore, "One surviv[ing bacterium] can produce new copies of itself, as well as recruit new resistant neighbors" (Levy 1992, p.78), and resistance spreads faster as more people are treated. If the erosion of susceptibility is specified as $\dot{E} = -\frac{\exp\left[\omega(n-\gamma)\right]}{\mathrm{P}+1}$, individual use has

increasingly high costs in terms of resistance. In this case, the optimal policy would be to increase the proportion of untreated people through time, even if the discount rate is zero. Therefore, the conclusion that, when the discount rate is zero, the optimal policy is to have a constant percentage of the population receiving treatment is a conservative one.

Second scenario: the existence of certain exhaustible substitutes

In this case, we will assume that there exists an alternative technology to the original antibiotic. Specifically, it is possible to develop another antibiotic, which is superior technologically to the existing one because it mines susceptibility more slowly than the original one. That is, the new chemical has a lower impact on resistance: $\omega_1 > \omega_2$, where ω_1 is the impact of the old technology on resistance and ω_2 is the impact of the new one. The development of this substitute is certain, but it requires investment in a capital stock. The structure of this model is similar to that of the second model developed by Vousden in the case of oil. We have three control variables: $\frac{\gamma}{n}$, the proportion of people treated with the new chemical, $\frac{\delta}{n}$, and the level of investment, I, and two state variables, E and the capital stock K. Investment increases capital, so that $\dot{K} = f(I)$, and $f' > 0, f'' < 0$, and investment presents increasing marginal costs because of the nature of the research and development process, so the cost of investment, $g(I)$, is such that $g' > 0$, $g'' > 0$. Because of the quasilinearity of the utility functions, the formulation is the same whether we assume that agents treated with the newer antibiotics

still pay the same price p and the government finances the difference or whether agents pay the full price for the newer treatment. Initially, the costs of using a new drug are very high: clinical trials require expensive Food and Drug Administration approvals, and are conducted by highly trained medical personnel. In addition to that, the production of new drugs itself is often very costly. As more resources are invested in the research of the new drug, costs decline. Therefore, we model the cost of the new antibiotic as an increasing function of the number of people treated with it, δ, and a decreasing function of the level of capital K: $c(\delta, K)$, such that $c_1(\delta, K) > 0$, $c_2(\delta, K) < 0$, $c_{11}(\delta, K) > 0$, $c_{22}(\delta, K) > 0$, $c_{12}(\delta, K) < 0$ for δ and $K > 0$, $c(\delta, 0) = c_2(\delta, 0) = \infty$, and $c(0, K) = c_1(0, K) = c_{11}(0, K) = 0$. Note that there is no capital depreciation, so the non-negativity constraint for capital is always satisfied. For simplicity, we will assume that $K_0 = 0$. The social planner problem is then:

$$\underset{\frac{\gamma}{n},\frac{\delta}{n},I}{\text{Max}} \int_0^{\infty} \left\{ \left[\begin{array}{l} \left(\frac{\gamma}{n}n+1\right)\alpha - \left[\left(\frac{\gamma}{n}\right)^3\frac{n}{3}+\left(\frac{\gamma}{n}\right)^2\frac{1}{2}+\left(\frac{\gamma}{n}\right)\frac{1}{6n}\right]\alpha \\ +\dfrac{\ln(1+E)}{\ln(2)}\left(1-\dfrac{\gamma}{n}\right)\alpha \\ +(n+1)(m-x')-p\left(n-\dfrac{\gamma}{n}n\right)-\mathrm{P}-c\left(\dfrac{\delta}{n}n,K\right)-g(I) \end{array} \right] \right\} e^{-rt}dt,$$

s.t.

$$\dot{E} = \frac{-\omega_1\left(n-\frac{\gamma}{n}n-\frac{\delta}{n}n\right)-\omega_2\left(\frac{\delta}{n}n\right)}{\mathrm{P}+1},$$

$$\dot{K} = f(I).$$

The Hamiltonian is:

$$H = \left[\begin{array}{l} \left(\frac{\gamma}{n}n+1\right)\alpha - \left[\left(\frac{\gamma}{n}\right)^3\frac{n}{3}+\left(\frac{\gamma}{n}\right)^2\frac{1}{2}+\left(\frac{\gamma}{n}\right)\frac{1}{6n}\right]\alpha + \frac{\ln(1+E)}{\ln(2)}\left(1-\frac{\gamma}{n}\right)\alpha \\ +(n+1)(m-x) - p\left(n-\frac{\gamma}{n}n\right) - \mathrm{P} - c\left(\frac{\delta}{n}n, K\right) - g(I) \end{array}\right] e^{-\pi} \qquad \text{(IV.9)}$$
$$+\mu\frac{-\omega_1\left(n-\frac{\gamma}{n}n-\frac{\delta}{n}n\right)-\omega_2\left(\frac{\delta}{n}n\right)}{\mathrm{P}+1}+\upsilon f(I).$$

The first order conditions are:

$$0 = \frac{\partial H}{\partial \gamma/n} = \left[n\alpha - \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\alpha - \frac{\ln(1+E)}{\ln(2)}\alpha + np\right]e^{-\pi} + \mu n\frac{\omega_1}{\mathrm{P}+1}, \qquad \text{(IV.10)}$$

$$\text{that is, } \mu = \frac{\mathrm{P}+1}{\omega_1}\left[-\alpha - p + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha\right]e^{-\pi}, \qquad \text{(IV.11)}$$

$$0 \geq \frac{\partial H}{\partial I} = -g'(I)e^{-\pi} + \upsilon f'(I), \qquad \text{(IV.12)}$$

$$0 \geq \frac{\partial H}{\partial \delta/n} = -nc_1\left(\frac{\delta}{n}n, K\right)e^{-\pi} + \mu n\frac{\omega_1-\omega_2}{\mathrm{P}+1}, \qquad \text{(IV.13)}$$

$$\dot{\mu} = -\frac{\partial H}{\partial E} = -\left(1-\frac{\gamma}{n}\right)\frac{\alpha}{(1+E)\ln(2)}e^{-\pi}, \qquad \text{(IV.14)}$$

$$\dot{\upsilon} = -\frac{\partial H}{\partial K} = c_2\left(\frac{\delta}{n}n, K\right)e^{-\pi}, \qquad \text{(IV.15)}$$

Note that (IV.10) is the same condition as in the first scenario (no technological change) as long as $\omega = \omega_1$ (see equation (IV.5)).

If $-nc_1\left(\frac{\delta}{n}n, K\right)e^{-r} + \mu n\frac{\omega_1 - \omega_2}{\mathrm{P}+1} = 0$, then $\mu = \frac{\mathrm{P}+1}{\omega_1 - \omega_2}c_1\left(\frac{\delta}{n}n, K\right)e^{-r}$.

PROPOSITION 2 – The dynamic path of the proportion of untreated people is the same as in the first scenario if the impact of the existing antibiotic on resistance is the same ($\omega = \omega_1$). This is due to the fact that the optimal policy is independent from the distribution of wealth.

PROOF:

We take the derivative of (IV.10) with respect to time, and equate it to (IV.11):

$$\dot{\mu} = \frac{\mathrm{P}+1}{\omega_1}\left\{\left[2\left(\frac{\gamma}{n}\right)n + 1\right]\frac{\alpha}{n}\left(\frac{\dot{\gamma}}{n}\right) - \frac{\alpha}{n(1+E)\ln(2)}\frac{\omega_1(n-\gamma)}{\mathrm{P}+1}\right\}e^{-r}$$

$$-r\frac{\mathrm{P}+1}{\omega_1}\left\{-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p\right\}e^{-r}, \text{ and also,}$$

$$\dot{\mu} = -\frac{\partial H}{\partial E} = -\left(1 - \frac{\gamma}{n}\right)\frac{\alpha}{(1+E)\ln(2)}e^{-r}, \text{ therefore}$$

$$\left[2\left(\frac{\gamma}{n}\right)n + 1\right]\frac{\alpha}{n}\left(\frac{\dot{\gamma}}{n}\right) = r\left\{-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p\right\}. \qquad \text{(IV.16)}$$

PROPOSITION 3 – Investment declines over time if the discount rate is zero. If the discount rate is positive, the time path of investment will depend on the importance that the stock of capital has on the reduction in the cost of producing the new drug.

PROOF:

Investment will not start as long as $g'(0)e^{-rt} > \upsilon f'(0)$. Once $g'(I)e^{-rt} - \upsilon f'(I) = 0$:

$$\dot{\upsilon} = \frac{g''(I)f'(I) - g'(I)f''(I)}{[f'(I)]^2}\dot{I}e^{-rt} - r\frac{g'(I)}{f'(I)}e^{-rt}, \text{ and } \dot{\upsilon} = c_2(\delta, K)e^{-rt}, \text{ therefore}$$

$$\dot{I} = \frac{[f'(I)]^2}{g''(I)f'(I) - g'(I)f''(I)}\left[c_2(\delta, K) + r\frac{g'(I)}{f'(I)}\right]. \qquad \text{(IV.17)}$$

If $|c_2(\delta, K)| > r\frac{g'(I)}{f'(I)}$, investment will decline over time. In this case, since the benefits of investment are certain, the level of investment will be initially high, so that its benefits can be captured as soon as possible, and then taper off.

The start of investment will not in general coincide with the beginning of use of the new technology. The date at which sufficient capital has been accumulated to make use of the new technology economically viable will depend on the structure of the cost function c. Specifically, treatment with the new technology will be delayed as long as $c_1 > \mu\frac{\omega_1 - \omega_2}{P+1}e^{rt}$. If, for low levels of capital stock, the marginal cost of treating even very few patients is high, adoption of the technology will be deferred. Figure IV.1 suggests a possible cost structure. For levels of capital below K_0, the cost of treatment is prohibitively high.

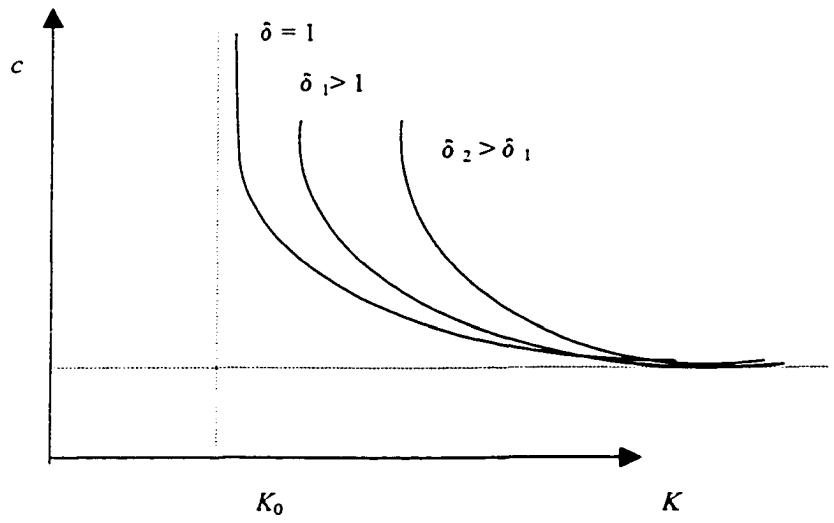

Figure IV.1 – A possible structure of the cost function for the new technology

PROPOSITION 4 – The time path of the proportion of agents treated with the new antibiotic depends on the net effect of a capital increase in the cost of administering the new drug and the impact of the use of the new drug on resistance.

PROOF:

We rearrange (IV.13) and take its derivative with respect to time, and equate it to (IV.11):

$$\dot{\mu} = \frac{\mathrm{P}+1}{\omega_1 - \omega_2}\left[c_{11}\left(\frac{\delta}{n}n, K\right)\left(\frac{\dot{\delta}}{n}\right)n + c_{12}\left(\frac{\delta}{n}n, K\right)f(I) - rc_1\left(\frac{\delta}{n}n, K\right)\right]e^{-rt}, \text{ and}$$

$$\dot{\mu} = -\frac{\partial H}{\partial E} = -\left(1-\frac{\gamma}{n}\right)\frac{\alpha}{(1+E)\ln(2)}e^{-rt}, \text{ therefore}$$

$$\left(\frac{\dot{\delta}}{n}\right) = -\frac{c_{12}}{c_{11}n}f(I) + r\frac{c_1}{c_{11}n} - \frac{\omega_1 - \omega_2}{\mathrm{P}+1}\left(1-\frac{\gamma}{n}\right)\frac{\alpha}{c_{11}n(1+E)\ln(2)}. \qquad \text{(IV.18)}$$

The long run behavior of the percentage of population treated with the new technology will depend on the difference between the reduction in costs brought about by a capital increase and the net effect of the use of the new drug on resistance buildup. Figure IV.2 shows a possible path for the portion of people treated with the old and new chemical, with a positive interest rate, and $\left(\frac{\dot{\delta}}{n}\right) > 0$ globally.

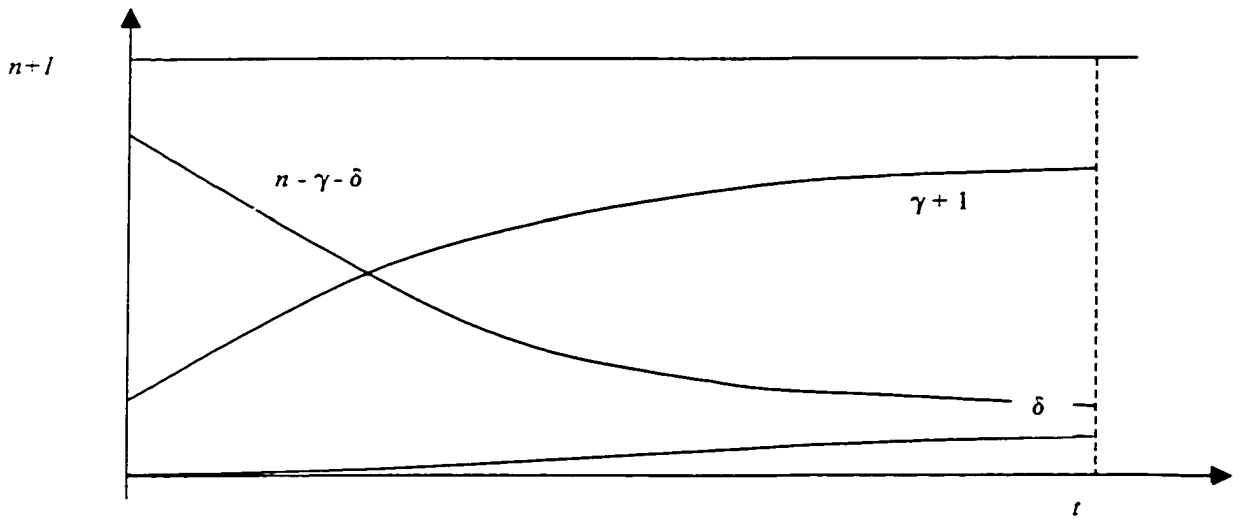

Figure IV.2 – Treatment with a positive discount rate in the second scenario

In this case, since the number of untreated people keeps increasing, as does the number of people treated with the second antibiotic, we must have that the slope of the latter is flatter, or $\dot{\delta} < \dot{\gamma}$. If, on the other hand, the discount rate for the future were zero, the number of untreated people would be constant but the number of people treated with the new antibiotic might still increase through time, albeit more slowly (see (IV.18)).

Third scenario: uncertain nonexhaustible substitutes

In this scenario, the discovery a backstop technology is not certain, and the probability of developing a new (nonexhaustible) technology is endogenous, depending positively on the cumulative amount of R&D effort. We suppose that the new technology is a real breakthrough, so that it renders the stock of susceptibility remaining at the time of the discovery worthless. A good example would be the discovery of "biospecific antibodies", which recognize harmful bacteria and take them to the human cells that can eliminate them (Nemecek). Define T as the time at which the new technology becomes available, and W as the maximum social welfare possible after the new technology is discovered:

$$W = \max \int_{T}^{\infty} \left(\sum_{i=1}^{n} U^i \right) e^{-r(t-T)} dt . \qquad \text{(IV.19)}$$

As we said above, the probability of discovering a backstop technology is endogenous, and depends positively on the cumulative amount of R&D effort. Define the level of R&D in each time period as I, and the cumulative level of R&D, or stock of knowledge capital, as K. We will assume that the dynamic relationship between stock and flow of knowledge has the same structure as in the previous scenario:

$$\dot{K} = g(I), \qquad \text{(IV.20)}$$

s.t. $K(0) = 0, f(0) = 0, f' > 0,$ and $f'' < 0.$

We define the probability of discovering the backstop as $\phi(K)$. $\phi(K)$ is such that $\phi(0)=0$, $\phi'(0)=0$, $\phi'\geq 0$, and $\lim_{z\to\infty}\phi(z)=1$ This is the same structure of the R&D function specified in Kamien and Schwartz (1978). The probability of discovering the new technology in the interval dt equals $d\phi(K(t))=\phi'(K(t))\dot{K}(t)dt=\phi'(K(t))f(I)dt$.

In their seminal 1974 paper, Dasgupta and Heal prove that if $W_E = 0$, as we have assumed here, a certain kind of certainty equivalence results, so that the maximization can be rewritten as:

$$\underset{\frac{\gamma}{n},I}{\text{Max}} \int_0^{\infty}\left\{\left[\begin{array}{l}\left(\frac{\gamma}{n}n+1\right)\alpha-\left[\left(\frac{\gamma}{n}\right)^3\frac{n}{3}+\left(\frac{\gamma}{n}\right)^2\frac{1}{2}+\left(\frac{\gamma}{n}\right)\frac{1}{6n}\right]\alpha \\ +\dfrac{\ln(1+E)}{\ln(2)}\left(1-\dfrac{\gamma}{n}\right)\alpha \\ +(n+1)(m-x)-p\left(n-\dfrac{\gamma}{n}n\right)-\mathrm{P}-g(I)\end{array}\right]\left(1-\phi(K)\right)+\phi'(K)f(I)W\right\}e^{-rt}dt,$$

s.t.

$$\dot{E}=\frac{-\omega\left(n-\frac{\gamma}{n}n\right)}{\mathrm{P}+1} \qquad \text{(multiplier } \mu\text{), and}$$

$$\dot{K}=f(I) \qquad \text{(multiplier } \eta\text{).}$$

The optimal control problem has two control variables: $\frac{\gamma}{n}$ and I, and two state variables, E and K. In general terms, utilization of the antibiotic shall cease in finite time at, say, T^* since the susceptibility that makes it effective is nonrenewable. The presence

of uncertainty might modify the optimal T^*, but, since the discovery of a backstop in the period [0, T^*] cannot be guaranteed, it might be the case that the susceptibility of the antibiotic is exhausted before an alternative technology is invented. We define the social welfare function before the introduction of the backstop as:

$$\Gamma\left(\frac{\gamma}{n}, I, E\right) = \left(\frac{\gamma}{n}n + 1\right)\alpha - \left[\left(\frac{\gamma}{n}\right)^3 \frac{n}{3} + \left(\frac{\gamma}{n}\right)^2 \frac{1}{2} + \left(\frac{\gamma}{n}\right)\frac{1}{6n}\right]\alpha + \frac{\ln(1+E)}{\ln(2)}\left(1 - \frac{\gamma}{n}\right)\alpha$$
$$+(n+1)(m-x) - p\left(n - \frac{\gamma}{n}n\right) - \mathrm{P} - g(I).$$

Then the Hamiltonian is:

$$H = \left\{\Gamma\left(\frac{\gamma}{n}, I, E\right)\left(1 - \phi(K)\right) + \phi'(K)f(I)W\right\}e^{-n} + \mu\frac{-\omega\left(n - \frac{\gamma}{n}n\right)}{\mathrm{P}+1} + \eta f(I).$$

The first order conditions are:

$$0 = \frac{\partial H}{\partial \gamma / n} = \left[n\alpha - \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\alpha - \frac{\ln(1+E)}{\ln(2)}\alpha + np\right]\left(1 - \phi(K)\right)e^{-n} + \mu n\frac{\omega}{\mathrm{P}+1}, \tag{IV.21}$$

$$0 \geq \frac{\partial H}{\partial I} = \left[-g'(I)\right]\left(1 - \phi(K)\right)e^{-n} + \phi'(K)f'(I)We^{-n} + \eta f'(I), \tag{IV.22}$$

$$\eta = \frac{g'(I)}{f'(I)}\left(1 - \phi(K)\right)e^{-n} - \phi'(K)We^{-n}, \tag{IV.23}$$

$$\dot{\eta} = -\frac{\partial H}{\partial K} = \phi'(K)\Gamma\left(\frac{\gamma}{n}, I, E\right)e^{-\pi} - \phi''(K)f(I)e^{-\pi}W, \tag{IV.24}$$

$$\dot{\mu} = -\frac{\partial H}{\partial E} = -\left(1-\frac{\gamma}{n}\right)\frac{\alpha}{(1+E)\ln(2)}(1-\phi(K))e^{-\pi}, \tag{IV.25}$$

$$\mu = \frac{\mathrm{P}+1}{\omega}\left\{-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p\right\}(1-\phi(K))e^{-\pi}. \tag{IV.26}$$

,

PROPOSITION 8 – The proportion of untreated people increases through time.

PROOF:

We take the derivative of (IV.26) with respect to time, and equate it to (IV.25):

$$\dot{\mu} = \frac{\mathrm{P}+1}{\omega}\left\{\left[2\left(\frac{\gamma}{n}\right)n+1\right]\frac{\alpha}{n}\left(\frac{\dot{\gamma}}{n}\right) - \frac{\alpha}{n(1+E)\ln(2)}\frac{\omega(n-\gamma)}{\mathrm{P}+1}\right\}(1-\phi(K))e^{-\pi}$$

$$-r\frac{\mathrm{P}+1}{\omega}\left\{-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p\right\}(1-\phi(K))e^{-\pi}$$

$$-\frac{\mathrm{P}+1}{\omega}\left\{-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p\right\}\phi'(K)f(I)e^{-\pi}, \text{ and}$$

$\dot{\mu} = -\frac{\partial H}{\partial E} = -\frac{(n-\gamma)\alpha}{n(1+E)\ln(2)}(1-\phi(K))e^{-\pi}$, therefore

$$\left[2\left(\frac{\gamma}{n}\right)n+1\right]\frac{\alpha}{n}\left(\frac{\dot{\gamma}}{n}\right) = r\left\{-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p\right\}$$
$$+\left\{-\alpha + \left[\left(\frac{\gamma}{n}\right)^2 n + \left(\frac{\gamma}{n}\right) + \frac{1}{6n}\right]\frac{\alpha}{n} + \frac{\ln(1+E)}{n\ln(2)}\alpha - p\right\}\frac{\phi'(K)f(I)}{(1-\phi(K))}. \tag{IV.27}$$

Note that the first term is identical to the expression on the RHS of equations (IV.8), and (IV.16) in the certainty cases. In this case, however, if $r = 0$, we have that $\left(\frac{\dot{\gamma}}{n}\right)>0$, since we can rewrite (IV.27) as $\left(\frac{\dot{\gamma}}{n}\right)=\frac{\omega}{\mathrm{P}+1}\frac{\mu}{\left[2\left(\frac{\gamma}{n}\right)n+1\right]\frac{\alpha}{n}}\frac{\phi'(K)f(I)}{(1-\phi(K))^2}e^{rt}$, and μ, the shadow value of susceptibility, is positive. The presence of uncertainty modifies a result that held for both the certainty cases. Since the date of discovery of an alternative technology is now unpredictable, the use of the existing technology is more prudent.

PROPOSITION 9 – The level of investment increases through time. The increase is higher if the discount rate is positive.

PROOF:

We take the derivative of (IV.23) with respect to time, and equate it to (IV.24):

$$\dot{\eta}=\left[\frac{g''(I)f'(I)-g'(I)f''(I)}{f'(I)^2}\dot{I}(1-\phi(K))-\frac{g'(I)}{f'(I)}\phi'(K)f(I)-\phi''(K)f(I)W\right]e^{-rt}$$

$$-r\left[\frac{g'(I)}{f'(I)}(1-\phi(K))-\phi'(K)W\right]e^{-rt}, \text{ and}$$

$$\dot{\eta}=-\frac{\partial H}{\partial K}=\phi'(K)\Gamma\left(\frac{\gamma}{n},I,E\right)e^{-rt}-\phi''(K)f(I)We^{-rt}, \text{ therefore}$$

$$\dot{I}=\frac{[f'(I)]^2}{g''(I)f'(I)-g'(I)f''(I)}\left\{\begin{array}{l}\frac{\phi'(K)}{(1-\phi(K))}\left[\frac{g'(I)f(I)}{f'(I)}+\Gamma\left(\frac{\gamma}{n},I,E\right)\right]\\ +r\left[\frac{g'(I)}{f'(I)}-\frac{\phi'(K)}{(1-\phi(K))}W\right]\end{array}\right\}. \qquad \text{(IV.28)}$$

Conclusions

The model's results on use of existing antibiotics are in general extremely robust to changes in the specification of the nature of research. They suggest that, no matter what the nature of the alternative technology to invest in, the optimal policy would limit the increase of people treated with the existing antibiotic. In practice, however, it appears that the number of people treated with the existing antibiotics is on the increase, at least in Western countries. This is particularly worrisome in the context of the results of the last scenario, that suggest that if the nature of the discovery process is uncertain, the number of people treated should be restricted through time, even in the more intergenerationally equitable case of a zero discount rate for the future.

The model also indicates that if the research process is certain, short, high bursts of investments might be optimal, while resources invested in R&D should increase through time if the discovery process is uncertain.

According to the American Society for Microbiology, in the mid 1990s, the short and medium terms prospects of new drugs' availability were not very good (ASM). More recently, the report of the July 1997 workshop of the Forum on Emerging Infections, created by a joint initiative of the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID) states that "Also, because general confidence in the existing antibiotic toolkit had muted any sense of urgency, there has been a distinct lag in producing new classes of antimicrobials, despite great advances in the fundamental science that is fueling pharmaceutical innovation in many other areas. This situation is changing, and the pharmaceutical industry has in the

past few years expanded its investment substantially, but public-sector investment awaits reinvigoration. What is needed now is sustained, sufficient support—for basic pioneering research, for the clinical research required to move truly new products from the laboratory to the pharmacy, and for the infrastructure underpinning both" (Harrison and Lederberg). This quote suggests research might be underfunded: both the level of investment and its time path appear to be suboptimal.

Linked to the issue of funding is that of the choice of the types of investment. We have been implicitly assuming that science determines in each instance the specific nature of the investment in which to direct research efforts. The social planner is presented with only one type of investment possibility, and can only choose the (continuous) amount of resource to devote to it. However, if various choices of investment were possible concurrently, the model could still be utilized to determine the optimal combination of investments.

CHAPTER V.
CONCLUSIONS

This dissertation examined the economics of resistance management for agricultural pesticides and antibiotics, with a particular focus on the common property nature of susceptibility and the endogeneity of technological change and their effects on the determination of the optimal use of the available biological capital of genetic susceptibility.

Chapter II presented a theoretical model of resistance development with a spatial dimension that allowed us to analyze the tradeoffs involved in the use of refuges in resistance management strategies. The analysis in Chapter II showed how the presence of more than one farmer might impact resistance management strategies based on refuges: farmers might either increase or decrease the dose of pesticide but it is in their self interest not to plant refuge. This will be true also in the case of a fixed dose.

The model presented in chapter II also illustrates how the presence of cross-resistance impacts optimal resistance management strategies by increasing the shadow value of susceptibility. The issue of cross resistance is likely to be an important one in the future since, as we will see in more detail below, many of the next generation of biotechnology products are going to be based on *Bt* toxins.

Chapter III introduced a specific example of the externalities resulting from the interaction of space and pest mobility discussed in the introduction of chapter II. The results presented in chapter III illustrate how pest mobility is the key parameter in determining the extent of the externalities and the development of resistance in the

context of *Bt* corn, and how market penetration and unstructured refuge impact resistance buildup. In terms of the optimal pest management strategy, the results of chapter III imply that some form of organization or regulation might be necessary only if market penetration of *Bt* crops increases dramatically, and entomologists establish that corn borers move very little. In general, the analysis presented in chapter III underscores the importance of quantifying externalities.

Chapter IV explicitly introduced technological change in the analysis. Though the analysis refers to the case of antibiotics, the model can be used for pesticides as well. The model developed in chapter IV explicitly characterized the common property aspects of susceptibility in a dynamic setting and it identified the optimal intertemporal usage problem from a social planner perspective.

The analysis in chapter II pointed out that, in the case of a fixed dose, the use of static refuges is not a first best policy, while the simulation results presented in chapter III illustrate how market penetration impacts the dynamics of resistance development. Together, these findings suggest three elements that might be included in the future to improve the refuge policy that the EPA mandates for *Bt* crops. Currently, resistance management plans for *Bt* crops do not take into account the dynamic nature of the economics of susceptibility mining, nor do they consider market penetration or low compliance to the policy due to the fact that susceptibility is common property. Including consideration of these factors is likely to improve the efficacy of the refuge policy. The introduction of dynamic refuges, for example, would bring two types of benefits: refuge requirements could be revised to take into consideration the level of

market penetration, and/or could be adjusted to decrease through time, as susceptibility becomes less valuable.

Indirectly, chapters II and III point to the importance of backstop technologies. The assumption that the time frame of reference is fixed implies that the outcome of ongoing research is certain, and that enough resources are being devoted to the development of new pesticides. The introduction of new pesticides in the US market has been relatively steady in the last decade (see EPA 1998b, 1998c, 1997, 1996, 1995, 1994). If historical precedent is of any guidance, the availability of alternative technologies is not likely to be an issue for US agriculture. However, this does not necessarily imply that susceptibility to existing pesticides is going to become obsolete. For example, over 10 percent of the 122 new pesticides registered in the US since 1994 are *Bt* products, either in spray form or plant-pesticides. Moreover, the EPA is in the process of approving or has already approved several new *Bt*-based bioengineered products: nine out of the 12 experimental use permits that the EPA granted in the year 2000 are for *Bt* toxins (EPA 2000).

The framework developed in chapter IV connects the issue of the discovery of backstop technologies – be they novel technologies or improvements of existing ones – with the socially optimal use of the resources we already have at our disposal. The model presented in chapter IV allows the identification of the time path of optimal number of people to treat through time while susceptibility to an existing antibiotic is positive, that is, it lets us specify the elements important to the trade-off between present and future use of a drug. The results presented in chapter IV suggest that the first best policy is to

restrict the increase of the number of people treated with available drugs, particularly if the discovery process for new pharmaceutical products is uncertain.

The second issue that the model developed in chapter IV focuses on is the allocation of resources for the development of new pharmaceutical products. The results indicate that the time path of investment will depend on the nature of technological change. If the discovery process is uncertain, it is optimal to increase the amount of resources invested in R&D through time.

These results have two types of policy implications. In terms of existing antibiotics, they point out that the study and implementation of mechanisms to contain the number of antibiotic prescriptions should be stepped up. The problem of over-prescription is even more dramatic in developing countries, since there antibiotics are available over the counter, and agents save by not completing antibiotic cycles.

In terms of research investment, these results indicate the importance of instruments that might increase the industry's development of new products. Also, the analysis presented indirectly points to the necessity for a clearer definition of the role of public vs. private investment in basic medical research and in drug development, particularly for diseases like tuberculosis and malaria, since they affect predominantly developing countries, and are less likely to attract private resources.

APPENDIX
THE TIME PATH OF REFUGE

We differentiate the first order condition (II.30) with respect to time:

$$
\begin{aligned}
0 &= \left\{D''[1-u(S)k(\tau)]Pk'(\tau)u(S) + D'k'(\tau)u(S)\right\}\dot{P} \\
&+ \left\{-D''\left[Pk'(\tau)u(S)\right]^2 + D'Pk''(\tau)u(S) - \rho\mu_2(t)h(S)r''(\tau)\right\}\dot{\tau} \\
&+ \left\{-D''P^2k(\tau)k'(\tau)u(S)u'(S) + D'Pk'(\tau)u'(S)\right\}\dot{S} - q_{\tau\tau}\dot{\tau} - \rho\mu_1(t)\theta Pk''(\tau)u(S)\dot{\tau} \\
&- \rho\dot{\mu}_1(t)\theta Pk'(\tau)u(S) - \rho\mu_1(t)\theta k'(\tau)u(S)\dot{P} - \rho\mu_1(t)\theta Pk'(\tau)u'(S)\dot{S} \\
&- \rho\dot{\mu}_2(t)h(S)r'(\tau) - \rho\mu_2(t)h'(S)r'(\tau)\dot{S}.
\end{aligned}
$$

We then substitute (II.31) and (II.32) into the expression above to get:

$$
\begin{aligned}
&\left\{D''\left[Pk'(\tau)u(S)\right]^2 - D'Pk''(\tau)u(S) + q_{\tau\tau} + \rho\mu_1(t)\theta Pk''(\tau)u(S) + \rho\mu_2(t)h(S)r''(\tau)\right\}\dot{\tau} \\
&= \left\{D''[1-u(S)k(\tau)]Pk'(\tau)u(S) + D'k'(\tau)u(S) - \rho\mu_1(t)\theta k'(\tau)u(S)\right\}\theta P[1-u(S)k(\tau)] \\
&- \left\{-D''P^2k(\tau)k'(\tau)u(S)u'(S) + D'Pk'(\tau)u'(S) - \rho\mu_1(t)\theta Pk'(\tau)u'(S) - \rho\mu_2(t)h'(S)r'(\tau)\right\}h(S)r(\tau) \\
&- \rho\left\{-D'Pu'(S)k(\tau) + \rho\mu_1\theta Pu'(S)k(\tau) + \rho\mu_2h'(S)r(\tau)\right\}h(S)r'(\tau) \\
&- \rho\left\{D'(1-u(S)k(\tau)) - \rho\mu_1\theta[1-u(S)k(\tau)]\right\}\theta Pk'(\tau)u(S).
\end{aligned}
$$

The LHS of this expression is positive. The RHS can be rewritten as:

$$
\begin{aligned}
&D''\theta P^2[1-u(S)k(\tau)]^2 k'(\tau)u(S) > 0 \\
&+D'\theta P k'(\tau)u(S)[1-u(S)k(\tau)][1-\rho] > 0 \\
&-\rho\mu_1(t)\theta^2 P k'(\tau)u(S)[1-u(S)k(\tau)](1-\rho) > 0 \\
&+D''P^2 k(\tau)k'(\tau)u(S)u'(S)h(S)r(\tau) > 0 \\
&+\rho\mu_2(t)h'(S)h(S)r'(\tau)r(\tau)(1-\rho) > 0 \qquad \text{if } h'(S) > 0 \\
&+D'Ph(S)u'(S)[\rho k(\tau)r'(\tau) - k'(\tau)r(\tau)] \\
&-\rho\mu_1(t)\theta P u'(S)h(S)[\rho k(\tau)r'(\tau) - k'(\tau)r(\tau)].
\end{aligned}
$$

If $\rho\dfrac{r'(\tau)}{r(\tau)} > \dfrac{k'(\tau)}{k(\tau)}$, the last two terms are positive as well. Therefore, $\dot{\tau} > 0$ when $h'(S) > 0$: the area treated increases (refuge decreases) through time.

BIBLIOGRAPHY

American Society for Microbiology, 1995, Report of the ASM Task Force on Antibiotic Resistance, Washington D.C.: American Society for Microbiology, URL: http://www.asmusa.org/pasrc/pdfs/antibiot.pdf, accessed October 19, 1999.

Andrews T.S.and I.N. Morrison, 1997, The Persistence of Trifluralin Resistance in Green Foxtail (Setaria viridis) Populations, *Weed Technology*, Vol. 11 n.2, pp. 369-372.

Brown G. and D.F. Layton, 1996, Resistance Economics: Social Cost and the Evolution of Antibiotics Resistance, *Environment and Development Economics*, Vol. 1 n. 3, pp. 349-355.

Byrne D.N., R. Isaacs and K. H. Veenstra, 1996, Local Dispersal and Migration by Insect Pests and Their Importance in IPM Strategies, in E. B. Radcliffe and W. D. Hutchison (eds.), *Radcliffe's IPM World Textbook*, URL: http://ipmworld.umn.edu, accessed November 18, 1998.

Caprio M.A., 1998, Evaluating Resistance Management Strategies for Multiple Toxins in the Presence of External Refuges, *Journal of Economic Entomology*, Vol. 91 n.5, pp. 1021-1031.

Cate, J. R. and M. K. Tinkle, 1994, *Integrated Pest Management: the Path of a Paradigm*, Washington D.C.: National Audubon Society.

Clark, J.S. and G.A. Carlson, 1990, Testing for Common Versus Private Property: The Case of Pesticide Resistance, *Journal of Environmental Economics and Management*, Vol. 19, pp.45-60.

Cohn D.L., Bustreo F, Raviglione MC, 1997, Drug-Resistant Tuberculosis: Review of the Worldwide Situation and the WHO/IUATLD Global Surveillance Project. International Union Against Tuberculosis and Lung Disease, *Clinical Infectious Diseases*, Vol.24 Suppl 1, pp.S121-130.

Croft B.A., and J.E. Dunley, 1993, Habitat Patterns and Pesticide Resistance, in: K.C. Kim and R.A.McPheron (eds.), *Evolution of Insect Pests: Patterns of Variation*, New York: John Wiley and Sons.

Croft B.A. and M.E. Whalon, 1983, Inheritance and Persistence of Permethrin Resistance in the Predatory Mite, Amblyseius fallacis (Acarina: Phytoseiidae) Apple Orchard Populations, *Environmental Entomology*, Vol. 12 n.1, pp. 215-218.

Dasgupta P.S. and G.M. Heal, 1979, *Economic Theory and Exhaustible Resources*, Welwin, U.K.: James Nisbet & Co.

Dasgupta P.S. and G.M. Heal, 1974, The Optimal Depletion of Exhaustible Resources, *The Review of Economic Studies*, Vol. 41, Issue Symposium on the Economics of Exhaustible Resources, pp. 3-28.

Dasgupta P.S., G.M. Heal, and M. Majumdar, 1977, Resource Depletion and Research and Development, in M.D. Intriligator (ed.) *Frontiers of Quantitative Economics*, Vol. 3 B, New York: North Holland, pp.483-505.

Davison R., 1978, Optimal Depletion of an Exhaustible Resource with Research and Development towards an Alternative Technology, *The Review of Economic Studies*, Vol. 45, pp. 355-367.

Diekema D.I. and R.N. Jones, 2000, Oxazolidinones: A Review, *Drugs*, Vol. 59 n.1, pp.7-16.

Dively G.P., P.A. Follett, J.J. Linduska, and G.K. Roderick, 1998, Use of Imidacloprid-Treated Row Mixtures for Colorado Potato Beetle (Coleoptera: Chrysomelidae) Management, *Journal of Economic Entomology*, Vol. 91 n.2, pp. 376-387.

Doessel D.P., 1998, The "Sleeper" Issue in Medicine: Clem Tisdell's Academic Scribbling on the Economics of Antibiotic Resistance, *International Journal of Social Economics*, Vol. 25, n. 6/7/8, pp.956-967.

Encyclopædia Britannica Online, 2000a, Antibiotic, URL: http://www.eb.com:180/bol/topic?eu=7912&sctn=1, accessed March 30, 2000.

Encyclopædia Britannica Online, 2000b, Drug, URL: http://www.eb.com:180/bol/topic?eu=108966&sctn=5, accessed March 30, 2000.

Environmental Protection Agency (EPA), 2000, Office of Pesticide Programs Biopesticide Experimental Use Permits Approved, URL: http://www.epa.gov/pesticides/biopesticides/reg_activ/new_eup_approv.htm, accessed August 20, 2000.

EPA, 1999, EPA and United States Department of Agriculture Position Paper on Insect Resistance Management in Bt Crops, URL: http://ww.epa.gov/pesticides/biopesticides/otherdocs/bt_position_paper_618.htm, accessed August 5, 1999.

EPA, 1999b, Letter to Bt Corn Registrants, 12/20/1999, URL: http://ww.epa.gov/pesticides/biopesticides/otherdocs/bt_corn_ltr.htm, accessed February 24, 2000.

EPA, 1998a, *The Environmental Protection Agency's White Paper on Bt Plant-pesticide Resistance Management*, Washington D.C.: Environmental Protection Agency.

EPA, 1998b, Chemicals Registered for the First Time as Pesticidal Active Ingredients Under FIFRA, URL: http://www.epa.gov/oppbead1/newais/, accessed October 21, 2000.

EPA, 1998c, Pesticide Program Highlights from Fiscal Year 1998, URL: http://www.epa.gov/oppfead1/annual/1998/fy98hlts.htm, accessed October 21, 1999.

EPA, 1998d, Pesticide Fact Sheet August 17, URL: http://www.epa.gov/fedrgstr/EPA-PEST/1998/August/Day-17/attri.htm, accessed October 30, 1999.

EPA, 1997, Office of Pesticide Programs Annual Report for 1997, URL: http://www.epa.gov/oppfead1/annual/1997/97annual.pdf, accessed October 21, 1999.

EPA, 1996, Office of Pesticide Programs Annual Report for 1996, URL:http://www.epa.gov/oppfead1/annual/1996/, accessed October 21, 1999.

EPA, 1995, Office of Pesticide Programs Annual Report for 1995, URL: http://www.epa.gov/oppfead1/annual/1995/95a_text.htm, accessed October 21, 1999.

EPA, 1994, Office of Pesticide Programs Annual Report for 1994, URL: http://www.epa.gov/oppfead1/annual/1994/94a_text.htm, accessed October 21, 1999.

Evans W. N. and W. K. Viscusi, 1991, Utility-Based Measures of Health, *American Journal of Agricultural Economics*, Vol. 73, n.5, pp. 1422-27.

Fauci A.S, 1999, Antimicrobial Resistance: The NIH Response to a Growing Problem, Statement of Anthony S. Fauci, M.D., Director of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Before the Senate Committee on Health, Education, Labor, and Pensions, Subcommittee on Public Health and Safety, February 25, 1999, URL: http://www.niaid.nih.gov/director/congress/1999/0225.htm, accessed October 19, 1999

Fuchs V.R. and R. Zeckhauser, 1987, Valuing Health-A "Priceless" Commodity, *American Economic Review*, Vol. 77, n.2, pp. 263-68.

Gambardella A., 1995, *Science and Innovation: The US Pharmaceutical Industry during the 1980s*, Cambridge: Cambridge University Press.

Georghiou G.P., 1986, The Magnitude of the Resistance Problem, in: Committee on Strategies for the Management of Pesticide Resistant Pest Populations, *Pesticide Resistance: Strategies and Tactics for Management*, Washington D.C.: National Academy Press.

Georghiou G.P., and C.E. Taylor, 1977, Operational Influences in the Evolution of Insecticide Resistance, *Journal of Economic Entomology*, Vol. 70 n.3, pp. 319-323.

Gold H.S. and R.C. Moellering, 1996, Antimicrobial Drug Resistance, *The New England Journal of Medicine*, Vol.335 n. 19, pp.1445-1453.

Goodin R.E., 1982, Discounting Discounting, *Journal of Public Policy*, Vol. 2 n.1, pp.53-72.

Gorddard R.J., D.J. Pannell and G. Hertzler, 1995, An Optimal Control Model for Integrated Weed Management under Herbicide Resistance, *Australian Journal of Agricultural Economics*, Vol. 39 n.1, pp. 71-87.

Hammock B.D. and D.M. Soderlund, 1986, Chemical Strategies for Resistance Management, in Committee on Strategies for the Management of Pesticide Resistant Pest Populations, *Pesticide Resistance: Strategies and Tactics for Management*, Washington D.C: National Academy Press.

Harrison P. F. and J. Lederberg, (eds), Forum on Emerging Infections, Antimicrobial Resistance: Issues and Options, Workshop Report, July 1997, URL: http://bob.nap.edu/html/antimicrobe/ accessed August 9, 2000.

Hartl D.L. and A.G. Clark, 1989, *Principles of Population Genetics* (second edition), Sunderland: Sinauer Associates.

Hastings A., 1997, *Population Biology : Concepts and Models*, New York: Springer.

Heap, I., 1998. International Survey of Herbicide Resistant Weeds Online, URL: www.weedscience.com, accessed November 12, 1998.

Hengeveld R., 1989, *Dynamics of Biological Invasions*, London: Chapman Hall.

Hueth D. and U. Regev, 1974, Optimal Agricultural Pest Management with Increasing Pest Resistance, *American Journal of Agricultural Economics*, Vol. 56, pp. 543-551.

Hurley T.M., B.A. Babcock and R.L. Hellmich, 1997, Biotechnology and Pest Resistance: An Economic Assessment of Refuges, Center for Agricultural and Rural Development, Working Paper 1997 WP 183, Iowa State University, Ames, IA.

Hurley T.M., S. Secchi, B.A. Babcock and R.L. Hellmich, 1999, Managing the Risk of European Corn Borer Resistance to Transgenic Corn: An Assessment of Refuge Recommendations, Center for Agricultural and Rural Development, Staff Report 99-SR88, Iowa State University, Ames, IA.

Kamien M.I. and N.L. Schwartz, 1982, Common Property Resources in Optimal Planning Models, in V.K. Smith and J.V. Krutilla (eds.), *Explorations in Natural Resource Economics*, Baltimore: Johns Hopkins University, pp. 47-71.

Kamien M.I. and N.L. Schwartz, 1978, Optimal Exhaustible Resource Depletion with Endogenous Technical Change, *Review of Economic Studies*, Vol. 45 n.1, pp. 179-196.

Kile J.D, 1989, *Research and Development in the Pharmaceutical Industry: The Impact of Drug Resistance*, Thesis, University of Wisconsin-Madison.

Kingston W., 2000, Antibiotics, Invention and Innovation, *Research Policy*, Vol. 29, pp. 679-710.

Jasieniuk M., Brûlé-Babel A.L., and Morrison I.N., 1996, The Evolution and Genetics of Herbicide Resistance in Weeds, *Weed Science*, Vol. 44, pp. 176-193.

Johnson C.G., 1969, *Migration and Dispersal of Insects by Flight*, London: Methuen.

Laxminarayan R. and G. Brown, 2000, Bacterial Resistance and the Optimal Usage of Antibiotics, University of Washington Economics Discussion Papers, URL: http://www.econ.washington.edu/econprelim/users/gbrown/abx_revised.pdf, accessed July 9, 2000.

Lazarus, W.F. and B.L. Dixon, 1984, Agricultural Pests as Common Property: Control of the Corn Rootworm, *American Journal of Agricultural Economics*, Vol. 66, pp.456-465.

Levy S.B., 1998, The Challenge of Antibiotic Resistance, *Scientific American*, Vol. 278 n. 3, pp.46-53.

Levy S.B., 1992, *The Antibiotic Paradox: How Miracle Drugs are Destroying the Miracle*, New York: Plenum Press.

Livingston M.J., G.A. Carlson and P.L. Fackler, BT Cotton Refuge Policy, Paper presented at the American Agricultural Economics Association Annual Meeting, July 30- August 2, 2000, Tampa, Florida, URL: http://agecon.lib.umn.edu/aaea00/sp00li01.pdf, accessed August 18, 2000.

Mason C.E., M.E. Rice, D.D. Calvin, J.W. Van Duyn, W.B. Showers, W.D. Hutchinson, J.F. Witkowski, R.A. Higgins, D.A. Onstad, and G.P. Dively, 1996, *European Corn Borer Ecology and Management*, North Central Regional Extension, Publication No.327, Iowa State University, Ames, IA.

Miranowski, J.A. and G.A. Carlson, 1986, Economic Issues in Public and Private Approaches to Preserving Pest Susceptibility, in: Committee on Strategies for the Management of Pesticide Resistant Pest Populations, *Pesticide Resistance: Strategies and Tactics for Management*, Washington D.C.: National Academy Press.

Murray B.E., 1994, Can Antibiotic Resistance Be Controlled?, *The New England Journal of Medicine*, Vol.330 n. 17, pp.1229-1230.

Nemecek S., 1997, Beating Bacteria. New Ways to Fend off Antibiotic-Resistant Pathogens. *Scientific American*, Vol. 276 n.2, pp.38-9.

Onstad D. W. and C. A. Guse, 1999, Economic analysis of Transgenic maize and Nontransgenic Refuges for Managing European Corn Borer (Lepidoptera: Pyralidae), mimeo, Center for Economic Entomology, Illinois Natural History Survey, Champaign, IL.

Organic Farming Research Foundation (OFRF), 1999, Final Results of the Third Biennial National Organic Farmers' Survey, Santa Cruz, CA: OFRF.

Pacala S.W. and J.A. Silander, 1985, Neighborhood Models of Plant Population Dynamics. I. Single-Species Models of Annuals, *The American Naturalist*, Vol. 125, pp. 385-411.

Peck S.L., F. Gould and S.P. Ellner, 1999, Spread of Resistance in Spatially Extended Regions of Transgenic Cotton: Implications for Management of *Heliothis virescens* (Lepidoptera: Noctuidae), *Journal of Economic Entomology*, Vol. 92 n.1, pp. 1-16.

Pedigo L.P., 1999, *Entomology and Pest Management* (third edition), Upper Saddle River, NJ: Prentice Hall.

Penrose L.J., 1990, Prolonged Field Persistence of Resistance to Benomyl in Monilinia Fructicola, *Crop Protection*, Vol. 9 n.3, pp. 190-192.

Perez C.J., A.M. Shelton, and R.T. Roush, 1997, Managing Diamondback Moth (Lepidoptera: Plutellidae) Resistance to Foliar Applications of Bacillus thuringiensis: Testing Strategies in Field Cages, *Journal of Economic Entomology*, Vol. 90 n.6, pp. 1462-1470.

Ramsey F.P., 1928, A Mathematical Theory of Saving, *Economic Journal*, Vol. 38 n. 152, pp. 543-559.

Regev U., A.P. Gutierrez and G. Feder, 1976, Pests as a Common Property Resource: A Case Study of Alfalfa Weevil Control, *American Journal of Agricultural Economics*, Vol. 58, pp.186-197.

Regev U., H. Shalit, and A.P. Gutierrez, 1983, On the Optimal Allocation of Pesticides with Increasing Resistance: The Case of the Alfalfa Weevil, *Journal of Environmental Economics and Management*, Vol. 10, pp.86-100.

Romero R.A., and T.B. Sutton, 1998, Characterization of Benomyl Resistance in Mycosphaerella fijiensis, Cause of Black Sigatoka of Banana, in Costa Rica, *Plant Disease*, Vol. 82 n.8, pp. 931-934.

Rook S. A. and G. A. Carlson, 1985, Participation in Pest Management Groups, *American Journal of Agricultural Economics*, Vol. 67 n.3, pp. 562-566.

Samuelson P.A., 1983, Thünen at Two Hundred, *Journal of Economic Literature*, Vol. 21 n. 4, pp.1468-1488.

Showers W. B., R. L. Hellmich, M. E. and W. H. Hendrix III, 2000, Aggregation and Dispersal Behavior of Marked and Released European Corn Borer (Lepidoptera: Crambidae) Adults, mimeo, Corn Insects and Crop Genetics Research Unit, USDA–ARS and Department of Entomology, Iowa Agriculture and Home Economics Experiment Station, Iowa State University, Ames IA.

Shigesada N., and K. Kawasaki, 1997, *Biological Invasions: Theory and Practice*, Oxford: Oxford University Press.

Stewart F.M., R. Antia, B.R. Levin, M. Lipsitch, J.E. Mittler, 1998, The Population Genetics of Antibiotic Resistance. II: Analytic Theory for Sustained Populations of Bacteria in a Community of hosts, *Theoretical Population Biology*, Vol. 53 n.2, pp.152-65.

Stinner R.E., M. Saks and L. Dohse, 1986, Modeling of Agricultural Pest Displacement, in: W. Danthanarayana (ed.), *Insect Flight: Dispersal and Migration*, Berlin, Heidelberg: Springer-Verlag.

Taylor, C. R. and J.C. Hadley, 1975, Insecticide Resistance and the Evaluation of Control Strategies for an Insect Population, *The Canadian Entomologist*, Vol. 107, pp. 237-242.

Tisdell C., 1982, Exploitation of Techniques that Decline in Effectiveness with Use, *Public Finance/Finances Publiques*, Vol. 37 n. 3, pp. 428-437.

USDA, 1999a, Agricultural Chemical Usage: 1998 Vegetable Summary, URL: http://usda.mannlib.cornell.edu/reports/nassr/other/pcu-bb/agch0799.pdf accessed September 8, 1999.

USDA, 1999b, Farms and Land in Farms–Final Estimates 1993-1997, Stat. Bulletin N. 955, URL: http://usda.mannlib.cornell.edu/usda/reports/general/sb/b9550199.pdf, accessed August 25, 2000.

Vousden N.J., 1977, Resource Scarcity and the Availability of Substitutes: A Theoretical Model, in M.D. Intriligator (ed.), *Frontiers of Quantitative Economics*, Vol. 3B, New York: North-Holland.

Willson, H.R., 1989, Corn Rootworms, The Ohio State University Estension, Ohio Pest Management Survey Circular # FC-16 CRW, URL: http://www.ag.ohio-state.edu/~ohioline/icm-fact/fc-16.html accessed June 6, 1999.

World Health Organization/World Bank, 1995, Operational Issues in Malaria Control, Report of a Working Meeting, Airlie, Virginia, USA, 6 to 8 September, 1995, URL: http://www.malarianetwork.org/index accessed April 3, 2000.