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Pesticides

Minimizing the Risks

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Foreword

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the Series parallels that of the continuing ADVANCES IN CHEMISTRY SERIES except that, in order to save time, the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. Papers are reviewed under the supervision of the Editors with the assistance of the Series Advisory Board and are selected to maintain the integrity of the symposia; however, verbatim reproductions of previously published papers are not accepted. Both reviews and reports of research are acceptable, because symposia may embrace both types of presentation.

Preface

PUBLIC CONCERN HAS GROWN STEADILY over the past three decades concerning the effects of pest control chemicals on human health and environmental quality. A substantial legislative base currently exists for regulation of these chemicals to protect the environment and promote human safety. The regulations that result from this legislative mandate are based on risk assessment and risk management. Risk is defined as the potential adverse health effects resulting from exposure to environmental hazards. Regulations to reduce risk influence the integration of agricultural research and technology into society and stimulate new technological developments in efforts to resolve the unanswered questions associated with the risk assessment process.

The National Academy of Sciences indicated in a recent study that the primary problem with risk assessment is the sparse data upon which decisions are based. Agriculture has an opportunity to meet the need for improved risk assessment and management through new research, new technology, and the use of that technology.

The symposium upon which this book is based focused on the new directions we must follow, based on our current level of understanding. The speakers identified research and educational opportunities that will strengthen the data base that is used to minimize risk while maintaining the necessary quality and quantity of food and fiber.

We would like to express our appreciation to the U.S. Department of Agriculture for its interest in and support of this symposium. We would also like to thank Herbert Cole, Richard Honeycutt, and Christopher Wilkinson for their excellent ideas in the planning phase.

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Chapter 1

Minimizing the Risk Associated with Pesticide Use: An Overview

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Although the benefits of pesticides are undeniable, attention in recent years has been focused on their impact on human health and environment. Although pesticide law requires that both risks and benefits be considered in all decisions, risk drives the process in terms of depth of analysis and allocation of federal resources. Two questions relative to risk are appropriate: "What is acceptable risk?" and "How can we minimize the risk?". No amount of research can eliminate all uncertainties associated with assessing the risks of exposure to pesticides or eliminate the controversial judgments inherent in any decision about control of pesticide exposures. Yet, there are opportunities to reduce the scientific uncertainties and to increase the public's confidence that health is protected and the economic consequences of imposed pesticide control are justified.

The decades of the 1940's and 1950's were characterized by major discoveries in the use of chemicals that aided the development of a highly successful agricultural system, promoted the economic strength of the nation, and secured the public's health from the dread of vector-transmitted diseases. In the early 1960's, tremendous progress was made in application technology for the dissemination of pesticides. Development in innovative equipment for applications accompanied major advances in formulation chemistry and the widespread efficacy testing of pesticide products. The late 1960's and 1970's were characterized by the concerns for the environment and the implementation of a massive regulatory program "that now governs all environmentally relevant aspects of our economy" (1).

Today, pesticides continue to play a major role in our society; yet, an unprecedented level of controversy over their use continues. The focus of the controversy is in the determination of "what is acceptable risk". The answer to this question cannot be provided by science - it is a social question. What can be addressed by the scientific community is the question of "how can we minimize the risk."

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Table I. Magnitude of Pesticide Use in the United States

Land Use Category	All Pesticides		Herbicides		Insecticides		Fungicides	
	Treated Hectares (x10 ⁶)	Quantity (x10 ⁶ kg)	Treated Hectares (x10 ⁶)	Quantity (x10 ⁶ kg)	Treated Hectares (x10 ⁶)	Quantity (x10 ⁶ kg)	Treated Hectares (x10 ⁶)	Quantity (x10 ⁶ kg)
Agricultural Lands	114	341	109	199	34	74	10	68
Government and Industrial Lands	28	55	30	44	--	11	--	--
Forest lands	2	4	2	3	1	1	--	--
Household Lands	4	55	3	26	3	25	1	4
TOTAL	148	455	144*	272	38	111	11	72

*Same land may be treated with several classes of chemicals.

SOURCE: Modified from Pimentel and Levitan (4), 1986.

This book, and the American Chemical Society's Symposium on which it is based, addresses this latter question.

Extent of Pesticide Use

A generally acceptable definition of pesticides includes key phrases such as "chemical substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pests" and "substances intended for use as a plant regulator, defoliant or desiccant (2,3). In 1980, some 530 million kg of pesticides were used in the production of food, clothing and durable goods for the more than 270 million persons living in the United States, that is 2 kg per person. Most recently, Pimentel and Levitan (4) have estimated that the current annual use of pesticides in the United States approaches about 500 million kg, primarily synthetic organic chemicals but also including 27 million kg of sulfur and copper sulfate fungicides. Table I shows the use by major land-use categories for herbicides, insecticides and fungicides. In 1983, the sites (users) of pesticide applications in the United States were agricultural lands (68%), industrial and commercial sites (17%), home and gardens (8%) and government lands (7%)(5). The use in the amounts of herbicides and insecticides has dramatically changed in the past two decades. Table II gives the amount of herbicides and insecticides for selected years, applied annually by U.S. farmers. The growth in herbicide use has been reflected in materials used in wheat, corn and soybean, e.g. 2,4-D, atrazine, and trifluralin, respectively. (Table III). As Ware (3) pointed out, pesticides are big business. The United States market is the world's largest, representing 34% of the total. In 1980, U.S. manufacturers produced 660 million kg of synthetic organic pesticides, valued at \$4.2 billion and the retail value of pesticide sales in the United States reached \$5.8 billion. Clearly, for such extensive demand and use there must be significant benefits associated with the use of pesticides. Conversely, such quantities used annually means that misapplications, accidents and improper use of pesticides constitute real, and documented risks associated with pesticide use.

Table II. Total Pesticides Used by U.S. Farmers on Crops

<u>Year</u>	<u>Herbicides (Million Kilograms)</u>	<u>Insecticides (Million Kilograms)</u>
1964	34.5	64.9
1966	50.8	62.6
1971	101.6	71.7
1976	178.7	73.5
1982	196.4	26.8

SOURCE: Council on Environmental Quality (1)

Table III. Selected Herbicides Used by U.S. Farmers on Crops, 1982

<u>Herbicide</u>	<u>Kilograms Used (Million)</u>	<u>Hectares Treated (Million)</u>
Atrazine	34	21
Alachlor	38	18
2,4-D	10	17
Trifluralin	16	17
All Other	99	73
TOTAL	197	146

SOURCE: Council on Environmental Quality (1)

Benefits of Pesticide Use

Pesticides are an integral and indispensable part of American (and world) agriculture. Hayes (5), Mellor and Adams (2), Pimental and Levitan (4), and Ware (14) have discussed the benefits derived from the use of pesticides. Ware (3) noted that the plants that supply the world's main source of food are susceptible to 80,000 to 100,000 diseases caused by viruses, bacteria, mycoplasma-like organisms, rickettsias, fungi, algae, and parasitic higher plants. They compete with 30,000 species of weeds the world over, of which approximately 1,800 species cause serious economic losses. Some 3,000 species of nematodes attack crop plants, and more than 1,000 of these cause severe damage. Among the 800,000 species of insects, about 10,000 plant-eating species add to the devastating loss of crops throughout the world. Pimental and Levitan (4) estimate that "total worldwide food losses from pests amount to about 45% (of total food production). Preharvest losses from insects, plant pathogens, and weeds amount to about 30%. Additional postharvest losses from microorganisms, insects, and rodents range from 10 to 15%.

In the United States crop losses due to pests are about 30% or \$20 billion annually, despite the use of pesticides and other current control methods (3). Ware (3) addresses the question of "what would the losses be without the use of insecticides?" Studies conducted in 1976-1978 compared the yields from test plots, where insecticides were used to control insects, to adjacent plots in which the insects were allowed to feed and multiply uncontrolled. Summary data from this study are shown in Table IV. These data suggested that, on the average, for the crops evaluated, half of the crops are lost to insects. Even with insecticides, 10% of the crop is lost. The issue, however, is what rate of return can a farmer expect from the use of insecticides on these crops? The data suggested an average increased yield of 36%. Pimental and Levitan (4) concluded that in economic terms, for the \$3 billion invested in the United States in controlling pests through the use of pesticides, about \$12 billion are returned in increased return on investment.

Table IV. Comparison of Losses Caused by Insects in Plots Treated by Conventional Use of Insecticides and Untreated Plots

<u>Commodity</u>	<u>Calculated Losses (%)</u>		
	<u>With Treatment</u>	<u>Without Treatment</u>	<u>Increased Yield (Percentage)</u>
Corn	17.7	42.2	24.5
Soybeans	5.5	20.8	15.3
Wheat	9.5	65.0	52.0
Cotton	14.5	51.1	39.1
Potatoes	1.0	48.0	47.0
Average of Above Crops	9.6%	45.4%	36.0%

SOURCE: Summarized from data presented by Ware (3)

Hayes (5) noted that although information is available on the benefits of pesticides to agricultural production, information is unfortunately fragmentary on the benefits of pesticides to the protection of stored products. Losses that occur during storage are caused mainly by insects, mites, rodents and fungi, all of which are susceptible to chemical control. It has been estimated that at least 10% of harvested crops worldwide - enough to feed 200 million people without additional land or cultivation - are lost during storage. In the tropics, the loss is mainly in the quantity of food stored. In temperate climates, the loss is mainly of quality and acceptability (5).

Hayes (5) has also reviewed the contribution of pesticides to the control of human diseases spread by arthropods and other vectors. Outbreaks of malaria, louse-borne typhus, plague, and urban yellow fever, four of the most important epidemic diseases of history, have been controlled by use of the organochlorine insecticides, especially DDT. In fact, the single most significant benefit from pesticides has been the protection from malaria. Today malaria eradication is an accomplished fact for 619 million people who live in areas once malarious. Where eradication has been achieved it has stood the test of time. An additional 334 million people live in areas where transmission of the parasite is no longer a major problem. Thus, about 1 billion people, or approximately one-fourth of the population of the world, no longer live under the threat of malaria.

In summary, pesticides have been and continue to be an integral part of American public health and agricultural programs. The benefits of the proper use of pesticides are enormous. Nevertheless, there are significant risks associated with widespread and intensive use of pesticides.

Risks Associated with Pesticide Use

Much attention in recent years has been focused on the social and environmental risks associated with pesticide use. Mellor and Adams (2) conclude that human poisonings are clearly the highest price paid for using pesticides. They reported that in many developing countries, improper use of pesticides by untrained workers has often led to poisonings during application. Also, workers who entered treated areas too soon after treatment to weed or harvest crops have been exposed to pesticides by brushing against contaminated foliage. Mellor and Adams estimated that in Central America a total of about 3,000 to 4,000 pesticide poisonings occur annually. Pimentel and Levitan (4) estimate that 45,000 total human poisonings occur annually worldwide, including about 3,000 cases admitted to hospitals and 200 fatalities, with approximately 50 of the latter being attributed to accidental death.

Mellor and Adam (2) pointed out that by disrupting natural controls, pesticides can have a detrimental impact on the environment. For example, the use of the fungicide benomyl to control fungi in soybeans may unleash damaging outbreaks of foliage-feeding caterpillars that the fungi might otherwise have destroyed. When outbreaks of new pests occur, additional control treatments must be used. About \$153 million is spent each year to control these newly created pests (4).

Pimentel and Levitan (4) estimated that less than 0.1% of the pesticides applied to crops actually reaches the target pests. Hence, they concluded that most of what is applied enters the environment, contaminating the soil, water, and air and perhaps poisoning or adversely affecting nontarget organisms. The figure of 0.1%, however, is calculated as the amount of insecticide, for example, that comes in direct contact with the insect. The bulk of the pesticide is certainly within the environment of the target pests. In the case of a herbicide, a far higher percent of the chemical intersects with the target plant. The point is that we have much to learn in how to direct the chemical to the target pest.

To comprehend the magnitude of environmental pollution by pesticides, Sun (6) recently reported on studies by the Environmental Protection Agency showing that 17 pesticides have now been detected in the ground water of 23 states; the concentrations typically ranged from trace amounts to several hundred parts per billion. Two years ago (1984) the count was 12 pesticides found in 18 states; but Agency scientists attributed the rise to an increase in the quality and quantity of studies rather than an increase in the problem. The goal of the EPA surveys is to obtain sufficient information to characterize pesticide contamination and to determine how pesticide concentration levels correlate with patterns of usage and ground-water vulnerability factors. While the studies are not designed to estimate individuals' pesticide exposure nor the resulting level of health risk, the data will allow inferences about populations potentially at risk.

Brattsten et al. (7) have reported on another problem associated with the widespread use of pesticides; namely, the rapid appearance of insecticide resistance. By 1980, 260 species of agricultural arthropod pests had insecticide-resistant strains, compared to 68 for disease vectors. They noted that some insects have developed resistance to all major classes of insecticides and will develop resistance to future insecticides as long as present application techniques and use patterns prevail.

In summary, the current widespread use of pesticides have resulted in problems involving human health, adverse effects on nontarget organisms, pesticide resistance in many major pests, and environmental contamination of air, soil and water. Many of these problems, however, result from the improper use, handling, or storage of pesticides. The recognition that pesticides pose risks to health and the environment is the salient reason for government and industry to undertake programs to minimize these risks.

Research Approaches to Minimizing Risks Associated with Pesticide Use

No amount of research can eliminate all the uncertainties associated with assessing the risks of exposure to potentially hazardous chemicals. No amount of research can eliminate the controversial judgments inherent in any decision about the control of chemical exposures. Yet, there are opportunities to reduce scientific uncertainties and to increase the public's confidence that health and environment are protected and that the economic consequences of imposed chemical control are justified. The following research areas have been identified for minimizing pesticide risks:

1. Minimizing Risk Through a Better Understanding of Toxicology
 - Toxicology requirements
 - Acute versus chronic toxicity testing
 - New methods for toxicologic evaluation
 - Simulating modeling
2. Minimizing Risk Through a Better Understanding of Pests
 - Physiological and biochemical considerations
 - Pests as part of the ecosystem
3. Minimizing Risks Through a Better Understanding of Potential Hazard
 - Proper protection and disposal
 - Educating the public
 - Perceptions through the media

The remainder of this book will focus on each of the above areas. Many of these areas have been the target of research teams and have already shown potential payoffs. In 1983, Nelson (8) identified five toxicology research needs; namely 1) improve the basis for dose and interspecies extrapolation to humans; 2) predict effects

of multiple chemical exposure; 3) develop cellular and molecular markers of exposure; 4) develop means to distinguish carcinogens on the basis of modes of action; and 5) expand use of existing federal data collection activities. As a consequence of Nelson's report, the Federal Government has committed major resources to the investigations of these areas. The key to minimizing risk is knowledge. The more we know and understand about the toxicology, mode of action and environmental fate of a pesticide, the more "management conscious" we can be about the use of that pesticide. Accordingly, in late 1983 the National Pesticide Information Retrieval System (NPIRS) was established. NPIRS is a computer data base that describes key characteristics of 50,000 pesticide products registered by EPA plus thousands of state registrations. This data base is currently updated weekly. NPIRS is maintained at Purdue University in Indiana and is supported through cooperative agreements with the USDA and EPA.

Research by Brattsten et al. (7) have stressed the need for managing the problem of insecticide resistance. They suggested that studies of the basic biology of insect-plant interactions in nature and in crop agroecosystems can produce ideas for improved use of chemicals and how they can best be integrated with nonchemical methods. Gebhardt et al. (9) have emphasized the need to devise improved pest management strategies for conservation tillage and to better understand the impact of conservation tillage on water quality, especially as it is related to use of agricultural chemicals. Boyer (10) has recognized that research into understanding the basic factors that influence plant productivity will significantly enhance our effectiveness of using plant protection chemicals.

Menn (11) has addressed the minimizing of risks through a better understanding of chemical structure-activity relations. He discussed strategies leading to the discovery of selective and biodegradable insecticides and insectostatic agents. Pimentel and Levitan (4) and Eue (12) have identified the need to understand chemical structure and the relationship to environmental mobility, bioaccumulation and persistence. Eue (12) also addresses the need for standardization of methods for studying the behavior of fate of herbicides in soil.

In 1985, Benbrook (13) challenged the scientific community to assist in the development of a national policy on pesticide residues. He identified two critical areas for scientific input: 1) expertise in developing the analytical and scientific insights needed to reform our existing patchwork of laws and programs, and 2) sound data needed for conducting reliable risk assessments to support regulatory decision making. He concluded his paper by stating: "Toxicologists need to clearly articulate the benefits to society that could result from more reliable up-to-date information on pesticide use patterns, and hence exposure. Such knowledge would make it possible to begin differentiating between significant potential hazards that deserve regulatory scrutiny, and truly insignificant, improbable risks that simply do not warrant the same degree of attention."

In assessing the regulation of pesticides, John Young (14), Chairman of the President's Commission on Industrial Competitiveness, stressed the need to balance environmental, health, and safety regulation with the needs of research, development and technological innovation. He concluded: "As the 21st Century approaches, Americans need to weigh more heavily the importance of maintaining a 'technology gap' in our favor if the Nation is to remain competitive in world markets and retain one of the highest standards of living in the world. Americans cannot (and do not) expect both absolute safety and a prominent position on the cutting edge of science and technology. Fear of the unknown and the unwillingness to accept small risks could make Government regulation an enemy of innovation. This could occur because a fundamental problem in our regulatory process is the failure to uniformly and properly balance safety concerns with the needs for innovation and industrial competitiveness."

Funding of Pesticide Research

The previous section identified numerous research areas. The funding and scientific staffing (in scientist years) of such research must be the responsibility of the entire scientific enterprise to include state and federal government and private industry. Data in Tables V and VI show FY 84 or CY 84 investments in pesticide research by government and industry, respectively. Table VII provides data for the federal expenditures for toxicology-related research.

Table V. Estimated FY 84 Federal and State Expenditures for Pesticide Research

<u>Area</u>	<u>Funding</u>	<u>SYS</u>
Fundamental Biology	\$ 86.4 M	618
Improved Means of Nonpesticidal Control	74.5 M	498
Improved Pesticide Use Patterns	33.8 M	232
Toxicology, Pathology, Metabolism and Fate of Pesticides	9.6 M	62
Economics of Pest Control	3.9 M	26
TOTAL	\$208.2 M	1,436

SOURCE: USDA Cooperative State Research Service

Table VI. CY 1984 Industrial Expenditures for Pesticide Research

<u>Areas</u>	<u>Total Dollars</u>	<u>Total SYS</u>
Synthesis and Screening	\$ 124 M	776
Product Development & Registration	308 M	1,925
TOTAL	\$ 432 M	2,701

SOURCE: Agricultural Research Institute (15)

Table VII. FY 85 Federal Expenditures for Toxicology-Related Research

\$ 194 M - Basic Research (e.g. Mode of Action)
 \$ 149 M - Toxicology Testing
 \$ 56 M - Methods Development

TOTAL \$ 399 M

88 Scientists Years

SOURCE: National Institutes of Health and National Science Foundation

In our society, the issue of risk from pesticide use is one where the level of public information is low and the potential for anxiety high -- a situation likely to confound the policy-making process. We do not have the luxury of discarding the "chemical tools" necessary for control of the many pests that threaten our food supply and health. Therefore, the task for agricultural scientists and policy makers is to effectively communicate risks and benefits impartially to the public. Only through such a process can we hope to retain the public's confidence in our abilities to safely use pesticides. To that end, universities, industries and governments must commit resources to the conduct of essential pesticide research; research that will meet the needs of the Nation's agricultural, industrial and public health programs.

Literature Cited

1. Council on Environmental Quality. 1986. Environmental Quality. 15th Annual Report of the Council on Environmental Quality. Superintendent of Documents, Washington, DC. 719 pp.
2. Mellor, J.W. and R.H. Adams, Jr. 1984. Feeding the Underdeveloped World. Special Report, Chem & Eng. News, April 23, 1984. P 32-39.
3. Ware, G.W. 1983. Pesticides: Chemical Tools. Chapter 1, P. 3-25. IN: Pesticides: Theory and Application. H.W. Freeman and Co., New York, NY.
4. Pimentel, D. and L. Levitan. 1986. Pesticides: Amounts Applied and Amounts Reaching Pests. BioScience 36:86-91.
5. Hayes, W.J., Jr., 1981. Toxicology of Pesticides. The Williams & Wilkins Co., Baltimore, MD.
6. Sun, M. 1986. Ground Water Ills: Many Diagnoses, Few Remedies Science 232:1490-1493.
7. Brattsten, L.B., C.W. Holyoke, J.R. Leeper, and K.F. Raffa. 1986. Insecticide Resistance: Challenge to Pest Management and Basic Research. Science 231:1255-1260.
8. Nelson, N. (Chairman). 1983. Research Briefing Panel on Human Health Effects of Hazardous Chemical Exposures. Committee on Science, Engineering and Public Policy. National Academy Press, Washington, DC P 100-110.

9. Gebhardt, M.R., T.C. Daniel, E.E. Schweizer, and R.R. Allmaras. 1985. Conservation Tillage. *Science* 230:625-630.
10. Boyer, J.S. 1982. Plant Productivity and Environment. *Science* 218:443-448.
11. Menn, J.J. 1983. Present Insecticides and Approaches to Discovery of Environmentally Acceptable Chemicals for Pest Management. *IN: Natural Products for Innovative Pest Management*. Whitehead, D.L. and W.S. Bowers (Eds). Pergamon Press, New York, NY P 5-31.
12. Eue, L. 1985. World Challenges in Weed Science. *Weed Science* 34:155-160.
13. Benbrook, C.M. 1985. National Policy Review. Panel on Pesticide Residues: Policy, Practices and Protection. Board on Agriculture, NAS/NRC. Presentation to the Toxicology Forum, July 17, 1985. Aspen, CO. 5 pp.
14. Young, J.A. (Chairman). 1984. Balancing Environmental, Health, and Safety Regulation with the Needs of Research, Development, and Technological Innovation. Appendix C, Vol. 2:279-293. Report of the President' Commission on Industrial Competitiveness. Government Printing Office, Washington, DC.
15. Agricultural Research Institute. 1985. A Survey of U.S. Agricultural Research by Private Industry III. ARI, Bethesda, MD., 26 pp.

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Chapter 2

Current Toxicology Requirements for Registration

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The Environmental Protection Agency (EPA) is responsible for pesticide regulation and for insuring the safety of pesticide products. To this end, the EPA has promulgated testing guidelines designed to fulfill pesticide registration requirements. Laboratory animal studies form the primary basis for predicting the potential hazards of pesticides to public health. EPA toxicology data requirements include acute testing, subchronic and chronic feeding/oncogenicity studies, a two generation reproduction and teratogenicity study, mutagenicity testing and a rodent metabolism study. These requirements and problems encountered in interpretation of data obtained from toxicity testing are discussed. Future directions of research to fulfill toxicology data requirements are described.

The Environmental Protection Agency (EPA), under the authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), is responsible for pesticide regulation. Data requirements for pesticide registration, and guidelines for evaluating the toxicity of pesticides to nonhuman organisms and for relating the results of these studies to human safety evaluations, have been developed by EPA(1,2).

Toxicity studies required by EPA for pesticide registration are listed in Table 1. The major toxicity categories include acute, subchronic, chronic and mutagenicity testing. Evaluation of teratogenicity and adverse reproductive effects are included under chronic testing. Animal metabolism and dermal penetration studies are found in a special testing category.

Acute Toxicity

The initial step in the safety evaluation of a pesticide product is the determination of its acute toxicity (Table I). Laboratory animals, usually rats and rabbits, are exposed to a single dose of the test substance. Toxic effects resulting from ingestion,

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inhalation, skin and eye contact are determined over a two to three week post-exposure observation period. If repeated dermal exposure is expected to occur, a dermal sensitization study in guinea pigs is required. An acute delayed neurotoxicity study is required only if the test substance is for food use and is an organophosphate, which causes acetyl cholinesterase depression, or if it is structurally related to a substance that causes delayed neurotoxicity. The purpose of acute toxicity testing is to establish relative toxicity to other chemicals by defining the median lethal dose (LD50 and LC50), to provide initial information on the mode of toxic action, to identify possible synergistic interactions and to evaluate design for subchronic tests. Data from these tests are used to determine the signal word and the hazard warning statements which appear on the pesticide product label; for example, if the pesticide is acutely toxic (oral LD50 in rat <50 mg/kg) the signal word Danger must be on the label.

Table I. EPA Toxicology Data Requirements

TEST	SPECIES
ACUTE	
°Oral/Dermal/Inhalation	Rat, Rabbit
°Primary Eye/Dermal Irritation	Rabbit
°Dermal Sensitization	Guinea Pig
°Delayed Neurotoxicity	Hen
SUBCHRONIC	
°90 Day Feeding	Rat and Dog
°90 Day Dermal/Inhalation	Rat
°90 Day Neurotoxicity	Hen
CHRONIC	
°Oncogenicity	Rat and Mouse
°Chronic Feeding	Rat and Dog
°Teratogenicity	Rat and Rabbit
°Reproduction, 2-Generation	Rat
MUTAGENICITY	
°Gene Mutation	
°Chromosome Aberration	
°DNA Damage and Repair	
SPECIAL	
°Metabolism	Rat
°Dermal Penetration	Rat

Subchronic Tests

Following the determination of its acute toxicity, the pesticide is then evaluated in subchronic studies (Table 1). Subchronic exposure usually lasts for 90 days and its objective is to generally evaluate and characterize the effects of the test substance when administered to laboratory animals on a daily basis. EPA requires that subchronic studies be performed in two species, the rat and dog, and at several dosage levels. The test substance is normally administered to the animals in their diet. However, when pesticide use involves purposeful application to or prolonged exposure of human skin, or if

its use results in repeated inhalation exposure at a concentration likely to be toxic, 90 day studies by the dermal and/or inhalation route will be required. If acute results show signs of neurotoxicity, a 90 day study is needed to further evaluate this end point.

Parameters which are evaluated in the subchronic testing phase include: general observation of test animals for clinical signs of toxicity, body weight changes, diet consumption, mortality, organ weight changes, clinical chemistry measurements, gross necropsy and histopathology. In addition to providing information on target organs and possible test substance tissue accumulation, the results serve to estimate the dosage levels to be used in long term or chronic toxicity tests.

Chronic Tests

Requirements under the category of chronic testing are listed in Table 1. Adverse effects resulting from long-term exposure to a pesticide are evaluated. Oncogenicity studies assess the potential of the test agent to produce malignant and benign tumors and pre-neoplastic lesions. They are performed in the rat and mouse and extend over the majority of the expected life span of the strain, about 2 years for rats and 18 months for mice. Chronic feeding studies, carried out in the rat and a non-rodent species, usually the dog, are designed to evaluate other chronic effects in addition to tumor formation. EPA believes that testing in a non-rodent species is necessary to provide an adequate evaluation of non-oncogenic effects. Chronic and subchronic feeding studies are similar except the period of exposure to the test substance is longer in chronic tests, i.e. 2 years duration for rats and 1 year duration for dogs.

EPA includes two tests in the category of chronic evaluation which are designed to examine the effects of a pesticide on the process of reproduction. A teratogenicity study is performed in two species, the rat and rabbit, to evaluate potential fetotoxicity or birth defects in offspring. Pregnant animals are exposed to the test substance daily by gavage during that part of pregnancy covering the critical period of organogenesis, or the time during the development or growth of organs, since teratogens are most effective at this stage of gestation. Organogenesis corresponds to days 6 to 15 of gestation for the rat and days 6 to 18 of gestation for the rabbit. In humans, it is complete during the first trimester of pregnancy. Parturition, the process of giving birth, occurs on day 21 and 32 for the rat and rabbit, respectively. Fetuses are delivered by cesarean section one day prior to parturition and examined for gross, visceral and skeletal abnormalities. A two generation reproduction study is conducted in the rat. The test substance is administered to male and female rats in their diet prior to mating. Treatment of inseminated females is continued during their growth into adulthood, mating and production of the second generation. Effects of a test substance on gonadal function, estrus cycles, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring are measured.

In general, chronic studies must incorporate several, usually

three, dosage levels. The EPA requires that the highest dose used in these studies must be the maximum tolerated dose (MTD) or one that produces some toxic or pharmacological effect in the test animal. Also, a lower dose level must be used which produces no evidence of toxicity. This is the "no observed effect level" or NOEL. The use of the MTD in chronic assays can cause problems in interpretation of test results especially when the MTD is responsible for overloading of metabolic pathways. Overloading enzymatic transformation of a test substance and/or metabolite results in disproportionate changes in blood and tissue levels and relative quantities of parent substance and metabolites. An expanding number of studies show that metabolic pathways can be overloaded, sometimes at doses well below a toxic level or MTD. When such overloading occurs in a toxicity study, the true hazard to another species cannot be reliably estimated (3). To avoid overloading of metabolic pathways, pharmacokinetic and metabolism experiments should be conducted prior to the start of chronic studies. Results from these experiments in conjunction with results from subchronic studies, should be used for determining the highest dose level used in chronic tests. In this way a better understanding of the actual hazard of the pesticide will be obtained since the chronic study will be carried out at dosage levels which will not alter the animals normal physiological response to the test substance.

Other Tests

Other toxicology requirements needed prior to registration include a battery of mutagenicity studies and a rodent metabolism and dermal penetration study (Table 1). The rodent metabolism and dermal penetration protocols are included under the category of special testing. Mutagenicity data is required to determine if the pesticide will affect genetic components in the nucleus of the mammalian cell. If a mutation is present in the genetic material of the egg or sperm at the time of fertilization, the resulting consequences may be embryonic or fetal death or congenital abnormalities. The battery of mutagenicity assays includes tests to detect gene mutations, structural chromosome aberrations and other genetic effects such as DNA damage and repair and mammalian cell transformation. These mutagenic assays are also used to screen for potential carcinogens since the initial step in chemical carcinogenesis is generally believed to be a mutagenic event. A rat metabolism study is required to determine the transformation, absorption, distribution and excretion of the pesticide. Dermal absorption evaluations are needed for pesticides having a serious toxic effect, as identified by oral or inhalation studies, or for which a significant route of human exposure is dermal penetration.

The main purpose of the toxicity tests just described is to provide a data base that can be used to evaluate the hazard and assess the risk associated with the use of a pesticide. In practice, the no observable effect level (NOEL) found in the most sensitive animal species tested in chronic studies is used. To extrapolate a safe dose for human consumption, a safety factor of 100 is usually used. For example, if the NOEL in the most sensitive animal species, e.g. the dog from the chronic feeding study, was 10 mg/kg of body weight, then the acceptable daily intake (ADI) for man would be

0.10 mg/kg of body weight. Since the NOEL is by definition a sub-threshold dosage level, this safety factor approach would not be applicable to pesticides that are carcinogenic and mutagenic and purportedly have no threshold dose. Hazard evaluation in these cases is performed by risk estimation. In this approach, mathematical models are used to determine the probability of tumor occurrence in man. However, there are a number of statistical issues that still need to be resolved before accurate risk estimations can be made.

Future Research Directions

Risks associated with pesticide use can be more accurately assessed through a better understanding of the current toxicology data base. This can be achieved by the development of new strategies designed to elucidate the biological mechanisms underlying toxicologic responses. For example, a number of shortcomings of traditional and present protocols render the prediction of carcinogenic risks to humans from animal experimentation unsatisfactory. New strategies should include incorporation of pharmacokinetic and metabolism data to allow elucidation of genotoxic mechanisms as a basis for better risk evaluation(4). Use of such data to assist in selection of dosage levels for chronic studies will ensure that normal metabolic processes are not overloaded and that biological responses of the test animals are more representative of the actual toxicity of the pesticide. This will allow for more precise extrapolation of data from animals to man.

A variety of liver culture systems are available for detecting genotoxic (DNA-damaging) and epigenetic (non DNA-damaging) effects of carcinogens. Current evidence indicates that carcinogens have distinctive properties and probably act by different mechanisms(5). Therefore, different risk assessments could be used for different types of carcinogens. While conservative one-hit risk models may be appropriate for some genotoxic carcinogens, other risk models, such as the Weibull model, may better approximate the risk associated with epigenetic carcinogens(6,7).

While the list of animal teratogens grows longer and longer, few significant advances have been made to increase our understanding of the mechanism of teratogenesis and our ability to extrapolate these findings to human reproductive hazard assessment. While no single test species can be said to accurately predict the true human response to a given test substance, tests in multiple species may increase the predictive reliability of animal test data. Increased basic research coupled with better monitoring of human populations will eventually lead to a better understanding of how animal data can best be used to predict human reproductive risks(8).

Finally, immunotoxicology has been a topic of much interest today, especially considering the drastic consequences of immunosuppression which can result in the loss of immune surveillance/protective mechanisms against infectious agents and cancer. However, no consensus exists on which test procedures are most suitable for incorporation into routine toxicology assays. One approach which has been considered is to conduct immunotoxicity testing during standard subchronic toxicity studies by collecting peripheral blood samples for immune function tests(9).

Conclusion

New strategies are required for carcinogenicity testing and risk estimation. Current testing requirements involve administration of pesticides to test animals at dosage levels which may be of such magnitude that they substantially alter the animals normal metabolic, physiologic or pharmacologic response. Clearly, doses which result in metabolic overload and are unrealistic, given typical human exposure patterns, should be avoided in chronic bioassays. Results of studies obtained at such doses cannot be reliably extrapolated to the low doses to which man will be exposed. Therefore, risk estimation should not be performed for toxic effects produced in test animals that are physiologically compromised. Also, extrapolation of results from a properly conducted study should be performed using the most appropriate risk model; for example, one which most accurately fits the experimental data and also takes into account the probable mechanisms of action of the test substance.

Improved test methods are needed to better assess potential adverse effects on the reproductive and immune systems. This can only be obtained through increased basic research and critical evaluation of adverse effects which are presently found in human populations. In this manner, results of animal testing can be better extrapolated to man.

Literature Cited

1. "Data Requirements for Pesticide Registration", Environmental Protection Agency, Federal Register, 1984, 49, 42856-905.
2. "Pesticide Assessment Guidelines, Subdivision F Hazard Evaluation: Human and Domestic Animals", Office of Pesticide Programs, Environmental Protection Agency, 1982.
3. Wolf, F. J. J. Environ. Path. Toxicol. 1980, 3, 113-134.
4. Henschler, D. Trends in Pharm. Sci. (FEST Supplement) 1985, 6, 26-8.
5. Williams, G. M. Reg. Toxicol. Pharm. 1985, 5, 132-44.
6. Carlborg, F. W. Fd. Cosmet. Toxicol. 1981, 19, 155-63.
7. Rodricks, J.; Taylor, M. R. Reg. Toxicol. Pharm. 1983, 3, 275-307.
8. Frankos, V. H. Fund. Appl. Toxicol. 1985, 5, 615-25.
9. Noebury, K. C. J. Am. College Toxicol. 1985, 4, 279-90.

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Chapter 3

Acute Versus Chronic Toxicity and Toxicological Interactions Involving Pesticides

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Selected examples of insecticides, herbicides, fungicides, nematocides and fumigants are discussed in regard to the similarities or differences in their respective acute, subchronic, and chronic toxicity. Similarity, in the sense of toxicity to the same target organ, is more likely an exception rather than the rule. For the purpose of this symposium, the area of toxicological interaction involving pesticidal chemicals is of relevance. The classical examples of synergism and/or potentiation between such binary mixtures as pyrethrin and piperonyl butoxide or malathion and EPN are well known. A review is given on some of the more recent examples of modulation of toxicity of chemicals involving pesticides. Finally, an approach is suggested to deal with the increasingly complex problems in toxicology.

Since this chapter is primarily dealing with the comparative aspects of acute and chronic toxicity of pesticidal chemicals, it is appropriate to begin with a discussion of the differences between acute and chronic toxicity. When one reads the readily available books, monographs, and other documents in toxicology (1-9), it is quite easy to find a clear-cut definition for acute toxicity, but not for chronic toxicity. For instance, the Organisation of Economic Cooperation and Development (OECD), in its Guideline for Testing Chemicals (5), defined acute toxicity as "the adverse effects occurring within a short time of administration/exposure of a single dose of a substance or multiple doses given in 24 hours". An actual definition was not given in the same document for chronic toxicity. In the proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules by the EPA (6), "chronic effects" was defined as "...disease processes which have a long latency period for development, result from long-term exposure, are long-term illnesses, or combinations of these factors." But ambiguity still exists; for instance, how long is "long-term"? The reason for the absence of a clear-cut definition for chronic toxicity is the complexity of events

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and factors involved in the development of chronic toxicity in animals. In Table I, a comparison of acute and chronic toxicity is given according to a variety of factors.

Table I. Comparison of Acute and Chronic Toxicity

Factors	Acute Toxicity	Chronic Toxicity
Exposure		
Frequency	Single/Repeated/ Continuous	Repeated and prolonged
Duration	Within 24 hrs	At least 1/2 of the life span; less in humans
Pharmacokinetics	Blood level high; bioavailable for a short time (i.e. hrs, days)	Gradual build up of blood level; bioavailability prolonged (i.e. months, yrs)
Responses	Immediate or in a short time (i.e. within days) Involving few target organs/systems	Delayed; prolonged (i.e. months, yrs); may be self-propagating Diversified target organs/systems
Experimental design	Many differences involving a number of parameters; see text	
References (1-9)		

It must be noted at the outset that certain grey areas do exist between acute and chronic toxicity and a sharp distinction may not be drawn between the two in certain cases. More detailed discussion on specific examples will be given later.

With respect to the frequency and duration of exposure, as indicated before, acute toxicity is the result of single or repeated or continuous exposure within a 24-hr period. On the other hand, chronic exposures, which are different from chronic effects (1,9), are defined as repeated or continuous exposures over a long period of time, generally more than half of the life span of the animal, although a shorter period is used for humans (9). Figure 1, although an oversimplification, illustrates the theoretical pharmacokinetic differences between acute and chronic exposure. In general, acute exposure, because of higher dosages, would result in higher blood levels in a relatively short time span. Chronic exposure, on the other hand, involves relatively low dosage levels with accumulation over a long period of time. If one compresses these blood kinetic profiles to the actual scales of a subchronic or chronic exposure, the theoretical differences become immediately apparent.

In Figure 1, every rise and fall reflects a dosing interval. When the time scale becomes "years", the blood level of the chemical may only be represented graphically as a solid block between the minimal and maximal concentrations.

With respect to toxicological responses or effects, there may be quantitative or qualitative differences between acute and chronic

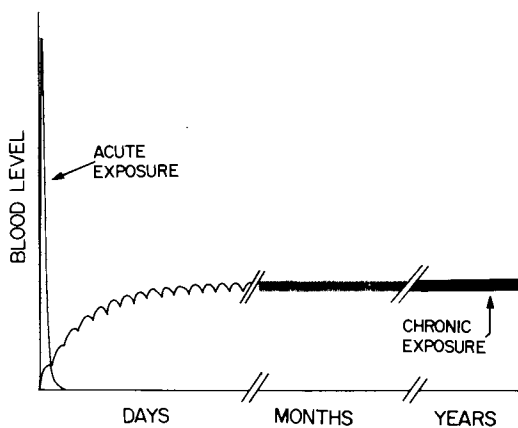


Figure 1. Theoretical pharmacokinetic profiles of a chemical in the blood of a mammal dosed via acute, subchronic, or chronic exposures in relation to different time scales.

toxicity. For many chemicals, the acute toxic effects are different from the toxicities resulting from chronic exposure (4,10). Chan *et al.* (11) summarized the common signs and the organs, tissues, or systems most likely to be involved in acute toxicity studies. An overwhelmingly large portion of the acute toxic effects was primarily related to the dysfunction of the nervous system. On the other hand, if one considers only one specific area of chronic toxicity, chemical carcinogenesis, the target sites may include hematopoietic, respiratory, digestive, endocrine, urinary, and reproductive systems comprising many different organs.

Two other points that deserve special mention are the self-propagating effects of certain types of chronic toxicity (i.e., neoplasm, advanced stages of cirrhosis) and the long, latent period for certain instances of chronic toxicity (i.e., delayed neurotoxicity, neoplasms). This latter category of chronic toxicity may be induced in some instances after only one single exposure. In experimental toxicology, the designs of acute and chronic toxicity studies vary greatly in regard to animal numbers, dosages, environmental conditions, modes and routes of exposure, duration of the studies, toxicological endpoints, and statistical analyses. These differences are beyond the scope of this presentation.

Acute and Chronic Toxicity of Pesticides

There are literally thousands of chemicals and/or formulations in the major categories (i.e., insecticides, herbicides, fungicides, rodenticides, fumigants, nematocides) of pesticides. Therefore, no attempt was made to provide a review of representatives of all the major classes of pesticides. In the section which follows, selected pesticides from three chemical classes, the organophosphates, the halogenated hydrocarbons, and the pyrethroids, will be discussed in regard to the differences and similarities between acute and chronic toxicity. The criteria for selection of the examples are mainly related to the availability of current information in the literature.

Organophosphates. The acute toxicity of organophosphate pesticides is basically derived from the anticholinesterase property of these chemicals. This property, which results in accumulation of acetylcholine at synapses and myoneural junctions, is responsible for both the insecticidal activity and mammalian toxicity. Early symptoms of organophosphate poisoning in humans include, among others, miosis (pinpoint pupils) and blurred vision, and a response known as the SLUD (salivation, lacrimation, urination, and diarrhea) syndrome; all of these are the result of muscarinic effects (12-15). Clinical manifestations of more severe poisoning involve predominantly nicotinic and central effects which include convulsions, paralysis, depressed respiration and cardiovascular functions, and coma (12-15). Death is usually due to respiratory failure, accompanied by cardiovascular failure (13).

Chronic toxicity of organophosphates may be discussed under four different areas: carcinogenicity, delayed neurotoxicity, experimental myopathy, and, in humans, psychiatric disorders. In 1983, the IARC (International Agency for Research on Cancer) evaluated the carcinogenic potential of, among other pesticides, five organophosphate insecticides/acaricides (malathion, methyl parathion, parathion,

tetrachlorvinphos, and trichlorfon) (16). One of these, tetrachlorvinphos, was considered to have provided limited evidence of carcinogenicity to experimental animals. This evaluation was based on the treatment-related increases of hepatocellular adenoma and carcinoma in B6C3F₁ mice, and C-cell adenoma of the thyroid and cortical adenoma of the adrenal in Osborne-Mendel rats (16). A recent oncogenicity study of tetrachlorvinphos in B6C3F₁ mice confirmed the carcinogenic potential of this chemical to the male mice at a very high dose level (i.e., 16,000 ppm, the highest level used in an earlier NCI study) but the investigators questioned the utility of results from a dose level which exceeded the maximum tolerated dose level (17). The four other organophosphates evaluated by the IARC were reported as either having inadequate evidence to evaluate its carcinogenicity to experimental animals (parathion, trichlorfon) or that the available data did not provide evidence for carcinogenicity in experimental animals (malathion, methyl parathion). Two recent publications (18,19) which appeared in the same issue of Environmental Research raised a controversy over the carcinogenicity of malathion and its oxygen analog, malaaxon. Reuber (18), a pathologist claimed to have made the histopathological examination of the National Cancer Institute (NCI) studies, felt strongly that both malathion and malaaxon are carcinogenic in Osborne-Mendel and Fischer 344 rats. However, the NCI Technical Reports (20-22), which did not list Reuber as a contributor, concluded that neither chemical was shown to be carcinogenic. The other publication, by Huff *et al.* (19), summarized the results of histopathology reexamination by a team of pathologists at and/or for the National Toxicology Program (NTP) following the renewed public health interests and concern about the increasing use of malathion in agriculture and especially its use to control Mediterranean fruit fly in California and Florida during the 1980s. The NTP team confirmed the original NCI interpretative conclusion that malathion was not carcinogenic. For the malaaxon study, the only difference between the original and subsequent interpretations was for C-cell neoplasms of the thyroid gland, in that the NTP concluded that there was equivocal evidence of carcinogenicity for male and female F344 rats (19).

The delayed neurotoxicity, experimental myopathy, and psychiatric disorders (human) represent some of the grey areas between acute and chronic toxicity. Since these effects may be induced with one or few exposures with a short latency period, they should be considered as acute effects. However, they are grouped under chronic toxicity in this presentation for three reasons: (a) there is reason to believe that at least one and possibly more of these toxic responses may be induced chronically; (b) the exposure periods to humans in clinical cases were often uncertain; (c) these responses are all considered as chronic effects in the medical literature (e.g. 14,15).

Delayed neurotoxicity results from degeneration of the axons followed by demyelination (14,15,23). Clinical manifestation includes sensory disturbances, ataxia, weakness, muscle twitching and, in severe cases, complete flaccid paralysis (15). A fair number of organophosphate compounds are capable of inducing delayed neurotoxicity. Of the 250 organophosphates (not all pesticides) tested for delayed neurotoxicity in chickens, 47% (117 chemicals) showed positive responses (23). Notable examples of pesticides which possess this neurotoxicity are leptophos, EPN, merphos, dichlorvos, and

trichlorfon (23). In general, delayed neurotoxicity may be induced by these chemicals after a single dose with a latent period of about 6 to 14 days (23). However, in HSD, ICR mice, two single oral doses of 1000 mg/kg of TOCP at a 21-day interval failed to induce neuropathy whereas daily dosing of 225 mg/kg TOCP for 9 months caused, among other toxic signs, muscle wasting, weakness and ataxia which progressed to severe hindlimb paralysis at the termination of the study (24). The development of neuropathy in this case was very slow; severe ataxia was not evident until after about 8 months of dosing (24). This may very well be an example where a similarity exists between acute and chronic toxicity.

Experimental myopathy following acute or repeated administration of certain organophosphates in laboratory animals is characterized initially by focal necrosis and subsequently by a generalized breakdown of muscle fiber architecture (14,15,25). The diaphragm appears to be the most severely affected (25). Myopathic alterations in humans following organophosphate poisoning have also been reported (14,26,27). Related toxic responses include muscle tenderness, changes in surface electromyography (EMG) and elevated muscle enzymes such as CPK (creatine phosphokinase) (14). Psychiatric disorders including acute psychosis or severe depressions were reported in greenhouse workers, farm workers and scientists working with organophosphate pesticides (14).

Halogenated Hydrocarbons. Three representative chemicals, 2,4-dichlorophenoxyacetic acid (2,4-D), hexachlorobenzene (HCB) and 1,3-dichloropropene (DCP), will be discussed in this section.

2,4-D, a well-known herbicide, is of low to moderate acute toxicity; depending on the salt forms used, the LD₅₀'s are in the order of several hundred to about 2000 mg/kg body weight (28). Animals given a lethal dose of 2,4-D appear to die from ventricular fibrillation. At sublethal doses, toxic responses to 2,4-D are indicative of neuromuscular involvement, including stiffness of the extremities, ataxia, paralysis and eventually coma (29-31). The central nervous system appeared to be a target organ in the acute toxicity of 2,4-D (31). A number of chronic toxicity studies were reviewed recently by Collins (31). Most of the experiments revealed no 2,4-D treatment-related chronic toxicity. In 1982, the IARC considered that there was inadequate evidence for carcinogenicity of 2,4-D to humans and animals (32) and that status is still true in 1986 (31). However, there is a report in which neurobehavioral signs, as well as changes in clinical chemistry parameters, were observed in pigs fed the triethanolamine salt of 2,4-D at 500 mg/kg of diet for up to one year (33). Kidney lesions (epithelial regeneration) of minimal severity were seen in male Fischer 344 rats on a 13-week subchronic study sponsored by The Industry Task Force on 2,4-D Research Data (31).

HCB has been used as a fungicide to control wheat bunt and smut fungi on other grains (34). However, the major source of environmental concern for HCB is derived from its being a byproduct or waste material in the production of many chemicals (34,35). HCB has a low order of acute toxicity; its oral LD₅₀ ranges from 1,000 to 10,000 mg/kg in several animal species (34,35). Toxic signs as a result of acute exposure to HCB are related to neurotoxic manifestations such as trembling, ataxia and paralysis (36). Death is due to neurotoxic effects (34,37).

Chronic toxicity of HCB involves three different areas: carcinogenicity, porphyria, and neurotoxicity. A number of carcinogenicity studies were conducted with Syrian golden hamsters, Swiss mice, and Wistar and Sprague-Dawley rats, and they were reviewed recently (35,38,39). HCB is carcinogenic in all three species, and the major target organs include liver, kidney, thyroid, parathyroid, adrenal, and the lymphohematopoietic system (35,38,39).

Experimental porphyria may be induced by a single dose of HCB (40) as well as by repeated or chronic exposure to HCB (34,35,40), another example of similarity between acute and chronic toxicity. An epidemic of about 4000 cases of human porphyria (porphyria cutanea tarda or porphyria turcica) occurred in Turkey between 1955 and 1959 as a result of consumption of grain that had been treated with HCB (34,35,41,42). Clinical manifestations included generalized hyperpigmentation and hypertrichosis, scarring on the cheeks and hands, and tight sclerodermoid changes of the nose with perioral scarring; and in children, painless arthritic changes with osteoporosis of carpal, metacarpal and phalangeal bones and atrophy or failure to develop in the terminal phalanges. In addition, neurologic symptoms including weakness, paresthesias, myotonia, and cogwheeling were observed (34,35,41,42). Neurotoxic signs such as ataxia and paralysis have also been observed in experimental animals treated with HCB subchronically or chronically (35). It is noteworthy that other toxic effects of HCB, including immunosuppression, body and organ weight changes, alterations of clinical pathology parameters, were also reported (34,35).

DCP is the main ingredient of a number of commercial fumigant formulations. Information on the toxicology of DCP is generally derived from the results of the commercial preparation Telone II (approximately 92% DCP) and/or D-D (approximately 52% DCP) (43). DCP, Telone II and D-D are moderately toxic to mammals in acute exposures. The primary target organs in rats following acute oral dosing of Telone are liver, kidneys and possibly lung (44). The acute toxic responses in rats and mice following peroral treatment of D-D include hyperexcitability, followed by tremors, incoordination, depression, and dyspnea. The pathological changes in animals that died from D-D exposure included distension of the stomach by fluid and gas, erosion of the gastrointestinal mucosa, occasional hemorrhages in the lungs, and fatty degeneration of the liver (45). Chronic toxicity of Telone II following gavage dosing (3 times/week) for two years in Fischer 344 rats and/or B6C3F₁ mice included neoplasms (forestomach, liver, lung, urinary bladder), epithelial hyperplasia (forestomach, urinary bladder) and hydronephrosis (43,46,47).

Pyrethroids. Pyrethroids, such as natural pyrethrins and synthetic analogs, allethrin, permethrin, and others, are well known for their neurotoxicity (48-59). However, as a major class of insecticide, they have a remarkable safety margin for mammals, principally because of the rapid metabolic degradation of pyrethroids in mammalian species (48-50). The acute toxicity of pyrethroids involves two distinct syndromes in rats and mice (49-51). The first one, I syndrome or tremor (Type I), is characterized by a rapid onset of tremor, initially in the limbs and gradually extending over the whole body. Death is associated with clonic seizures. The second

syndrome, CS-syndrome or choreoathetosis with salivation (Type II), is characterized by profuse salivation followed by a gradual development of a coarse whole-body tremor and a splayed gait of the hind legs. Clonic and tonic seizures in both species usually result in death.

Despite their popularity as a major class of insecticides, information on chronic toxicity of pyrethroids is limited. Of the several studies mentioned or reported (49,50,52-57), there appeared to be no evidence for carcinogenicity nor were there any significant morphological or ultrastructural alterations in the nervous system. Neurotoxic signs were observed in some of the studies, but they either disappeared after a short period of time or were not accompanied by any significant neuropathy (53,55). Hepatic changes as a result of repeated or chronic exposure to pyrethroids were reported quite consistently (49,52-55). These changes included hypertrophy, bile duct proliferation and multifocal microgranulomata (52-55). Multifocal microgranulomata were also observed in lymph nodes and spleen in mice exposed to fenvalerate chronically (54).

Toxicological Interactions Involving Pesticides

The classical examples of synergism and/or potentiation between such binary mixtures as pyrethrin and piperonyl butoxide or malathion and EPN are well known (60,61). The effects of solvents and impurities on the insecticidal activity of commercial preparations has also been studied (62,63). In a number of recent articles (64-68), toxicological interactions of pesticides and other chemicals were discussed with respect to specific target organs, to dietary and nutritional factors and in light of the possibility of designing safer chemicals. Since, without an exception, all pesticidal chemical formulations are chemical mixtures, the following two examples are presented in the hope of bringing additional attention to this very important area of toxicology.

Mehendale and associates have conducted a series of studies on the effects of pretreatment of Kepone (chlordecone) on the acute toxicity of carbon tetrachloride (69-79). After the discovery of the dramatic potentiation of carbon tetrachloride hepatotoxicity by pretreatment of Kepone (69), Klingensmith and Mehendale (73) and Mehendale (74) demonstrated that pretreatment of young male Sprague-Dawley rats with a very low level (10 ppm) of Kepone in the diet for 15 days enhanced acute toxicity of carbon tetrachloride 67-fold (Table II).

This is probably the first report where a chemical at an environmentally realistic level (i.e. 10 ppm) caused a dramatic potentiation/synergism in the toxicity of another chemical. This potentiative or synergistic effect of Kepone was apparently rather specific in that close structural analogs such as mirex and photomirex do not share this property (74). The underlying mechanism for this phenomenon is being pursued actively in Dr. Mehendale's laboratory, it probably involves the excessive accumulation of intracellular calcium ion and the disruption of hepatocellular repair-regeneration processes (77-79).

Toxicological interactions may occur in chronic toxicity and carcinogenicity studies (80,81). Wong et al. (80) examined the influence of disulfiram on the chronic toxicity of EDB (ethylene

Table II. Enhancement of Acute Toxicity of Carbon Tetrachloride by Low Level Dietary Pretreatment of Kepone

Dietary Pretreatment	48 hr LD ₅₀ (ml/kg)	Increase in Mortality
Carbon tetrachloride		
Control diet	2.8	--
Kepone (10 ppm) diet	0.042	67-fold

Condensed from Klingensmith and Mehendale (73) and Mehendale (74)

dibromide) in a long-term inhalation study. This work came about because the National Institute of Occupational Safety and Health had been interested in minimizing hazards related to workers' exposure to EDB, particularly to those who were in alcohol control programs under disulfiram (antabuse) treatment. The rationale for this concern was derived from the enzyme inhibitory properties of disulfiram toward acetaldehyde dehydrogenase. Since this enzyme plays a key role in the biotransformation of EDB, it was thought that its inhibition might modify the toxicity of EDB, including its carcinogenicity.

Table III. Experimental Design of the EDB/Disulfiram Interaction Study

Animal:	Sprague-Dawley rats
Test groups:	Control EDB (20 ppm, inhalation) Disulfiram (0.05% in diet) EDB + Disulfiram
Group size:	48 rats/group/sex
Duration of exposure:	18 months
Exposure frequency:	7 hr/day, 5 days/week (inhalation) Diet given <u>ad libitum</u> except chamber exposure period
Endpoints	Body weights Food consumption Mortality Hematology Gross and Histopathology

Condensed from Wong et al. (80)

The experimental design of the study by Wong et al. (80) is summarized in Table III. Dramatic enhancement of mortality was observed as early as 9 months in the EDB/Disulfiram combination group and the results of the cumulative mortality of the last 9 months of the study are summarized in Table IV.

Table IV. Cumulative Mortality in Rats of the EDB/Disulfiram Interaction Study

	Month							
	Male				Female			
	9	12	15	18	9	12	15	18
Control	0	0	1	5	0	2	3	6
Disulfiram	1	2	4	6	1	2	2	3
EDB	1	5	30	43	1	4	19	37
EDB + Disulfiram	8	23	48	48	12	40	48	48

Condensed from Wong *et al.* (80)

Toxicological interactions were seen also in the marked increases of tumor incidences (except mammary tumors) as well as in the shortening of the latent period. Table V is a summary of the major histopathological findings in the EDB alone group and the EDB/disulfiram combination group. Control and disulfiram alone groups were not included to conserve space. Other than the significant increase of mammary tumors in the disulfiram alone female rats, no other tumor incidences were different from the background in these two control groups.

Table V. Major Histopathological Findings in Rats Exposed to EDB or EDB/Disulfiram (EDB+DS) in the EDB/Disulfiram Interaction Study

	EDB		EDB+DS	
	Male	Female	Male	Female
No. of Animals Examined	46	48	48	45
Liver				
hepatocellular tumors	2	3	36*	32*
Mesentary or omentum				
hemangiosarcoma	0	0	11*	8*
Kidney				
adenoma and adeno- carcinoma	3	1	17*	7*
Thyroid				
follicular epithelial adenoma	3	1	18*	18*
Mammary				
all tumors	---	25	---	13*
Lung				
all tumors	3	0	9*	2
No. of Rats with Tumor	25	29	45*	45*
No. of Rats with Multiple Tumors	10	8	37*	32*

* $P < 0.05$ Condensed from Wong *et al.* (80)

A Possible Approach For Dealing With Toxicological Interactions

Having reviewed these two examples of toxicological interactions involving pesticides, let us put things into perspective. Are we in imminent danger because of potential toxicological interactions due to environmental pollution or occupational exposure to pesticides and/or other chemicals? The answer is probably "no". Dr. John Doull stated some reasons why the answer is no in the Proceedings of the 5th International Congress of Pesticide Chemistry "...As a group, the pesticides have been subjected to a more thorough toxicologic investigation in animals than any other class of chemicals, including drugs..." and "...Considering the extreme toxicity of some of the pesticides and the severity of their adverse effects, their overall safety record is remarkably good..." (82). Should we then ignore the issue of toxicological interactions? The answer is obviously a "no" because, as long as we use these chemicals to enhance the quality of our life, we can not possibly afford to have a detrimental surprise in the human population. What are we to do then? The long-range answer, in my view, lies in the application of some of the recent advances in pharmacokinetics and computer technology.

As shown in Figure 2, the concepts of "physiologically-based pharmacokinetics" and "animal scale-up" were initiated in the late 1960s and early 1970s by Bischoff *et al.* (83-85), Dedrick *et al.* (86), and Dedrick (87,88). Physiologically-based pharmacokinetics differ from the classical pharmacokinetics in that: (a) the utilization of a large body of physiological and physicochemical data which are not chemical specific; (b) interspecies extrapolation may be attempted with more confidence; (c) the pharmacokinetic behavior of certain chemicals may be predicted *a priori* or from very limited data; and (d) compartments correspond to anatomical entities such that organ or tissue specific biochemical interactions can be incorporated (88).

If one draws an analogy of the "scale-up" from a mouse to a human to the scale-up of a chemical plant or a chemical engineering process, one finds that both situations are governed by a great number of physical and chemical processes (87). In mammals, the physical processes (i.e., mass balances, thermodynamics, transport, and flow) often vary in a predictable way. However, chemical processes such as metabolic reactions may vary greatly and unpredictably among species. The physical and chemical processes interact such that the pharmacokinetics of any given chemical between one species and another may be predictable depending on the amount of background information available (87).

In the past, the application of physiologically-based pharmacokinetics was limited by the complexity of the mathematics involved because of the large number of parameters in the models. In recent years, the advances in computer software have overcome this limitation. Thus, earlier this year, Clewell and Andersen (89) reported that by using the Advanced Continuous Simulation Language (ACSL), physiologically-based pharmacokinetic modelling may be carried out on personal computers with reasonably short turn-around times (i.e., execution time, 0.6-8 minutes) and in a user-friendly manner.

Presently, the application of these techniques in toxicology is being actively pursued for the extrapolation between routes, between

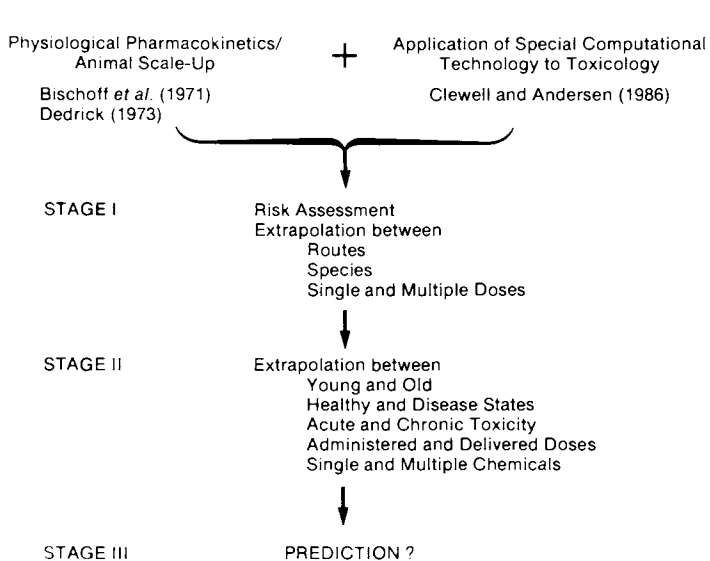


Figure 2. A suggested approach utilizing physiologically based pharmacokinetics and computer technology for the extrapolation and prediction of various situations in toxicology.

species, between single and multiple doses, and in its application to the risk assessment process (90-95). All these efforts are combined in Figure 2 as a Stage I effort. It is conceivable that in the foreseeable future, with the availability of more research data, further extrapolation may be made between the young and the old, the healthy and the diseased, acute and chronic toxicity, the administered (exposure) and delivered (effective) doses, and between single and multiple chemical exposures (Stage II effort, Figure 2). The ultimate hope is, of course, to "predict" the possible outcome of toxicity for one or more chemicals (including toxicological interactions) in one or more species with little or no need of doing the actual tedious animal experimentation such as the chronic toxicity studies.

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Literature Cited

1. Doull, J.; Klaassen, C. D.; Amdur, M. O. "Casarett and Doull's Toxicology. The Basic Science of Poisons"; 2nd Edition; Macmillan Publishing Co., Inc.: New York, 1980; 778 pp.
2. Hayes, A. W. "Principles and Methods of Toxicology"; Student Edition; Raven Press: New York, 1984; 750 pp.
3. Loomis, T. A. "Essentials of Toxicology"; 3rd Edition; Lea & Febiger: Philadelphia, 1978; 245 pp.
4. Klaassen, C. D. In "Goodman and Gilman's The Pharmacological Basis of Therapeutics"; 6th Edition; Gilman, A. G.; Goodman, L. S.; Gilman, A.; Mayer, S. E.; Melmon, K. L., Eds.; Macmillan Publishing Co., Inc.: New York, 1980; Chap. 68.
5. "OECD Guidelines for Testing of Chemicals," Organisation for Economic Co-operation and Development, 1981.
6. "Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules," U. S. Environmental Protection Agency, Fed. Reg. 1979, 44, 27334-375.
7. "Proposed Guidelines for Registering Pesticides in the United States; Hazard Evaluation: Human and Domestic Animals," U. S. Environmental Protection Agency, Fed. Reg. 1978, 43, 37336-403.
8. "Principles and Procedures for evaluating the Toxicity of Household Substances," National Academy of Sciences, 1977.
9. "Drinking Water and Health," Vol. 1, National Academy of Sciences, 1977.
10. Klaassen, C. D.; Doull, J. In "Casarett and Doull's Toxicology. The Basic Science of Poisons"; 2nd Edition; Doull, J.; Klaassen, C. D.; Amdur, M. O., Eds.; Macmillan Publishing Co., Inc.: New York, 1980; Chap. 2.
11. Chan, P. K.; O'Hara, G. P.; Hayes, A. W. In "Principles and Methods of Toxicology"; Student Edition; Hayes, A. W., Ed.; Raven Press: New York, 1984; Chap. 1.
12. Haddad, L. M. In "Clinical Management of Poisoning and Drug Overdose"; Haddad, L. M.; Winchester, J. F., Eds.; W. B. Saunders: Philadelphia, 1983; Chap. 67-68.

13. Gossel, I. A.; Bricker, J. D. "Principles of Clinical Toxicology"; Raven Press: New York, 1984; Chap. 9.
14. Stopford, W. In "Industrial Toxicology. Safety and Health Applications in the Workplace"; Williams, P. L.; Burson, J. L., Eds.; Van Nostrand Reinhold Co.: New York, 1985; Chap. 11.
15. Taylor, P. In "Goodman and Gilman's The Pharmacological Basis of Therapeutics"; 6th Edition; Gilman, A. G.; Goodman, L. S.; Gilman, A.; Mayer, S. E.; Melmon, K. L., Eds.; Macmillan Publishing Co., Inc.: New York, 1980; Chap. 6.
16. "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Miscellaneous Pesticides," International Agency for Research on Cancer, 1983, Vol. 30.
17. Parker, C. M.; Van Gelder, G. A.; Chai, E. Y.; Gellatly, J. B. M.; Serota, D. G.; Voelker, R. W.; Vesselinovitch, S. D. Fundam. Appl. Pharmacol. 1985, 5, 840-54.
18. Reuber, M. D. Environ. Res. 1985, 37, 119-153.
19. Huff, J. E.; Bates, R.; Eustis, S. L.; Haseman, J. K.; McConnell, E. E. Environ. Res. 1985, 37, 154-173.
20. "Bioassay of Malathion for Possible Carcinogenicity, CAS No. 121-75-5," Technical Report Series, No. 24, National Cancer Institute, 1978.
21. "Bioassay of Malaoxon for Possible Carcinogenicity, CAS No. 1634-78-2," Technical Report Series, No. 135, National Cancer Institute, 1979.
22. "Bioassay of Malathion for Possible Carcinogenicity, CAS No. 121-75-5," Technical Report Series, No. 192, National Cancer Institute, 1979.
23. Abou-Donia, M. B. Ann. Rev. Pharmacol. Toxicol. 1981, 21, 511-48.
24. Lapadula, D. M.; Patton, S. E.; Campbell, G. A.; Abou-Donia, M. B. Toxicol. Appl. Pharmacol. 1985, 79, 83-90.
25. Laskowski, M. B.; Dettbarn, W. D. Ann. Rev. Pharmacol. Toxicol. 1977, 17, 387-409.
26. De Reuck, J.; Willems, J. J. Neurol. 1975, 208, 309-14.
27. Wecker, L.; Mrak, R. E.; Dettbarn, W. D. J. Environ. Pathol. Toxicol. Oncol. 1985, 6, 171-6.
28. "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals," International Agency for Research on Cancer; Vol. 15; 1977.
29. Gehring, P. J.; Betso, J. E. Ecol. Bull. 1978, 27, 122-33.
30. Hill, E. V.; Carlisle, H. J. Ind. Hyg. Toxicol. 1947, 29, 85-95.
31. Collins, J. J. Rev. Environ. Contam. Toxicol. Manuscript submitted.
32. "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans," International Agency for Research on Cancer, 1982, p. 101, Supplement 4.
33. Bjorkland, N. E.; Erne, K. Acta Vet. Scand. 1966, 7, 364-90.
34. "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Halogenated Hydrocarbons," International Agency for Research on Cancer, 1983, Vol. 20, pp. 155-78.
35. "Health Assessment Document for Chlorinated Benzenes," U.S. Environmental Protection Agency, 1985.

36. Gehring, P. J.; MacDougall, D. "Review of the Toxicity of Hexachlorobenzene and Hexachlorobutadiene;" Dow Chemical, U.S.A.; 1971.
37. Booth, N. H.; McDowell, J. R. J. Amer. Vet. Med. Assoc. 1975, 166, 591-5.
38. Cabral, J. R. P.; Shubik, P. International Symposium on Hexachlorobenzene, International Agency for Research on Cancer, Lyon, France, June 24-28, 1985. (Abstract).
39. Erturk, E.; Lambrecht, R. W.; Peters, H. A.; Morris, C. R.; Bryan, G. T. International Symposium on Hexachlorobenzene, International Agency for Research on Cancer, Lyon, France, June 24-28, 1985. (Abstract).
40. Sweeney, G. D.; Janigan, D.; Mayman, D.; Lai, H. S. A. J. Lab. Clin. Med. 1971, 17, 68-72.
41. Goemen, A. International Symposium on Hexachlorobenzene, International Agency for Research on Cancer, Lyon, France, June 24-28, 1985. (Abstract).
42. Peters, H. A.; Cripps, D. J.; Goemen, A.; Erturk, E.; Bryan, G. T.; Morris, C. R. International Symposium on Hexachlorobenzene, International Agency for Research on Cancer, Lyon, France, June 24-28, 1985. (Abstract).
43. Yang, R. S. H. Residue Rev. 1986, 97, 19-35.
44. Torkelson, T.; Oyen, F. Amer. Ind. Hyg. Assoc. J. 1977, 38, 217-23.
45. Hines, C. H.; Anderson, H. H.; Moon, H. D.; Kodama, J. K.; Morse, M.; Jacobsen, N. W. Arch. Ind. Hyg. Occup. Med. 1953, 7, 118.
46. "Toxicology and Carcinogenesis Studies of Telone II in F344/N Rats and B6C3F₁ Mice (Gavage Studies)," National Toxicology Program, Tech. Rep. No. 269, 1985.
47. Yang, R. S. H.; Huff, J. E.; Boorman, G. A.; Haseman, J. K.; Kornreich, M. J. Toxicol. Environ. Health 1986, 18, 377-92.
48. Casida, J. E. Environ. Health Perspect. 1980, 34, 189-202.
49. Casida, J. E.; Gammon, D. W.; Glickman, A. H.; Lawrence, L. J. Ann. Rev. Pharmacol. Toxicol. 1983, 23, 413-38.
50. Aldridge, W. N. Proc. 5th Int. Congr. Pesticide Chem., 1982, 3, 485-90.
51. Gray, A. J. NeuroToxicology 1985, 6, 127-38.
52. Miyamoto, J. Environ. Health Perspect. 1976, 14, 15-28.
53. Litchfield, M. H. Proc. 5th Int. Congr. Pesticide Chem., 1982, 2, 207-11.
54. Parker, C. M.; McCullough, C. B.; Gellatly, J. B. M.; Johnston, C. D. Fundam. Appl. Toxicol. 1983, 3, 114-20.
55. Parker, C. M.; Piccirillo, V. J.; Kurtz, S. L.; Garner, F. M.; Gardiner, T. H.; Van Gelder, G. A. Fundam. Appl. Toxicol. 1984, 4, 577-586.
56. Dyck, P. J.; Shimono, M.; Schoening, G. P.; Lais, A. C.; Oviatt, K. F.; Sparks, M. F. J. Environ. Pathol. Toxicol. Oncol. 1984, 5, 109-117.
57. Parker, C. M.; Patterson, D. R.; Van Gelder, G. A.; Gordon, E. B.; Valerio, M. G.; Hall, W. C. J. Toxicol. Environ. Health 1984, 13, 83-97.
58. Hallenbeck, W. H.; Cunningham-Burns, K. M. In "Pesticides and Human Health"; Springer-Verlag: New York, 1985; 166 pp.

59. Parker, C. M.; Albert, J. R.; Vaan Gelder, G. A.; Patterson, D. R.; Taylor, J. L. Fundam. Appl. Toxicol. 1985, 5, 278-286.
60. Murphy, S. D. In "Casarett and Doull's Toxicology. The Basic Science of Poisons"; 2nd Edition; Doull, J.; Klaassen, C. D.; Amdur, M. O., Eds.; Macmillan Publishing Co., Inc.: New York, 1980; Chap. 16.
61. Matsumura, F. "Toxicology of Insecticides"; Second Edition; Plenum Press: New York, 1985; 598 pp.
62. Brattsten, L. B.; Wilkinson, C. F. Science 1977, 196, 1211-3.
63. Ryan, D. L.; Fukuto, T. R. Pestic. Biochem. Physiol. 1985, 23, 413-24.
64. Wilkinson, C. F.; Murphy, M. Drug Metab. Rev. 1984, 15, 897-917.
65. Hook, J. B.; Serbia, V. C. Proc. 5th Int. Congr. Pesticide Chem., 1982, 3, 515-20.
66. Charbonneau, S. M.; Munro, I. C. Proc. 5th Int. Congr. Pesticide Chem., 1982, 3, 521-5.
67. Kaloyanova, F.; Tasheva, M. Proc. 5th Int. Congr. Pesticide Chem., 1982, 3, 527-9.
68. Kaloyanova, F. In "Health Effects of Combined Exposures to Chemicals in Work and Community Environments"; Proceedings of a Course; European Cooperation on Environmental Health Aspects of the Control of Chemicals-Interim Document 11; World Health Organization: Copenhagen, 1983, pp. 165-95.
69. Curtis, L. R.; William, W. L.; Mehendale, H. M. Toxicol. Appl. Pharmacol. 1979, 51, 283-93.
70. Curtis, L. R.; Mehendale, H. M. Drug Metab. Dispos. 1980, 8, 23-7.
71. Agarwal, A. K.; Mehendale, H. M. Fundam. Appl. Toxicol. 1982, 2, 161-7.
72. Agarwal, A. K.; Mehendale, H. M. Toxicology 1983, 26, 231-42.
73. Klingensmith, J. S.; Mehendale, H. M. Toxicol. Lett. 1982, 11, 149-154.
74. Mehendale, H. M. Fundam. Appl. Toxicol. 1984, 4, 295-308.
75. Lockard, V. G.; Mehendale, H. M.; O'Neal, R. M. Exp. Mol. Pathol. 1983, 39, 230-45.
76. Lockard, V. G.; Mehendale, H. M.; O'Neal, R. M. Exp. Mol. Pathol. 1983, 39, 246-56.
77. Agarwal, A. K.; Mehendale, H. M. Toxicol. Appl. Pharmacol. 1986, In press.
78. Bell, A. N.; Lockard, V. G.; Young, R. A.; Mehendale, H. M. Fourth Int. Congr. Toxicol. Tokyo, Japan; July 21-25, 1986. (Abstract).
79. Bell, A. N.; Mehendale, H. M. FASEB, April, 1986. (Abstract).
80. Wong, L. C. K.; Winsteon, J. M.; Hong, C. B.; Plotnick, H. Toxicol. Appl. Pharmacol. 1982, 63, 155-165.
81. Huff, J. E. Environ. Health Perspect. 1983, 47, 359-63.
82. Doull, J. Proc. 5th Int. Congr. Pesticide Chem., 1982, 3, 433-6.
83. Bischoff, K. B.; Brown, R. G. Chem. Eng. Prog. Symp. Ser. No. 66 1966, 62, 32-45.
84. Bischoff, K. B.; Dedrick, R. L.; Zaharko, D. S. J. Pharm. Sci. 1970, 59, 149-54.
85. Bischoff, K. B.; Dedrick, R. L.; Zaharko, D. S.; Longstreth, J. A. J. Pharm. Sci. 1971, 60, 1128-33.
86. Dedrick, R. L.; Bischoff, K. B.; Zaharko, D. S. Cancer Chemotherapy Rep. Part I 1970, 54, 95-101.

87. Dedrick, R. L. In "Pharmacology and Pharmacokinetics"; Teorell, T.; Dedrick, R. L.; Condliffe, P. G., Eds.; Plenum Publishing Corp.: New York, 1973; pp. 117-45.
88. Dedrick, R. L. J. Dynamic Syst. Measurement Cont. September, 1973, pp. 255-258.
89. Clewell, H. J.; Andersen, M. E. Proc. Soc. Computer Simulation Winter Multi-Conf., San Diego, CA, Jan. 23-7, 1986.
90. Andersen, M. E.; Clewell, H. J. III; Gargas, M. L.; Smith, F. A.; Reitz, R. H. Toxicol. Appl. Pharmacol. Submitted.
91. "Drinking Water and Health," Vol. 6, National Academy of Sciences, 1986, Chap. 6.
92. Clewell, H. J., III; Andersen, M. E. Toxicol. Ind. Health 1985, 1, 111-31.
93. Hoel, D. G.; Kaplan, N. L.; Anderson, M. W. Science 1983, 219, 1032-7.
94. Hoel, D. G. In "Toxicological Risk Assessment"; Vol. 1. Clayson, D. B.; Krewski, D.; Munro, I., Eds.; CRC Press, Inc.: Boca Raton, FL, 1985; Chap. 10.
95. Lutz, R. J.; Dedrick, R. L. In "New Approaches in Toxicity Testing and Their Application in Human Risk Assessment"; Li, A. P., Ed.; Raven Press: New York, 1985; pp. 129-49.

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Chapter 4

New Approaches for the Use of Short-Term Genotoxicity Tests To Evaluate Mutagenic and Carcinogenic Potential

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Two international collaborative studies sponsored by the International Program on Chemical Safety to evaluate short-term tests for genotoxicity have been completed. The first IPCS study was designed to evaluate in vitro eukaryotic assay systems for use as a complement to the Salmonella reverse-mutation assay system. The second IPCS study was designed to evaluate in vivo assay systems and their ability to discriminate between carcinogens and structurally-related noncarcinogens. The results of both of these international trials have been used to develop a unified testing strategy for the evaluation of new test chemicals to evaluate their mutagenic and carcinogenic potential.

It was about ten years ago that short-term tests with Salmonella were first recommended for use in screening environmental chemicals for mutagenic and carcinogenic potential. Since then, the Ames test has been put into widespread use all over the world and thousands of chemicals have been tested to evaluate their mutagenic and carcinogenic potential. Many additional short-term tests were developed to detect other types of genetic damage, as well as nongenotoxic damage that would lead to cancer. With the advent of in vitro metabolic activation, it seemed certain that the metabolism of the whole animal could be mimicked on the Petri plate or in the test tube and that whole animal assays would no longer be necessary.

As a result of large international collaborative studies to evaluate various short-term in vitro and in vivo tests, it has become clear that both approaches are needed and that any battery of assays designed to evaluate environmental chemicals must include both in vitro and in vivo short-term tests. The use of the Ames assay in isolation has resulted in premature, and sometimes false, indictment of potentially useful chemicals. A data base developed with the use of this test alone is inadequate for the evaluation of a chemical's mutagenic and carcinogenic potential in laboratory animals and humans.

In this paper, I intend to review the results of three international collaborative studies to evaluate the general utility

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of short-term tests for mutagenicity and carcinogenicity and the impact of the data base developed in these studies on the design of testing schemes used in the safety evaluation of pesticides and environmental chemicals in general.

International Collaborative Study to Evaluate Short-Term *In Vitro* Tests for Carcinogens

Two international collaborative studies (sponsored by the International Program on Chemical Safety [IPCS] a collaborative program of the World Health Organization, the International Labor Organization and the United Nations Environmental Program) to evaluate short-term tests for genotoxicity have recently been completed (1,2). The first IPCS study was designed to evaluate eukaryotic *in vitro* assay systems for use along with the Salmonella reverse-mutation assay system. The Salmonella assay was shown to be particularly suitable for use in screening environmental chemicals for potential mutagenic and carcinogenic activity in the International Program To Evaluate Short-Term Tests for Carcinogens (IPESTTC) that was started in 1977 (3). In that study it was clear that the Ames Salmonella test could not detect all known carcinogens and it had to be used along with some other short-term test as yet to be identified. In the IPCS *in vitro* study a total of 10 chemicals, consisting of 8 carcinogens that are difficult to detect with the Salmonella assay and 2 noncarcinogens, were used to evaluate the utility of a wide variety of eukaryotic assays for genotoxicity. The 10 chemicals tested are as follows: carcinogens (acrylonitrile, benzene, diethylhexylphthalate, diethylstilboestrol, hexamethylphosphoramide, phenobarbitone, safrole and o-toluidine) and noncarcinogens (benzoin and caprolactam). The eukaryotic systems tested included; assays for gene mutation, gene conversion, crossing-over and aneuploidy in fungi; assays for somatic cell recombination and gene mutation in *Drosophila*; and assays for metabolic cooperation, transformation, single-strand breaks, unscheduled DNA synthesis, chromosome aberrations, sister-chromatid exchange, micronucleus, polyploidy, aneuploidy and gene mutation in mammalian cells in culture. An evaluation of the data base developed in this study showed that the best overall performance was given by the fungal assay for aneuploidy and the chromosome aberration assay in mammalian cells in culture. Since the aneuploidy assay has had limited use outside of the laboratory contributing test data to the collaborative study, a recommendation for more general use will have to await studies to evaluate interlaboratory reproducibility. Assays for chromosome aberrations in mammalian cells in culture, which are in widespread use, were suggested to complement the Salmonella reverse-mutation assay (1). It is important to note, however, that this recommendation was based on a study limited to only ten test chemicals.

In principle, justification for including tests complementary to the Ames test is based on knowledge that genotoxic agents cause damage through various mechanisms that may not be detectable in the Ames test alone. For example, neither structural damage to chromosomes nor the induction of aneuploidy can be detected in the Ames test. As a result of such considerations, it follows that a battery of short-term *in vitro* tests is required to provide a

comprehensive evaluation of the spectrum of genetic damage induced by a genotoxic chemical.

In the initial reports on the utility of the Salmonella assays for identifying carcinogenic potential (4-6) a high percentage of known chemical carcinogens and a low percentage of known chemical noncarcinogens were shown to give a positive response. One of the problems encountered in IPESTTC (3) was the high frequency of positive responses observed *in vitro* for 7 of the 14 chemicals classified as noncarcinogens. The number of *in vivo* short-term tests in IPESTTC was somewhat limited, but the total data base developed in this experiment suggested that, although some noncarcinogens were positive *in vitro* they were negative in *in vivo* short-term tests. Two good examples of these differences were provided by the noncarcinogens in the benzo(a)pyrene and pyrene (BP/P) and the 2-acetylaminofluorene and 4-acetylaminofluorene (2AAF/4AAF) pairs as indicated in Table I.

Table I. Results of Assays on the Two Pairs of Chemicals BP/P and 2AAF/4AAF Reported in IPESTTC

Type of Assay	Number of + Responses/Total Number of Assays			
	BP	P	2AAF	4AAF
<i>in vitro</i>	40/47	17/40	32/36	27/35
<i>in vivo</i>	5/5	0/5	2/2	0/2

Thus, the rationale for the second IPCS study on *in vivo* short-term tests was derived from IPESTTC and it was decided to evaluate the ability of an even broader range of *in vivo* short-term tests to determine which of these show the best discrimination between known chemical carcinogens and noncarcinogens.

International Collaborative Study to Evaluate Short-Term *In Vivo* Tests for Carcinogens

The second IPCS study on *in vivo* assay systems utilized the two test chemical pairs BP/P and 2AAF/4AAF to evaluate a wide range of whole animal short-term tests for genotoxicity and carcinogenicity. In IPESTTC all 4 test chemicals gave positive results in a wide range of *in vitro* short-term tests, and the objective of this second IPCS study was to determine which *in vivo* assays were capable of distinguishing the 2 carcinogens from the two noncarcinogens. The results of this study have only recently been compiled in terms of a final report (2), but the data show clearly that, in general, the collective body of *in vivo* assays does discriminate between the two carcinogens and the two noncarcinogens as shown in Table II.

Table II. Results of Assays on the Two Pairs of Chemicals BP/P and 2AAF/4AAF Reported in the IPCS Collaborative Study on in vivo Assays

Type of Assay	Number of + and +/- Responses/Total Number of Assays			
	BP	P	2AAF	4AAF
<u>in vivo</u>	64/72	2/73	54/75	10/75

Particularly useful in vivo assays were the mouse bone marrow micronucleus assay and the assay for unscheduled DNA synthesis in cultured rat liver cells. Both assays showed good interlaboratory reproducibility and they provide a reasonable battery of in vivo short-term tests for further evaluation of in vitro genotoxins.

Effective Deployment of In Vitro and in Vivo Short-Term Tests for Carcinogenicity

The effective deployment of short-term tests for individual chemicals or their use in mass-screening programs has been the subject of considerable debate in the recent literature (7). Obviously, if in vitro genotoxins can be negative in vivo, a sequential scheme of testing may be required to develop a data base that will permit a comprehensive evaluation of mutagenic and carcinogenic potential. One possible approach to this problem is given in Figure 1.

In this scheme a chemical is subjected to an in vitro battery of tests (the Salmonella assay and an assay for chromosome aberrations in mammalian cells in culture) to determine whether it is a genotoxin in vitro and produces the type of genetic damage that can be detected by each of these assays. A positive result in one or both of the assays classifies the chemical as a genotoxin and the chemical is then tested with a battery of in vivo assays. If both of the in vitro assays are negative, then the chemical is tested in the appropriate battery of assays to detect nongenotoxic carcinogens. These tests may include assays for in vitro transformation, unscheduled DNA synthesis, etc. Positive results with any of these assays will classify the chemical as a potential carcinogen.

In vitro genotoxins are then subjected to a battery of in vivo tests (e.g. the mouse bone marrow micronucleus test and the rat liver assay for unscheduled DNA synthesis). Since enzymatic detoxification may well be organ-specific, one of the main problems in the in vivo assays is the development of a group of tests that will permit a comprehensive evaluation of the activity of the chemical being tested in the appropriate target organs (liver, lung, kidney, bone marrow, etc) as well as the gonads (ovary and testis). The dominant lethal test in the rat has been used extensively to evaluate the mutagenic effects of chemicals on germ cells, but positive results do not always indicate genotoxicity (8). The data base on other germ cell assays is much more limited and, in general, these tests involving the use of rodent assays for genotoxicity are too costly for general use (9). However, the data base on a new assay for unscheduled DNA synthesis in the testis developed by Sega and presented as an

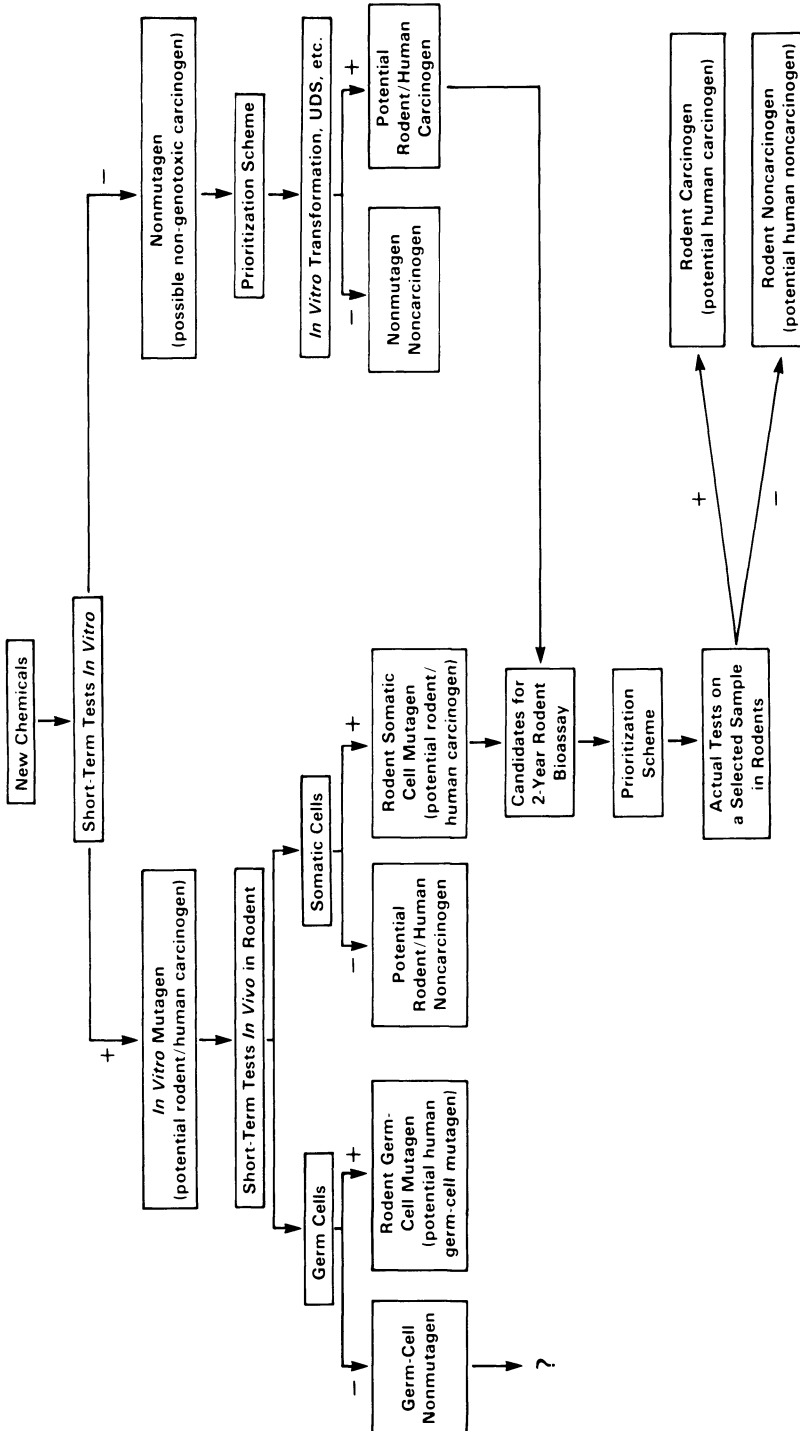


Figure 1. Proposed testing scheme for identification and classification of test chemicals with short-term in vitro and in vivo assays.

appendix to the Russell paper (9), looks promising. The development of a sufficiently comprehensive battery of in vivo assays will eventually permit the classification of those chemicals that give negative results as potential rodent/human nongenotoxins and as germ-cell nonmutagens. Chemicals that give positive results in one or more assay will be classified as potential rodent/human carcinogens and will have to be tested in the traditional two-year rodent bioassay for cancer.

In summary, these studies have demonstrated the general utility of short-term tests to evaluate the mutagenic and carcinogenic potential of environmental chemicals. It is now clear that to provide a comprehensive evaluation, it will be necessary to supplement such short-term in vitro assays as the Ames Salmonella test and an in vitro assay for chromosome aberrations in mammalian cells in culture with short-term in vivo assays. At present, the best candidates for these in vivo assays are (1) the mouse bone marrow micronucleus assay, and (2) the assay for unscheduled DNA synthesis in rat liver cells.

Literature Cited

1. Ashby, J.; de Serres, F. J.; Draper, M.; Ishidate, M., Jr.; Matter, B. E.; Shelby, M. D., Eds. "Evaluation of Short-term Tests for Carcinogens: Report on the International Programme on Chemical Safety's Collaborative Study on in vitro Assays"; Progress in Mutation Research, Vol. 5, Elsevier: North Holland, Amsterdam, 1985.
2. Ashby, J.; de Serres, F. J.; Shelby, M. D.; Margolin, B. H.; Ishidate, M., Jr.; Becking, G. C., Eds. "Evaluation of Short-term Tests for Carcinogens: Report on the International Programme on Chemical Safety's Collaborative Study on in vivo Assays"; Cambridge University Press: Cambridge (in press).
3. de Serres, F. J.; Ashby, J., Eds. "Evaluation of Short-term Tests for Carcinogens: Report of the International Collaborative Study"; Progress in Mutation Research, Vol. 1, Elsevier: North Holland, Amsterdam, 1981.
4. McCann, J.; Choi, E.; Yamasaki, E.; Ames, B. N. Proc. Natl. Acad. Sci. USA 1975, 72, 5135-9.
5. McCann, J.; Ames, B. N. Proc. Natl. Acad. Sci. USA 1976, 73, 950-4.
6. Sugimura, T.; Yahagi, T.; Nagao, M.; Takeuchi, M.; Kawachi, T.; Hara, K.; Yamasaki, E.; Matsushima, T.; Hashimoto, Y.; Okada, M. IARC Scientific Publ. No. 12, International Agency for Research on Cancer; Lyon, 1976, pp. 81-101.
7. Ashby, J.; Purchase, I. F. H. Environ. Mutagen. 1985, 5, 747-758.
8. Green, S.; Auletta, A.; Fabricant, J.; Kapp, R.; Manandhar, M.; Sheu, C.; Springer, J.; Whitfield, B. Mutat. Res. 1985, 154, 49-67.
9. Russell, L. B.; Aaron, C. S.; de Serres, F.; Generoso, W. M.; Kannan, K. L.; Shelby, M.; Springer, J.; Voytek, P. Mutat. Res. 1984, 134, 143-157.

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Chapter 5

Simulation Modeling in Toxicology

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Attempts to understand and manage toxicological manifestations are generally a reactive rather than a predictive endeavor. Although we have responded by addressing untoward reactions with no effect levels and safety factors and oncogenic responses with quantitative and qualitative risk modeling, little has been established as a foundation for prediction of responses. The purpose of this paper will be to present a summary of the state-of-the-art on structure activity modeling; this process may assist in the evolution of predictive approaches to toxicology.

The performance of mechanistic studies to determine how xenobiotics produce their toxic responses is a promising approach for the understanding of risks (1). This technique would appear equally appropriate for a proactive, as well as reactive, examination of the factors involved. Understanding is based on experience; this commodity is as invaluable in proactive reasoning as reactive scrutiny. As we explore approaches to Structure-Activity-Relationship and biotransformation kinetics, it will become apparent that the foundation for the future is firmly anchored to the past. The link between similarity of structure and similarity of biological response is the key to making predictions on biological and/or toxicological properties. Our ability to simulate in models is only as good as our ability to accurately establish that link.

For this consideration of simulation modeling, some of the currently available approaches for prediction of toxicity through chemistry will be examined--looking at both integrated knowledge and empirical evaluation.

Structure Activity Relationships

The information base between toxicological response and chemical structures has been growing exponentially. The integration of these data into a comprehensive and reliable structure activity

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relationship system (SAR) has, generally, been linear. Although computers have assisted greatly in this evolution, development has required that certain basic criteria for effective assessment be met. These requirements are included in Table I.

Table I. Criteria for Reliable Structure Activity Modeling

<ul style="list-style-type: none"> • Broad data base (>60 compounds) <ul style="list-style-type: none"> - Congeneric chemistry (good prediction only within the same class of chemistry) - Same mode/mechanism of action • Relevant test/organism

The incorporation of these criteria into a structure activity model is no simple task. Although it is not necessary to have either congeneric chemistry or the same mode of action for practical SAR models, these data provide a foundation for greater accuracy. A wide variety of biological reactions must be considered.

Quantitative structure activity relationships (QSAR) have been used in designing structures for efficacy for both pharmaceuticals and agricultural chemicals. Hansch (2) was one of the first to attempt to integrate the congeneric chemistry, mathematically, with biological activity; a generalized Hansch regression equation resembles the following (3):

$$\text{Log} \frac{1}{\text{Effective Dose}} = \text{Constant} + (\text{coefficient}_1 \times \text{parameter}_1) + (\text{coeff.}_2 \times \text{par.}_2) + \dots + (\text{coeff.}_n \times \text{par.}_n)$$

Hansch incorporated several chemical/physical chemical characteristics into this approach (4). He found Log P values (log octanol/water partition coefficient) were usually applicable with other parameters, such as Hammett linear free-energy relationships and Van der Waals radii selectively applicable. Continued work in this area by Hansch and other workers (5) has expanded the number of relevant characteristics to include molecular orbital calculations and diffusion parameters. Still, this quantitative approach embodies continuous parameters as an endpoint, a parametric philosophy.

On the other hand, several investigators (6, 7) have taken another approach, based on pattern recognition. These dichotomous models search for agreement between dependent variables; i.e., whether a chemical entity or substructure can be associated with a particular toxic property. For example, certain N-nitrosamine groups are associated with tumors in animals. Since this consideration is not dependent on a relationship between the endpoint and the dose, the quantitative term is dropped from QSAR and the effort simply named SAR. This approach is best expressed by the dependent equation:

$$\text{Toxic Response} = f(\text{Chemical Structure})$$

This is an overwhelming concept when one envisions the number of permutations possible. The Food and Drug Administration (FDA) has tackled this formidable task with just 33 questions to define three presumptive toxicity categories (8). The categories are used to determine the degree of testing required by the FDA. This scheme, though basic and very pragmatic, represents a potentially useful tool for toxicologists, biologists and synthesis chemists. It offers a mechanism to recognize the potential hazard of a compound or to change the molecule to avoid unnecessary toxicity.

The 33 questions on structure are answered by a yes or no (Appendix 1). Each answer leads either to a further question or to the classification into one of three classes of presumptive toxicity (Table II).

Table II. FDA Presumptive Toxicity Classifications

Description	Classification
Relatively innocuous	I
Intermediately toxic	II
Presumptively mostly toxic	III

The requirements for this approach are simple. The structural formula, as well as a knowledge of chemistry and biology are used to make judgements on metabolism.

The FDA has evaluated the reliability of the scheme, using literature data and FDA's inventory of over 1,500 substances and the no observable effect levels derived from subchronic and chronic studies. Thus far, in a retrospective and prospective review, based upon the available information at the Agency, the FDA has no indication that these 33 questions do not adequately classify compounds (cross-comparison of structure to findings) into the three presumptive classes.

However, it is obvious that the FDA approach is a generalized toxicity classification and cannot supply the answers to questions such as, what are the metabolites and which compounds will be teratogens, mutagens or oncogens. Although the FDA approach has built its foundation on a broad data base, it does not narrow its spectrum to a precise toxicological response or mode of action.

It has been clear for some time that pattern recognition approaches would not go far without the computer (9). Utilizing techniques, such as regression, discriminant, and factor analyses progress in SAR (10) has been further enhanced. This evolution has led to such useful tools as described in Table III.

Table III. Computer Assisted Research Models

Model	Function
• Computer Assisted Synthesis Planning (CASP)	• Can predict precursor's need for synthesis as well as most likely metabolites
• Constrained Structure Generation (CONGEN)	• Can generate all possible isomers if the substructure elements and the molecular formula are provided
• ADAPT (11)	• Affords an opportunity to predict the activity and properties of unstudied structures through application of pattern recognition and statistics

Although to the synthesis chemist, CASP and CONGEN may seem highly intriguing, to the biologist, a system such as ADAPT opens the door to the design of new and efficacious molecules for a myriad of uses. In fact, many of the major chemical industries have begun to incorporate such computer assisted systems into their research programs as a component of informed design, rather than the formerly predominant serendipitous discovery. These SAR techniques have not supplanted standard biological efficacy models; however, the information gained helps to establish the foundation for enhanced pattern recognition.

In pattern recognition modeling, such as ADAPT, it is difficult to effectively visualize and manipulate chemical structure. Instead, there has been an effort to translate abstract structure into quantities and/or numerical entities (10), referred to as molecular descriptors. Such descriptors have been classified as presented in Table IV.

Table IV. Molecular Descriptors Used in SAR

Classes of Descriptors	Examples
• Geometric/Biophysical	Rotation axes, molecular volume and surface area
• Physiochemical	Log P, atomic charges, linear-free energy relationships
• Structural	Molecular weight, atomic numbers, types of bonding, molecular orbital calculations, ring structures
• Substructural/topological	Topological and physiochemical properties of substructural arrangements, molecular symmetry and/or bonding

It is obviously not possible to unravel the entire complexity of the physical, chemical and biological properties of even the simplest of molecules. However, focusing on the apparently pertinent descriptors for structures, one can, via pattern recognition, begin to equate toxicological response with structures:

Toxicological response = f(structure) = f(molecular descriptors)

Jurs et al (10) qualitatively and quantitatively examined the correlation of a variety of molecular descriptors for polycyclic aromatic and nitroamine compounds with carcinogenesis. The result of these efforts has been the evolution of predictive equations which capture the oncogenic response for these classes of compounds as a function of the molecular descriptors.

Enslein and coworkers (12, 13, 14, 15) have utilized this approach to develop predictive models for carcinogenicity, teratogenicity and mutagenicity, as well as for acute toxicity endpoints.

This approach in predictive toxicology has manifest itself by the incorporation of certain key principles. These include:

- Marker compounds, compounds with a known biological endpoint, used to produce predictive equations.
- Equations are used for comparison of unknown compounds and to test the system.
- Finally, a statistical approach, such as stepwise regression (if endpoint is continuous) or discriminant analyses (if the endpoint is categorical) to verify the quality of fit.

Despite the great success that has been achieved with the approach taken by Enslein and coworkers, the utility of the system is limited by the depth of the database available in the open literature. If proprietary data were available from the files of pharmaceutical and agricultural companies, a new dimension to the reliability might be added. The possibility that new compounds can be examined for toxicity before they are synthesized is intriguing. However, the release of proprietary information from the bulwark of inherently competitive organizations is not likely in the near future. Therefore, Dr. Enslein plans to make his software available by mid-1987. Then, perhaps, the criteria for reliable structure activity modeling in the area of toxicology may be better served. However, until these criteria are achieved, it will be essential to rely on the more pragmatic approaches to simulation modeling; that is, bioassays.

Predictive Empirical Systems

With pressures from the animal rights movement, an impetus has been generated for the development of in vitro and/or computer models to reduce the level of in vivo testing. In the seventies, the hope of the future was placed in what was then considered a potential replacement technique for the lifetime rodent bioassay for cancer assessment--the short-term mutagenicity tests, particularly the Ames Evaluation (16). Brusick (17) has shown that the correlation between a positive mouse bioassay and a positive rat bioassay for a selected group of materials is no better than the

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match for a positive Ames and/or a positive rat or mouse bioassay (Table V). In addition, a comparison of the Enslein's SAR Carcinogen model (18) for these same human carcinogens is provided.

Table V. Chemicals Evaluated as Positive for Carcinogenicity in Humans Compared to the Response in Rodent and Bacterial Predictive Assays, D. Brusick (17)

Chemical	Rat Bioassay	Mouse Bioassay	Ames Test	Enslein's Model
4-Aminobiphenyl	+	+	+	+
Arsenic	-	-	-	0
Asbestos	+	+	-	0
Benzene	-	-	-	0
Benzidine	+	+	+	+
Bis(chloromethyl)ether	+	+	+	0
Chromium and some chromium compounds	+	-	+	0
Cyclophosphamide	+	+	+	+
Diethylstilbestrol	+	+	-	0
Melphalan	+	+	+	+
Mustard Gas	No Data	+	+	+
2-Naphthylamine	-	+	+	+
Soot, tars	-	+	+	0
Vinyl chloride	+	+	+	+
Percent predictability of humans	69	79	71	100
+ = positive - = negative 0 = cannot be evaluated				

The data from Enslein's Model show that a good match with the rodent bioassays is possible for organics upon which the SAR model is based. The SAR model is ineffective for metals, simple hydrocarbons like benzene, mixtures and hormones. Within these limits, the prediction is 100%. Considering the reliability of rodent and in vitro bioassays to predict the human response, it is possible, with continued development, that in the future, SAR may become a powerful tool to supplement our other sources of toxicological information.

Appendix 1

	If 'No'	If 'Yes'
	...Proceed to...	
1. Normal body constituent?	___ 2	___ I
2. Certain nitrogen <u>FG's</u> ?	___ 3	___ III
3. "Non-physiological" elements?	___ 5	___ 4
4. Innocuous salt of above?	___ III	___ 7
5. Simple <u>...</u> HC or common CHO?	___ 6	___ I
6. Certain p-alkoxy benzenes?	___ 7	___ III
7. Heterocyclic?	___ 16	___ 8
8. Lactone or cyclic diester?	___ 10, 20,10	___ 9
9. Certain lactones?	___ 23	___ III
10. Three-member heterocycle?	___ 11	___ III
11. Hetero ring; strange <u>FG's</u> <u>...</u> ?	___ 12	___ 33
12. <u>Heteroaromatic</u> ?	___ 22	___ 13
13. Any substituents?	___ III	___ 14
14. More than one aromatic ring?	___ 22	___ 15
15. <u>Readily hydrolyzed</u> <u>...</u> ?	___ 33	___ 22(16)
16. <u>Common terpene</u> ?	___ 17	___ I
17. <u>Readily hydrolyzed</u> <u>...</u> ?	___ 19	___ 18
18. Is it one of <u>-----</u> ?	___ I	___ II
19. <u>Open chain</u> ?	___ 23	___ 20
20. <u>Linear or simply branched</u> <u>aliphatic</u> <u>...</u> ?	___ 22	___ 21

	If 'No'	If 'Yes'
	...Proceed to...	
21. Three or more types of FG's?	___ 18	___ III
22. <u>Common component of food or structurally closely related ...?</u>	___ 33	___ II
23. <u>Aromatic?</u>	___ 24	___ 27
24. Monocarbocyclic; certain FG's ...?	___ 25	___ 18
25. Cyclopropane or cyclobutane ...?	___ 26	___ II
26. No unusual <u>FG's</u> ; certain ketones?	___ 22	___ II
27. Any ring substituents?	___ III	___ 28
28. More than one <u>aromatic</u> ring?	___ 30	___ 29
29. <u>Readily hydrolyzed</u> ...?	___ 33	___ 30,18
30. Other than certain substituents?	___ 18(19)	___ 31
31. Acyclic acetal, -ketal, -ester ...?	___ 32	___ 18,19
32. Only certain <u>FG's</u> , plus ...?	___ 22	___ II
33. Enough sulfonate/sulfamate?	___ III	___ I

Literature Cited

1. Stevens, J. T.; Sumner, D. D. J. Toxicol.-Clin. Toxicol. 1983, 19,781.
2. Hansch, C. Chem. Res. 1969, 2, 232.
3. Enslein, K. Pharmacol. Rev. 1984, 36, 131s.
4. Leo, A; Jow, P.Y.C.; Silipo, C.; Hansch, C. J. Med. Chem. 1975, 18, 865.
5. "QSAR and Strategies in the Design of Bioactive Compounds," Seydel, J. K., ed. Verlagsgesellschaft, Weinheim, FRG. 1985.
6. Jurs, P. C.; Chou, J. T.; Yuan, M. J. Med. Chem. 1979, 22, 476.
7. Tinker, J. F. J. Computational Chemistry. 1981, 2, 231.
8. Rulis, A. The Toxicology Forum; 1982 Annual Summer Mtg. 1982, p. 352.
9. Jurs, P. C.; Ham, C. L.; Brugger, W. E. In "Odor Quality and Chemical Structure"; Moskowitz, H. R.; Warren, C. B; Eds.; ACS Symposium Series No. 148, American Chemical Society: Washington, D.C., 1981; pp. 143-160.

10. Jurs, P. C.; Hasan, M. N.; Henry, D. R.; Stouch, T. R.; Whalen-Pederson, E. K. Fund. Appl. Toxicol. 1983, 3, 343.
11. Stuper, A. J.; Brugger, W. E.; Jurs, P. C. In "Computer Assisted Studies of Chemical Structure and Biological Function;" Wiley-Interscience, New York, 1979.
12. Enslein, K.; Craig, P. N. J. Toxicol. Environ. Health 1982, 10, 521.
13. Enslein, K.; Lander, T. R.; Strange, J. R. Teratog. Carcinog. Mutagen. 1983, 3, 289.
14. Enslein, K.; Lander, T. R.; Tomb, M. E.; Landis, W. G. Teratog. Carcinog. Mutagen. 1984, 6
15. Enslein, K.; Lander, T. R.; Tomb, M. E.; Craig, P. N. Benchmark Papers Toxicol. 1983, 1, 1.
16. Wolff, G. L.; J. Environ. Pathol. Toxicol. 1977, 1, 79
17. Brusick, D. In "Application of Biological Markers to Carcinogenicity Testing"; Milman, H. A.; Sell, S.; Eds. Plenum Press, N.Y., 1983; pp. 153-163.
18. Enslein, K., personal communication.

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Chapter 6

Vulnerability of Pests: Study and Exploitation for Safer Chemical Control

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Despite considerable improvements in their safety, the current use of pesticides causes an uncertain but disturbing level of toxicity to non-target organisms on a worldwide basis. A better knowledge of the biochemistry and physiology of pests could reduce this threat by decreasing unintended exposure to existing pesticides and by aiding in the discovery of new and more selective ones. Such knowledge can help in the discovery process in several ways -- in the development of new control concepts, in the rational design of novel compounds, and by providing tools for their efficient evaluation and optimization. Scientifically-based strategies to slow the onset of resistance to such rare and valuable materials must be developed. Here, too, a better knowledge of their biochemical modes of action and of pest vulnerability and defenses will be indispensable. However these goals can be fully realized only if there is greater investment in research into pesticidal mechanisms and responses in target and non-target species.

For the last 25 years and more the use of pesticides has been a controversial and troubled subject of continuing public concern. This concern has been based on the feeling that pesticides, as presently used, may be seriously hazardous to man and to the environment. The degree to which this is true is not clear. On the one hand reasonably complete statistics indicate that in the USA, which uses about 30% of the pesticide produced in the world, less than 50 people a year are killed by accidental exposure to these materials (1), fewer than the number killed by lightning or by insect stings. Statistics for other developed nations show similar mortality rates. However, worldwide estimates of the number of accidental deaths from pesticides, though very uncertain, are much higher, ranging from 5,000 to over 20,000 per year in the early 1970's (2), and indicating a considerable degree of misuse in developing nations. Nor has this situation clearly improved in the last decade. About 13,000 pesticide-related

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hospitalizations and 1000 deaths (73% as suicides) were recorded in the island of Sri Lanka each year from 1975 to 1980 (3), and 500-650 such deaths were recorded in the Phillipines in 1980-1981. The herbicide paraquat accounted for 93 known fatalities in the small island of Trinidad in the single year of 1984 (4).

Estimates of the number of people injured by pesticides vary widely but may be 100-times the accidental death rate on a worldwide basis (5,6). In 1985, 2500 occupationally-related accidental pesticide poisonings were officially reported in California and the real number of injuries may be considerably higher. Neither is the record of safety in pesticide manufacturing in the USA unblemished. Serious injuries to workers involved in manufacturing the insecticide chlordecone, the nematocide dibromochloropropane (DBCP), and, possibly, the insecticide leptophos have been reported in the last 15 years (4,5). There is preliminary but disquieting epidemiological evidence that frequent users of some herbicides may have an elevated risk of contracting cancer, particularly if standard safety precautions are not observed (e.g. 7,8).

The toll on wildlife is uncertain, but the role of DDT and other organochlorine residues in the decline of some raptorial bird populations is reasonably well established and there are regular reports of the death of birds due to exposure to organophosphate insecticides such as diazinon and famphur during normal use, among many other incidents and concerns (9).

It is estimated that at least 50% of food items in the USA contain detectable pesticide residues (6). A considerable segment (77% in a recent poll) of the US population is concerned about pesticide residues in food, and, increasingly, about residues in groundwater and other water that is used for drinking, even though the toxicological significance of such low level exposure is dubious and the results may be mainly a tribute to the sensitivity of modern analytical equipment. These and parallel examples of exposure through spray drift lead to concern and are poorly tolerated by those involved because of their involuntary nature, despite (or perhaps because of) the unclear nature of the degree and type of hazard involved.

Yet pesticides are regarded as essential for modern society -- as a necessary economic investment in agriculture and as a vital tool in the control of vector-borne diseases such as malaria and onchocerciasis. This leads to a tense and adversarial situation between proponents and opponents of pesticides. The situation is appropriately characterized as "you can't live with them and you can't live without them".

In part, the increased pesticidal potency of newer compounds is helping to solve some of these problems. Use rates of such compounds as the photostable pyrethroid and avermectin insecticide/acaricides, the sulfonylurea herbicides, and ergosterol biosynthesis inhibitors as fungicides are a few ounces of active ingredient per acre at most. This greatly reduces residues and decreases the chance of accidental poisonings. However, these compounds are not entirely without hazard. Many of the pyrethroids are exquisitely toxic to aquatic species, including fish, and some avermectins have an acute oral toxicity to rats considerably higher than that of parathion. The problem, even in these examples of modern highly potent insecticides is that they act on biochemical target sites which are also present and critical in

vertebrates i.e. the sodium channel of excitable tissues in the case of pyrethroids and GABA-ergic inhibitory neurotransmission in the case of avermectins.

Insecticides as a class present the greatest risk of acute poisoning in man and other vertebrates. They are the most difficult class for the discovery of new and safer materials. At the same time the usefulness of the limited range of existing compounds is continually threatened by the development of resistance. Consequently, insecticides represent both the biggest need and the greatest challenge in devising safer pest control technologies, and special emphasis is laid on insect control in the discussion that follows.

This article addresses the question of how we may increase the safety of pesticide use through a knowledge of pest biochemistry and physiology. Such research and knowledge can lead to improved safety both in terms of compounds currently registered for use and, more particularly, in helping guide the search for new and safer materials to replace them. In this, it deals with possibilities only. Which, if any, of these possibilities will come to fruition depends on many factors including the level of investment in their development and potentially severe technical, economic, and regulatory constraints.

Enhancing the Safety of Existing Compounds

The risk from pesticide use depends on two factors -- toxicity and exposure. Since the toxicity of an existing compound is an innate property, it cannot be altered, but the toxicity of the final formulation may be improved and this will alter the risk. To make the use of current compounds safer, then, is mainly to concentrate on the reduction of exposure or the improvement of formulations and application methodologies for greater safety. Knowledge of pest biochemistry and physiology could help to achieve this in several ways.

Minimizing exposure through reduced application rates or frequency. Attractants and baits for mobile pests may greatly safen the use of existing compounds by allowing the localized placement of an insecticide or by decreasing the overall concentration needed in the formulation. An excellent example is the use of bait formulations of the insecticide, mirex, which reduced the amount of this organochlorine material needed to control imported fire ants from about 1 kg to about 1 g per acre (10). Unfortunately, even this reduction was not judged to be enough to allow the continued use of mirex for this purpose because of its environmental stability and potential carcinogenicity. Also, the use of insect pheromones to monitor insect populations and thereby reduce the frequency and improve the timing of pesticide applications is well established (11). Applications may be reduced by as much as 50% and this in turn increases the contribution to control by beneficial insects, further decreasing the need for insecticide treatment. In some favorable cases, pheromones can be used to attract insects to localized insecticide-treated sites for safer control. It is salutary to remember that early basic research on insect sex pheromones was essential for these benefits, but was derided in some quarters as a waste of public funds on studying the sex lives of insects.

It is probable that through a better understanding of such examples of chemoreception and the feeding behavior of pests, new, improved attractants and bait formulations could be produced. Particularly important in this regard are such insects as the Heliothis complex on cotton which are exposed to foliar insecticides only briefly as they hatch from the egg and migrate to the cotton boll. Much insecticide is wasted in trying to ensure that a lethal dose is picked up by contact during this short time. The brief window of vulnerability also imposes a severe limitation on the efficacy of such highly safe materials as the Bacillus thuringiensis endotoxin, which must be ingested by the larvae to be toxic.

Compounds that alter insect behavior in other ways may also be useful e.g. chemicals that increase insect locomotor activity should enhance the uptake of pesticides from treated surfaces. Such compounds are already known among the formamidines insecticides and their relatives that stimulate octopamine receptors (12), and further research in this area of pest biochemistry could reveal other locomotor stimulators such as phosphodiesterase inhibitors (13,14). A similar philosophy underlies recent studies showing that alarm pheromones increase the motility of aphids and that this results in the enhanced efficacy of contact insecticides such as pyrethroids and organophosphates (15).

It is also probable that a more detailed study of the factors governing the uptake of pesticides from treated surfaces could lead to improved formulations of higher efficiency and lower concentration. From the limited data available it is clear that events on the surface of the leaf or insect and the type of formulation applied may radically affect the performance of herbicides (16) and insecticides (17).

Modification of the Toxicity of Pesticides with Formulation Additives. Potentially the use of additives to modulate the toxicity of pesticides could lead to a considerable increase in their safety to non-target species, man included. This concept has been well explored and exploited in adding safeners to certain herbicides such as the thiocarbamates. These compounds stimulate defensive metabolic reactions in the crop species but not in weeds (18,19). This principle has also been applied to vertebrates, but only to a very limited degree. Under some circumstances the thiocarbamate rice herbicide, molinate, may show toxicity to carp in nearby ponds. Based on a knowledge of the safeners that are active in plants, a compound was discovered that, when applied with molinate, acted as an antidote/safener for the carp (20). Little effort, either theoretical or empirical, seems to have gone into developing other such examples.

Since "safening" involves transiently changing the biochemistry of non-target species, the alternative strategy of making the pesticide selectively more active with synergists that alter the pest's biochemistry may be more appealing. Numerous examples of synergism with all types of pesticides are known, but the present applications of the principle are limited by several factors including a lack of selectivity for non-target species in the synergistic process (19,21). The discovery and application of pest-specific synergists is a realistic goal which, if exploited, could lead to considerably reduced formulation and application rates

and thus to a higher level of safety to the applicator and environment. One compound for which such an approach is justified is the herbicide paraquat which, based on the known number of human poisonings, is one of the most hazardous pesticides currently in use. In both plants and animals its toxic actions result from the catalytic generation of reactive forms of oxygen in the tissues. Success in the use of copper and zinc chelators to synergize its toxicity by inhibiting the antioxidant enzymes (e.g. superoxide dismutase) that tend to protect the plant is therefore promising (22). Synergists that are relatively selective between plants and animals in this regard would be particularly valuable. Such synergists, selective or not, could not have been devised without a thorough knowledge of the mechanism of action and physiological responses to paraquat in plants. The concept of selective synergism of pesticides has considerable potential but, as yet, has hardly been exploited.

Strategies to Overcome Pesticide Resistance

The development of resistance is a process which inexorably eliminates existing pesticides from the market, safe and dangerous alike. Even if they are not eliminated, application rates may have to be raised as resistance develops leading to enhanced levels of exposure for non-target organisms. Even with herbicides, resistance is now starting to become a practical problem; it is an established one for insecticides and the modern selective fungicides. It is probably a worse threat to safer compounds since these often are selectively toxic by attacking a single enzyme or receptor peculiar to the pest group. A single mutation at this site may then render the target insensitive and the pest highly resistant. Compounds acting at multiple essential sites are less open to the development of target site resistance, but by the same token are less likely to be selective in their toxic actions. Preserving safe pesticides by slowing, preventing, or reversing the onset of resistance depends absolutely on understanding the biochemistry and physiology of the pest and the biochemical and population genetics of the resistance process.

After many years of relative passivity in the face of resistance, a more aggressive concept of "resistance management" has developed considerable momentum in the last decade as it has become clear that new pesticides will not be readily available to replace those lost to resistance. This approach is reviewed elsewhere much more fully than is possible here (21,23-26). There are several critical areas of resistance management where a knowledge of pest biochemistry and physiology is essential:

1. Definition of existing and potential resistance mechanisms and their genetic basis.
2. Development of rapid, simple, and cheap methods to monitor resistance levels and mechanisms occurring at a low level in the field.
3. Development of chemical strategies to alleviate or prevent resistance.

Resistance to pesticides arises primarily through changes in the sensitivity of the site of action or in the metabolism of the pesticide (25,27,28). Many pesticides are activated metabolically. While it is theoretically possible to generate resistance through reduced activation, it seems much more common to observe increased detoxification in resistant strains. In some cases decreased uptake or enhanced excretion also contribute. It is an obvious prerequisite for any type of scientifically-based attempt to combat resistance that the resistance mechanism and its genetic basis must be defined.

There is a clear need for rapid, simple and cheap methods to monitor the status of resistance mechanisms and levels while they are still at a low incidence in field populations. If this can be achieved, early warning of changes in resistance gene frequency within the population will be possible. This should allow a shift to alternative control measures before the gene frequency and associated development of a supportive genotype progress to a stage which results in the irreversible loss of a desirable pesticide. The same survey methods will also be essential for monitoring the success of these alternative strategies. To be successful, alterations in gene frequency need to be detected when no more than a few percent of the population has the resistance gene. This demands a high degree of sensitivity and reliability at the population level that is not possible with typical bioassay methods. However biochemical tests for the presence of the resistance gene in individuals in the population may meet these requirements.

Some examples of approaches to such tests are already available e.g. assays for esterase levels in individual leaf- and planthoppers, mosquitoes, and aphids that could be run under field conditions or in local laboratories in the search for individuals with an elevated activity that provides resistance to organophosphates and other esters (29,30). Other simple tests for enzymological markers of resistance seem feasible based on the catalytic activity of the resistance site such as changes in the sensitivity of acetylcholinesterase (AChE) to inhibitors (29), mixed function oxidase (MFO) activity, and glutathione transferase activity. In the herbicide area, a field test for altered sensitivity to photosynthesis inhibitors has been described (31). However, developing specific diagnostic methods for some other traits involving changed target sites such as the *kdr* resistance mechanism for pyrethroids will be more challenging. With the purification of the changed enzymes or receptors responsible for resistance has come the possibility of gene cloning and the development of highly sensitive and specific diagnostic tests based on immunological methods such as ELISA assays (32,33).

The third element in resistance management is the development of strategies to alleviate resistance. Several possibilities can be envisioned (Table I). The various approaches in Table I and their difficulties have all been discussed previously (21,25,26), and some have been exploited on occasion by an essentially empirical approach. The intelligent use of mixtures or alternations of dissimilar materials could be viewed as an attempt to gain the resistance-delaying advantages of a pesticide with multiple sites of action. Although widely used in fungicidal treatments, the rational development of this approach is still in its infancy. Besides the desired suppression of the onset of resistance, it also carries the

hazard of the rapid development of resistance to both types of pesticide, e.g. by the selection for a detoxification mechanism that affects both compounds. Predictions of which of these outcome may occur are still hazardous because of our lack of basic knowledge. All of the methods in Table I will be more accessible and predictable only as our understanding of pest biochemistry and physiology increases.

Table I. Some Chemical Strategies to Alleviate Resistance.

1. Use of pesticides with multiple sites of action.
 2. Use of mixtures of compounds with dissimilar modes of action that lack cross-resistance potential.
 3. Alternations and rotations of such dissimilar compounds.
 4. Use of additives that antagonize the adaptive value of the resistance mechanism.
 5. Use of compounds that display negatively-correlated cross-resistance.
-

In a number of instances the use of synergists to antagonize the adaptive advantage of a metabolic resistance mechanism has been tried, but with varying results (34). One successful example is the use of esterase inhibitors to prevent resistance to organophosphates in leaf- and planthoppers in Japan (35). Once the mechanism of resistance is understood at the biochemical level, strategies to combat other types of resistance can be envisioned e.g. the use of mitochondrial poisons to prevent the energy-dependent expulsion of sterol biosynthesis inhibitors by some fungi (36).

It is harder, but not impossible, to envision synergists that act to oppose a loss of sensitivity at the site of action. However, in these cases, other strategies are available since a biologically-essential target site (enzyme, receptor) generally cannot disappear but is only changed somewhat in its properties in the mutant form. This implies that in some cases, other compounds may be found that are effective against the changed site and which therefore are toxic to the resistant pest. This situation, which should be powerful in preventing or even reversing the effects of resistance, is an example of negatively-correlated cross-resistance i.e. the higher toxicity of a compound to the resistant than the susceptible strain. Such compounds have been discovered and are already being utilized in a limited number of situations. For example, it has been found that resistance to typical carbamate insecticides in the green rice leafhopper often involves the development of a mutant form of AChE which is insensitive to inhibition by *N*-methylcarbamates. However, a site on the changed AChE is now sensitive to *N*-propylcarbamates which are relatively inactive on the native enzyme (37; Figure 1). Presumably this site has undergone a change in topography that allows

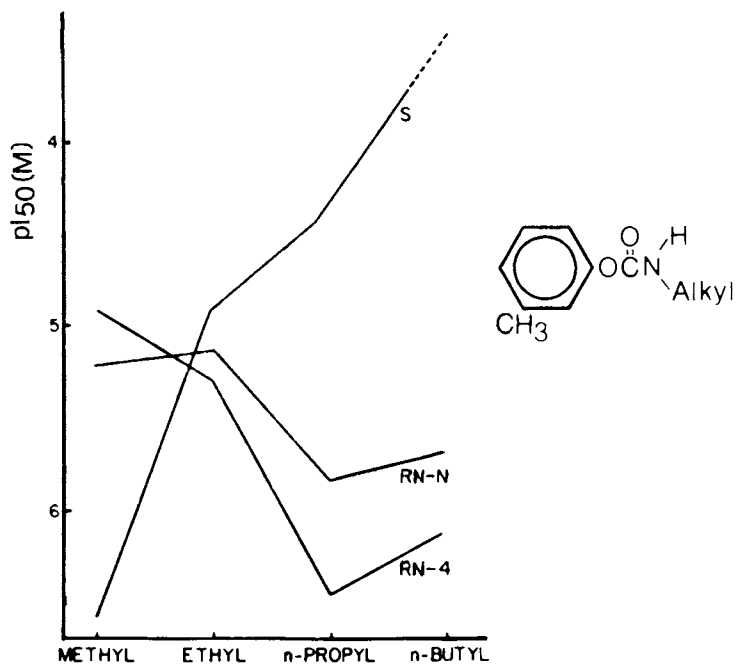


Figure 1. Comparative inhibition (pI₅₀) of acetylcholinesterase from susceptible (S) and two resistant (RN-N and RN-4) strains of green rice leafhopper by *m*-tolyl *N*-alkylcarbamates in which the *N*-alkyl group varies from methyl to *n*-butyl. Reproduced with permission from Ref. 37. Copyright 1983 Plenum Press.

greater bulk in this N-alkyl part of the inhibitor molecule. The difference in sensitivities of the forms of AChE to inhibition is paralleled by differences in the toxicity of N-methyl and N-propylcarbamates to susceptible and resistant leafhoppers (27). More recently a comparable enhanced inhibition in resistant strains has been observed with aryloxadiazolone anticholinesterases (38). A second promising example is the discovery that some natural and synthetic isobutylamides are selectively toxic against houseflies that carry the super-kdr resistance trait (39). This gene causes an alteration in the sensitivity of the site of action for DDT and pyrethroids and is a major threat to the continued efficacy of synthetic pyrethroids in many of their applications.

Turning to the fungicide area, it has been shown that resistance to benzimidazole fungicides often results from a change in the benzimidazole binding site on beta-tubulin or from enhanced stability of the microtubules. Some herbicidal N-phenylcarbamates which affect microtubule functioning in plants have been found to be specifically toxic to benzimidazole-resistant strains of fungi (28). Field tests are currently being conducted with one analog that is not herbicidal, S-32165 (diethofencarb; isopropyl 3,4-diethoxyphenylcarbamate), to evaluate its use as a "resistance breaker" (40). Another example of negatively-correlated cross-resistance among fungicides involving phosphorothiolates and phosphoramidates has been described (41).

As information on the molecular architecture and mechanisms of pesticide sites of action becomes more generally available and the nature and effect of mutations on their sensitivity to pesticides is defined, it should become possible in some cases to design agents that specifically interfere with the altered site of the resistant forms. The same line of reasoning suggests that the design of specific and selective synergists to block individual metabolic resistance mechanisms may eventually be possible.

New and Safer Pesticides - Exploiting Pest Vulnerability

The defects of current pesticides, regulatory actions resulting from them, the natural desire of chemical companies to discover new and better compounds than their competitors, and the regular loss of pesticide efficacy due to resistance and changes in agricultural technology all provide impetus to the search for new compounds. However, increased research and regulatory demands are expensive and the difficulty of finding molecules with clearly superior properties to those of existing compounds has made the discovery of new compounds with improved safety characteristics an increasingly costly and rare occurrence. It has been pointed out that the peak of innovation in the introduction of new pesticides was seen in the late 1960's at about 20 compounds per year. Since then it has declined precipitously (25,42,43). Recently the success rate is estimated to be one compound commercialized for every 15,000 to 20,000 synthesized with the total cost of developing this single new compound being anywhere from \$20 million (25) to \$45 million (44). Pesticide discovery is a game of roulette on a wheel with many thousands of numbers. To stay in this game long enough to hit winners and recoup investment is extremely expensive. An increasing number of companies have decided that they cannot afford to play and have cashed in their chips. In itself, this decreases our chances of discovering safer pesticides.

On the basis of the old advice to know thy enemy, can studies of pest physiology and biochemistry aid in the struggle to find new and safer chemicals for pest control? The answer is by no means clear, but it is obvious that the figures for success using past methods of blind screening and analog synthesis are increasingly unfavorable and uneconomical. The only alternative in sight is to attempt to apply the growing knowledge of pest biochemistry and physiology to define specific vulnerabilities in the pest and thus to decrease the odds in our search for better materials. This prospect has been discussed recently by a number of authors (19,20,43,45-48). Although the topic of the genetic engineering as a means of pest control is beyond the scope of this chapter, it equally depends on such a knowledge of the enemy. Fortunately it is likely that research on pest biochemistry and physiology can help improve our chances of finding novel compounds, particularly safer ones, at several different levels.

Improved Bioevaluation and Optimization of Leads. At the simplest level, such information provides improved methods for screening and optimizing the activity in a new series of potential pesticides, and to some extent in the discovery of such leads also.

Compounds with novel chemistry and marginal biological activity appear more or less frequently in screening, and it is important to decide whether these represent important leads for new products or dead ends. Low activity may be due to any one of several factors singly or in combination. Studies on pest physiology and biochemistry provide a battery of tools to aid in making this decision. Poor uptake can often be detected if the compound is injected into the organism or applied in a special solvent such as dimethyl sulfoxide, too-rapid metabolism is indicated by the synergistic effect of co-application with specific enzyme inhibitors, and low intrinsic activity can be detected by specific assays of the action on the target site, when this is known. This modest goal of integrating our present knowledge of the pest and its defenses into the discovery and optimization process sounds simple but even now is not always achieved.

A good example of how this process can work is provided by the discovery of the nitromethylene heterocyclic (NMH) insecticides at Shell Development Co., Modesto, CA. The initial NMH's were obtained from an outside source as random screening items. In the screen it was found that one NMH had 1% of the activity of parathion against houseflies. This is not a very impressive level of activity, but since the NMH's were new chemistry, there was a rapid follow up in which the compound was injected into houseflies to subvert penetration barriers and in the presence of the synergist, sesamex, to inhibit oxidative degradation. This increased its activity against the housefly to 50% of parathion's activity, which encouraged further analog synthesis. At the same time, mode of action studies were initiated. The strong excitatory symptoms in vivo suggested that the nervous system was involved. The compound was applied to the 6th abdominal ganglion preparation from the American cockroach where a massive increase in nerve activity was observed followed by a block of neurotransmission (Figure 2). These observations, supplemented by further study based on the known properties of this preparation, suggested that the NMH's acted to stimulate acetylcholine receptors

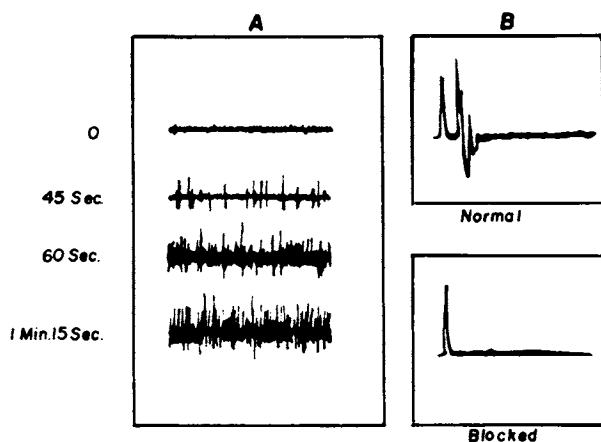
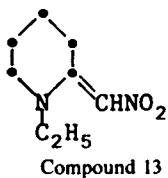


Figure 2. The development of spontaneous giant fiber discharges (A) and the subsequent block of the response evoked by electrical stimulation (B) in the central nervous system of the American cockroach treated with a $3 \mu\text{M}$ solution of NMH compound 13 illustrated. Reproduced with permission from Ref. [49](#). Copyright 1984 Academic Press.

(49). This is a target site for very few current insecticides, and resistance to compounds acting there has not been developed. This discovery gave additional momentum to the synthesis program. Eventually compounds with activity comparable to the synthetic pyrethroids were discovered (50) and investigations in this area continue.

The discovery of a mechanism of action is not always so readily achieved, and may be very challenging if it is completely novel. However, here pesticide resistance can offer some notable advantages. Strains of pests with carefully defined single resistance mechanisms involving insensitive sites of action, such as pyrethroid resistant insects with the *kdr* gene or plants with an altered triazine-binding site in the chloroplasts, can, by their relative resistance to a new compound, be a useful and very rapid diagnostic aid for evaluating its mode of action. Comparative studies with strains having elevated levels of such defensive enzymes as MFO and GSH transferase could help to define the susceptibility to metabolism as a limiting factor in new compounds, and indicate the potential for resistance to them by existing genetic mechanisms.

Rapid in vitro tests for actions at sensitive target sites, such as enzyme and receptor binding assays, are needed to help in defining modes of action early in the development of a new series, and in guiding the chemist as changes in intrinsic activity occur during its optimization. Currently we do have good assays for some enzymes and for ACh receptors in insects, but methods for other sites need to be developed for routine use. This is in strong contrast to the pharmaceutical industry where in vitro tests are advanced and widely used e.g. batteries of receptor binding assays to help define not only the primary activity of a new compound but also its effects on other receptor types as an indicator of potential side-effects. Further basic research is essential to provide this capability with pesticides. This may eventually allow us to use in vitro assays to aid in predicting at an early stage of development not only the intrinsic activity of compounds, but also their potential side effects such as impact on important non-target species including beneficial insects and vertebrates.

In some cases, such automated biochemical methods may help in the discovery process since many more samples can be run through assays for AChE inhibitors, receptor binding, Hill reaction inhibitors, and metabolism inhibitors as potential synergists than can be put through a normal biological screen in the same time period. As long as such biochemical screens are relevant for the biological activity desired (43), and are not meant to replace whole animal screening, but simply to augment it and provide information on potentially interesting intrinsic activity for further evaluation, their utility may be considerable. For example, such automated screening with AChE as the target resulted in the discovery of a novel series of inhibitors (51), although unfortunately with selective activity against mammalian forms of the enzyme.

Discovery of the mode and site of action of existing compounds. This is a second way in which studies on pest biochemistry and physiology can aid in the discovery of new and safer compounds. The discovery of the site and mechanism of action of a group of pesticides inevitably stimulates new thinking, particularly if the site is a novel one.

A recent example from the area of herbicides illustrates this possibility very well. Two recent new groups of herbicides with very high commercial potential are the sulfonylureas and imidazolinones. It was found that, though quite different structurally, these compounds inhibit the same enzyme in plants, acetoxyacid synthase (AHAS), which is essential for the synthesis of the branched chain amino acids valine, leucine and isoleucine. The mechanism of inhibition is still under study, but probably both groups of compounds act on a regulatory site rather than on the active site of the enzyme (52). Valine itself is known to exert feedback inhibition on the activity of some forms of AHAS. Using this information on the potential site and mode of action, Huppatz and Casida (53, Figure 3) noted that the imidazolinones contain a 2-methylvaline substructure and postulated that other valine derivatives might therefore also interact at the regulatory site to inhibit AHAS activity. A series of valine analogs were synthesized, and the most active one, *N*-phthaloyl-L-valine anilide, was found to inhibit AHAS and plant growth in the micromolar range.

It must be stressed that the contributions of pesticide mode of action studies are not limited to their undoubted practical significance in pesticide discovery. The definition of modes of action in pests generally has considerable significance in the safety evaluations of a pesticide. Further, the elucidation of a new mechanism of action may produce remarkable benefits for basic biological research. It frequently stimulates research in that field, often generates new insights into essential biological processes, and provides indispensable tools for their study. It would be safe to say that many of the most significant advances in modern biology depended on the use of natural and man-made poisons as probes.

An even higher degree of sophistication in pesticide discovery is now within sight. The increasingly detailed understanding of enzyme mechanisms sometimes allows the design of inhibitors that interact very strongly or irreversibly as well as specifically with them e.g. transition state analog inhibitors and suicide substrates (48). Remarkable advances in biochemical and molecular genetic techniques and X-ray crystallography allow the amino acid sequences and prediction of 3-dimensional structures of important target sites to be generated with increasing facility. The computer-assisted definition of the structure and chemistry of binding domains of potential target receptors and enzymes and of their interactions with ligands is already being practiced (43, 54, 55). This is discussed by Dr. Vorpagel in another chapter in this volume.

The best developed example of this process with pesticides currently lies in the herbicide area. Triazines, ureas, and many other herbicides inhibit photosynthesis by competitively displacing plastoquinones from their binding site in photosystem II, thus diverting electron flow from its normal pathway and resulting in the generation of reactive intermediates that are cytotoxic (19, 52). Recently the position of this binding site has been localized to a 32 kDa polypeptide and the molecular architecture of the site has been elucidated using such techniques as photoaffinity labelling, gene sequencing of herbicide-resistant mutants, the development of a plausible model of the amino acid sequence and its folding within the membrane, and comparison with the structure of the related region in the bacterial photosystem determined by X-ray crystallography

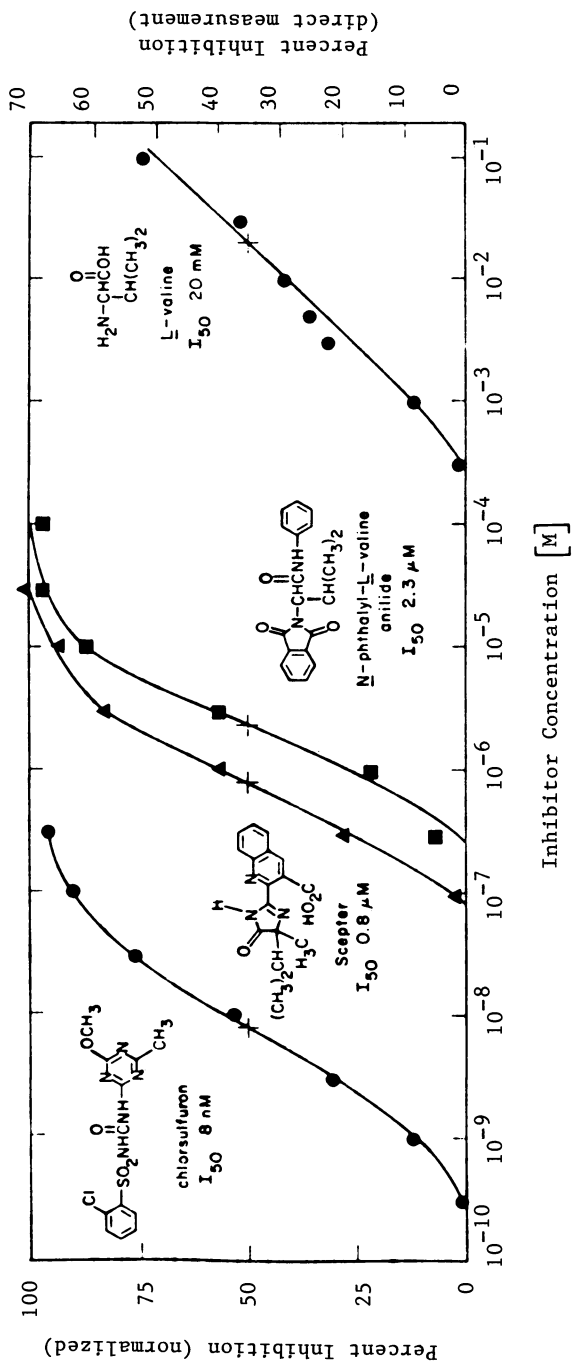


Figure 3. Relative potencies of N-phthalyl-L-valine anilide, L-valine, the imidazolinone herbicide, Scepter, and the sulfonylurea herbicide, chlorsulfuron, as inhibitors of acetoxyacid synthase from *Zea mays*. (Reproduced with permission from Ref. 53. Copyright 1985 Verlag der Zeitschrift für Naturforschung.)

(52,56,57; Figure 4). This information is now being used in industry to design novel inhibitors for this site as potential herbicides.

Returning to the topic of ACh receptors, preliminary three-dimensional models are available for this receptor from *Torpedo* electroplax (58,59). Figure 5 shows the possible structure of the ACh binding site and the residues likely to be involved in ACh binding. Considerable progress can be expected in developing the structure of the comparable receptor from the locust CNS (60). Notable differences exist in the subunit structure of these two receptors, although they may not extend to all types of mammalian ACh receptors. Information of this type may eventually allow the design of agonists and antagonists having a high degree of specificity for insect receptors. In addition to revealing the topography of the ACh binding site, it is possible that such studies will reveal new binding areas at which ligands could either trigger or inhibit the normal receptor-activated opening of ion channel. The ion channel itself offers such an opportunity since several pharmacologically active agents have been shown to interact with this pore (58) including some insecticides (61).

In the area of fungicides, the binding site for benzimidazole fungicides on fungal beta-tubulin in both sensitive and resistant fungi is now beginning to be understood at the molecular level (28). Additionally, a group of enzymes with great significance for pesticide action and resistance is the cytochrome P-450 based family of monooxygenases. These act both as a major metabolic force for pesticides, and as a potential target site e.g. they are the established site of action for many fungicidal ergosterol biosynthesis inhibitors and a potential site for inhibitors of juvenile hormone biosynthesis in insects (19). It is therefore significant that the structure of one form of P-450 has recently been revealed by X-ray crystallography (62). Further developments along these lines could eventually open the way for the computer-assisted design of several types of pesticides, growth regulators and pesticide synergists. Applications of this approach to aid in developing inhibitors of sterol biosynthesis in fungi (63) and gibberellin biosynthesis in plants (64) have been described.

The information regarding these and other binding sites should be invaluable for the design of improved and new types of ligands. At present the discovery and optimization of effectors is very much a hit and miss phenomenon, akin to the old game of pinning the tail on a donkey while blindfolded. To have the 3-dimensional structure and reaction mechanism of a critical site fully elucidated is to remove the blindfold. To appreciate the potential of this site-directed molecular design one has only to remember that, by adding to an existing molecule a strategically located functional group which forms an additional hydrogen bond with the receptor surface, one can increase its affinity by two or three orders of magnitude (65). Unfortunately, knowledge of most potential target sites at this sophisticated level in most target species is very limited or completely lacking and a great deal of effort will be needed to develop it to a usable level.

New Concepts in Pest Control - The Discovery of Pest Vulnerability. Further back in the chain of discovery, but of extreme importance for future developments, studies of pest biology, physiology and

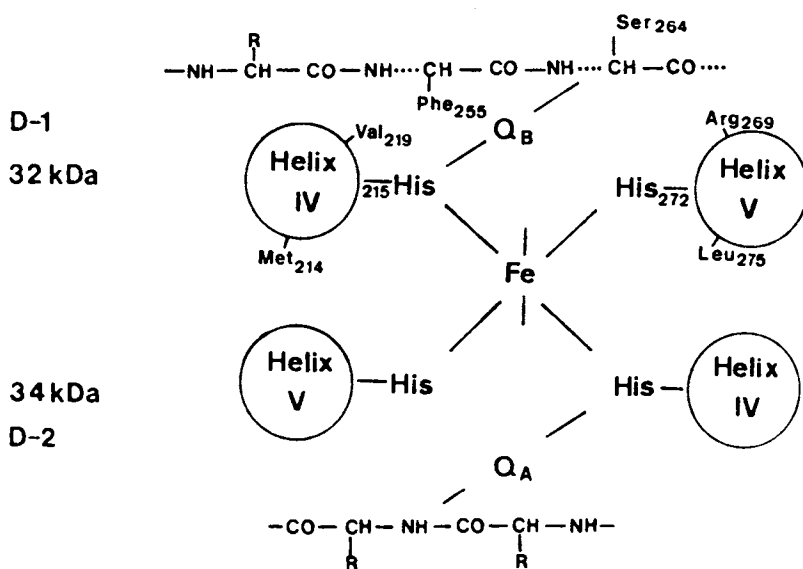


Figure 4. Proposed plastoquinone (QB) and herbicide binding site on the 32 kDalton D-1 polypeptide of photosystem II. The quinone is bound through an iron-complexed histidine residue (his 215) and hydrogen bonding to ser 264. Further interactions occur with arg 269 and phe 255 lying above and below the binding site. Amino acid substitutions in herbicide-tolerant mutants have been identified at the residues numbered 219, 255, 264 and 275. Reproduced with permission from Ref. 57. Copyright 1986 Verlag der Zeitschrift fur Naturforschung.

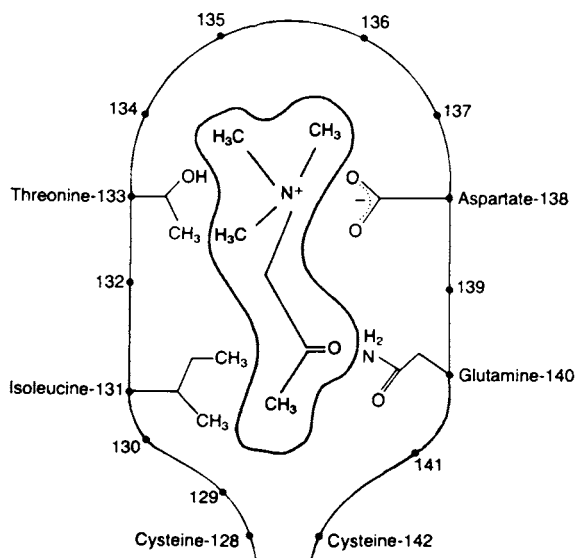
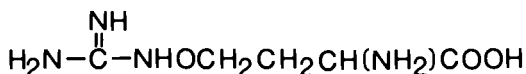


Figure 5. Model of the proposed acetylcholine recognition site on the alpha subunit of the Torpedo ACh receptor in the region between Cys 128 and Cys 142. An ACh molecule is shown in relation to the four residues postulated to interact in its binding. Reprinted with permission from Ref. 59. Copyright 1985 Elsevier Science Publishers.

biochemistry lead to new concepts in pest control by defining basic differences between target and non-target species. As examples, the discovery of the control of insect development by juvenile hormones, and of mating and aggregation behaviors by insect pheromones, were eagerly and rapidly exploited for new and very safe approaches to insect control. These areas continue to attract research aimed at novel applications of this basic knowledge. Even restricting the discussion to insect pests, many other significant differences in their biochemistry and physiology compared to vertebrates are already known. These represent potential areas for the development of safer pesticides, some of which are currently under study with this end in view e.g. peculiarities of sterol metabolism in insects, their reliance on octopamine and specific neuropeptides as neuroeffectors, and their cuticular biochemistry and waterproofing (45,46,48,66). Further, selectivity and mammalian safety can be achieved just as readily by the development of compounds which are degraded at differential rates in friend and foe as by attacking biochemical targets peculiar to the pest, as illustrated by the pyrethroid insecticides. Lack of ability to rapidly degrade a toxicant is clearly a serious vulnerability factor. There is a great need for studies on the basic physiology and biochemistry of all types of pests to continue and be expanded in order to better understand existing sites of vulnerability and to discover new ones which can lead to novel concepts for control.

To provide but a single example from many, the defense responses of insects against invading pathogens represents just such a promising topic of current research. Results in this area have recently been reviewed by Dunn (67). In lepidopterous larvae, these defenses are multiple and include both humoral and cellular elements. Invading organisms are subject to phagocytosis and encapsulation in cellular networks derived from hemocytes. Over a period of 24 to 48 hours, these initial defenses are augmented by the synthesis and release into the blood of lysozyme and lysine- and arginine-rich polypeptide antibiotics (bactericidins) from the fat body. It is premature to suggest that such information currently provides obvious opportunities for exploitation in insect control, but the potential is clear. If means could be found to turn off or obviate some or all of these defenses, the insect would be more likely to succumb to natural infections. This could be particularly useful if applied in combination with an infectious agent such as a bacterium or virus. Such a concept is more than a pipe-dream since it has been shown that a virus associated with the eggs of parasitic wasps prevents the encapsulation response of the host which would otherwise tend to occlude the egg (68). An unidentified component from the venom of other parasitic wasps has also shown immunosuppressant properties in insects (69) and two immunosuppressants active on giant silkworm moths have been detected in preparations of Bacillus thuringiensis (70). Further, Dunn and his coworkers have found that quite small peptidoglycan fragments of the bacterial cell wall are recognized as "foreign" in Manduca sexta and will trigger the production of humoral defenses. Can we find low molecular weight analogs to block these "receptor" sites and thus inhibit this aspect of immunity? Finally, the defensive antibiotics are rich in arginine. Canavanine, an analog of arginine which occurs in some legume seeds, can be toxic by replacing arginine in essential proteins and peptides (71).



Canavanine

Manduca larvae treated with canavanine produce antibiotic peptides in which arginine is replaced by canavanine. Their intrinsic biological activity is greatly diminished and these larvae may be unusually susceptible to infection by bacteria (P. E. Dunn, personal communication).

It is only realistic to admit that the chances of eventually being able to exploit any such example of basic research are highly uncertain and require a long lead time for development. Even the discovery of mechanisms to disrupt essential biochemical processes peculiar to pest groups does not offer a panacea for several reasons.

1. Though we may avoid acute toxicity to most non-target species, there are no guarantees that we will avoid chronic toxicity: the two are not correlated. In fact there may be a negative correlation since current protocols for safety evaluation employ the maximum tolerated dose in long term studies with vertebrates. Hence compounds which can be given at high doses because of their low acute toxicity are at a disadvantage in lifetime chronic tests.

2. Though the site of action may be peculiar to the pest, there may be parallel processes in non-target species that also are affected.

3. Even if after enormous effort and investment a new approach clears all these hurdles and can be used in practice, we shall find no victory over pests to be permanent. The loss of vulnerability through the development of resistance will always be a threatening possibility. This is why it is so crucial that much greater effort be devoted to understanding the population, genetic, and biochemical basis of the development of resistance to control measures in general.

However, on the basis of past experience, it is reasonable to conclude that with faith, patience, and a sufficient investment, at least some such basic studies of pest biochemistry will pay off in novel and safer pest control strategies.

The Clouded Future

Since the Second World War the US has invested large amounts of money on research into basic biological mechanisms and their control, largely spurred by medical goals, but also, to a lesser extent, by the motivation to understand potential pests and their essential characteristics. This investment by government and industry has proved remarkably fruitful. There is reason to hope that we are now on the threshold of an era where we will be able to design compounds that are both highly potent and highly specific in their toxic effects, and to prevent resistance from negating them. Although much remains to be done to achieve these ends there is cause for optimism that we can achieve them. However, such advances, starting from basic studies, are increasingly costly and demand a team effort

and cooperation between industry and academia. This comes at a time when the agrochemical industry is experiencing lowered profits and a decreased ability to invest in such basic and expensive research. A third essential partner in this process is government, particularly, because of its agricultural mandate, the USDA. However, governmental research support is also experiencing financial stringency and uncertainty.

The USDA, even in the past, has not, from the perspective of this article, invested its limited resources optimally. When it became clear in the 1960's that society correctly regarded many current pesticides as too flawed for continued use, two logical approaches to the development of safer pest control strategies could be envisioned: (1) to develop alternatives to chemical pesticides, and (2) to support basic research aimed towards the discovery of new and safer chemical compounds to replace those that were unsatisfactory. The USDA chose to emphasize the former approach heavily at the expense of the latter. Though politically popular, this may have been short-sighted, and has not radically changed our approach to pest control which continues to depend very heavily on pesticides. Meanwhile funding from this potentially primary source to support research into the better understanding of the biochemical sites and modes of action of pesticides, to aid in the discovery of new methods to develop improved and safer compounds, and to spur efforts to understand and alleviate resistance to pesticides has been negligible in comparison to the needs and opportunities. This viewpoint has been independently expressed by others also (48). It is to be hoped that the emphasis on strategies for developing safer pest control technologies can soon be brought into a more rational balance.

When one considers the immense sums being invested in weapons and medical research, or elsewhere in agriculture, the amount needed to support such work at a realistic level is miniscule. Just 0.01% of the amount expected to be spent to subsidize agricultural production in the USA in 1986 would provide \$3 million as a firm foundation for pesticide-related basic research. This same amount represents 2% of what is spent to maintain military bands in the USA. Currently, there is a minimum of encouragement or opportunity in the USA to work on these topics, and a large proportion of the research is done in other nations. At the recent IUPAC International Congress of Pesticide Chemistry, which attracted a worldwide attendance and was held close to the USA in Canada, 78% of the papers on fungicide modes of action were given by speakers with non-US affiliations, as were 89% of the papers on herbicide modes of action, and 82% of those on fungicide and insecticide resistance. While it is encouraging that such work is thought worthy of support in many nations around the world, the clear indication is that, despite its huge agricultural industry with a continuing dependence on pesticides, the USA is lagging seriously in such necessary research efforts.

The combination of financial stresses that currently threaten all sources of funding for agricultural research is in danger of leaving us with fruit ripe for the picking as a result of our prior investments in biological research, but with few harvesters in the orchard. If so, others may then profit from our lack of vision.

Acknowledgments

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Literature Cited

1. Hayes, W. J., Jr.; Vaughan, W. K. Toxicol. Appl. Pharmacol. 1977, 42, 235-52.
2. Copplestone, J. F. In "Pesticide Management and Insecticide Resistance"; Watson, D. L.; Brown, A. W. A., Eds.; Academic: New York, 1977; pp. 147-55.
3. Jeyaratnam, J.; de Alwis Seneviratne, R. S.; Copplestone, J. F. Bull. World Health Org. 1982, 60, 615-9.
4. Davies, J. E.; Doon, R. In "Silent Spring Revisited"; Marco, G. J.; Hollingworth, R. M.; Durham, W. W., Eds.; American Chemical Society: Washington, D.C., 1986, In Press.
5. Davies, J. E.; Freed, V. H.; Whittemore, F. W. "An Agromedical Approach to Pesticide Management"; Univ. Miami Press, 1982; pp. 8-9.
6. Pimentel, D. In "Chemistry and World Food Supplies: The New Frontiers"; Shemilt, L. W., Ed.; Pergamon: Oxford, 1983, pp. 185-201.
7. Barthel, E. J. Toxicol. Environ. Health 1981, 8, 1027-40.
8. Hoar, S. K.; Blair, A.; Holmes, F. F.; Boysen, C. D.; Robel, R. J.; Hoover, R.; Fraumeni, J. F., Jr. J. Am. Med. Assoc. 1986, 256, 1141-7.
9. Hall, R. J. In "Silent Spring Revisited"; Marco, G. J.; Hollingworth, R. M.; Durham, W. W., Eds.; American Chemical Society: Washington, D.C., In Press.
10. Knipling, E. F. "The Basic Principles of Insect Population Suppression and Management"; Agric. Handbook No. 512; U.S. Dept. Agric.: Washington, D.C., 1979, pp. 425-7.
11. Campion, D. G. In "Techniques in Pheromone Research"; Hummel, H. E.; Miller, T. A., Eds.; Springer-Verlag: New York, 1984, pp. 405-49.
12. Hollingworth, R. M.; Lund, A. E. In "Insecticide Mode of Action"; Coats, J. R., Ed. Academic: New York, 1982, pp. 189-227.
13. Hollingworth, R. M.; Lund, A. E. In "Pesticide Chemistry: Human Welfare and the Environment"; Miyamoto, J.; Kearney, P. C., Eds.; Pergamon: Oxford; 1983, Vol.3, pp. 15-24.
14. Nathanson, J. A. Science 1984, 226, 184-7.
15. Griffiths, D. C.; Pickett, J. A. Entomol. Exp. Appl. 1980, 27, 199-201.
16. Hess, F. D.; Bayer, D. E.; Falk, R. H. Weed Sci. 1981, 29, 224-9.
17. Schouest, L. P., Jr.; Umetsu, N.; Miller, T. A. J. Econ. Entomol. 198, 76, 973-82.
18. Pallos, F. M.; Casida, J. E. "Chemistry and Action of Herbicide Antidotes"; Academic: New York, 1978.

19. Corbett, J. R.; Wright, K.; Baillie, A. C. "The Biochemical Mode of Action of Pesticides"; Academic: New York, 2nd Edn., 1984.
20. Menn, J. J. J. Agric. Food Chem. 1980, 28, 2-8.
21. Brattsten, L. B.; Holyoke, C. W., Jr.; Leeper, J. R.; Raffa, K. F. Science 1986, 231, 1255-60.
22. Shaaltiel, Y.; Gressel, J. In "Pesticide Science and Biotechnology"; Greenhalgh, R.; Roberts, T. R., Eds.; Blackwell: London, In Press.
23. Georghiou, G. P.; Saito, T. "Pest Resistance to Pesticides"; Plenum: New York, 1983.
24. Dover, M.; Croft, B. "Getting Tough: Public Policy and the Management of Pesticide Resistance"; World Resources Institute: Washington, D.C., 1984.
25. "Pesticide Resistance: Strategies and Tactics for Management", National Research Council, National Academy Press, Washington, D.C., 1986.
26. Sawicki, R. M. Phil. Trans. R. Soc. Lond. B 1981, 295, 143-51.
27. Oppenoorth, F. J. In "Comprehensive Insect Physiology, Biochemistry and Pharmacology"; Kerkut, G. A.; Gilbert, L. I., Eds.; Pergamon: Oxford, 1985; Vol. 12, pp. 731-73.
28. Davidge, L. C. Ann. Rev. Phytopathol., 1986, 24, 43-65.
29. Miyata, T. In "Pest Resistance to Pesticides"; Georghiou, G. P.; Saito, T., Eds.; Plenum: New York, 1983; pp. 99-116.
30. Pasteur, N.; Georghiou, G. P. Mosquito News 1981, 41, 181-3.
31. Ali, A.; Souza Machado, V. Weed Res. 1981, 21, 191-7.
32. Devonshire, A. L.; Moores, G. D.; French-Constant, R. H. Bull. Entomol. Res. 1986, 76, 97-107.
33. Hemingway, J.; Rubio, Y.; Bobrowicz, K. E. Pestic. Biochem. Physiol. 1986, 25, 327-335.
34. Georghiou, G. P. In "Pest Resistance to Pesticides"; Georghiou, G. P.; Saito, T., Eds.; Plenum: New York, 1983; pp. 769-92.
35. Ozaki, K. In "Pest Resistance to Pesticides"; Georghiou, G. P.; Saito, T., Eds.; Plenum: New York, 1983; pp. 595-614.
36. de Waard, M. A.; van Nistelrooy, J. G. M. Pestic. Sci. 1983, 15, 56-62.
37. Yamamoto, I.; Takahashi, Y.; Kyomura, N. In "Pest Resistance to Pesticides"; Georghiou, G. P.; Saito, T., Eds.; Plenum: New York, 1983; pp. 579-94.
38. Yamamoto, I. Abst. 6th IUPAC Int. Cong. Pestic. Chem., Ottawa, Canada, 1986. Abst. 3E-20.
39. Elliott, M.; Farnham, A. W.; Janes, N. F.; Johnson, D. M.; Pulman, D. A.; Sawicki, R. M. Agric. Biol. Chem. 1986, 50, 1347-9.
40. Nakamura, S.; Kato, T.; Noguchi, H.; Takahashi, J.; Kamoshita, K. In "Pesticide Science and Biotechnology"; Greenhalgh, R.; Roberts, T. R., Eds.; Blackwell: London, In Press.
41. Uesugi, Y. In "Pest Resistance to Pesticides"; Georghiou, G. P.; Saito, T., Eds.; Plenum: New York, 1983; pp. 481-504.
42. Braunholtz, J. T. Phil. Trans. R. Soc. Lond. B, 1981, 295, 19-34.
43. Geissbuehler, H.; Mueller, U.; Pachlatko, J. P.; Waespe, H. R. In "Chemistry and World Food Supplies: The New Frontier"; Shemilt, L. W., Ed.; Pergamon: Oxford, 1983; pp. 643-56.

44. Storck, W. J. Chem. Eng. News 1984, 62 (April 9), 35-57.
45. Magee, P. S.; Kohn, G. K.; Menn, J. J. "Pesticide Synthesis through Rational Approaches"; ACS Symposium Series No. 255; American Chemical Society: Washington, D.C., 1984.
46. von Keyserlingk, H. C.; Jaeger, A.; von Szczepanski, C. "Approaches to New Leads for Insecticides"; Springer: Berlin, 1985.
47. Schwinn, F.; Geissbuehler, H. Crop Protect. 1986, 5, 33-40.
48. Hammock, B. D.; Soderlund, D. M. In "Pesticide Resistance: Strategies and Tactics for Management"; National Academy: Washington, D.C., 1986; pp. 111-29.
49. Schroeder, M. E.; Flattum, R. F. Pestic. Biochem. Physiol. 1984, 22, 148-60.
50. Soloway, S. B.; Henry, A. C.; Kollmeyer, W. D.; Padgett, W. M.; Powell, J. E.; Roman, S. A.; Tieman, C. H.; Corey, R. A.; Horne, C. A. In "Advances in Pesticide Science; Geissbuehler, H., Ed.; Pergamon: Oxford; 1979, Pt. 2, pp. 206-17.
51. Voss, G.; Neumann, R. Experientia 1979, 35, 583-4.
52. Fedtke, C.; Trebst, A. In "Pesticide Science and Biotechnology"; Greenhalgh, R.; Roberts, T. R., Eds.; Blackwell: London, In Press.
53. Huppatz, J. L.; Casida, J. E. Z. Naturforsch. 1985, 40C, 652-6.
54. Gund, P.; Andose, J. D.; Rhodes, J. B.; Smith, G. M. Science 1980, 208, 1425-31.
55. Richards, W. G. Endeavour 1984, 8, 172-8.
56. Deisenhofer, J.; Epp, O.; Miki, K.; Huber, R.; Michel, H. Nature 1985, 318, 618-24.
57. Trebst, A. Z. Naturforsch. 1986, 41C, 240-5.
58. Changeux, J.-P.; Devillers-Thiery, A.; Chemouilli, P. Science 1984, 225, 1335-45.
59. White, M. M. Trends in NeuroSci. 1985, 8, 364-8.
60. Breer, H.; Kleene, R.; Hinz, G. J. Neurosci. 1985, 5, 3386-92.
61. Eldefrawi, M. E.; Sherby, S. M.; Abalis, I. M.; Eldefrawi, A. T. Neurotoxicol. 1985, 6, 47-62.
62. Poulos, T. L. In "Cytochrome P-450"; Ortiz de Montellano, P. R., Ed.; Plenum: New York, 1986; pp. 505-23.
63. Marchington, A. F. Proc. 10th Internat. Congr. Plant Protect. 1983, 1, 201-8.
64. Ebert, E.; Huxley, P.; Mueller, U. Abst. 6th IUPAC Internat. Congr. Pestic. Chem. Ottawa, Ontario, Abst. #1C-15.
65. Andrews, P. Trends Pharm. Sci. 1986, 7, 148-51.
66. Hollingworth, R. M. In "Pesticide Selectivity"; Street, J. C., Ed.; Dekker: New York; 1975, pp. 67-111.
67. Dunn, P. E. Ann. Rev. Entomol., 1986, 31, 321-39.
68. Stoltz, D. B. J. Insect Physiol., 1986, 32, 347-50.
69. Kitano, H. J. Insect Physiol., 1986, 32, 369-75.
70. Edlund, T.; Siden, I.; Boman, H. G. Infect. Immun. 1976, 14, 934-41.
71. Rosenthal, G. A. Q. Rev. Biol. 1977, 52, 155-78.

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Chapter 7

Pests as Part of the Ecosystem

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Diseases, insects, and weeds are important constraints to crop production; their combined effect has been "estimated" at 25-45%, on a world-wide basis. Pesticides comprise one of the major means of pest control. In the U.S., insecticides, herbicides, or fungicides are used on more than 90 million hectares of crop land. Percentages of crop area treated with pesticides range from <1 to >90% for crops ranging from pasture to apples. The amount of chemicals used and the seriousness of plant pests mandate that pesticide usage be based on sound biological data and principles. Pest control decisions ideally are based on: 1) precise estimates of pest density and aggregation; 2) interaction of pests with crop plants and the environmental and biotic environment; 3) quantification and modeling of pest population dynamics; and 4) effects of pests on crop yields. Optimal timing, amount, and selection of pesticides (e.g., type of activity), as well as selection of alternate controls, can be determined based on these four considerations. Pesticide risks to humans as well as the environment can be reduced through an understanding of the pest as part of the ecosystem.

Pests are inescapable parts of an ecosystem. No crop can be grown anywhere in the world without concern about damage due to at least one pest. For this paper, the term pest is used in a gross sense to include all organisms that are detrimental to agricultural production, weeds, insects and other arthropods (e.g., mites), and pathogens. Pathogens include fungi, viruses, nematodes, bacteria, and other prokaryotes such as spiroplasma and mycoplasma like organisms (MLO's) that cause plant diseases. Pathogens of crop plants are dominated by fungi, although the other groups are extremely important. There are other pest types such as mammals (e.g., deer, rodents) and birds, but these are somewhat less widespread and will not be specifically discussed any further.

The impact of pests is immense but quantitative data is notoriously poor (1). In an attempt to understand losses caused by

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plant diseases, Zadoks and Schein (2) classified losses as being direct or indirect; their classification system is pertinent to all pests and not just pathogens. Direct losses are reductions in quantity or quality of produce, as well as reduction of yielding capacity. Direct losses include: losses incurred pre- and postharvest and costs of control (primary direct losses); contamination of sowing and plant material; soil infestations, and other factors that reduce yield in future seasons (secondary direct losses). Indirect losses encompass economic and social effects of pests, including economic impacts on farmers, communities, consumers, and the environment.

In general, agricultural scientists cannot give accurate estimates of the above losses. This is due partly to the lack of detailed field experiments relating pest levels to loss, and partly to the lack of extensive survey data on the level of pests in grower's fields. The published estimates of losses are better called "questimates" and should only represent general ranking of pest effects. On a world-wide basis, primary losses due to pests are in the range of 35% (3), fairly evenly attributable to insects, diseases and weeds (Table I).

Table I. Some Published Percentage Losses Due to Pests
(reported in McEwen (3))

	Insects	Diseases	Weeds	Total
North America	9	11	8	28
World	11.6	12.6	10	34.2
Wheat	5	9	10	24
Potato	5	22	4	31
Rice	27	9	11	47

Other published values may be found in the literature, but the values presented herein likely are just as accurate. In North America, losses are somewhat less than for all continents. These numbers for continents, however, mask many interesting results. For instance, diseases and weeds cause more losses in wheat than do insects; the opposite is true for rice (Table I). Obviously, these losses will vary with location, year, and cropping practices.

Due to impact of pests, considerable expenses are incurred in controlling insects, weeds, and pathogens. One such control practice is the use of pesticides. In the U.S., over 90 million hectares are treated with herbicides, as an example (4), considerably less insecticides and fungicides are used (Table II). In 1982, herbicides accounted for more than three-quarters of all pesticide sales.

Table II. Pesticide Use on Major Food Crops in the U.S. for 1982 based on Schaub (4)

Pesticide	Amount (million kg a.i.)	Hectares (millions)
Herbicides	190.7	90.0
Insecticides	24.8	21.9
Fungicides	2.4	1.5

Hectares covered and the amount used vary tremendously with crops and locations. For instance, in 1976 nearly 50% of the insecticide use on major field crops was on cotton (4). The greatest fungicide use is on fruit and vegetable crops. However, this use varies with geographic location. For example, although ~50% of potatoes in the U.S. are sprayed with fungicides, but close to 100% are sprayed in the eastern U.S. (5).

The above figures should indicate that pests have a serious impact on crop production and that pesticides comprise a major means of control. To minimize risks due to pesticide applications, a clear understanding of the biology, ecology, and population dynamics of pests is imperative. It is no longer economical or environmentally desirable to apply excessive and poorly timed chemicals. Pesticide application strategies should be based on: 1) precise estimates of pest density and aggregation; 2) interaction of pests with crop plants and the physical and biotic environment; 3) quantification and modeling of pest population dynamics; and 4) effects of pests on crop yield.

Pest Density and Aggregation

A trivial principle of biology is that organisms are not equal in number at all locations. This infers that plant pests are not equally important in all geographic regions. For instance, one of the most serious constraints to potato production in the eastern U.S. is the disease, late blight, caused by the fungus Phytophthora infestans. Without regular fungicide applications, potatoes could not be grown. However, in many western U.S. states the disease is not of major concern, mainly because of much drier weather conditions. Another example is the weed johnsongrass (Sorghum halepense), a major pest in the southern U.S., which is not found in high numbers in the northern U.S. This large-scale geographic variation in pest numbers and impact results in differing control practices.

At a much smaller scale, pest density can vary tremendously within a given region. This is particularly true with soil-borne fungi and arthropods. Two adjacent fields may have densities that vary by several orders of magnitude. With pests that move in the air, there will be less aggregation than this, but differences can still be large. Unfortunately, it is still not a wide-spread practice to assess pest densities in fields in order to properly determine the need to use a pesticide. There are obvious exceptions, however, which fall under the concept of Integrated Pest

Management (IPM). Initiated in the 1950's to better control insects of cotton, IPM blossomed in the 1970's with a wealth of federal government (USDA, NSF, and EPA) backing (6-7). IPM encompasses a holistic, multidisciplinary management system that integrates control methods on the basis of ecological and economic principles for pests that coexist in an agroecosystem. It involves much more than assessing pest density, but these assessments, nevertheless, are critical. Although pests, especially insects, of cotton and tobacco were originally studied in pilot projects, many crops in many states were eventually included.

An implicit assumption of IPM is that pesticides should only be used when necessary. Absence, or anticipated absence, of a given pest is a situation in which a pesticide application is not necessary. Even when a pest is present, control decisions can be made on the anticipated pest increase and the relationship between pest numbers and yield (see sections below). In practice, trained scouts can sample a given field by counting, measuring, or assessing pest density at selected locations. Growers themselves can also make the assessment.

The degree to which IPM is practiced and scouts are used varies with the crop and geographic area. Scouts are heavily used in some states (e.g., California) and rarely used in others (e.g., Ohio). Although usually lower expenditures for pesticides are required with IPM, sometimes greater expenditures are necessary in favorable years (4). For example, apple growers participating in an IPM program in North Carolina used less insecticides but more fungicides, resulting in an increase in total pesticide expenditures (8). However, increased fruit quality produced a net revenue increase for IPM growers compared to non-IPM growers.

One generally wants to determine the mean pest density per field with a given degree of precision. To do this, one must take a number of samples that is dependent on the aggregation of the pest. At any given time, a pest might have a uniform, random or clustered pattern in a field (9) (Fig. 1). Uniform patterns are not expected to occur, and even random patterns are not common. Although randomness is an absolute, clustering is a matter of degree--from low to high clustering. For a given level of precision, the lowest number of required samples is with a random pattern. Sample size increases as clustering increases.

There are many ways to assess or characterize the degree of clustering (9-10). For our purposes, the simplest measurement will be presented. If one is counting number of individual insects, infected plants, or lesions, and some statistical assumptions are met, the variance (\underline{v}) will equal the mean (\underline{m}) if there is a random pattern. With clustering, $\underline{v} > \underline{m}$, or the variance-to-mean (VTM) ratio exceeds one. The VTM is a useful yet simple index of aggregation; if VTM is known, one can sample accordingly. Obviously, the exact degree of aggregation will not be known until after sampling, but based on prior studies, one can assume a "worst-case" scenario and collect the necessary number of samples. Formulae for sample sizes are available (9).

Interaction of Pests with the Environment

Insects, pathogens, and weeds respond to their physical and biotic environment in predictable ways. For instance, growth of many fungal pathogens varies with temperature in a well-established manner. Growth starts low, increases to a maximum at the optimal temperature and then declines to zero (Fig. 2). In fact, most plant pests will respond to temperature in a similar manner. Fungal pathogens often require free moisture for infection to occur; infection increases with increased time of wetness (Fig. 2). The duration of free moisture is dependent on temperature (Fig. 2), as well as other physical factors.

Development of insects and pathogens is highly dependent on the plant host cultivar. Both physical and physiological host factors influence or limit the life cycle of insects and the disease cycle of pathogens. In fact, the first line of defense against many pathogens is host resistance. Although chemicals are more often used to control insects, host resistance to insects can be very effective (11).

Figure 2 depicts just some of the known response-stimulus relationships for plant pests. Collection of the fundamental data and description of the responses with mathematical models can lead to a better understanding of pests in the field. If one knew the current environmental conditions, one could predict whether or not the potato leafhopper would increase during the next week. Final decisions would also be based on the known population dynamics of the pests of interest (see below), as well as the known interaction between the plant host and pest.

Another component of the biotic environment is the collection of organisms that interact with the pests. Some of these interactions, including competition, parasitism, and predation, are exploited by man to achieve biological control. The range and numbers of interactions are immense. Researchers are accustomed to conducting experiments with perhaps two or three interactions. But when considering pests as part of the ecosystem, there are thousands of interactions (or relationships) among organisms within and between crops, as well as with crop cultivars, cultural conditions, and the physical environment. It is revealing to note that most pesticide use is aimed at curtailing interactions by the high specificity of the utilized chemicals. Van Enden (12) discusses some interesting interactions of pesticides with other factors, including biological control agents. An area in which interactions are critical for crop management is minimum or no-tillage systems. Here, interactions in the soil are relied on to result in reduced pest levels. The long-term consequences of the use of herbicides with minimum tillage cropping systems is still not known. Perhaps pest interactions should be exploited rather than eliminated with pesticides to benefit growers. Obviously much more work needs to be done in this area.

Population Dynamics

Numbers of pests are seldom static for long periods of time. Usually, population growth can be described precisely with one or more mathematical models. Such models permit the prediction of

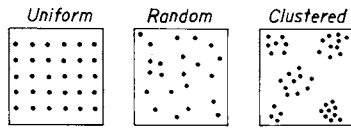


Fig. 1. Example patterns of pests in field plots.

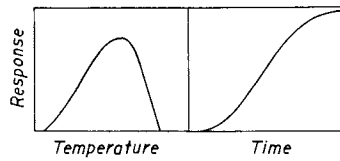


Fig. 2. Typical relationships between pests and physical factors.

future population levels based on past population growth and current environmental and biotic conditions. Knowledge of pest population dynamics is paramount for correctly using pesticides. Knowing that a certain pest will or will not reach a level at which losses occur can completely determine whether or not a pesticide is applied. Pests that increase slowly can be efficiently controlled at planting time, whereas pests increasing at a high rate need to be controlled throughout most of the growing season (2).

There is a wealth of literature on pest population dynamics (e.g., 13-14). Only some rudimentary concepts can be given here. The growth of a population is a dynamic process that needs to be described by its rate of change with time (dY/dt):

$$dY/dt = rY(K-Y)/K \quad (1)$$

in which: Y is the number of pests (e.g., insect adults, fungal lesions, or even infected plants); t is time, r is a rate parameter; K is the maximum population size, i.e., the carrying capacity; and dY/dt represents the absolute rate of increase. Integrating this equation results in a sigmoid-shaped curve which analytically can be written as:

$$Y = K/(1+\exp(-(\ln(Y_0/(K-Y_0))+rt))) \quad (2)$$

in which Y_0 represents initial population size. Equations 1 and 2 are very simple models for population growth, but, nevertheless, are often used, both for prediction and interpretation. For instance, it can be shown that reducing Y_0 with some control measure is not efficient if r is high (2).

Equation 1 can be generalized considerably to make it more realistic. The rate parameter r is influenced by generation time, reproductive and dispersal capacity, and how the biotic and abiotic environment influences these components. One can refine eq. 1 to account for all of these aspects by dividing Y into reproductive and nonreproductive parts (e.g., latent and infectious lesions), and also by making r a variable that is a function of the environment. K can also be made a variable that can vary with host changes and other factors.

Effects of Pests on Crop Yields

Obviously, pests would not be important if they did not reduce crop yields. A great deal of recent work has been conducted to relate pest density at various times to yield loss (e.g., 15-17). Pests can be classified into various categories, including: stand reducers (e.g., damping-off fungi), photosynthetic rate reducers (viruses), leave senescence accelerators (pathogens), light stealers (weeds), assimilate sappers (nematodes, sucking insects), tissue consumers (chewing insects, fungi) and turgor reducers (root feeding insects and pathogens) (15). Any given pest can act in one or more of the above categories.

The combined effects of plant pests will result in measurable direct primary loss if a threshold pest density is surpassed. Below this level (injury or disease damage level), crops theoretically are capable of "compensating" for the injurious effects of the pests.

Such thresholds, however, are difficult to determine experimentally. For instance, at low pest density (where the threshold is likely to be) there is great within-field variation and pest aggregation. Taken together with the natural variation in yield among healthy plants and the fact that other factors such as weather and nutrient availability influence results, researchers will find it difficult to precisely determine a threshold.

Above the threshold, whether precisely known or not, there is a proportionate reduction in yield with increases in pest densities. Eventually, a minimum yield could be reached in which further increases in pests do not produce additional yield losses. More complicated aspects of the yield/pest relationship are discussed by Teng (16). Ideally, one attempt to maintain pest density below the threshold level, provided that the threshold exists and is known. In practice, such a feat may require more pesticides than are economically feasible. If one cannot eliminate losses in quantity or quality of yield, then an economically optimal yield should be strived for. Such an optimum is achieved by maximizing the difference between cost of control and price of the harvested crop. Those interested in this topic should read Main (18) and Shoemaker (19).

Conclusions

There are many complex interactions among pests and their biotic and abiotic environment. Knowledge of these interactions, pest population dynamics, yield losses, and pest density and aggregation should improve our ability to properly use pesticides in the ecosystem. Despite their world-wide importance, much of this information on pests in the ecosystem still needs to be determined. Agricultural researchers, mainly at land grant schools and experiment stations, are continuing a long tradition of working in these areas. At present, our knowledge of the pest as part of the ecosystem is substantial only for a relatively few species. In an era when large percentages of new research dollars are being spent on biotechnology, researchers, unfortunately, may have a difficult time in acquiring the supplies, equipment, and personnel needed to carry out large field studies. Administrators must be made aware of the importance of this research.

One benefit of additional research is the expansion of our knowledge and understanding of such factors as damage thresholds, pest population dynamics, and how pests interact with other organisms in the ecosystem and react to changes in the environment. The other benefit of this work is that agricultural researchers will have the data to better educate others. Obviously, graduate and undergraduate students, as well as co-workers, will be the first to benefit from a better understanding of pests in the ecosystem. Some of these studies eventually will have positions with pesticide producers or IPM programs where they can apply their knowledge and also educate many others. Fortunately, this education is currently being carried on and will continue and improve only if universities, the federal and state governments, and industry continue to support researchers and teachers concerned about understanding pests as part of the ecosystem.

Literature Cited

1. James, W. C.; Teng, P. S. In "Applied Biology. Vol IV"; Coaker, T. H., Ed.; Academic: New York, 1979; pp. 201-267.
2. Zadoks, J.; Scheen, R. D. "Epidemiology and Plant Disease Management"; Oxford: New York, 1979; Chap. 8.
3. McEwen, F. L. BioScience 1978, 18, 773-777.
4. Schaub, J. R. In "Agricultural Chemicals of the Future"; Hilton, J. L., Ed.; Rowman and Allanheld: Totowar, 1985.
5. Pimentel, D.; Krummel, J.; Gallahan, D.; Hough, J.; Merrill, A.; Schreiner, J.; Vittum, P.; Koziol, F.; Back, E.; Yen, D.; Fiance, S. BioScience 1978, 28, 772-784.
6. "Integrated Pest Management"; Council of Environmental Quality, 1972.
7. Stern, V. M.; Smith, R. F.; van den Bosch, R.; Hagen, K. S. Hilgardia. 1959, 29, 81-101.
8. Carlson, G. A. In "Tar Heel Economit"; Agriculture Extension Service, North Carolina State University, Raleigh.
9. Ruesink, W. G. In "Sampling Methods in Soybean Entomology"; Kogan, M.; Herzog, D. C., Eds.; Springer-Verlag: New York, 1980; Chap. 3.
10. Campbell, C. L.; Noe, J. P. Annu. Rev. Phytopathol. 1985, 23, 129-148.
11. Tingery, W. M. In "The Leafhoppers and Planthoppers"; Nault, L. R.; Rodriguez, J. G., Eds.; Wiley: New York, 1985; Chap. 9.
12. van Emden, H. F. Proc. Symposium IX Int. Congr. Plant Prot., 1981, pp. 5-7.
13. Kranz, J. "Epidemics of Plant Diseases"; Springer-Verlag: Berlin, 1974; Chap. 1-5.
14. Southwood, T. R. E. "Ecological Methods"; Chapman and Hall: London, 1978; Chap. 9-12.
15. Boote, K. J.; Jones, J. W.; Mishoe, J. W.; Berger, R. D. Phytopathology 1983, 73, 1581-1587.
16. Teng, P. S. In "Advances in Plant Pathology, Vol. 3, Mathematical Modelling of Crop Disease"; Gilligan, C. A., Ed.; Academic: London, 1985; Chap. 8.
17. Cousens, R. Ann. Appl. Biol., 1985, 107, 239-252.
18. Main, C. E. In "Plant Disease, An Advanced Treatise, Vol. I, How Disease is Managed"; Horsfall, J. G.; Cowling, E. B., Eds.; Academic: New York, 1977; Chap. 4.
19. Shoemaker, C. In "Modeling for Pest Management"; Tummala, R. L.; Hayes, D. L.; Croft, B. A., Eds.; Michigan State University: East Lansing, 1976; pp. 32-39.

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Chapter 8

Principles Governing Environmental Mobility and Fate

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During the past several years, much attention has been devoted to understanding the physical and chemical properties, processes, and principles governing the environmental behaviour and fate of chemicals. The goal is to be able to predict how chemicals behave before release occurs and to use this capability in the design and regulation of chemicals proposed for use in pest control and other environmental applications. This effort has included improving the data base of key physical and chemical properties, understanding the processes which underly movement to air, biota, and groundwater, and developing models for predicting mobility and persistence. The modelling approach will be illustrated with examples of pesticide volatilization from water and the fate of pesticides in aquatic field use situations. The role of field experiments in validating predictive models will also be discussed.

Predicting how chemicals behave in the environment is a major task facing science today. Society is no longer satisfied to know that we can provide answers on where chemicals go and how long they persist by conducting analyses of environmental samples after use occurs. Rather, it demands premarket or preuse tests which can lead to prediction, with a high degree of certainty, that the chemical in question will not pose adverse environmental risks. Such processes as food chain accumulation, contamination of surface or groundwaters, undue persistence in soil or water, and movement to sensitive environments through the air are of particular concern. Fulfilling these expectations for premarket environmental safety testing is a large order; it requires that much information be available on physicochemical properties, the environmental compartments available to the chemical in its zone of use, processes which can transfer the chemical between compartments and transform the chemical within each compartment, and those extrinsic properties of the environment which influence both the course and

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rate of such processes. Given the complexity and heterogeneity of the environment--functions of both location from one environment to another and time within any given environment--it is presently not possible to provide quantitatively accurate prediction. Yet the demands of society, ever more frequently contained in regulations, require that science do the best job possible in this area. The subject of this chapter is the measurement of the key physicochemical properties which govern fate, and the use of these properties for predicting the environmental behaviour of pesticides.

Our ability to identify and measure the key physicochemical properties which influence behaviour and fate has improved considerably (1). There exist guidelines and, in some cases, detailed directions for determining such physical properties as water solubility (S), octanol-water partition coefficient (K_{ow}), bioconcentration factor (BCF), vapor pressure (P_{vp}), Henry's law constant (H), and soil sorption coefficient (K_d or K_{oc}), and the rates of such chemical processes as hydrolysis, photolysis, oxidation, metabolism by plants and animals, and biodegradation (2-4). As illustrated in Figure 1, this information along with several parameters which describe the "environment" into which the chemical is to be placed (a pond in the example) provide the starting point for making predictions on intercompartmental distribution and persistence -- the first step in defining the environmental fate for a given chemical or group of chemicals.

The second step often involves the use of physical or mathematical/computer models. Combining the "benchmark" properties (first step) with data from models (second step) allows one to draw a profile of expected behaviour. This information can be very useful to those developing chemicals for eventual release to the environment or proposing new uses for existing chemicals (5).

Certainly, if one is to rely on models, a third step must occur which involves validating the model predictions by comparing them with results from field studies. It is model validation that perhaps is in most need of immediate attention, particularly if one is aiming to regulate based upon model information as appears to be the case for EPA and several state regulatory agencies. Unfortunately, the ability of models to provide numbers may have engendered the notion that field tests are no longer needed, a notion that must be dispelled if we are to improve predictive capability to the point of regulatory reliability.

Physicochemical Properties

Polarity. A basic concept underlying virtually all physical properties, and the associated distributions involving them, is that of molecular polarity. Strictly speaking, polarity refers to the unevenness of charge in a molecule. Water is considered to be polar because it is relatively negative in the region of the oxygen atom and positive in the region of the two hydrogen atoms in the non-linear structure. The relatively high dipole moment (1.85 deByes), measured by observing the extent to which water molecules align themselves when placed between the plates of a charged condenser, and the high dielectric constant (80), measured as the ability of water to act as an insulator when placed in an electric

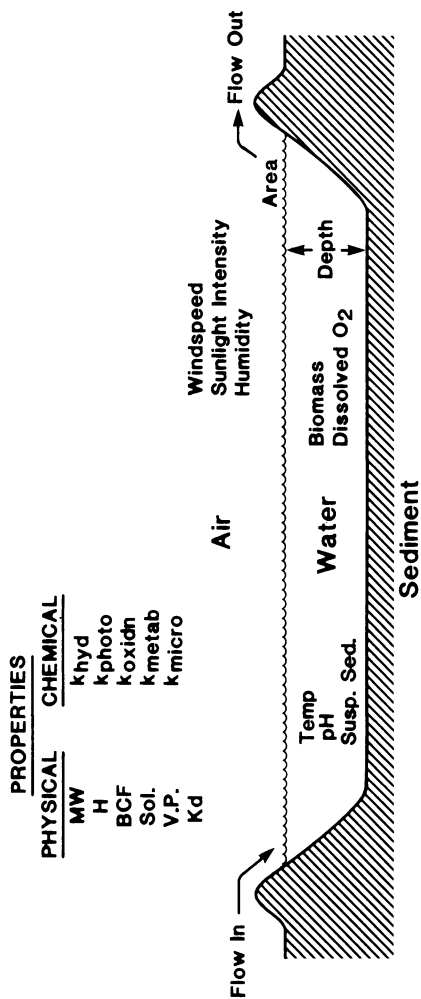


Figure 1. Intrinsic and extrinsic properties governing the distribution and fate of a chemical in a pond environment.

field, confirm this inherent polar character. Nitrobenzene is similarly considered to be a polar aromatic compound, with a dipole moment of 4.21 deByes and a dielectric constant of 35.7. These values are reasonable based upon the strong polarizing effect of the nitro substituent. We have no problem ranking nitrobenzene, chlorobenzene ($\mu = 1.7$ deByes, $D = 5.7$) and toluene ($\mu = 0.37$ deByes, $D = 2.4$) in a polarity series based upon this part of the polarity concept, and their water solubilities fall roughly in the order expected based upon it. It is even possible to do some ranking in simple structural series using the dipole moment contributions for various substituent groups (nitro, amino, nitrile, etc.). Useful generalizations among otherwise similar compounds are that symmetrical ones (eg, carbon tetrachloride) are less polar than unsymmetrical ones (eg, chloroform), and that compounds containing oxygen, nitrogen, and sulfur (eg organophosphate and carbamate esters) are more polar than hydrocarbons and chlorinated hydrocarbons. The total interaction of solute with solvent (or with solid surface in a heterogenous environment) involves several kinds of forces: Polar interactions (dipole-dipole, dipole-induced dipole), hydrogen bonding, and the dispersion interactions which exist between every pair of adjacent molecules. The latter, referred to as London or van der Waal's forces, explain the ability of even apolar substances to associate in condensed phases.

A polarity ranking is not possible based only on dielectric constant and dipole moment because they do not take into account H-bonding; thus, polarity series are often constructed empirically, using such factors as the solvent strength parameter obtained from the observed ability of various solvents to elute solutes from aluminum oxide absorbent. However, for environmental chemicals, a numerical index for polarity does not exist; only the consequences of polarity, as reflected in measureable properties such as water solubility and octanol-water partition coefficient, are available for fate predictions.

Water Solubility (S). The measurement of water solubility is relatively straightforward for most organic compounds, involving observation of the amount dissolved in water when an excess of the chemical is allowed to reach equilibrium with water at constant temperature. Centrifugation or filtration removes suspended material from the solution prior to measurement. Experimental variations on this basic method can produce rather large discrepancies (6). While precision appears to be lowest with hydrophobic compounds of very low solubility, a recent re-measurement revealed discrepancies with literature values of up to a factor of two for several pesticides of moderate water solubility and a factor of 100 for two of them (ronnel and bromophos) (7). A recently introduced column method offers the potential of generating solubility data of good precision and accuracy much faster than possible with the conventional method (8). This may stimulate an effort at re-measuring all pesticides under identical conditions.

Water solubility is influenced by temperature (T), and the direction generally is toward an increase in solubility with an increase in temperature. A rule of thumb is that solubility of

solids and liquids increases by a factor of 2 for a 14° rise in temperature from 10-24°C. However, there are exceptions to this. The solubility of thiocarbamates decreases with increasing temperature (9), an effect ascribed to an increase in resonance contribution of the uncharged $-S-C(O)-N=$ form at higher temperatures over the $-S-C(O^-)=N^+$ form which predominates at lower temperatures (10). Unfortunately, solubilities in the literature are usually given at just a single temperature so that there is no basis for judging whether a regular or inverse relationship exists between S and T for a given chemical. Furthermore, the temperature may not always be specified in the literature citation, leaving a large potential for error when using such values in fate calculations.

Among organophosphates paraoxon has a water solubility of 3640 ppm compared with only 12.4 ppm for parathion (7), reflecting the much greater polarizing effect of the $P=O$ moiety when contrasted with $P=S$. Similarly, phorate sulfoxide (>8000 ppm) is much more soluble than phorate (17.9 ppm) because of the presence of the polarizing $S \rightarrow O$ group in the former. It is thus not possible to estimate the water solubility of a compound based upon the value for a close analog. The effect of very small changes in structure may also help to explain some of the discrepancies in reported solubilities in the literature, where a small contamination with an analogue of much higher solubility than the compound being subjected to measurement can produce a large error in the measured value.

The water solubility of the supercooled liquid exceeds that of the solid for a given chemical above its melting temperature (t_m). An approximate formula for converting from one to the other is (11):

$$\text{Log } S_{\text{solid}} = \text{Log } S_{\text{liquid}} - 0.0095 (t_m - 25)$$

This may be an important correction in environmental fate calculations because the liquid form, rather than the solid (upon which solubility determinations are usually based), may be the state of interest in environmental processes. Obviously, the correction becomes larger for compounds of higher melting point.

Considering the above factors as well as water pH and water purity, it is clear that reported water solubilities, particularly those done at a single temperature with no indication of replication or of solute and solvent purity, must be assigned a fairly large uncertainty (at least $\pm 100\%$) when used for calculating distribution coefficients or other environmental fate parameters. When water solubility is not reported in the literature, it may be estimated from the octanol-water partition coefficient (K_{ow}) or from structural parameters (11); in either case an even larger uncertainty exists in the value.

Octanol-Water Partition Coefficient (K_{ow}). This partition coefficient is perhaps the most used distribution constant in environmental chemistry, underlying calculations of bioconcentration and bioaccumulation, several structure-activity relationships, and the choice of solvent conditions for extractions.

Partition coefficient has been studied in great detail and compilations are available in the literature (12). The laboratory measurement of K_{OW} is fairly straightforward, although again error can creep in due to such things as failure to use equilibrated solvents, non-constant temperature, and inaccuracy of the measuring technique, contributing to a fairly large uncertainty in literature values. A not atypical case is that for methyl parathion, where the literature provides at least 4 values of $\log K_{OW}$ (11):

$\log K_{OW}$	K_{OW}
2.04	109.6
2.99	977.2
1.91	81.3
3.22	1659.6

In light of this example, literature values of K_{OW} must be given a fairly broad latitude (± 1 order of magnitude) unless they have been confirmed by more than one laboratory or by calculation from structure.

The relatively new area of property estimation has been perhaps best developed for K_{OW} . The methods of estimating $\log K_{OW}$ include:

- a. Estimation from Reverse Phase - HPLC retentions
- b. Estimation from water solubility
- c. Estimation from structure via fragment constant method

Correlation with reversed phase HPLC retention data is attractive as a rapid estimation method because the sample requirements of HPLC in terms of purity and quantity are not stringent. A popular estimation method is from water solubility (S) data, given a log-log regression between S and K_{OW} for a series of compounds. An example of a regression equation applicable to mixed classes of chemicals (11) is:

$$\log S = 1.37 \log K_{OW} + 7.26$$

where S is expressed as $\mu\text{mol/L}$. Forty-one compounds, ranging from $K_{OW} = 8$ to 10^6 , were used in the regression with a correlation coefficient (r^2) of 0.903. Other equations might be more apt for specific types of organic chemicals (11). The advantage of using the solubility correlation to obtain K_{OW} is that no chemical is required, and one only needs a literature value of S. The disadvantage is that it is just an estimation, and there is no way of assessing the accuracy of it given the uncertainty in literature values of S described above.

Related to the above is the intriguing possibility that physical properties can be calculated knowing only molecular structure, completely obviating the need for a sample of the substance or any prior laboratory work with it. For K_{OW} , the calculation from structure uses the fragment constant approach (13) or early versions of it (12). Briefly, the method employs empiric-

ally derived atomic or group fragment constants (F) and structural factors (f):

$$\log K_{ow} = \text{sum of fragments (F) and factors (f)}.$$

Values for F and f are compiled in tables (11, 13). The calculation becomes more tedious (and uncertainty in the result increases) for more complex structures. A computer program has been developed to aid in the calculation (C. Hansch and A. Leo, personal communication).

Bioconcentration Factor. The bioconcentration factor (BCF) is defined as the ratio of the concentration of a chemical in an organism to the concentration in the surrounding medium. While BCF is used most commonly as a measure of direct partitioning of chemical from water to fish, it also has some applicability to terrestrial species (plants and animals) in contact with contaminated soil or water (14).

Some confusion exists in the literature regarding the term "bioconcentration" which, as defined above, implies uptake across membranes from the medium (usually water), and "biomagnification", "bioaccumulation", and "ecological magnification". In the latter three, dietary transfer of chemical can occur along with direct partitioning. The major experimental distinction is that bioconcentration experiments are run such that no dietary intake is involved, while bioaccumulation experiments include contributions from both direct partitioning and dietary intake. In biomagnification, the use of an intact food chain involving two or more trophic levels is implied.

The measurement of bioconcentration is difficult because the water concentration must remain constant during the run and contact must be maintained until equilibrium is reached in the organism. Equilibration, signalled by a plateau in the concentration vs time plot, may take several days. This entails, particularly in the case of relatively hydrophobic compounds of low water solubility, dosing in a flow-through chamber at levels well below the toxic threshold. A complete experiment involves analysis of samples during the exposure, or "uptake phase", and also following transfer to a clean environment where release (depuration) occurs. Both the parent chemical, from which the bioconcentration factor is calculated, and known metabolites are analyzed (15).

Experimental variables include, in addition to those implied above, temperature and species of test organism. The species-to-species variation alone contributes a variability of $\pm 50\%$ for the same chemical. Another variable is the type of tissue sampled. When account is taken of all error sources, values differing by much less than 1 order of magnitude may not have biological significance (15). This still leaves room for a reasonable scale as BCF for most organic chemicals fall over a wide range, from about 1 (hydrophilic compounds) to over 1,000,000 (hydrophobic chemicals).

If BCF is not available from experimental measurements, it can be estimated via correlation equations from water solubility (S), octanol-water partition coefficient (K_{OW}) or soil adsorption coefficient (K_{OC}). Of the three, correlations from K_{OW} are considered the most reliable because they are currently based on the largest body of bioassay data and because K_{OW} measurements involve a water-lipophilic phase partitioning which bears obvious similarity to water-to-fish partitioning. One recommended correlation equation is (11):

$$\log BCF = 0.76 \log K_{OW} - 0.23$$

It is based on data from several investigators using a variety of fish species and 84 organic chemicals. The log-log plot of this correlation shows substantial scatter, underscoring the order-of-magnitude accuracy expected in results from the use of the correlation.

Volatility. For vapor pressure, the fundamental property governing condensed phase-vapor phase distributions, the experimental measurement can be quite tedious and prone to several sources of error particularly for compounds of low volatility. Of the available methods, gas saturation appears to be the most convenient and accurate (16), while estimation based upon GC retention data promises a more rapid (though perhaps less accurate) method worth further development (17).

Henry's law constant, the air-water distribution ratio, is needed when computing either the direction of equilibrium or the rate of volatilization from water. It may be measured experimentally or calculated as the ratio of vapor pressure to water solubility (18).

Rate Constants. Distribution coefficients of the type mentioned above tell the direction of transfer but not the rate of transfer or overall dissipation. As noted, the data for distribution coefficients are imprecise and frequently difficult or impossible to find in the literature, and their estimation techniques in need of further improvement. The situation is even less satisfactory for rate constants, with the possible exception of rate of volatilization from water (Table I). Linear Free Energy Relationships (LFER) offer potential as estimation techniques for reaction rate constants, with examples being provided by estimation of the second order rate constant for hydrolysis of organophosphate esters from the pKa of the leaving group's conjugate acid or of benzoic esters from Hammett sigma-rho values (11). There are currently just a few LFER's available, for just a few classes of chemicals and reaction types, and the data base upon which they have been built is fairly small particularly for pesticides. This is definitely an area in need of a greatly expanded effort.

Table I. Availability of Rate Constant Data from Literature Sources and from Estimation Techniques

Rate Constant	Literature Data Base of Experimental Values	Estimation Techniques
Volatilization	Good	Good (from H)
Hydrolysis	Fair	Fair (LFER, k vs pH)
Photolysis	Fair	Fair (UV-Vis ϵ vs λ , solar irradiation data)
Uptake by fish	Poor	Fair (LRE from K_{ow})
Excretion by fish	Poor	Poor (LRE from K_{ow})
Uptake by soil	Fair	Not available
Desorption from soil	Poor	Not available
Biodegradation	Poor	Qualitative only

LFER = Linear Free Energy Relationship

LRE = Linear Regression Estimation

Environmental Relevance

The availability of reliable measurements or estimates of water solubility, octanol-water partition coefficient, bioconcentration factor, rate constants and the like allows one to make qualitative judgements or, through the use of mathematical simulation models such as EPA's EXAMS (19), quantitative calculations of environmental distribution and persistence. In the qualitative use, Swann and coworkers (20) classified chemical mobility in soil based upon reversed-phase HPLC retention data which in turn is related to S . The approximate water solubility equivalents in this first-estimate classification, with chemical examples, are in Table II. This classification holds for chemicals whose primary adsorption in soil is to organic matter, and excludes those chemicals (such as paraquat) which bind ionically to the soil mineral fraction. A recent tabulation of pesticides found in groundwater had 11 entries, 8 of which represented compounds with water solubilities in excess of 200 ppm with the remaining three falling in the range of 3.5 to 52 ppm (21).

Table II. Relationship Between Soil Mobility (Leaching) and Water Solubility (20)

Mobility Class	Water Solubility	Examples
Very High	>10 ⁶ -3000 ppm	Aldicarb (5730 ppm)
High	3000-300	Bromacil (815 ppm)
Medium	300-30	Carbofuran (257 ppm)
Low	30-2	Simazine (3 ppm)
Slight	2-0.5	Ethion (1.1 ppm)
Immobile	<0.5	DDT (0.0023 ppm)

Of course, water solubility alone is not an adequate criterion for soil movement, and must be tempered with a knowledge of soil sorption, volatility, and chemical reactivity, competing processes that can remove a chemical from the soil water phase, and the method of application to soil. An attempt to build in the important factors which govern leaching (as well as a similar approach to volatilization from soil) has been described (22). Their "leaching index" can be calculated from the simple ratio:

$$\text{LEACH} = \frac{s \cdot t^{1/2}}{P_{vp} \cdot K_d}$$

Simple indices such as this can be quite useful for ranking chemicals according to inherent leaching potential, but fall short of direct environmental relevance because they make no account of the soil and groundwater characteristics which exist in a given use zone. To factor in the latter, Aller et al. (23) developed a weighting scheme ("DRASTIC") which combines seven hydrogeological parameters into a score which can serve as an indicator of relative groundwater contamination potential for a given region of the country. The parameters are:

Depth to groundwater
Recharge rate
Aquifer media
Soil media
Topography
Impact of the vadose zone
Conductivity of the aquifer

The results of both the LEACH and DRASTIC calculation can provide important leads for selecting monitoring sites, as well as serving to flag potentially troublesome pesticide use situation (24). The development of "triggers" by EPA, which take into account many of these same groundwater contamination characteristics, indicates that regulation based upon physicochemical properties is in the offing. In fact, California recently passed a groundwater contamination prevention act (the "Connelly Bill", 25) which mandates the setting of numerical standards for those physicochem-

ical properties involved in downward movement of chemicals through soil, with a relatively short time deadline for defining the standards. This is a relatively new development, breaking new ground in the regulatory process.

Examples of Prediction: Air-Water Distributions Involving Pesticides

The atmosphere represents an important environmental compartment for receiving and distributing residues of organic chemicals. Pesticides, for example, may enter the atmosphere during application to soil, crops, and forests by the process of drift and by volatilization of residual deposits after application (26). The concentration and form of airborne residues are of concern from the viewpoint of human exposures and for the possible damage they might cause to sensitive plants and animals downwind from the treated areas. There is also considerable evidence that the atmosphere may be an important medium for moving pesticides through the environment far from the original sites of application, and for breakdown processes.

While these points are now understood qualitatively, there is a general lack of quantitative information on specific processes for specific pesticides. The lack of such information has hampered the development of capability for predicting the relative role of atmospheric processes in overall pesticide environmental fate, and specifically of equations correlating atmospheric processes with pesticide physicochemical properties and environmental variables.

As part of a long-term study of pesticide residue dynamics in the atmosphere, we gathered and analyzed environmental samples from two situations and then compared the experimental data with results predicted by equations or models which fit the situations.

Volatilization from Flooded Fields. One instance involved the measurement of volatilization flux of pesticides from flooded rice fields in California's Central Valley. We obtained quantitative information on how much pesticide is lost to the air by post-application volatilization, at what rate the loss occurs, and what factors control it for individual chemicals.

The methodology for measuring rate of volatilization, or flux from soil, water, or crop surfaces, has been summarized by Taylor (27). In practice, one or more multiple sampling towers is placed near the center of a field or study plot, and air samples are collected at intervals for several days after application. The resulting concentrations are used to calculate flux for each sampling period, and the data from several sampling periods are then integrated to give the rate and amount volatilized. This "aerodynamic" method may be supplemented by analyzing for loss of chemical from condensed media (soil, water, foliage); the two methods should give results which are equivalent for stable chemicals or results which differ by the amount of breakdown occurring in the condensed media. While the aerodynamic method has found widespread use for measuring pesticide flux above bare soil and field crop canopies, it had not been used above water surfaces probably because of the technical difficulty in maintaining samp-

lers at constant height and in changing sampler contents frequently without disturbing the water body. These difficulties were circumvented by making measurements in a shallow, flooded rice field with a narrow wooden pier constructed as a pathway to the air sampling and meteorological masts.

An available aquatic fate computer model, EXAMS (Exposure Assessment Modelling System, 19), provided predictions for comparison with the field-measured volatilization flux. EXAMS inputs include:

Chemical	Environment
Molecular weight	Water depth
Water solubility	Water surface area
Vapor pressure	Water temperature
	O ₂ exchange constant

These parameters were known or measurable for the chemicals studied. The EXAMS model was previously used successfully for modelling volatilization processes from waste ponds (28), a somewhat similar application.

The EXAMS program is an interactive system that allows a user to specify and store the properties of chemicals and ecosystems, modify the characteristics of either using simple English-like commands, and conduct rapid evaluations and sensitivity analyses of a chemical's probable aquatic fate (19). Starting from a description of the chemistry of a toxicant, and the relevant transport, physical and chemical characteristics of the ecosystem, EXAMS computes:

- 1) Exposure: the ultimate (steady-state) environmental concentrations resulting from a specified pattern of pollutant loadings,
- 2) Fate: the distribution of the chemical in the system and the fraction of the loadings consumed by each transport and transformation process (volatilization, in the case studied here),
- 3) Persistence: the time required for effective purification of the system (via export/transformation processes) once the pollutant loadings terminate.

Field-measured herbicide volatilization from flooded rice fields, results from a laboratory simulation chamber (28), and predictions from the EXAMS computer program, led to several conclusions (29). Both the laboratory chamber and EXAMS computer model showed good potential for predicting the volatilization flux of pesticides applied to flooded fields. EXAMS calculations agreed fairly well, and laboratory chamber measurements agreed very well with field results for the thiocarbamate herbicides, thiobencarb and molinate (Table III). For MCPA, neither EXAMS nor the laboratory chamber gave flux values approaching those observed in the field, but in this case the major sources of volatilized residue were deposits on dry foliage and soil surfaces rather than from solution in water. The MCPA case also showed the potential

Table III. Summary of Normalized Flux Values For Chemicals in Flooded Rice Fields (29)

Chemical	H (atm·m ³ /mole)	Flux (ng/cm ² ·hr·ppm)			
		EXAMS	Laboratory Chamber	Rice Field	
				Day 1	\bar{x} Days 1-3
MCPA (acid)	1.0×10^{-9}	8.1×10^{-3} (pH 3.5)	4.1×10^{-3} (pH 3.5)	2.8	1.9
MCPA-DMA (salt)	$<10^{-13}$	0.0000	----	----	----
4-Chloro- o-cresol	1.1×10^{-6}	---	---	330	243
Thioben- carb	1.7×10^{-7}	4.5	23.8	23	23
Molinate	9.6×10^{-7}	51.5	62.8	66	47

importance of a relatively minor contaminant/conversion product 4-chloro-o-cresol having much higher volatility than the parent pesticide as a contributor to airborne residues.

Although the objective was to compare results from EXAMS, the laboratory chamber, and field in this evaluation, the findings do allow for assessment of the relative importance of volatilization as a fate process for the three herbicides studied, showing clearly that volatilization rate decreases in the order molinate > thioben-carb > MCPA which is in agreement with the prediction based upon Henry's law constant. The ability of the model to generate data supporting the field measurement bodes well for the further use of such models in the future. In the case of volatilization, which is so difficult to measure experimentally, the availability of a predictive model would be a welcome development.

While this study showed the potential of EXAMS for forecasting volatilization over fairly broad time intervals, a more refined study was needed to supply experimental flux data to test the capability of EXAMS to model variations in flux with time of day, windspeed, and temperature. This was conducted for molinate using the same basic field design as before but with more sampling intervals and heights, and better micrometeorological equipment. EXAMS was provided with inputs of temperature, windspeed, and with molinate water solubility and vapor pressure corresponding to the temperatures at each sampling interval. The results (30) showed that EXAMS correctly forecast the flux maxima and minima measured by the aerodynamic method. The experimental measurements from the field were somewhat lower than predicted by EXAMS and by the loss in field water concentrations of the herbicide.

Overall, EXAMS appeared to be quite promising as a predictive tool for estimating volatilization loss from flooded rice fields. It may be useful for estimating loss from other dissipation routes as well, a capability of the model not tested in these experiments, and for estimating overall dissipation in water from all routes of loss. This capability could be quite useful for calculating the effect of water holding intervals on the concentration of herbicides in rice field effluent reaching public waterways--a subject of much interest in the extensive rice growing regions of California's Sacramento Valley (31)--and, more generally, the concentration of virtually any organic pollutant in bodies of water at various times following contamination.

Pesticides in Fogwater. A second set of experiments dealt with the fate of pesticide in the atmosphere, and more specifically with the distribution between vapor and atmospheric moisture in the form of fog. The ways by which residues can be removed from the air include dry deposition, that is, by impaction of particles or direct air-surface exchange of vapors, and wet deposition following entrainment of particles or dissolution of vapors in fog, snow, and rainwater (32). Hundreds of organic chemicals have been identified in rainwater (33, 34) and a smaller number in fogwater (35), but aside from the more persistent halogenated materials and herbicides in rainwater (36, 37), practically no measurements have been made of other pesticides.

In 1983-84, a collection system designed by USDA-ARS personnel Glotfelty and Liljedahl at Beltsville, MD, was used to collect fogwater from Maryland. In this collaborative project, an analytical method (adapted from 38) was developed for ppt concentrations of representative pesticides, and positive findings were made of five organophosphates (including diazinon, malathion and methyl parathion), two triazines (atrazine and simazine), an organochlorine (DDT), and several phthalate esters and polycyclic aromatic hydrocarbons. In 1984-85, the fog sampler was brought to California for sampling fog from the Central Valley. These "tule fogs" may linger for several days in the December-March season and, in the process, entrain airborne dusts and partition chemical vapors. A total of 16 phosphorus- and nitrogen-containing compounds were measureably present in fogwater collected at the Kearney Agricultural Center near Fresno (Table IV) and 16 in another sample collected near Corcoran in the cotton-growing region of Kings County; similar findings were obtained for samples from other parts of the Central Valley (39). The concentrations of several of these chemicals--notably, p-nitrophenol, diazinon, ethylbenzimidazole, parathion, paraoxon, chlorpyrifos, and DEF--were suprisingly high, extending to 30 ppb in the extreme case of p-nitrophenol. For diazinon, Central Valley fog had approximately 20 times the concentration measured in Maryland fog during the preceding winter. We were particularly intrigued by two findings:

1. Breakdown products of parathion (paraoxon and p-nitrophenol), trifluralin (ethylbenzimidazole), and chlorpyrifos (chlorpyrifos oxon) were suprisingly significant residues.

TABLE IV. Distribution of Chemicals Between Fog Water and Interstitial Air - Kearney Agricultural Center, January 13, 1985 (39)

Chemical	Concentration, ng L ⁻¹		Distribution Ratio (X10 ⁶)	
	Fog Water	Air (X10 ³)	Experimental	Literature
Diazinon	16,000	2.2	0.12	60
Parathion	12,400	3.2	0.25	9.5
Chlorpyrifos	1,020	3.3	3.2	500
Methidathion	840	<0.03	<0.04	0.07
DEF	250	<0.03	<0.12	320
Malathion	70	<0.03	<0.4	1.0
p-Nitrophenol	32,800	<1.2	<0.04	0.084
Simazine	390	<0.1	<0.3	0.025
Atrazine	270	<0.2	<0.7	0.2
Paraoxon	9,000	0.21	0.023	0.25
Methidathion Oxon	120	<0.03	<0.25	----
Diazoxon	190	<0.03	<0.16	----
Chlorpyrifos Oxon	170	<0.03	<0.18	----
Trifluralin	<350	1.3	>3.7	3.2 x 10 ³
Ethylbenzimidazole	14,000	2.2	0.15	----
PCNB	<3,000	113	>40	1.8 x 10 ³

2. Unlike the Maryland findings, the distribution of chemicals between vapors and fogwater in California samples differed considerably from that predicted by Henry's Law constants, being much more enriched (100 to 1000 x) in the water than predicted.

The observation of breakdown products may reflect hydrolysis or oxidation of residues on surfaces prior to volatilization or conversion in the vapor phase (40). The unexpectedly high water phase distribution is more difficult to explain and, in the present context, shows that our ability to predict behaviour is far from perfect. Apparently, partitioning in fog atmospheres is not simple, and might involve a contribution from particle entrainment or from surface-active solutes which enhance dissolution in the water phase. The encouraging point is that pesticides were correctly predicted to be measurably present in fogwater; this finding may have pinpointed an environmental medium (fogwater) that can be used advantageously to measure movement and dispersion of pesticides, and also provide basic information on an environmental fate pathway previously unrecognized. Although it is doubtful that

fogwater will concentrate pesticides to an extent that poses a health hazard, it certainly should not be overlooked when assessing the total exposure for humans, wildlife, and plants.

Conclusions

The study of the behavior and fate of chemicals in the environment -- environmental chemodynamics -- has moved from reliance on retrospective analytical data toward an ability to predict quantitatively based upon properties which can be determined in the laboratory or estimated from structure. The important physical properties and the corresponding distribution coefficients may be measured directly or estimated by linear regression equations. The advantage of this approach is that it allows one to screen for chemicals that are likely to show adverse environmental behaviour characteristics (eg, leaching or biomagnification) early in the development phase, and in fact to build in desirable properties (eg, by addition of appropriate functional groups) to prevent unwanted persistence or contamination. The disadvantages at the present are that (1) literature values of the key properties, as well as those obtained by regression correlations, are only approximate so that conclusions drawn from calculations based upon them are usually rough estimates, and (2) some environmental processes (such as leaching) are not well enough understood presently to allow quantitative predictions even if physical properties of high accuracy were available.

Certainly the trend toward refining our ability to measure or estimate the appropriate properties, to correlate these with structure, and eventually use them to calculate environmental behaviour and fate of existing chemicals or to design new alternative chemicals will continue. For the present, field testing is still needed both to point out adverse behavior not fully understood or anticipated and to provide data to ensure that our property-based estimations are headed in the right direction. It is important that such validation studies be pursued vigorously given the rush toward adopting models, and the results of models, for regulatory purposes. Regulating pesticide uses based upon physicochemical properties and models poses new challenges which, if successfully met, will ensure a steady improvement in the development and use of agrochemicals posing minimal risks to man's environment.

Literature Cited

1. Seiber, J.N. In "Agricultural Chemicals of the Future"; Hilton, J.L., Ed; Rowan and Allanheld: Totowa, NJ., 1985; Chapt. 31.
2. "Test Protocols for Environmental Fate and Movement of Toxicants," Association of Official Analytical Chemists, Arlington, VA., 1981.
3. "Annual Book of ASTM Standards, Part 3, Method D," American Society for Testing and Materials, Philadelphia, 1970, p. 1193.

4. "Chemical Fate Test Guidelines," Office of Pesticides and Toxic Substances, USEPA Report EPA560/6-82-003, PB82-233008, Washington, D.C., 1982.
5. Swann, R.L.; Eschenroeder, A., Eds. "Fate of Chemicals in the Environment - Compartmental and Multimedia Models for Predictions"; ACS SYMPOSIUM SERIES No. 225, American Chemical Society: Washington, D.C., 1983.
6. Gunther, F.A.; Westlake, W.E.; Jaglan, P.S. Residue Rev. 1968, 20, 1-148.
7. Bowman, B.T.; Sans, W.K. J. Environ. Sci. Health 1979, B14(6), 625-34.
8. Wasik, S.P.; Miller, M.M.; Teari, Y.B.; May, W.F.; Sonnefeld, W.J.; Devoe, H.; Zoller, W.H. Residue Rev. 1983, 85, 29-42.
9. Freed, V.H.; Hague, R.; Verneti, J. J. Agric. Food Chem. 1967, 15, 1121-3.
10. Rummens, F.N.A.; Louman, F.J.A. J. Agric. Food Chem. 1970, 18, 1161-4.
11. Lyman, W.J.; Reehl, W.F.; Rosenblatt, D.H. "Handbook of Chemical Property Estimation Methods"; McGraw-Hill: New York, 1982.
12. Leo, A.; Hansch, C.; Elkins, D. Chem. Revs. 1971, 71, 525-621.
13. Hansch, C.; Leo, A.J. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; John Wiley: New York, 1979.
14. Kenaga, E.E. Environ. Sci. Technol. 1980, 14, 553-6.
15. Macek, K.J.; Petrocelli, S.R. In "Test Protocols for Environmental Fate and Movement of Toxicants", AOAC: Arlington, VA., 1981; pp 168-76.
16. Spencer, W.F.; Cliath, M.M. Residue Rev. 1983, 49, 1-47.
17. Kim, Y.-H.; Woodrow, J.E.; Seiber, J.N. J. Chromatogr. 1984, Vol. 314.
18. Mackay, D.; Shiu, W.Y.; Sutherland, R.P. Environ. Sci. Technol. 1979, 13, 333-7.
19. Burns, L.A.; Cline, S.M.; Lassiter, R.R. "Exposure Analysis Modeling System (EXAMS): User Manual and System Documentation"; U.S. Environmental Protection Agency; Environmental Research Laboratory: Athens, GA., 1981.
20. Swann, R.L.; Laskowski, D.A.; McCall, P.J.; Vander Kuy, K.; Dishburger, H.J. Residue Rev. 1983, 85, 17-28.
21. Cohen, S.Z.; Creeger, S.M.; Carsel, R.F.; Enfield, C.G. In "Treatment and Disposal of Pesticide Wastes"; Krueger, R.F.; Seiber, J.N., Eds.; ACS SYMPOSIUM SERIES No. 259, American Chemical Society: Washington, D.C., 1984; pp 297-326.
22. Laskowski, D.A.; Goring, C.A.I.; McCall, P.J.; Swann, R.L. In "Environmental Risk Analysis For Chemicals"; Conway, R.A., Ed.; Van Nostrand Reinhold Co.: New York, 1982.
23. Aller, L.; Bennett, T.; Lehr, J.; Petty, R. "DRASTIC: A Standardized System for Evaluating Groundwater Pollution Potential using Hydrogeologic Settings"; USEPA, Office of Research and Development: Washington, D.C., 1985; 384 pp.
24. RaO, P.S.C.; Hornsby, A.G.; Jessup, R.E. Soil Crop Sci. Florida Proc. 1985, 14, 1-8.

25. "AB 2021, California Legislature," State of California, Sacramento, CA., 1985.
26. Seiber, J.N.; Kim, Y.H.; Wehner, T.; Woodrow, J.E. In "Pesticide Chemistry: Human Welfare and the Environment"; Miyamoto, J.; Kearney, P.C., Eds.; Pergamon Press: Oxford, 1983; Vol. 4.
27. Taylor, A.W. J. Air Pollut. Control Assoc. 1978, 28, 922.
28. Sanders, P.E.; Seiber, J.N. In "Treatment and Disposal of Pesticide Wastes"; Krueger, R.F.; Seiber, J.N., Eds.; ACS SYMPOSIUM SERIES No. 259, American Chemical Society: Washington, D.C., 1984; pp 279-96.
29. Seiber, J.N.; McChesney, M.M.; Sanders, P.F.; Woodrow, J.E. Chemosphere 1986, 15, 127-38.
30. Seiber, J.N.; McChesney, M.M.; Woodrow, J.E. "Experimental validation of model-predicted volatilization rates of pesticides from water"; Paper presented at the 190th National Meeting of the American Chemical Society (AGRO 99), Chicago, IL, Sept. 8-13, 1985.
31. Cornacchia, J.W.; Cohen, D.B.; Bowes, G.W.; Schnagl, R.J.; Montoya, B.L. "Rice Herbicides: Molinate (Ordram) and thiobencarb (Bolero)"; California State Water Resources Control Board: Sacramento, CA, April, 1984; Special Projects Report No. 84-45P.
32. Galloway, J.N.; Eisenreich, S.J.; Scott, B.C., Eds. "Toxic Substances in Atmosphere Deposition: A Review and Assessment"; National Atmospheric Deposition Program, NC-141: July, 1980; 146 pp.
33. Gill, P.S.; Graedel, T.E.; Weschler, C.J. Rev. Geophys. Space Phys. 1983, 21, 903.
34. Duce, R.A.; Mohnen, V.A.; Zimmerman, P.R.; Grosjean, D.; Cautreels, W.; Charfield, R.; Jaenicke, R.; Ogren, J.A.; Pellizari, E.D.; Wallace, G.T. Rev. Geophys. Space Phys. 1983, 21, 921.
35. Munger, J.W.; Jacob, D.J.; Waldman, J.M.; Hoffman, M.R. J. Geophys. Res. 1983, 88, 5109.
36. Eisenreich, S.J.; Looney, B.B.; Thornton, J.D. Environ. Sci. Technol. 1981, 15, 30.
37. Pankow, J.F.; Isabelle, L.M.; Asher, W.E.; Kristensen, T.J.; Peterson, M.E. In "Precipitation Scavenging, Dry Deposition, and Resuspension"; Pruppacher et al., Eds.; Elsevier: New York, 1984; pp 403-14.
38. Wehner, T.A.; Woodrow, J.E.; Kim, Y.H.; Seiber, J.N. In "Identification and Analysis of Organic Pollutants in Air"; Keith, L.H., Eds.; Ann Arbor Science: Ann Arbor, MI., 1983.
39. Glotfelty, D.E.; Seiber, J.N.; Liljedahl, L.A. Submitted for publication, 1986.
40. Woodrow, J.E.; Crosby, D.G.; Seiber, J.N. Residue Rev. 1983, 85, 111-25.

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Chapter 9

Mammalian Metabolism

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While pesticide risk assessment should never become totally a predictive process, it is essential that our prior knowledge of xenobiotic metabolism be used to help predict the hazards of chemicals before they are introduced into the environment. It is important to realize, however, that even a complete knowledge of the metabolism of a pesticide in mammals does not necessarily alert one to the potential safety or risks that might be associated with the use of that particular compound. This can be accomplished only when the metabolism data can be related to toxicological significance. Consequently, greater emphasis in the future must be placed on defining the influence of given metabolic reactions on toxicity, while at the same time continuing the awesome task of individual metabolite identification and toxicity assessment.

The recent space shuttle disaster which claimed the lives of seven American astronauts resulted in one of the most extensive and expensive investigations ever conducted. Every phase of the space program was included in the investigation and flaws causing, or at least contributing to, the accident were eventually revealed that seemingly would never occur in such a sophisticated undertaking. This dreadful event is mentioned here just as one example where proper caution, even amongst the best, sometimes is not practiced. Like most after-the-fact investigations, the space shuttle incident raises a point that is germane to all whose actions and reactions may impact upon the safety of others. That is, it is not only important that the right questions are being asked, it is essential that the right questions are being asked at the right time.

One of the most important aspects of the symposium on pesticide risk is the opportunity it provides for those in the pesticide chemistry and toxicology field to think about whether the right questions are being asked and if they are being asked at the right time. Such is not always the case as evident by the numerous incidences where caution and, indeed, most of our regulations

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concerning pesticide safety, have resulted largely from after-the-fact considerations. Fortunately, the frequency of scientists reacting to pesticide-related crisis, in lieu of sound planning towards their prevention, seems to be decreasing. As amply evidenced by the recent situation regarding pesticide-contaminated ground water, however, all is not well and it is clear that there are still many cases where the right questions have not been asked, or at least asked of the right people. Ideally, the right people would be those scientists who are experts in the area of pesticides and who, if specifically asked, could accurately predict many hazards before they occur. That this is not always done, even when the expertise exists, attests to avoidable weaknesses in the present hazard assessment system.

The present paper is concerned with pesticide metabolism and in keeping with the issue of question-asking as heretofore discussed, the question which must be addressed is as follows:

Can and will a better understanding of mammalian metabolism of pesticides minimize pesticide risk?

On the surface a simple question seemingly deserving a simple answer, this question is very difficult and potentially exceedingly complex because of some apparent and some not so apparent associated ramifications. Since an answer would depend upon a precise and perhaps very different personal interpretations of the question, some analysis of the question is in order.

Metabolism and Risk

Understanding vs Knowledge. The term "understanding" takes on paramount importance in any attempt to relate pesticide metabolism to the issue of hazards and pesticide risk. A thorough knowledge of pesticide metabolism in mammals is essential to any fundamental understanding of the processes involved, but it is safe to say that we have a far greater knowledge than understanding of the subject. Although a monumental task and one that is far from complete, it is presently quite possible to identify essentially all metabolites of most pesticides in any given system. This in itself, however, does not mean that the risk associated with the use of the chemical involved, or its analogs, has been minimized.

When the products formed by metabolic processes are toxicologically insignificant and, when this is a known fact, the findings may be valuable in assessing pesticide risk. Contrarily, a number of pesticides yield metabolites known to be highly toxic and these materials may be taken into account in the risk assessment process. Too many times, however, the isolation and identification of pesticide metabolites tell us very little about risks that may be associated with the use of a particular chemical because the information can not be related to in vivo toxicological significance.

Time, economic, and technical limitations make the proper testing of all metabolites for all types of toxic action virtually impossible. Consequently, few metabolites, per se, are thoroughly tested and, even then, the type of toxicity assessed is usually limited to acute in vivo situations and to select batteries of

short-termed bioassays. Moreover, one must be especially mindful that the possibility always exists that the tests utilized do not allow expression of the specific toxic characteristics of the compound being evaluated. Furthermore, there is the ever-present possibility that the test system is not applicable to humans. The conclusion must be drawn, therefore, that it is far easier to correctly predict what metabolite will be formed than to predict what affect its formation will have on the hazards of the pesticide being evaluated.

Using Knowledge to Predict Risk. Before declaring the whole situation hopelessly disastrous, a brighter side of the metabolism and risk should be considered. That is, when sufficient knowledge of pesticide metabolism in mammals is accumulated to begin to understand the basic processes involved and predict how these processes are likely to influence toxicity, then, we may begin to use that knowledge in an intelligent manner as suggested by Williams (1). In 1968 this metabolism scientist wrote that "The intelligent use of our knowledge of the biochemistry of foreign compounds should permit us to predict what compounds are safe to use and to avoid those, like thalidomide, which produce adverse effects". While the intelligent use of our knowledge of pesticide biochemistry is not likely to ever allow us to always predict which compounds are safe and to avoid those which produce adverse effects as proposed by Williams, great strides towards this ultimate objective have been made in recent years.

For example, it is presently well recognized that many nitroso compounds are highly carcinogenic chemicals (2) and to see today a nitrosoamine or nitrosoamide introduced as a potentially new pesticide would be very unlikely. Additionally, while many pesticides in use today undergo nitrosation, any new compound which might do so would be viewed with great skepticism by most toxicologists should such a chemical be proposed as a new pesticide. At a minimum, such a compound would be marked by our knowledge and understanding of the toxicological properties of nitroso compounds as a product to receive special attention from a risk assessment viewpoint. Knowing when to exercise particular caution is the most vital component of predictive toxicology.

Along these same lines, we would never today consider a compound like 2-AAF (2-acetylaminofluorene) as a commercial pesticide. This compound is listed as a carcinogen by the Environmental Protection Agency (3) and is used by many as a positive control in the Ames mutagenicity assay. Nonetheless, this compound was screened for its insecticidal action after its synthesis in 1933, long before its carcinogenic properties were known. Fortunately, its pesticidal activity did not merit commercial development. The probability is extremely low that a compound as highly carcinogenic as 2-AAF would escape detection as a carcinogen today. Not only would the chemical structure alert the toxicologist of such a possibility, cancer is the most dreaded of all diseases and society has demanded that science develop tests which, with great accuracy, identify carcinogenic substances before commercial introduction. Unlike what often appears to be the case, however, cancer is not the only possible adverse effect of human pesticide

exposure. In time, other aspects of xenobiotic toxicity to humans must be given the same thorough treatment by medical science as has cancer.

Special Problems: New Compounds. A major challenge presently is to make certain that our current knowledge and understanding of pesticide risks be effectively put to use in the development of new materials. The synthetic pyrethroid insecticides which are rapidly replacing many of the older products may be used to illustrate the point. While these compounds are insecticidal at almost unbelievably low rates, their mode of action is the same or similar to that of DDT (4). When chlorinated, as is the case with some of the more effective ones, they indeed become chlorinated hydrocarbons and, as such, they must be scrutinized just as carefully as if DDT itself was the compound under consideration. One trusts that this is being done, but it is important that the low-rate phenomenon not be allowed to have an undue influence as the overall toxicology of these new pesticides are being assessed.

Chemicals capable of killing insects at rates far below those around which our present criteria for safety evaluation were based do pose a special problem. If they are insecticidal at such low doses, are other aspects of their toxicological properties perhaps as equally spectacular? The problem is not so much related to those toxicities detected using conventional testing protocols, but to those which have not evolved as problems with chemicals that are far less insecticidal. Chemicals which might adversely affect the mental state or immune capacity of humans fall within this latter category. As often the case, it is the unknown that is most frightening and the knowledge accumulated from years of experience with the older materials is of little comfort when attempting to estimate all harmful effects of new chemicals proposed as pesticides.

Metabolites and Toxicity

As previously pointed out, the problems associated with using metabolism data to assess risks are enormous. Knowing that one cannot accurately predict the acute toxicity of a chemical to laboratory mice, or to different strains even after the toxicity in one strain is known, vividly demonstrates how vulnerable our predictions may be relating to more elusive issues such as reproductive disorders, growth and development, mental health, aging processes, immune deficiencies, and genetic integrity of individuals and populations. Because of the numerous potential risks associated with each pesticide metabolite, it is difficult to comprehend a system that would reasonably assure adequately testing. That metabolites do indeed influence toxicity, however, can be illustrated using specific metabolites and a given type of toxic response. A few common examples will serve to make the point.

Heptachlor and Heptachlor Epoxide. Heptachlor is a cyclodiene insecticide introduced around the same time as DDT and, until recently, was used extensively. It is important to the present discussion because it was the first case where a metabolite of a pesticide was proven to be involved in the toxic response assumed

initially to result solely from the applied chemical. The situation came to light when heptachlor-specific means of residue analysis revealed that the "toxicant" was no longer present, but that bioassays showed otherwise. Solvent extracts of soils and treated plants continued to kill houseflies and other test species long after the heptachlor had dissipated below levels detected by chemical and instrumental analysis. Subsequent analyses demonstrated that the culprit was heptachlor epoxide, a metabolite just as toxic, if not more so, as heptachlor and much more persistent in the environment. The result of this discovery was that all future risk assessments of heptachlor had to include the metabolite, and, ultimately, the epoxide was largely responsible for the demise of heptachlor as a major agricultural chemical.

Whether the discovery of heptachlor epoxide has ever saved a human life or contributed to the prevention of a "Silent Spring" will never be known for certain. That is not important. The important thing is that the discovery, and hundreds of a similar nature which followed, provided new information applicable to most chemicals that improved the validity of the risk assessment process.

Parathion and Paraoxon. Again, this represents a reaction (the sulfur oxidation of a thiophosphate pesticide) that is familiar to most in the pesticide area. Unlike heptachlor epoxide, paraoxon is not a stable compound and its actual presence in a poisoned animal was very difficult to demonstrate. The oxons of other organophosphorothioates are not so elusive. In any event, the paraoxon metabolite is an excellent example of where an understanding of metabolic processes and their potential toxicological significance alerted scientists to the likelihood that such a metabolite existed. Many years of work with similar compounds had established that the insecticidal thiophosphates required oxidation to the P=O form in order to inhibit the neurotransmitter acetylcholinesterase, the biochemical basis of their toxic action. Paraoxon was eventually isolated in vivo and now consideration of the oxon is a vital part of the overall risk assessment of this group of pesticides.

Carbaryl and 1-Naphthol. The mode of action of the carbamate insecticides is, like the organophosphorus compounds, inhibition of acetylcholinesterase. However, no metabolic activation is required as with the latter insecticides. Carbaryl is the most widely used carbamate and, in fact, is one of the most widely used pesticides in the world. Its acute oral LD50 to rats is usually reported to be in the 400 to 600 mg/kg range. Because chemical hydrolysis of the ester linkage yields 1-naphthol, carbon dioxide, and water, metabolism via this route would be expected to yield products of little toxicological significance to mammals. Both carbon dioxide and water are obviously of no hazard and 1-naphthol has an acute oral LD50 to rats of over 2500 mg/kg. While the metabolism of carbaryl is now known to be extremely complex and to involve formation of toxic oxidative metabolites as well as the nontoxic hydrolytic products, the latter were once thought to predominate and early risk assessments were based on this assumption (5).

Metabolic Processes and Toxicity

Isolation, identification, and determination of the toxicity of all metabolites of a pesticide may appear to be necessary to properly assess risk, but this is not possible and perhaps not always true. The time and resources that would be required to do so would mean almost certain death to those chemicals presently under development, and no such consideration could be given to the hundreds of pesticides already on the market. This means that other methods for estimating the toxicity of individual metabolites must be employed.

The process would be made rather simple if given types of in vivo chemical and biochemical reactions were known to always have the same effect on toxicity. That is, that all ester hydrolysis resulted in detoxification, that all sulfur oxidations were activations, and that all conjugations rendered a compound nontoxic and readily excretable from the body. Unfortunately, this is not the case. However, when applied to specific types of chemicals, our knowledge and understanding of how certain reactions likely affect toxicity are sufficient to be extremely valuable in estimating pesticide risk. The more that is known about a particular chemical group in this regard, the more likely the prediction will be an accurate one.

Overall Metabolic Processes. In general, metabolic processes which facilitate elimination of a pesticide from the body are considered desirable. This is based a great deal on our long history of associating toxicity with chemicals that accumulate in the body. Arsenic, lead, mercury and other metals substantiate these concerns as do more modern synthetic organic chemicals such as DDT and mirex. Because so many chemicals rapidly voided from the body are now known to be extremely hazardous, risks and excretion rates are evaluated very carefully. Still, storage of metabolites is not a positive characteristic even for those compounds like DDE whose danger, if any, as a body burden has not been established.

Nonetheless, so long as pesticides and their metabolites remain in the body, the potential for damage remains. Once removed, the potential ceases and emphasis may be placed on determining the toxicological consequences of the chemical having passed through the body. It should be clear, therefore, that the actual metabolic processes which are responsible for clearance of the pesticide need not always be known in order to be useful in risk assessment. Such information, routes and rates of excretion, is usually available from radiotracer studies long before the number and chemical nature of the metabolites have been defined. A thorough evaluation of the data at this stage is critical to the proper planning of further metabolism studies and, combined with other data, might very well provide a basis for conducting only a fraction of the studies which are "recommended" in registration guidelines.

Processes vs Products. While it is often stated that certain metabolic reactions generally represent either activation or detoxification, care must be taken to differentiate between that which is assumed and that which is known for certain. For example, the metabolic conversion of thiophosphates (P=S) to phosphates (P=O)

is recognized as an activation step and, as mentioned earlier for parathion, this is certainly the case for some thiophosphates. Since the thiophosphates are weak inhibitors of acetylcholinesterase, it is probably safe to say that all compounds of this type which induce death by severe inhibition of acetylcholinesterase undergo activation via sulfur oxidation. Death without this enzyme inhibition would suggest an alternate mode of action. Does this mean, then, that metabolism of all thiophosphates to phosphates effects greater risk to the organism involved? Certainly not. Many oxons produced in the body are so unstable that the reactant is destroyed before reaching the site of detoxification. The point here is that a product may be formed which, based on similar compounds and even in vitro testing, should be highly toxic but, in fact, is not.

A situation opposite to that is seen with the carbamate insecticides. As shown in Table I, data from studies in our laboratory demonstrate that carbamate insecticides most toxic to rats are also hydrolyzed at a faster rate. Ester hydrolysis in these studies was measured by quantitation of radioactive carbon dioxide in the respiratory gases of animals treated orally with the carbamate radiolabeled on the carbonyl carbon. Yet, hydrolysis of

Table I. Carbamate Ester Hydrolysis (0-24 Hour) Following Oral Treatment (0.2 Mg/Kg) of Rats Compared with Toxicity

Insecticide	Percent of Dose	Acute Oral LD50, Mg/Kg
Aldicarb	71.5	1
Carbofuran	54.3	5
Croneton	39.9	400
Carbaryl	27.8	600

carbamate insecticides is always considered as a detoxification reaction. The reason for this obviously is the fact that the products of hydrolysis, 1-naphthol from carbaryl, for example, are always much less toxic to mammals than the parent compound. One possibility that naturally comes to mind when the in vivo data are examined is that either hydrolysis yields a more active product or that oxidation does so and it is the latter which is hydrolyzed to carbon dioxide. This is not supported by our data to date. None of the hydrolytic products tested has demonstrated any anticholinesterase activity. Moreover, hepatic enzyme induction using mirex and other inducers, and confirmed by a number of in vitro reaction, did not alter radioactive carbon dioxide production as would have been expected if hydrolysis resulted from the formation of an oxidative metabolite.

In similar studies, we have compared the toxicity of the same carbamate insecticide to several laboratory animal species that varied considerably insofar as rates of *in vitro* ester hydrolysis was concerned. Again, it was the more susceptible species which demonstrated the faster rates of hydrolysis (6). Neither absorption from the gut, or total metabolism as evidenced by excretion rates and metabolites excreted, was significantly different when the same carbamate was administered to either rats, mice, guinea pigs, or gerbils. At this point, it can only be surmised that the same properties that make the carbamates excellent *in vivo* inhibitors of acetylcholinesterase also make them excellent substrates for other esterases.

Minimizing Risk

There is little question at this point that a better understanding of mammalian metabolism of pesticides can minimize pesticide risk. There remains, however, considerable concern about the effectiveness of the use of metabolism data in this regard and of the lack of coordinated efforts to improve the design of metabolism studies to more appropriately address the issue of risk assessment.

One of the biggest obstacles to assuring that a better understanding of pesticide metabolism in mammals will be useful in minimizing pesticide risk is the absence of any designated group of experts whose mission it is to do just that. Compound-by-compound review involving, by necessity, a few regulatory scientists and some number of industry representatives is a very inefficient and potentially dangerous means of determining pesticide risk. Different chemical groups pose different problems and it is unreasonable to expect a reviewer, or a series of reviewers, to keep abreast of the latest developments within a particular field, much less to render a decision as to whether its proposed use is allowed or disallowed.

The tendency may be to play it safe and to delay a decision as long as apparent rational reasons to do so could be devised. Groups of experts would have the same tendency, but such a group would benefit from the knowledge that is available only when those who best know a subject are brought together. While imperfect, the peer review system of NSF and NIH, and the EPA's procedure for developing Water Criteria Documents, etc., are the types of decision-making processes which instill confidence of the nature required for making pesticide risk assessments.

With pesticide registration, it would not be feasible for a scientific review panel to rule on day-to-day matters. The role of such a panel on metabolism would be to periodically examine the requirements, or guidelines, for registration and, using select chemicals then being reviewed, determine if the process is working in the most effective and efficient manner. Ideally, there would be a general metabolism panel to consider issues pertinent to the overall topic of metabolism and pesticide risk. Similar panels of experts would then be formed to deal with each major chemical group of pesticides, and an ad hoc panel to address metabolism-risk issues of miscellaneous pesticides.

The ad hoc panel might consist of, among others, one member from each chemical-group panel, and the general panel could consist

of, among others, one member from each chemical- or panel. In addition to risk matters pertaining to pesticide registration, the chemical-group panels would hopefully become the national advisory body for all major problems that arise with chemicals falling within their area of expertise. The problems are just too diverse for one panel of advisors to adequately address all pesticide issues.

For some, a proposal to "panelize" the risk assessment process may be taken as a criticism of individuals presently responsible for such matters, and/or a mechanism to share the blame. The former is totally untrue and the latter only partially true. A regulatory reviewer is somewhat like a judge; that is, one who renders a decision based on that which has been deemed proper by appropriate authorities. Their role is not to make the rules. Panels of experts would serve to assist in making the rules and in lending advice to the reviewers. Thus, the views of the reviewer, backed by the panel, would become stronger. If not backed by the panel, then, the reviewer should take comfort in the fact that she/he, or they, do not stand alone but are making a decision representative of those who are most qualified to render a judgement.

Whether a reviewer, a panel member, an industry representative, or just a concerned citizen, it is essential that each recognize that there are severe risks involved in decision making. Risk assessment of pesticides is difficult and not all decisions related thereto will be flawless. Only those who are extremely secure in their roles as scientists and as caring human beings should dare take on such awesome responsibilities.

Literature Cited

1. Williams, R. T. In "The Biochemistry of Foreign Compounds"; Parke, D. V., Ed.; Pergamon Press: London, 1968; p. ix.
2. Mirvish, S. S. J. Toxicol. Environ. Health 1977, Vol.2, 1267-77.
3. "The Merck Index", Merck: Rahway, NJ, 1983; 10th ed., p.4058.
4. Casida, J. E.; Gammon, D. W.; Glickman, A. J.; Lawrence, L. J. Ann. Rev. Pharmacol. Toxicol. 1983, Vol. 23, 413-38.
5. Kuhr, R. J.; Dorough, H. W. "Carbamate Insecticides: Chemistry, Biochemistry and Toxicology"; CRC Press: Cleveland, 1976; p. 146.
6. Benson, W. H.; Dorough, H. W. Pestic. Biochem. Physiol. 1984, Vol. 21, 199-206.

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Chapter 10

Molecular Modeling: A Tool for Designing Crop Protection Chemicals

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Application of molecular modeling techniques to the biorational design of selective and environmentally safe crop protection chemicals is addressed. Sulfonylurea herbicides are used as an example to illustrate the kinds of biological information that can be known with modern technologies. An example of selective inhibitor design using computer graphics is presented.

Crop protection chemicals (CPC) are an important component in the high yield production of crops. Future trends in agriculture and CPC technology will necessitate the discovery of agrichemicals with high selectivity, high mammalian and environmental safety, low use rates, and low costs.

Traditionally, agrichemicals are discovered by empirical synthesis and evaluation. Although this approach has been (and is currently) very successful, its efficiency continues to decline. For example, in 1950 about 2,000 compounds were screened to produce one product. In 1970, the ratio was 7,500 compounds screened per product and today an estimated 20,000 compounds must be screened for every new type of product introduced. The discovery and development process can take five to eight years and cost tens of millions of dollars.

These efficiency, economic, and time realities suggest that the empirical discovery process be complemented by a chemical design program based on a molecular understanding of key biological processes related to weed, disease, and insect control (i.e., biorational design). Computer-assisted molecular modeling techniques can play an important role in both understanding these biological processes and aiding in chemical design. These techniques include a wide variety of operations associated with molecules and model building. It encompasses the generation, manipulation, and representation of three-dimensional structures of molecules and associated physicochemical properties. Because of the complexity of the systems, computers are mandatory. Since all

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molecular interactions are essentially electronic, any biological activity expressed by a molecule comes from its electron density distribution and polarizability. Computer-assisted molecular modeling techniques allow the researcher to model chemical interactions at this level (for instance, the interactions between enzyme and substrate or enzyme and inhibitor).

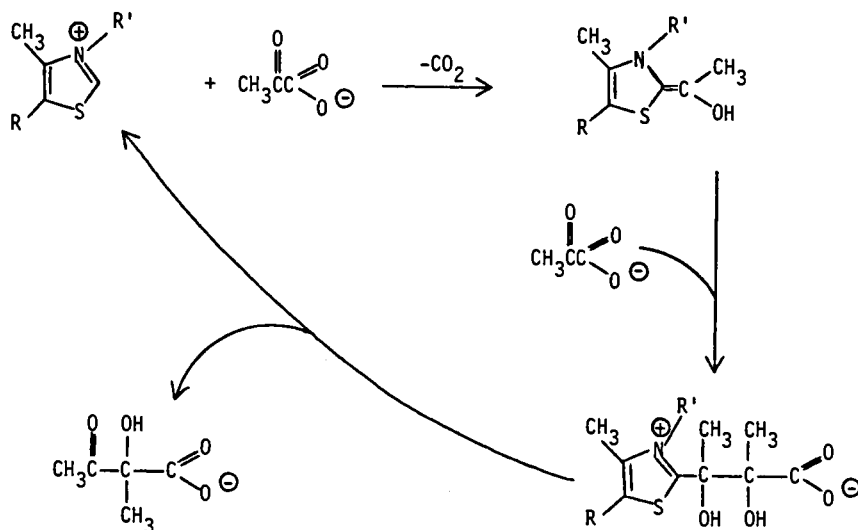
In this chapter, I will address how molecular modeling tools can be applied to the biorational design of selective and environmentally safe crop protection chemicals. To do this effectively, the fundamental biological processes must be understood. First I will discuss the kinds of biological information that can be known with modern technologies. The sulfonylurea class of herbicides that we at Du Pont are commercializing will be used as an example. These "sulfonylurea herbicides" are ushering in a new era of herbicide technology. They will be used to illustrate how biological understanding at the molecular level can provide valuable insight into herbicide design strategies. Next, I will reverse the sequence and discuss how an understanding of biochemical processes can be combined with molecular modeling techniques to provide general principles that can be used to design crop protection chemicals.

Sulfonylurea Herbicides

Sulfonylureas are a new class of high potency herbicides which show excellent weed control activity at extremely low application rates (4 - 35 grams per hectare). Their high potency and low use rates combined with their high mammalian safety and crop selectivity make them extremely attractive in terms of efficacy and the environment. We have carried out extensive studies aimed at understanding the factors that govern the intrinsic biological activity, crop selectivity, and soil degradation properties of sulfonylureas. These three properties are essential for effective and environmentally safe herbicides.

Biological Activity. We have shown that the site of biochemical action for sulfonylureas is the enzyme acetolactate synthase (1,2). This enzyme catalyzes the first common step in the biosynthesis of the essential branched chain amino acids valine and isoleucine. Plants must synthesize these amino acids for protein synthesis and subsequent growth. Therefore, this is a vulnerable or critical enzymatic pathway. It is important to note that plants contain these essential amino acid biosynthetic pathways (and the associated enzymes) while mammals do not. Mammals obtain these amino acids from their diet. This largely explains why sulfonylureas are so non-toxic to mammals [LD₅₀ of >5000 mg/kg in male rats (3)].

Acetolactate synthase (ALS) catalyses the reaction of two pyruvate molecules to give acetolactate and carbon dioxide. It also catalyses the reaction of pyruvate and α -ketobutyrate to give α -aceto- α -hydroxybutyrate and carbon dioxide. The enzyme requires three coenzymes for activity; flavin adenine dinucleotide, thiamin pyrophosphate, and magnesium ion. The reaction takes place in several steps.



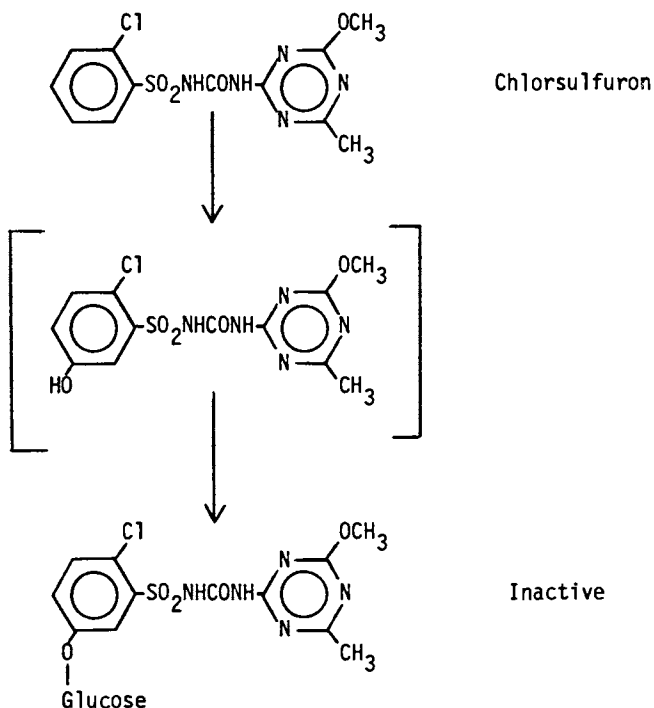
First a pyruvate molecule condenses with thiamin pyrophosphate at the thiazolium ring carbon with subsequent loss of carbon dioxide. Then a second pyruvate (or α -ketobutyrate) condenses followed by loss of acetolactate and regeneration of the thiazolium ring.

Studies on enzyme kinetics show that sulfonylureas act as slow tight-binding inhibitors. They appear to bind most tightly to the enzyme after binding of the first pyruvate molecule (4). Since detailed enzyme mechanistic studies are facilitated by having large quantities of pure enzyme, bacteria have been genetically engineered to over produce the ALS enzyme. Following large scale fermentation and purification procedures, large amounts of pure ALS enzyme have been obtained. Pure enzyme is also required for growing crystals which can be used to obtain the enzyme's three-dimensional structure by X-ray diffraction. In addition we have cloned the genes coding for bacterial, yeast, and plant ALS enzymes, determined their DNA base sequences and deduced the amino acid sequences of the enzymes. These are important steps in understanding the molecular architecture of enzymes and the design of new inhibitors.

An *in vitro* assay for intrinsic sulfonylurea activity has been developed using isolated plant enzyme (5). The I_{50} for ALS inhibition is defined as the concentration of sulfonylurea that

inhibits ALS activity by 50%. A good correlation exists between the herbicidal activity of sulfonylureas and their ability to inhibit acetolactate synthase (2). This *in vitro* assay using the target enzyme along with the three-dimensional structure of the enzyme should aid in the generation of a substantial data base that can be used to design potent inhibitors.

Crop Selectivity. I_{50} values for inhibition of the ALS enzyme from a variety of crop and weed species have been determined (2). In all cases the highly active herbicides proved to be potent inhibitors of plant ALS enzyme. Crop tolerance results from rapid metabolism of



the sulfonylureas by the crop but not the weeds. Our studies have shown (6) that the biological mechanisms for metabolic inactivation of various sulfonylureas differ from crop to crop. For example, a major factor responsible for the selectivity of chlorsulfuron as a post-emergence herbicide for small grains is the ability of crop plants, such as wheat, to metabolize the herbicide to polar, inactive products. Sensitive broadleaf plants show little or no metabolism of chlorsulfuron. Tolerant plants such as wheat, oats, and barley rapidly metabolize chlorsulfuron via hydroxylation at the 5-position of the phenyl ring. This intermediate is converted to the inactive O-glycoside by a glycosyl transferase enzyme.

Other detoxification mechanisms are also known. This diversity of metabolism by different plants and for different sulfonylurea molecules is responsible for the high selectivity found in different crops. Understanding this enzymatic and chemical diversity can facilitate the design of sulfonylureas with optimal selectivity for a particular crop.

Soil Degradation. Soil residual properties are (and will continue to be) an important parameter for herbicides and other agrichemicals. Soil degradation of sulfonylureas under field conditions occurs at rates which are similar to conventional soil active herbicides (7). Structural modification of the molecules can be used to modify the rate of degradation and thereby adjust the residual properties of the product as illustrated in Figure 1. Thus, changing from the ortho-chlorophenyl moiety in chlorsulfuron to the ortho-carboxymethylphenyl moiety in Ally causes some increase in degradation rate. However, substituting a thiophene ring for the phenyl ring gives Harmony a very rapid degradation rate. Breakdown of sulfonylureas in soil is a combination of chemical hydrolysis and microbial action (8). Knowledge of these mechanisms at the molecular level is very useful in the design of crop protection chemicals with the desired soil residual properties.

Biorational Design

Sulfonylureas, as a class of herbicides were discovered as part of an empirical synthesis and screening program (9). After much structural modification and further biological evaluation, several herbicides have been commercialized by Du Pont. The site of action, mechanisms for selectivity, and soil degradation were determined subsequent to the initial leads generated from the traditional approach. As mentioned earlier, the chances of finding another crop protection compound with the same potency, selectivity, and environmental safety are slim. The remainder of this chapter will address how an understanding of biological processes at the molecular level can be combined with computer-assisted molecular modeling techniques to design new crop protection chemicals.

Identify Target. A chemical design program usually begins by identifying a critical biological pathway in the target species. The pathway must be essential for the survival of the organism so that inhibition will cause death. The pathway should not be easily circumvented or replaced by some other process. For enzymes this means that the reaction products can not be obtained from other metabolites. Ideally, there should be differences in the intrinsic bioactivity between pest and non-pest species. For example, mammals and non-pest species should not depend on the same pathway. Some known critical biological pathways for plant species are essential amino acid biosynthesis, photosynthesis, and either the synthesis or site of action of plant hormones. For example, sulfonylureas inhibit the biosynthesis of the essential amino acids valine and isoleucine. This pathway is not present in mammals, but it is present in both crop and weed species.

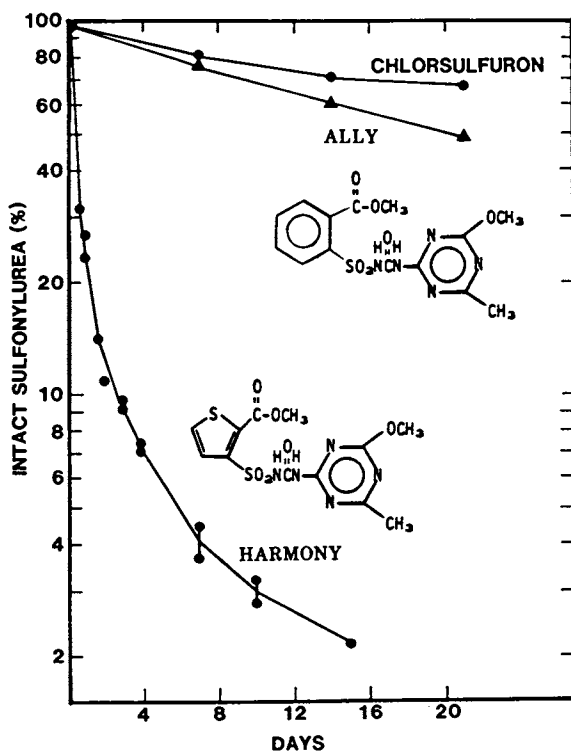


Figure 1. Sulfonylurea Soil Degradation.

Second, a key enzyme or receptor in the pathway should be identified as the target. It is best to select enzymes whose products are important for several functions in the species. Cellular response to such a metabolic blockade should also be considered (e.g., cascading effects). Often end-product limitation results in more metabolites entering the pathway. After sufficient substrate accumulation, catalysis may occur even in the presence of an inhibitor (10). However, accumulation of toxic intermediates would prevent this cellular response and lead to death. Again using sulfonylureas as an example, acetolactate synthase is a common enzyme in the pathway for two essential amino acids rather than just one. Also, inhibition of acetolactate synthase leads to high levels of α -ketobutyrate which is thought to have deleterious effects (11).

Once an enzyme or receptor has been identified, ideally it should be isolated and characterized. A three-dimensional structure is very useful and can be determined from X-ray crystallography, NMR or by some other means which may include computer-assisted molecular modeling. The mechanism for the normal catalytic activity of the enzyme should be understood. This includes knowing the natural substrates, any natural inhibitors, and any coenzyme requirements. An *in vitro* assay method must be developed to quantitatively test the effectiveness of potential inhibitors. At this point molecular modeling techniques can be used in the design process.

Inhibitor Design. Several approaches have been used to design enzyme inhibitors. Structural modifications of known substrates can be constructed which compete with the natural substrate. An example for the ALS enzyme would be analogues of pyruvate. Enzyme-activated irreversible inhibitors, often referred to as suicide substrates, can be designed based on some intermediate in the normal catalytic reaction. An example for the ALS enzyme would be a molecule that would react with the active site carbon atom in the thiazolium ring but could not undergo any further reaction. Transition-state analogues can be designed based on some high-energy, metastable intermediate which exists during the normal catalytic reaction. An example for the ALS enzyme would be thiamin thiazolone pyrophosphate, a known thiamin pyrophosphate analogue which has been reported in the literature (12).

Depending on the enzyme, there may be regulatory sites which can be exploited. Structural modification of known inhibitors which bind tightly can be used to permanently shut off the enzyme. For example, the amino acid valine is known to inhibit the ALS enzyme in bacteria and plants by a feedback mechanism (13). Three-dimensional molecular modeling could be used to identify a suitable cleft or pocket in the enzyme into which an inhibitor would fit and stop normal catalytic activity. Such a method has been used in drug design (14).

Because of certain proprietary considerations, a protein other than the ALS enzyme will be used to demonstrate how molecular modeling techniques can be applied to the design of crop protection chemicals. Human serum prealbumin has been used by Blaney, et al (15) to model drug-receptor interactions. Its function is to transport the hormone thyroxin. The binding site for thyroxin will

be used in the following examples. Figure 2 is a computer generated representation of the three-dimensional structure of the binding site. Thyroxin is shown as a stick structure in red. A series of dots has been added to the surface of the binding site. This solvent-accessible surface is generated (16) by mathematically rolling a probe sphere over the surface of the molecule. It is displayed as a continuous envelope of dots which can be color coded to show various physiochemical properties at the surface.

Molecular modeling techniques can be used to fit novel compounds into the binding site. They need not be structurally similar to the natural substrate but the dominant physiochemical properties should be similar. Modifications can be made to the molecule to improve the fit. This will increase specificity for the target enzyme. Substituents can be added or modified so that regions in the enzyme interact favorably with parts of the inhibitor. Electrostatic interactions, hydrophobicity, and hydrogen-bonding can be included in the fitting process. By judicious choice of substituents, both *in vitro* and *in vivo* activity can be optimized. Substituents could be added or modified to improve uptake, translocation, and accumulation in the appropriate parts of the pest species provided the molecule still fits in the binding site.

Selectivity of the compound for pest and non-pest species can also be designed into the molecule with the aid of computer-assisted molecular modeling techniques. There are several ways to affect this selectivity; differential inhibition of the enzyme, differential uptake, or rapid metabolism of the inhibitor by the tolerant species. Differential inhibition of the enzyme is preferred because it is less susceptible to the metabolic states of the pest and non-pest which can be influenced by environment, stage of development, and behavior.

If the target enzymes for both pest and non-pest species have been isolated and characterized, they can be used to design compounds which are specific for the pest species. For example, Figure 3 shows the binding sites for both the pest (left) and non-pest species (right). The shape of the binding site (blue dot surface) is slightly different in the lower left part of the binding site (see arrows). This is the result of a single amino acid residue change near the binding site. This modification was made to prealbumin using computer-assisted molecular modeling techniques. There is precedent for such an amino acid change affecting enzyme inhibition (11). Yeast mutants have been isolated which are highly resistant to sulfonylureas. There is a single amino acid change in their ALS enzyme.

An inhibitor has been included in the two binding sites (red dot surface). Notice the extra space present in the pest species enzyme at the *ortho*-position (see arrows). This space is not present in the non-pest species. This suggests that an analogue with an appropriately-sized substituent in this position should inhibit the pest species enzyme but not the non-pest enzyme.

Figure 4 shows the two binding sites with an *ortho*-substituted analogue. Based on shape, this analogue does not fit in the non-pest enzyme (see arrow). The surface of the inhibitor goes

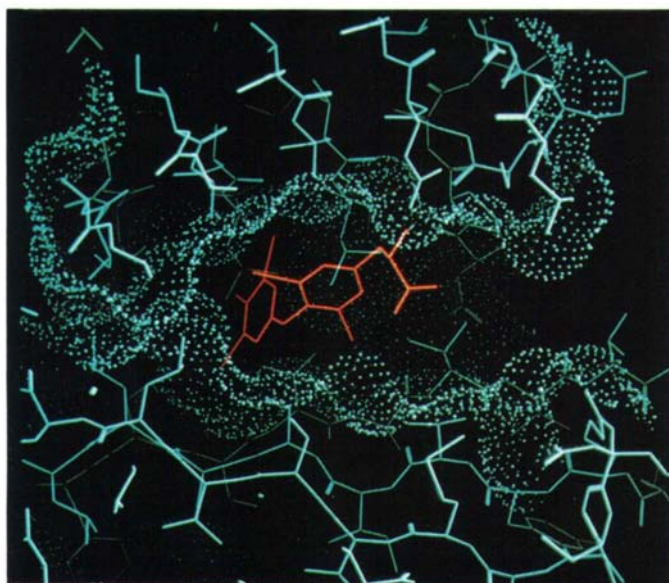


Figure 2. Cross Section of the Thyroxine-Prealbumin Binding Surface.

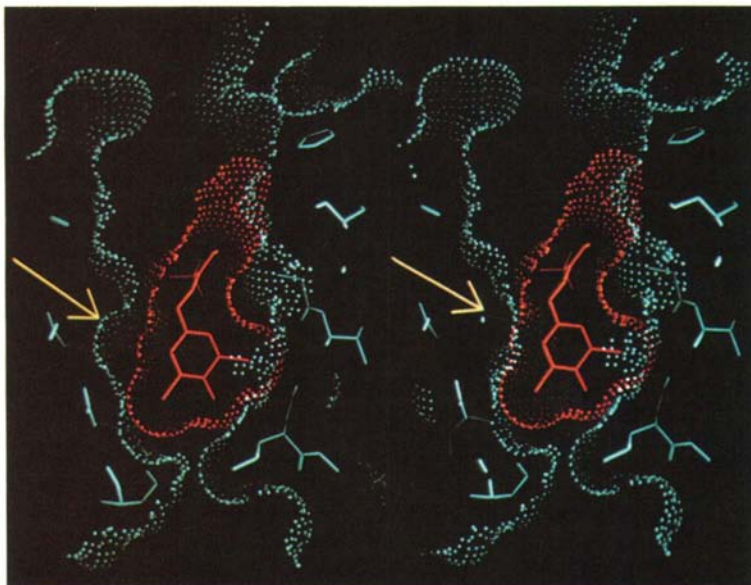


Figure 3. Cross Section of the Pest and Non-Pest Binding Sites with a Non-Selective Inhibitor.

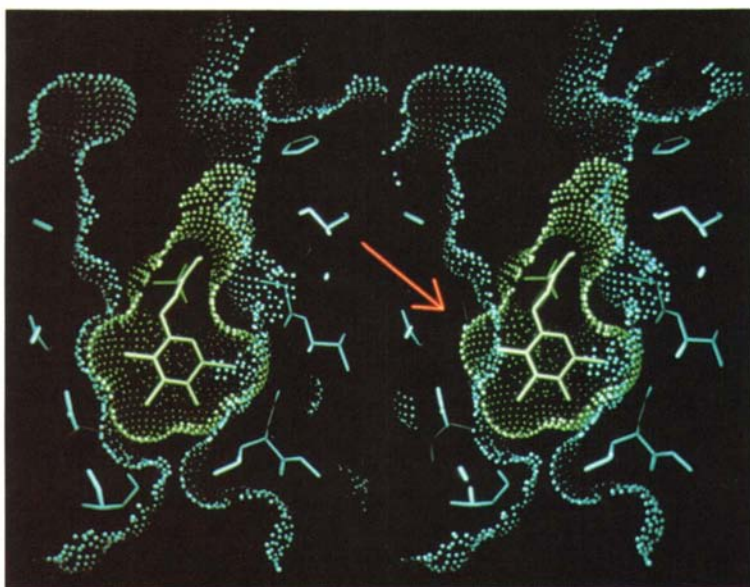


Figure 4. Cross Section of the Pest and Non-Pest Binding Sites with a Selective Inhibitor.

beyond the surface of the enzyme. This compound should show selectivity in the in vitro assay. Also, compounds with larger substituents in the ortho-position probably would not be inhibitors of either enzyme.

Ultimately, the final crop protection compound will require the best combination of potency, uptake, translocation, selectivity, metabolism, degradation, and minimal toxicity to non-pest organisms. This is the same set of criteria that all crop protection chemicals have to meet. The only real difference with the methods detailed here is that the lead compound and the decisions of how to modify its chemical structure came from a knowledge of the biochemistry. This approach may significantly decrease the number of analogues that must be made and result in a more efficient discovery of crop protection chemicals which are potent, selective and of minimal risk to the environment.

Is this approach practical? We believe so, even though this field is in its infancy. Similar approaches have been used in medicinal chemistry where X-ray structures of key enzymes are known (14,17). Their success in the design of potent inhibitors using molecular modeling techniques is encouraging. The biggest difficulty in applying these techniques to design crop protection chemicals is the limited amount of basic scientific knowledge. We need to know more about the physiology, biochemistry, and molecular biology of insects, fungi, and plants. As more is learned about these systems, computer-assisted molecular modeling will become a more useful and effective tool.

Literature Cited

1. La Rossa, R. A.; Schloss, J. V. J. Biol. Chem. 1984, **259**, 8753-8757.
2. Ray, T. B. Proc. British Crop Protection Conf.-Weeds, 1985, **3A-1**, 131-138.
3. Levitt, G.; Ploeg, H. L.; Weigel, R. C., Jr.; and Fitzgerald, D. R. J. Agric. and Food Chem. 1981, **29**, 416.
4. Schloss, J. V. In "Flavins and Flavoproteins"; Bray, R. C.; Engel, P. C.; Mayhew, S. G., Eds.; Walter de Gruyter & Co.: Berlin, 1984; pp. 737-740.
5. Ray, T. B. Plant Physiol. 1984, **75**, 827-831.
6. Sweetser, P. B.; Schow, G. S.; Hutchison, J. M. Pest. Biochem. and Physiol. 1982, **17**, 18-23.
7. Palm, H. L.; Riggleman, J. D.; Allison, D. A. Proc. British Crop Protection Conf.-Weeds, 1980, **1**, 1.
8. Joshi, M. M.; Brown, H. M.; Romesser, J. A. Weed Science 1985, **33**, 888-893.

9. Saures R. F.; Levitt, G. In "Pesticide Synthesis Through Rational Approaches"; Magee, P. S.; Kohn, G. K.; Menn, J. J., Eds.; ACS SYMPOSIUM SERIES No. 255, American Chemical Society: Washington, D.C., 1984; pp. 21-28.
10. Christopherson R. I.; Duggleby, R. G. Eur. J. Biochem. 1983, **134**, 331-335.
11. La Rossa, R. A.; Falco, S. C. Trends Biotechnol. 1984, **2**, 158-161.
12. Gutowski J. A.; Lienhard, G. E. J. Biol. Chem. 1976, **251**, 2863.
13. De Feliece, M.; Lago, C. T.; Squires, C. H.; Calvo, J. M. Ann. Microbiol. (Paris) 1982, **133A**, 251-256.
14. Godford, P. J. J. Med. Chem. 1984, **27**, 557-564.
15. Blaney, J. M.; Jorgensen, E. C.; Connolly, M. L.; Ferrin, T. E.; Langridge, R.; Oatley, S. J.; Burrige, J. B.; Blake, C. C. F. J. Med. Chem. 1982, **25**, 785-790.
16. Connolly, M. L. Science 1983, **221**, 709-713.
17. Hopfinger, A. J. J. Med. Chem. 1985, **28**, 1133-1139.

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Chapter 11

Pesticide Use: The Need for Proper Protection, Application, and Disposal

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Current pesticide management practices can result in three categories of human exposure situations--acute, chronic high or occupational, and chronic low or incidental. Pesticide exposure, whether direct or via chemical trespass from treated areas, can be reduced, if not eliminated entirely, by utilizing: (a) adequate personal protective equipment, (b) technologically superior application equipment and techniques, and (c) improved and economically affordable disposal processes. New lightweight and inexpensive protective clothing and equipment need to be developed if applicators are expected to comply with personal protection requirements on pesticide labels. Research in application technology needs to address the issue of applicator exposure as well as that of efficacy and economics, and reliable cost efficient disposal techniques need to be developed for small volume pesticide users.

By design, pesticides are biologically active and, in most cases, toxic. Thus, they pose potential risks to human beings and other living organisms (1). As is the case with toxic substances in general, pesticides pose several different kinds of threats to health. These adverse effects are commonly considered as either "acute" effects, developing quickly after exposure but of usually short duration, or "chronic" effects, which may appear after a delay, often years, but then persist for extended periods (2). Chronic adverse effects occur as a result of sustained exposures but are much more difficult to evaluate than are acute effects (Table I). Such exposures are often classified as "chronic high" resulting from occupational exposures, or "chronic low" occurring from low level, incidental exposure (3). We know that there are some chronic effects from particular chemicals, but securing the documentation for possible long-term effects such as increased prevalence rates of cancer, vascular disease, and organ injury is extremely difficult, and may well be impossible to obtain (2).

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Table I. Chronic Adverse Effects of Pesticides

Chronic effects (delayed onset, or protracted, recurrent, or irreversible course)
A. Peripheral neuropathy
B. Effects on reproduction
C. Sensitization
D. Suspected, but generally unconfirmed effects:
1. Effects on brain, heart, liver, kidney, lung, blood, reproductive organs
2. Accelerated atherosclerosis, hypertension
3. Carcinogenesis
4. Teratogenesis
5. Impaired immunity and immunopathies

Source: Ref. 2.

With an excessive, single exposure, the result will be either a systemic pesticide poisoning or a topical lesion frequently observed on the skin or in the eyes. Since most acute intoxications are from the carbamate and organophosphate insecticides, the systemic manifestations are cholinergic and are due to the inhibition of acetyl cholinesterase and the resultant accumulation of the neurotransmitter acetylcholine, at the synapse. Topical effects, in contrast, either are the result of the irritant properties of the chemicals in the formulation or have an allergenic basis for their occurrence (3). However, topical effects are not necessarily exclusively the result of exposure to the active ingredient in the formulation but may result from a reaction to one or more inert as well.

With chronic or sustained exposure to pesticides, the populations at risk are those who receive repetitive exposures during the manufacture, formulation, mixing, application, or disposal of pesticides. Another type of chronic exposure is persistent residue contact by workers in the field during the harvesting and thinning of fruits, vegetables and other agricultural commodities. The outcome of these repetitive exposures can result in a number of different diseases.

Although of considerable public concern, the chronic incidental exposure that the general public receives from trace amounts of pesticide residues in air, food, and water, does not usually result in a public health crisis to the population at large. In such instances a pesticide exposure profile is required to determine the extent and/or severity of this incidental, involuntary pesticide exposure (3).

With pesticides being used currently at a rate approaching one billion pounds per year in the United States alone, the risks to agricultural workers and to the general public alike are significant, especially if one considers that only 1-3% of an agricultural chemical may actually reach the intended site of action (4). Just where is the other 97-99% going? Clearly, the application of liquid sprays to some agricultural crop canopies is a very inefficient process. Unfortunately, the relationships between the spray process, the target pests, and the crops themselves are very complex and certainly not well understood. The same can be said about the

state of the art involving hazardous waste disposal which, of course, includes pesticide waste management. Pesticide handling, from inception in the test tube to ultimate disposal of wastes by applicators is not without risk . . . to the user, to the general public, and to the environment.

All pesticide users and handlers need to keep abreast of current innovations in personal protective equipment, application technology and disposal techniques.

Personal Protective Equipment

Pesticides as a class of chemicals are toxic. But pesticides need not be hazardous to the user if ways can be found to reduce exposure. Whether we are driving an automobile, cutting firewood with a power saw, or using pesticides, the risks or hazards associated with these modern technological innovations can be substantially reduced by effectively utilizing appropriate risk reduction techniques and practices. One such practice, at least with regard to pesticides, is to use all appropriate protective clothing and other safety equipment. Such protective devices can reduce and, in some instances, eliminate exposure to pesticides altogether (1). The type of protective clothing and equipment needed depends on the job being done and the type of chemical being used. With some of the more hazardous chemicals such equipment is often mandatory.

As a minimum the following protective items should be available when handling pesticides:

- (1) Clean clothing, including a long-sleeved shirt, long trousers, and/or coveralls or a spray suit made of a tightly woven fabric or a water-repellent material.
- (2) Waterproof gloves, unlined and without a fabric wrist band. Shirt sleeves should be worn over gloves in most instances, not tucked inside.
- (3) Waterproof boots. Pants legs should be worn over boots, not tucked inside.
- (4) Wide-brimmed waterproof hat.
- (5) Goggles or full-faced shield.
- (6) Respirator with a clean cartridge or canister. The correct type of cartridge or canister must be used for the specific chemical being applied; they differ for particular kinds or groups of toxicants.

Considerable difficulties unfortunately remain with both the design and use of these protective devices. The independent farmer who regularly handles and applies pesticides tends to shy away from using protective garments, often complaining that such clothing is uncomfortably warm. In hot weather, some types of protective clothing may actually contribute to heat exhaustion. The same complaints are often directed against pesticide respiratory protective devices as well. Unfortunately, the protective equipment that provides the best protection for the pesticide applicator is also usually the most uncomfortable and cumbersome to wear, not to mention frequently the most costly.

There are now, however, reasons for optimism. Inexpensive disposable or limited-use lightweight clothing and accessories have now become commonplace in industry as personal protective items;

i.e. coveralls, coats, shirts, pants, and hoods (5). Spunbonded olefin (Tyvek) is the most commonly used fabric for industrial disposable or limited-use protective clothing. Such fabric is made by spinning continuous strands of very fine, interconnected polyethylene fibers, and then bonding them together with heat and pressure (6). The fabric can also be coated or laminated with a polyethylene coating for added protection. For example, breakthrough of a methyl parathion field spray through uncoated Tyvek, polyethylene-coated Tyvek, and Saranex-laminated Tyvek fabrics was less than 5 min., 30 to 45 min., and greater than 240 min., respectively (7). The coated/laminated spunbonded olefin fabric is clearly an effective particle barrier and resists liquid splash penetration, properties absolutely essential when applying pesticides.

One of the most desirable attributes of this fabric is its lightweight property. A typical nonlaminated coverall weighs only about five ounces, thus eliminating or, at least, reducing the "fatigue factor" commonly associated with heavy rubberized spray suits. Because of their superior liquid hold-out properties, durability, comfort, and low cost, spunbonded olefin and other nonwoven fabrics are now being used widely in limited use or disposable protective garments. In the future, with the development of new fabrics, new combinations, and new style modifications, these lightweight garments will find even wider usage among pesticide users as a way to minimize occupational exposure.

If protective garments can minimize dermal deposition of chemicals, then respiratory protective devices can aid in reducing pulmonary exposure to airborne volatiles and particulates. As with protective garments, the most common excuse for not wearing a respirator when applying pesticides is comfort. It is generally easier and certainly much more comfortable not to wear a respirator. Here again manufacturers must address the comfort factor if pesticide users are expected to wear even the most basic air-purifying device, the chemical cartridge respirator.

Application

Whereas protective clothing and equipment attempt to reduce applicator exposure by intercepting spray droplets or dust particles prior to deposition on the skin or transfer to the lungs, pesticide application technology tends to focus on improving penetration and deposition of agrichemicals into crop canopies or, in other words, reducing movement off target. New pesticide application innovations depend on many factors, of which safety is only one. Factors such as cost, convenience, labor time requirements, and, of course, efficacy usually take precedence (1). Few types of application equipment have been tested for their exposure impact, and very few of the many combinations of formulations and active ingredients have been tested with each type of equipment.

During the past 30 years there has been phenomenal progress in the development of highly active and effective agrichemicals, yet we have not kept pace in either the development of efficient pesticide delivery systems or in developing a basic understanding of the components of efficient pesticide application (8). If development indeed lacks in these areas, no wonder then that so little research

has been done on how application methods affect pesticide exposure levels.

Although we are well aware that there is an exposure potential from any type of formulation, we generally relegate our major concerns to the liquid or sprayable formulations. When liquid application is essential, the formulation can be modified to assure that droplets remain large enough to minimize drift (1). The worst drift problems result from the smallest, nonvisible particles or droplets, generally those under 100 microns (Table II). The smaller the particle, the greater the drift potential.

Table II. Drift of an Oil/Water Emulsion¹

Particle Diameter (microns)	Drift Distance Downwind (Ft.)
800	25-50
400	50-100
200	150-300
100	500-1,000
50	Indefinite

¹2.8 oil/water emulsion applied during a strong inversion at a boom height of five feet and wind speed at 5 MPH.

Spray nozzles designed for both aircraft and ground equipment can also be used to enlarge droplet size of the spray. Application equipment can also be modified to reduce drift. For example, shrouding the spray booms of ground equipment keeps droplets from swirling up into the air, thus reducing the potential for drift and applicator exposure.

A look at two recent technological innovations in spraying systems as well as a current application practice will bring the issue of applicator exposure in relation to application practices and technology into better focus.

Electrostatic sprayers propel charged pesticide droplets to the target crop. In most field tests, significantly improved deposition coupled with a reduction in drift occurred with charged droplets (9). These droplets are propelled at high velocity from the spray nozzle to the target and, because they are positively charged, they are mutually repellent to one another and attracted to the crop. Although more extensive applicator exposure studies are needed using electrostatic sprayers, preliminary results suggest that such equipment improves safety as well (1) (Table III). Significantly improved deposition associated with these sprayers means more chemical is deposited on the target plant (and possibly adjacent soils) with less to drift in the environment and presumably less deposition on the applicator.

Another new method of spray application which may improve foliar deposition is called air-assist spraying (10). This application system involves spraying air along with the pesticide to enhance penetration of crop canopies. With more spray impacting the plant, not only is environmental impact reduced but the performance of insecticides, fungicides, foliar fertilizers, and growth regulators is vastly improved.

The new air-assist system has been shown to improve overall

Table III. Applicator Exposure Using Conventional and Electrostatic Sprayers

Country	Device	Grams active applied per hour	Formulation	Crop height (cm)	TDC* mg/hr	TDC* as % of active ingredient applied
Tanzania	Electrodyn sprayer	16	Cypermethrin	30-60	26.9	0.17
	Spinning disc	116	Cypermethrin	30-60	369.9	0.32
Ivory Coast	Electrodyn sprayer	21.6	Cypermethrin	120-160	8.9	0.04
	Spinning disc	23.4	Cypermethrin	110-180	17.8	0.08
Paraguay	Electrodyn sprayer	6.6	Cypermethrin	66-125	3.0	0.05
	Knapsack	13.1	Cypermethrin	75-180	29.5	0.22

*TDC--Total dermal contamination

Source: T. B. Hart, "The Hand-Held 'Electrodyn' Sprayer: Worker Hazard," ICI Plant Protection Division (Fernhurst, England: undated).

coverage of chemicals on crop foliage by 234 percent on soybeans and 100 percent on corn. The air-assist sprayer uses fan nozzles to produce the spray. About 8 inches beyond the nozzle the spray mixes with swirling air generated by a centrifugal fan to form a mist around the target plant. These accelerated droplets enter the target area of the plant and are deposited where directed. Air-assist spraying can also be done inside a metal shroud, giving good spray saturation plus spray recirculation.

Spray droplets generated by air-assist sprayers are obviously better able to penetrate dense canopies of foliage because of accelerated droplet velocity. But does this added spray momentum also increase topical and inhalation exposure for applicators? The exposure issue with this new technology has not been adequately addressed, yet must be examined before this or any new spray system can be classified as an unqualified success.

A popular current practice is the use of vegetable oils as carriers in the application of crop pesticides. As long as the product label specifically includes instructions that permit the use of vegetable oils, such as cottonseed and soybean oils, as diluents or carriers in place of water, it is perfectly acceptable to use the pesticide in this manner. This applies to diluents used in conventional, low volume, and ultra-low volume applications. As this practice rapidly increased, EPA expressed concerns about the practice relevant to applicator/farm worker safety (11). The use of vegetable oils as spray diluents/carriers might result in chemical residues on crops in excess of permissible amounts as well as increase farmworker exposure to the pesticides when handling treated crops. EPA officials noted that vegetable oils evaporate more slowly than water, and there are longer-lasting residues after the materials have been applied. The oil may also increase the human body's absorption rate of the active ingredient, further prompting worker safety concerns.

In response to these concerns, the Office of Pesticides and Toxic Substances, EPA, issued FIFRA Compliance Monitoring Policy No. 12.5 on February 27, 1984 (11), which in summary states that in such instances where no diluent is specified on the label, water must be used as the diluent. Clearly, this response was prompted by health and safety concerns for pesticide applicators and farmworkers.

Pesticide Waste Disposal

The issue of pesticide waste disposal has been recognized as a national problem for years, yet today remains as one of the foremost problems confronting most pesticide users. In any Extension meeting that addresses pesticide safety issues, the most frequently discussed topic is that of pesticide waste disposal. The undisputable fact is that adequate hazardous waste disposal facilities do not presently exist for small volume pesticide users. Improper, albeit not necessarily irresponsible, handling of pesticide wastes and containers often results in unacceptable levels of environmental contamination and excessive exposure to the applicators themselves.

Pesticide waste disposal policy and practices have been dealt with recently by three national workshops (12, 13, 14). These conferences defined the problem and examined the state-of-the-art

technology for pesticide waste disposal. The sources of potential problems include the containers; unwanted, unuseable and unidentifiable products; tank rinse waters; leftover materials; equipment wash waters; incompatible mixtures; spilled materials from accidents; stormwater and run-off from natural occurrences; and toxic debris from fires (15). Defining the problem is relatively easy; it's the solutions that are so difficult to develop.

Speakers at these national workshops described container collection programs and various techniques for waste treatment and disposal. Much of the discussion was devoted to pioneering efforts to deal with disposal problems. For the most part, however, the issues of environmental and human health concerns were not addressed.

Of the dozen technologies that are being investigated for disposing of pesticide wastewater, only four methods are currently available commercially (13, 16) (Table IV). But, the question must be asked, available to whom? Often even the simplest technology is not priced in the range that farmers and small commercial applicators can afford.

Recycling pesticide rinsewater seems to be a wastewater management system that could be available to most pesticide users. The basic design of a wastewater collection/recycling system includes a wash pad and some type of receptacle for rinsewater containment. The rinsewaters can then be mixed as needed into subsequent spray solutions as an alternative to treatment or disposal. However, this practice does elicit some concerns especially where more diverse and sensitive specialty crops are grown. The main concerns arise from tank mixing of pesticides not labeled for such use, phytotoxicity to some crops, and residues in excess of established tolerances (17). The potential for excessive applicator exposure must also be viewed as a significant concern because the rinsewaters, laden with these chemicals, are used much the same as tap water is used for mixing chemicals in a spray tank. This presents an additional exposure risk to the applicator every time the rinsewater is handled during the recycling process.

Closed system technology for transferring pesticide concentrates into a spray tank is designed to empty shipping containers of liquid pesticides, rinse these containers, and transfer both product and rinsate to the application equipment while effectively reducing applicator exposure by minimizing spilling and splashing of pesticide concentrates during mixing and application. Possibly a modified type of "closed system" would be appropriate for storing and ultimately recycling pesticide-contaminated rinsewater to the spray tank. Such handling and storage techniques would certainly reduce the potential for applicator exposure.

Aboveground soil disposal beds may ultimately provide an environmentally safe and economical means of disposing of pesticide contaminated rinsewater (18). Rinsewater would be collected initially in a sump and pumped into a specially designed tank with a lower liquid storage container and an upper layer of soil suspended on a perforated platform. A sump pump would be used to apply daily doses of the accumulated liquid to the soil surface via a surface distribution system. Although it remains to be seen if these aboveground soil digestion systems will be practically functional, it is interesting to observe that such a system that includes wastewater

Table IV. Categorization of Pesticide Wastewater Disposal Technologies

Technology	Category		
	Proven Technology ¹	Technology ² Transfer	Emerging ³ Technology
Physical/Chemical Treatment & Recycling			
1. Pesticide Rinsewater Recycling	X		
2. Granular Carbon Adsorption	X		
3. UV-Ozonation		X	
4. Small-Scale Incineration			X
5. Solar Photo- Decomposition			X
6. Chemical Degradation		X	
Biological Treatment & Land Application			
1. Evaporation, Photo- degradation & Biodegradation in Containment Devices	X		
2. Genetically Engineered Products			X
3. Leach Fields	X		
4. Acid & Alkaline Trickling Filter Systems			X
5. Organic Matrix Adsorption & Microbial Degradation			X
6. Evaporation & Biological Treatment with Wicks			X

¹Technology is currently being utilized on a commercial basis to treat and dispose of dilute pesticide wastewater.

²Technology is being utilized commercially to treat other types of waste and offers promising opportunities for pesticide wastewater.

³Technology is not being utilized commercially but experimental data indicates it is a promising candidate technology for pesticide wastewater.

collection and storage capabilities as well as automatic transfer of the liquid waste to a digester would also reduce direct applicator exposure significantly.

At the January 1985 workshop in Denver, O.R. Ehart said, "Although this conference has dwelt upon the regulation of pesticide waste disposal, it is shortsighted not to recognize that the purpose of these regulations is not, or at least should not be, to regulate pesticide waste per se but to protect the environment" (19). The term environment as used in this sense most certainly also includes persons who are subject to pesticide contamination through occupational exposure as well as persons who are exposed inadvertently through incidental exposure such as might occur through contact with contaminated potable water sources.

Affordable, innovative technology to remedy the pesticide disposal dilemma will, with time, be available to the farmer and other pesticide users. However, as with any new information or technology, the focus will have to be on education if such technical innovations are to be used in an efficacious and responsible manner. Any program on pesticide waste management must also include information on minimizing the risks to the applicator as well as to the environment. Nothing less will be acceptable.

Summary

EPA's guidelines do not presently address the issue of measuring direct exposure to pesticide applicators (20). Rather, the Agency often takes the "surrogate chemical approach," which uses data from one compound to set exposure standards for another. The problem arising from this kind of approach is that such procedures often fail to provide us information about the permeability properties of the compounds. The EPA needs to develop a standard methodology for assessing applicator exposure and issue relevant guidelines to address the problem.

Pesticide manufacturers and user industries need to place greater emphasis on health surveillance programs for their employees. Research programs need to be expanded and coordinated on assessing exposure to pesticides. While the work on exposure should be conducted by pesticide manufacturers, university-based agricultural scientists, and research-oriented governmental agencies, it still remains the responsibility of those agencies concerned with occupational safety and health to take the overall responsibility for establishing research guidelines and coordinating research objectives. However, to accomplish these objectives, the overall research climate and support for such programs need to improve rather dramatically in the immediate future.

Literature Cited

1. Dover, M. J. "A Better Mousetrap: Improving Pest Management for Agriculture"; World Resources Institute: Washington, D. C., 1985; p. 84.
2. Morgan, D. P. In "Residue Reviews"; Gunther, F. A., Ed.; Springer-Verlag: New York, 1980; Vol. 75, pp. 97-102.
3. Davies, J. E. In "Determination and Assessment of Pesticide Exposure"; Siewierski, M., Ed.; Studies in Environmental Science No. 24, Elsevier: New York, 1984; pp. 67-77.

4. Hall, F. R.; et. al. In "Improving Agrochemical and Fertilizer Application Technology"; Hall, F. R., Ed.; Agricultural Research Institute: Bethesda, MD, 1985; pp. 15-23.
5. Goldstein, L. Natl. Safety News 1980, 50-1.
6. "The Properties and Processing of TYVEK Spunbonded Olefin," DuPont Tech. Inf. Bull. S-10, 1973.
7. Schwope, A. D. "The Effectiveness of TYVEK and TYVEK Composites as Barriers to Methyl Parathion," Arthur D. Little, Inc., 1980.
8. Bukovac, M. J. In "Improving Agrochemical and Fertilizer Application Technology"; Hall, F. R., Ed.; Agricultural Research Institute: Bethesda, MD, 1985; pp. 25-38.
9. Matthews, G. A. In "Improving Agrochemical and Fertilizer Application Tehnology"; Hall, F. R., Ed.; Agricultural Research Institute: Bethesda, MD, 1985; pp. 39-52.
10. Richardson, L. Agrichemical Age 1985, 29(9), 8-9, 12.
11. "The Use of a Diluent Not Specified on the Product Label," FIFRA Compliance Monitoring Policy No. 12.5, U.S. EPA, 1984.
12. National Workshop on Pesticide Waste Disposal: Denver, CO; Jan. 28-29, 1985.
13. Pesticide Wastewater Research Workshop: Cincinnati, OH; July 30-31, 1985.
14. National Workshop on Pesticide Waste Disposal: Denver, CO; Jan. 27-29, 1986.
15. Ehart, O. R. Proc. Natl. Workshop on Pesticide Waste Disposal, 1985, pp. 2-11.
16. Bridges, J. S.; C. R. Dempsey. "Proceedings: Research Workshop on the Treatment/Disposal of Pesticide Wastewater"; U.S. EPA: Cincinnati, OH, Jan. 1986; p. 55.
17. Taylor, A. G. Abstr., Pesticide Wastewater Research Workshop: Cincinnati, OH; July 30-31, 1985.
18. Brown, K. W. Agrichemical Age 1986, 30(1), 14, 44.
19. Ehart, O. R. Proc. Natl. Workshop on Pesticide Waste Disposal, 1985, pp. 120-3.
20. Wasserstrom, R. F.; Wiles, R. "Field Duty: U.S. Farmworkers and Pesticide Safety"; World Resources Institute: Washington, D. C., 1985; p. 78.

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Chapter 12

Educating the Public Concerning Risks Associated with Toxic Substances

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A comprehensive program modeled after the present Department of Health and Human Services (DHHS) recommendations for a problem-solving approach in risk assessment/risk management would be useful in educating the public about the risks from exposures to certain chemicals, e.g., pesticides. Documents on the nature of risk and risk perception, as suggested in the DHHS recommendations, can be useful in putting risk into perspective. Suggested is a "problem-solving approach", which not only separates the evolution of a risk management decision into an analysis of the risk assessment, but also clearly states the uncertainties in the risk assessments. This "problem-solving" approach also attempts to provide comparison and justification to other governmental risk assessments and the analysis of possible options, e.g., government regulation, risk reduction by technologic means, etc. Additionally, in order to make clear the nature of the risk, it offers a plan for informing the affected parties, other health-related agencies, e.g., federal, state, and local health agencies, primary care physicians, and suggests a plan for the evaluation of the option selected. It is suggested that these issues be explicated in special sections of a risk management document, and in language aimed at the layman. It is strongly suggested that the risk assessment/risk management document be used as an instructional tool to assist both the public and risk manager in deciding how to evaluate the significance of the risk.

The ancient Babylonian lived in a world populated by terrifying spirits, a world fraught with perils derived from the slighting of jealous gods. In the villages, mystical shamen/prophets interpreted the will of the gods in capricious and whimsical ways based on bizarre extrapolations from personal observations. In such an

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atmosphere, the Asipu, the first risk assessors known to us (1), delivered pronouncements on proper planting times, risky ventures, etc., based on a complex system using pluses and minuses derived from divination results. The Asipu thought they divined the will of the gods, and their authority, bulwarked by the regency, convinced the public to comply with the results of their assessments. The authority of the king and priests was important as a counterweight to a frightening cosmos.

Although this example is from the beginning of recorded history, aspects of it are uncannily familiar. The terrifying spirits now are toxic agents (the "sea" of carcinogens) (2). The mystics in the public marketplace today speak of idiosyncratic interpretations of test results (e.g., human danger from the marginal observation of chromosomal changes in fungi) or of personal experiences ("My cow stopped supplying milk when she was exposed"). The assessors, speaking with the authority of government, now use computers, and quantitate economic dislocation as well as physical destruction. Similarity to both the ancient and modern situation is that unknowable phenomena are being interpreted through ways approaching magic to the general public.

A fundamental break with this tradition has been recommended recently by the Department of Health and Human Services (DHHS) "Report on Risk Assessment and Risk Management in DHHS" (3). Instead of requesting that the public "trust us", or requiring a personal mystical union with some embodiment of "Nature", this document recommends that the public be brought in as a partner to understand the meaning of risk, the method for assessing risk, and the response to risk. This "democratization" was not to occur by mindless extrapolation of a single test result, such as cancer induction in a single test, but by promoting a true understanding, as much as possible, of the state-of-the-science of a complex process. This is to be done by a "problem-solving approach" to risk assessment and management, which seeks, to educate the public, as much as possible, concerning the risks from chemical exposure in order to achieve an effective risk management strategy.

Although originated for DHHS, the approach has potential for use throughout government when it is necessary to communicate risks to an interested public. This is especially true for pesticides. These chemicals, which are an important part of the armamentarium against that aspect of nature which would take the very bread from our mouths, have acquired a somewhat unsavory reputation because of the potential risk associated with some of their chronic effects. The method chosen to explain the context of a pesticide risk (health hazards, etc.) to the public is a vital part of effective pesticide use management.

A tactic in the educative process is to use risk assessment and risk management documents as teaching tools to train the public to understand and manage risk, as noted below.

Definitions

There is no surer block to communication than using "common" terms which have different meanings for different individuals. This is especially true in risk assessment, especially for different

government agencies. For instance, if one agency is discussing risk in terms of adverse human health effects, while another is addressing the issue in terms of the effects in animal studies, this can lead to one agency saying there is no risk, while another declares an emergency. One of efforts in the DHHS document (3) was to develop a common set of definitions for the different agencies in DHHS. These definitions are adapted from the NAS report on risk assessment (4) and the OSTP Report on chemical carcinogenesis (5).

Risk - The probability of an adverse health effect as a result of exposure to a hazardous substance(s).

Risk Assessment - The use of available information to evaluate and estimate exposure to a substance(s) and its consequent adverse health effects. Risk assessment consists of one or more of the following four elements:

Hazard Identification - The qualitative evaluation of the adverse health effects of a substance(s) in animals or in humans.

Exposure Assessment - The evaluation of the types (routes and media), magnitudes, time and duration of actual or anticipated exposures and of doses, when known; and, when appropriate, the number of persons who are likely to be exposed.

Dose-response Assessment - The process of estimating the relationship between the dose of a substance(s) and the incidence of adverse health effects.

Risk Characterization - The process of estimating the probable incidence of an adverse health effect to humans under various conditions of exposure, including a description of the uncertainties involved.

Risk Management - The process of integrating risk-assessment results with engineering data and social, economic and political concerns, then weighing the alternatives to select the most appropriate public health action, ranging from public education to interdiction, that will lead to reduction or elimination of the identified risk.

In the DHHS report, it was suggested that these definitions be the ones generally used when communicating the risk from chemical materials to the public. Some general consensus definitions, agreed to across government can be very useful in preventing inconsistency when presenting the information on hazard from a chemical, e.g., a pesticide, to the public.

Factors in Understanding Risk

To understand the nature of the societal response to risk, it is important to appreciate a number of factors which influence this response.

Acceptability of Risk. Although risk has always been part of life, the acceptability of different kinds of risk has varied considerably. For instance, deadly outbreaks of infectious diseases were once a sign of God's displeasure and, therefore, acceptable. However, with the advent of modern public sanitation, vaccines, and other modern technologies, very limited outbreaks, such as that experienced with Legionnaire's Disease, which would have hardly been noticed in the recent past, are now considered national emer-

gencies. Mining, once done by "disposable" slaves because of the attendant hazards, has become an occupation in which substandard working and health conditions are not tolerated. Much of this change is the fruit of the efforts of countless physicians, politicians, labor leaders, regulators and journalists. As a result of efforts such as these, and the improvement in living standards, the major focus now is on non-infectious diseases, such as most cancers, and the health consequences of the industrial processes from which this improved standard of living is derived, such as the consequences of pesticide use. An important factor in the public acceptability of a risk is also the confidence in the societal ability to control it (6). Risks which are not readily controllable strike much more fear than those that are. As exposures alter, as mores change, as prevention and control techniques improve, as laws evolve, as needs change, as alternatives become available, as information on hazards improves, so then the acceptability of a risk changes.

Estimation of Risk. The estimation of risk contains uncertainties, based on the lack of specific data (such as exposure information) and/or the lack of understanding of the mechanism of toxic action of a compound. Between the extremes of actuarial risk, which is based on enough information that "time has removed the uncertainty," such as the probability of death as cited in an insurance table, and theoretical risk, which is based on probabilistic calculations of events which have never actually occurred (e.g., nuclear "winter" (7)) lies a wide continuum into which most estimates of human health effects fall. In real-life situations, many assumptions are made in evaluating risk in order to make a conclusion, and these assumptions lead to uncertainties in the final result. These uncertainties should be understood as limitations to the best guess science can presently make. Although one response to this uncertainty, in the face of an outcome as fearsome as cancer, is to deny that there is a lack of certainty, the more reasonable response is to try to estimate the uncertainty, making it clear that any estimate is bracketed by these possible errors.

Also important to consider is the nature of the risk. When a physician recommends that a patient change his lifestyle to reduce risk of heart attack, the physician is synthesizing clinically-oriented human research and personal experience with an expert evaluation of the relevant personal characteristics which bear upon the hazard. This personalized risk management, based on what can be termed "personal risk," is very different than the approach based on population risks contained in risk assessments. The population risks are almost always upper confidence bounds, often based on "worst-case" scenarios. Many important characteristics in assigning risk have not been identified, and personal qualifiers are ignored. Frequently, there is little, if any, epidemiological data to demonstrate human effects. A source of confusion is to consider risks of all types as immediate and personal risks. Personalizing inferential population risks can lead to the conclusion that everything is dangerous, that one is treading in a veritable minefield where the slightest misstep can explode into a horrible cancer. This perception does not accurately see population risks

simply as part of the process of prioritizing and managing risks on a broad scale.

Voluntary Aspects. People voluntarily accept some risks, such as driving a car, and have others imposed upon them, such as water pollution. The line between voluntary and involuntary risks is often hard to define and is frequently determined by availability of resources and social practices, e.g., if one has a filter, one could drink only filtered water. In general, the American public, probably reflecting our individualistic biases, is more tolerant of voluntary risks (8). Americans do not readily accept their government to be the arbiter of personal risk, demonstrated by the brouhaha that developed over governmental attempts to mandate use of seat belts and motorcycle helmets (9). (For a good discussion of the broader concept of risk and consent, see 10). Much more acceptable appears to be government efforts to protect the public from imposed risks.

Perception of Risk. Fairly recently, it has been appreciated that public perception of risk is important in risk policy (11). Some of the major conclusions that can be drawn about public perception are (12,13):

a) Cognitive limitations, coupled with anxieties generated by the feeling that one is gambling with one's life, cause uncertainty to be denied, risks to be distorted, and statements of "fact" to be believed with unwarranted confidence.

b) Perceived risk is influenced by the imaginability and memorability of the hazard. In this aspect the media has a special role since it can make the unimagined real, vivid, and fearsome. For instance, publishing a series of articles on birth defects, with pictures of deformed babies, is likely to heighten the sensitivity of a community to information about contaminants in water that may be teratogenic.

c) While safety experts tended to perceive risk in a manner closely responding to the statistical frequencies of death, lay persons' risk perception included aspects such as dread, the likelihood of fatality, and the degree of catastrophic potential. For instance, the public perception of the risk of death by flood is high compared to the danger of asthma, a much more significant killer (14). This difference in perspective is especially evident for chemicals. For instance, a synthetic chemical such as trichloroethylene (TCE) is treated as a very dangerous entity, while aflatoxin contamination of food or the effects of drinking alcohol, both with orders of magnitude greater cancer risk than TCE (15), is considered relatively benign.

Public perception of risk, therefore, can vary significantly from that of safety experts. This difference in perception is important to evaluate in a risk management strategy.

Understanding Risk. It is important that the public understand the nature of risk. Explaining and illustrating the risks involved in toxic exposure, plus relating them to the risks of everyday life, is crucial if the public is to understand how to put risks for toxic exposures in context. Context is vital if people are to get

an accurate picture of what threat a hazard presents and to whom. It is useless to note that the upper limit on the risk associated with a particular substance is on the order of 10 unless one also gives the appropriate context for such a number. The population at elevated risk may be miniscule, however, the risk could be misinterpreted as a general population danger. A risk assessment/risk management document should do this, and provide the scientific bases for the explanation by risk managers of the risk to the public. This information, placed in an organized fashion in the document, provides the bases for those who interpret the meaning to the public directly, such as private physicians, health departments, company health managers, etc. The object is not to turn the public into professional risk assessors and/or managers, but, understanding the many-faceted interests in the many individuals who comprise the public, is to encourage active participation by interested parties in managing risk and participation by as many members of the public as possible.

Problem-solving Approach to Risk Management

The major challenge in risk management is to enhance public welfare through effectively managing the risk of a chemical that has toxic effects under practical conditions of use and exposure, i.e., a successful risk management decision. In order to manage risk effectively, one must have an adequate assessment of the situation, and realistic plans for coping with the hazards that derive from the situation. A crucial element for success is public understanding and cooperation in all aspects. A systematic process separates the analysis of a risk assessment/management decision into four sections:

- 1) analysis of the risk assessment;
- 2) analysis of possible options;
- 3) promotion of understanding and acceptance of risk-management decisions; and
- 4) evaluation of the effectiveness of the options chosen.

and asks whether each section completes its task in terms of leading to a effective risk management strategy.

This process can be termed a problem-solving approach to risk management. Some of the formal rubrics termed "problem-solving" tend to be quite general, e.g., using such concepts as problem-identification, determining important parameters, etc. Problem-solving referred to here is quite specific to risk assessment/risk management as presently performed and focuses on its goal, a successful risk management decision, with the appreciation that public understanding is a key portion of an effective strategy. It is an approach that attacks each risk management decision as a "clinical research experiment" in resolving toxic-related situations in a manner most conducive to public welfare. The scientific method is incorporated as much as possible and the approach "learns" in order to expedite the next decision. Aspects of this approach are currently being used in different contexts by different units in government, and this systemization seeks to place these efforts in context.

Analysis of the Risk Assessment. In answering the question of whether the risk assessment is adequate for basing a risk management decision, a number of issues arise. Some are listed below.

1) A risk management decision should be based on the clear understanding of the limitations of the risk assessment. This is difficult, if not impossible, if the risk assessment doesn't characterize the uncertainties comprehensively, e.g., identify the result of altering different assumptions which are bases of contention; the major sources of uncertainty, etc. This could become a special section of the risk assessment document and would be invaluable to risk managers and the public in understanding the validity of the assessment.

2) In order to evaluate options, it is important to understand what could be done to limit the uncertainty, especially when this radically changes the options. For example, if the exposure level for safety is based on a conservative approach, necessitated by the uncertainty in an assessment, and an experiment could reduce the uncertainty by a factor of ten, then the control level may be able to be set much lower. This could change the control options significantly. A level of 10 ppb could require destruction of 1/2 of a crop, while a level of 100 ppb could have little, if any, economic consequences. For the present data deficiencies which contribute to the major uncertainties in the assessment, it is useful to identify the research, if any, which could limit uncertainty. Research such as this could lead to re-evaluation of a risk assessment after data are obtained, making delay of a decision unnecessary, and leading to increased use of relevant information in a risk assessment.

In the special category of contributing to public understanding of the risk management decision, understanding of the risk assessment would be heightened by:

1) The bases of the risk assessments, i.e., the assumptions which underlie the process, should be elucidated in plaintext (i.e., simple, straightforward common language) as much as possible. A special section in the risk assessment document should be written to comprehensively discuss the assumptions, and could also be in plaintext.

2) Understanding risk management decisions in light of major differences in risk assessments by various agencies is particularly difficult when the reasons for the differences are not clearly presented, and can be a major stumbling block to public cooperation. It is crucial for public understanding that the assessment be compared with other risk assessments for the same compound. Plaintext explanations of the reasons for any differences (probably a result of different assumptions being used) will be very important in the education process.

Analysis of Possible Options. The next step is to question whether the risk management decision actually considers all possible options and chooses one which maximizes public welfare and effectiveness. The decision is seen as an opportunity for government expertise to protect public health with minimal losses (better if everybody gains). Analysis should not be limited to economic and

social benefits, but should also include health benefits (e.g., it would make little sense to transport a material across the country if the public health dangers of the transfer exceeded those of letting the material remain where it was).

Some examples of the range of options to be considered are:

1) Agency regulatory action - which can range from public education, warning labels, etc. to interdiction and total ban, with plaintext explanations of why the particular route was chosen;

2) Regulation by other governmental units - Evaluation of the role that state, local and other federal agencies play should be clearly set forth. This leads to coordinated action, with removal of any contradictory regulations and different units working at cross-purposes. Discussing how different control possibilities would impact on different agencies is an important part of this evaluation.

3) Risk reduction by technologic means - Technologic strategies to reduce risks should be considered, e.g., detoxification, filtration, alternatives, etc. Personal protective gear, changes in application procedures, changes in formulations are technological solutions especially relevant to minimizing pesticide risk. However, when discussing technologic solutions, it is useful to discuss them in context of the new risks. For instance, a new application using different ingredients may simply exchange chemicals with no relevant information for those for which we have limited information that they are toxic.

4) Voluntary actions by the private sector - "Jawboning", i.e., discussion of the problem with concerned interests, e.g., the manufacturer, applicator, etc., can be very effective in maximizing compliance and speeding up the removal of any health hazard. This approach also maintains maximum flexibility as the "regulations" are not fixed.

5) Actions by professional societies - A long history of public service characterizes the professional societies. This avenue should be formally considered when faced with the need to resolve especially complex issues. These societies are a valuable resource in reviewing documents, assisting in clarifying consensus positions, etc. and as a source of ideas for coping with difficult situations.

6) Risk management research - Similar to the need to identify research in the risk assessment, identifying risk management research involving the social sciences, research into the factors which contribute to the success of various options, especially in public health terms is important. It has been relatively neglected. However, when risk management decisions are considered attempts to resolve situations, an obvious question is how to maximize application of management strategies.

Again, in the special case of increasing public understanding, it is important to demonstrate that a wide range of options was considered, and those with the least risk and most benefit chosen. It is useful for acceptance to clearly state the reasons for choosing a particular option, both its advantages and disadvantages, especially in the health area, as the different segments in the society will seek out the reason for a decision which will have impact on it. Very useful would be a plaintext statement of the

nature of the risks, benefits, options, and factors (e.g., statutory mandates). A special section in plaintext would be very useful for this.

Promotion of Acceptance of Risk-Management Decisions. In a risk management decision, it is important to ask how to maximize acceptance of and compliance with a risk management decision, although this is often overlooked. Too often it is forgotten that a reasonable explanation can sometimes be more effective than police action. Examples of actions are below.

1) Getting the affected parties to participate in and understand the major aspects of the decision as soon as possible. This is different than general public understanding since the response to the issues will probably be much more volatile and heated. Crisis teams especially trained to explain and adapt decisions, when possible, are probably the best way to accomplish this. What is needed is not spokesmen, but active participants who can modify and adapt the risk management.

2) Getting information to local units. Dissemination of information to health-related agencies in the area, as well as primary care physicians on who is likely to be affected and in what way, is important. These individuals will probably be the front line addressing many of the questions involving health, and need all the health information the federal government can provide. Working with these individuals as partners, as soon as possible (perhaps when options are being considered) can mitigate problems beforehand.

Evaluation of the Effectiveness of Options Chosen. When considering a risk management decision, it is important that the question of how to evaluate the decision is addressed. Information on the efficacy of the option chosen is important both to the process of choosing future options and to evaluating the need for corrective action. Factors to evaluate:

1) Effect on health should be evaluated. It would also be useful to evaluate the cost-effectiveness of the option. A follow-up provides a record for any corrective options. Further, if conditions change or the follow-up shows the resolution is ineffective, the risk manager may decide to alter the decision. This is an important part of the problem-solving approach which would lead to improvement. In this sense, the process "learns."

2) For increased public understanding, it is important to show how effective an option was to improve future compliance. It also can lead to improvement of the solution through direct public input and participation.

Conclusion

The role of the public in risk assessment and risk management in a democracy such as ours is as a partner. Government has an obligation to explain its actions in a manner as conducive to public understanding as possible. Part of the societal investment in any risk assessment/risk management decision should be dedicated to explanation to those who are to live with the decision. In terms

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of efforts to derive experimental results to use in risk assessment/management, broad-based support across the regulatory agencies should be primarily for programs for research to limit the uncertainty in the critical assumptions used in risk assessment and for basic information in risk management (such as evaluation of risk management options). These routes are the best avenues to provide the information necessary to assess and manage risk effectively, and allow cogent presentations to the public. Approaches which attempt to maximize public understanding and participation, coupled with a strong research program to confine many of the uncertainties in the complex process of risk assessment/management, are necessary to truly accomplish the objective of an effective risk management strategy.

Literature Cited

1. Covello, V. T.; Mumpower, J. Risk Analysis 1985, 5, 103-120.
2. Efron, E. "The Apocalypitics- The Big Cancer Lie"; Simon and Schuster, 1985.
3. "Risk Assessment and Risk Management of Toxic Substances A Report to the Secretary Department of Health and Human Services," U.S. Department of Health and Human Services, April 1985.
4. "Risk Assessment in the Federal Government: Managing the Process," National Academy of Sciences, 1983.
5. Office of Science and Technology Policy. Fed. Reg. 1985, 50, 10372-442.
6. Starr, C. Risk Analysis 1985, 5, 97-102.
7. Carrier, G.F. Issues in Science and Technology 1985, 1, 114-117.
8. Thompson, S. C. Psychol. Bullet. 1981, 90, 89-101.
9. Robertson, L. S. J. Communication 1976, 26, 41-45.
10. MacLean, D. Risk Analysis 1985, 2, 59-67.
11. Covello, V. T.; Menkes, J.; Nehnevajsa, J. Risk Analysis 1982, 2, 53-58.
12. Slovic P.; Fischhoff, B.; Lichtenstein, S. Risk Analysis 1982, 2, 83-93.
13. Slovic P.; Fischhoff, B.; Lichtenstein, S. Environment 1979, 21, 14-39.
14. Lichenstein, S., Slovic P., Fischhoff, B., Layman, M., Combs, B. J. Exp. Psychol.: Human Learn. Mem. 1978, 4, 551-563.
15. Ames, B.N. Science, in press.

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Chapter 13

Mass Media's Effect on Public Perceptions of Pesticide Risk: Understanding Media and Improving Science Sources

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Mass media rarely change existing attitudes, but through reinforcing messages and repetition they do strengthen public perceptions thereby impacting behavior. In assessing the role of media in public perceptions of pesticide risk, this presentation examines the process of mass communication and the relationship between journalists and the science community. Accuracy, objectivity and sourcing are identified as problems. The author offers as solutions an understanding of the media process and the constraints faced in covering science stories, as well as, an improved performance by scientists as sources of information. Major questions considered include how media define news, who media use as sources, and whether media can be expected to cover risk. The presentation relies on available studies and analyzes recent cases of media attention to pesticides. Print and broadcast media are discussed.

At a recent gathering of journalists and representatives from science and industry, one biologist snapped from the audience, "I don't understand your business and I don't expect you to understand mine!" That's the sort of useless attitude guaranteed to continue the current cold war that exists between mass media and science. Just as journalists are training themselves to better understand the process of scientific thinking, science professionals ought to be working at understanding how mass media function.

Reporters are consciously struggling with the liabilities of not enough time and inadequate knowledge to cover science stories. And they are doing well according to the findings of the Twentieth Century Fund's 1984 Science in the Streets study, and more recently, the Scientists' Institute for Public Information (SIPI) survey. In SIPI's 1986 study, over 90 percent of the scientists queried felt that journalists were performing with accuracy and appropriateness, and were helpful in improving the public's understanding of science.

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So what is the problem with media's science coverage, and in particular, are there problems with media's coverage of pesticides or the risk associated with pesticide use? Stuart Diamond of The New York Times reasons, "Zero risk does not exist...risk is basic to technology." This reporter sees his task as one of balancing risk with benefits and resisting the short hand explanation, the convenient line that may not be accurate in each case. But in the effort to find the answers and detail, what many journalists confront is experts who are afraid of the press, and scientists who don't understand media process or pressures. In reality, the information vacuum gets filled, even if it comes from non-experts who are willing to talk to the media rather than stonewalling with a "no comment."

Government or industry employed chemists as well as scientists in general are considered "a hostile audience" by media. It is believed that scientists have no respect for reporters. "There's no learning in the face of all of that hostility." But since I decided some time ago that I'd rather work with those who are attempting to act as sources for media--trying to access media--rather than singularly side with journalists, I took this assignment. This symposium and the long term efforts of the American Chemical Society such as the ACS news service make it clear that many scientists as sources do want to improve their relationship with media representatives and improve their ability to use mass media to effect the public perception of pesticide risk.

BACKGROUND

Journalists are not comfortable with the what-if story. There's greater safety and potential for objectivity in reporting what has already happened. Uncertainty in a response from an expert usually does not get into the story. Even worse is the scientists' reluctance to speculate. Journalists are beginning to recognize that the potential risk question probably should not be aimed at the scientist. But at whom then? Who will speculate in regard to risk for the next morning's paper? What you do wrong as sources hurts. What you do right as sources will make the difference.

Reporters know that readers probably will not understand the water and phosgene and methyl isocyanate reactions covered in the Bhopal story. The story gets summed up as an unnatural disaster and pesticides become only a party to the larger issues of worker training, safety regulations, corporate responsibility, and so on. Whether the product is pesticides, nuclear power or poultry becomes secondary, although the association can become enormously detrimental. However, blaming coverage of a tragedy for the actual event is absurd. In the Bhopal story, the press managed to obtain the all important company manual that defined methyl isocyanate (MIC) and provided the instructions for its safe use and production. That manual was essential to the coverage of the story. The residents of Bhopal on the other hand reported to journalists that they thought the Union Carbide plant was producing "medicines for the crops" and had never been given brochures about MIC or provided with educational or even public relations literature before the accident. Effective mass communication means more than answering press questions after something has happened.

A journalist's human sense perception is operative in covering any story. What looks are on the faces of those involved? How do things in general look? How does the air smell? Some of the best reporting comes in the form of analogies. Diamond wrote in covering Bhopal: "To make the pesticide (Sevin) carbon tetrachloride is mixed with methyl isocyanate and alpha-naphthol, a coffee-colored powder that smells like mothballs." Where did he get that description? Did the sources he was interviewing treat him as a human observer and offer some assistance in explaining complex chemicals and procedures to his readers, or is Diamond on his own expected to be a good science writer?

Jim Detjen of the Philadelphia Inquirer acknowledges the hard feelings and difficulty in confronting these complex stories when he says, "No one wants to sound foolish." Experts are ego-involved in a professional ethic that does not prepare them for quick, simple responses. So, "they clam up." Oftentimes an expert really isn't sure and doesn't want to say, "I don't know." There's a sense that reporters have fried too many experts with a printed, "No comment."

Editors and reporters want to get the story right. There were changes in the New York Times Bhopal series, even changes in the lead paragraph, up to the very last minute--at one point a change in the lead between editions of the paper. Journalists are as committed to accuracy as a science researcher. The overwhelming difference is the immediacy of the journalists' need for answers.

"We're covering issues that are suddenly thrust into the public domain; we dig and find untruths, we still go for a balanced story and then we get attacked by the chemical industry and the American Chemical Society," one reporter told me. It comes as no surprise that respect is lacking in the relationship from both sides. What needs to be confronted here is that the industry is ultimately responsible for its own image. The messenger can't be shot for the problems carried in the mailbag.

THE PROBLEM

The American Chemical Society is not the first to look for flaws in the media. The American print and electronic media catch the blame from computer manufacturers for the furor over a faulty chip, from bankers for contributing to bankruptcy rumors, from the nuclear industry for the failure of nuclear power, and from the government for everything that's wrong. Yet studies continue to show that the public have faith in the media and research indicates that media coverage is in fact fair and unbiased. This paper attempts to offer a very basic understanding of media's approach to coverage of pesticide risk and how the American Chemical Society can work with media to improve that coverage.

Ronald Kuhr, an editor of this book and the head of the Department of Entomology at North Carolina State University told me, "I myself don't like to talk to reporters. It destroys your credibility as a scientist." Kuhr echoes a common complaint when he accuses journalists' translations of what was said of being wrong. He believes, as do some other scientists, that while scientists tend to be very precise, journalists are not precise, and their translations change meanings. Before the translation, it is important to understand the reporter's involvement in the first place.

Where does news begin? What are the news pegs? (What are the significant events or what is it that's new?) The answer usually is that news begins with an accident. (Fires are usually a guaranteed news story.) Reports are released to the press, or leaks reach reporters of not-yet-released reports. Someone gives a speech, a press conference is held or one of the thousands of press releases arriving on an editor's desk gets attention. Or someone makes a phone call. It is possible that a concerned citizen's letter to an editor plants the seeds for a story, but the usual initiation of coverage is an involved source. Unfortunately, there seems to be a paranoia, especially among government sources, about looking pro-pesticide. The attitude seems to be that any coverage leads to unnecessary concern by the public. Scientists are afraid to release information to the press and therefore don't, leaving the flow of information to accidents and leaks.

I do not want to misrepresent this as a formal survey because in preparing this paper I have only reviewed the existing literature and talked to an unscientific sampling of reporters who cover pesticide stories. My judgement is that their comments are fairly representative. Journalists I spoke with generally cited the same sources for pesticide stories. They look for someone from a responsible agency who can talk, a company representative, a victim or a witness. Primarily they depend on authorities. They go to local experts for translations of jargon, background information and better understanding, and they are using hot lines such as SIPI's Media Resource Service as much as possible. They report that most pesticide related stories are breaking stories--news happening right now--not in depth follow ups or features. They also list the usual constraints of time and available sources. Reporters say they feel their coverage has made the public aware of pesticides and maybe a little more cautious--"scared of the stuff." They complain of poor relations between scientists and journalists and lament that they "don't get any respect." They're not sure how to improve the science/media relationship, but they want the experts to be willing to talk more. Everyone I spoke with rates his or her publication's or station's coverage of pesticides as accurate and fair. They think they're doing the best possible job. Sadly, a few report they are beginning to share the public's lack of faith in the industry's openness to change. Along with the public, reporters are asking, "If it's safe why are you telling me about it?" or, "If it's dangerous why is it in my universe?" Standing in the middle sounds unresolved, too technical, too hard to sell to either editors, or the public.

Very little research exists on how the public use the mass media for risk information. The psychology literature examining what affects nonscientists' perceptions of risk is useful, but mass communication and media scholars are just beginning to gather data in this area. Sharon Dunwoody at the University of Wisconsin is finishing a content analysis of media risk stories to see how such information affects individuals' risk perceptions.

In New Jersey Peter Sandman and a group of researchers from Rutgers University are involved in a far reaching project examining that state's environmental risk reporting. Their work so far has

found, most importantly, a lack of reporting about environmental risk (1). Experts involved in the New Jersey study suggest reporters are more at ease covering environmental politics than environmental risk. Other important findings from this research effort include: an unmeasured "feeling" that when risk is reported in New Jersey newspapers, it is more alarming than reassuring; reporters rely primarily on the government (over half of the cited sources were local, state or federal government) and industry sources who were found to be the least likely to pay attention to risk and were the leading sources for risk-denying; risk is assessed by journalists in terms of extremes rather than quoting intermediate or tentative positions; and, bias, when it occurs, results from overreliance on a single source or a failed effort to translate jargon into lay terms. One of the key recommendations of this report for editors and reporters is more reliance on expert sources who are uninvolved in a particular story. It is reassuring that this New Jersey study did find experts, who were among the most likely to assert risk, being cited in over one fourth of the articles analyzed.

Prominent in laying the foundation for how people deal with risk is Paul Slovic. The conclusions and recommendations Slovic, with Baruch Fischhoff, Sara Lichtenstein and other risk perception experts offer are very important to those who are now focusing on how media might inform and impact public perceptions. (See for example Acceptable Risk (2).) What does it mean to consider media's role when the subject demands attention to values, beliefs, and issues rather than events? Issues of fact and issues of value are not generally debated in newsrooms; the two are clearly separate to the journalist. However, as we all know, a clear separation is not always possible. Judgement calls are made regularly by experts when confronted with perceived vs. objective risks. The public or nonexperts bring an even more diverse set of viewpoints to the analysis. Value judgments, uncertainties, complexities, fallibility, and even inconsistencies all play a part in assessing acceptable risk. Tell that to a fact-finding journalist and you're in trouble.

MEDIA'S ROLE

What impact do media have? There are five effects generally cited. The first impact is persuasion, but there is much misunderstanding about media's powers to persuade. What is hard for most non-media professionals--and some media pros as well--to accept is that regardless of the issue, mass media cannot convert their readers, listeners or viewers. Mass media reinforce the existing attitudes of the audience; they are not a force for change. Media cannot be used to force conversion. What can be done is to attempt to understand which existing attitudes should be maintained in working toward a goal. What beliefs and opinions forming the status quo are only slightly different from the desired new view? What current audience attitudes can be moved in the direction that would be acceptable to the established goals? Psychologists call this ability to maneuver around an attitude and create a new view a "latitude of acceptance." In mass communication theory, it is also acknowledged that mass media can be used to guide an audience toward a new attitude that is rooted essentially in what they (the audience or

message receivers) have already accepted, what they already believe. For example, if people are already fearful of pesticides but only in reference to plant accidents, fires or other disasters, consider the potential usefulness of such fears to promote the safe use of chemicals. Don't deny the fear. Use the existing caution induced by fear to establish the desired new attitude or behavior.

Media's second impact comes in the form of agenda-setting, which means that editors and reporters respond to what they think the public is interested in, not what they think the public ought to be interested in. It is probably true that media are often ahead of their audiences and are in reality "bringing the public along," but it is nonetheless important to understand what is selected for coverage and where it shows up. If pesticide risk is to be an agenda item, editors and reporters must be convinced that the public considers pesticide risk an important issue. If neither the public nor editors list such risk among their concerns, the story will never see the light of day...until there's an attention getting disaster. The industry it seems is faced with a serious educational task. Recall that nuclear power was not much of an agenda item until Three Mile Island (TMI). Pesticides--not even the manufacturing sites--were not on many lists until Bhopal. As do journalists, the industry waited for a disaster before attending to the issue. It is ironic that both media and industry failed to respond to what was clearly a concern for the public (3).

The risk stories to which media seem to have attended of late are the dangers of smoking, the risk of getting Acquired Immune Deficiency Syndrome (AIDS), and the problems of hazardous waste disposal. Those news items are for the most part the result of legislation, industry press releases, advocacy group campaigns and real events covered by reporters. Perhaps now that Caesar Chavez, President of United Farm Workers of America, has undertaken a strategy which calls more public attention to pesticide use in America, editors will begin to add pesticides--perhaps even pesticide risk--to their agendas. That of course casts industry in the role of respondent rather than initial source. Some sources have learned the lessons of media power better than others.

The third area of media impact is in presenting norms; media attempt to reflect our arts and social customs. There is no question that media homogenize culture in a regrettable way. There are those who devote their lives to improving this content and form dilemma. The fourth and fifth areas of media impact are also less than desirable. Media are held responsible for modeling--fashions are straight out of "Miami Vice"; our children think in Smurf. And, media induce apathy. Until more can be done with the interactive potential of TV, media area passive experience. And worse, that passivity is satisfying the total experiential need. Even the most ardent advocate of television reacts with horror to the statistic showing the percentage of people who rely solely on the six o'clock news for all of their information. A 1982 study indicated that 41 percent of the American public rely on television as their only source of news and that 53 percent feel television is more credible than other media (4). It would be of immense value to society if simply viewing the tragedy of farmworkers' exposure to pesticides initiated actions that led to real safety measures. It would be useful if reading a story about

the dangers of pesticide residue in produce resulted in an overwhelming consumer demand for better labeling and rethinking of costs vs. benefit. But in fact, such programs and stories are experienced as a whole--the readers/viewers/listeners feel they have the beginning, the middle and the end of the story, and there is no need to act further. The audience is either lulled or numbed into passivity by mass media.

These general media impacts have been understood for some time (5). What we can say about specific perceptions of the audiences reached by media is less clear. But before we move whole-heartedly into researching what the results of the message on the receiver might be, it seems to me more effort can be put into improving how sources are delivering the messages, and what is being said. The relationship between sources of science information and the translators who send the messages is not yet the best it can be.

MORE PROBLEMS

The usual charges when criticizing media coverage of risk issues do not differ so greatly from problems cited for media coverage of science and technical issues in general. First, the complexity of the information requires science literacy. Accuracy is difficult to achieve. Science reporting in general is incomplete. Assessing risk requires good judgement and, as St. Petersburg Times president and editor Andy Barnes points out, some of today's new journalists don't even know the norms (6). The second category of charges suggests reports are biased, superficial, sensational, negative, distorted, and generally lack objectivity. The third general charge is that the "good" news story is always bad news.

In discussing media constraints when covering or presenting science, June Goodfield (7) also points to financial pressures, especially in television. Goodfield sees the sword of Damocles hanging over producers, threatening to cut off funds. Any documentary or expanded programming requires financing and sponsorship. Intervention in terms of content is not so much the issue here as is initial funding and eventual marketability of the idea.

I don't find journalists denying that accurate science reporting is difficult. Those in media are working to provide better training for future science writers, and better support resources such as SIPI are becoming more available. I do not take seriously charges that editors and news directors have a "startle-amaze-amuse-them" mindset, and insist on simplicity and negativism. Such criticism reflects an unwillingness to understand or respect the process and constraints of mass media. Neither do I accept the charge that somehow the public's mindset is to blame for missing or mis-understanding. The public knows scientists can be wrong. TMI for example, or a failed shuttle launch, do much to reinforce that attitude. And, experts have noted there is often much to be learned from the general public's common-sense wisdom. Rather than accuracy, objectivity, or motivation, what seems the more serious problem for journalists and science sources seems to lie in basic values.

Several very different "world views" between journalists and sources have been noted. The comparison (see Table 1) foretells difficulties. For example, whereas journalists search for facts and

are triggered into action by events, scientists, as do most sources, look for truth and confront issues. Whereas journalists report what happened (a yesterday focus), scientists see time as forever. Sources are allowed to feel strongly about their work, whereas journalists are bound by a creed of objective, unfeeling rationality. Reporters have a commitment to the process of news gathering regardless of results, whereas sources are clearly focused on the end message--what appears in print. Journalists record events and balanced quotes in a point by point, one fact on another (atomistic) style, whereas a source has a more coherent vision. And so on.

<u>Journalists</u>	<u>Sources</u>
facts/events	truth/values/issues
yesterday	forever
rationality	feeling
peers	audience
process	result
fast	timeless
atomistic	coherent
interesting	important

Source: Sandman, April 1984, lecture at University of Tampa.

Each of these sets of views offers very different integrities, and very different sets of values.

Television of course further complicates the attention to different values because of its reliance on good pictures. TV is primarily a visual medium. As Roger Peterson of ABC news points out, "Bophal was dynamite television (8)." The impact on innocent people provided what television needed--shocking pictures full of emotion. In comparison, TMI was not such a good picture story, but the immediacy of impending diaster made up for the lack of visuals. The problem in covering pesticide risks is similar to TMI in that there is no way to really show ethylene dibromide (EDB). Television can show people reacting to or talking about EDB dangers, but it's simply not a good picture story. Unless, of course, there's a fire.

To many of us the more serious difficulty is that it seems impossible to get on the air with the issues between crises. The long term problems don't get coverage. Series or in-depth features are few and far between, and then, some journalists bemoan the task of finding angles that make interesting pictures. Regardless of content, television can still be counted on to choose good pictures first, and immediacy is primary.

It may be frustrating to the experts, but reporters simply do not have the time to understand it all. News on deadline is not a think piece. It's enough to "develop a feel for what's dangerous," and "find an expert and pick his brain for a translation." And that means the front page story is more likely to be incomplete while the Sunday supplement story offers far more background and information.

Any attempt to extend information requires looking to documentary or news analysis treatment.

THE MEDIA PROCESS

Some of the best science writers get their leads from reading scientific journals and publications. They read and review reports, and check with experts in an effort to understand the process and findings of research. But, pursuing such stories--those not pegged on a specific event--is a luxury in the world of media. There is a difference between a publication of record and a thorough examination of an issue. And, there's a difference between the straight science story--that's the usual bread and butter story--and an issue story or a science policy story. Reporting pesticide risk is an issue and policy story, unless there is a fire, a spill, or another clear newspeg.

Although the earlier described newspeg is core to the Who, What, Where, When, Why and How, the standard formula for newsworthiness to a journalist also includes proximity, prominence, unusualness, human drama, consequences and immediacy. An editor and the reporter make these judgement calls, and then, they turn to sources. "If I can, I will avoid the PR person...I want to go to the scientist who did the study, the person who made the decision," any good reporter will tell you. A good public relations person knows that original sources are imperative and will act as a liaison for media to that quotable expert source. Sandman's research in New Jersey tells us a lot about who journalists use as sources (9). It is useful to note what these sources say about risk coverage.

Environmentalists label the results of risk coverage in terms of "who cares?" and "so what?" In general they feel the coverage is so poor and unarousing that only an occasional headline has any impact. Industry PR representatives seem dismayed with the editing. The stories are so full of holes that the public can not possibly make intelligent decisions. Experts feel reporters do not have even the basic understanding to explain the information, but that the inaccuracies reflect a lack of knowledge rather than bias. Reporters themselves admit to not asking enough questions but are overwhelmed by the lack of standard assessments of risk and uncooperative sources.

Journalists want non-adversary interpreters, someone to help formulate the question as well as communicate with ease for public consumption. They're asking for "user friendly" expert sources, not fact sheets, but real people who can be interviewed and quoted. I hear repeatedly from science and environment reporters about the difficulty in finding "leading experts with no ax to grind." In Scientists and Journalists Dunwoody cites research pointing to three major credibility factors a journalist looks for in selecting a source for a pesticide story. Journalists look for a source with mainstream status, administrative credentials, and previous media contact (10). These sought after traits seem far more manageable, I would think, than Goodell's description of the fittest visible scientist for media as one who is relevant, controversial, articulate, colorful and reputable (11). SIPI has a list of 150 experts who might respond to a reporter's inquiry in a pesticide risk story.

Of these, 70% are affiliated with universities or research centers, 10% are with environmental groups, 10% are employed in government agencies and the rest are in a variety of other positions (12).

It is ironic that reporters do assume bias on the part of every expert. That's probably a healthy suspicion that can only lead each assignment to include more sources. Expert bias and the well founded belief that experts can't talk to people leave journalists more than content with their roles as translators, sometimes floundering around, but doing their job as they see it. Multiple sourcing--more translators--may even offer better long term understanding for journalists. The more complicated obstacle to overcome seems to be a reporter's difficulty in accepting that an expert may truly not know the needed answer. Too many journalists have routinely assumed a cover-up or general unwillingness to provide information when the answer is, "I don't know." Not knowing may not be so difficult for a long-range-thinking scientist to admit, but "I don't know" is near impossible to get past an editor.

THE EDB EXAMPLE

For the Tampa Tribune, EDB began as a local story. Two counties in the newspaper's circulation area were among the first to be cited for contamination with the pesticide. Tribune reporters, particularly a very enterprising young woman from the newspaper's Lakeland bureau, interviewed state health officials, government agencies, local millers and farmers, Florida Citrus Mutual, and scientists before they even began to note the importance of the breaking story. "It was tempting to wonder if this pesticide, which was widely used for more than two decades on groves, fruit and grains, wasn't simply the latest "'chemical of the month'," wrote Tribune state editor Bill Gueskin (13). The Tribune ultimately saw EDB as "both a frightening danger to public health and a vivid example of the difficulties government agencies encounter in protecting citizens." That was in early 1984. Almost exactly two years later the same newspaper's Lakeland bureau business writer has no difficulty reporting, "The fumigant [EDB], used to destroy fruit-fly larvae, is essential in maintaining Japanese markets for Florida grapefruit (14)." Again the sources for the current stories were Florida Citrus Mutual, the EPA and now, Great Lakes Chemical Corporation.

The EPA commissioned study on how the public received the message that EDB was unsafe (15) used content analysis of 50 newspapers, news programs, national press stories and weekly magazines to arrive at a conclusion that indicts "macro-risk and micro-risk" perceptions on the part of EPA's specialists vs. the public's vision. According to this study, neither the EPA nor the public were in error about risk perceptions. The difference between perspectives (macro vs. micro) caused a barrier. Nonetheless the report characterizes the public during this six month period in 1983-84 as "confused and antagonistic (16)."

What NBC's chief censor Ralph Daniels knows, this EPA document does not tackle: there is no mass audience in spite of the mass media. Individuals view programs and that presents endless problems for people like Daniels whose job it is to be not only accurate, but a respectful guest in someone's living room. Reporters translating

government agency messages about EDB were only trying to provide understandable information for each media consumer. No editor or reporter set out to create a science fiction monster. If the New York Times or Wall Street Journal have superior coverage of a story, it reflects lessened constraints and more expertise on the part of their journalists, not a macro view as opposed to a local newspaper's micro view.

EPA's EDB report clearly notes that the pesticide had been exempted from all regulations as long ago as the mid-fifties and had been "in our universe" since the forties. Why then should it seem amazing that the public some thirty to forty years later was unsoothed by assurances that the risk from this chemical was only long range and chronic? It did not take television's image of grain elevator workers overcome by toxic effects, being rushed to a hospital (where it is later reported they have died) to create alarm. The EPA's own, original, untranslated communications were adequately fear arousing.

The irony is that regardless of media "sensationalism" the public, at least in Florida, apparently remained disbelieving, uninterested and generally uncooperative with local task forces. Some light might be shed on this public reaction if sources for the EDB study are considered. The Miami Herald for example, as did other state newspapers, relied on the State's Department of Agriculture, industry sources such as Monsanto Chemical Company, and interviews with citrus farm owners for sourcing. With rare exception, reporters ignored workers and consumers. Even in the wake of a recall order, three months into the EDB scare, all was relatively quiet in the state. And nationally, media all but dropped the issue, not when public anxiety declined or when EDB disappeared, but when the press releases and press conferences stopped. The "event" had been covered and it was over. There were no rioting or hysterical hoards. Even the EPA report notes without insight that NEWSBANK stopped indexing EDB articles after February 1984. As with nuclear anxieties, economic scares and other over-sized fears, the public accepted media's closure on the issue, or became numbed (17).

THE PROBLEM SUMMARY

The more general outcome of this information complexity, lack of expertise, no clear and immediate answer, and multiple, media-process constraints is the reporters' ethic that admonishes them to err on the side of public safety. And, as Paula Lyons of WCVB-TV in Boston sums up, if media are making people more afraid--more careful--"that's okay (18)." Accusations of being alarmists concern reporters far less than being caught missing the story. And to cover the risk story, a bit of fear or a measure of alarm might be the only news peg.

SOLUTIONS

One key to improving communication between journalists and scientists is a clearer understanding of the media process. As stated earlier, the story idea is generated, usually by a press release, an event, a study or report, but a leak can substitute as the trigger. The idea is evaluated and assigned by an editor. The story is covered by a

reporter or team of reporters. (And here is where scientists as sources play a critical role.) Space and time are allotted. The story is edited and processed.

The overshadowing professional demands at each step of the process are honesty, accuracy and fairness. The mass communication demands are clarity, readability and style. These demands for delivering information to the public need not conflict, but in covering science and the complexities of risk, they often do. The dilemma is real but can hopefully be resolved.

Dr. Vincent Covello, Director of the National Science Foundation's Risk Analysis Program, has developed a list of ten questions he believes a reporter should ask to assess risk (19):

1. What is the probability that people might be harmed and to what degree?
2. How much of the assessment of risk is based on assumption or guesswork?
3. If there is an uncertainty in the data, do the conclusions reflect that?
4. Does the study consider the number of people exposed to the problem?
5. What are the study's limitations?
6. Do the researchers consider such things as individual sensitivities, exposures to multiple hazards and cumulative effects?
7. Are all the scientific data open to the public scrutiny?
8. Does the analysis distinguish between voluntary and involuntary exposure?
9. Is the process of doing research kept separate from the process of making policy decisions?
10. Who provided the funds for the study?

Rather than Covello's approach, however, the norm now is to find risk--if included at all--in a single paragraph answering:

1. How much is there?
2. What's the standard?
3. What's the health relationship?
4. Who objects or disagrees?

Either formula for good coverage requires digging, phone calls and understanding. None of this is initiated using either formula if risk or science issues are not assigned as stories. And nothing gets covered without access to good sources.

Burson-Marsteller and Hill & Knowlton, leaders in the public relations (PR) industry, are impacting the public's perception of pesticide risk, and they are premier in knowing how to use media. Perhaps the American Chemical Society should use this public relations expertise just as Union Carbide and Dow have, but I do not think such reliance on these giants of PR is the only or even the best solution. Uncovered PR-generated articles are neither journalists' nor the public's favorites; such stories do little for long term creditility.

Better suggestions come in a very recent report on risk communications, again by Covello, listing communication problems with the message, the channel, or the receiver (20). In other words, something goes wrong with understanding and assessing what has been said or what has happened, something goes wrong because of the risk

assessment experts, something goes wrong because of the media process, or something goes wrong because of characteristics inherent in the mass audience--the public.

Let's consider how well media might fare if the tasks of risk communication are as outlined in Covello's report:

1. The task is treated as one of information and education.
Some mass media do well as sources of information, but there are format and process constraints on how messages will be presented. There are serious concerns about media's educational role.
2. The task is seen as behavior change and protective action.
Media rarely change behavior, particularly for strongly held beliefs. It is necessary to look to the advertiser's model for persuasion and understand mass communication theory, especially in regard to fear appeals for success in this type of communication.
3. The task is to send disaster warnings and emergency information.
Experience and conditioning indicate media have strengths in this role, but sources must have a good track record on these occasions. Media are relinquishing control under prearranged plans for such communications.
4. The task is one of joint problem solving and conflict resolution.
Media may play a supportive role in, for example, announcing public hearings, but in an effort to balance a story, confusion or undue alarm is often generated.

Rather than hiring Hill & Knowlton or Burson-Marsteller, Covello's report suggests a very useful list of what communication can do to effectively inform people about risk. Effective risk communication requires simplicity; relevant, personalized comparisons; an understanding of the audience; complete honesty; and a perspective that acknowledges political and ideological conflicts. It is also useful to remember all media channels, such as pamphlets and alternate video uses, instead of an exclusive focus on commercial television and newspapers. (Beyond news coverage of pesticide risk, someone needs also to look at how entertainment programming represents such issues.) If sources followed the offered guidelines, media's translation and transmittal would be less suspect as the culprit for public misconception.

A ranking of the most popular topics presented at the 1977 AAAS annual meeting listed "world food losses to insect pests" as in the top ten for experienced science journalists, who ranked the story at #6. Scientists did not rank the topic as popular (21). In 1984 the annual Associated Press poll placed the Bhopal disaster at #2 in the top ten stories of the year. Many reporters still use a time reference labeled TMI to Bhopal. In 1984 the only stories ranked as tops by national editors and broadcasters that came close to being science related were the Ethiopian famine (#6) and heart transplants (#8). The Mexico City gas explosion and space shuttle satellite retrieval were both ranked among the second top ten. Five out of twenty top stories for one year in somewhat of a science category is actually a dramatic rise in attention to science news.

In 1985 the top ten stories included an earthquake and a volcano in addition to a famine and the AIDS epidemic, but economic and

political stories were again dominant. The obvious note to make is that disasters, natural and unnatural, are considered the best news. A 1982 Gannett poll showed that newspaper readers rated natural disasters and tragedies as most popular, with local and national economic stories as second and third. Stories about the environment, energy or conservation ranked seventh. There are no risk stories in the top ten, not the risk of economic depression or even the risk of an air disaster. The news is the actual stock market crash, or hijacking. Even a meeting is more likely to be considered news than is a risk story.

It is no wonder most scientists prefer magazines to other news media. Not only are magazines somewhat similar to the more familiar journals, but the magazine medium is less hampered by the constraints of newspapers or electronic news media (22). And now in the 1980's there is an explosion of popular science magazines fueling the public's demand for more information. That may be a factor in the fact that newspapers have increased the number of pages devoted to science coverage (23). Magazine articles can be longer features, more reflective and verified. Whether working with a magazine writer or a reporter from another medium, Barbara Gastel's Presenting Science to the Public (24) offers a good primer. More seasoned veterans of encounters with media professionals may find it useful to simply make the time to talk one on one--get to know these people as people. Or, participate in opportunities to encounter journalists at events such as Boston University's one day seminar on media coverage of public health issues, or Northwestern University's seminar on science and health reporting, cleverly titled, "Risky Business." Far more attention has been paid lately by universities, the AAAS, and professional organizations such as ACS to getting science specialists and media professionals together. The common goal is to have a more informed public able to make more informed decisions.

It seems to me the public feels trapped by a system that tells them pesticides are essential to adequate food production and at the same time suggests pesticides are carcinogens. They would like to believe the scientists who assure them that Temik is not harmful, but they fear the worst. Although disastrous physiological consequences have not yet resulted, there is an uneasiness in the land and more frequent reference to Rachel Carson's Silent Spring (25). Mothers no longer tell their children to wash the fruit and eat that vitamin-rich peel; now caution and uncertainty have promoted avoiding the skin where "all those pesticides concentrate." Public perceptions appear to range from paranoid to cavalier, although little real measurement data exists.

For the public, mass media are the dominant sources of information about risks. Media set the agenda, shape and frame the reality by accurate and timely treatment through coverage or non-coverage, and reinforce what the public already believes. Policy and public opinion leaders respond to media coverage and in turn try themselves to influence media content. The media are critical in any risk communication effort.

The majority of expert media watchers do seem to feel media have done a good job in reporting risk, although excesses, errors, and bias are noted. There is general agreement that to suppress media coverage of risk would deny the public's right to know and violate

the freedom and responsibility of the press. I'd like to summarize what I've tried to say by offering a list of what I believe can be done to make better media coverage and indirectly, clearer public perception of the pesticide risk issue, more possible:

1. Understand how public perceptions are formed. Do you have public relations campaigns to inform the public? Media are not totally, if at all, responsible for public perceptions.
2. Don't blame the press for actions taken by others as a result of information provided in the media.
3. Understand that the reporter covering the respective risk story may not necessarily be a science journalist; the general assignment reporter will require much more patience and translation and even science writers may need assistance in developing better thinking skills.
4. Drop unessential jargon and clearly define science terms.
5. Provide as much information as available.
6. Learn to stop hating the press and respect their professionalism. Forget and forgive their past mistakes.
7. Cooperate. It can only help. Remember that reporters are also apt to have an unforgiving memory for deliberate or perceived omissions and lies.
8. Don't confuse alarm with sensationalism.
9. Don't expect media to do the slow buildup stories. And don't expect the seemingly necessary follow-up story. (Do encourage such coverage and help make it happen.)
10. Don't expect television to provide what a Wall Street Journal article might provide. Know which medium to lean on for what.
11. Allow reporters their humanity. Journalists care very much about consequences and are generally very active members of society. Some of them will even confess to resenting their editors' demands for inhuman impartiality, disinterest in issues and commitment to being uninvolved in the news. A job that requires a separation of facts and values is neither an easy one, nor one with which scientists should have difficulty empathizing.
12. Try encouraging compassion rather than cynicism. In the November 1983 issue of The Quill Gene Goodwin noted the substantial newsroom lore creating that hard-nosed, macho, dispassionate person demanding that two quotable facts be handed him or her, and now. Without superiority or subterfuge, try treating reporters as people who care as much about accurately informing the public about risks as you do.
13. Understand the process and constraints of mass media.
14. Offer statistical comparisons for a reporter attempting to translate and put into perspective a risk message. Certainly a statistical comparison is more relevant and more sensible than leaving someone to ask, "Do you want worms or EDB in your pancake mix?"
15. Do not wait to release weighty background papers, definitions and fact sheets in the middle of a breaking story. That is at best too much too late. Those resources and that understanding should be available and reinforced on a

continuing basis. As the story breaks, references then become a refresher rather than an impossible task.

16. Remember that being on deadline does not allow time for a lengthy explanation or "the history of..." Try to find out specifically what the reporter needs to know, then provide answers (or help restructure their questions) without lecturing. Their impatience is not with the subject; they're facing white space or dead air and the clock's ticking.
17. Encourage and participate in workshops or other efforts to bring scientists and journalists together for mutual "training" sessions.

Overall, rather than post disaster planning, I recommend a better understanding of the public's fear and confusion, and a more cooperative posture toward media. If the public is uninformed, media can play an important role in providing information. If the public is misinformed and overly fearful, media can be useful in turning that fear into positive action.

Literature Cited

1. Sandman, P.M.; Sachsman, D.B.; Greenberg, J.; Jurkat, M.; Gotsch, A. R.; Gochfeld, M. "Environmental Risk Reporting in New Jersey Newspapers," Environmental Risk Reporting Project, Industry/University Cooperative Center for Research in Hazardous and Toxic Substances, New Jersey Institute of Technology, January, 1986.
2. Fischhoff, B.; Lichtenstein, S.; Slovic, P.; Derby, S.L.; Keeney, R. L. "Accpetable Risk"; Cambridge University Press: Cambridge, 1981, pp. 28-35.
3. Allman, W. "Staying Alive in the 20th Century"; Science 85, 1985, 6, 31-41.
4. Hiebert, R.E.; Reuss, C. "Impact of Msss Media"; Longman: NY, 1985.
5. Sandman, P.M.; Rubin, D.M.; Sachsman, D.B. "Media"; 3rd Ed. Prentice-Hall: Englewood Cliffs, NJ, 1982.
6. Barnes, A., personal communication.
7. Goodfield, J. "Reflection on Science and Media", American Association for the Advancement of Science: Washington, D.C., 1981, AAAS Pub. No. 81-5.
8. Peterson, R.; Invitational Symposium on Environmental Risk Reporting, 1985.
9. Sandman, P.M.; Sachsman, D.B.; Greenberg, M.; Jurkat, M.; Gotsch, A.R.; Gochfeld, M. "Environmental Risk Reporting in New Jersey Newspapers", Environmental Risk Reporting Project, Industry/University Cooperative Center for Research in Hazardous and Toxic Substances, New Jersey Institute of TEchnology, January, 1986.
10. Dunwoody, S. In "Scientists and Journalists: Reporting Science as News"; Friedman, S.M.; Dunwoody, S.; Rogers, C.L., Eds.; Free Press: New York, 1986; p. 7.
11. Goodell, R. "The Visible Scientist"; Little-Brown: Boston, 1975; p. 18.
12. SIPI, personal communication.

13. Grueskin, B., "Stories Uncover the Problems with EDB". Tampa Tribune, February 4, 1984, D, p. 1, Col. 1.
14. Garmond, G., "Feds OK Seasonal Use of EDB". Tampa Tribune, February 14, 1986, E, p. 2, Col. 5-6.
15. Sharlin, H.I., "EDB: A Case Study in the Communication of Health Risk," Office of Policy Analysis, U.S. Environmental Protection Agency, January, 1985.
16. Sharlin, H.I., "EDB: A Case Study in the Communication of Health Risk," Office of Policy Analysis, U.S. Environmental Protection Agency, January, 1985, p. 13.
17. Sandman, P.M.; Valenti, J.M. Bulletin of the Atomic Scientists, January, 1986, 42, 12-16.
18. Lyons, P. Hazards or Hype. Video Tape Seminar, "Public Health and the Media". Boston University: Ketchum Public Relations, 1984.
19. Covello, V. Science and Health Reporting: Risky Business. Video Tape Seminar. Northwestern University, Medill School of Journalism, 1985.
20. Covello, V.; von Winterfeldt, D.; Slovic, P. "Risk Communication: An Assessment of Literature on Communicating Information About Health, Safety, and Environmental Risks". Draft Preliminary Report to the EPA, Institute of Safety and Systems Management, University of Southern California, January 11, 1986.
21. Dunwoody, Sharon. In "Reporting Science: The Case of Aggression". J. Goldstein, Ed. LEA Publisher: London, 1986, pp. 75-76.
22. Dunwoody, S.; Scott, B. Journalism Quarterly, 1982, 59, 52-59.
23. SIPISCOPE, Scientists' Institute for Public Information, 1984, 23, 1-16.
24. Gastel, B. "Presenting Science to the Public"; ISI Press: Phila., 1983.
25. Carson, R. "Silent Spring"; Houghton-Mifflin: NY, 1962.

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Chapter 14

Summary and Discussion

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In the overview to this book Dr. Alvin L. Young presented a striking item of information: when one considers the investment in pest control versus the gain in productivity that results in the United States, a \$9 billion estimate of the value of pest control is obtained. In spite of that we are still losing 30% of our total agricultural production to pests in this country, and an even higher percentage on a world-wide basis (1). This fact embodies the challenge in minimizing the risks of using pesticides: if we could somehow increase by only a few percent the amount of pesticides that reach the target and expand our knowledge base to support effective use of pesticides, we could save, in the first place, billions of dollars, but we would also be minimizing to a significant extent the risk of pesticides to the environment.

Minimizing Risk by Understanding Toxicology

The U.S. Environmental Protection Agency (EPA) requirements impose on us a certain understanding of toxicology before a pesticide can be registered. Dr. Ray Cardona has very effectively presented the specifics of the guidelines for developing toxicology information for registration which were adopted by EPA several years ago. The question is raised, however, whether the rigidity, or lack of flexibility, of those guidelines prevents or in any way inhibits the application of new technologies, including biotechnology, to the development of the new compounds which will be needed in the future to lower or minimize the risk of pesticide use.

The question of our focus on acute versus chronic toxicology is a problem area in the continued use of pesticides. We have put our major research and data-gathering emphasis in the past on acutely toxic chemicals and acute toxicity problems. When we started considering chronic problems, as with the chlorinated hydrocarbons, we discovered major problem areas. That led to quite significant changes in our perceptions of the ways we ought to be using pesticides in general, certainly insecticides specifically.

A question which is perhaps just as significant as the switch from concern about acute toxicology to chronic toxicology, is the

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coming emphasis on the question of interactions. Very little is known about interactions of pesticides in the environment, with each other or with endogenous chemicals. Dr. Raymond Yang gave several examples of some interactions that could be harbingers of what may be occurring in the environment that have not been recognized. The need for research to address this matter is great.

Several chapters present information on the possibilities for simulation and modeling, both in terms of understanding the data which have already been accumulated, but also in terms of developing new techniques for discovering new compounds, based on information which has been obtained from structure-activity relationship studies. If we can predict the effects of compounds before we actually put them into the field, obviously the risk of the toxicology of these compounds to both agricultural workers and consumers of the products, and to the environment, will be minimized.

Minimizing Risk by Understanding the Pest

Understanding the biochemistry and physiology of the pest and exploiting that as the search for new compounds proceeds is receiving much attention today, as well it should. In the past, that generally has not been the case. It was just 20 years ago that we talked about the "spray and count" pest scientists, who really knew very little about the habits of the pest; all they were really concerned about was how many would die given a specific dose of pesticide as applied in the field. We have now progressed beyond that approach, as several chapters point out.

The interaction of the pest with its environment must be taken into account in order to use pesticides optimally. We have, of course, considered the environment in development and use of pesticides, but frequently we have been more concerned with the non-target species which also happen to inhabit the pest's environment and not so much with target species-environmental relationships. If we knew more about the way pests behaved in the environment, we would be able to direct pesticides to their targets better and in a timely manner that would give more effective results.

In addition, we are increasingly concerned about pest resistance to pesticides, which has been a matter of some concern for a long time. The intriguing idea that we might be able to exploit and overcome the pests' resistance mechanisms was discussed. By taking some of the pests' traits which are negative for resistance into account, one might "trick" the pest as it develops resistance to one pesticide by using another compound in conjunction with it that would exploit these negative resistance factors and thus overcome the resistance. A recent National Academy of Science report (2) has emphasized the need to focus more resources on understanding and overcoming the resistance problem.

Minimizing Risk by Understanding the Chemical

In order to minimize the risk of pesticides by understanding the chemicals, Dr. James Seiber maintained that we must understand the chemodynamics. We have only just begun to consider factors such as water solubility, octanol-water partition coefficients, soil

adsorption constants, etc., to understand the behavior of existing compounds in the environment and to try to design better compounds in the future. If we had really paid attention to the chemical and physical properties of pesticides and stopped to think about some of the things that should have been obvious to us, and were obvious once we did think about them after the crises had erupted, we would probably not have used certain compounds under some circumstances. We had a very dramatic example of that in the case of the use of aldicarb on Long Island. Following extensive use of this highly toxic insecticide for the control of the Colorado potato beetle, it was noted that the material readily leached through the coarse sandy soils characteristic of Long Island and finally reached the ground water. Contamination of the only source of drinking water for the area must be classed as a severe environmental crisis.

Another illustration of our failure to use existing knowledge is presented by Dr. Wyman Dorough in the discussion of mammalian and other animal metabolism of pesticides. Much of what we know about metabolism of pesticides in mammals and other organisms was not predictable prior to the development of the chemicals. We have now come to the point, however, where we can make some predictions. Although our regulatory approach requires us to actually do the research, we must also think about the implications of what we are learning. Then we could apply our knowledge to the design of new compounds and for minimizing the risk of both old and new compounds. Information gained about comparative toxicology and comparative metabolism of these chemicals will minimize the risk to the ultimate non-target species, man.

Finally, the ultimate benefit of the accumulation of this chemical information is to apply it, using some of the really elegant new computer techniques now available, to the design of new compounds that will nicely fit the specific biochemical target sites of pest species, while at the same time not fitting targets, or similar targets, of non-pest species. Thus we can achieve what might be called the ultimate selectivity.

Minimizing Risk by Understanding the Hazards of Pesticides

One might consider two separate populations of people who need to understand pesticide hazard: those who are occupationally exposed and the general public. The hazards of pesticides, and specific steps taken to minimize them, have been the focus of environmental activist groups, farm workers' unions, and the Cooperative Extension Service. Great strides have been made toward minimizing exposure of workers to pesticides, both by providing protective clothing and improving the design of application equipment, and by information programs designed to encourage workers to improve their own work practices to minimize their own exposure.

Communication of the realistic hazards of pesticides to the general public has been more difficult. Dr. Ronald Hart's statement that risk assessment techniques must be upgraded to use them more effectively, is an illustration. The approach using several orders of magnitude difference in numerical risk assessments simply is untenable when one tries to apply this in practice and communicate the idea to the public. Clearly, the techniques of risk

assessment must be brought into focus before the results will be useful. The application of such techniques to regulatory decision-making is a major public policy issue.

Attention must be called to the NPIRS system (3), the National Pesticide Information Retrieval System, which has been established to provide information on the registration of pesticides, specifically to the scientific, regulatory, and extension communities. NPIRS might be called upon by the news media to provide some of the background information which is presently lacking in the short time-lines which face reporters in collecting information on late-breaking stories. This is an on-line data base which requires only a telephone and a computer terminal to access and a little money for access charges. The system can provide the basic background information which should be translated into an understanding of the hazards associated with the use of pesticides.

Finally, although mass media rarely change existing attitudes, they do strengthen public perception. Scientists and journalists must work together to promote a better informed public sector. Accuracy, objectivity, and sourcing are identified as problems. The scientific community must endeavor to understand the media process and the constraints faced in covering scientific issues.

Commentary

Following the conclusion of the formal paper presentations in the Symposium on which this book is based, four individuals were asked to comment on the ideas and information presented from their own unique perspectives.

Anne E. Lindsay, Chief of the Policy and Special Projects Staff, Office of Pesticide Programs, U.S.E.P.A., speaking from the perspective of a regulatory official, was struck by the amount and complexity of information needed to answer what seem to be simple questions pertaining to whether we can use a product safely or whether food treated with pesticides is really safe to eat. As a regulatory agency, it is EPA's role to perform that task on the public's behalf: to take a lot of different kinds of information, evaluate it, and produce a very basic, public decision that a pesticide can or cannot be used.

The actual process of reaching such decisions is largely unknown outside EPA, and may seem to be a "black box." EPA engages in all three of the basic approaches to pesticide safety discussed in this book, namely hazard identification, exposure assessment and reduction, and communication efforts. Hazards are identified by requiring extensive testing before a pesticide is registered for use. One hundred or more individual tests for health and environmental effects are now required, depending on proposed uses. These requirements can be a "black box" for the industry, but EPA is trying to correct that impression by encouraging companies to consult with them early in the process to clarify any data development problems which might arise before making expensive testing commitments which might be inappropriate or unnecessary.

In the area of exposure, we are dealing with the variable on which we can really have an effect through regulation (unlike

toxicity of a chemical). EPA is finding also in reviewing older pesticides that exposure was often not very carefully evaluated in the past, and applicators are frequently found at greater risk than previously thought. We can reduce the risk of exposure through changes in application rates and methods, geographic restrictions, protective clothing and other label precautions, and restricting use to trained applicators. The question of the adequacy of label precautions must be addressed.

Carol N. Scott, Executive Director of the Committee to Coordinate Environmental Health and Related Programs, U.S. Department of Health and Human Services, speaking from the perspective of the public policy analyst, noted that in an ideal political and social climate a risk assessment should, in advance of a crisis, present to knowledgeable risk managers a quantitative risk assessment which expresses all of the uncertainties incorporated in the assumptions. However, too often the crisis occurs first, and the public-press-politician synergistic relationship takes over, as in the case of the ethylene dibromide situation, or someone leaks misinformation to the press, as in the case of Alar, or politics takes over, as in the case of the controversy over the appropriate ways to use and regulate biotechnology.

The results of conducting the process of risk management in the public arena are all too often irrational decisions without the benefit of good scientific data. This can result in the commitment of resources and the expenditure of large sums of money to "control" emotionally volatile risks to the benefit of almost no one.

We cannot hope to change the press or the politicians, but we can educate the public. Risk managers should develop public policies in advance of the next crisis. No one in the public realm wishes to subject the public to unnecessary risk. But a small risk with a large benefit may be quite acceptable to the public, if the public is effectively presented with all the data. This emphasizes the need for effective public communication.

Dr. Donald D. Kaufman, Chief, Soil-Microbial Systems Laboratory, Agricultural Research Service, U.S.D.A., Beltsville, Maryland, expressed his belief that the bench scientist involved in pesticide research has in the past had too provincial a perspective with respect to the risks associated with pesticide use. Frequently these scientists are working with the chemicals early in the development process before introduction to the market. The bench scientist has a perspective on what the realistic risk of a future pesticide is and how that risk might be perceived. This perspective should be communicated and factored into the regulatory decision-making process. In the past this has not always been done effectively.

Have we asked the right questions? Have we asked the right questions at the right time? The pendulum seems to have swung back from past practice, and now many questions which should have been asked, are being asked. It is now acceptable for the researcher, the developer, the regulator, and the policy analyst to sit down together, consider the data, and make decisions. Rather than focusing on the negative, which is society's propensity, we need to take a balanced approach, using all the data available, both the positive

and negative aspects of a candidate pesticide's behavior, to develop a realistic risk assessment.

We need to research how to use effectively our existing pesticides, how to conserve them, and how to fit them into new strategies for pest control. In the past it was difficult to consider the use of pheromones, other alternative controls, or biological controls of pests because there was no funding incentive for development. Now it is becoming a very realistic part of our research because it has become apparent that there are fewer and fewer new pesticides coming into the market. We must literally look at how we can get basic principles back into the system in terms of control and save some of the pesticide chemicals we have. We feel that we are in danger of losing a major part of them, and we cannot afford that. Wise use practices and intelligent assessment of the risks of pesticide use will permit us to prolong their life. Research is essential to achieve this.

Dr. James M. Witt, Extension Specialist in Chemistry and Toxicology, Department of Agricultural Chemistry, Oregon State University, Corvallis, expressed his feeling that communication is a difficult art. The final and most important aspect of the search for knowledge is its communication. This is especially so in the area of risk from pesticides, where there are many simple assertions and questions but no simple answers. The nature as well as use patterns of pesticides and consequently their associated risk is governed by how they are regulated. This in turn is governed by both the regulating agency's perceptions and the perceptions of the public. Dr. Young identified an important reality when he quoted the ancient maxim, "Perception is more important than reality."

The argument of risk from pesticides is expressed in the language of toxicology and chemistry, but the issue is often one of philosophy. In our communication we must first teach the elements of toxicology and chemistry necessary for understanding and interpretation of the reality of the data, provide an accurate summary of the data, and attempt to isolate or separate the toxicological arguments and risk evaluations from the philosophical and emotional arguments. This is not easy; few audiences have either the time or interest requisite to understanding the elements of risk evaluation. We have consistently failed to teach the concept of dose/response - that as you increase the dose, you increase the severity, frequency, and nature of the effects and as you decrease the dose, the opposite happens.

We can identify pesticide risks and we can reduce them. But can we adequately define to what level we wish to reduce them? This is a philosophical as well as a social issue. At present there may be no socially acceptable risk from chemicals similar to the acceptable risks from food-borne infections, occupational injuries, or injuries incurred around the home. The public often occupies an extremist position - from "It can't hurt you; I've bathed in it," to "I don't care what you say, I don't want any exposure; I want zero risk."

Society will decide what is a socially acceptable risk. Toxicologists should learn to communicate with the public to provide the basis for such decisions. The chemical risks are summarized in

terms of margins of safety (for obvious chemical injury) and probability (for injury which might occur some time in the future). Until we can communicate the significance of a margin of safety of 10 versus 1,000, or a probability of 1×10^{-4} versus 1×10^{-9} , the social decisions on acceptable risks will be made from fear on the basis that any level of exposure is significant and all risks are equal.

Conclusion

This book, I believe, has identified many areas where we need substantially more data, highlighted some problem areas, and certainly given us new ways to look at some problems we have today. If the solution to a problem lies first in its identification, I believe we have taken a positive step forward.

Literature Cited

1. Ware, George W. "Pesticides: Theory and Application"; W. H. Freeman and Co.: San Francisco, 1983; p. 5-6.
2. National Research Council. "Pesticide Resistance: Strategies and Tactics for Management"; National Academy Press: Washington, D. C., 1986; 471 pp.
3. National Pesticide Information Retrieval System, an on-line data base managed by Purdue University, West Lafayette, Indiana.

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