Staff Papers Series

P83-14

June 1983

INNOVATION AND REGULATION IN THE PESTICIDE INDUSTRY: FOUR CASE STUDIES

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Acknowledgments

This study was made possible by the very generous support of the United States Department of Agriculture, Economic Research Service, Natural Resource Economics Division (Research Agreement 58-319U-0-0076X, between the University of Minnesota and the USDA.) Both John Schaub and Clark Burbee contributed to the development of the research plan. Katherine Reichelderfer and Ted Eichers provided helpful advice regarding the conduct of the research.

The project was carried out under the direction of Vernon W. Ruttan of the University of Minnesota Department of Agricultural and Applied Economics. He has provided continuous guidance and advice.

The project could not have been completed without the generous cooperation of pesticide industry scientists, especially Cleve Goring of Dow Chemical; Larry Magill and Tom Fridinger of Minnesota Mining and Manufacturing; Steve Krzemski and Art Ballard of Rohm and Haas; Susan Merritt and Eric Ummel of Sandoz. Comments by Carlo Ignoffo of USDA Biocontrol Laboratory on a preliminary draft were particularly useful. Frequent consultations with Larry Magill and Tom Fridinger were essential to the successful completion of this project. William Hollis and Lawrence Norton of the National Agricultural Chemicals Association were especially helpful in making as much industry information available to us as possible without infringing upon rights of confidentiality.

The advice of Arnold Aspelin and Gary Ballard of the Environmental Protection Agency was beneficial to the assessment of the important

economic relationships involved in pesticide regulations and their detailed comments to a draft of this study were very useful.

I would like to express my appreciation to all the industry and government officials who were interviewed or contacted as part of this project. Also, I am grateful for the patience of Mary Jane Luedtke, Elaine Reber, and Janet Cardelli who typed the numerous drafts and revisions of this report.

These case studies are drawn from my thesis, entitled "The Effect of Environmental Protection Agency Regulation on Research and Development in the Pesticide Industry" (1982). A copy of the thesis is available through University Microfilms International.

INNOVATION AND REGULATION IN THE PESTICIDE INDUSTRY: FOUR CASE STUDIES

Introduction

Pesticide policy has evolved in response to the U.S. political climate and the development of new technology. The U.S. Congress created EPA to oversee the publicly-mandated task of environmental protection. Pesticide policy has sought to maintain a reasonable degree of consistency between the interests of pesticides manufacturers and agricultural producers and concerns about the public health and the environmental impact of pesticide use.

Not only is the technology of producing pesticides and agricultural products continually changing but also the technology of monitoring environmental hazards. To a large degree, the increase in pesticide regulation is a result of the immense success agrichemical firms have experienced in developing pest control products. These products have contributed substantially to the growth in crop and animal productivity. The increased use of chemical pesticides in crop and animal production has also contributed to public apprehensions concerning the purity of its food supply. This public concern has resulted in stricter regulatory control over the use of traditional pesticides and the introduction of new pesticides.

Recently, the development of new pesticides has required more time, money, and personnel, and has faced increased economic risks. (U.S. Environmental Protection Agency, 1975; Conservation Foundation, 1980; Office of Technology Assessment, 1981; Hatch, 1982). The time needed for research and development of a new active ingredient has risen sharply, in part as a result of increased time in regulatory review. Risks have increased in relation to the number of materials screened, problems gaining registration, and restrictive regulatory actions. R&D funds, personnel,

and equipment requirements have risen as a result of the more stringent regulatory regime. The number of new products and their uses has fallen in the 1970's, especially in minor use markets. The percentage of R&D funds allocated to discovery has decreased while the share going to regulatory and environmental studies has increased sharply. Also, more effort is being exerted in defense of existing products to the detriment of new product development. Management decisions have been made more difficult resulting in an earlier decision on which compounds to pursue and a decrease in the likelihood that "radical", high risk compounds will receive attention. (Hatch, 1982).

Case studies of four products - chlordane, acifluorfen, fluoridamid-mefluidide, and Heliothis NPV -- will be used to examine some of the impacts of regulation on pesticide innovation. Regulatory effects will be illustrated by reviewing the R&D history of particular products.[1/] Case studies are useful as a compliment to a statistical analysis particularly in assisting with the formulation of testable hypotheses. Although all conclusions drawn from these case studies can not be statistically analyzed, several economic relationships will be examined that might involve testable hypotheses. Thus, these case studies are intended to provide insight on the regulatory effects on pesticide innovation and serve as a basis for the formulation of hypotheses that might be examined with an appropriate data base.

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[1] Because chlordane was developed in the 1940's during a much different regulatory climate from the other three case studies, the emphasis of the chlordane case is placed on the history of the use cancellation, not on its R&D history.

The four products selected for the case studies are not intended to be sufficiently similar to make direct comparisons. They are in fact quite dissimilar, representing the diversity of products that are included in the pesticide industry. The first case study involves an older generation chlorinated hydrocarbon -- Chlordane[R] 2/ -- which has had most of its major uses cancelled. Chlordane is a broad spectrum, highly persistent chemical produced by Velsicol Chemical Corporation. As a member of the chlorinated hydrocarbons its regulatory fate has been closely linked to the actions against other members of this family of chemicals, particularly DDT, aldrin, and dieldrin. Consequently, chlordane's regulatory history provided an opportunity to delve into the mechanics of the cancellation process.

Acifluorfen is the second case study; its trade name is Blazer Herbicide[R] 3/ and it is produced by Rohm and Haas Company. Blazer Herbicide is a broad spectrum, post-emergence herbicide, principally used on soybeans. As a post-emergence herbicide it has a considerable potential market. Its exceptionally rapid R&D and regulatory history make it a good reference point as a lower bound of the range of time required to develop a new product.

Fluoridamid-mefluidide were developed by 3M. Although three product names and two active ingredients are involved, the effort represents essentially a single R&D project. Sustar[R] Plant Growth Regulator (PGR) 4/ (fluoridamid) was first to be registered but was not

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2/ Chlordane is a Reg. T.M. of Velsicol Chemical Corporation.

3/ Blazer is a Reg. T.M. of the Rohm and Haas Company.

4/ Sustar is a Reg. T.M. of the 3M Company.

pursued because of Embark® Plant Growth Regulator (PGR)'s[5] (mefluidide) increased activity and herbicidal potential. Vistar® Herbicide[6] (mefluidide) was recently registered as a herbicide on soybeans. The fluoridamid-mefluidide case represents a very highly research oriented firm's ability to exploit its technogical skills to enter a new market. The plant growth regulator mode of action is highly innovative.

The last case study -- Heliothis NPV -- is a new biological agent (virus) whose early development was pursued in a USDA laboratory and which is presently produced under the trade name, Elcar®,[7] by Sandoz. The viral pesticide is highly specific to the Heliothis species and is principally used on cotton. Biological pesticides have been praised as the third generation and much success has been expected in this area; however, the development of new biologicals has not been an easy process and the number of new biological pesticides has not increased as rapidly as expected by many market observers. Heliothis NPV illustrates some of the R&D roadblocks that have slowed the widespread acceptance of biologicals.

These case studies examine the R&D and regulatory histories of four individual pesticide products to analyze the effects of EPA regulatory policy on the pesticide industry with special emphasis on new product development and use cancellation. The objectives of this analysis are to provide concrete

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[5] Embark is a Reg. T.M. of the 3M Company.
[6] Vistar is a Reg. T.M. of the 3M Company.
[7] Elcar is a Reg. T.M. of Sandoz, Inc.

examples of the regulatory effects often mentioned by industry officials and to develop economic relationships from the experiences with these products that might suggest testable hypotheses.

Chlordane

Chlordane is a chlorinated hydrocarbon insecticide which has been most extensively used in soil applications against a broad spectrum of economic pests, particularly for the control of insects in corn. However, by the time of the EPA restrictive action, chlordane's role as a major insecticide for agricultural crops had greatly diminished. Its most important remaining use was against termites. (Eichers, et al., 1978). It is a stomach and contact insecticide whose registered uses have been restricted to subterranean termite control and dipping of roots for quarantine purposes. Velsicol Chemical Corporation developed chlordane in 1945. The Environmental Protection Agency restricted its use in 1978.

U.S. agriculture in 1945 had not evolved to its present capital intensive state. Pesticides had not become an essential input in farm production but their usefulness was becoming apparent. As agriculture evolved, the chlorinated hydrocarbons had a comparative advantage in pest control due to their persistence and nonspecificity. Pesticidal activity that lasted the length of the insect infestation was desired to decrease the need for additional applications. Also, a pesticide which demonstrated activity against a broad spectrum of pests was the goal of agricultural chemical research and development. A broad spectrum, persistent pesticide allowed farmers to achieve a reasonable level of pest control with a minimum number of sprayings. Chlordane is such a pesticide and was a great success for its developer and producer and users.

Further evolution in agricultural production and concern over public health and safety have undermined the status of certain of these pesticides as important agricultural production inputs (Headley and Lewis, 1967).

Current pest control strategies often focus on the use of pesticides in anticipation of insect infestations. The evolution of U.S. farm policy has been toward fewer farm producers, more food production and less agricultural land. Broad spectrum, persistent pesticides have been an essential element in this evolution. Concurrently, public debate over environmental hazards has escalated. The policy implication of this debate has been the formation of a comprehensive regulatory regime, principally administered through the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA).

The rather strict interpretation and implementation of legislatively mandated restrictions on the production and use of products demonstrating potential environmental hazards have begun to affect the evolution of agricultural production. Regulatory and production policy has developed in response to changes in technology. As chemical technology has permitted the detection or identification of materials at vanishingly small levels, regulatory agencies have tightened restrictions. The more restrictive policy is inducing the development of production technology that decreases human exposure to potential hazards. Policy and technology are inextricably intertwined. The case history of chlordane illustrates this relationship.

Regulatory action against chlordane was greatly affected by its membership in the family of chlorinated hydrocarbons with DDT, aldrin, dieldrin, and heptachlor. The history of the cancellation of DDT has been well documented (Dunlap, 1981). Communication between industry and environmental groups was totally adversarial. Armed with the successful move against DDT and later dieldrin and aldrin, environmentalists brought pressure on EPA for cancellation of chlordane and heptachlor. Industry

officials reacted in an understandably defensive manner. Thus, the cancellation proceedings reported in this case study were carried out in the adversary environment that had developed as a result of previous regulatory activities concerning other chlorinated hydrocarbons. Data pertaining to human health hazards and economic benefits from chlordane and heptachlor were presented in open hearings, subjected to cross-examination, and upheld as the basis for a regulatory decision.

The criteria used to make the judgement in the cancellation hearings and the scientific evidence presented to confirm the need for action are outlined in this study to illustrate the implementation of environmental policy. Several alternative regulatory courses were considered and the impact of each was analyzed to determine the environmental, social, and economic effects. The discussion of the testimony at the hearings provides an indication of the complexity of the scientific evidence and its interpretation.

Regulatory History

Concern over the potential environmental hazards of chlordane was given official recognition in 1969 by the U.S. Department of Health, Education and Welfare Commission on Pesticides and their Relationship to the Environmental Health. The commission recommended "restricting the use of certain persistent pesticides, including chlordane, in the United States to specific essential uses which would create no known hazard to human health or to the quality of the environment" (HEW, 1969). A review of chlordane was initiated by the EPA in 1971; however, it was judged that the scientific evidence assembled at that time was insufficient to justify restriction of uses (EPA, 1972).

In 1975, the scientific evidence was updated (EPA, 1976a) and a report was issued summarizing the economic and social impacts of cancellation of registered uses (EPA, 1975). The additional scientific data and the experience of the aldrin/dieldrin cancellation and suspension process precipitated a reversal of the earlier judgement. In the aldrin/dieldrin hearings,[8/] a more precise definition of the evidence needed to justify use restrictions and an amplified concept of carcinogenicity based on the growing body of cancer research was established. The EPA Administrator under Section 6(b) of FIFRA, as amended, issued a notice of intent to cancel[9/] certain registered uses of products containing chlordane and heptachlor. Public hearings were initiated.

In the related aldrin/dieldrin case, all uses were cancelled with some restricted exemptions. Because chlordane/heptachlor are substitutes for aldrin/dieldrin in many uses, it was assumed that without restrictive action, the use of chlordane/heptachlor would increase substantially. Suspension of registration of chlordane/heptachlor for uses in lawns, gardens, turf and for household pest control was issued to prohibit use during the cancellation proceedings.

8/ Under Section 3 of FIFRA, as amended, if evidence exists that a pesticide poses "unreasonable adverse effects on the environment," the burden of proof is placed on the prospective producer to demonstrate that registration should not be denied.

9/ If the Agency has determined that unreasonable adverse effects are occurring, the notice of intent to cancel is designed to instigate the gathering of relevant information and the voicing of public concerns by the registrants or other affected parties. The decision to issue a notice is based on evidence that supports the possibility of hazards. The notice does not represent a judgement that the pesticide has been found to cause "unreasonable adverse effects on the environment;" however, it implies that sufficient evidence has been brought forth to question the assertion that no unreasonable adverse effects exist and that all relevant evidence should be amassed and analyzed for a final judgement.

Product Characteristics and Scientific Evidence

Chlordane is a persistent pesticide. Two metabolites of chlordane,[10/] heptachlor epoxide and oxychlordane, have raised concerns among scientists. Chlordane's persistence has been documented: as much as 16% of the compound remained in the soil after 15 years for crop application and 15% after 12 years for subterranean termite control (EPA, 1976a). In addition to residues in the air, rainwater, dust, fish, birds, and mammals, residues of metabolites from chlordane/heptachlor were found in 90% of human tissue samples. (United States Environmental Protection Agency, 1976).

Chlordane was most extensively used in soil applications for control of a broad spectrum of insects; consequently, its properties in the soil are the most studied and analyzed. Fortunately, chlordane is water insoluble and becomes tightly bound to soil particles. This property tends to lessen the possibility of contamination of ground water, but some residues have been found in private wells as a result of termite control or other uses around the home. Chlordane is fairly volatile; some residues have been detected in air, rainwater, and dust (EPA, 1976a). Studies with fish, birds and mammals have shown low-level residues and toxic

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10/ Heptachlor epoxide is not a significant or routinely detectable metabolite after application of technical chlordane. Although chlordane contains about 7% heptachlor, and heptachlor is metabolized to heptachlor epoxide, in most environmental substrates analyzed, heptachlor epoxide is either obliterated by other materials that show in the chromatogram or is seen in extremely small quantities. Also, oxychlordane is only a metabolite known to occur in certain animals and in alfalfa plants. (Velsicol, 1978).

effects, particularly in aquatic environments. These short term effects have not yet been substantiated for longer time periods.

FDA and USDA have established tolerance levels for human consumption; the World Health Organization of the U.N. has set acceptable daily intake levels (0.001 mg/kg body weight for man). FDA and USDA monitoring of food and feed crops has consistently found residues, particularly heptachlor epoxide. EPA surveys indicate the presence of the principal metabolites in adipose (fatty) tissue, stillborn infants, and human milk.

EPA's evidence against registration was summarized in the Environmental Impact Statement.

> "1. They (chlordane and heptachlor) have been used for over 20 years in considerable quantities for a variety of crop and non-crop pest control purposes.
> 2. They are chemically similar; chlordane contains about 10% heptachlor.
> 3. They and their toxic breakdown products are very persistent in the environment, resisting chemical or biological breakdown into harmless substances.
> 4. They or their toxic breakdown products are found as residues throughout the environment, i.e., in soil, water, air, wildlife and food.
> 5. Their toxic breakdown products are found to have accumulated in human adipose tissue and in human milk.
> 6. They and some of their breakdown products are acutely toxic to many forms of life, in addition to target species.
> 7. Heptachlor epoxide has been found to have accumulated in the organs of stillborn infants.
> 8. Heptachlor, heptachlor epoxide and chlordane induce tumors in laboratory animals, and thus pose a cancer threat to man (EPA, 1976b)."

Interpretation of laboratory studies has not been unanimous. The results of four studies (Figure 1) summarized the scientific evidence for the hearings: U.S. Food and Drug Administration (FDA), International Research and Development Corporation (IRDC), National Cancer Institute (NCI) and The Kettering Laboratory (University of Cincinnati).[11/]

11/ The IRDC and Kettering studies were sponsored by Velsicol.

Scientists from IRDC and Kettering unanimously assessed the results as not demonstrating carcinogenicity. The FDA study was reviewed in 1969 by the HEW Commission on Pesticides and Their Relationships to the Environment; at the time, it was considered insufficient evidence to warrant restrictive actions. During the cancellation hearings the study was again reviewed and, in some cases, was used to support the claim of carcinogenicity. Dr. Kent Davis, who conducted the FDA study, testified that the second reviewers were not able to observe the tissue from which the samples were taken or observe the animal or its life history.

> "If EPA had focused on the total number of tumors and on malignant tumors in particular, in comparing test groups to the control groups, it could not have come to the conclusion that heptachlor and chlordane are chemical carcinogens (Davis, 1975)".

The EPA witnesses, however, came to different conclusions. Dr. Melvin Reuber, a consultant for EPA and NCI concluded:

> "1. Heptachlor, heptachlor epoxide and chlordane are carcinogenic in mice.
> 2. Heptachlor epoxide is carcinogenic in rats.
> 3. Since these chemicals are carcinogenic in mice and rates, they should be considered potential carcinogens for human beings (Reuber, 1975)."

His statement is representative of the EPA witnesses.

The administrative Law Judge requested that the National Academy of Science arbitrate. The studies were reviewed by the Pesticide Information Review and Evaluation Committee for the Advisory Center on Toxicology, Assembly of Life Sciences National Research Council, National Academy of Sciences. It was concluded that chlordane is carcinogenic in the mouse but that no "statistically significant evidence exists to support carcinogenicity in rats (National Academy of Sciences, 1977)". The extrapolation of laboratory study results to potential human risks was addressed as follows:

Figure 1. Laboratory Studies Used in Chlordane Cancellation Hearings

Laboratory	Year	Test Animal	Compound	Feeding Levels
FDA	1965	CH3 Mouse	Heptachlor	10 ppm
			Heptachlor epoxide	10 ppm
NCI	1975	B6C3F1 Mouse	Heptachlor	6.1-18 ppm
			Chlordane	29.9-63-8 ppm
		Osborne-Mendel Rat	Heptachlor	25.7-77.9 ppm
			Chlordane	120.8-407 ppm
IRDC	1973	CD-1 Mouse	Heptachlor(25%) Heptachlor epoxide (75%)	1, 5 and 10 ppm
			Chlordane	5, 25 and 50 ppm
Kettering	1959	CFN Rat	Heptachlor epoxide	0.5, 2.5, 5. 7.5 and 10 ppm

SOURCE: Velsicol Chemical Corporation, "Summary of the Toxicological Evidence of Heptachlor and Chlordane Presented in Administrative Hearings called by the United States Environmental Protection Agency (November 18, 1974-March 6, 1968)", 1978.

> "There are no adequate data to show that these compounds are carcinogenic in humans, but because of their carcinogenicity in certain mouse strains and the extensive similarity of the carcinogenic action of chemicals in animals and in humans, the Committee concluded that chlordane, heptachlor and/or their metabolites may be carcinogenic in humans. Although the magnitude of risk is greater than if no carcinogenicity had been found in certain mouse strains, in the opinion of the Committee the magnitude of risk cannot be reliably estimated because of the uncertainties in the available data and in the extrapolation of carcinogenicity data from laboratory animals to humans (National Academy of Sciences, 1977)".

A further issue in the hearings was the feasibility of establishing a virtually safe dose (VSD).[12/] The report of the Carcinogen Assessment Group (CAG) of EPA, "Interim Procedures and Guidelines for Health Risk and Economic Impact Assessment of Suspected Carcinogens" was used in the hearings as a basis of EPA's position. Dr. Roy Albert, Chairman of CAG, concluded that:

> "It is possible that the socioeconomic value of heptachlor and chlordane may ultimately be considered to justify the risk ... There is no question that the evidence provides a warning signal that heptachlor and chlordane could be a cancer hazard to humans. The magnitude of the risk is probably not very large, but neither is it negligible."

Velsicol witnesses argued for the existence of a virtually safe dose but this issue was never resolved due to the compromise nature of the final agreement. Evidence was also brought forth by Velsicol to support the record of safety established by chlordane with application and manufacturing workers (Mac Mahon, 1975). The NAS Advisory Committee stated that these research efforts needed to be extended to more workers over more time. Also, this approach (used by the Public Health Service) of conducting population surveys on heavily exposed groups had been set aside in favor of long term animal tests to determine chronic effects.

12/ The National Academy of Sciences was unwilling to set a virtually safe dose and EPA concurred with the decision.

Velsicol defended chlordane's safety at great length. In addition to the testimony of the FDA scientist that did the original FDS study and the data on workplace and farmer safety, the judgement of experts of the Food and Agriculture Organization of the United Nations was brought forward. The latter reached more favorable conclusions on the safety of chlordane use. It concluded that "the production of hepatic tumors by dieldrin and chlordane in the mouse was a species-related phenomenon and were, therefore, able to confirm the acceptable daily intake (ADI) for these pesticides (FAO, 1978). It also set a no-effect level of 5 mg/kg in the rat and 3 mg/kg in the mouse and an ADI for man of 0.001 mg/kg body weight.

The final decision, with the consideration of the factors described in the next section, was to cancel all uses of chlordane except subterranean termite control and dipping of roots for quarantine purposes. Several exceptions were included in the final compromise agreement between EPA and Velsicol.

Criteria for Cancellation Decision[13/]

Environmental, social and economic factors pursuant to the judgement on cancellation were assembled by EPA for the four most feasible policy alternatives in the "Environmental Impact Statement Concerning Notice of Intent to Cancel Registered Uses of Products Containing: Chlordane and Heptachlor" (EPA, 1976b). The alternatives considered were: no action, cancel all uses, cancel all uses with exception of subterranean termite control and dipping of nonfood plants, and cancel only food and feed crop uses. Beneficial and adverse effects associated with each alternative were outlined.

13/ This section is taken in large part from the EPA environmental impact statement concerning chlordane/heptachlor cancellation and other EPA documents.

Adverse environmental effects of no action result primarily from Chlordane's persistence. Chlordane and its toxic metabolites, principally heptachlor epoxide and oxychlordane, have been found to persist in the soil for many years after application (EPA, 1972; EPA, 1976a). Greater persistence results from subterranean application but it was believed that human exposure would be reduced. With the cancellation of aldrin/dieldrin and because of chlordane's substitutability for these cancelled products, the quantity used of chlordane was expected to increase sharply. In addition, a greater quantity and frequency of application of chlordane would be required to achieve the same level of pest control formerly achieved with aldrin/dieldrin.

Scientific evidence suggested that hazards to drinking water, human diet, wildlife and applicators and production workers may be posed by the production and use of chlordane (EPA, 1976a). Social costs in terms of fatalities or medical expenses of no action were difficult to quantify. Tolerance[14/] and acceptable daily intake (ADI)[15/] levels had been established. Also some research suggested that chlordane was overused (EPA, 1975). Chlordane's low price, easy availability and proven effectiveness had led to overuse that increased the trend toward pest resistance, killed nontarget organisms (especially beneficial parasites) and increased environmental hazards.

The benefits to agriculture of the use of chlordane were numerous. Its use was responsible for higher agricultural production yields, lower pest control costs, lower farm and consumer prices, and decreased crop and

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14/ The maximum level of a pesticide allowed in foods for human consumption. The level is set by EPA and enforced by FDA and USDA.

15/ The ADI is set by the Food and Agriculture Organization (FAO) and the World Health Organization of the United Nations.

structural damage. The important statistic was the difference in benefits attributed to chlordane in excess of the benefits associated with its closest substitute. It should be noted that chlordane use may have significant inequalities in the geographical distribution of benefits. Its greatest agricultural use was on corn and benefits were, therefore, concentrated in certain corn-producing regions.

The analysis of the environmental, social, and economic effects associated with the cancellation of all uses focused on the nature and extent of substitutes for chlordane in its many uses. Of particular interest was its uses on corn and for termite control. In the absence of chlordane (and heptachlor, aldrin, and dieldrin) what pest control products would be available for use on corn and termites and what effect would these alternative products have on the environment, society and economy?

In general, the substitutes[16/] would be less persistent, more mobile, and more acutely toxic. Short term risk to applicators, formulators and manufacturing workers would increase as a result of the probable greater acute toxicity of substitutes but the long term risk to the general population resulting from the lower persistence would decrease. Greater precaution with the handling of the more acute substitutes for chlordane should be required.[17/] The improved sophistication in handling acute pesticides should be achieved through the EPA sponsored program to train and certify applicators.

16/ Probable substitutes included: diazinon, carbaryl, carbofuran and toxaphene.

17/ Care in handling and proper protective clothing would be expected to minimize hazards. Such exposure is voluntary and manageable, as compared with persistant chemicals in the crop production ecosystem.

Chlordane is very immobile in the soil; the greater mobility of substitutes is mitigated by their decreased persistence. If chlordane/heptachlor were not cancelled for termite use, benefits gained from cancelling aldrin/dieldrin for that use would be lost. All four of these products would have to be removed from the market to achieve a significant decrease in hazards from this use. Even with the cancellation of the four chlorinated hydrocarbons, residues would persist. Residues in the diet and hazards to wildlife would decrease rapidly. Residues in the soil would decline in trace levels within 25 to 30 years; subterranean application would cause slower elimination of residues (EPA, 1976a). A further effect of the cancellation of use on corn is an increase in the corn acreage for which no pesticide is used. This increase would result both from a rise in corn acres with no pesticide use and a shift of corn acreage to crops not requiring pesticides. Therefore, the cancellation of chlordane for use on corn would cause a shift to less persistent pesticides and a decrease in the overall level of pesticide use.

Cancellation could have an impact on employment and income in the producing enterprise, Velsicol. Although the lost jobs and labor income would be replaced by new jobs and income in the enterprises which produce the substitutes, the imperfect mobility of labor would cause adjustment problems for the production workers laid off by Velsicol. In addition, substitutes may be relatively less available, more expensive, more difficult to use, and less effective. Because pesticides are a small part of the farm budget, price responsiveness may be low. Any of these relative disadvantages might induce the farmer to use his land for another purpose; consequently, some change in cropping patterns may result and may represent inefficient use of the land resource.

Several attempts have been made at estimating the economic impact of cancelling the use of a pesticide (Cashman, et al., 1980; Burton and Martin, 1980; Eichers, et al., 1975). These analyses gave estimates for the decline in corn acreage, increase in acreage for other grains, decrease in price of other grains, and increase in consumer and farm prices. Certain special situations were mentioned in the EPA report, including Florida citrus[18/] and strawberries. Concern was expressed but sufficient information to make a judgement on the impacts on these crops was not available.

The economic impact of cancellation on termite control is substantial. Substitutes (BHC, lindane, pentachlorophenol, creosite, and coal tar neutral oils) were considered less effective and short-lived (EPA, 1976b); BHC and lindane were the only other registered termite control products. The short life of substitutes would require more frequent application, thereby increasing the cost of termite control. Termite damage would probably increase. The termite control industry could benefit from cancellation through a rise in sales volume. In summary, cancellation of all uses would speed the decline in residue levels; cause an increase in the use of more acutely toxic, less persistent, more expensive, less effective pesticides; have difficultly-quantified economic effects on corn and termite control; decrease level of pesticide use.

The alternatives of cancelling all uses with exception of subterranean termite control and dipping of new food plants and of cancelling only food and feed crop uses were, in effect, combinations of the two alternatives already outlined. The exemption of subterranean termite control was justified by concerns over substitutes. Dipping of roots or taps of nonfood

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18/ There were no known substitutes to control Fuller's Rose Beatle on citrus.

plants is required by USDA for quarantine of nursery plants. This use involved small quantities of chlordane and did not represent a significant exposure problem. Cancellation of only food and feed crop uses would allow the continuance of usage for termite control, lawn and garden, household, and nonfood field crops.

The environmental Impact Statement summarized the criteria for recommending the cancellation of all uses except subterranean termite control and dipping of nonfood plants:

1. Beneficial
   a. Probable substantial reduction in long-term risk to human health and wildlife.
   b. Probable substantial reduction in economic and social loss due to long-term human health effects of clordane and heptachlor.
   c. Substantial reduction in environmental contamination.
   d. Avoidance of the economic impact in the area of termite control that would result from cancellation of that use.
2. Adverse
   a. Some possible long-term risk to human health and the environment due to a presumably slight, but not fully defined, hazard from continued use of chlordane and heptachlor for termite control.
   b. Some possible risk to human health and the environment from increased use of substitute pesticides which, while generally less persistent, may be more acutely toxic.
   c. Minor economic and social impact on a national scale, with moderate impact in a few sectors of agriculture and a few non-agricultural activities.
   d. Minor economic impact on the pesticides industry" (EPA, 1976b, pp. 36-37).

Two further aspects of this issue might be raised: time frame and reversibility. All of the benefits outlined above are both long term and short term; some of the adverse effects may be rectified over time. Disruptions of agricultural production would dissipate with the development and adoption of new pest control techniques and the adjustment in land allocation. Job and income losses should not be long term. The recommended alternative is in general reversible because cancelled

uses could be reinstated or exempted uses cancelled. Human health damage is not reversible but is expected to be minimal under this alternative. Irreversible impacts on wildlife are not expected.

Summary and Conclusions

Was regulation of agricultural chemicals adequate to protect public health in 1945? A short review of the history of pesticide regulation leading up to the introduction of DDT, chlordane, and the "new generation" of chemical insecticides indicates the convergence of several factors that resulted in the widespread use and determined defense of these products.[19/] Public sector institutions, agricultural producers, technical change, and the scientific community were all important participants in the historical evolution of pesticide regulation.

In the early 1900's several agricultural pesticide crises, particularly those involving the boll weevil, the gypsy moth, and lead arsenate, set the stage for the emergence of chemical insecticide as the most viable means of pest control and of public concern over their potential harm to public safety. The widespread use of persistent chemical pesticides, especially the chlorinated hydrocarbons, precipitated the need to evaluate environmental residues for potential harmful effects to man and the environment. New technology in measuring residues has greatly increased the ability to detect trace amounts of a chemical. Consequently, the wide-

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19/ For a more complete discussion of the history of pesticide regulation see: Upton Hatch, The Effects of EPA Regulation on R&D in the Pesticide Industry, University of Minnesota, Ph.D. Dissertation, 1982, pp.185-245.

spread use of chemical pesticides aroused public concerns and public involvement in the creation and implementation of environmental policy while technological change allowed the implementation of stricter regulatory policy. Regulation was not adequate in 1945 because the experience with use of persistent chemicals and the technology to monitor residues was not available; however, regulation in the 1970's became more strict. Thus, chlordane was developed during a period of lenient regulation and most of its uses were cancelled during a period of strict regulatory policy.

This case study has illustrated the adversarial proceedings in which the scientific evidence concerning human hazards of chlordane use was judged and has described the economic, social and environmental factors that were analyzed to determine the optimal regulatory policy alternative. The evaluation of the scientific basis for restrictive action and the various policy alternatives that were considered was greatly affected by the prior regulatory actions against DDT, aldrin, and dieldrin. The presentation of scientific data followed the precedent of non-cooperative proceedings set in these earlier regulatory activities.

Acifluorfen

Acifluorfen is the active ingredient of Blazer Herbicide, developed and produced by Rohm and Haas and used primarily on soybeans. Its post-emergent capabilities and its extremely rapid R&D time horizon are aspects of this pesticide product that makes it of particular interest to this inquiry into the effects of EPA regulation on R&D in the pesticide industry. In the previous case study, chlordane, the evolution of technology and regulation were briefly discussed. While chlordane is an older generation pesticide developed under the lenient regulatory regime of the 1940's and restricted under the stricter regulation of the 1970's, acifluorfen may be seen as a new generation pesticide whose development may be in some part attributed to the stricter regulatory regime under which it was developed and registered.

This case study clearly illustrates the relationship between regulatory policy and technology. Agricultural pest control strategies have centered around pesticide application in anticipation of pest infestation. In the case of soybean herbicides, the evolution of agricultural technology had tended to dictate the need for pre-emergent pesticide applications to destroy weed populations. As a part of its attempt to reduce environmental residues, EPA policy has attempted to induce a reduction in quantities of pesticides used. Acifluorfen's post-emergent capability fits this objective to the extent that it decreases dependence on anticipatory application. Regulatory policy's ability to alter the evolution of agricultural technology is demonstrated by the restrictive actions against chlordane and the registrations of acifluorfen, mefluidide, and Heliothis NPV.

The short time horizon of the project to develop and register Acifluorfen was a result of both EPA's inclination to register a post-emergent herbicide and Rohm and Haas' early realization of its potential market share. The firm's R&D management committed additional resources and started some testing phases early to take advantage of the product's expected high commercial ability. Consequently, the firm's early commitment to undertaking all possible tests that might be required by EPA and the latter's favorable predisposition to the product resulted in a short project time horizon that should be viewed as a minimum under the present regulatory regime.

Research, Development and Regulatory History

Synthesis and screening for Blazer Herbicide (code number RH-6201) and the many other compounds that were potential products was done in 1974. Both a random screening and the more directed synthesis approach were used in this effort to find a herbicide with activity against the important soybean weeds - morningglory, pigweed, and cocklebur - that did not also injure the soybean plant. Through the directed synthesis approach, Colin Swithenbank developed the chemical characteristic that led to the synthesis of acifluorfen. The primary screening phase involved several thousand compounds to determine activity; the most successful compounds were put through a secondary phase to continue the selective process. Both of these initial phases were completed in the greenhouse. The secondary phase has succeeded in narrowing the possibilities down to several hundred. Only a very small quantity of each compound is synthesized for the primary screening, usually 1/2 gram, while 100 grams of each compound selected is synthesized for the secondary

phase. Dosage rates and plant growth stages are varied and initial toxicology tests are completed to screen out compounds that are too hazardous.

Initial field testing was started in 1975 at the firm's facilities in Newton, Pennsylvania. It was clear to management, even at this early stage, that RH-6201 was special. Test results were so impressive in Pennsylvania that more tests were done in Arkansas that same season. During the field testing, soybean fields are infested with various weeds known to be a problem to soybean growers; the tests in another region allowed testing to be done on different species of weeds under different soil and climatic conditions. Of particular significance was acifluorfen's ability to demonstrate activity post-emergence without decreasing potential yield. Although some superficial damage to leaves was found the plant recovered quickly and yields were unaffected. Acifluorfen's specificity, activity at low dosages, and post-emergence capabilities were the important factors in management's decision to commit an inordinate level of resources to attempt to shorten the R&D and regulatory processes.

As a result of this decision the common procedure of a second year of field testing to confirm the earlier results was altered. The retesting stage was eliminated. Instead activities were set in motion to expedite commercialization. The synthesis of the active ingredient, acifluorfen, was increased for use in the expanded effort. Process development was undertaken to determine the optimal manufacturing process. Construction of a pilot plant facilitated the estimation of production costs and the required

capacity of a full scale plant. The appropriate formulation was also pursued. Long term tests were begun much earlier in the R&D process than usual, including residue, toxicology and environmental chemistry.

Before the scale of testing is widened a patent is sought. Acifluorfen's patent protection commenced in 1976 and will be in effect for 17 years. The short R&D time necessary to register Blazer's herbicide in affect extended the time of patent protection over the average product. Because the patent is applied for and legally binding before a product is actually marketed commercially, the effective time of the patent protection is reduced by the time period between the issuance of the patent[20/] and commercialization.

Testing was broadened to many soybean growing areas in the U.S. and worldwide and to other crops.[21/] Confidence in the potential market success of Blazer continued with the demonstration of its broad spectrum of activity, especially against important soybean weeds such as morning-glory and pigweed, its ability to control some grasses, and its residual as well as contact activity.

An experimental use permit (EUP) was applied for on January 12, 1977. The EUP is necessary to expand testing to include commercial farmland. Innovative farmers were sought to provide a demonstration of Blazer's

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20/ A "patent restoration" bill is presently under consideration in Congress that would allow the patent protection to start when the product is registered.

21/ Registration was actively pursued for use on rice and peanuts. The peanut registration was approved in December, 1981 and the rice registration was approved in August, 1982.

ability to control important weeds in soybeans without harming yield potential. In this phase testing is extended to understand any problems farmers participating in the EUP program may have had with the new product. Although the EUP program cannot commence in the U.S. until EPA has granted approval, similar activities can be undertaken in the less stringent climates of many foreign countries, particularly less developed countries. Particular attention was placed on experimentation under actual field conditions in Latin America where the cultivation of soybeans is growing rapidly. Rohm and Haas was not only able to continue the R&D process, while the EUP was under consideration for eventual registration in the United States, but was also taking aggressive action to assure a larger market share of the increasingly important Latin American soybean herbicide market. Argentina, Paraguay, Ecuador, and Bolivia quickly gave permission to sell the new product in time for the winter season of 1977-1978.

The EUP request was granted on November 1, 1977; along with this decision, a temporary tolerance was established. The EUP is granted either on a one or two year basis. With EPA's acceptance, full scale field testing by actual farmers and university researchers could be undertaken. In addition Brazil, Colombia and Uruguay registered Blazer Herbicide in 1978. Armed with the test results that indicated acifluorfen's safety under reasonable precautions and its efficiency against a broad spectrum of weeds and some grasses inadequately controlled by existing products, Rohm and Haas applied for full registration on December 1, 1978.

Testing did not stop with the submission for registration. In fact, in 1979, Blazer was given further opportunity to demonstrate its efficacy in

six states through emergency exemption requests. Use of Blazer was requested against morningglory in Delaware, Maryland and Virginia; against hemp sesbania in Louisiania and Texas; and against hemp sesbania and showy crotalaria in Mississippi. Also Mexico accepted Blazer on a provisional basis until full registration was received in the U.S. Full registration was received on April 10, 1980.

Product Characteristics and Use Recommendations

Acifluorfen is a broad spectrum, post-emergence soybean herbicide. It controls weeds principally through a contact mode of action and is formulated as a liquid concentrate in which surfactant[22/] is added. Actively growing weeds in early growth stages are the most susceptible to Blazer. Adherence to recommended dosage rates (Figure 2) is essential for optimal control. Even at the recommended dosage soybeans may exhibit some response (burn, crinkle or bronze); however, new growth is unaffected and yield potential is not reduced.

Blazer Herbicide is formulated with 2 pounds of active ingredient per gallon and 20 gallons of water per gallon of product per acre is generally recommended as a minimum. Because it may pose eye or dermal hazards, certin precautions in handling are required, especially the use of goggles.

22/ "Factors involved in the selection of a (surfactant) include the homogeneity of concentrate, storage stability of concentrate or powder, corrosion factors on storage or packaging of a concentrate, the ease of mixing in water, effect of water hardness on emulsion stability or dispersion, and use end cost of ingredients," (Farm Chemicals Handbook, 1980, 1981, p. D293).

Figure 2. Blazer Herbicide 25 Weed Control and Use Rate Table.

Weed		2.0 Pints/Acre Leaf Stage (maximum)[1]
AMARANTH, PALMER	Amaranthus palmeri	6
AMARANTH, SPINY	Amaranthus spinosus	6
BALLOONVINE	Cardiospermum halicacabum	4
BUR CHERKIN	Cucumis angùria	4
CARPETWEED	Mollugo verticillata	multi 8" diameter
CITRON (WILD WATERMELON)	Citrulius vulgaris	4
COCKLEBUR, COMMON	Xanthium pensylvanicum	4
COPPERLEAF, HOPHORNBEAM	Acalypha ostryaefolia	4
COPPERLEAF, VIRGINIA	Acalypha virginica	4
CROTALARIA, SHOWY	Crotalaria spectabilis	
CROTON, TROPIC	Croton glandulosus	2
CROTON, WOOLLY	Croton capitatus	2
CUCUMBER, SPINY	Cucumis dipsaceus	4
FLORIDA PUSLEY	Richardia scabra	2
GALINSOGA, SMALLFLOWER	Galinsoga parviflora	4
GROUNDCHERRY, CUTLEAF	Physalis angulata	4
GROUNDCHERRY, LANCELEAF	Physalis landeifolia	4
INDIGO, HAIRY	Indigofera hirsuta	3
JIMSONWEED	Datura stramonium	8
LADYSTHUMB	Polygonum persicaria	4
MORNIGHGLORY		
CYPRESVINE	Ipomoea quamoclit	4
ENTIRELEAF	Ipomoea hederacea var. integriuscula	3
IVYLEAF	Ipomoea hederacea var.hederacea	3
PURPLE MOONFLOWER	Ipomoea muricata	4
SCARLET	Ipomoea coccinea	4
SMALLFLOWER	Jacquemontia tamnifolia	4
SMALL WHITE (PITTED)	Ipomoea lacunosa	4
TALL (COMMON)	Ipomoea purpurea	3
WILLOWLEAF (PALMLEAF)	Ipomoea wrightii	4
MUSTARD, WILD	Brassica kaber	6
NIGHTSHADE, BLACK	Solanum nigrum	4
PIGWEED, REDROOT	Amaranthus retroflexus	6
PIGWEED, SMOOTH	Amaranthus hybridus	6
PURSLANE, COMMON	Portulaca oleracea	multi 8" diameter
RAGWEED, COMMON	Ambrosia artemisiifolia	6
RAGWEED, GIANT	Ambrosia trifida	4
SESBANIA, HEMP	Sesbania exaltata	
SMARWEED, PENNSYLVANIA	Polygonum pensylvanicum	4
SMELLMELON	Cucumis melo	4
SPURGE, PROSTRATE	Euphorbia supina	multi 2" diameter
TEXAS GOURD	Cucurbita texana	3

Figure 2 (Continued). Blazer 25 Weed Control and Use Rate Table

Weed		1.5 Pints/Acre Leaf Stage (maximum)[2]
AMARANTH, PALMER	Amaranthus palmeri	4
CARPETWEED	Mollugo verticillata	multi 6" diameter
JIMSONWEED	Datura stramonium	6
MORNINGGLORY		
PURPLE MOONFLOWER	Ipomoea muricata	4
SMALL WHITE (PITTED)	Ipomoea lacunosa	4
MUSTARD, WILD	Brassica kaber	4
PIGWEED, REDROOT	Amaranthus retroflexus	4
PIGWEED, SMOOTH	Amaranthus hybridus	4
PURSLANE, COMMON	Portulaca oleracea	multi 6" diameter
RAGWEED, COMMON	Ambrosia artemisiifolia	4

[1] Do not count leaves as pairs...count each leaf separately. Do not count cotyledon leaves. Spraying weeds in the cotyledon growth stage is not recommended.

Source: Rohm and Haas, "Blazer Herbicide", Research Report, January, 1980.

Also, all application equipment should be thoroughly cleaned to avoid potential corrosive damage. The label provides information on medical treatment and environmental hazards. Directions concerning storage and disposal to avoid drift or contamination, particularly of water, are given; these cautions are routinely displayed on the labels of chemical pesticides. Hollow cone or flat fan sprayers calibrated to apply at least 20 gallons per acre at a pressure of 40 to 60 psi are recommended to provide high gallonage and pressure to achieve the necessary contact with weeds.

It should be emphasized that any circumstances that put weeds under stress are not conducive to optimal control with Blazer Herbicide; the weeds should be young and actively growing. Cultivation before or during application will not achieve optimal results; however, cultivation 7 days after application may actually improve performance. Also, temperature, rainfall and other pest problems all complicate the effective use of Blazer Herbicide through the ability to cause stress to the soybean crop. If the maximum daily temperature does not exceed 70°F some degree of crop injury may result and preclude the timely use of acifluorfen. Drought conditions place the crop in stress and rainfall 6 hours after application may reduce response. In addition, any injury caused by recent application of other pesticides or resulting from disease or insects has the potential of increasing the response of the soybeans to the herbicide, i.e., decreasing yield.

In addition to avoidance of application during stress, adequate coverage of weed population is essential because of Blazer Herbicide's contact mode of action. Thorough coverage may not result if the soybean crop has

exceeded the third leaf stage because the crop may interfere with the spray pattern. Optimal control of weeds is achieved in the early growth stages approximately 14 to 21 days after planting.

Summary and Conclusions

Acifluorfen was developed and registered in minimum time because its post-emergent capabilities both convinced Rohm and Haas' management of its potential market success and also fit EPA's general objective of decreasing pesticide use through the reduction of anticipatory applications. The firm was willing to undertake all possible tests to meet EPA requirements because of the size of the expected market. It appeared to the management of Rohm and Haas to be the type of new product that EPA policy makers wanted to see developed. The use of acifluorfen in pest control strategies could be viewed as another step toward EPA's attempt to slow the increasing dependence of U.S. agriculture on chemical pesticides.

Fluoridamid - Mefluidide

This case study involves the efforts of a highly research oriented firm to diversify into the pesticide market with an innovative new pest control product.[23/] The effective, working relationship that developed between 3M officials and EPA officials illustrates the improved effectiveness in the registration process that can be achieved when a less adversarial strategy is undertaken. The fluoridamid - mefluidide case history involves not only the introduction of a new pesticide but the entry of a new firm into the small group of basic agricultural chemicals producers who actively pursue innovative pest control through aggressive R&D investments.

The basic research that led to the agricultural chemical effort at 3M was initiated in the Central Research Laboratory. In the period 1963-1969, 3M scientists explored new chemical possibilities including fluorochemical derivatives for possible biological activity. Pharmaceutical and agricultural chemical research was pursued jointly because of certain similarities in chemical and biological processes in plants and animals. In 1970 3M acquired a drug company, Riker, and in 1973 the agricultural chemical research was moved from the Central Research Laboratory to the Commercial Chemical Divison. Thus, the agricultural chemical effort at 3M was begun as an attempt to take advantage of the basic chemical knowledge of fluorochemicals and pharmaceuticals research.

23/ Because fluoridamid and mefluidide are close chemical analogs and because only mefluidide was eventually marketed, the R&D effort to develop these two chemicals should be viewed as a single R&D project.

The decision to pursue research and development in the agrichemical area involved both scientific and marketing considerations. In the past 3M's research policy has encouraged scientists to diversify into different areas. Scientists saw the opportunity to apply basic research in the application to biological activity in agrichemical products. Research teams were established in the weed, insect and plant disease control areas. Chemists and biologists were assembled to develop new agrichemical product possibilities. Knowledge obtained in other 3M research and in the drug research effort was used in the agrichemical effort. Chemists pursued candidates for biological activity.

Table 1 shows some of the candidates that were synthesized and screened and the product label decision. The first column gives the general description of the product; the middle columns give some indication of the considerations in pursuing a product label. The last column indicates the ultimate decision on these product candidates. The second column classifies each candidate on its uniqueness. Because 3M was a new entry to the agrichemical industry, it did not want to enter the market with a "me-too" product. It was felt that 3M's major strength was its ability to apply its research activities to diverse market opportunities; consequently, some degree of uniqueness was considered essential. The third column shows the relative performance of each candidate in research testing. The fourth column provides 3M's preliminary estimation of market potential. Possible toxicity problems are indicated in column five. The economic considerations shown in column six include manufacturing costs, yield improvements, and rate of application. The

Table 1. Product Candidates Discovered and Product Label Decision.

Product	Unique	Performance	Market Potential	Acute Toxicity Problem 1/	Economic Considerations	Patent	Decision
Herbicide (Broad Spectrum)	Yes	?	?	No	+	Yes	Drop
Herbicide (Nutsedge Control)	Yes	+	+	No	+?	Yes	Develop
Plant Growth Regulator	Yes	+	?	No	?	Yes	Develop
Foliar Fungicide	No	No Advantage	?	No	+	Yes	Drop
Soil Fungicide	Yes	+	?	No	-	Yes	Drop
Nematicide	No	+	?	Yes	-	Yes	Drop
Bacteriocide	Yes	+	?	?	-	Yes	Drop

Source: Tom Fridinger, Laboratory Manager, 3M Corporation, 1979.

1) By definition, in the early stages of R & D, possible chronic toxicity can not be known.

seventh column demonstrates that 3M considered only products for which it had the patent.

Until 1970 pharmaceutical and agrichemical R & D were pursued jointly in the Central Research Laboratory; in that year 3M purchased a pharmaceutical enterprise. The agrichemical R & D remained as a "team" in the Central Research Laboratory. The Commercial Chemical Division was formed in 1973; the agrichemical effort thus became a "project" in a newly-formed division. Resources and personnel were added to develop and register agricultural chemical products. These new resources were applied to:

1) field development,
2) formulations,
3) process development,
4) analytical, metabolic, and residue testing, and
5) regulatory.

The management of 3M demonstrated the importance it placed on the regulatory process by hiring personnel with special training in regulatory science. 3M's "newness" to the agrichemical industry gave it an opportunity to avoid the adversarial relationships that were created between producers and EPA, when restrictive actions were taken against existing products by EPA. 3M had no products to defend against possible cancellation of uses; consequently, it was able to nurture a cooperative relationship by submitting thorough registration packages and judiciously selecting when to fight EPA regulatory policies. A new entrant into the industry will not necessarily achieve success through its "newness" alone; expertise in assembling an effective registration package is an essential element of success. Research efforts have focused on the herbicide and plant growth regulator areas. This concentration in relatively new areas of R&D was presumably the result

of 3M's desire to avoid the development of "me-too" products. The aggressive, innovative research effort combined with the cooperative relationship with EPA and the effectiveness of testing package submittals has provided the ingredients for a potentially successful entry into the agrichemical industry.

The first 3M registration of a new agrichemical was achieved in 1975 when Sustar PGR received full registration as a plant growth regulator for turf. The R&D effort was complemented with marketing, sales, distribution, and production efforts.

Research, Development and Regulatory History

Sustar PGR (fluoridamid) was first synthesized in 1967. From first synthesis until application for the experimental use permit (EUP), initial testing was undertaken to determine structure vs. activity relationships (SAR). Small plot field testing on turf was conducted and toxicological and environmental testing was initiated. An EUP was applied for in November, 1971, "for use on certain grasses for growth retardation and seedhead suppression on highway right of ways, golf courses, industrial sites and cemeteries." The EUP was granted in March, 1972, for a one year period, limited to certain states, and prescribing a limit of 730 gallons of the product. In January, 1973, 3M applied for an expansion and extension of the EUP program; a greater quantity - 4,000 gallons - was requested and use was expanded to include "non-bearing orchards, parks, recreational areas and residential lawns involving multiple applications and wider dosage range." The extension was approved in April, 1973 but the one year extension was to begin in March. Consequently, there was a short period in which some uncertainty existed as to whether the EUP would be extended and the resultant managerial indecision, expecially during the spring season, had the potential to cause planning problems. The tradename,

Sustar PGR, was registered in December, 1973. An additional extension until November, 1974, was requested by 3M to allow testing for the entire season. EPA approved a six month extension through September, 1974.

Application for full registration was submitted in May, 1973. Efficacy, residue, metabolism, toxicity and environmental data supported the application; no tolerance petition was necessary since this was a non-food use. During the course of the registration review process, numerous telephone calls and letters by 3M to determine the status of the submittal received no written response. Eventually, it was determined that EPA would not make any comments until the review was completed. It was learned in January, 1974 that the Sustar PGR review was "on hold" over the resolution of noncrop persistence criteria. An internal EPA debate was causing delay and uncertainty for 3M R&D planning decisions. EPA was unsure itself of the testing requirements necessary to demonstrate nonpersistence for nonfood crops: the development of Sustar PGR was being impeded but more importantly the Embark PGR project was also threatened. However, the eventual resolution of the issue assisted in the development of Embark PGR. In April, 3M was notified by phone that several problems had arisen, in particular, insufficient efficacy data and inadequate testing of environmental dissipation; in May, a formal letter was sent by EPA to list and explain the reasons Sustar PGR had not received registration. The letter also indicated that EPA felt that registration package was poorly organized and needed a good summary. In September, a revised registration package was resubmitted by 3M and the last additional requested test - a bioaccumulation study for channel catfish was completed and sent to EPA in October. Informal approval was received in February with the proviso that identification was needed for the major photodegradation products in water.

The relationship between the reviewer and the product manager was found to be an important element in the registration review process. This relationship enhanced the firm's ability to estimate the possibility of additional required tests and the date of registration. These estimates are the prime concerns of the firm's regulatory personnel. Marketing and production decisions can be greatly facilitated if these two issues can be predicted. The personal contact between industry and EPA and the former's understanding of the interrelationships involved in the review process and coordinated by the registration division are essential elements in developing reliable predictions of tests required and registration date.

3M's attention had shifted to Embark PGR; consequently, effort to develop Sustar PGR was not pursued and the additional test proviso became relatively unimportant. Despite the management decision to develop Embark PGR instead of Sustar PGR, 3M felt its corporate responsibility was to submit the photo alteration and teratongenicity studies in order to consummate the condition for registration of Sustar PGR. 3M felt there was scientific validity in certain of EPA's requests for data; consequently, some of the studies were submitted to support the continued registration of Sustar PGR. However, 3M felt certain other studies indicated by EPA as "data gaps" should not be required - in particular, the studies typically requested only for food uses. Accordingly, 3M argued against certain long-term studies for non-food use. The issue was finally closed in June, 1978, when 3M submitted the test results and EPA accepted the results.

3M places great value in the maintenance of its good rapport with EPA. 3M made a commitment to this good relationship in 1974 by hiring a regulatory scientist, trained specifically in the dealings between private industry and government regulators. This change was particularly apparent

in the comparison of the first Sustar PGR and the Embark PGR registration packages. The former was "poorly organized and lacked a good summary;" in fact, the problem lay in 3M's lack of experience in submitting for pesticide registration. Because of 3M's previous regulatory experience in the pharmaceutical area it was not surprising that the first Sustar PGR submittal was organized similar to a new drug application (NDA). Although this format is acceptable to the Food and Drug Administration (FDA) for the registration of new pharmaceutical products there is one important difference between drugs and pesticides that demands a significantly different format. Drugs are usually developed for a specific use; pesticides are generally developed for the most important uses and, over time, use is extended where possible. Consequently, the registration package for a pesticide must be organized in such a way as to facilitate the review of the particular segments of testing to accomodate periodic expansion of new uses. Different testing areas (e.g., efficacy, wildlife, and toxicity) were submitted under separate cover and summaries of each testing area were provided to facilitate the reviewer's ability to shift back and forth between the different areas to check relevant tests for the additional use. The importance of the different format was appreciated by the regulatory scientist and, in turn, the reviewer and product manager.

Mefluidide (Embark PGR and Vistar Herbicide) was pursued over fluoridamid (Sustar PGR) principally because mefluidide was demonstrated more active and economical to apply on turf, and has a broader spectrum. Less chemical per acre is required for mefluidide; depending on the grass species, it is 8 to 16 times more active than fluoridamid. Later, mefluidide demonstrated plant growth regulator and herbicidal activity in soybeans and sugarcane. There was no evidence that Sustar had potential as a commerical herbicide.

Embark PGR (mefluidide) was first synthesized in 1971. Much of its early development stages were proceeding, with a one to two year lag, in concert with the Sustar PGR (fluoridamid) effort. Early field testing and development and toxicology and residue analysis were undertaken in the 1972-1974 period; testing was expanded with the EUP program in 1975-1976. The two new products were pursued even though 3M management had decided that only one would eventually be produced and marketed. Even before Sustar PGR received full registration the decision in favor of Embark PGR had been made. It was felt that the task of registration of Sustar PGR should be nonetheless completed, especially because of the close chemical similarity of the two products.

In October, 1976 efforts were made to develop a registration package for Embark PGR. Application for full registration of Embark PGR was submitted in November, following the regulatory requirements as specified in 40 CFR 162.1 - .12, including sample product, label draft, "Offer to Pay Statement," "Confidential Statement of Formula," "Label Technical Data," "Application for New Pesticide Product Registration," and cover letter. Sample product was sent to the USDA Beltsville Laboratory, including 2 grams of the 100% purity analytical standard and 20 grams of the technical product of 93% purity. A label draft was submitted containing the reason for issue: "to provide label text proposing the registration of product for use on turfgrasses and broadleaf vegetation to regulate growth and suppress seedhead formation." An "Offer to Pay Statement" was contained in the registration package offering to conpensate for any additional data "used in support of the registration application for the subject pesticide". The "Confidential Statement of Formula" provided the components of the commercial product. The "Label Technical Data" summarized the general characteristics of the new product: application

sites - turf, outdoor (residential, commercial) and outdoor (non-agricultural); pest type - not applicable; mode of action - growth regulator; user type - unspecified general use, homeowner use, and commercial applicator use; Formulation - soluble concentrate. Data concerning product chemistry, environmental chemistry, efficacy, phytotoxicity, human safety, and fish and wildlife safety were submitted in the "Application for New Pesticide Product Registration." A cover letter was attached to summarize the data. Since the common name of mefluidide was not approved by the American National Standards Institute (ANSI) until later in November this information was not included in the registration package and a short delay and exchange of correspondence resulted. EPA chemistry review section also questionned the composition of technical mefluidide because of the technical Embark PGR down to the level of 0.1%. EPA stated that "only 94% - 96.2% of the composition is accounted for. You must name every compound down to 0.1%. They must add to 100%." It was agreed that if more testing was needed to achieve the improved accountability, analytical work could be completed while the rest of the package was reviewed. Except for the late common name approval and the lack of total accountability, the Embark PGR package was well received. At this time, 3M was sent the official notice of "Received" by EPA. In December, 3M submitted an improved accounting of impurities and the notice of the submittal of Embark PGR was made in the Federal Register. In February, an EUP on soybeans and a temporary tolerance were submitted (in support of the eventual Vistar Herbicide registration). A revised disclaimer statement was required that was more suitable to an EUP program[24/] and several label revision, not requiring additional studies, were also re-

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24/ The disclaimer on a registered product usually absolves the company of all liability associated with uncontrolled use, i.e. not in acordance with the label. However, in an EUP program it is assumed that the compnay has a much greater degree of control over the use of the experimental product.

quired. Minor label changes were also made indicating no animal grazing and caution against drift.[25/]

The toxicology and efficacy review was completed in March. Additional required tests included a mutagenicity study, subacute dermal and skin sensitization tests, and phytotoxicity, discoloration and reseeding interval tests. The subacute dermal and skin sensitization tests were requested because the product would be used as a spray. The improved accounting of concomitants was completed and submitted by 3M in March and officially accepted in May. 3M regulatory personnel and EPA efficacy staff reviewers met to discuss areas of concern, especially discoloration of turf. EPA asserted the importance of check plots, statistical analysis, weather conditions at treatment time, and effects of weather stress (drought). 3M pursued coloration ratings from different geographical regions.

The need for subacute dermal and skin sensitization tests were dropped in April because the product will be applied only once a season by professional applicators. The guidelines for registration specify such tests nonetheless for expanded uses but did not feel the tests should be required for the registration of Embark PGR. The questions raised by EPA in March are addressed in an additional submission by 3M in June. The results of the mutagenicity study were reported and the phytotoxicity and efficacy issues were answered. A complete registration package was resubmitted with the revised label and improved efficacy and toxicological testing in which 3M discoloration tests satisfied EPA's initial concern.

[25/] These were relatively routine cautions that were not an indication of a problem associated with the use of Embark® PGR.

EPA discovered in July an industry wide concern regarding significant deficiencies in the quality of research completed at Industrial Biotest Laboratory (IBT) and recalled all IBT tests submitted in registration packages to EPA. Each company relying on IBT testing was required to audit and validate their studies. 3M had contracted IBT for several studies.

3M learned in August that environmental chemistry review had a large backlog because of the reregistration process. It was probable that this review of Embark PGR might be significantly delayed because of the higher priority placed on reregistration of existing products. 3M's concerns over the delay were heard and the review continued and was eventually completed in November.

In January, 1978 EPA required analysis of the product formulation for nitrosamines. As a result of the toxicological review EPA indicated in the "Notice of Registration" that as a condition of registration the mouse study must be reviewed by two independent laboratories. It was later determined that the formulation did not contain nitrosamine at the specified level of sensitivity and in August, this review accepted the mouse study reviews by independent laboratories.

Vistar Herbicide has the same active ingredient, mefluidide, as Embark PGR but is marketed as a soybean herbicide and needed additional testing because it is a food use. As discussed previously, mefluidide was pursued over fluoridamid, in part, because of its herbicidal activity. Registration, production, and marketing of Vistar Herbicide was the culmination of that earlier decision.

The registration package for Vistar Herbicide similar to the one submitted for Sustar PGR and Embark PGR was first submitted in December, 1978.

In addition, a petition for the establishment of a tolerance of 0.01 ppm for mefluidide in or on soybeans was submitted. Formal notice of the receipt of the package was made by EPA to 3M in January, 1979 and 3M submitted the $10,000 fee required for the tolerance petition. Also in January, the Federal Register announced the 3M request for registration and establishment of tolerance for Vistar Herbicide. Radiometric data were submitted in May indicating no residues in rotational crops of analytical sensitivity of 0.01 ppm. A multigeneration rat study, a lifetime carcinogenicity mouse study, and a 2-year rat feeding study all conducted by the International Research & Development Corporation (IRDC) were also sent to EPA. A revised data package was submitted including "promised" mouse and chronic rat studies. The "Offer to Pay Statement" used the cite-all method of compensation because there were no other producers who might have relevant data. Time was saved from listing of all data. The residue chemistry review was delayed by turnover in EPA personnel. An addendum to the two year rat feeding study by IRDC was submitted in December.

With the review complete in February, EPA notified 3M of the need for additional testing. The reviewers asserted that a definitive no effect level had not been demonstrated in the two year rat feeding study. 3M responded quickly and thoroughly. The results of the rebuttal was the elimination of the demylenation and subacute dermal studies and the agreement to complete a longer term dog study and to conduct a 1 - year rat feeding study for the sole purpose of measuring animal weight gain and loss. Further delay was caused in part by a turnover in EPA personnel, specifically the toxicological reviewer. In response to this delay 3M stressed the importance of a timely registration in order to plan for the upcoming season.

When it appeared that the registration would not be forthcoming four states submitted an emergency petition (18) requesting the use of 100,000 gallons of Vistar - EPA assured 3M that review could be completed by May. 3M responded to EPA's points of rejection and through negotiations agreed to undertake the following studies as part of the terms for conditional registration: 1-year rat feeding, 6-month dog, and rat teratology studies. Both EPA and 3M preferred a full registration as a means of marketing the product as compared to a state controlled Section 18 marketing program.

The official "Notice of Registration" was received in April with the agreement that the three tests will be completed and adherence to the following statement:

> "You will submit and/or cite all data required for registration/ reregistration of your product under FIFRA Section 3 (C) (5), when the Agency requires all registrants of similar products to submit such data" 26/

The petition was submitted on April 29 and approved by EPA on May 2. The Federal Register announcement of the establishment of a tolerance on soybeans at 0.01 pp. appeared in April.

Since the original registration approval and tolerance setting for Vistar Herbicide, several amended registrations for Embark PGR and Vistar Herbicide have been submitted and accepted. In general the amendments are additional uses or changes in the rate of application. For an amendment, only the "Application for Amended Pesticide Product Registration" is submitted with previous and additional testing relevant to the changes. The entire package of tests, the "Offer to Pay," the "Label Technical Data" and the "Confidential Statement of Formula" are not necessary for the label amendement application.

In February 3M applied for the addition of red fescue and chewings fescue species, a recommendation of 2, 4-D tank mix, a reduction in the rate of application to one pint/acre on specified turfgrass species, and increased gallonage. These label changes were accepted in May. Further amendments were submitted in December, 1979 to increase the species of plants for which Embark PGR was registered, to change the application rate for certain species, and to specify season-long seedhead suppression of cool season grasses. EPA reviewed and accepted the amendments within two weeks pending the receipt of a final label. In this case, 3M caused the delay. The final label was sent on March 27, 1980 and approved April 8, 1980. More minor amendments were submitted in February, 1981. For subsequent amendments to the Embark PGR label only efficacy data was relied upon to support these uses. Because of the waiver of efficacy data required for submissions these registrations were expeditiously approved.

Product Characteristics

Sustar is a plant growth regulator whose active ingredient, fluoridamid, has demonstrated activity on many grasses, broadleaf plants, trees, and ornamentals (Figure 3). Suppression of foliar growth and interruption of reproductive process have resulted. It is formulated as a water solution

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26/ This statement is required of all conditional registrants.

Figure 3. Species that Have Responded to Applications of Fluoridamid

Grasses

Good to Excellent Supression	Fair to Good Supression
Kentucky bluegrasses	Bermudagrass
Tall fescue	Common
St. Augustinegrass	Hybrid, some
Smooth bromegrass	varieties
Timothy	Orchardgrass
Reed canarygrass	Zoysiagrass

Inconsistent Supression	Possible Injury
Bahiagrass	Bentgrass
Dallisgrass	Ryegrass
Quackgrass	

Trees and Ornamentals

Ligustrum	Green Ash
Burford Holly	Sycamore
Oleander	London Plane Tree
Purpleleaf	Silver Maple
Honeysuckle	Hybrid Poplar
Dwarf Yaupon	Honeylocust
Algerian Ivy	Groundsel-tree
Ice Plant	Cotoneaster
Boxwood	

SOURCE: Minnesota Mining and Manufacturing, "Sustar 2-S Plant Growth Regulator", technical data bulletin, 1976

containing the equivalent of 2 pounds of pure active ingredient per gallon; in addition, it is stable when protected from sunlight. Sustar is capable of corroding metals over prolonged periods of contact. Consequently it is recommended that all application equipment be rinsed immediately after use with amonia and water. Toxicological testing results are summarized in Figure 4.

Sustar retards grass growth and suppression of seedhead formation (as described in Figure 2), suppresses growth of clover and dandelion, and reduces mowing requirements for ornamental turf. The latter use is especially important for highway right-of-way, golf courses, industrial sites, and cemeteries. Traffic or slope can make maintenance of highway right-of-ways difficult, expensive, and hazardous. Mowing can be difficult in golf course roughs and fairways. In heavily obstructed areas on industrial sites Sustar can greatly facilitate turf maintenance.

Sustar should be applied only to healthy actively growing turf. To achieve uniformity in growth patterns an accurately calibrated sprayer is essential. Recommended rate of application is 1.5 to 2.0 gallons with 40 to 80 gallons of water per acre. Growth and seedhead suppression generally lasts four weeks. Application is not recommended until after the first mowing and the desired height and color is obtained. Sustar is registered for one application per year. Several cautions are mentioned on the Sustar label (Figure 4) including: avoidance of use on golf greens, newly seeded areas and newly mowed to heights less than one inch; slight discoloration might be evident for short periods even at recommended use rates; avoidance of contact with certain ornamentals whose growth, flowering and fruit may be negatively affected. The label also states that Sustar is not registered for grazing.

Figure 4. Acute Toxicology of Fluoridamid

Test	Species	Route	Technical	Sustar 2-S
LD_{50}	Rat (female)	Oral	2580 mg/kg	
LD_{50}	Rat (male)	Oral		9230 mg/kg
LD_{50}	Mouse	Oral		9700 mg/kg
LD_{50}	Rabbit	dermal	>4000 mg/kg	>8000 mg/kg
Primary Skin Irritation	Rabbit			non-irritating
Eye Irritation	Rabbit			non-irritating
LD_{50}	Mallard Duck	Oral		>10,000 mg/kg
LD_{50}	Bobwhite Quail	Oral		>10,000 mg/kg
LD_{50}	Pheasant	Oral		8250 mg/kg
LC_{50}	Channel Catfish			5365 ppm
LC_{50}	Bluegill			4469 ppm
LC_{50}	Rainbow Trout			8180 ppm

SOURCE: Minnesota Mining and Manufacturing, "Sustar 2-S Plant Growth Regulator", technical data bulletin, 1976.

There is no evidence that drift will harm vegetation; however, direct spraying of adjacent areas may retard growth. Tank mixes with Dicamba, MCPA, and 2,4-D has shown satisfactory results. Questions persist concerning the optimal rate of application for additional sprayings (although it is presently only registered for one).

Foliar application to trees and woody ornamentals has demonstrated growth suppression ability. As in the case of turf, application should not be undertaken until the plant has reached its desired size. New growth can be injured. Recommended rate of application is one to ten ounces per gallon of water. Hawaiian sugarcane increases its sugar content when treated with Sustar. Two gallons per acre are applied 6 to 8 weeks before harvest.

Mefluidide and fluoridamid are highly related chemically; consequently, much of the information discussed in the previous section will be, to varying degrees, relevant also in the case of Embark (mefluidide) and Vistar (mefluidide). Embark is also a plant growth regulator that has demonstrated activity on grasses, broadleaf plants and trees, ornamentals, and brush (Figure 5). Mefluidide shows promise for the following uses: "grass growth regulation and seedhead suppression, tree and ornamental plant growth regulation, weed control and suppression, sucrose enhancement in sugarcane and other crops, increased quality of forage crops, increased yields of grain crops, and control of tobacco suckers" (Technical Data Bulletin, 1980). Embark is formulated as a diethanolamine salt containing 2 lbs. of mefluidide per gallon. The recommended application rate is one to four pints per acre diluted in 15-150 gallons of water. The higher range is generally necessary in southern and dry regions. Spring application should be restricted to actively growing turf several days before or after mowing. Fall applica-

Figure 5. Species that Have Responded to Applications of Mefluidide

Grasses

Barley, Common
Barley, Foxtail
Barley, Little
Barley, Wild
Barnyardgrass
Bentgrass, Creeping
Bermudagrass
Bluegrass, Annual
Bluegrass, Kentucky
Brome, Downy
Brome, Red
Brome, Ripgut
Brome, Smooth
Canarygrass, Reed
Centipede, Common
Crabgrass, Smooth
Fescue, Foxtail
Fescue, Red
Fescue, Tall
Foxtail, Giant
Foxtail, Green
Foxtail, Yellow
Goosegrass
Johnsongrass
Kikuyugrass
Lovegrass, Orcutt
Orchardgrass
Quackgrass
Ryegrass, Common
Ryegrass, Italian
Ryegrass, Perennial
Shattercane
St. Augustinegrass
Timothy
Wild Oats
Nutsedge, Purple
Nutsedge, Yellow

Broadleaf Plants

Alfalfa, Common
Cheeseweed (Little mallow)
Clover
Clover, Sour (annual yellow sweetclover)
Fiddleneck, Coast
Filaree, Redstem
Iceplant
Ivy, Algerian
London Rocket
Mustards'
Nightshade, Hairy
Pineappleweed
Radish, Wild
Shepherd's Purse
Vetch, Common

Volunteer Crops

Corn
Oats

Figure 5. Species that Have Responded to Applications of Mefluidide (cont'd)

Trees, ornamentals and brush

Abelia	Maple
Apple	Oak, Live
Azalea	Oleander
Camellia	Osmanthus
Elder	Peach
Ginkgo	Pear
Grape	Pecan
Holly	Plum
Honeysuckle	Prune
Juniper	Pyracantha
Ligustrum	Willow
Locust	

SOURCE: Minnesota Mining and Manufacturing; "Mefluidide (Formerly MBR 12325) Experimental Plant Growth Regulator/Herbicide", technical data bulletin, April, 1980.

tion will retard growth and seedhead formation the next spring. Also, spraying should not be repeated in less than a six week period. Tank mixing with 2,4-D or MCPP is recommended. Uniformity of application is essential; rainfall or irrigation within 8 hours may decrease the effectiveness. Root growth has been stimulated by Embark.

Foliar application to trees, ornamentals, and brush has demonstrated growth regulation. Embark should be applied in bands around the stem or trunk of the plant using 0.5 to 4.0 ounces per gallon of water. With application 8-12 weeks before harvest, Embark has shown the ability to increase sucrose content in sugarcane. Improved quality in certain pasture grasses, especially fescue, has been demonstrated; the measure of quality was a decrease in non-digestible cellulose and an increase in sugar and protein. Greater weight gain of cattle on treated plots has resulted. Further possibilities for quality improvement are silage corn, sorghum, bluegrass, bermudagrass, and alfalfa. Increased yields on wheat have also been recorded.

Certain limitations, cautions, and recommendations are presented on the Embark label. Applications should be limited to 4 months after seeding and 2 weeks before reseeding. Turf can be mowed one day before or 3 to 7 days after application. Animals should not graze on treated areas and drift onto other areas should not be allowed. Toxicology testing results are presented in Figure 6.

Vistar contains the same active ingredient, mefluidide, as Embark. Consequently, the toxicology testing (Figure 4.6) and many of the cautions are the same; however, Vistar is marketed as a herbicide. As noted in the earlier section on the regulatory histories of these products, Vistar's use on soybeans requires the establishment of a tolerance. More extensive

Figure 6. Toxicology of Mefluidide

Test	Species	Route	Technical	Mefluidide 2-S
LD_{50}	Mouse	Oral	1920 mg/kg	
LD_{50}	Rat	Oral	>4000 mg/kg	>5000 mg/kg
LD_{50}	Dog	Oral	Emesis at 500 and 2000 mg/kg	
LD_{50}	Rabbit	Dermal	>4000 mg/kg	>20,000 mg/kg
LC_{50}	Rat	Inhalation		>8.5 mg/L air
Primary Skin Irritation	Rabbit	Dermal -		
		Intact Skin	Nonirritating	Nonirritating
		Abraded Skin	Nonirritating	Nonirritating
Eye Irritation	Rabbit	Ocular	Minimal Irritation	Minimal irritation
Teratology	Rabbit	Oral	Nonteratogenic	
Mutagenicity	*Salmonella typhimurium*		Nonmutagenic	
Subchronic	Rat	Oral	NOEL*=6000ppm	
Subchronic	Dog	Oral	NOEL*=1000ppm	
LD_{50}	Mallard Duck	Oral	>4640mg/kg	
LC_{50}	Mallard Duck	Oral	>10,000ppm	
LC_{50}	Bobwhite Quail	Oral	>10,000ppm	
LC50	Rainbow Trout	Water	>100 ppm	>1000 ppm
LC_{50}	Bluegill Sunfish	Water	>100 ppm	>1000 ppm

*NOEL = No observable effect level.

SOURCE: Minnesota Mining and Manufacturing; "Mefluidide (Formerly MBR 12325) Experimental Plant Growth Regulator/Herbicide", technical data bulletin, April, 1980.

testing, especially chronic, was necessary to gain registration and the tolerance for this food use.

Vistar is a postemergence herbicide used to control seedling and rhizome johnsongrass. A non-ionic surfactant is recommended to achieve optimal results. Control of johnsongrass is accomplished by growth retardation which decreases competition between the soybean and the weed. Ten days may elapse before these effects are evident. For ground application 10-40 gallons of water should be mixed per acre and for aerial application the gallonages can be reduced to 5-10 gallons per acre. First spraying should be made when the soybeans are actively growing and full coverage of weeds less than 15 inches tall. If the soybean canopy is able to shade the weed foliage a second application will probably not be necessary; however, if needed, a second spraying should be made 3-4 weeks after the first and no less than 60 days before harvest. Temporary superficial effects on the soybeans may occur and optimal results will not be obtained if rainfall occurs within 8 hours following application. Animals should not be grazed on treated areas and rotation with another crop must allow at least 4 months. Synergistic effects on hemp sesbania and red rice have been demonstrated with tank mixes of mefluidide and bentazon. Mefluidide has a growth retarding effect while "traditional" herbicides use a burn effect to control weeds. It has been found that the combination of these two modes of action achieves excellent results, especially when mefluidide is applied first and given a short time to take effect.

Summary and Conclusions

The fluoridamid-mefluidide case history provides evidence of the learning process in pesticides R&D in several ways. The development

and registration of mefluidide was greatly aided by 3M's experience with fluoridamid. In addition, the link between basic research and applied is illustrated by the exploitation of basic research knowledge developed in 3M central research laboratory through the foundation of an agricultural chemicals project and development of a new pesticide. The learning process is also demonstrated by 3M's ability to adapt to the regulatory regime and develop EPA confidence in its registration submittals.

Resource mobility in pesticide R&D is indicated by the movement of basic research output into a new applied R&D enterprise. This mobility will tend to increase industry responsiveness to EPA policy. Industry may respond by moving into the pesticide market as in the case of 3M or by moving out of pesticide activities. Within these two extremes, greater resource mobility will result in the greater ability of firms to adjust their levels of investment in pesticide R&D to changes in the regulatory regime.

The manner in which regulatory activities were pursued by 3M indicates the possibility of improved efficiency in the regulation process. A less adversarial relationship between the regulated and the regulator will improve the the effectiveness of the regulatory regime.

Heliothis NPV

Research and Development History

The development of a viral pesticide was originated in a USDA laboratory (Ignoffo, 1965), pursued for commercialization by several firms, and is presently produced under the trademark, Elcar, by Sandoz. Introduction of this innovative pest control technique represents a significant step in the development of biological pesticides. The notion that pathogens might be employed for pest control was first suggested by Bassi in 1835 and viral pesticides were first studied in the 1940's (Balch and Bird, 1944; Steinhaus and Thompson, 1949). In the late 1950's applied research was conducted on cotton, tobacco, and corn (Coaker, 1958; Chamberlain and Dutky, 1958; Tanada and Reiner, 1962). The *Heliothis* virus was first isolated in 1961 on cotton (Ignoffo, 1965). Early development and pilot plant effort was completed in the late 1960's (Ignoffo, 1968; Greer *et al*. 1971; Ignoffo, 1973) and two companies, International Minerals and Chemical Corporation (IMC) and Nutrilite Products, Inc., pursued commercialization. IMC sold its experimental program to Sandoz in 1973 and Nutrilite obtained limited commercial success under its tradename, Biotrol VHZ, and terminated production in 1980. At this time Sandoz is the sole producer of a commercial viral pesticide. Figure 7 presents an outline of the development of Elcar, Figure 8 provides a list of some potential useses of a *Heliothis* viral insecticide, and Table 2 gives estimates of losses and control costs associated with *Heliothis* on selected crops.

The production of a viral pesticide is complicated by certain properties of viruses. Especially relevant to the chances of commercialization

Figure 7. Chronology of Development of Elcar

1961	isolation of Heliothis virus
1966	experimental use permit (EUP) temporary exemption from tolerance on cotton
1971	IMC petitions EPA for full registration under tradename Viron H (registration denied)[1]
1973 (May)	permanent exemption from tolerance on cotton
1973	Sandoz acquires product development rights from IMC
1974	Sandoz develops and produces viral pesticide
1975 (June)	Sandoz resubmits for full registration
1975 (Dec.)	EPA approval
1976-77	streamlining of production process
1979 (June)	production plant opened in Wasco, California

[1]Registration was denied due to certain safety considerations and the virus' inability to equal the effectiveness of a chemical insecticide under heavy infestations (Ignoffo and Couch, 1981).

Figure 8. Some Economic Plants Attacked by Species of Heliothis

Field Crops		
Cotton	Oats	Sunflower
Corn	Sunflower	
Flax	Sorghum	
Millet	Soybean	
Vegetables		
Asparagus	Lettuce	Pepper
Beans	Melangana	Squash
Carrot	Okra	Tomato
Cole plants	Onion	
Cucumber	Peas	
Fruits		
Apple	Gooseberry	
Citrus	Strawberry	
Miscellaneous		
Hemp	Pines	Tobacco
Peppermint	Poppy	

SOURCE: Ignoffo, C. M., "Development of a Viral Insecticide: Concept to Commercialization," Experimental Parasitology, Vol. 33, No. 2, April, 1973.

Table 2. Estimated Losses and Costs for Control of *Heliothis* sp. Attacking Various Crops in the United States (1965)[1]

Crop	Acreage (millions)	Estimated % loss	Control Cost (millions $)
Cotton	9.5	9.2	38.0
Sweet corn	0.6	13.8	7.8
Tobacco	0.8	5.0	4.4
Tomato	0.5	8.1	1.8
Lettuce	0.2	2.3	0.4
Soybean	36.6	2.5	0.1
Sorghum	15.9	4.1	0.1

[1]The acreage figures can be updated but the losses and cost figures cannot. These data are provided to give an indication of the losses associated with *Heliothis* species.

SOURCE: United States Department of Agriculture, "Losses in Agriculture," USDA Handbook 291, Washington, D.C., 1965; United States Department of Agriculture, "Crop Production," annual summary, Washington, D.C., 1965.

is the need to produce the virus in living cells, in vivo.

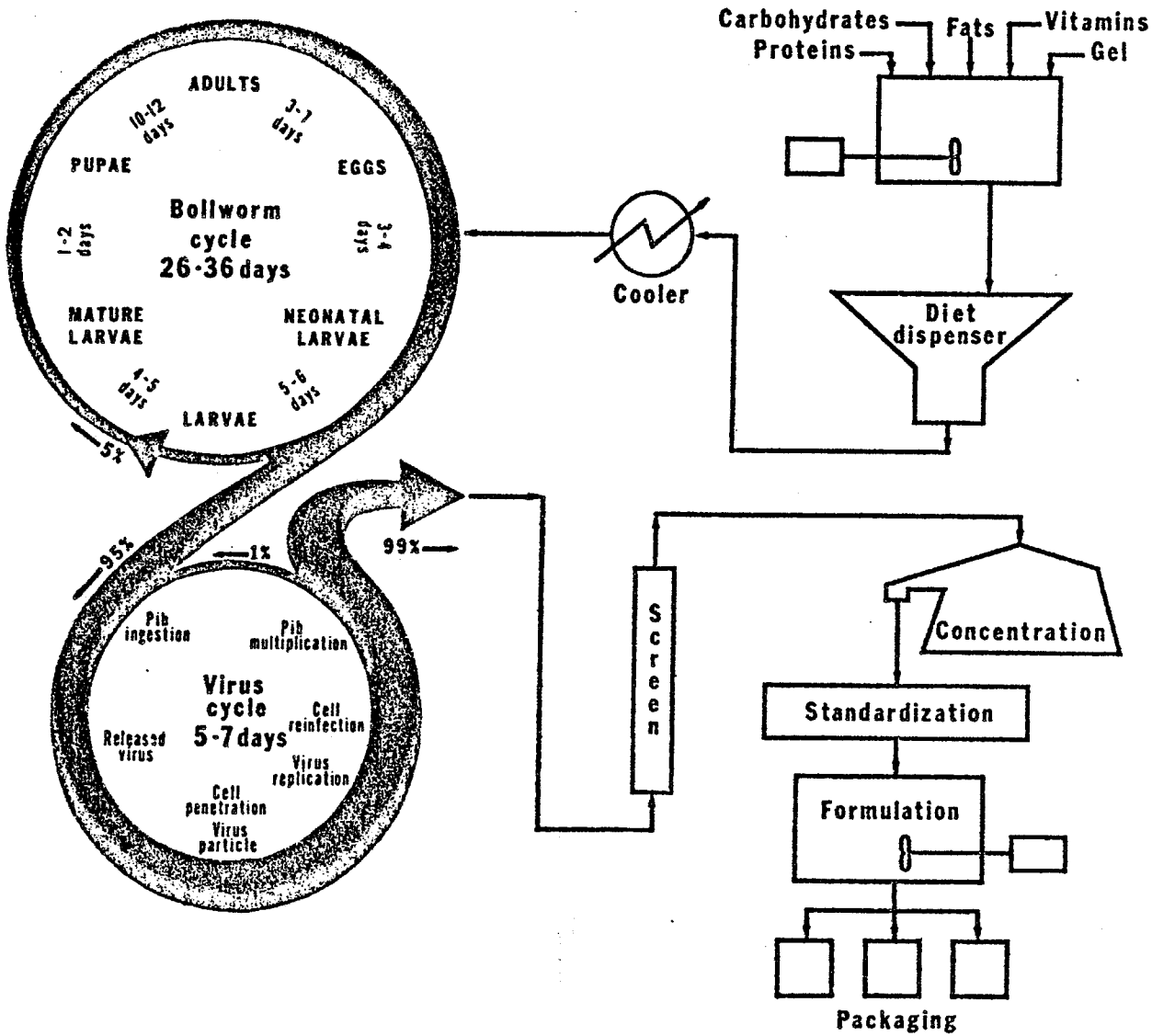
> "A semisynthetic diet containing essential nutrients and vitamins is prepared as a liquid. A gelling agent such as agar or gelcarin is added to solidify the liquid diet. Prior to gelling the liquid diet is dispensed into suitable containers. Newly hatched caterpillars or eggs are individually placed in each container. The new caterpillars are incubated at a constant temperature (30±1C) for 5-7 days. Approximately 95% of all larvae produced are used for propagation of the virus. The other 5% is used to perpetuate the culture to provide additional larvae for virus production. Larvae for virus production are fed on the diet surface -- contaminated with virus for 6-8 days (26±1C). During this period the virus replicates within the caterpillars and produces 5,000-10,000 times more virus than that originally used. An individual caterpillar can produce as much as 36 billion inclusion bodies, which is ca. 30% of the dry weight of a mature caterpillar.
>
> Virus-killed caterpillars are collected, triturated, screened, and processed into a dry or wet technical product. This preparation, standardized as to activity and purity, formulated with various additives to increase stability and efficacy, is then packaged for sale." (Ignoffo, 1973, pp. 392-3)

The production process is summarized in Figure 9. All virus production is descended from the original isolate of 100 diseased bollworm larvae on cotton in 1961. Virus was annually produced from a standardized sample to maintain a consistent product activity. Diet for rearing the bollworms was blended in 2 oz. containers. After 5 to 6 days, the larvae are exposed to virus so as to obtain mortality in the last instar;[27/] 6-8 additional days are required to kill the larvae.

Labor requirements for the pilot production of the viral pesticide were six persons: four for bollworm production and two for propagation of the virus. Labor accounted for 70% of total cost with a unit cost of $.07 per larva (Ignoffo, 1973). Estimates of various production levels (laboratory, pilot, and commercial plant) and unit costs are presented in Table 3.

[27/] An instar is an insect development stage.

Figure 9. Schematic of Viral Pesticide Production Process



SOURCE: Frances Greer, Carlo M. Ignoffo, and Ralph F. Anderson,"The First Viral Pesticide: A Case History," Chemtech, June, 1971.

Table 3. Estimated Production Levels and Costs of Producing Heliothis NPV in Bollworm Larvae

Production phase	Production level (10^3 larvae/ month)	Estimated cost per larva (¢)
Laboratory	54	7.0
Pilot-plant	1000	4.8
Commercial plant	4200	< 2.0

SOURCE: Ignoffo, C. M., "Development of a Viral Insecticide: Concept to Commercialization," Experimental Parasitology, Vol. 33, No. 2, April, 1973.

With the completion of the early development phase by government research groups in 1965, three companies -- Hayes-Sammons, IMC, and Nutrilite -- showed interest in commercializing a viral pesticide under the trademark Virex for sale only in Texas but problems with viral contamination of the stock culture of insects caused the firm to discontinue production. IMC and Nutrilite invested in a long term R & D program to develop viral products. Production techniques were largely borrowed from food industry processes. Small condiments containers were used to incubate the larvae. Large trays of 2 oz. containers were sealed with plastic and stored in controlled environment rooms. Hundreds of these trays could be stacked on mobile racks. The most important constraint on production was infesting each container with the newly hatched larva (Ignoffo, 1973). Pilot plant production was about 1 million larvae per month and the unit cost from the laboratory phase was reduced by 46% (Table 2). Early field testing demonstrated the viral pesticide's ability to increase average yield relative to the check but generally was not as effective or consistent as chemical insecticides when used against heavy population of the bollworm-budworm complex (Table 4).

Development efforts during the pilot phase were directed not only at streamlining the production process but also at demonstrating safety and efficacy. Laboratory data on production, safety, and efficacy were supplemented by data obtained in greenhouse and field testing. Formulation and process development efforts were aimed at developing a production technique and marketable product for large scale production and sale. Relationships receiving the greatest attention included: compatability with pesticides, phytotoxicity, and effects of temperature, light, water, rain, relative humidity, and pH on virus stability (Ignoffo, 1973).

Table 4. Average Yield and Range of Average Yields for 1969 Field Tests Conducted in Alabama, Arkansas, California, Mississippi, North Carolina, and Texas

Formulations[a]	No. tests[b]	Yield (kg) seed cotton/acre	
		Average	Range
Virus	7	852.6	261-1488
Virus + carbon	5	925.2	440-1449
Virus + IMC90001	7	971.6	445-1628
Standard insecticide	5	989.3	497-1656
Check	7	747.8	178-1271

[a]All tests conducted using Viron/H at 40 LE/acre or 240×10^9 PIB/acre.

[b]Number of field tests in which specific formulation was used.

SOURCE: Ignoffo, C. M., Bradley, J. R., Jr., Gilliland, F. R., Jr., Harris, F. A., Falcon, L. A., Larson, L. V., McGarr, R. L., Sikorowski, P. W., Watson, T. F., and Yearian, W. C. "Field Studies on Stability of the Heliothis nucleopolyhedrosis virus at various sites throughout the cotton belt," Environmental Entomology, pp. 388-390, 1972.

Viron/H and Biotrol were sold on a limited basis while further refinements of the production process and reductions in unit costs were pursued. A large scale plant was constructed by Sandoz in Wasco, California and opened in June, 1979.

Product Characteristics

Elcar is a selective biological insecticide against Heliothis species insects. It is formulated as a wettable powder registered for use on cotton against tobacco budworm (Heliothis virescens) and cotton bollworm (Heliothis zea). Its specificity allows effective control of the target pest without harmful effects ot humans, wildlife, and beneficial insects. Target insects have not developed resistance in laboratory tests involving more than 25 generations.[28/] (Ignoffo and Allen, 1972). The active ingredient is a nuclear-polyhedrosis virus (NPV) and is referred to as Heliothis NPV or Baculovirus heliothis. Heliothis NPV is morphologically and biologically dissimilar from vertebrate and plant virses (Sandoz, 1978); this characteristic tends to infer that human and plant susceptibility to the virus or a mutation will not be a problem. Six species of Heliothis have demonstrated susceptibility -- H. zea, H. virescens, H. armigera, H. phloxiphaga, H. punctigera, and H. obtectus. Only H. zea and H. virescens are economic pests in the United States. H. armigera and H. punctigera are important pests in Europe, Australia and Asia.

28/ Twenty-five generations is approximately 12 years.

Elcar's mode of action requires ingestion by the target pest. When the active ingredient, Polyhedral Inclusion Bodies (PIB), enters the stomach of the insect, infectious bodies called virions are released. The diseased larva reduces its eating pattern and dies. Only insects at late stages of larval development (fourth or fifth instars) have a reasonable chance of surviving the infection; surviving insects will nonetheless be diseased and experience reduced eating habits. Death of young larvae generally requires 3 days and death of older larvae occurs after 4 to 5 days.

Oral, inhalation, and subcutaneous toxicity tests on the purified active ingredient and the technical formulation containing 20% active ingredient demonstrated neither toxic nor pathogenic effects in rats, dogs, or monkeys (Ignoffo, 1975). Testing for skin irritation also indicated no effect. Fish, avian, apian, and plant toxicity were investigated in the environmental toxicology phase. No adverse effects were shown in fish, avian, and apian tests. Economic plants demonstrating no phytotoxicity or pathogenicity when administered Elcar at the recommended rate (2-4 ounces per acre) include: bean, corn, cotton, kidney bean, peanuts, radish, snapbean, sorghum, soybean, tobacco, and tomato. "Based on the results of the toxicological investigations, the United States Environmental Protection Agency has officially granted, in 1976, an exemption from the requirement of a tolerance for residues in or on cotton." (Sandoz, 1978, p. 5).

Light to moderate infestations can be controlled by the use of Elcar applied by the individual farmer. Most efficient use is achieved

under the direction of a pest management consultant and Elcar is well suited for integrated pest management (IPM) programs. Elcar should be applied when eggs or newly hatched worms are detected. Spraying should be continued at 3-7 day intervals until no eggs are present. The recommended quantity (2-4 ounces per acre) should be diluted and continuously agitated (before use) in 2-20 gallons of water and applied with a properly calibrated air or ground sprayer. Elcar does not require any special equipment or handling. It is essential, however, to attain thorough, even coverage. Spraying programs should commence early in the season to facilitate the increase of target pest predators and beneficial populations. As long as infestation stays at low to moderate levels, this strategy can reduce the use and cost of chemical applications. Spray mixture should be used within 12 hours and the reuse of old containers and storage at temperatures exceeding $80^{o}F$ are not recommended. Much of the above information is given on the product label.

Elcar can be used in combination with most other products and adjuvants. Sandoz markets its specially developed adjuvant, Gustol, that increases the rate of insect ingestion of Elcar. Recommended minimum acreage for Elcar use is 40 acres; the larger the area treated, the greater the effect of beneficials. Testing has demonstrated the stability of Elcar, showing no loss of potency under varying field temperatures; however, it is recommended that under field conditions it be stored in a cool, dry place and not exposed to direct sunlight and for prolonged storage it should be kept under $50^{o}F$.

Elcar's regulatory history has been influenced by its innovative nature and its classification as a biorational pesticide.[29/] Until recently, registration officials were wary of such new concepts as viral pesticides because they didn't feel they knew enough about them; however, registration officials are now encouraging the development and registration of biologicals as an alterantive to the highly toxic traditional chemicals. Registration of traditional chemicals has become more difficult during the 1970's and some products, particularly the organochlorines, have faced either cancellation of registration or restricted registration. Biologicals are seen by some regulatory officials as a nontoxic alternative to traditional chemicals for some uses.

The new guidelines (Subpart M) under consideration for registration of biologicals center around a tier system. If a product passes the first tier (all 15 currently registered biorationals would pass the first tier), no further testing is required (see Appendix A). If, however, it fails the first tier it is required to complete a second tier of testing. This system should help reduce uncertainty caused by not being sure what tests will be required. The status of biological control agents is summarized in Figure 10.

29/ Biorational pesticides are all nontraditional chemical pesticides. Biorationals can be further subdivided into microbials, pheromones, and juvenile hormones. Bacteria and viruses are subsets of microbials. Juvenile hormones are actually chemicals but their mode of action differentiates them from traditional chemicals. Pheromones have generally not been used as insecticides, their primary use has been to survey insect populations.

Figure 10. Status of Biological Control Agents

Pesticide	Use Pattern	Registration Status
Bacillus thuringiensis -- B.t.	Lepidopterous larvae on several crops	Registered 1962
Altosid (Juvenile hormone analog)	Larvae of flies and mosquitoes	Registered 1972
Virus of H. zea (corn earworm nuclear polyhedral virus) -- Elcar	Heliothis species on cotton	Registered 1975
Virus of tussock moth larvae.	Forest use	Registered 1977
Bacillus popilliae	Japanese bettle grubs in lawns	Registered 1975
Bacillus popilliae	Japanese bettle grubs in pastures	Petitioned 1975
Virus of Gypsy moth larvae	Forest use-hardwoods	Registered 1978
Gossyplure (Pheromone)	Pink bollworm in cotton	Registered 1978
Colleotrichum gloeodiosporidoes (mold)	Weed control in rice	EUP (experimental use permit)
Nosema locustea (Protozoan)	Grasshoppers in rangeland	Registered 1980
Hirsutella thompsonii (mold)	Mites on citrus	Registered 1981
Phytophthora citropthora (mold)	Milkweed vine in citrus	Registered 1981
Nomuraea rileyi	Lepidopterous larvae on row, pasture and truck crops	EUP application
Bacillus sphaericus	Mosquito larvae	Field research
Virus of Autographa californica	Broad spectrum against Lepidopterous larvae	Field research
Virus of Sawfly larvae	Forest use	Field research
Agrobacterium radiobacter	Crown gall	Registered 1979
Disparlure (Pheromone)	Gypsy month in forests	EUP
Multilure (Pheromone)	Pine bark beetle in forests	EUP

SOURCE: United States Department of Agriculture, "IR-4 Project Status Report 1979," Washington, D.C., 1979.

The R & D costs associated with biologicals are significantly less than traditional chemicals because they are nontoxic and because regulation has shifted in favor of biologicals. If Elcar had been registered using the current revised tier system for an evaluation of safety, the cost for safety tests would represent less than 5% of the total cost of obtaining registration (Ignoffo, 1980). Testing requirements for biologicals have lessened since the development of Elcar. Precedents for testing have been established; the number of tests required has been reduced. The recent development of biological products aimed at the gypsy and tussock moths was accomplished with no long term residue or toxicity testing. Consequently, it is much easier now to register microbials than it was during the period in which Elcar received registration (Dec. 1975).

Filing costs for an exemption from establishing a tolerance are $10,000 for the first crop and $2,000 for each additional crop, unless a product receives a "blanket exemption." If such a waiver from the tolerance requirement is granted, the basic producer can pursue use of his product on any crop without paying the filing fee. The precedent for "blanket exemptions" has been in cases identified as the "public good." Several biologicals, including B.t., have received this waiver because of the public priority to reduce toxic chemicals in the environment. Elcar has recently received this exemption. The requirement of efficacy data can be waived under the 1978 revisions. Efficacy data is only required with health related pests (e.g. fleas and cockroaches). The producer will keep efficacy data on file but the data is not subject ro review. Label amendments can be easily gained. Three to five years should be sufficient time to

develop a candidate microbial if it does not have any problems related to safety (Ignoffo, 1980). A major stumbling block for early microbials was the development of protocols for testing; however, this problem should be solved by the new tier system. Previously, researchers had to develop their own protocol. Traditional chemicals have established protocols but scientific ability to measure toxicity is increasing (always chasing zero). The cost of safety data is usually dependent upon the length of the study, not what is done to the animal.

Process, formulation, or use patents provide protection for the biological innovator. Elcar is presently produced under a process patent. Based on the restrictive regulatory environment existing at that time, the management of IMC decided not to conduct R & D on any agricultural pesticides, either chemical or biological. Sandoz research concentrated on achieving consistent field results. Sandoz management is concerned about competitors' ability to enter the market, especially if new uses on such major crops such as soybeans, sorghum, corn and tomatoes are demonstrably effective. With the blanket exemption, effort on other uses is imminent. An advantage of the waiver is the ability to sell the crop produced under the experimental conditions. Farmers will be more likely to try Elcar.

Because of Elcar's specificity no protective equipment is needed for field applicators. At present there is no evidence to suggest that mutations might occur that might endanger other species or cause resistance. It is impossible to prove mutation of harmful effects will not occur but testing has shown that resistance will occur faster with chemicals. In experiments

to breed resistance, chemical pesticides developed resistance after 8 generations while no resistance was found after 25 generations with the B. heliothis (Ignoffo and Allen, 1972). Also, pests resistant to one chemical will be more resistant to a similar chemical, however, this relationship has not been found with microbials. Because biologicals tend to experience less pest resistance their anticipated product life should be greater.

Mammalian viruses are more specific than insect viruses. Insect tissue cell cultures might accept mammalian viruses, the implication being that more concern is placed on the possibility of production workers contaminating the insect virus than the potential harm insect viruses could cause to mammals. This issue is relevant in the effort to produce a virus in vitro (culture) as opposed to the current techniques, in vivo (living organism). The in vitro process cannot compete economically at present. The in vitro production process may be easily contaminated because the potential contaminant need only penetrate the cell; however, in the in vivo process, the virus would have to be ingested by the insect and passed from the insect's digestive system into a particular susceptible cell to be a contaminant. Consequently safety testing might be more vigouous for in vitro produced than for in vivo produced viral pesticides.

In response to possible public concern over the introduction of viruses into the environment, it should be noted that a higher concentration of virus may exist in the environment after a natural epidemic than with the application of a viral pesticide. Viral pesticides are aimed at the insect in the early stages of its development, under such

circumstances, death of the target insect can be achieved at rather low concentrations. In a naturally occurring epidemic the virus must be more concentrated to kill a particular insect.

Concentration is not important for viruses, one particle or 1000 particles may successfully infect an organism. Consequently, with a virus there is no issue of some level of negligible effect as with traditional chemicals. Viruses are capable of producing more of their own, but chemicals are not. The quantity of artifically used viruses, under consideration as microbials, is no greater than the level of viruses found naturally in the environment (Ignoffo, 1968).

Production technology is sufficiently flexible to produce different viruses in the same pilot plant. Thus the same capital investment can be applied to the production of different viruses with small modifications of the basic plant. The pilot plant for Heliothis was built on a modular basis to achieve greater production flexibility.

Heliothis has an ample shelf life, no refrigeration is necessary, but it should be kept dry. It has a half-life of less than three days -- this is true of 90% of all microbials without additional formulations. The half-life increases to 5-7 days with the proper formulation. The issue of short UV-light stability of viruses may be an overstated problem because most insects' feeding occurs within 24 hours of application. As long as field application achieves complete coverage of the plant, the applied virus should be effective. Optimal application techniques for coverage and timing are continually being researched (Smith, et al., 1979). Presently viral

pesticides are applied in the same way as traditional chemicals, but such techniques are probably not best suited for biologicals. Preliminary results indicate that smaller droplets and high plant hit will cause slower evaporation and thereby greater efficacy (Smith, et al., 1977, 1978, 1979). Researchers must always keep in mind not only what achieves optimal coverage but also what will be accepted by farmers. The biggest problem is how to apply and use viruses more effectively -- the solution may involve covering every leaf. It is essential to be aware of the different crop situations in terms of the way the insect attacks the crop. The feeding behavior of insects on different crops determines the optimal pest control techniques.

A possible application strategy might involve the early prophylactic use of Heliothis and then remedial use of chemicals later in the growing season. If the virus is unsuccessful chemicals can be used. This strategy should decrease the amount of chemicals applied. Costs could be reduced by reducing the frequency of pesticide application. Heliothis does not kill beneficial insects. For use on cotton, insect leaf eating does not hurt yield, principally because the insect is attacked before the boll forms. The most damaging stages are the third to fifth instar when the insect is mature enough to fight off the effects of virus and may be able to damage the plant before dying. There is no reason to spray chemicals before a dangerous population level is reached because chemicals not only

kill target pest but also beneficial insects. Strategies must be developed to introduce and augment beneficial insect populations and watch thresholds of economic damage. For soybeans, most often the threshold is never reached; unfortunately, many farmers spray anyway (Thomas, et al., 1974). Many extension advisers do not recommend pest control at all on soybeans except for every 5-6 years.

Elcar kills slower than chemicals -- the label says for suppression, not control. It has little control in the fourth instar,[30/] is slower acting (5 days), and achieves 50-60% control. Its primary advantage is its specificity, beneficial insects are not reduced. If some Heliothis are spotted in the field a farmer has three alternatives: wait (and his risks increase), use chemicals (and be locked into regular spraying program for rest of season), or use Elcar early in season (and potentially decrease pest control costs). Small losses early will not necessarily hurt yield. Heliothis is important early in the season. Where low chemical pressure exists, Elcar might be sufficient for the entire season. Also, if pest control costs have declined, the farmer can afford some low level of yield loss. Elcar requires farmer education because it should be used early in a preventive way (maybe even before seeing insects) and because of the long term benefits that accrue from its use (build up of beneficials). Elcar is more effective against H. zea (mainly found in the southeastern U.S.) and equally effective against H. virescens (mainly found in the western U.S.).

Because of possible UV degradation problems, spraying is recommended in early morning or late afternoon. There is the need to cover foilage to

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[30/] The fourth instar is a late stage of larval development.

reach insect feeding. Even if the insect does not die, it will reduce feeding and not reach the moth stage (reproductive stage).

Elcar's slow acting mode of action can be a source of confusion for interpretation of research results and for farmer determination of the success of an application of Elcar. Because of a latent incubation period, determined in part by the size of the larvae, virus concentration, and temperature, the insect virus disease may not be detected until 24 hours before the death of the larvae. Consequently, 3-4 days may be required for the symptoms to become apparent. Researchers and farmers may get misleading performance information if the proper time is not allowed. (Merrit, et al.,1980)

Many small plot experiments have been undertaken (Ignoffo and Couch, 1981). The effect of beneficial insect populations will be underestimated in small plot testing; however, such experiments do give an indication of the activity of the active ingredient against the target pest. In addition, the small plot testing was conducted with varying insect populations, including heavy infestations and was continued throughout the season. In contrast, Elcar is recommended for low to moderate infestations (2000-8000 worms per acre) and principally for early season use to avoid or eliminate the need for chemical insecticides later. Table 5 demonstrates the performance of Elcar against an untreated check and a chemical insecticide. It showed a 25 percent yield improvement over the untreated check but indicated a 17 percent decrease in yield from the chemical standard. These results support the recommendation of using Elcar principally in the early season against low to moderate infestations. Tables 6 and 7 indicates the viral pesticide's ability to equal the effectiveness of the standard insecticide under light to moderate infestations and its inability to achieve this equality under heavy infestations. Table 8 indicates that Elcar used

Table 5. General Performance of Elcar Used Full Season in 14 Small Plot Trials (1975-1978)

	Standard (%)	Elcar (%)	Check[1] (%)
Square damage	7	11	15
Boll damage	5	7	16
Yield (lb. seed cotton/acre)	1516	1250	996

[1]All means are significantly different (P 0.05)

SOURCE: Eric L. Ummel and Thomas O. Blythe, "Elcar: Biological Insecticide for Heliothis spp. Control in Cotton," Proceedings of Cotton Council, St. Louis, 1980.

Table 6. Efficacy Ratios for Yields of Cotton from Virus Treatment to the Untreated Check for 22 Heavy and 16 Light to Moderate Infestations of Heliothis spp. from 1963-1967

Dose/0.4 ha	Infestation Level[1]	
(X 10^{10} PIB)	Light to moderate	Heavy
6	1.06	1.77
60	1.24	2.17
600	1.34	2.26

[1]Criteria: Untreated checks for heavy levels averaged < 453.6 kg. of seed-cotton/0.4 ha; and for moderate to light > 453.6 kg.

SOURCE: Ignoffo, C. M. and T. L. Couch, "The Nucleopolyhedrosis Virus of Heliothis Species: A Microbial Insecticide," Microbial Control of Pest and Plant Diseases 1970-1980, H. D. Burges (ed.), Academic Press, 1981.

Table 7. Efficacy Ratio of Virus Treatment for Yields of Cotton and Different Levels of Infestation of Heliothis spp., 1960 to 1978

	Ratio virus: untreated check[1]			Ratio virus: insecticide[1]		
Dose/0.4 ha x 10^{10} PIB	Heavy	Moderate	Light	Heavy	Moderate	Light
6	1.77(3)	----	----	0.89(4)	1.08(4)	----
12	----	----	1.07(5)	----	----	0.97(15)
24	2.08(35)	1.68(6)	1.03(15)	0.90(15)	1.12(24)	0.91(17)
30	----	----	1.17(4)	----	1.16(4)	1.10(8)
48	----	----	1.12(8)	0.98(3)	0.85(4)	0.95(8)
60	2.37(38)	1.27(9)	1.18(9)	0.96(30)	0.83(4)	0.94(10)
600	2.26(5)	----	----	1.14(2)	----	----
Mean	2.22	1.48	1.11	0.97	1.01	0.97

[1]Mean yield for untreated checks for heavy infestations < 453.6 kg. seed-cotton/0.4 ha; for light, > 680.4 kg. Figures in parantheses are the numbers of comparisons.

SOURCE: Ignoffo, C. M. and T. L. Couch, "The Nucleopolyhedrosis Virus of Heliothis Species: A Microbial Insecticide," Microbial Control of Pest and Plant Diseases 1970-1980, H. D. Burges (ed.), Academic Press, 1981.

Table 8. General Performance of the Combination Elcar + Chlordimeform in Small Plot Trials (1975-1977) Full Season, 17 Trials

	Elcar 2 oz.	Elcar + Chlordimeform 1-2 oz. + .125 - .25	Std.[1] n
% square damage	8	6	6
% boll damage	6	3	4
Yield (lb. seed cotton/acre)	1433	1663	1631

[1]Means followed by the same letter are not significantly different (P 0.05)

SOURCE: Eric L. Ummel and Thomas O. Blythe, "Elcar: Biological Insecticide for Heliothis spp. Control in Cotton," Proceedings of Cotton Council, St. Louis, 1980.

Table 9. Performance of the Combination Elcar + Chlordimeform in a Large Scale Trial in North Carolina (30 Acres, 1979)

	No. of Appl.	No. Larvae /Acre	No. Damaged Bolls/50 Ft.	% Damaged Bolls
Elcar (2 oz. + chlordimeform 125-lb + adjuvant)	6	2400	21	3
Elcar (2 oz. + adjuvant)	7	3185	39	6
Check	0	5620	105	17

SOURCE: M. C. Ganyard, "

season-long in combination with chlordimeform was as efficacious as the chemical standard. In large scale plot testing the combination of Elcar, chlordimeform, and an adjuvant demonstrated its ability for suppression of Heliothis on cotton (Table 9).

Heliothis virus has a sufficiently large potential market to be a commercially successful pesticide. In addition to its already registered use on cotton it has demonstrated efficacy on other large market crops -- corn, soybeans, sorghum, and tomatoes. Four microbials have now been developed for use as commercial insecticides. These are the Heliothis NPV, Bacillus thuringiensis, Hirsutella (a fungus) and Nosema (a protozoan). The gypsy and tussock moth viral pesticides have been produced under U.S. Forest Service license agreements because the gypsy moth causes significant problems only about every two years and the tussock moth about every five. These two viral pesticides are consequently not commercially viable but nonetheless extremely important when these particular pest epidemics arise. The IR-4 program is designed for such pesticides.

The virus isolated from Autographa californica is a broad spectrum virus that may compete with B.t. and Heliothis NPV, however, it is not commercially available. The concept of broad spectrum is different for microbials than for chemicals. Before widespread chemical use, Heliothis zea was the most important pest of cotton, now Heliothis virescens appears to be more of a problem. Both species are equally susceptible to the virus. This is not the case with the Autographa californica virus (Ignoffo and Garcia, 1979). H. zea is more resistant to Autographa californica than is H. virescens. Thus, relative susceptibility and use of the virus is an important concept that could make broad spectrum biologicals less commercially attractive since different doses might be

required to make a broad spectrum virus equally susceptible for all pest species.

The farmer has a limit he will spend for pest control, he will respond to a cost reducing product. Chemicals develop dependence throughout the crop season, thereby requiring frequent application. Elcar has a comparable relative cost for an application but has the possibility of reducing the number of applications. The education process should concentrate on convincing farmers that some low level of insect population causes minimal harm (threshold of economic damage). With Elcar some low level of insects must be tolerated. Agricultural consultants are the best source of education that biological producers must reach (Merrit, et al., 1980). On high cash crops (including cotton) consultants have a significant voice in decisions on planting, spraying, and harvesting. The bad public inage given chemicals has helped in educating and changing attitudes about biologicals.

Area wide use of biologicals is important. If neighbors are using chemicals, the benefits of beneficial insects might be minimized. Distribution and storage are not significantly dissimilar to chemicals; if kept in cool, dry storage, timing of application is unaffected. Other companies do not necessarily want to jump into the market -- they must have microbiologists, insectary, and insect colonies. Growers' and distributors' attitudes are the big stumbling block, not competition (Merrit, et al., 1980). Biologicals can be used with traditional chemicals in a spraying program; biologicals are not necessarily replacing chemicals but may become complements.

Summary and Conclusions

The Heliothis NPV case history is used to examine the difficulties that new biological products faced before the implementation of the new tier system of regulations. The special characteristics of biologial pest control methods and integrated pest management (IPM) are illustrated through the development, registration, and marketing of the new viral pesticide, Elcar. Biologicals are not expected to take a large share of the pest control market away from traditional chemicals; nonetheless, the Heliothis NPV pesticide is an example of a growing number of biological control agents that are demonstrating an ability to compete with traditional chemicals in some segments of the market. The new tier system for biorationals has provided a clear incentive to continued investment in the developing and marketing of these innovative products. Although regulation is being reduced as a barrier to commercialization, problems of non-patentability, limited market size, user acceptance and technological constraints persist.

Summary and Conclusions

The changing regulatory climate between the 1940's and 1970's is clearly illustrated in the changing regulatory status of chlordane. As one of the new generation of chemical insecticides after World War II it was praised for the great benefits it could accrue to farmers and consumers. Food production and quality could be greatly increased with the elimination of economic pests. Risks associated with the widespread use of persistent chemicals were largely unknown and ignored in favor of the great benefits these new pesticides could deliver. In addition, the public was largely uninvolved in determining environmental policy.

By the 1970's the picture was totally different. The benefits of chemical insecticides were less often stressed and the risks became the major emphasis. The public had entered the debate over safety and health and its presence was reflected in a much tighter regulatory regime. Several important chemical insecticides had been removed from the market. Thus, before the 1970's emphasis was placed on the benefits of pesticides to agricultural production and the risks were little emphasized or understood.

Regulation in 1945 was not capable of handling the complex scientific issues that were faced in the 1970's. The technology to detect small amounts of a chemical were not sufficiently sophisticated and no body of evidence was at hand to point to any human risk associated with chlordane. The short summary of the scientific evidence and its interpretation that was used in the chlordane cancellation hearings makes it clear that the data were not clear-cut in their condemnation of chlordane. It was concluded by EPA that chlordane may be carcinogenic and that the risk to

humans is not negligible. The Food and Agriculture Organization's decision to approve an acceptable daily intake level is evidence that the data were subject to more than one interpretation. Once EPA had made its decision on carcinogenicity, socio-economic criteria were employed to determine the appropriate regulatory action: certain uses were allowed to continue due to the lack of viable substitutes.

The political power associated with an aroused public over safety and health concerns resulted in a stricter regulatory policy. The scientific evidence indicated that the potential cancer risk was not negligible. Economic criteria were considered in making the final judgement among the viable regulatory alternatives on the restriction of uses. Chlordane's R&D and regulatory history is consequently a reflection of dramatic changes in technology and environmental policy.

Blazer Herbicide (acifluorfen) is an innovative product in terms of its capabilities but not its mode of action. Its ability to control important weeds in soybeans after rather than prior to the emergence of the weeds held out the possibility of reducing the intensity of pesticide use. The feature of acifluorfen convinced R&D managers at Rohn & Haas that the new active ingredient deserved special attention. By shortening the prelimimary field testing and adopting more rapid toxicological testing procedures, the new product was brought to commercialization in a very short time. Under the present regulatory regime a firm cannot expect to move a potential new product from discovery to commercialization at a faster rate.

It should also be noted that the acifluorfen's first introduction was not made in the U.S. but in Latin America. Strict regulations in the U.S. have tended to make this a common occurrence. The more lenient regulatory regumes of

most less developed countries allow international firms to market a new product at an earlier stage of its development and to assess its advantages and disadvantages in a large scale, private market setting.

The "poorly-organized, lacks a good summary" comment of EPA reviewers to the first Sustar registration package provides a clear indication of 3M's inexperience, at that time, in registering new pesticides. The submittal was organized in the format of a new drug application (NDA) simply because 3M had experience in the registration of pharmaceuticals, not pesticides. Also, 3M's decision to hire specially trained personnel to handle regulatory matters was a key to the non-adversarial relationship - that presently exists between EPA and 3M. The Embark PGR registration application was highly complimented by EPA reviewers for its thoroughness and its good organization. 3M's "newness" to the industry, its high level of competence in submitting registration packages, and its significant pool of research possibilities in a very innovative area of pest control has allowed it to register several products during a period when few registrations were being accepted.

The handling of the mouse study (in which preliminary test results indicating a possible risk were reported to EPA by 3M and the EPA Registration Division opted to assess the risk internally) is an indication of the evolution of EPA policy toward consideration of "the effect of regulation on production and prices of agricultural commodities, retail food prices and otherwise on the agricultural economy" (Aspelin, 1983). This policy change was reflected in the amendments to FIFRA in 1978, and more recently, in attempts to improve operational efficiency in the regulatory process

under the special review of Vice President Bush's Task Force on Regulatory relief. This latter effort has targeted as problems: delays in registration decision making and inflexibility of data requirements and their cost. Solutions under consideration include "involving industry more closely and frequently in the regulatory process, examining (EPA's) approach to issuing data requirements for registration, finding more efficient ways to regulate, and streamlining internal processes" (Aspelin, 1983). The decision in early 1978 by the Registration Division to evaluate the potential risk utilizing its internal expertise, thereby reaching a more timely decision, was a precursor of the legislative and executive changes in regulatory policy. Also, this case demonstrates that policy tends to evolve and does not represent discreet, sudden shifts in policy. EPA was beginning its move toward greater consideration of economic impacts before the amendments to FIFRA in 1978 and the Vice President's Task Force on Regulatory Relief. Because the basic program operations that implement policy are constantly reacting to new technology, regulatory policy is constantly changing. Legislative or executive actions often either make official a policy that has already been evolving or attempt to guide the evolution of the basic program operations, consequently these actions must not be viewed as discreet regulatory policy changes. The mefluidide case study provides evidence of the evolution of pesticide regulatory policy.

Vistar's registration was speeded up by the emergency (18) and special local needs (24C) petitions filed by some states. This fact illustrates the impact state governments can have on national regulatory policy. Without the petitions the marketing of Vistar Herbicide would most likely have been delayed through the season, thereby losing an retire year.

The non-adversarial relations between 3M and EPA and 3M's recent entry into the agricultural chemical market are the overriding factors shaping agrichemical development and regulatory events at 3M. Great effort at 3M has been placed in nurturing confidence in its relationship with EPA regulators and EPA has responded positively. 3M's recent entry has aided the establishment of the good rapport. 3M does not have any "old" traditional chemicals to defend in the reregistration or RPAR process; consequently it neither is required to expend extra effort to maintain the registration of such products nor is it involved in adversarial interface with EPA. Both factors contribute substantially to the maintenance of the rapport.

At several points during the development and registration of Sustar/ Embark/Vistar, we have documented evidence of the good rapport between 3M and EPA. On several occasions it appeared that the review process was beginning to slow for internal EPA reasons, each time personal contact was able to get things moving again. Excluding the first Sustar submittal, all registration packages were well organized and summarized to facilitate the review job. It is clear that both EPA and 3M have gained from a cooperative relationship. EPA's review effort is facilitated by the well organized submittals and 3M has registered its new products with success.

The impact of regulation on the development of Elcar is strongly influenced by the involvement of public sector research effort in its early development and the changing attitude of EPA regulations toward biologicals. In the early years, research was undertaken by USDA laboratories and lack of knowledge concerning biologicals tended to bias regulatory decision makers against biologicals. The relatively tough regulatory regime might have had a more negative effect on early develop-

ment if research had not been conducted by the public sector. Although early phases of research were undertaken at USDA the principal scientist actually left USDA to join industry (IMC) to improve the chances of the product's commercialization (Ignoffo, 1980). Private sector research effort would not have been as inclined to take the associated risks if a large payoff was not forthcoming. Consequently, the relatively restrictive regulatory environment that existed during the early development of Elcar combined with significant uncertainty concerning its potential market success would probably have discouraged private sector R&D.

Initial isolation and characterization and preliminary field and safety tests were done almost entirely within USDA; regulation had little impact on this initial stage. Additional field testing and development, toxicology and metabolism, and formulation and process development were initiated by USDA then IMC and eventually refined by Sandoz. Because of the nonpersistent nature of Elcar certain toxicological and residue testing were not relevant. The special characteristics of Elcar were not, however, always recognized by regulatory officials in its early development.

Four crucial elements that pervade any analysis of the R&D process of Elcar are the extent of public sector input, its unique mode of action as a biological control agent, the willingness of industry to become involved, and the changing philosophy of EPA regulators toward biorationals. The uncertainities associated with the development of such a unique pest control technique and with the eventual acceptance of the product by the end user mandated the involvement of public sector research; it is clear that private industry would have been unwilling to face the development

problems inherent in such an innovative product without some high level of confidence that, once developed, a major market success would be forthcoming. The lack of basic understanding of biologicals on the part of regulators further impeded early development efforts. Testing protocols for biorationals had not been implemented. Early developers were forced to develop their own protocols as they proceeded. Many tested were undertaken that would not have been required under the new tier system. This regulatory innovation should provide a clear inducement to the development of new biorational products.

Early stages of Elcar's development were slowed by the hesitancy of regulatory decision makers. The later development and present marketing efforts have been advanced by EPA's more favorable view of biologicals.

The required sophistication of users of biologicals is a major stumbling block to market penetration. It is not evident that these products can be commercially successful outside an IPM program; the status of biorationals as substitutes or complements to traditional chemical pest control methods is equally unsure. Elcar's development and marketing represents a major element in the evolution of biological control.

Some Policy Implications

The four case studies give a strong indication of the influence of pesticide policy on agricultural technology. Each of the new products analyzed - acifluorfen, fluoridamid-mefluidide, and Heliothis NPV - are highly innovative characteristics that fit the general EPA policy of decreasing exposure to potentially hazardous chemicals through the reduction of farmers' use of pesticides. In addition the one case study involving an older traditional chemical - chlordane - illustrated EPA policy makers' commitment to the reduction in the use of persistent pesticides.

EPA policy is inducing a trend toward less persistent, more specific pesticides whose use will in general reduce the total amount of pesticides applied. Acifluorfen achieves this objective by allowing farmers to wait until certain weed species have emerged to begin herbicidal strategies. Mefluidide's plant growth regulator mode of action represents a new, creative approach to weed control that attacks the growth pattern of the target species so opposed to the more traditional method of "burning" the undesired plant. Heliothis NPV is a member of the growing number of biological pest control agents.

The importance of the relationship between the regulator and the regulated is particularly apparent in the chlordane and fluoridamid-mefluidide cases. In the chlordane regulatory preceeding both EPA and Veliscol went to great lengths to prove their point. Conversely, in the fluoridamid-mefluidide case each side made special efforts to be sensitive to the objectives of their counterparts. These cases tend to indicate that society is better served by the mutual respect and coopera-

tion that can be used in a professional examination of potential environmental hazards and social benefits associated with the use of a new pesticide product.

The acifluorfen and Heliothis NPV cases provide support to the notion that industry can be very responsive to the objectives of government policy. The management of Rohm and Haas were quick to judge not only the potential market success of acifluorfen but the favorable manner in which this proudct might be viewed by EPA. In the Heliothis NPV case the original developers were scientists employed in the public sector. They were convinced of the potential marketability of the viral pesticide and were also able to convince a private firm to invest in the development of the pesticide. In both cases private industry invested in a new product upon which EPA was expected to look favorably.

A consistent regulatory policy is needed. Uncertainty created by frequent changes in policy or its implementation serve as a significant disincentive to investment in new pesticide products. The large up-front costs and high interest rates of recent years have made the development of new pesticides more expensive. If EPA adds to this difficult investment environment, significant uncertainty through tightening and loosening of regulation, R&D managers decisions to proceed with potential new products are further complicated. A more consistent regulatory policy would allow industry management to make more efficient "go" decisions; this increased efficiency would provide a significant stimulant to pesticide R&D. These case studies have demonstrated the ability of

industry to respond to regulatory policy. The social goal of environmental quality, pursued in a way that minimizes social costs, can be more easily achieved with a consistent regulatory policy.

The importance of time to productivity and costs in pesticide R&D is evident. R&D project time horizons can be reduced by decreasing the uncertainty faced by industry management. More precise guidelines for the registration of new products and the tier system are two means of reducing time horizons. Amendments to the Federal, Insecticide, Fungicide and Rodenticide Act of 1978 called for the writing and implementation of guidelines for the testing requirements for new product registration. This goal has been achieved for only four product testing phases - product chemistry, environmental chemistry, fish and wildlife, and human hazard - of the 12 testing phases generally involved in pesticide R&D.

The tier system that has been developed for registration of biorationals is an institutional innovation that should provide clear incentive to the development of this new pesticide group. Where possible this system might be adapted to test requirements for chemical pesticides. Implementation of clear data requirements through the tier process [31] should greatly decrease uncertainty and thus be an incentive to investment in pesticide innovation.

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[31] In general, the greatest roadblock to the use of the tier system for traditional chemicals is the lack of short term tests that might indicate the need for more long term testing. Public research expenditures could be usefully invested in basic research to aid in the search for technology that would allow the development of such short term tests.

A less adversarial relation between EPA and industry would greatly improve the efficiency of the regulation process. Regulatory proceedings (e.g., DDT and chlordane cancellation hearings) can be transacted under mutual respect and expect consideration of scientific and economic evidence. Also, a less adversarial relation can contribute to a decrease in delay time as evidenced in the 3M case study. Greater consideration of economic impacts by EPA will serve to improve its relations with industry. Environmental quality can be pursued in a way that minimizes the economic costs to producers and consumers.

Appendix A. Proposed Changes in Guidelines for Registering Biorational Pesticides.

The "Guidelines for Registering Pesticides in the United States, Subpart M: Data Requirements for Biorational Pesticides" is being proposed as an incentive to the developments of biorationals. A new tier system is being developed.

"To fulfill the proposed data requirements for registering a biorational pesticide the applicant would have to, at a minimum, submit Tier I data obtained from testing in three general areas: Product Analysis (section series 163.151), Toxicology (section series 163.152), and Nontarget Organism Hazard (section series 163.154). Tests in each of these areas, except Product Analysis, are arranged in a hierarchial or tier system as illustrated in the diagram that follows this discussion. Toxicology and Residue Chemistry testing would be conducted under one tier testing arrangement; likewise, testing under Nontarget Organism Hazard and Environmental Fate and Expression would be combined under a separate tier scheme.

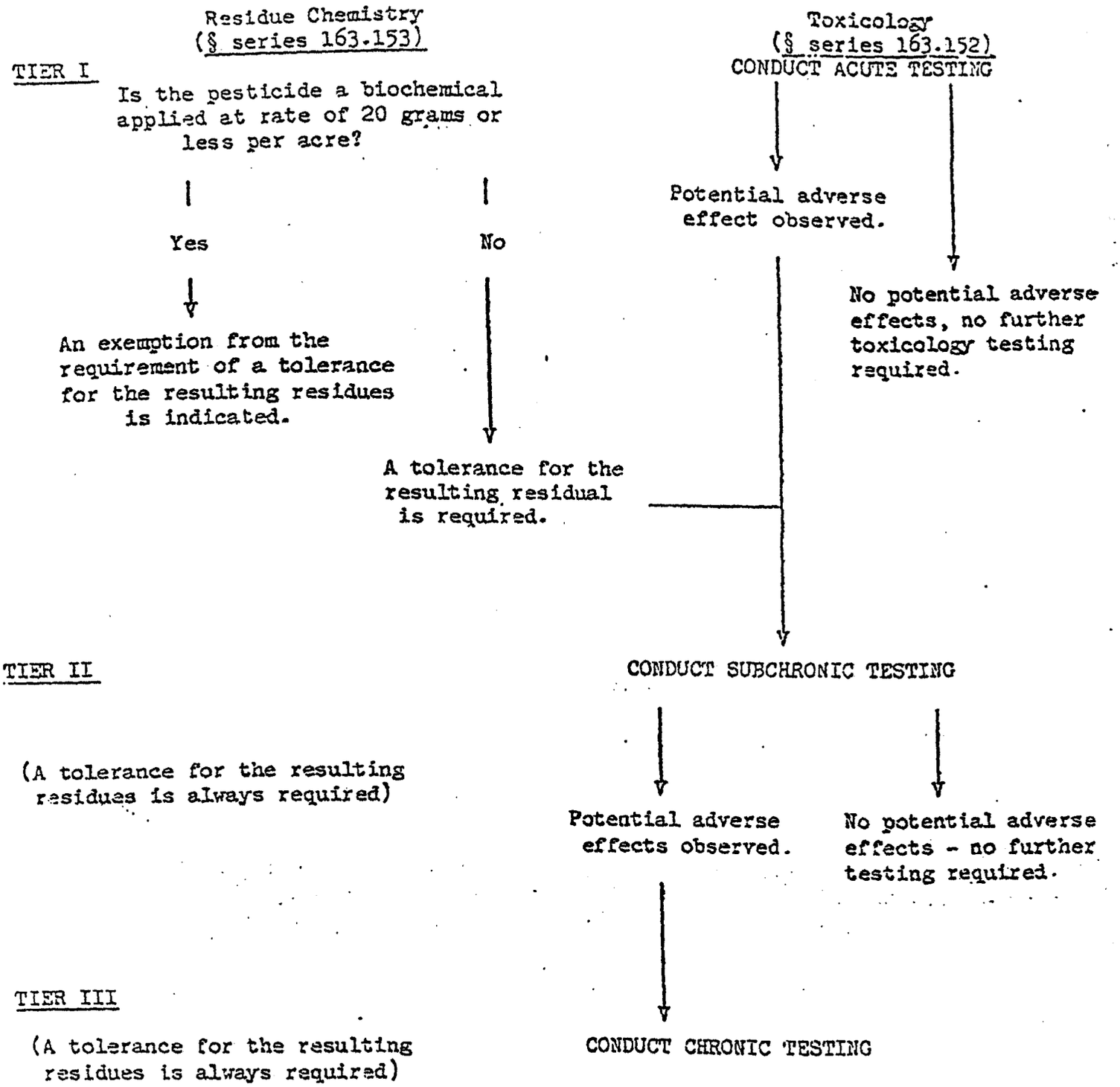
The Toxicology/Residue Chemistry testing scheme commences with short-term toxicology studies in Tier I as shown in Appendix Figure 1. The decision to proceed to Tier II would depend on the results of Tier I studies. If Tier II Toxicology testing (subchronic and further acute testing) is required, then, in addition, the Residue Chemistry data requirements for a tolerance would be required. Ordinarily, Residue Chemistry data would be required only if Toxicology testing results would mandate testing beyond Tier I. For biochemicals, however, residue chemistry data would be required under certain circumstances (product application of 20 grams active ingredient or more per acre) regardless of the results of Tier I Toxicology testing. Depending on the results of Tier II tests, further Toxicology testing may be required at Tier III. Tier III involves acute and long-term laboratory testing and is the final level of Toxicology testing.

The first tier of tests in the Nontarget Organism Hazard/ Environmental Fate and Expression testing scheme consists of short-term laboratory studies to determine pesticidal effects on wildlife, aquatic animals, plants, and beneficial insects (Appendix Figure 2). When no adverse effects are found in the first tier, no Environmental Fate and Expression Testing would be needed, except in the case of biochemicals applied to water. The decision as to whether the second tier of tests would be required is based on the potential toxicity or pathogenicity demonstrated in the Tier I tests in combination with other pertinent information

such as use pattern available environmental chemistry information, product analysis, and toxicological data for mammals.

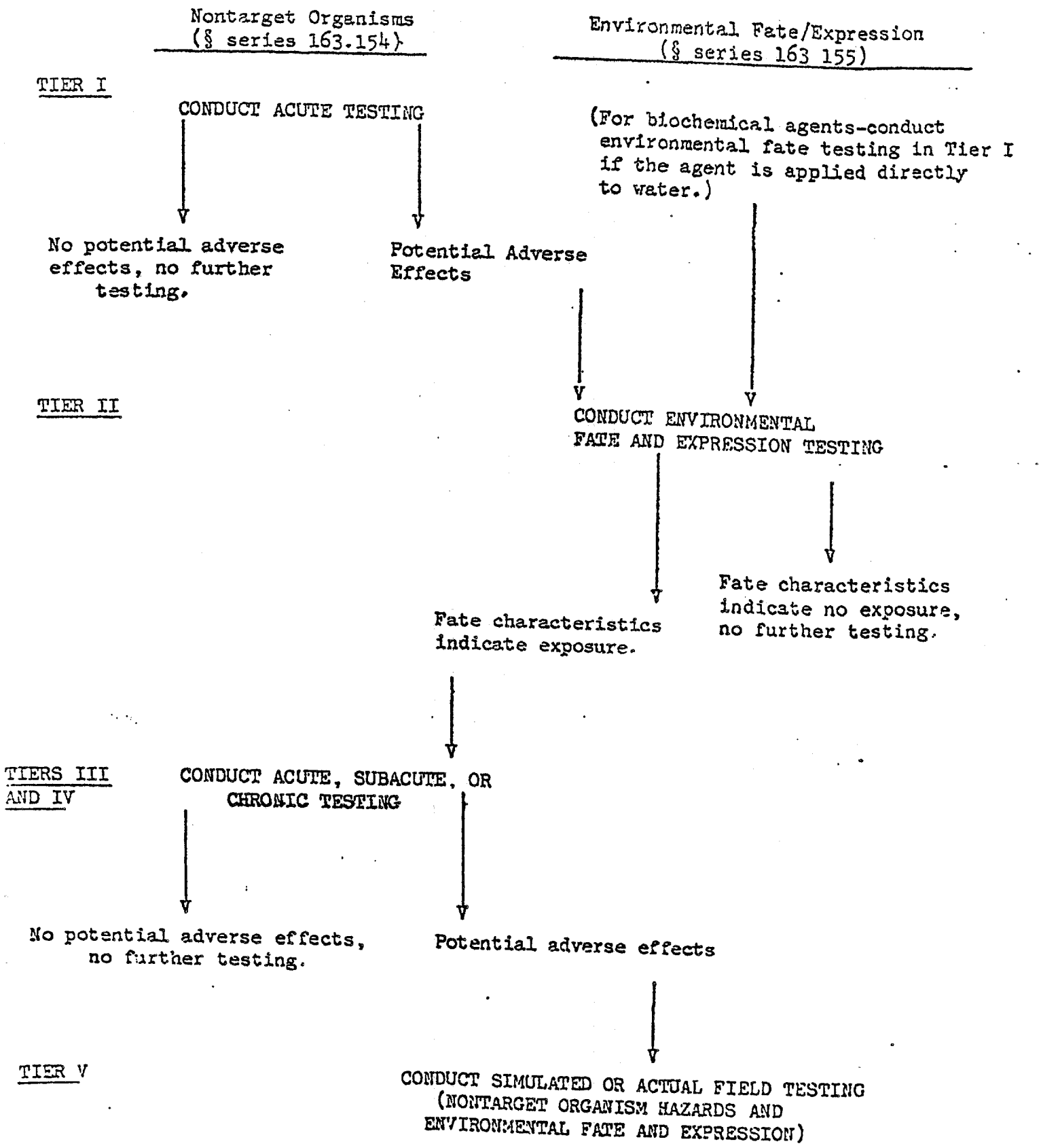
Tier II tests for this scheme would consist of studies to determine pesticidal fate or expression. These data, along with use pattern information, would be used to estimate the environmental concentration of the pesticide. The toxicity/pathogenicity data developed in Tier I and the estimated environmental concentration(s) developed in Tier II would be used in combination to estimate pesticide hazard. When a potential hazard is indicated, Tier III and IV tests are designed to promulgate development of additional nontarget organism data with respect to adverse results or conditions reported in prior tier studies. Tests at Tier V evaluate pesticide hazards under actual or simulated field conditions and consist of both Nontarget Organism Hazard and Environmental Fate and Expression studies. The Agency anticipates very few tests beyond Tier I, because most questions concerning hazards of biorational pesticides should be answered by the first tier tests." (Environmental Protection Agency, 1980, pp. 10-12)

Appendix
Figure 1. Summary of Toxicology and Residue Chemistry Tier Testing Schemes



SOURCE: Environmental Protection Agency, "Guidelines for Registering Pesticides in the United States, Subpart M: Data Requirements for Biorational Pesticides," Office of Pesticide Programs, 40 CFR Parts 163, October, 1980.

Appendix
Figure 2. Summary of Nontarget Organism/Environmental Fate and Expression Testing Schemes



SOURCE: Environmental Protection Agency, "Guidelines for Registering Pesticides in the United States, Subpart M: Data Requirements for Biorational Pesticides," Office of Pesticide Programs, 40 CFR Parts 163, October, 1980.

Appendix Figure 3. Definition of Pesticide R & D Stages

1. Synthesis - Invention of compound and preparation of quantities for primary and secondary testing.

   Screening -

   Primary - testing of gram quantities at high dosage rates in laboratory or greenhouse biological evaluations.
   Secondary - testing of gram quantities in series dilution laboratory or greenhouse tests to determine thresholds of biological activity.

2. Field plot testing - The range of biological testing in this category is from small, replicated field plots using logarithmic dosages or single dosage rates and small scale application equipment to full commercial scale equipment on one or more acres. Tests provide information on minimum effective dosage under commercial conditions, as well as information on host plant tolerance and crop yield.

3. Toxicology -

   Mammalian - conduct all acute and chronic studies on parent compound and significant metabolities required to support establishment of residue tolerances and to determine product labeling requirements for safe handling.
   Environmental/Wildlife - tests on nontarget organisms in environments where the pesticide is used or where exposure may occur.

   Metabolism (Radiosynthesis) - Preparation of radiolabelled pesticide and use in studying pesticide metabolism in animals, plants, soil and water.

4. Environmental Chemistry - Conduct studies on the fate of residues in soil, water, nontarget organisms, etc.

   Residue Analysis - Conduct residue studies on crops, animals and process foods to support establishment of residue tolerances or food/feed additive clearances. Include designing a residue method(s) for detecting and measuring minute quantities of residues of parent compound and/or significant metabolites in plant, animal, soil, water, etc.

Appendix Figure 3. Definition of Pesticide R & D Stages (continued)

5. Formulation Development – Prepare and study formulation characteristics and design appropriate packages for these formulations.

   Process Development – Design and develop production methods for pilot plant and commercial scale production.

6. Registration – Prepare applications for registration and establishment of residue tolerances and food and feed additives. Include fees for establishing EPA tolerances.

   Administration/Overhead – Include only those expenditures appropriately allocated to new product development, product expansion and registration and product defense. Include expenditures or estimated expenditures for facilities and personnel that are utilized full or part-time in support of the R & D effort, which are not included in the other specific categories. Examples: market research, patent or legal expenses, other technical support, executive overhead.

Source: Ernst & Whinney (accountants), "Industry Profile Study," prepared annually for the National Agricultural Chemical Association, Washington, D.C., 1981.

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