Insect Control of the Future: Operational and Policy Aspects

What common factors make significant advances in insect and human population control so difficult?

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Much has been written (*1*) about the economic importance of insect control, the relation between such control and the available food supply, the need to prevent environmental degradation, and the theoretical availability of various alternative approaches to insect control which could or should be developed. We shall assume that this background is generally known and we shall also tentatively accept the premise that the desire for integrated pest management (*2*) is not just pious preaching but actually represents a real goal of government policy-makers, scientists, and eventual users. Integrated pest management refers not to the abolition of chemical agents for insect control, but to the judicious use of such agents together with biological, biochemical, and microbial methods as well as the application of other control techniques (*3*). The questions that we wish to answer in this article are: when, if at all, can we expect the widespread availability of such new methods, what will it cost—especially in terms of time—to create them, and what policy changes, if any, should be made in order to expedite or even make possible the practical realization of such goals? If one considers the plethora of books and papers written on insect control, it is amazing how deficient the literature is in contributions dealing with operational and policy questions (*4, 5*).

In 1970, Djerassi (*6*) analyzed some of the operational problems (cost, time, regulatory barriers, for example) and policy questions in the field of human fertility control that have to be considered in converting laboratory discoveries (of which there are many) into practical methods (of which there are very few) suitable for millions of people. The conclusion was reached that 15 years and many millions of dollars would be a conservative estimate of the time and financial costs that would be required to create a practical new agent of birth control. Hardly any attention seems to have been paid by the layman or the scientist to the many similarities that exist between insect and human fertility control in terms of either the operational aspects of such research or governmental policy in these areas. It is also interesting that in both human fertility control and insect control most of the important methods now used are of relatively recent origin (that is, post World War II) and are largely chemical in nature, and that many current attempts to develop new methods center on trying to develop nonchemical alternatives. Policy-makers in both fields generally do not recognize how difficult it is to accomplish such changes and improvements.

Let us first consider some of the similarities and differences between insect and human fertility control in order to determine to what extent the methodology and conclusions from the earlier study (*6*) of human birth control can be applied to insect control.

Similarities between Human and Insect Population Control

1) The development and eventual commercialization of agents for human fertility and insect control is governed by regulatory agencies: the Food and Drug Administration (FDA) in the first instance and the Environmental Protection Agency (EPA) in the latter, although the FDA and the U.S. Department of Agriculture (USDA) may also participate in the regulation of insect control agents under certain circumstances. In contrast to the situation in the 1960's, currently these regulatory agencies not only monitor existing products on the market or decide on the release of new agents to the public but, much more importantly, they wield an enormous prospective effect on research and development. Because this impact is not generally recognized by the public, and sometimes not even by the regulatory agencies themselves, the concept of research impact statements has been proposed (*7, 8*).

2) Virtually all agents in practical use for human fertility or insect control have been brought to the marketing stage by industry rather than by academic, governmental, or nonprofit organizations, even though nonprofit organizations have frequently contributed heavily at the research level. This situation in free enterprise countries has several important consequences which are usually given scant or no attention by government policy-makers. One such consequence is that return-on-investment (ROI) calculations become important, and if the developer (that is, industry) does not see a potential market which is attractive enough to permit recovery of his research investment he presumably will not even start working in that area (*9*). Because of the very long lag times in the development of human fertility control agents (*6*) and insect control agents (see Fig. 1), the costs and risks are such that in general only very large companies with substantial financial and manpower resources are active in these two fields. Another important consequence of industry's key function in the development of these agents is that patents play an important role, and this we will discuss in our recommendation section.

3) There is little formal inquiry into the reluctance of industry to perform research in certain areas of fertility control, be it for human beings (for example, male fertility agents) or insects (for example, biological or biochemical methods). At best one hears that the ROI does not justify such efforts, but to us it seems essential that these reasons be defined more clearly.

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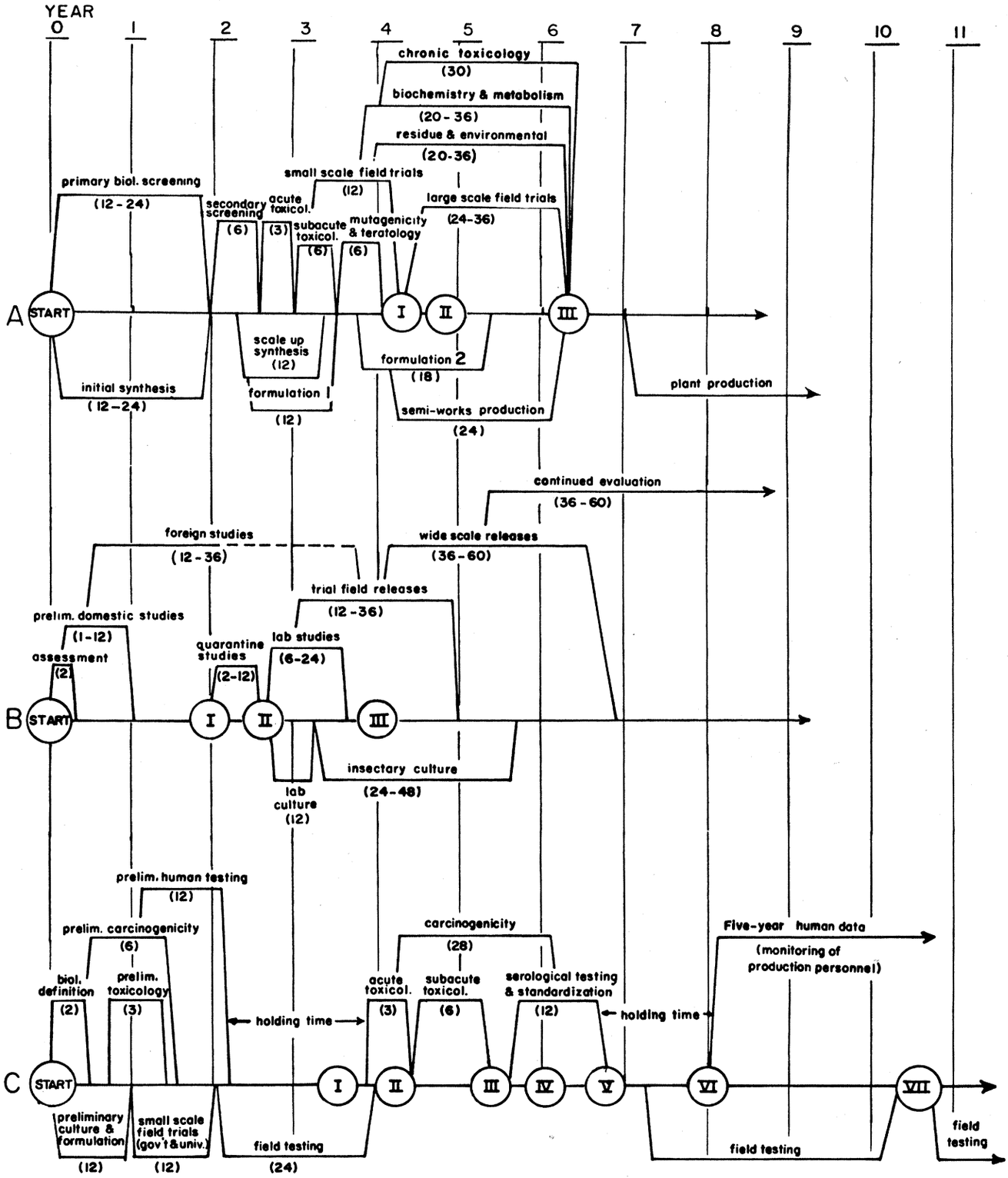

Fig. 1. Critical path maps for development of some insect control agents. Numbers in parentheses indicate time in months. (A) Biorational chemical agents: I, application for experimental permit; II, approval of experimental permit; III, application for full permit. (B) Beneficial insect predators and parasites: I, importation; II, release from quarantine; III, initial establishment. (C) Nucleopolyhedrosis virus (NPV): I, application for USDA registration; II, denial of USDA registration; III, reapplication for USDA registration; IV, rejection by USDA; V, reconsideration by USDA; VI, temporary permit and exemption from tolerance approved by EPA; VII, full exemption from tolerance. The data for biorational chemical agents (A) were obtained from Zoecon Corporation, Palo Alto, California. The data for beneficial predators and parasites (B) are based on information provided by R. van den Bosch (College of Agricultural Sciences, University of California, Albany), J. Laing (Department of Environmental Biology, University of Guelph, Guelph, Ontario), and J. Coulson (Beneficial Insect Introduction Laboratory, Agricultural Research Service, USDA, Beltsville, Maryland). The data for the NPV (C) were provided by C. Rehnborg and E. B. Westall (Nutrilite Products, Incorporated, Buena Park, California) and C. M. Ignoffo (Biological Control of Insects Research Laboratory, USDA, Columbia, Missouri). Both (A) and (C) are based on the actual experience of the pioneering developers.

Policy-makers then ought to consider whether special incentives (*4*) are needed to stimulate the conduct of practical work in these areas or whether other sectors of the R&D community could contribute effectively to practical new approaches in these fields. *We make the categoric prediction that, if this is not done promptly, most current public pronouncements on the likelihood of fundamentally novel human or insect population control agents will represent grossly optimistic exaggerations.*

4) The great public clamor for improved agents is associated with an equally great clamor for absolute safety (*10*). Since nothing is absolutely safe, a statement about safety is purely an estimate of degree which should enable us to choose among alternatives. However, this choice is never based on scientific considerations alone, but also on political ones. The difficulties of making such risk-benefit decisions are especially serious in the fields of human and insect population control. In these two fields, it is not at all clear whether society in the 1970's is willing to assume the necessary risks and costs associated with the development and eventual use of fundamentally new agents for these purposes.

5) In spite of the virtually unquestioned necessity for improved agents for human and insect population control and in spite of the urgency of the situation, practically no financial support or other incentives are provided to industry by the U.S. government (in marked contrast to the situation in countries such as Germany and Japan) for research and development in these fields.

Differences between Human and Insect Population Control

1) The public's concern for the environment is one of the factors motivating the development of new agents for both insect and human population control. However, such concern is really very different in the two areas. Contraceptives involve primarily the microenvironment of the individual and, furthermore, their use involves voluntary decisions by the consumer. Insect control has macroenvironmental consequences. Furthermore, in the case of pesticides, the ultimate consumer of a crop that has been treated has usually not participated in making the decision to treat that crop. Thus it is even more difficult to make risk-benefit determinations in the field of insect control than it is in the field of human population control.

2) The scope for financial return on R&D investments is much more circumscribed in the insect control area than it is in the field of drugs, such as contraceptives, for human beings. Thus, if one develops a fundamentally new drug for human disease, the subsequent commercial price for this drug usually can generate a return that is commensurate with the original research and development expenditure, because a higher economic limit is placed upon cures of diseases or prevention of death than upon the control of insects. In the case of insect control, even if one develops a fundamentally new and environmentally superb agent, its cost is immediately controlled by the economics of the crop that one is going to protect. In other words, with the possible exception of certain public health pests, the economic cost-benefit is a prime determinant in insect control while in human fertility control "humane" as well as "human" factors (for example, cultural, religious, or political) intervene heavily.

3) Another difference between ROI calculations in the two fields concerns the potential overall market. Demonstration of clinical efficacy is essentially applicable anywhere in the world and most human applications of drugs, including contraceptive ones, have potentially a global market. This is hardly true of new insect control agents, although it may have been the case at one time with DDT. The understandable insistence by public and also many scientific groups for nonpersistent and much more selective insect control agents implies that in the future there will be numerous small- or medium-sized markets for many different agents and that ROI considerations and market dollar volumes will, therefore, be even more crucial. As will be elaborated later, registration requirements are the same whether the pesticide being developed will have a small or a large ROI (*11*). Development costs are now so high that industry is reluctant to develop narrow spectrum pesticides unless the pest species is of major economic importance (*12*). Clarke (*13*) emphasized the truism that the larger the company, the larger the market must be in order for a project to be sufficiently attractive. As development costs for new pesticides increase, the large companies who can best afford the expense will avoid small, specialized markets, whereas the small company that might be interested in the small market will no longer be able to afford to enter it. It follows that in the field of insect control, the progress and extent of R&D will be even more sensitive to the regulatory climate and to the length of development times than it will in the human field. This is another justification for the rapid introduction of research impact statements (*7*) into the regulatory process.

4) Another important difference between human and insect population control is that, in general, local factors play a much smaller role in human beings than they do in insects. In the former, an effective cancer cure or a male contraceptive developed in London is almost certain to be effective also in San Francisco or Johannesburg. On the other hand, an effective control agent developed in one geographical area for a particular insect does not at all mean that the same insect will be controlled in another geographical setting, because of differences in climatic conditions, agricultural practices, or the presence of other insects. It is therefore particularly important to conduct trials of such insect control agents in many different geographical locations. Toxicological tests, however, provide results that do not vary according to where the tests are conducted, and regulatory practices should be designed to facilitate the worldwide acceptance of such toxicological data (Japan, for example, usually does not accept the results of toxicological tests performed in other countries). Unless one deals within the legislative borders of a large geographical entity, international cooperation is required to avoid duplication and delay. At present such cooperation is largely nonexistent.

5) As already pointed out, regulatory agencies now operationally determine when serious applied research can be started with human beings (that is, when clinical research can be conducted under an "investigational new drug permit") or with insects (that is, when substantial field trials can be conducted under an "experimental permit"). This similarity, however, introduces *one of the most significant differences in the two areas and one where the regulatory process can have a disastrous effect.* With relatively few exceptions, it does not make a great deal of difference when the FDA permits the initiation of clinical work since studies on cancer or tuberculosis, for

instance, can be started in January as well as in June. This is not at all the case in the field of insect control where a delay of only a couple of months by a regulatory agency in acting on an application for an "experimental permit" may cause a project delay of an entire year since most insect life cycles are restricted to relatively short seasons, except in tropical regions.

6) Once the newly developed agent has been approved for public use, there is a great difference in the manner by which it is disseminated. In human fertility control, the distribution system is under constant regulation and surveillance by members of the medical profession. In insect control—in actuality a more complex field—decisions are frequently made by lay persons. Recent legislation (see Table 1) has been addressed to this problem and certification of pesticide applicators is now being instituted.

Nature of Insect Control Agents

Given the right research climate, advances can be expected in the following four areas of insect control which are subject to government regulatory scrutiny:

Chemical insecticides. At the present time most research, notably in industry, is still concentrated on chemical insecticides, especially on modifications of existing structural types such as organophosphates, chlorinated hydrocarbons, and carbamates. The emphasis is on agents with less persistence, improved efficacy, and greater specificity to target organisms, but in the process a price is frequently being paid in terms of toxicity to man or mammals. Thus the persistent DDT is less toxic than the nonpersistent organophosphate parathion. Both are relatively nonspecific agents—an economic advantage but an ecological hazard.

"Biorational" chemical agents. Another chemical approach, which is associated with a considerable amount of scientific glamour but where practical applications are only just being demonstrated, can best be categorized as the use of "biorational" chemical agents. We have coined this term in order to avoid the great confusion in the literature between chemical and biological control of insects. Typical examples of biorational chemical agents would be pheromones (that affect insect behavior), insect hormones (for example, insect growth regulators), and hormone antagonists, all of which are frequently classified (*14*) as "biological" control agents. A pheromone, which is an insect secretory product, is as much a chemical as DDT, but its mode of action is based on a completely different rationale. Thus the use of a pheromone, by its definition, usually involves a species-specific agent which is often active in very low concentrations and generally is neither persistent nor toxic.

Insect hormone mimics, currently referred to as insect growth regulators (*1*, *15*), usually lack the extreme specificity of pheromones; therefore their potential commercial applications are clearly wider. Their unique biochemical mode of action appears to limit their effect to members of the phylum Arthropoda while rendering them relatively innocuous to man and other animals (*16*). Recent studies have indicated that some of them are the least toxic and least persistent chemical insect control agents currently known.

Microbial agents. This is an area in which a substantial amount of academic and government research has been conducted for many years (*17–19*) and to which industry has also made some significant contributions. Two bacterial agents, *Bacillus thuringiensis* and *B. popilliae*, are already being used commercially. Also (and this is an indispensable first step toward the ultimate open use of such agents), an exemption from the requirement of a tolerance (*20*) has been granted for the nucleopolyhedrosis virus (NPV) of *Heliothis zea* (the corn earworm).

Some experience has already been gained concerning the cost of developing microbial agents (*17–19*) and the possible barriers to our putting them rapidly into use. While few investigators believe that microbial agents will replace chemical methods, there is a general consensus that they may play an important role as supplementary agents in many integrated pest management programs.

Biological control procedures. Classically, the biological control of pest insects refers to the introduction of natural predators and parasites of accidentally imported pest species or, in some instances, of endemic pest species. In principle, biological control offers nontoxic, nonpolluting, relatively inexpensive, long-lasting, and self-perpetuating protection. Sometimes erroneously called a biological control procedure is the use of genetically modified insects, such as the use of sterile males in controlling (*21*) screwworm flies. This technique does not constitute true biological control because new batches of sterilized males must be released periodically and thus continual intervention by man is required—a feature that makes the technique more expensive. Furthermore, it is most likely to work when applied to very large areas or areas with natural geographical barriers (for instance, islands) where continuous outside infestation is prevented.

The use of natural enemies is a vital facet of integrated pest control. These purely biological procedures are being studied almost exclusively by academic institutions and some government researchers; except for some companies that have established insect rearing facilities, interest on the part of industry has been negligible, probably because of the lack of proprietary protection and the very short shelf life of most insects. Unfortunately, as with all other approaches discussed in this article, biological control is not a panacea. First, the introduction of beneficial parasites and predators usually does not offer immediate control. Second, some level of insect damage must be expected since a certain minimal pest population must be maintained if the predators and parasites themselves are to survive. This unavoidable level of crop damage may not be acceptable economically to farmers or esthetically to buyers. Finally, estimates of crop pests that are of foreign origin and are thus potentially more amenable to classical biological control range from 30 percent (*22*) to 50 percent (*23*) of currently important pest species. Use of foreign beneficial insects against pests of domestic origin has been little explored since such an introduced natural enemy would not only be poorly adapted to the target pest but would have to contend with an unfamiliar and perhaps less hospitable environment and compete with already adapted domestic natural enemies of the pest species.

"Cultural" control practices for insects are also of potential value. Such practices include the adjusting of planting and harvesting dates to avoid insects, the use of plant varieties resistant to insects, the implementation of deadlines for destruction of crop residues at the end of the growing season, and the careful control of irrigation water to avoid the breeding of mosquitoes. All of these cultural practices can be improved by research and all are or can be subject to government regula-

tions that may enhance or hinder their development and adoption. Research advances in cultural control practices are almost certain to come from the public sector.

Regulatory Requirements

In 1947, the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) was passed which called for USDA registration of economic poisons prior to their interstate sale or transport. Approval of registration applications was based upon review of safety and efficacy data. It also required that product labels contain instructions for use and warning statements to prevent injury to human beings, other animals, and plants. In 1954, the Miller Amendment to the Food, Drug, and Cosmetic Act required the FDA to establish tolerance limits for pesticide residues remaining on raw agricultural products by review of toxicological, metabolic, and persistence data. In 1970, full regulatory powers (that is, registration and establishment of tolerances) over economic poisons was transferred to the EPA.

It was felt that FIFRA had a number of weaknesses [including lack of direct federal control over pesticide use, lack of any enforcement powers other than lengthy, cumbersome cancellation procedures, and lack of authority to regulate intrastate manufacture and shipment of economic poisons (*24*)] so in 1972, the Federal Environmental Pesticide Control Act (FEPCA), generally referred to as "FIFRA as amended," substantially changed FIFRA. In Table 1 we summarize relevant provisions of FEPCA and discuss the potential impact that individual sections of the law will have on the development of innovative insect control agents. [Note that the right-hand column of Table 1 illustrates what research impact statements (*7*)

Table 1. Summary of the relevant provisions of the Federal Environmental Pesticide Control Act (FEPCA), and examples of the impacts of these provisions on the development of innovative methods; FIFRA, Federal Insecticide, Fungicide and Rodenticide Act.

Summary of FEPCA	Potential impact on development of innovative methods
Sec. 3(c)(1)(D): *Establishing of proprietary rights to test data.* Test data submitted by an applicant shall not be used in support of another applicant without the permission of the first applicant and the payment of "reasonable compensation" by the second applicant	The establishment of proprietary rights to test data and protection of trade secrets provides much needed incentive and insurance to the developer of novel agents, especially where patent protection is impossible (that is, microbial insecticides and pheromones)
Sec. 3(c)(5)(C & D): *Inclusion of a benefit vs. environmental risk evolution when considering applications.* The EPA is required to base its decisions on data showing that the product performs its intended function without *unreasonable* adverse environmental effects	The explicit inclusion of environmental risk in the benefit vs. cost evaluation should be advantageous to those insect control agents which offer lower environmental hazards. At the same time, developers should be protected against excessive demands for proof of safety by the phrase "unreasonable effects" which acknowledges the inherent risk of *any* agent
Sec. 3(c)(5)(D): *Prohibition of essentiality as a criterion for registration.* When two pesticides meet the regulatory requirements, one pesticide is not to be registered in preference to the other	The stipulation that developers need not prove "essentiality" over a competing product in order to register a new product is fundamental to the development of *any* alternative insect control agent
Sec. 3(d) and 4(a): *Establishment of use classifications.* Pesticides would be classified as "restricted use," "general use," or both. Restricted pesticides could be used only by or under the direct supervision of a certified applicator	
Sec. 5: *Issuance of experimental use permits and temporary tolerances* for the purposes of obtaining experimental information required for full registration of a pesticide	This is potentially the most significant incentive or hindrance to R & D. Experimental use permits and temporary tolerances, available under FIFRA and retained by FEPCA, expedite early experimentation and decrease the cost of obtaining experimental data because treated crops may be sold rather than destroyed. The availability of such permits is especially crucial for smaller firms. Larger companies often own experimental farms where large-scale field testing can be performed without requiring experimental use permits and temporary tolerances. Small firms must rely on noncompany owned crops and farms and therefore could not conduct the required field testing without experimental permits
Sec. 6: *Cancellation and suspension procedures.* Pesticide registration is automatically cancelled after 5 years unless the registrant petitions the EPA for a continuance. Administrative procedures are spelled out. Other criteria for cancellation or emergency suspension are established	Streamlined cancellation and suspension procedures provide reasonable and justifiable consumer protection. These procedures, however, generate increasing "defensive research" in order to maintain existing registrations (*31, 46*). Money and facilities devoted to "defensive research" is obviously unavailable for research on novel technology. The question may be asked why there exists no equivalent provision for the automatic cancellation of drugs
Sec. 9, 12, 13: *Expanded enforcement powers.* Unlawful acts are listed. The EPA is authorized to enter and inspect any establishment where pesticides are produced, stored, or sold. Civil and criminal penalties for violations are increased	
Sec. 10: *Protection of trade secrets.* Applicants may mark information which in their opinion are trade secrets or commercial or financial information and the EPA is forbidden to release such information except under certain conditions delineated in this section	

ought to contain if they were made obligatory.]

A pesticide is defined by FEPCA as "any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest. . . ." This all-encompassing definition calls for EPA registration not only of chemical agents (traditional insecticides and biorational agents), but also of living organisms (microbial agents and conceivably even beneficial insect predators and parasites). In actual practice, the EPA does control microbial and biorational and traditional chemical agents, but developers and users of insect predators and parasites are regulated to a considerable extent by the USDA and some state agencies. This arbitrary grouping of traditional chemical insecticides and biorational agents with microbial methods under EPA regulations and predatory and parasitic insects under USDA regulations is probably undesirable because, in this latter area, the USDA is both a research and a regulatory agency. As discussed below, USDA regulations are much less time-consuming and expensive to fulfill than are EPA regulations. The legislative basis for USDA regulation of beneficial predators and parasites is the Federal Plant Pest Act of 23 May 1957 and the Plant Quarantine Act of 1912. These acts provide for regulation of plant pests and do not explicitly empower the USDA to regulate nonpest species. However, since cultures and shipments of beneficial insects could harbor pest species, the USDA has included predators and parasites under regulatory guidelines.

Beneficial insects are not "registered" with the USDA in the same sense that other insecticidal agents are "registered" by the EPA. Instead, USDA control is administered by way of the issuance of permits to those who wish to ship or import insects. There are three categories of permits (specific, general, and courtesy) covering five categories of insects (*25*). The USDA guidelines primarily call for assurances that the imported or transported insect will not pose a potential hazard to crops, human beings, other animals, or beneficial insects, and that no hyperparasites or other insect species are included in the shipment. Safeguards to prevent escape during shipment are required. Thus, the USDA requires assurances of safety, but not necessarily efficacy, in the use of beneficial insects as a means of insect control, unlike the EPA which spells out detailed safety and efficacy requirements for the other agents discussed.

Time and Cost Estimates for the Development of New Agents

Because of industry's and government's long experience with chemical pesticides, the registration requirements and development procedures are best defined for this "traditional" class of insect control agents. Even here some authors (*26, 27*) have justifiably questioned whether a reasonable return on research investment can still be realized, although specific guidelines for necessary efficacy and safety studies can most easily be defined in these areas. Unfortunately, these are precisely the agents which are most likely to lead to "me-too" products or only to minor modifications of existing agents. Safety, efficacy, and environmental requirements which have evolved for chemical insecticides are the standards by which practically every new insect control agent is judged by the EPA, even though such agents may bear little resemblance to classical insecticides. In our opinion the cost of developing any new method of insect control falling within the scope of the EPA is going to be at least as expensive as the cost of developing a traditional chemical insecticide. In addition to the baseline requirements established by the chemical insecticides, new agents (even in the "experimental permit" and "temporary tolerance" phase) will be required to undergo unique and additional studies because of their novelty. Table 2 outlines in general the regulatory requirements for a full-scale operational and commercial introduction of chemical insecticides and biorational and microbial agents (*28, 29*) [proposed unofficial guidelines (*30*) for viral agents are also

Summary of FEPCA	Potential impact on development of innovative methods
Sec. 15: *Payment of indemnities*: Holders of pesticide stocks prior to issuance of suspension notices of pesticides whose registration is eventually cancelled are reimbursed for the face value of their holding. Manufacturers are not reimbursed or compensated for development and production costs, and are not compensated at all if the manufacturer has knowledge that the pesticide registration should be suspended or cancelled and fails to so notify the EPA	This section is primarily designed to provide protection to small farmers and businessmen and is not really an incentive to developers. It does not really provide "insurance" against cancellation or suspension of registration of a product
Sec. 20: *Expansion of research and monitoring participation.* The EPA is authorized to undertake research, make grants, or form contracts with other federal agencies, universities, or other parties for research relevant to the purposes of this act, giving priority to research "to develop biologically integrated alternatives for pest control"	Expansion of EPA research activity and funding provides incentives to the development of alternatives, especially in fields where industry is inactive because of the inability to obtain a strong proprietary and/or patent position. Unfortunately, industry develops virtually all new insect control agents and procedures; the impact of increased government spending on the insecticide field as a whole therefore will be minor under the present system
Sec. 24: *Uniform registration regulations.* States are prohibited from establishing additional or different labeling and packaging requirements. States are given the right to register a pesticide for special local needs only if the EPA deems the state capable of adequately controlling the use of the pesticide in accordance with FEPCA *and* if registration of the pesticide has not previously been denied, suspended, or cancelled by the EPA	Standardization of state registration of pesticides should facilitate the development of alternatives by reducing administrative marketing and distributing costs. However, the following adverse aspects of this provision more than counterbalance the positive aspects. Environmentally, a specific pesticide is preferable to a broad spectrum agent and insect control agents of the future will likely be geared toward such micro- and semimacro markets. State authorities, who are familiar with localized agricultural practices, are not authorized to register a new agent which effectively controls a localized, specific pest for use in one state, unless this agent passes all EPA requirements. Thus, companies will tend to develop agents with large markets and higher ROI to the detriment of more specific agents with small ROI's because development costs for the two agents will be very similar despite different potential markets

included]. Depending upon the nature and projected use patterns of the individual agent, it may not be necessary to conduct all of the studies outlined in Table 2. For instance, issuance of an experimental permit for use of a chemical insecticide on a nonfood crop requires no establishment of temporary tolerance limits for that pesticide and only limited efficacy studies as well as acute toxicological investigations on animals and nontarget organisms. Experimental permits for insecticides used on food crops require establishment of temporary tolerances. To establish tolerances to negligible residues, studies of the following must be made in addition to the studies already mentioned: crop residues; subacute toxicology (for 90 days); plant, water, soil, and animal metabolism; photodecomposition; microorganism and nontarget residues. In most instances, the absence of mutagenicity and teratogenicity also has to be demonstrated. Establishment of nonnegligible temporary tolerances requires also that long-term 2-year toxicological and three-generation reproduction investigations be near completion. As in the case of experimental permits and temporary tolerances, the requirements for full registration are slightly less stringent when the insecticide is applied to a nonfood crop or results in negligible residues.

Table 2. Outline of regulatory requirements for registration of insect control agents.

Traditional and biorational chemical agents (*28*)	Microbial agents* (*18, 19, 29, 30*)
	Efficacy
Scope†: Lab trials; small- and large-scale field trials	*Scope*: Same as traditional and biorational agents
Data†: Demonstration of degree and duration of pest control at requested use rate; definition of use rate; efficacy in all geographical locations; optimization of formulation and packaging	*Data*: Same as traditional and biorational agents
	Safety
Acute toxicology‡§: Oral (rat, other species): dermal (rabbit); eye and skin irritation (rabbit); inhalation (two species)	*Acute toxicology*: Oral‖ (two species‖); eye irritation‖ (rabbit‖); skin irritation‖ (man, guinea pig, rabbit‖); inhalation‖ (rat); intraperitoneal injection (rat, mouse); subcutaneous injection (rat)
Subacute toxicology§: 90-day oral (rat, one other mammal); 21-day dermal (rabbit); skin sensitization (guinea pig); 21-day inhalation (one species)	*Subacute toxicology*: 21-day oral (mouse); 90-day oral (monkey, dog, dog, rodent); 21-day inhalation‖ (monkey, dog, rodent); subcutaneous injection and sensibility‖ (monkey, dog, mouse, rat, newborn rat); 120-day intravenous injection (rat); 120-day intraperitoneal injection (mouse)
Chronic toxicology†: Reproduction—3 generations (one species); carcinogenicity 2 years (rat) 18 months (one other rodent)	*Chronic toxicology*: Carcinogenicity—subcutaneous and 18 months feeding (mouse), 120 days and 2 years (rat)
Mutagenicity†: Dominant lethal or cytogenic assay, or both; and host mediated or microbial assay, or both	
Teratogenicity†: (rat or rabbit)	*Teratogenicity*: (rat or mouse)
	Other safety: Replication potential (man and primate tissue culture); mutability (passage through mallard duck gut); stability (monitoring through 20 generations of *H. zea*)
	Human effects‖: Medical-clinical records of production personnel‖; effects of human gastrointestinal juice on pathogenicity
	Metabolism†
Blood levels; tissue storage; biological half-life; detoxification mechanisms; structure of metabolites (rodent and occasional large animal)	
	Environmental
Acute and subacute toxicology†§: Avian oral (bobwhite quail and mallard duck); fish (rainbow trout and bluegill sunfish); nontarget species (insects, crustaceans, earthworms, and so forth)	*Acute toxicology*‖: (bees‖, oysters, shrimp, fish, grass shrimp, sheepshead minnows, rainbow trout‖, black bullhead, white sucker, bluegill sunfish‖, English sparrows, bobwhite quail‖, mallard duck‖)
Chronic toxicology: (fish, crustaceans, livestock, and so forth)	*Chronic toxicology*: (fish, birds, chickens)
Reproduction†: (ducks, quail)	*Reproduction*: (mallard duck, bobwhite quail)
Residues†§: (Nontarget insect, fish, and animal species)	
Phytotoxicity†: Agricultural crops	*Phytotoxicity*‖: Agricultural crops
Water metabolism§: (Pure, with suspended particles, with bottom sediment, moving)	
Soil metabolism, leaching, and binding	
Photodecomposition	
Microorganism degradation	
	Other
Antidote; secondary hazard; neurotoxicity; interaction	

* Guidelines for the safety testing of microbial agents apply only to NPV's because these were the first such agents to be developed. † Active or formulated compound. ‡ Active and formulated compound. § Active and significant metabolites. ‖ Studies that would be required under the unofficial proposed guidelines (*30*) for safety testing NPV's and possibly granulosis viruses. Species requirements for the various tests may differ from present requirements but are indicated whenever possible. Acute oral studies should include some immunodepressed animals. Tissue culture studies involving six species total are proposed, including vertebrate cells at lower temperatures and homologous invertebrate cells. Three blind passages should be made and the last passage reinjected into a host animal of the original species. A chromosomal analysis is required. Note: Long-term teratogenicity and reproduction studies would *not* be required if acute and subacute studies showed the viruses to be neither nontoxic nor capable of reproduction in vertebrates.

Chemical insecticides. Despite the recent publication of many papers concerning the high cost of developing new pesticides, figures are hard to generate for individual products because of the proprietary nature of such information. In 1970, a survey of the pesticide industry claimed an average cost of $5.5 million for the development of a new pesticide (*31*). The time required for commercialization was 77 months. A similar survey of 14 companies reported an average cost of $4 million in 60 months in 1969 (*32*). As pointed out correctly by Johnson and Blair (*33*), these figures are too low since they do not include the cost of pilot plants, process development, or studies of waste control and other environmental factors. Their more realistic estimate leads to a figure of $11 million over 10 years, which includes not only the cost of developing unsuccessful compounds, which must be borne by successful ones, but also the additional cost involved in the failure to invest $11 million at 8 percent interest if the company had instead chosen merely to deposit the money in the bank.

Biorational chemical agents. Pheromones and insect growth regulators (juvenile hormone analogs) are the only two types of biorational chemical agents which have reached the stage of development that warrants formal regulatory approval by the EPA. Insect molting hormones and hormone antagonists have not proceeded beyond the laboratory research stage and the former appear in any event to be outside the realm of economic feasibility.

While the use of pheromones (*1, 14*) for pest detection and population assessment does not require regulatory approval—pheromones are, in fact, al-

ready being used operationally on a modest scale—consideration of the use of these compounds for control purposes immediately places them within the present regulatory process as described below. It appears that little, if any, attention is paid to the fact that these agents are much less toxic and much more species specific than classical insecticides and that, because they interfere with the insect's own communication mechanism, their use can be described as "biorational." By treating them as standard insecticides and ignoring their species specificity, which generally implies that their marketability will be limited, the likelihood that many pheromones will be developed for control (in contrast to monitoring) purposes is slight unless substantial changes are made at the regulatory level.

In 1971, USDA scientists (*34*) isolated and elucidated the structure of a housefly sex attractant from fecal and cuticular extracts. Because of its weak attractancy, this straight chain hydrocarbon (*cis*-9-tricosene) was not developed as a housefly control agent. In November 1972, Thuron Industries (a subsidiary of Zoecon Corporation) filed a registration application with the EPA for a standard chemical insecticide fly bait to which had been added small amounts of this sex attractant, muscalure. The incorporation of muscalure permitted a reduction of concentration of the chemical pesticide in the bait and also increased the efficacy of the product. Twelve months later the EPA approved this mixture, and this constituted the first registration of a pheromone for insect control. The regulatory delays (1 year) were not due to the presence in the bait of the standard organophosphate insecticide (which had been in commercial use for many years), but rather to the less toxic hydrocarbon muscalure. Extensive and expensive toxicological investigations on duck, quail, and fish were requested.

In 1970, a USDA group (*35*) successfully elucidated the structure of the sex attractant (disparlure) of the gypsy moth, whose larvae defoliate millions of hectares of trees in the northeastern United States. Since that time, extensive field experiments have been conducted (*36*) to assess the potential of disparlure in controlling the gypsy moth by disruption and confusion techniques. In November 1973, the USDA filed a registration petition with the EPA for utilization of disparlure, but no action has been taken to date. Applications for experimental permits for two other natural sex attractants (Codlemone, a sex attractant for the codling moth and grandlure, the boll weevil aggregation pheromone) were filed recently with the EPA; the Codlemone petition was approved in early 1974.

In December 1972, the first application for an experimental permit and temporary tolerance status for a modified insect juvenile hormone was filed for the use of Altosid insect growth regulator (*15*) in controlling floodwater mosquitoes. Although extensive toxicological investigations (including mutagenic, teratogenic, and subacute studies) show that Altosid is relatively harmless (administered orally to the rat, the acute lethal dose, LD_{50}, is more than 34,600 milligrams per kilogram of body weight) and studies of its residues and biochemistry indicate that it is nonpersistent (its half-life in water is less than 24 hours), the EPA imposed toxicological, environmental, residue, and biochemical requirements that were practically identical to those for a full registration and permanent tolerance status. Zoecon Corporation estimates an expenditure of at least $8 million to develop this new insect control agent to the experimental permit stage. In other words, the regulatory requirements were at least as severe as they are for classical insecticides, probably because of the relative novelty of such approaches to insect control. Such situations, in which the innovator is delayed or penalized for understandable reasons and where "me-tooism" is thus encouraged, occur frequently both during the development of insect control agents and in the human pharmaceutical field.

Figure 1 shows a critical path map outlining the steps required to register and commercialize a new biorational agent. Many costs, such as those for synthesis, production, and formulation, are considerably higher than those reported for traditional chemical insecticides. Biorational agents differ totally in chemical structure from standard organophosphates, carbamates, and chlorinated hydrocarbons; thus, existing synthetic procedures, pilot plants, and manufacturing facilities cannot be slightly and inexpensively altered to meet the demands of each new chemical. Instead, entire new processes, equipment, and facilities must be developed and constructed. The same is true of biological evaluation because the mode of action of biorational agents differs considerably from traditional agents, necessitating more manpower for the development of new techniques.

Microbial agents. The use of microbes as insect control agents is of relatively recent origin (*17*). Although *Bacillus popilliae* was the first microbe agent registered (in 1948, for use in controlling the Japanese beetle), *Bacillus thuringiensis* Berliner has been the most widely used agent of this kind, but considerable manpower and financial resources were expended in obtaining its registration. Here we will concentrate on the costs and time expenditure involved in the development of viral agents, because they have been developed more recently and the cost and time requirements are thus most indicative of the present situation.

In 1960, Cornell University first indicated an interest in obtaining clearance for use of the NPV of *Trichoplusiani* (the cabbage looper). The first petition for a temporary exemption from the requirement of a tolerance (*20*) for a virus was submitted to the FDA by the Agricultural Research Service of the USDA in 1963. In 1966, the USDA's petiton was denied because of insufficient proof of safety. The USDA decided to discontinue its effort and allow industry to further develop the virus (*17*).

In 1968 two companies, International Minerals and Chemical Corporation and Nutrilite Products, Incorporated, initiated formal regulatory procedures which resulted, in 1970, in the official granting of a temporary exemption from the requirement of a tolerance for the *Heliothis* NPV provided that the host was found in or on cottonseed. Experimental permits were granted for two commercial products, Biotrol VHZ and Viron H. Between 1970 and 1973, temporary exemptions were extended and in May 1973 the first full exemption was granted. However, as of February 1974, no full registrations have been obtained for the NPV's because of problems associated with the demonstration of efficacy. Detailed accounts of the attempts to register the NPV (*18, 19, 29, 30, 37*) indicate that the most difficult and time-consuming phases of development were the attempts to establish protocols for determining safety. Because this was a precedent-setting case, the EPA acted with great caution in establishing its criteria for safety. Unlike traditional chemical pesticides, questions arose not only concerning toxicity but also infectivity.

Table 2 lists the safety evaluations that the *Heliothis* NPV underwent. It was tested (*18, 19*) against 19 insect, 2 invertebrate, 19 vertebrate, and 10 plant species, with positive toxicity or

pathogenicity occurring only in *Heliothis*. Ignoffo, in commenting that the most serious difficulty encountered during the registration process was the cost of delay and indecision on the part of regulatory officials, stated (*19*): "Tests originally agreed upon were completed and new tests sequentially added several times. These tests, requiring a total sequential period of 5 years could have been completed within 2 and a half years." One of the corporations developing the *Heliothis* NPV was, in fact, actually in the process of disbanding its entire research group because of the high holding-time costs incurred by regulatory delays when the initial temporary exemption from tolerance was finally issued (*29*). Because viral agents are expensive to produce, have a relatively narrow range of activity, and are essentially nonpatentable, extraordinary regulatory delays act as strong impediments to the introduction of such insect control agents. Much of the caution exercised by the regulatory agencies in passing on the first viral agent is probably understandable, but we believe it to be unlikely that the development cost can be recovered economically in a reasonable time. Unless some economic incentive for this type of work is created, it is doubtful whether much additional research will be performed by industry in the area of new viral control agents.

It is ironic that FEPCA specifies that the EPA "give priority to research to develop biologically integrated alternatives for pest control" while the law as it is actually administered operates as a major disincentive. The EPA has recently proposed some unofficial guidelines (*30*) for the safety testing of NPV's (see Table 2). These guidelines apply only to NPV's and possibly granulosis viruses; other types of viruses and bacteria will probably experience the same difficulties as the first NPV.

Biological control (beneficial predators and parasites). Historically, 81 completely or partially successful biological control programs have been achieved worldwide (*38*). It is claimed (*22, 39*) that 20 introduced species have offered "significant" control in the United States. The current rate of successful introduction is 1.4 per year (*38*). The development of beneficial insects as a method of insect control differs greatly from the other three approaches previously discussed. First, the regulatory agencies involved are the USDA and certain state agricultural departments, rather than the EPA. Second, the universities of California and Florida, the State of Hawaii, and to some extent the USDA are the leading groups now engaged in the introduction and establishment of beneficial insects. The role of private industry is by and large limited to that of dissemination, by some small firms, of insects raised from cultures obtained from government or university sources. Thus the situation is somewhat more analogous to the Atomic Energy Commission in that the regulatory agency (USDA) is both a proponent of and developer in the field being regulated with all the obvious advantages and pitfalls of such an arrangement.

It is difficult to compare the reported time and cost estimates for biological control with those of other insect control agents because, among other reasons, government and university accounting methods are very different from those used in industry. Figure 1 contains a critical path map outlining the steps for the introduction and establishment of a new beneficial entomophagous insect species. Estimated costs range from $127,150 for the University of California (*40*) to $200,000 for the USDA (*41*). Neither one of these figures includes the cost of unsuccessful attempts (*42*).

The costs involved in the development phase of a biological control agent are very much lower than for the other agents discussed. The nature of the agent involved (insect as opposed to chemical) precludes the need for expensive facilities, such as sophisticated analytical instrumentation for residue determination or quality control, for example. The capital investment in building an insectary is much less than that in building a pilot plant or factory for producing a chemical insecticide. The respective critical path maps (Fig. 1) reveal another reason for the wide disparity between the costs of developing beneficial insects as opposed to microbial and chemical insecticides. Efficacy testing (that is, field testing) is very similar for all the agents discussed in this article. The difference lies in the required safety testing, residue tolerance determinations, and especially the administrative procedures involved in registration.

Recommendations

Almost all of the following policy recommendations are equally applicable to insect control and human fertility control—indeed some of them are adaptations of suggestions made earlier (*6*) in the context of new birth control developments. They are based on the premise that it is desirable to encourage continued or even increased involvement of the private sector in the field of insect control. Otherwise, steps should be taken to make the government control of research, development, and production of new types of insect control agents more effective.

1) Research impact statements should be prepared (*7*). Since regulatory agencies now play a de facto and frequently even a de jure role in deciding how and what research should be done, it is imperative that they also take the responsibility for determining the effect of given regulations upon the conduct of research. In matters as critical as those under examination here, it is no longer reasonable simply to promulgate some rules and regulations and then to ignore their consequences (*8*). Regulatory personnel should be required to examine in a prospective fashion the impact of given regulations on future research—especially on that research which policymakers would like to see emphasized (for example, in the field of insect control, the development of nonpersistent, safe, and more selective agents)—and to determine whether the introduction of such regulations would discourage or completely inhibit certain fields of research. Such a negative impact has clearly occurred in the human contraceptive field (*6, 43*) and for that reason we also suggest that regulatory agencies be required to prepare at periodic intervals retrospective research impact statements to determine what impact a given set of regulations had upon research in a certain field over a given period of time.

2) There should be new funding mechanisms of long-term toxicology. Many applications of insect control agents, especially those where the crop involved is somewhere in the food chain, require 2-year toxicological studies. The cost of these and the related investigations probably falls in the $200,000 to $300,000 range. If such studies could be postponed until the developer were certain that the product would be of commercial value, then no major objection would be raised to this additional financial burden. However, frequently such results are required before extensive practical field trials are even feasible (for example, in the control of insects in stored grain) and, since in the search for specific insect

control agents several such products would have to be examined, the cost very rapidly escalates to such an extent that some potentially promising products are never put to practical test. This is especially true if the potential market is relatively small. Alternatively, only one product at a time is tested, thus extending the development time by years.

The high burden of such toxicological requirements is even now being felt by some of the giant companies in the field, and has led to the suggestion (*26*) that "if the requirements for presale testing are to be increased primarily to satisfy public demand, it is proper that the public should bear a part of the cost . . . we must be assured of the assumption of this responsibility by federal agencies if the new, more stringent, requirements now being discussed become regulations or laws." This burden, of course, becomes a much more significant one for smaller R&D groups and this may be one of the reasons why, during the past decade or two, only one new company has been created with a substantial R&D commitment to the insect control field while several large companies have dropped out of this area. The resulting penalty of decreased research and reduced competition is one that the public may not have bargained for.

Our own recommendation is more closely adapted to the one made earlier (*6*) in the context of the requirements for 7-year toxicological studies in dogs and 10-year studies in monkeys in the development of steroid oral contraceptives for human beings. We suggest that the developer of the potential insect control agent should have the option of applying to the appropriate government agency—ideally the EPA—to fund initially the long-term toxicological studies which would then be conducted in an outside laboratory. The performance of these studies by a third party is desirable in any event to assure completely unbiased interpretation. If the product eventually led to a commercial entity, then the manufacturer would be obligated to pay a royalty to the government agency which would continue to be paid for the life of the product or until the entire costs (with interest) of the toxicological studies had been repaid. Such advance funding by the taxpayer through the government agency should not restrict the proprietary position of the developer, because he would have already expended hundreds of thousands of dollars of his own on chemical, biological, analytical, and acute toxicological studies before he reached the stage where long-term toxicological studies were justified and required. The taxpayer is simply asked to share the risk of additional safety requirements so as to make ROI calculations somewhat more attractive in a field where social goals (for example, species specificity) automatically imply smaller markets (*44*) and hence considerably lower return on the original research and development investment. If a product actually reached the commercial stage, then the taxpayer would be repaid for this advance. To put a possible qualitative as well as quantitative ceiling on such requests for partial government funding of toxicology studies, a peer review system (excluding industrial participants) would have to be instituted. Ample precedent for such review exists already in government support to academic institutions.

3) The experimental permit phase should be expedited. The experimental permit phase in insect control research is directly analogous to phases II and III of clinical research in the drug field. It is easy to demonstrate efficacy in the insectary laboratory but it is a completely different matter to demonstrate such efficacy under actual field conditions which frequently involve large areas (hundreds of hectares) in order to make the results meaningful. Government permission has to be secured for such experimental permits and the required regulatory procedures introduce two kinds of delays. The first one, already alluded to in this article, is that insects are generally active during very limited periods of time and sometimes a delay of just a couple of months in securing an experimental permit may lead to a year's delay in actual work. Second, residues of an agent may remain either on a crop or in an animal's meat or milk and, consequently, great caution is exercised both by the regulatory agency and the developer before field trials are attempted because under certain circumstances that crop or those animals may have to be destroyed. In many instances this has led to hypercaution and inordinate delays before serious testing could be started. We think that the granting of such experimental permits could be expedited if two conditions were met: (i) Instead of relying on reports made by the developer after the completion of field trials, the regulatory agency should actually assign a member of its own staff to participate in the monitoring of the experimental permit work. This would have the enormous advantage of exposing regulatory personnel to the actual problems encountered in field testing, and of making them cognizant of the many practical problems that arise during the development of practical insect control agents, particularly of the fundamentally new kinds of agents. Such direct exposure would make regulatory personnel much more experienced in the preparation of research impact statements (*7*). (ii) Funds should be made available, possibly through some type of experimental crop insurance program (*45*), which would assure the developer, and the owner of the crop or animals to be used for the testing, that they could carry out experiments at an earlier date without an inordinate risk of having to pay for the destruction of a crop or group of animals because they contained unacceptable residues. The actual cost of such an insurance system would probably be negligible compared to the social benefits of expediting field research concerned with insect control agents.

The preceding three recommendations are designed to expedite and facilitate the research and development of new insect control agents. The following two refer to incentives once the product has reached the granting of a full registration by the EPA and the stage of actual public use.

4) The regulations for patent protection should be modified. This suggestion was first made (*6*) in the context of human contraceptive development where the time lags between agents being discovered and applied are even longer than in the insect control field. The common denominator behind this recommendation is that under current law the lifetime of a patent is 17 years. However, when one deals with long development times, frequently one-third to even two-thirds of the patent protection time is actually consumed by the development phase and frequently the inventor or developer of the product who bore the brunt of the intellectual and financial gamble has only a few years left of proprietary patent protection. We therefore suggest that for agents actively under regulatory review, the 17-year patent lifetime be reduced to 10 years, but that the 10-year clock start running only from the day that a full registration is issued. A related recommendation is included in the "Mrak Report" (*4*).

5) Bonuses should be paid to en-

courage the use of environmentally desirable agents. The social goals associated with man's ever-increasing concern for the environment require that an insect control agent be relatively nonpersistent, specific to certain harmful insects, relatively harmless to beneficial ones, and, of course, harmless to man, wildlife, and domestic animals. Nonpersistence generally entails more frequent administration, and specificity to certain harmful insects frequently means "biorationality," which in turn often implies administration at a very specific time of the insect's life cycle. In any event, any such new agent—be it a biorational chemical one, a microbial one, or biological one—may require that substantial education be given to the applicator and the user. In a number of instances such personnel may have to be completely retrained. All of these features, whether operational or educational in nature, must be included in calculating the cost of insect control. As already pointed out, the development of insect control agents differs from the development of drugs for human beings in that the finite economic limit for the former is directly associated with the market value of the crop or the socially perceived value of a natural resource such as a forest. Until now, it is primarily lip service that has been paid to such concerns, while funds for paying the increased cost of environmentally more desirable agents have been very limited. There seems to be no evidence that government agencies are aware that the payment of subsidies to users, as an incentive for them to employ environmentally more desirable but also more expensive techniques, would be better than allowing the economics of the market to dictate whether or not new agents are developed.

Summary

Human and insect population control have several features in common, all of them indicating that the lag times in converting laboratory discoveries into practical agents are increasing greatly and that ROI calculations are becoming more and more significant in decisions related to the development of new agents. ROI calculations are particularly important in the field of insect control because, by being more specific, the agents of the future are likely to cover smaller markets. Several recommendations for stimulating the development of new methods of insect control are proposed which are addressed primarily to policy-makers. If they are not implemented, then our suggestions should at least stimulate others to make alternative proposals. If neither event occurs, then it is unlikely that there will be any fundamentally new approaches to practical insect control in this decade; a similar prediction (*6*) that was made 4 years ago in the field of human birth control is rapidly proving to be correct.

References and Notes

1. *Pest Control: Strategies for the Future* (National Academy of Sciences, Washington, D.C., 1972).
2. Council on Environmental Quality, *Integrated Pest Management* (Government Printing Office, Stock No. 4111-0010, Washington, D.C., 1972).
3. In addition, integrated pest management places heavy emphasis on cultural, physical, and mechanical measures, notably the introduction of insect-resistant plant varieties. Such pest management requires a high level of professional competence because it involves the making of decisions based on continuing accumulation, analysis, and utilization of information. In one of our recommendations (No. 5) we discuss this further.
4. *Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health* (Department of Health, Education, and Welfare, Washington, D.C., December 1969). Recommendations 10 (increase federal support of research on all methods of pest control, the effects of pesticides on human health and on the ecosystems, and on improved techniques for prediction of human effects) and 11 (provide incentives to industry to encourage the development of more specific pest control chemicals) are related to some of our recommendations, although we differ in terms of their detailed implementation.
5. The last report of the President's Science Advisory Committee (PSAC) to be released (9 January 1974) by the Science and Technology Policy Office of the National Science Foundation entitled *Chemicals and Health* (Government Printing Office, Stock No. 3800-00159, Washington, D.C., 1973) is the most recent paper addressed to policy matters applicable to pesticides (see pp. 19, 22, 53–61, 173–179). While the PSAC panel recognize implicitly and even explicitly some of the factors we outline in this article, it is curiously ambivalent in some of its recommendations. Thus it proposes (p. 19) that "research development devoted to pest control methods which reduce the need for pesticides with notable adverse health effects should be markedly expanded," yet states (p. 60) that "alternatives to narrow-spectrum pesticides and pesticides generally do not offer as much attraction" to the private sector which bears "a high proportion of the R & D expenditures associated with pesticides." Given this crucial fact, nowhere in the PSAC report are any incentives suggested for greater involvement in the pesticide field by the private sector. In our recommendations (Nos. 2 to 5) we address this point and suggest alternatives that are also likely to be economic bargains for the taxpayer. If our recommendations are not accepted, it is important that alternative policies for effective government-operated research and production facilities be considered for the insect control field.
6. C. Djerassi, *Science* **169**, 941 (1970).
7. ———, *ibid.* **181**, 115 (1973). The research impact statement here proposed is not unlike the "white paper" concept outlined subsequently in the PSAC report (*5*), except that the PSAC report surprisingly omits consideration of the effects of regulating decisions on future research and development.
8. Section 102(2)(C) of the 1969 National Environmental Policy Act can actually be construed as a legal mandate for research impact statements by government regulatory agencies.
9. J. M. Utterback, *Science* **183**, 620 (1974).
10. These pressures are exerted primarily in the more highly developed countries (DC's), but political, economic, and even moral implications for lesser developed countries (LDC's) are grossly underplayed. Thus in the human birth control field attention has already been drawn [C. Djerassi, *Science* **166**, 468 (1969)] to the problems that arise when clinical work on new fertility control agents is carried out in an LDC rather than in the country where the initial basic discovery was made. Similarly, let us consider the problems of an LDC with a predominantly agricultural economy and no facility for developing new insect control agents which is informed by a DC that the use of some important conventional insecticide is now banned and will not be manufactured any more because of environmental considerations.
11. E. Deck, *Food Drug Cosmet. Law J.* (1973), p. 628.
12. An actual example of this situation was described by G. K. Kohn of Chevron Chemical Company at the American Chemical Society Symposium on Pesticide Selectivity (Chicago, Ill., 29 August 1973): Chevron synthesized a modified insecticidal carbamate (RE 11,775) which was found to be an effective mosquito larvicide even against strains resistant to conventional pesticides. Further tests by the University of California confirmed these findings and suggested that no extraordinary problems would be encountered with respect to toxicology and ecological impact. Since the mosquito vector for viral encephalitis in the San Joaquin Valley was known to be developing resistance to most organophosphates and chlorinated hydrocarbons and some carbamates, Chevron proposed that RE 11,775 might be an effective control agent. After consideration of the market potential (estimated to be 115,000 kilograms in California and 450,000 kg worldwide) Chevron decided it could not afford to develop RE 11,775. Exploratory conversations were then initiated whereby the company offered to donate the process patents and all rights to the State of California for manufacture by the state or, alternatively, proposed to manufacture the pesticide on a cost plus basis. California had no mechanism for accepting such an offer and Chevron discontinued work on this promising lead. Kohn concluded that chances for development of a new agent are minimal if the product is too specific for only one or a few target organisms of the total market potential is small. Development would proceed only if certain registration requirements were relaxed, thus reducing development costs, or certain subsidies introduced such as cost plus production programs, sharing of development costs, tax rebates, or state production.
13. R. Clark, *Chem. Technol.* **2**, 656 (1972).
14. J. L. Marx, *Science* **181**, 736, 833 (1973).
15. Among others, C. A. Henrick, G. B. Staal, J. B. Siddall, *J. Agric. Food Chem.* **21**, 354 (1973); R. G. Strong and J. Diekman, *J. Econ. Entomol.* **66**, 1167 (1973); J. J. Menn and M. Beroza, Eds., *Insect Juvenile Hormones: Chemistry and Action* (Academic Press, New York, 1972).
16. J. D. Diekman and L. Senior, *Abstracts of the Annual Meeting of the Entomological Society*, Dallas, 1973, p. 73; R. W. Bagley and J. C. Bauernfeind, in *Insect Juvenile Hormones: Chemistry and Action*, J. J. Menn and M. Beroza, Eds. (Academic Press, New York, 1972), p. 113.
17. H. D. Burges and N. W. Hussey, Eds., *Microbial Control of Insects and Mites* (Academic Press, New York, 1971); L. A. Bulla, Jr., Ed., "Regulation of Insect Populations by Microorganisms," *Ann. N.Y. Acad. Sci.* **217**, 1–243 (1973); see especially pp. 234–237 by W. M. Upholt, R. E. Engler, L. E. Terbush.
18. C. M. Ignoffo, *Exp. Parasitol.* **33**, 380 (1973); *Insect Pathology and Microbial Control*, P. A. Van der Laan, Ed. (North-Holland, Amsterdam, 1967), pp. 91–117; *Misc. Publ. Entomol. Soc. Am.* **9**, 57 (1973); *Ann. N.Y. Acad. Sci.* **217**, 141 (1973); *Environ. Lett.*, in press.
19. ———, in *Proceedings of the Tall Timbers Conference on Ecology and Animal Control by Habitat Management*, 26 to 28 February 1970.
20. An exemption from the requirement of a

tolerance is granted by the EPA when it is judged that any crop residues resulting from the use of the insecticidal agent according to label directions will not be harmful.
21. For some recent comments on practical limitations of this technique, see J. Calman, *Science* **182**, 776 (1973); R. H. Smith, *ibid.*, p. 776; R. C. Bushland, *ibid.* **184**, 1010 (1974).
22. R. I. Sailer, *Proc. North Cent. Branch Entomol. Soc. Am.* **27**, 35 (1972).
23. R. E. Pfadt, Ed., *Fundamentals of Applied Entomology* (Macmillan, New York, ed. 2, 1971), p. 172.
24. B. H. Holmes and W. D. Anderson, *Laws and Institutional Mechanisms Controlling the Release of Pesticides into the Environment* (Pesticides Study Ser. 11, Government Printing Office, Stock No. 514-147/52 1–3, Washington, D.C., 1972).
25. U.S. Department of Agriculture, Agricultural Research Service, *Issuing Permits for the Movement of Plant Pests, Pathogens, and Vectors*, PA 967 (Government Printing Office, Stock No. 0-408-757, Washington, D.C., 1970); L. Andres, U.S. Department of Agriculture, Albany, Calif., personal communication.
26. K. R. Fitzsimmons, "Role of industry in advancing new pest control strategies," in *Pest Control: Strategies for the Future* (National Academy of Sciences, Washington, D.C., 1972), pp. 352–361.
27. P. J. Gehring, V. K. Rowe, S. B. McCollister, *Food Cosmet. Toxicol.* **11**, 1097 (1973).
28. Environmental Protection Agency, Criteria and Evaluation Division, *Guidelines for Registering Pesticides in the United States* (Environmental Protection Agency, Washington, D.C., draft dated 1 May 1972 and 4 November 1973).
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30. R. A. Engler, Registration Division, Office of Pesticide Programs, Environmental Protection Agency, Washington, D.C., personal communication.
31. Ernst & Ernst Trade Association, *Pesticide Industry Profile*, a study prepared for the National Agricultural Chemicals Association (Ernst & Ernst Trade Association, Washington, D.C., 1971).
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37. M. Rogoff, Sandoz-Wander Corporation, Miami, Fla., personal communication.
38. R. van den Bosch, *Annu. Rev. Ecol. Syst.* **2**, 45 (1971).
39. G. Irving, Jr., *J. Wash. Acad. Sci.* **62**, 240 (1972).
40. R. van den Bosch, College of Agricultural Sciences, University of California, Albany, and J. Laing, Department of Environmental Biology, University of Guelph, Guelph, Ontario, personal communication.
41. J. Coulson, USDA Agricultural Research Center, U.S. Department of Agriculture, Beltsville, Md., personal communication.
42. R. van den Bosch (*38*) estimates a success rate of 16 per 100 species attempted for entomophagous insects at the University of California, Albany.
43. "The Food and Drug Administration: Law, Science and Politics in the Evaluation and Control of New Drug Technology," *Northwest. Law Rev.* **67**, 858 (1973).
44. It may be more cost effective to reduce safety standards for smaller markets, but this is unlikely to be acceptable to the public.
45. This is closely related to the concept of "Insurance for technological injury" proposed in *Chemistry in the Economy* (American Chemical Society, Washington, D.C., 1973), p. 7.
46. M. J. Sloan, "Regulation and adversary action—the pesticide industry's dilemma," paper presented at the 5th Stanford University Industrial Affiliate Symposium entitled "Effect of Regulatory Agencies on Scientific and Industrial Productivity," 13 to 14 November 1972; F. H. Tschirley, "Pest research by the public sector: Control and management," paper presented at the American Chemical Society Meeting, Boston, Mass., 13 April 1972.
47. We are indebted to many persons in academic, government, and industrial circles for valuable suggestions in reviewing an earlier draft of this article.

Energy and Life-Style

Massive energy consumption may not be necessary to maintain current living standards in America.

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One strategy for countering persistent shortages of energy is to increase the supply. Another strategy—the one that concerns us here—is to reduce the demand. The United States consumes more energy—on both an absolute and a per capita basis—than any other country. There is no doubt that a reduction in our current rate of increase of energy consumption would have short-term negative effects on the society, for example, increased unemployment and decreased pleasure driving. On the other hand, it is equally clear that we waste substantial amounts of energy and that we could use it more efficiently than we do, getting the same output with less consumption (*1*). Perhaps—after a painful short-term adjustment—we would be better off with reduced but more efficient energy consumption. Some obvious advantages would be reduced dependency on foreign oil suppliers, less pollution from power generation, less need to extract fuels from the earth and the oceans, reduction of the massive need for investment capital for the energy industry, and less need to devote large land areas to power generation and transmission facilities. Would these be outweighed by a long-term deterioration in our life-style as an industrialized nation?

We really have very little knowledge of the effect of decreased energy consumption on life-style, but there is sufficient cause for concern. Many observers have pointed to the close relation between per capita energy consumption and per capita gross national product (GNP) (*2*). One can argue that a long-term decrease in energy consumption would lead to a long-term decline in GNP with an associated decrease in the economic (and other) benefits of American life. On the other hand, many aspects of American life seem no better than comparable aspects of life in some countries that consume much less energy than we do.

Here we will report our analysis of energy consumption in a large number of countries. We have used readily available national statistics in order to estimate some of the long-term effects of reduced energy consumption on life-style. There are many shortcomings to this sort of analysis, some obvious and some subtle. We will point to these problems as we proceed, providing a sort of running critique of our own results.

Data and Method

Our sample of 55 countries (Table 1) consists basically of the United Nations member nations with population size of at least 7 million; we have also included three smaller ones—Israel, Denmark, and Switzerland—and we have excluded Communist China, North Korea, and Iran because of lack of data. We have focused on 1971, which is the most

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