PESTICIDES

1. Introduction

A pesticide is any substance or mixture of substances used to control living organisms that cause damage or economic loss, or transmit or produce disease, including such animals as insects or mice, unwanted plants, microorganisms such as those causing plant disease or viruses. Early pesticides were simple, often toxic inorganic compounds having a broad spectrum of activity, and often applied indiscriminately at high rates. Newer crop protection agents are generally complex organic chemicals, which may bind to a specific enzyme receptor. Some commercial pesticides are biological agents.

1.1. History. Devastation caused by pests has troubled both ancient and modern humans often changing the course of history. The bubonic plague in Europe and the great potato famine in Ireland were both caused by pests. In 1884, grasshoppers caused such a food shortage in the midwestern United States that a national disaster was declared.

Early attempts to control fungus on foliage relied on dusting with sulfur (qv), and Paris Green (cupric acetoarsenite) was applied on a large scale to kill the destructive Colorado potato beetle. Another highly toxic mixture used as a crop protectant was London Purple containing arsenic trioxide, aniline, lime, and ferrous oxide. By the early 1900s, chemicals used to control insect infestations included Bordeaux mixture (lime and copper sulfate) for downy mildew on grapes, nicotine sulfate for sucking insects, and lead arsenate and calcium arsenate for chewing insects. Increasing use of such toxic chemicals led to the passage of the Federal Insecticide Act in 1910, the first of many rules and regulations governing the sale and use of these pesticides, which were designated economic poisons at that time (see FUNGICIDES, AGRICULTURAL; INSECT CONTROL TECHNOLOGY).

Plants can also be pests that need to be controlled, particularly noxious weeds infesting food crops. Prior to 1900, inorganic compounds such as sulfuric acid, copper nitrate, sodium nitrate, ammonium sulfate, and potassium salts were used to selectively control mustards and other broadleaved weeds in cereal grains. By the early 1900s, Kainite and calcium cyanamid were also used in monocotyledenous crops, as well as iron sulfate, copper sulfate, and sodium arsenate. From 1915 to 1925, acid arsenical sprays, carbon bisulfate, sodium chlorate, and others were introduced for weed control use. Total or nonselective herbicides kill all vegetation, whereas selective compounds control weeds without adversely affecting the growth of the crop (see HERBICIDES).

When in World War II American farmers were called on to feed half the world population, research efforts led to development of more effective compounds. The first organochlorine insecticide, dichlorodiphenyltrichloroethane [50-29-3] (DDT) was soon followed by mixed isomers of benzene hexachloride (BHC), principally gamma-hexachlorocyclohexane [319-86-8] (lindane). Other insecticides included organophosphorus derivatives such as parathion [56-38-2] (*O,O*-diethyl *O*-4-nitrophenyl phosphorothioate) and malathion [121-75-5] (diethyl (dimethoxythiophosphorylthio)succinate), and carbamates such as carbaryl [63-25-2] (1-naphthyl methylcarbamate). Also recognized at this time were the plant growth regulating properties of compounds such as 2,4-D

[94-75-7] (2,4-dichlorophenoxy acetic acid) and MCPA [94-74-6] (4-chloro-2-methylphenoxy acetic acid) (see GROWTH REGULATORS, PLANTS).

In early 1995, the U.S. Environmental Protection Agency (EPA) summarized its role in the regulation of pesticides:

> All pesticide products created for use by homeowners and farmers in the U.S. must be registered by EPA. This process includes extensive testing to determine the toxicity of the product and its potential for threatening the health of people, wildlife, and the environment. Laws and regulations apply to all pesticides, including disinfectants, fungicides, insecticides, and weed-killers. When a pesticide is registered by EPA, the manufacturer is required to label it with specific instructions as to use, disposal, and special precautions. The label requires agricultural employers to provide their employees with many safety protections. If later scientific developments indicate unsuspected dangers, the registration can be suspended, canceled, or amended. EPA is expediting re-examination of the hundreds of pesticides registered during the Agency's early years using sound scientific standards. The Agency sets specific limits on pesticide residues in food, the limits depending on toxicity, and the quantity of those residues. Once EPA establishes the levels of pesticide that may remain on food, the Food and Drug Administration (FDA) and the Department of Agriculture (USDA) monitor the levels.

The original Insecticide Act of 1910 was replaced in 1947 by the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), which also regulated agents used to control fungi and animal pests such as rats and mice (see FUNGICIDES, AGRICULTURAL). In 1959, an amendment added herbicides (qv), nematicides, plant growth regulators (see GROWTH REGULATORS, PLANTS), defoliants, and desiccants. Another amendment in 1962 declared certain forms of plant and animal life, and viruses, to be pests under certain conditions. Principal revisions to FIFRA were enacted in 1972 and in 1988. Most of the genetically engineered microorganisms that are used in the environment are pesticides that are regulated by EPA, using existing regulations under the pesticide law FIFRA (7 U.S. Code 136). A number of naturally occurring microorganisms have been used for decades as pesticides because their natural properties give such strains the ability to selectively kill or inhibit growth of certain agricultural pests. More recently, genetically modified or engineered microorganisms have also been used or proposed as pesticides. Using principles established for the earliest (nonengineered) microbial pest control agents, microbial pesticides are regulated by EPA under the same regulations used for chemical pesticides. Some of the required testing data is different for living biological agents, but for genetically modified biopesticides the key issue became the identification of those modified microorganisms that required additional oversight at the level of small-scale field–testing. Types of pesticides regulated under pesticide laws include the following (see also SOIL CHEMISTRY OF PESTICIDES).

acaricides	algicides	animal dips
antimicrobials	attractants	avicides
bactericides	baits	biological agents
defoliants	desiccants	disinfectants
fumigants	fungicides	herbicides
insect growth regulators	insecticides	ixodicides
larvicides	microbiale miticides	molluscicides
nematicides	pheromones	piscicides
plant growth regulators	repellents	rodenticides
safeners	seed protectants	soil sterilants
synergists	wood preservatives	wound protectants

Each pesticide product used in the United States must be evaluated and registered by the EPA. Labeling must be approved for each use and each product must be registered in each state where it is sold and used. Pesticides are used for many diverse purposes, including the following.

Crop Protection: insects and weeds in fields, gardens, greenhouses, nurseries

Disinfection: bacteria in homes, hospitals, on medical and dental equipment

Domestic Animals: pests on dairy and beef cattle, sheep, goats, hogs, horses, poultry, and pets such as dogs, cats, and birds

Forest Restoration: conifer release; selective weed and brush control

Fuel Preservation: diesel oil, gasoline, heating oil, jet engine fuel

Fumigation: stored fruit and grain; quarantine of export and import crops

Indoor Pests: cockroaches, fleas, flies, lice, carpet beetles, clothes moths, silverfish, centipedes, millipedes, termites; mice, rats; mildew

Outdoor Pests: biting flies, fire ants, hornets, mosquitoes, ticks, wasps; mice, moles; snails, slugs; mildews, molds, mosses

Pests in Aquatic Sites: weeds clogging navigable streams, infesting recreational areas; predator eels and fish; zebra mussels

Post-Harvest Treatment: fresh produce during transportation, distribution, storage

Seed Treatment: prevent spoilage, premature germination, sprout growth

Transport Equipment: insects and rodents carried by trucks, trains, ships, aircraft

Tree Preservation: gypsy moths, caterpillars, borers, leaf miners, mites; wounds from pruning or other damage to bark

Turf Protection: insects and weeds in lawns, parks, golf courses; moles

Vector Control and Plagues: rodents, mosquitoes, tsetse flies, grasshoppers, locusts

Vegetation Control: rights-of-way along fence rows, roads, highways, railroads, utility lines, pipelines

Water Purification: reservoirs, swimming pools, cooling towers

Wood Preservation: construction lumber, fence posts, railroad ties, utility poles

2. Technology

Pesticide use has undergone many changes since toxic products containing arsenic and mercury were dusted indiscriminately in attempts to control pests infesting crops or homes. Advances in pesticide technology have occurred in discovery, production, formulation, and application. The relatively few pesticides available to previous generations of farmers have been replaced by hundreds of highly active agrochemicals targeted to control specific pests in specific sites under specific conditions, such as selective inhibition of certain enzymes in plants and insects.

2.1. Discovery. The traditional approach to new pesticide discovery was to make intuitive changes in the substituents on a promising primary chemical structure. Initially, materials from any source were subjected to screening for biological activity as insecticides, herbicides, or fungicides. Experience showed that, on average, only one in about 20,000 chemicals tested achieved commercialization (1). The challenge to speed up discovery of novel pest control agents effective at low application rates, highly selective in biologic action, and having demonstrably low impacts on the environment, is being met. Optimization in selection of discovery pathways has been enhanced through use of tools such as quantitative structure activity relationship (QSAR) and computer-aided molecular design (CAMD) (see Refs. 2–4).

2.2. Manufacturing. Early pesticides (Table 1) were simple compounds, often easy to make. Some of these have a high mammalian toxicity and present unacceptable hazards to farmers and other agricultural workers. In contrast, the manufacture of new chemical classes of pesticides having complex structures generally requires multistep synthesis processes, any of which can lead to side products or impurities (5–9). Also, concern about the fate of bioactive chemicals introduced into the environment has led to strict regulations on release of vapors into air or of manufacturing waste into effluent water, as well as for proper disposal of containers and wastes from pesticide use (10).

Some of the newer compounds may contain both saturated and unsaturated rings, heteroatoms such as oxygen, nitrogen, or sulfur, and halogen substituents. Others, such as synthetic pyrethroids, may have one or more chiral centers, often needing stereospecific methods of synthesis or resolution of isomers (9). Table 2 lists examples of some more complex compounds. Structures are shown in Figure 1 (11).

2.3. Formulation, Packaging, and Distribution. Advanced technology is needed to formulate pesticides to meet the needs of farmers and commercial applicators who must operate under regulatory constraints for protection of the environment. Basic producers of pesticide active ingredients (AIs) can formulate their own products or have the products formulated by secondary companies. Some formulators also manufacture pesticides that are no longer covered by patents, or import AIs from foreign producers. However, each AI and pesticide product formulated in the United States must be registered by the EPA before

it can be distributed and sold. It must have approved labeling for each recommended use, and must also be registered by each state where it is sold and used.

Much progress has been made. Historically compounds containing arsenic and mercury were applied as dusts in orchards and cotton fields (12). Wettable powders and emulsifiable concentrates were developed that could be applied by spraying, as were granular products suitable for application with equipment used for solid fertilizers. More recently, dry flowable formulations have been developed. These are easier to use, safer for mixer/loaders to handle, and generally perform better than wettable powders. Water dispersible granules are also easier to measure than powders and can be applied using conventional spraying equipment (13–15). Newer innovations include premeasured amounts of concentrates in water-soluble pouches packaged in recyclable paper that applicators can handle without contacting the product (14). Some companies have also developed proprietary encapsulated formulations and slow-release products that allow pesticides to become activated in the soil by trigger mechanisms such as moisture or temperature (see CONTROLLED RELEASE TECHNOLOGY, AGRICULTURAL).

Inert ingredients include solvents, emulsifiers, surfactants (qv), dispersants, stabilizers, preservatives, sequestrants, and other substances. These are not AIs, but aid in ensuring consistent action of one or more AIs in a formulated product. The products must remain stable during storage and distribution under a variety of environmental conditions, ranging from extreme heat in southern regions to subzero temperatures in northern areas. Containers must not rust or leak, must withstand rough handling, and must not collapse when stacked in warehouses. The openings must be childproof and liquid contents should not gurgle or splash when being poured. Totally enclosed systems were introduced by some companies for highly toxic products so the contents could be transferred directly to the mixing tanks, but the special equipment required is often not available at the general user level (14). Since 1990, closed containers have been widely used for bulk packaging units for new potent herbicides.

In 1987, EPA issued a policy statement regarding inert ingredients in formulated pesticide products, and in 1992, published a list of inerts in four categories according to the degree of toxicological concern. Labeling on any product containing a List 1 inert had to be revised to show the statement: "This product contains the toxic inert (name of inert)." Also, the EPA strongly encouraged registrants to substitute or remove from their products any List 1 or List 2 inert ingredients and to submit revised confidential statements of formula to amend these registrations. Updated Lists 1 and 2 are given in annual editions of the *Farm Chemicals Handbook*.

List 2 inerts are considered to be potentially toxic and at high priority for testing. List 3 includes about 800 inert ingredients that have no basis for being on Lists 1, 2, or 4, and List 4 contains inerts which are generally regarded as safe (GRAS). This latter group includes about 300 inert ingredients, such as clays (qv), cookie crumbs, corn cobs, etc.

As more effective pesticides were discovered, application rates dropped from kilograms or liters of formulated products per acre to grams of active ingredient per hectare (g/ha of AI). Highly active, low volume products are easier to ship to dealers, take up less storage space until sold to customers, and are easy to deliver to farmers. The smaller quantities needed can be supplied in

0.5–10 L (pint to 2.5 gal) plastic jugs that can be triple rinsed easily as required before proper disposal, or in some cases can be returned to the manufacturer for reuse (10). On the other hand, the large quantities needed for older, less active products were generally distributed in bulky metal drums, such as those formerly disposed of improperly in ditches, along streams, or in domestic landfills. Bulk shipments of tank-car lots can be made to large-scale commercial applicators having approved diked platforms for mixing and loading, such as for herbicide products to be applied by aircraft.

2.4. Application of Pesticides. Older, less active pesticides were often applied using backpack tanks and hand-held wands to direct the spray onto target weeds and brush. For somewhat larger projects, the sprays were applied from tractor-drawn rigs with booms extending over several rows of field crops or onto adjacent rights-of-way. Tractor-drawn mistblowers dispense insecticides into the foliage canopy of trees in fruit and nut orchards (see NUTS), but this procedure is hazardous to the driver unless the tractor cab is completely enclosed, air-conditioned, and equipped with charcoal filters on air intake vents. Formulations that provide large droplets are necessary for herbicides applied by aircraft, including helicopters, under low wind conditions to avoid drift from the target area. Fogging sprays can be used to control insect pests such as mosquitoes in urban and recreational areas, and destructive insects like gypsy moths in forests. Very dilute ready-to-use products are packaged in aerosol spray cans and are registered for use around homes and institutions.

More efficient application systems have been developed, including longer spray booms to cover a greater area per pass and installation of movable or permanent tanks to dispense the prepared sprays. More sophisticated equipment is essential for accurate and even application of highly effective pesticides, particularly for products formulated for low volume or ultralow volume (ULV) spraying. All equipment must be carefully calibrated to ensure that the rates of application are the same from nozzles located at the end of a boom as from those near the spray rig. In some cases, prescription amounts can be applied according to need, based on computer calculations using satellite systems to outline contours and provide information on moisture and temperature conditions in different areas of large fields (13). Some products have also been approved by the EPA for drip application in irrigation water, or from central pivot sprayers above artesian wells on the circular fields of the arid Great Plains area in the United States.

3. Economic Aspects

World use of pesticides in 1999 was an estimated $28 billion, an increase of 1% from 1994. The market for herbicide-tolerant and insect-tolerant crops expanded to over $2 billion in 1999, representing a total crop protection market of over $30 billion. This increase was mainly a result of market expansions in the United States, Europe, parts of Asia, and Latin America.

By 2004, world pesticide sales declined to $27 billion annually. This represents a real decline in worldwide use of pesticides at an average rate of 1% per year. The decline in pesticide usage will likely be offset by increases in pest- and pesticide-tolerant crops.

The 1999 sales of pesticides are estimated at 2 million metric tons active ingredient, including user-level sales and exports. Volumes were expected to decrease about 1.0–1.5%, while inflation and higher-unit-value products could add a 2–3% rate of growth per year to the dollar value of the industry over this period.

Herbicides are the biggest sector in the U.S. Because planted crops and treated acres have not grown substantially in the last few years, retail price competition continues at a high level. The introduction of herbicide-tolerant crops has resulted in a significant change in the mix of herbicide products used by farmers.

Exports are a major factor in the market for U.S.-produced pesticides, with the 1999 volume reaching an estimated 310 thousand metric tons of active ingredient. Non-U.S. markets currently represent about 30% of total U.S. pesticide production. Imports in 1999 amounted to 82 thousand metric tons of active ingredient (16).

3.1. Aggregate Trends in the United States. Synthetic organic pesticide use grew rapidly from the late 1940s to the early 1980s as farmers treated a greater percentage of crop acres. By the late 1970s, the rate of growth was slower because high percentages of crop acres were treated each year, and large percentage increases were no longer possible. Trends in pesticide use since 1980 have been heavily influenced by changes in crop acreage and the replacement of older compounds with new ones that are applied at lower per-acre rates. During the 1990s, synthetic organic pesticide use grew more slowly than in the years before 1980.

The U.S. Environmental Protection Agency (USEPA) estimated that agricultural pesticide use increased from 366 million pounds active ingredient (AI) in 1964 to 843 million pounds in 1979, fell to 658 million pounds in 1987, but rose to 770 million pounds in 1997 (17) (estimates exclude sulfur, petroleum oil, wood preservatives, biocides, and other nonconventional chemicals). However, analyses that take into account changes in the materials used and their properties, such as toxicity, persistence, and reduced application rates to control the same pests, showed a threefold increase in pesticide use from 1968 to 1992, while the unadjusted USEPA estimates showed that quantities increased 1.6 times (18).

Economic Research Service analysts developed aggregate use estimates for major crops from 1964 to 1997 based on US Department of Agriculture (USDA) pesticide surveys (19,20). Pesticide use on these selected crops grew from 215 million pounds AI in 1964 to 572 million pounds in 1982, fell to 478 million pounds in 1991, and rose to a high of 588 million pounds in 1997 (Fig. 2). Increases in herbicide quantity through 1982, especially on corn and soybeans, and insecticide quantity through 1976, especially on corn and cotton, followed by declines are major factors in these changes. Aggregate pesticide quantity on potatoes and vegetables, as well as the quantity of fungicides and "other pesticides" on all crops, generally increased over the entire period.

3.2. Insecticides. Insecticides were widely applied to such high-value crops as cotton, tobacco, fruits, potatoes, and other vegetables in the 1950s and continued to be applied in the 1990s (20). Insecticide use grew rapidly on other major field crops between 1950 and 1980. Corn acreage treated with insecticides

increased from less than 10% during the mid-1950s to 35% to 45% during the mid-1970s to mid-1980s, before declining to 25% to 30% in the 1990s.

The quantity of insecticide use on the major crops increased from 1964 to 1976 but declined to less than 50% of the 1976 level by 1997. Lower use on cotton and corn was a major contributor to the overall decline. The quantity applied to cotton fell from 73 million pounds AI in 1971, to 64 million pounds in 1976, to 19 million pounds in 1982, and varied between 10 and 30 million pounds since then. The quantity applied to corn fell from 30 million pounds AI in 1982 to less than 21 million pounds AI in the 1990s.

A factor in the reduction of insecticide quantity was the use of newer compounds with reduced per-acre application rates. In the 1960s and 1970s, organophosphates and carbamates replaced organochlorines (20). Synthetic pyrethroids, introduced in the late 1970s, were rapidly adopted and accounted for over 20% of insecticide acre treatments by 1982, but less than 5% of the quantity of insecticide used (acre treatments are the number of acres treated with a pesticide multiplied by the average number of treatments per acre). However, many of the organochlorines, organophosphates, and carbamates were still widely used in the 1990s and accounted for over 90% of insecticide quantity. Synthetic pyrethroids and other newer, low rate insecticides accounted for less than 5% of quantity of insecticide used in 1997 but also for about one-third of insecticide acre treatments.

The introduction and adoption of genetically modified crops since the mid-1990s may influence future insecticide use trends, as well as crop yields and pest control costs. Genes have been incorporated into some crops to produce the *Bacillus thuringiensis* (Bt) toxin that helps control Lepidopteran pests, such as European corn borer (*Ostrinia nubilalis*), a target for insecticides on a small portion of corn acreage; and bollworm (*Helicoverpa zea*); tobacco budworm (*Heliothis virescens*); and pink bollworm (*Pectinophora gossypiella*), major targets for cotton insecticide use. Fernandez-Cornejo and McBride (21) analyzed cotton in the southeastern States in 1997 and found that planting Bt cotton increased yields and profits, had no significant impact on the use of organophosphate and pyrethroid insecticides as measured by acre treatments, but reduced the use of other insecticides. USDA estimated that Bt seed was planted on 19% of corn acreage and 35% of cotton acreage in 2000 (22). However, recent domestic and international controversies about the pest control, environmental, and health effects of this technology, which have limited sales of the commodities, could slow or limit further adoption.

3.3. Herbicides. Herbicide use grew rapidly from the late 1950s until it stabilized in the 1980s. Approximately 10% of corn and wheat and 5% of cotton acres were treated with herbicides in the early 1950s, and, by 1980, herbicide use on corn, cotton, and soybeans stabilized in the range of 90% to 97% of planted acres (20). Winter wheat herbicide use has varied in the range of 30% to 60% of planted acreage since 1986, while spring wheat use has varied between 80% and 95%. Limited data show increases in percent of acres treated for potatoes, peanuts, rice, and sorghum, as well as for other fruits and vegetables.

The estimated quantity of herbicides used on the major crops increased by 8.9 times between 1964 and 1982, but quantities in the 1990s were 15% to 20% lower than the 1982 level. The amount used on corn and soybeans grew from

30 million pounds AI in 1964 to 377 million pounds AI in 1982, before falling to 296 million pounds in 1997. The amount used on cotton, wheat, vegetables, and fruit generally increased between 1964 and 1997, but these crops accounted for a declining share of herbicide use.

Reduced crop acreage, particularly during the 1980s, and lower application rates for commonly used herbicides, such as atrazine, account for much of the decline in herbicide use since 1982. But the change in use to compounds with reduced average application rates per acre also contributed (20). Shares of total quantity of herbicide used declined for phenoxys, phenyl ureas, and benzoics between 1964 and 1997 and for carbamates since 1982, while shares grew significantly for amides and anilines. The share for triazines increased until 1976, then declined, but still exceeded 20% in 1997. New families introduced since the 1970s, such as phosphinic acids, bipyridyls, benzothiadiazoles, benzoxazoles, oximes, pyridazinones, pyridines, sulfonyl ureas, and imidazolinones, account for increasing shares of use. Herbicide groups reported on USDA surveys in the 1960s accounted for over 80% of herbicide quantity in 1997. Phosphinic acids, sulfonyl ureas, and other new groups not reported until 1976 or later accounted for about 40% of acre treatments in 1997. In particular, shares for phosphinic acids and sulfonyl ureas have grown dramatically since 1982.

The introduction and adoption of genetically modified herbicide-tolerant crops may influence future herbicide use trends by encouraging the use of specific herbicides that might otherwise kill the crop. Herbicide-tolerant corn, cotton, soybeans, and canola have been developed. The most commonly planted for these crops are glyphosate-tolerant, but glufosinate ammonium-tolerant corn and bromoxynil-tolerant cotton are also available. The Fernandez-Cornejo and McBride study (21) showed that planting herbicide-tolerant cotton in 1997 increased yields and returns but had no significant impact on herbicide use. That study showed that planting herbicide-tolerant soybeans in 1997 caused a small increase in soybean yields, had no significant impact on soybean returns, increased glyphosate use, had no impact on the use of amide herbicides, and decreased the use of other herbicides as measured by acre treatments. USDA estimated that herbicide tolerant seed was planted on 7% of corn, 54% of soybean, and 46% of cotton acreage in 2000 (22). The adoption of herbicide-tolerant crops may be a factor in the dramatic increase of glyphosate use, the primary phosphinic acid, in the 1990s. However, as in the case of genetically modified crops incorporating Bt genes, domestic and international controversies about environmental and health effects of this technology, and the development of herbicide-resistant weed species, could slow or limit further adoption.

3.4. Fungicides. The estimated quantity of fungicides used on the major crops increased by about 2.3 times between 1964 and 1997. Fruits and vegetables, including potatoes, accounted for over 94% of fungicide use over that time period. Much of the increase took place on potatoes and vegetables; use on those crops was 4.5 times greater in 1997 than 1964. Potato acres treated with fungicides increased steadily from 24% in 1966 to 85% to 98% in the 1990s (20). An estimated 20% of the acres of "other vegetables" were treated with fungicides in 1966 and 1971, and, by the 1990s, much higher proportions of the acreage of many vegetables, such as celery, tomatoes, lettuce, melons, strawberries,

and green peas, were treated. By the early 1970s, a high proportion of fruit acreage was treated, including about 70% of apple acreage and over 50% of citrus acreage, and even higher proportions were treated during the 1990s.

The introduction of newly developed compounds, as occurred with insecticides and herbicides, contributed to lower per-acre fungicide application rates (20). Shares of quantity declined for inorganics (primarily copper compounds) and dithiocarbamates since the 1960s but increased for phthalimides. However, phthalimides, inorganic materials, and dithiocarbamates together accounted for over 90% of fungicide quantity in the 1960s and still accounted for almost 90% in 1997. The shares of newer groups, such as benzimidazoles, azoles, dicarboximides, metal organics, and acyclalanines, accounted for about 10% of quantity but 35% of acre treatments in 1997.

3.5. Other Pesticides. Estimated use of "other pesticides" on the major crops increased by more than fivefold between 1964 and 1997. This category includes soil fumigants, desiccants, harvest aids, and growth regulators. Of the crops included in the estimates, cotton, fruits, and vegetables account for virtually the total amount (estimated use on tobacco, a major use of "other pesticides" excluded from these totals, was 18 million pounds in 1964, 19 million pounds in 1976, and 25 million pounds in 1996). Much of the growth is due to increased use of fumigants on potatoes and other vegetables and use of sulfuric acid as a harvest aid on potatoes. These materials are used at very high per-acre rates and currently account for 85% of the quantity of "other pesticides," but they account for less than 5% of the treated acres. In 1997, about 30 million pounds of sulfuric acid, which was not reported in the early USDA surveys, was applied to only 14% of potato acreage. The quantity of fumigants (methyl bromide, 1,3-D, chloropicrin, and metam-sodium) on crops included in this category increased from about 10 million pounds during the period from 1964 to 1971 to over 60 million pounds in the 1990s. The use of growth regulators, desiccants, and harvest aids on cotton and other crops account for most of the acres treated with "other pesticides."

Use on potatoes and vegetables accounts for most of the increased quantity of "other pesticides," which increased by 15 times between 1964 and 1997. The proportion of potato acreage treated with such materials increased from 9% in 1966 to 55% to 60% in the late 1990s. The limited information available indicates that acreage of other vegetable crops treated with these materials has also increased. Cotton is a major site for growth regulators and harvesting aids; the quantity used increased 50% from 1964 to 1997, which is a small proportional increase as compared with the increase for potatoes and vegetables. The percentage of cotton acreage treated increased from 26% in 1966 to over 60% in the late 1990s. The increase in percentage of acreage treated was accompanied by changes in use from older materials, such as arsenic acid, sodium chlorate, and tribufos, to new ones applied at lower peracre rates, such as ethephon, mepiquat chloride, thidiazuron, paraquat, and dimethepin. Growth regulators are also used on various fruit crops including apples, pears, lemons, and tart cherries.

4. Regulatory Policy

Pesticide use has grown within the context of regulatory law and policy, which have been shaped by changing public attitudes and political pressure. The regulatory process defines what pesticides can be used and what use practices are legal. In the United States, there have been many public concerns about potential health and environmental hazards of pesticide use, including farm worker safety, cancer risks, birth defects, wildlife mortality, water quality, endangered species, and food safety. One important issue has been the balance of production benefits, such as higher output or lower costs, against the health and environmental hazards of pesticide use.

Before a pesticide can be used in the United States, it must be registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), administered by USEPA. Registrations specify sites (such as specific crops or livestock) where pesticides can be applied, application rates, methods of use, personal protection requirements, or locations of use for pesticide products. For a pesticide to be registered for use on a food crop, the Federal Food, Drug, and Cosmetic Act (FFDCA) requires residue tolerances, which are limits, or exemptions from tolerance for the raw commodity and all processed foods and feeds, rotational crops, and livestock on which residues can be found. USEPA establishes residue tolerances, while FDA monitors residues and enforces the tolerances. Under these laws, USEPA decides whether or not to register new uses of previously registered or unregistered pesticides, modify existing pesticide registrations, or cancel some or all registered uses of pesticides on the market. The Clean Air Act, Clean Water Act, Endangered Species Act, and the Occupational Safety and Health Act also affect pesticides.

U.S. pesticide regulatory policy recognizes a role for pesticides in crop production but emphasizes protection from hazards. The current regulatory approach is to mitigate risks of pesticide use by modifying use rates and practices, canceling uses of pesticides that do not meet safety standards, and registering "reduced-risk" pesticides. The focus is on meeting safety standards, especially for dietary risks, rather than on weighing risks and benefits.

Over time, regulatory requirements have influenced the types of pest control products developed and submitted for registration, as well as the structure of markets for those products. Ollinger and Fernandez-Cornejo (23) estimated that the research and development for a new pesticide takes 11 years and costs between $50 and $70 million. Their results indicated that regulation encourages the development of less toxic pesticide materials, such as biological pesticides; discourages new registrations; encourages firms to abandon pesticide registrations for minor crops; and favors large firms over smaller ones. Important impacts have been the development and registration of genetically modified crops and pesticides with low application rates.

4.1. A Review of Changing Legislation. From the early 1900s, before pesticide use was widespread, until the 1960s, when pesticide use was growing rapidly, U.S. pesticide legislation facilitated adoption of the new technology by regulating product effectiveness, labeling contents, and warning users about acutely toxic ingredients (24,25) (Table 3 lists important pesticide legislation).

Concerns about the presence and safety of chemical residues in food emerged in the 1950s, resulting in FFDCA amendments in 1954 and 1958 to require pesticide residue tolerances for raw food and feed commodities and processed products. The 1958 amendment included the Delaney Clause that prohibited food additives found to induce cancer in humans or animals.

Public concerns about potential environmental hazards of chemical use emerged in the 1960s, when pesticide use was growing rapidly. FIFRA amendments in the 1960s and 1970s focused the regulatory process on protection from health and environmental hazards. These laws created a role for considering risks and benefits in registration decisions. The result was a series of formal reviews of the risks and benefits of registered pesticides.

Reregistration became a major focus in the 1980s and 1990s. The review of previously registered pesticides was identified as reregistration in the 1978 amendments, and 1988 amendments were passed to speed the process and provide additional financial resources through fees. During this process, EPA identified many pesticide risk issues, and registrants, in many cases, voluntarily changed labels or canceled uses to meet safety standards without going through a costly formal review. An important impact was to focus the regulatory process on the data and procedures of risk assessment and to reduce the role of formal risk and benefit comparisons.

During the 1980s and 1990s, there were increasing public concerns about the health effects of pesticide residues in food, especially to children, the enforcement of the Delaney Clause, and the availability of pest control alternatives for fruits, vegetables, and other small acreage crops. These concerns led to important provisions in the Food Quality Protection Act of 1996 (FQPA).

4.2. Dietary Risks, the Delaney Clause, and the FQPA. Two important National Academy of Sciences reports recommended changes in pesticide legislation. One described the unique sensitivity of children to pesticide risks and recommended changes in risk assessment procedures (26). The other described the regulatory confusion created by the "Delaney Paradox" where a no carcinogenic-risk rule applied to residue tolerances for pesticides that concentrate in processed food (the Delaney Clause) and a benefit-risk rule applied to those that do not concentrate (27). Under its policy, USEPA would revoke or deny tolerances for a raw commodity if the tolerance for a processed product was revoked or denied under the Delaney Clause, leading to the cancellation of the pesticide's registration for those crops. The National Academy of Sciences recommended a negligible risk rule for pesticide residues because strict application of the Delaney Clause would reduce USEPA's flexibility to reduce dietary cancer risks. Strict application would have prevented registration of new pesticides with slight cancer risks that could displace more hazardous materials and focus regulatory activity on negligible dietary risks instead of other, more significant health risks.

The FQPA resolved the Delaney Paradox, created new dietary risk standards, and required a reassessment of residue tolerances against the new standards. Pesticides are no longer subject to the Delaney Clause but to a uniform safety standard for raw and processed foods: "a reasonable certainty of no harm from aggregate exposure to the pesticide chemical residue." For carcinogens treated as nonthreshold effects, this standard means negligible risk, instead

of no risk, for both raw and processed foods. For threshold effects, the standard is satisfied if exposure is lower by an ample margin of safety than the no-effect level.

In setting tolerances, USEPA must consider dietary exposures to a pesticide from all food uses, drinking water, and nonoccupational exposure, such as homeowner use of a pesticide. USEPA must also consider increased susceptibility of infants and children or other sensitive subpopulations and can use an additional 10-fold margin of safety in setting residue tolerances to protect infants and children. USEPA must consider the cumulative effects when two or more substances have a "common mechanism of toxicity," a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. By 2006, USEPA must review all residue tolerances in effect when the law passed, giving priority to pesticides that may pose the greatest risk to public health. If risk of a pesticide exceeds the standard, USEPA will reduce or revoke tolerances for uses of the pesticide until the standard is met. If a common mechanism of toxicity is identified for a group of pesticides, the acceptable risk for one pesticide can be reduced by risks from other pesticides.

The FQPA changed the role of benefits of use in pesticide regulatory decisions. Benefits can no longer be considered when setting new residue tolerances. When evaluating existing tolerances, benefits can justify, for a limited time, an aggregate dietary cancer risk for a pesticide that is slightly greater than negligible. But to qualify, the pesticide must protect consumers against adverse health effects greater than it creates or it must prevent a significant disruption in the domestic food supply. Although the role of benefits of use estimates for justifying higher dietary risks is likely to be small, benefits can be considered to decrease the economic impact of risk reduction decisions (28).

4.3. Minor Use Pesticides. Growers of minor crops, such as fruits, nuts, and vegetables, argued that the pesticide regulatory process created inadequate incentives to register and reregister pesticides for use on those crops. These small-acreage crops represent relatively small markets for pesticides, except for fungicides and some "other pesticides," even though per-acre crop values and use of pesticides are often very high. Registrants have a financial incentive to register or reregister pesticides for major crops, such as corn, soybeans, cotton, and wheat, which represent large markets for pesticides, and to cancel minor uses as a cost-effective way to reduce risks to acceptable levels. A registrant might also decide not to incur the costs of conducting toxicology tests to retain registrations, so that minor use registrations may be canceled for procedural reasons. Similarly, registrants often choose to pursue new registrations for major crops, but not for minor crops, to avoid the cost of registration and low potential for sales.

The FQPA created incentives to register pesticides for minor uses by providing additional time to submit registration data, waiving data requirements in some cases and extending the period of exclusive use of data by the registrant. Minor uses were defined as crops grown on less than 300,000 acres or where use provides insufficient financial incentive for registration (but other conditions must apply). While these provisions reduce costs of registering pesticides for minor uses, it is unclear if they will offset the loss of registrations resulting from tolerance reassessment (29).

4.4. Role of International Organizations in Pesticide Regulation. Most developed countries have established laws and regulations that outline policies for the production, registration, and use of pesticides. Much as in the United States, these determine the risks and benefits associated with pesticides, and promote safe and effective use. The harmonization of regulatory standards has become of greater importance with the expansion of world agricultural trade and the movement of agricultural commodities among nations, particularly in compliance with the General Agreement on Tariffs and Trade (GATT) adopted in 1994.

The U.S. GAO has also reviewed pesticide standards and regulations among member countries of the expanded. European Union and the Organization for Economic Cooperation and Development (OECD). A high degree of uniformity exists among the surveyed nations, including the United States, with regard to the kinds of test data required to register food-use pesticides. However, similar data requirements do not necessarily mean that countries receive the same information about a pesticide product or evaluate it in a similar manner. For example, there is a divergence of scientific opinion concerning what regulatory approach is most appropriate for dealing with substances that show some oncogenic effects (tumors) only at very high, near-lethal doses as compared to those that cause cancer through a genotoxic mechanism (31). Also, most other countries do not require analyses of commodities for pesticide metabolites and do not include metabolite residues in the expression of tolerance levels (32,33).

There is strong support for harmonization of pesticide regulations among countries to avoid having to repeat expensive studies to meet each country's requirements. Steps toward this goal were marked by development of OECD's Guidelines for Testing of Chemicals and their Principles of Good Laboratory Practice updated in 1992 (74) and by issuance in 1991 of the European Council Directive 91/414/EEC known as the Registration Directive (62). In some cases, new data is expected to be needed to fill gaps which arise as a result of new data requirements imposed by the Directive (34).

Several other international agencies also take part in activities related to the safe use of pesticides, particularly in developing countries (35). The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme (UNEP), the World Health Organization (WHO), and the International Labour Organization (ILO). IPCS conducts and disseminates evaluations of how chemicals can influence the environment and human health. IPCS staff also develop different methods of assessing risk related to chemicals using data from laboratory, epidemiological, and related studies. The principles, concepts, and definitions used by panels of experts selected by the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) to evaluate residue data and toxicology data, respectively, were published in 1990 (36). These expert panels hold an annual joint meeting on pesticide residues (JMPR) to review selected pesticides using data from all study reports provided by manufacturers and governments. The FAO panel recommends maximum residue limits (MRLs) for each pesticide in those commodities of importance in international trade. The WHO panel proposes an acceptable daily intake (ADI) for the pesticide, having an adequate margin of safety (generally 100-fold or more) over the lowest no-effect-level (NOEL) observed in the toxicology studies. Monographs summarizing all the data used in

the evaluations are prepared and distributed to governments around the world. The recommended MRLs are reviewed by delegations from many countries during annual meetings of the Codex Committee on Pesticide Residues (CCPR). These MRLs are revised, if necessary, and are eventually accepted by the Codex Commission as standards for foodstuffs in international trade. This process can take several years, mainly because of different pesticide use patterns in various countries, depending on climate, the pests to be controlled, and the relative prices of available pesticides.

FAO has also developed a series of guidelines related to pesticide control that cover legislation, registration, efficacy data, post-registration surveillance, and environmental criteria (34). Its Working Party of Experts on the Official Control of Pesticides recommends specifications and methods of analysis for pesticide technical products and formulations to help prevent distribution and sale of illegal or fraudulent products in remote areas. In 1985, FAO adopted the International Code of Conduct on the Distribution and Use of Pesticides (78). FAO also shares operational responsibility with UNEP for overseeing the Prior Informed Consent (PIC) program, which was incorporated into the Code of Conduct in 1989. PIC is based on the principle that chemicals that are banned or severely restricted for health or environmental reasons should not be exported without the consent of relevant authorities in the recipient country. Although a long list of pesticides was initially proposed for PIC, an international panel reduced the number to those that are truly hazardous. However, the EPA's pesticide export policy has been strengthened (40 CFR 168.65–85) by requiring the exporter to notify the recipient if the product is not registered in the United States. Moreover, the EPA must receive a signed acknowledgment statement from the responsible authority in the recipient country before the product can be shipped.

4.5. EPA Biotechnology Regulation. EPA is using Toxic Substances Control Act (TSCA) to regulate the microbial production of certain chemicals or enzymes not regulated elsewhere in the government, and planned introductions of microorganisms into the environment that are not regulated under other federal statutes. TSCA (15 U.S. Code 2601) is a law requiring manufacturers to notify EPA at least 90 days before commencing manufacture of any "new" chemical, that is, one that is not already in commerce for purposes not subject to regulation as a pesticide or under the food and drug laws. In the Coordinated Framework, EPA decided to use TSCA in this same "gap-filling" way to capture those microorganisms that were not regulated by other federal agencies. The primary areas that therefore became subject to the TSCA biotechnology regulations were (*1*) microorganisms used for production of non-food-additive industrial enzymes, other specialty chemicals, and in other bioprocesses; (*2*) microorganisms used as, or considered to be, pesticide intermediates; (*3*) microorganisms used for nonpesticidal agricultural purposes; and (*4*) microorganisms used for other purposes in the environment, such as bioremediation.

Procedures under the TSCA biotechnology regulations are similar to existing practice for new chemical compounds. Manufacturers of chemicals new to commerce must file premanufacture notices (PMNs) with EPA at least 90 days prior to the first intended commercial sale, use, or importation. Manufacturers must submit all relevant health and safety data in their possession, and although

EPA has published guidance documents, specifying the types of data that it wants to see in PMN submissions, there are no formal data or testing requirements under TSCA. As applied to new chemical entities, TSCA is a "screening" statute: the 90-day review period is sufficient only to allow EPA to identify chemicals that might pose an environmental or public health risk, and in such case it can take any of several actions to extend the time period and keep the product off the market until suitable data is submitted to show its safety. The large majority of PMNs are approved within the 90-day period after only brief agency review (37).

4.6. Biotechnology Regulation outside the United States. *Canada.* Canada's regulatory approach resembles that of the United States, in that existing laws and regulations are used to regulate biotechnology in a product-specific way. Therefore many products of biotechnology would be regulated in Canada under federal laws, such as the Pest Control Products Act (pesticides), the Seeds Act (plants), and the Fertilizers Act (nitrogen-fixing microbes and inorganic fertilizers). In November 1997, after several years of deliberation, Environment Canada issued biotechnology regulations under the Canadian Environmental Protection Act (CEPA) that are similar in scope and approach to the U.S.EPA's TSCA regulations. Environment Canada will use CEPA to conduct risk assessments of certain biotechnology products that are new to commerce in Canada and are not regulated by other federal agencies. Among products that would fall within the scope of this law would be microbial cultures used for bioremediation.

Environment Canada considers microorganisms as being potentially subject to these "New Substance Notification" (NSN) regulations if they meet the definition of "new substance." Under the NSN regulations, any person who manufactures or imports substances subject to notification must provide a notification package to Environment Canada, which contains certain information specified in the regulations. Environment Canada uses this information to conduct a risk assessment prior to entry into commerce. These requirements are generally similar to those used by the U.S. EPA. Information on the Canadian biotechnology rule is available at www.ec.gc.ca/ccebl/eng/biohome.html and the regulations themselves can be found at www.ec.gc.ca/ccebl/eng/nsnregejan-1597a.html. A Guidelines document that is similar to the EPA "Points to Consider document" can be accessed at www.ec.gc.ca/ccebl/eng/97gle2.html.

European Union. Many countries now in the European Union have adopted biotechnology regulatory policies following the same historical pattern as that seen in the United States: early concerns over public health issues, leading to controls over contained uses, followed by commercial regulation triggered largely by environmental concerns. For example, many European countries have adopted laboratory and manufacturing guidelines similar to the U.S. NIH Guidelines. Most of these laws were initially aimed at laboratory research but some covered commercial activities as well.

Within the European Union these individual country laws have been subsumed by two Union-wide biotechnology directives adopted by the European Commission's (EC's) Environmental Directorate, DGXI, in April 1990 (EC directives are not themselves laws or regulations but require each EU member state to adopt its own implementing laws to achieve the result specified in the

directive). The first is a directive, covering contained uses of genetically modified organisms. This directive is similar to the NIH Guidelines in establishing appropriate procedures, both at small-scale and large-scale, for the use of engineered organisms in contained systems. Regulatory authorities in the member states must be notified or must actually approve certain biotechnology activities.

The other directive DGXI adopted was aimed at outdoor uses of genetically manipulated organisma. This directive required each member state to appoint a regulatory agency with the authority to review and approve environmental introductions within its jurisdiction. Proposals for R&D field tests must address similar environmental issues as are considered in the United States.

The approach adopted by the EU for implementation by its member states differs from the product-specific approach adopted by the United States and Canada. It creates a single biotechnology law to govern all field releases of engineered organisms regardless of end use. In some countries this has created the situation where a GEM might be subject to dual regulation, under the biotechnology law and the product-specific law applying to the use for which the GEM is intended (eg, a pesticide law). This was among the early criticisms levied against the DGXI directive by industry spokespersons.

However, during the years this directive has been in effect it has worked reasonably well to allow for research field tests of genetically modified plants and microorganisms, although certain countries within the EU have been less than hospitable to outdoor uses of GEMs. More recently, however, this directive has allowed individual nations to ban commercial use or shipment of transgenic plants intended for food use, leading to significant uncertainties and consumer concerns throughout Europe about engineered plants in foods. These concerns seem not to be directed to environmental uses of GEMs or plants for the most part (37).

5. Requirements for Pesticide Registration in the United States

Pesticide registration decisions are based primarily on EPA evaluations of test data provided by applicants to ensure that, when used according to label directions, the pesticide does not cause unreasonable adverse effects to human health or the environment. Testing is needed to show whether the pesticide has the potential to cause adverse effects to humans, wildlife, fish, and plants, including endangered species. Potential human risks, which are identified using laboratory tests in animals, include acute toxic reactions such as poisoning and skin and eye irritation, as well as possible long-term effects such as cancer, birth defects, and reproductive disorders. Data on the fate of pesticides in the environment are also required so that scientists in OPP can determine, among other things, whether a pesticide poses a threat to groundwater or surface water (lakes, rivers, and streams). Extensive analytical studies are also required to establish maximum residue levels anticipated from recommended uses in food or feed crops.

FIFRA Sections 3 and 4 pertain to registration and reregistration of pesticides, with clearly defined data requirements as outlined in Title 40 of the *U.S. Code of Federal Regulations* (38). About 120 different studies are listed, most of which are to be done on technical-grade active ingredients (TGAIs). Some must

also be done on formulated products containing inert ingredients. All studies must be done according to a published series of Pesticide Assessment Guidelines (PAGs) and must meet supplementary requirements delineated in various Data Reporting Guidelines (DRGs), Standard Evaluation Procedures (SEPs), and additional guidance documents available from the EPA (see *General References*). All studies must be conducted under conditions to meet Good Laboratory Practice (GLP) standards (40 CFR 160), regardless of whether carried out in-house by registrants or by outside testing facilities. The group of tests that must be performed for each pesticide depends on how that pesticide is to be used. For example, if a pesticide is not used on food or feed crops, extensive residue and metabolism tests in plants and domestic animals might not be required. Similarly, if a pesticide is not used in field crops nor on other extensive outdoor areas, all the environmental fate studies might not be required.

5.1. Product Chemistry. Data and information from product chemistry studies (40 CFR 158.150–190 and Subdivision D Guidelines) are used by the EPA primarily to establish the composition of each manufacturing and user product as commercially produced. Product composition is reported in the Confidential Statement of Formula (CSF) which identifies and gives the amounts of the AI(s), intentionally added inert ingredients, and in some cases the impurities contained in each product. This basic information is needed to assess toxicity to humans and hazards to the environment resulting from use of the product, and to assess the physical and chemical hazards such as corrosiveness, explosiveness, and flammability. Analysis of the technical-grade active ingredient (TGAI) must account for all components present at 0.1% or more, and should account for >98% of the product used for manufacturing the product. The composition of all commercial products must be within certified limits set at the time of registration.

5.2. Residue Chemistry. Residue chemistry studies must be carried out according to 40 CFR 158.240 Subdivision O Guidelines. The data are used by the EPA to estimate the exposure of the general population to pesticide residues in food, and for setting and enforcing tolerances for pesticide residues in raw agricultural commodities or processed fractions that can be used as food or feed. Uses that can result in residues in meat, milk, poultry, or eggs are also considered to be food uses. Samples to be analyzed are obtained from extensive field studies in which the product is applied at the maximum recommended rate and frequency, using the shortest interval between the last treatment and harvest for each crop on which that product is to be used. The analytical method(s) must account for the total residue, including significant metabolites, and must be sensitive to a quantitation limit in the low parts per billion (ppb) range for any item used as food for humans (32,38–43). The method must have been validated by an outside laboratory and by an EPA laboratory, and must be suitable for enforcement purposes when used in monitoring studies conducted by the FDA and USDA.

Section	Topic
171-2	Chemical identity
171-3	Directions for use
171-4(**a**),(**b**)	Nature of residue in plants, livestock
171-4(**c**),(**d**)	Residue analytical method (plants, animals)
171-4(**e**)	Storage stability
171-4(**f**)–(**h**)	Magnitude of the residue in potable water, fish, irrigated crops
171-4(**i**)	Magnitude of the residue in food handling establishments
171-4(**j**)	Magnitude of the residue in meat/milk/poultry/eggs (feeding/dermal treatment)
171-4(**k**)	Crop field trials (for each crop use, in each geographic location)
171-4(**l**)	Magnitude of the residue in processed food/feed
171-5	Practical methods for reduction of residues (by washing, peeling, cooking, etc)
171-6	Proposed tolerance (in each crop and crop by-product)
171-7	Reasonable grounds in support of tolerance petition
171-13	Analytical reference standard(s)

Subdivision O guidelines for residue chemistry data were originally published by the EPA in 1982. These have been supplemented to improve the rate of acceptance by EPA reviewers of the many reports submitted by registrants in support of tolerances for pesticides in foods. The residue chemistry studies most frequently rejected include metabolism in plants, food processing (qv) studies, and studies on storage stability of residues in field samples (44). All tolerances (maximum residue levels) established under FIFRA are listed in 40 CFR under Sections 180 for individual pesticides in/on raw agricultural commodities, 180 for exemptions from tolerances, 185 for processed foods, and 186 for animal feeds.

5.3. Environmental Chemistry. Requirements for data on pesticides in the environment include both laboratory and field studies. The purpose of these studies is to identify and assess the potential hazards associated with each use of a pesticide in the environment in which it is to be used (45). These studies, governed by 40 CFR 158.290 and Subdivision N Guidelines, are generally conducted by or on the behalf of the basic manufacturer, using technical-grade chemical (TGAI), typical product, or a radioactively labeled analytical-grade chemical for studies where a material balance is needed. Studies include the following.

Section	Topic
160-5	Chemical identity
161-1	Hydrolysis studies
161-2,3,4	Photodegradation studies in water, soil, air
162-1	Aerobic soil metabolism studies
162-2	Anaerobic soil metabolism studies
162-3	Anaerobic aquatic metabolism studies
162-4	Aerobic aquatic metabolism studies
163-1	Leaching and adsorption/desorption studies
163-2,3	Volatility studies (laboratory, field)
164-1	Terrestrial field dissipation studies
164-2	Aquatic field dissipation studies: soil and sediment
164-3	Forest field dissipation studies
164-4	Dissipation studies for combination products and tank mix uses
164-5	Long-term soil dissipation studies for products
165-1	Accumulation studies in confined rotational crops
165-2	Accumulation studies in field rotational crops
165-3	Accumulation studies in irrigated crops
165-4	Bioaccumulation studies in fish (laboratory)
165-5	Bioaccumulation studies in aquatic nontarget organisms (field)
166-1	Groundwater monitoring study (small-scale prospective)
166-2	Groundwater monitoring study (small-scale retrospective)
166-3	Groundwater monitoring study (large-scale retrospective)

Controlled laboratory studies are required to examine the persistence, mobility, and potential for accumulation of a pesticide and its primary degradates. Persistence studies examine the behavior of a pesticide as it interacts with water, soil, air, sunlight, and microrganisms. Mobility studies attempt to predict the potential of the pesticide to volatilize into the atmosphere, move into ground or surface waters, or bind to the soil. Accumulation studies examine the potential for a pesticide to accumulate in rotational crops and fish. These studies are designed to help identify which dissipation processes are likely to occur when the pesticide is released into the environment and to characterize the significant degradates likely to result from these processes. From the results of these studies, EPA scientists develop a preliminary, qualitative assessment of environmental fate and transport. The data are then used to design and/or trigger appropriate field studies and to provide parameters needed in simulation modeling of the environmental fate of pesticides (46) (see SOIL CHEMISTRY OF PESTICIDES).

Field studies are required to provide a more realistic picture of the dissipation of the parent compound and those degradates determined to be significant. Under field conditions pesticides are exposed simultaneously to the individual dissipation processes that were examined separately in the laboratory studies. Thus, in field studies, some dissipation processes may be altered due to competition and interaction. Requirements for spray drift data were outlined in draft Subdivision R, but the EPA agreed that data generated on a generic basis by an industry consortium could represent the potential for drifting of individual pesticides.

Data from field and laboratory studies are then integrated to characterize the persistence and transport of the pesticide and its degradates in the environment, and to develop a quantitative environmental assessment (47). Environmental concentrations of the pesticide in different media under various pesticide application and site scenarios are also calculated using computer modeling. These estimates of exposure are used in conjunction with toxicity data to assess the risks to nontarget species associated with the use of the pesticide. Computed risks are used by the EPA to determine the required degree of regulatory action which can include label advisories, use restrictions, denial of registration for a new pesticide, or suspension or cancelation of a registered pesticide. If the data warrant, a pesticide can also be placed in the Special Review process (40 CFR 154) to undergo a more extensive examination of specific problems uncovered during reviews.

Many of these studies require tremendous expenditure of time and effort, and should not be initiated until after consultation with scientists in the EPAs Environmental Fate and Groundwater Branch (45). As for residue chemistry data requirements, the environmental fate guidelines have been supplemented by DRGs and SEPs (46). Although the rejection rate for all environmental fate studies dropped from 54% for pre-1986 studies to 28% for studies submitted after 1988 (48), many problems still remain (49). Critical evaluations of the environmental fate guidelines were conducted by task forces consisting of scientists from the EPA, USDA, industry, and academia, who recommended how laboratory and field studies should be conducted to provide a more scientific basis for environmental risk assessment (45). Available data for many pesticides can be combined in computer modeling systems to predict the environmental behavior of individual pesticides without having to conduct costly and time-consuming field studies that provide only limited additional information for those pesticides (47). The EPA recognizes the need for revising these guidelines (50), and for harmonizing U.S. requirements with those in the European Union (51) and those developed by the International Organization for Economic Cooperation and Development (OECD).

5.4. Hazard Evaluation. *Humans and Domestic Animals.* Data from toxicology studies are used to evaluate hazards to humans from the use of pesticides (40 CFR 158.340 and Subdivision F Guidelines).

Section	Topic
81-1	Acute oral toxicity (rat)
81-2	Acute dermal toxicity (rabbit)
81-3	Acute inhalation toxicity (rat)
81-4	Primary eye irritation (rabbit)
81-5	Primary dermal irritation (rabbit)
81-6	Dermal sensitization (guinea pig)
81-7	Acute delayed neurotoxicity (hen)
82-1(**a**),(**b**)	Subchronic 90-d feeding (rodent, nonrodent usually dog)
82-2	Subchronic 21-d dermal toxicity (albino rabbit)
82-3	Subchronic 90-d dermal toxicity (rat)
82-4	90-d Inhalation (rat)
82-5(**a**)	28-d Delayed neurotoxicity (adult hen)
82-5(**b**)	90-d Neurotoxicity in the mammal (rat preferred)
83-1(**a**),(**b**)	2-yr Chronic feeding study (rat; nonrodent, dog)
83-2(**a**)	2-yr Oncogenicity study (rat)
83-2(**b**)	Oncogenicity study (lifetime) (mouse)
83-3(**a**),(**b**)	Teratogenicity (development toxicity) (rat, rabbit)
83-4	Reproduction study (two generations) (rat)
83-5	Combined chronic feeding/oncogenicity study (rat)
84-2(**a**)	Gene mutations
84-2(**b**)	Structural chromosome aberrations
84-2(**c**)	Other genotoxic effects
85-1	General metabolism (biotransformation)
85-2	Dermal penetration
86-1	Domestic animal safety

The acute studies provide information on health hazards likely to arise soon after, and as a result of a single exposure. These data are used to classify the pesticides as highly toxic (Category I), toxic (Category II), moderately toxic (Category III), or low in toxicity (Category IV), all of which require precautionary labeling using signal words such as Danger and Poison, Warning, or Caution (40 CFR 156.10). Acute data are used to set reentry intervals for farmworkers, to require protective clothing for applicators (40 CFR 170), and determine the need for child-resistant packaging (40 CFR 157). These data also provide information for establishing appropriate dose levels in the subchronic and other studies, and provide initial information on the mode of toxic action(s) of a substance.

Subchronic testing provides information on health hazards that might arise from repeated exposure to a chemical over a limited period of time. These studies can identify target organs and accumulation potential, and are also useful in selecting the maximum tolerated dose (MTD) levels for chronic studies and for establishing safety criteria for human exposure. The chronic toxicity studies are intended to determine the effects of a substance in mammalian species following prolonged and repeated exposure, and should detect effects which have a long latency period or are cumulative. The daily doses given to the animals should span a level that causes no observed effect (NOEL), the lowest effect level (LEL), and the maximum tolerated dose (MTD), just below the level that causes lethal effects. In oncogenicity studies in rats and mice, the test animals are observed for the development of neoplastic lesions (cancer) or benign tumors

during or after feeding doses including the MTD over their normal lifespans (51,52).

The developmental testing sequence is designed to determine the potential of the test substance to induce structural and/or other abnormalities in the fetus as a result of exposure to the mother during pregnancy. The two-generation reproduction test is designed to provide information concerning the general effects of a test substance on gonadal function, estrus cycles, mating behavior, conception, parturition, lactation, weaning, and the growth and development of offspring. The data generated from these studies are the NOEL, LEL, and the developmental toxicity potential, as well as the margins of safety for dietary and nondietary exposure.

The purpose of mutagenicity testing is to assess the potential for the pesticide to affect the qualitative or quantitative integrity of the mammalian cell's genetic components. The assays are selected to detect the capacity of a chemical to alter genetic material in cells, to determine the relevance of these mutagenic changes to mammals, and when mutagenic potential is detected, to incorporate these findings in the assessment of heritable effects, carcinogenicity, and possibly other endpoints. Other special tests are required as needed, such as delayed neurotoxicity for organophosphate and thiophosphate pesticides, and dermal penetration of substances for which the assumption of 100% absorption does not produce an adequate margin of safety for workers exposed to the substance.

Wildlife and Aquatic Organisms. Studies required to provide ecological effects data to determine the toxicological hazards of pesticides to various terrestrial and aquatic nontarget organisms are summarized (40 CFR 158.490 and Subdivision E Guidelines).

Section	Topic
71-1(**a**)	Acute avian oral toxicity (LD_{50}) in bobwhite quail or mallard duck
71-1(**b**)	Acute avian oral toxicity (LD_{50}) in bobwhite quail or mallard duck (using typical product)
71-2(**a**)	Acute avian dietary toxicity (LC_{50}) in bobwhite quail
71-2(**b**)	Acute avian dietary toxicity (LC_{50}) in mallard duck
71-3	Wild mammal toxicity test
71-4(**a**)	Avian reproductive toxicity in bobwhite quail
71-4(**b**)	Avian reproductive toxicity in mallard duck
71-5(**a**)	Simulated terrestrial field study
71-5(**b**)	Actual terrestrial field study
72-1(**a**),(**b**)	Fish toxicity in bluegill sunfish
72-1(**c**),(**d**)	Fish toxicity in rainbow trout
72-2(**a**),(**b**)	Invertebrate toxicity freshwater LC_{50} (daphnia preferred)
72-3	Toxicity to estuarine and marine organisms (six tests)
72-4(**a**)	Early life stage in fish
72-4(**b**)	Life cycle in aquatic invertebrates (daphnia/mycid)
72-5	Fish life cycle study
72-6	Aquatic organism accumulation study
72-7(**a**),(**b**)	Field tests for aquatic organisms, simulated, actual

A risk characterization for a pesticide use is performed by comparing these effects data with data on environmental fate and exposure. The eco-effects

tests include acute, subacute, chronic, and field studies that are part of a tiered testing scheme. The results from one tier are evaluated to determine potential toxicological hazards, and if further testing is required in the higher tiers. The adverse effects examined include mortality, reduction in growth, reproductive impairment, changes in number of species, bioaccumulation of residues in nontarget organisms, and in higher tier studies, structure and function changes in the ecosystem. The data are used by the EPA to determine whether product labeling should carry warning statements pertaining to toxicity to birds, fish, or wildlife, and whether the product can be registered or should be subjected to special review.

5.5. Occupational and Residential Exposure. *Nontarget Insects and Nontarget Plants.* Additional ecological hazard evaluation studies might be needed, using honey bees and certain plants including terrestrial and aquatic species (40 CFR 158.540 and 590, and Subdivision J and L Guidelines).

Incidents of illness in field workers, particularly in California, led to requirements for data to establish safe reentry intervals after treatment of fields with acutely toxic pesticides (40 CFR 158.390 and Subdivision K and U Guidelines). In addition to post-application data, such as foliar and soil residue dissipation, the EPA has also required development of monitoring data to estimate exposure in mixer/loaders who handle pesticide concentrates, and in applicators who handle large quantities of the pesticide as diluted for use. Passive testing using absorbent patches fastened to clothing can lead to inaccurate estimation of exposure. Most exposure occurs on the hands of the workers. Data from many exposure studies conducted by individual companies, contract laboratories, academia, and government groups in the United States and Canada have been compiled on a generic basis to provide a better estimate of the amount likely to reach the skin of mixer/loader/applicators under actual working conditions. Studies have also been done on levels of certain pesticides or metabolites in blood or excreted in urine of exposed workers. These latter data cannot be interpreted without adequate information about metabolism and pharmacokinetics of the pesticide in humans (53).

6. Benefit, Risk and Environmental Issues

As world population increases, urban expansion encroaches more and more on productive land areas used for growing food and fiber to feed and clothe all these people. Whereas crop yields may continue to increase with advances in agricultural technology, crop protection agents are needed to avoid losses owing to weeds, insects, and fungi (see General References). Pest infestations can affect the economies of entire regions.

Although employment of chemicals for insect pest control is essential to modern society, the extensive and injudicious use of chemical insecticides since 1946 has resulted in many problems, including (*1*) widespread insect resistance, (*2*) emergence of resurgent and secondary pests whose regulating natural enemies have been adversely affected, (*3*) hazards to human health, (*4*) environmental pollution, and (*5*) exponentially increasing costs of new insecticides.

Pesticides are subjected to extensive testing for residues in food, toxicology in laboratory animals, and fate in the environment before being registered for use. Moreover, uses are closely regulated by governmental agencies worldwide. Concerns exist about residues in food, especially for those pesticides classified as probably or possibly carcinogenic, based on studies in test animals given maximum tolerated doses over most or all of their respective lifetimes (31,52).

When illegal residues have been found in monitoring studies conducted by the FDA or USDA, the reason has often been that no U.S. tolerance had been requested for that particular pesticide in that specific crop. For example, an imported crop would be deemed to be adulterated and would be seized at the port of entry into the United States if found to contain a pesticide residue in the absence of a tolerance in that crop. This is so even if tolerances have been set for the same pesticide in several crops grown in the United States and the pesticide had been used to control a pest that does not exist in the United States. Furthermore, an international maximum residue level (MRL) might already have been established for that pesticide–crop combination under the Codex system of standards for food of importance in international trade.

Concern about pesticides contaminating surface or groundwater used for drinking purposes has resulted in groundwater monitoring (qv). Levels above health advisories (HAs) recommended by EPA have been found in samples taken from streams receiving runoff from freshly treated fields following heavy rainfall in the spring (54). This peak declined rapidly during the growing season. The rates of decline of herbicide residues in or on soil depend on the climate and on the chemical and biological nature of the soils being tested, as well as on the physical and chemical characteristics of individual pesticides (55,56).

6.1. Integrated Pest Management. Management systems have been proposed that will direct insect pest control away from exclusive reliance on insecticides and toward the optimization of pest control tactics in an ecologically and economically sound way. Integrated pest management (IPM has been variously defined as (*1*) "a system in which all available techniques are evaluated and consolidated into a unified program to regulate pest populations so that economic damage is avoided and environmental disturbances are minimized," (*2*) as "the intelligent selection of and use of pest control actions that will ensure favorable economic, ecological, and sociological consequences," or (*3*) as "the selection, integration, and implementation of pest control based on predicted economic, ecological, and sociological consequences"). IPM is similar to or synonymous with the term integrated crop management (ICM) in Europe. This has been defined as follows: "An approach to farming which aims to balance production with economic and environmental considerations by means of a combination of measures including crop rotation, cultivations, appropriate crop varieties and careful use of inputs" (http://glossary.eea.eu.int/).

Integrated pest management (IPM) is an approach that can reduce counterproductive pesticide applications. Stern and others (57) originally defined integrated control as "applied pest control which combines and integrates biological and chemical control." IPM focuses on optimizing the use of chemical, biological, and cultural controls, such as varietal resistance to pests, trap crops, augmentation of natural enemies and crop rotation, to manage pest problems rather than relying solely on pesticide use (58). IPM programs often include

pest monitoring and economic thresholds. Biological control methods, which can be included in IPM programs, include the use of pest predators, parasites, and other beneficial organisms, as well as pheromones or microbial organisms that may be regulated as pesticides. Organic crop production and sustainable agriculture are approaches that may incorporate various pest management techniques to reduce or eliminate pesticide use. Certification of organic production generally implies that synthetic organic pesticides and genetically modified crops have not been used.

IPM was originally developed as an approach to control pests more cost-effectively over time, and it has influenced the science and practice of pest control. More recently, IPM has become a policy tool to reduce the use and risks of pesticides. In the late 1980s, some advocacy groups in the United States began to argue for a policy of restricting or reducing the total amount of pesticides used in order to reduce the adverse environmental and health effects. Many proponents argued that some pesticides were overused and that more efficient application technology, nonchemical practices, pest monitoring and economic thresholds, or crop rotations may reduce pesticide use with relatively small economic losses and, at the same time, significantly reduce adverse environmental and health effects (59). Some European countries, including Denmark and Sweden, passed legislation that mandated the reduction of pesticide use by 50% (29). Some groups have argued that the practice of IPM has become overly oriented to using pesticides to control pests rather than reducing pesticide use (60). As a response, the concepts of biointensive IPM and ecologically based IPM have focused on reducing the use of synthetic organic pesticides, increasing the emphasis on reduced-risk pesticides and nonchemical practices, and understanding crop and pest ecology (61).

The United States instituted a policy of encouraging IPM adoption to help reduce health and environmental risks from pesticides, but the policy did not include a goal of reducing pesticide use by a specified percentage.

6.2. Impacts of Introducing Engineered Microorganisms into the Environment. Although magnified and possibly distorted by the concerns of the general public and several legitimate scientific issues underlie the concern over the use of genetically engineered microorganisms. There are numerous historical instances where exotic or nonindigenous plants or microbial species dramatically outcompeted native flora or fauna after intentional or accidental introductions into a new environment, with resulting adverse effects. Although not an ideal model for the introduction of microorganisms possessing only a few genetic differences from wild type, this paradigm shaped the early debate. Accordingly, among the issues identified as important to assess in proposed uses of genetically engineered materials (GEMs) in the environment were (*1*) the toxicity, infectivity, or other risks inherent to the GEM itself; (*2*) the ability of the GEM to persist or become established in the environment; (*3*) the ability of the GEM to compete with or displace natural microflora at the release site; (*4*) the possibility that the GEM could spread or be dispersed from the release site; and (*5*) the possibility that genes introduced into the GEM could themselves spread through horizontal gene transfer to be taken up by and expressed in different microbial species (1).

This scientific debate continued for much of the 1980s and many scientific issues remain for investigation. For the purposes of the development of regulations, much of the debate was settled in the late 1980s by the appearance of peer-reviewed reports (62,63) that generally concluded that the behavior of GEMs in the environment would be similar to that of nonengineered strains introduced into new environments and that such behavior could be predicted and monitored using appropriate risk assessment tools. The results of many of the earliest GEM field tests and the monitoring programs that accompanied them have generally borne out the predictability and low risks of many uses of GEMs in agriculture (64).

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Table 1. **Examples of Simple Early Pesticides**

Compound	CAS Registry number	Molecular formula	Pesticide class
formaldehyde	[50-00-0]	HCHO	bactericide
bromomethane	[74-83-9]	CH_3Br	fumigant
dimethylarsinic acid	[75-60-5]	$(CH_3)_2AsO_2H$	herbicide
dalapon	[75-99-0]	$CH_3Cl_2CO_2H$	herbicide
trichloroacetic acid	[76-03-9]	Cl_3CCO_2H	herbicide
acrolein	[107-02-8]	$CH_2{=}CHCHO$	herbicide
2-phenylphenol	[90-43-7]	$C_{12}H_{10}O$	fungicide
biphenyl	[92-52-4]	$C_{12}H_{10}$	fungicide
diphenylamine	[122-39-4]	$C_{12}H_{11}N$	fungicide
mercuric oxide	[21908-53-2]	HgO	fungicide
mercurous chloride	[7546-30-7]	Hg_2Cl_2	fungicide
sodium fluoride	[768-49-4]	NaF	insect bait

Table 2. **Examples of Complex Pesticides**[a]

Compound	CAS Registry number	Molecular formula	Structure number[b]	Pesticide class
abamectin	[71751-41-2]	$C_{48}H_{72}O_{14}$	(1)	acaricide
bifenthrin	[82657-04-3]	$C_{23}H_{22}ClF_3O_2$	(2a) plus (2b)	acaricide
cyphenothrin	[39515-40-7]	$C_{24}H_{25}NO_3$	(3a) plus (3b)	insecticide
imazalil	[73790-28-0]	$C_{14}H_{14}Cl_2N_2O$	(4)	fungicide
imazamethabenz	[81405-85-8]	$C_{15}H_{18}N_2O_3$	(5a) plus (5b)	herbicide
imazosulfuron	[122548-33-8]	$C_{14}H_{13}ClN_4O_5S$	(6)	herbicide
imibenconazole	[86598-92-7]	$C_{17}H_{13}Cl_3N_4S$	(7)	fungicide
imidacloprid	[105827-78-9]	$C_9H_{10}ClN_5O_2$	(8)	insecticide
prallethrin	[23031-36-9]	$C_{19}H_{24}O_3$	(9)	insecticide
thiazopyr	[117718-60-2]	$C_{16}H_{17}F_5N_2O_2S$	(10)	herbicide

[a]Ref. 11.

[b]See Fig. 1.

[c]Abamectin was first isolated from seeds of the neem tree as a mixture of (1), as shown in Fig. 1, plus (1, $R = CH(CH_3)_2$).

Table 3. **Important Pesticide Legislation**

The Insecticide Act of 1910—Prohibited the manufacture, sale, or transport of adulterated or misbranded pesticides; protected farmers and ranchers from marketing of ineffective products.

Federal Food, Drag, and Cosmetic Act of 1938 (FFDCA)—Provided that safe tolerances be set for residues of unavoidable poisonous substances, such as pesticides, in food.

Federal Insecticide, Fungicide, and Rodenticide Act of 1947 (FIFRA)— Required pesticides to be registered before sale and that the product label specify content and whether the substance was poisonous.

Miller Amendment to FFDCA of 1954—Amended the Federal Food, Drug, and Cosmetic Act (FFDCA) to require that tolerances for pesticide residues be established (or exempted) for food and feed (Section408). Allowed consideration of risks and benefits in setting tolerances.

Food Additives Amendment to FFDCA of 1958—Amended FFDCA to give authority to regulate food additives against a general safety standard that does not consider benefits (Section409); included the Delaney Clause, which prohibited food additives found to induce cancer in humans or animals. Pesticide residues in processed foods were classified as food additives, while residues on raw commodities were not. When residues of a pesticide applied to a raw agricultural commodity appeared in a processed product, the residues in processed foods were not to be regulated as food additives if levels were no higher than sanctioned on the raw commodity.

FIFRA Amendments of 1964—Increased authority to remove pesticide products from the market for safety reasons by authorizing denial or cancellation of registration and the immediate suspension of a registration, if necessary, to prevent an imminent hazard to the public.

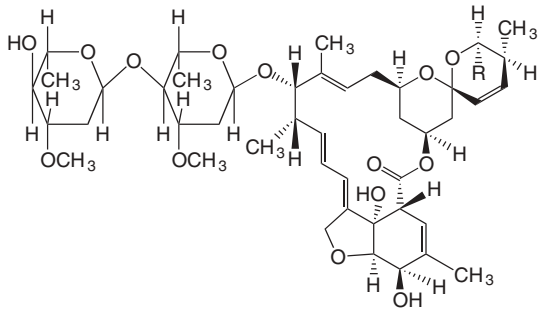
Federal Environmental Pest Control Act (FEPCA) of 1972—Amended FIFRA to significantly increase authority to regulate pesticides. Allowed registration of a pesticide only if it did not cause unreasonable adverse effects to human health or the environment; required an examination of the safety of all previously registered pesticide products within 4 years using new health and environmental protection criteria. Materials with risks that exceeded those criteria were subject to cancellation of registration. Specifically included consideration of risks and benefits in these decisions.

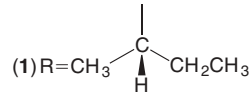
FIFRA Amendment of 1975—Required consideration of the effects of registration cancellation or suspension on the production and prices of relevant agricultural commodities.

Federal Pesticide Act of 1978—Identified review of previously registered pesticides as reregistration; eliminated the deadline for reregistration but required an expeditious process.

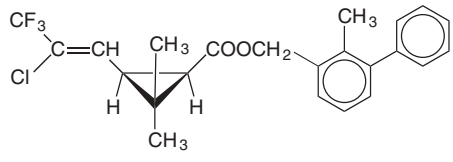
FIFRA Amendments of 1988—Accelerated the reregistration process by requiring that all pesticides containing active ingredients registered before November 1,1984, be reregistered by 1995; provided EPA with additional financial resources through reregistration and annual maintenance fees levied on pesticide registrations.

The Food Quality Protection Act of 1996 (FQPA)—Amended FIFRA and FDCA. Set a consistent safety standard for risks from pesticide residues in foods: "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure." Pesticide residues are no longer subject to the Delaney Clause of FDCA; both fresh and processed foods may contain residues of pesticides classified as carcinogens at tolerance levels determined to be safe. EPA is required to reassess existing tolerances of pesticides within 10 years, with priority to pesticides that may pose the greatest risk to public health. Benefits no longer have a role in setting new tolerances, but may have a limited role in decisions concerning existing tolerances. Included special provisions to encourage registration of minor use and public health pesticides.





(**1**) R=CH_3 CH_2CH_3



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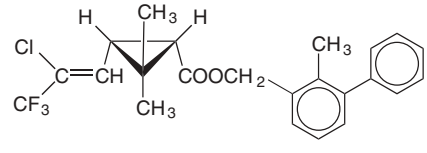

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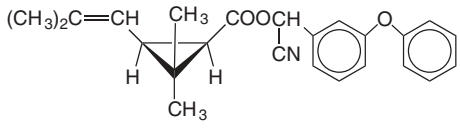

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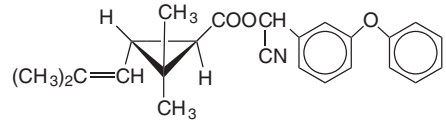

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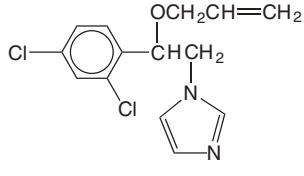

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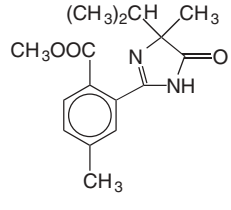

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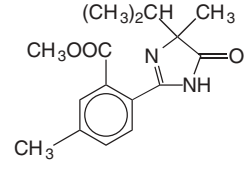

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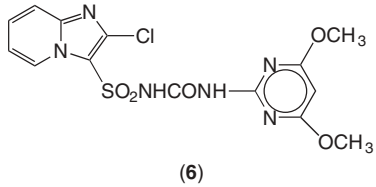

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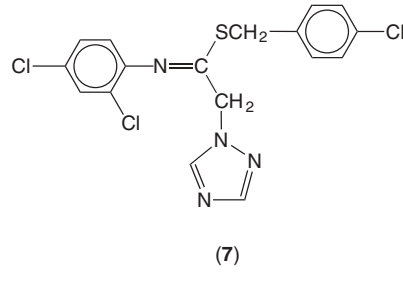
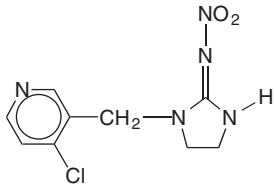
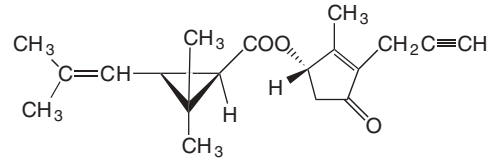


(**7**)

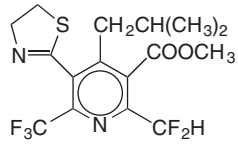
Fig. 1. Structures of more complex pesticides. See Table 2. Structures (**2a**) and (**2b**) are the (*Z*)-(1*R*)-cis and (*Z*)-(1*S*)-cis isomers, respectively; (**3a**) and (**3b**) are the (1*R*)-cis and (1*R*)-trans isomers, respectively.



(**8**)



(**9**)



(**10**)

Fig. 1. (*Continued*)

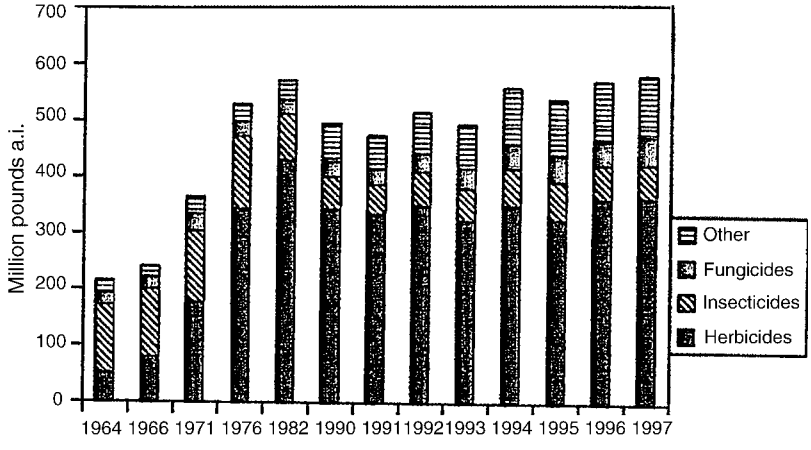


Fig. 2. Pesticide use on major crops (19,20).