HERBICIDES

1. Introduction

Herbicides are important for many reasons. Cultivation of plants for economic or ornamental purposes entails an incessant struggle against losses from pests. Weeds not only reduce yields by competing for sunlight, water, and nutrients, but they also reduce the quality of products and overgrow adjacent areas and bodies of water. Some of them actually produce phytotoxins (allelochemicals) that reduce crop growth. Uncontrolled weed infestations drastically reduce crop yields and decrease crop, turf, timber, and forage quality. For example, the post-harvest presence of weed seeds reduces crop quality, ie, cocklebur in soybeans, wild mustard in canola, and red rice and Northern jointvetch in rice. Weeds also serve as alternative hosts for crop-infesting fungi and harbor insect pests such as whiteflies. Furthermore, certain weeds, such as nightshade, produce toxins that can have severe health consequences for both livestock and humans.

The broadest definition of "herbicides" includes all agents that destroy or inhibit plant growth. Thus, an herbicidal agent may be animal, ie, a homegardener with a hoe or a grazing herbivore; vegetable, ie, a parasitic weed or one plant species competing successfully with another; or mineral, ie, chemicals with herbicidal activity. The definition of a weed as "a plant growing where it is not wanted" is convenient, although perhaps not scientific. It focuses on one of the basic problems of weed control, ie, selectively killing weeds without crop damage. Whether a plant is considered a weed depends entirely on the circumstances.

Weeds can be controlled by crop rotation, mowing, tilling the soil, and crowding out by crop competition. Extensive infestations of certain single weed species can be controlled by biological methods. Insects, herbivores, or diseases destroy certain weeds. However, these techniques have the disadvantage that weed seeds remain dormant in the soil and are unaffected. Cultural practices

are important, but the use of chemicals for weed control has been adopted globally.

Pest-control chemicals, ie, pesticides, have contributed significantly to agricultural productivity in the United States and often provide the farmer's first line of defense against pests. The term "pesticide" includes all classes of chemicals used against insects, weeds, plant pathogens, rodents, algae, snails, and other pests. Legally, it also includes growth regulators. The term "herbicide" refers specifically to weedkillers.

Modern agriculture demands that herbicides and other crop-protection chemicals be integrated into a production system that includes the development of pest-resistant and high yielding crop varieties, crop management, plant nutrition, and mechanization of farming methods and pest-control techniques. In this system, chemical control is an important component. Pesticides have been stated to increase production of crops, livestock, and forest products by 25% and thus contribute to the stability of food prices.

The widespread introduction of chemicals for weed control (herbicides) brought about major changes in agriculture affecting not only the economics of farming, but also the communities that were founded and based on crop production. Populations shifted from rural areas as labor demands decreased. The changes came about initially in the United States where this technology developed rapidly but parallel developments took place in Europe. Chemical control of pests was widely adopted by large-scale agricultural systems in areas throughout the world. There were many benefits from the use of chemicals. Not only was there increased potential for food production at lower cost, but also there was potential for conservation of soil resources through reduced tillage. The reduction in tillage that was made possible by the use of herbicides has resulted in a dramatic reduction in soil erosion. The application and development of the technology required sophisticated users. Industrial research and development received increasing support, as did the efforts of counterparts in government and academia. The quantity of herbicides used grew throughout the last decades of the twentieth century, and the industry that supported this growth flourished. The major companies became multinational corporations.

The chemical inputs were expensive. Adverse environmental effects and other problems gradually offset some of the benefits. Regulatory agencies both national and international have called for more stringent regulations on the types and amounts of chemicals that could be used. There was little initial understanding of the implications of the widespread use of chemicals in the environment, but the growth of this field of science soon paralleled progress in pesticide research. Increased costs of safety tests and the introduction of government-mandated requirements to reduce pesticide use made some industries reluctant to continue investing in development of new pesticides. It had become very costly to introduce new herbicides. The fact that farmers were already treating large acreages successfully meant that the market had become extremely competitive and there was a general reduction of effort by major companies, many of whom have separated or divested themselves of their agrochemical departments.

Reductions in the use of herbicides have been driven to some extent by regulation, but more significant changes in the patterns of herbicide use are due to

progress in the applications of biotechnology to agriculture. The understanding of metabolic processes in plants, modes of action of herbicides, and plant genetics coupled with the ability to manipulate genes and facilitate their expression in plants are major factors in these changes. Industrial research emphasized the potential of biotechnology, and industry invested heavily. Some developments, such as herbicide-resistant crops and plants incorporating insecticides, are currently approved and widely adopted. Such new directions are the current focus of the major North American and European chemical industries whereas outside Europe and the United States, manufacturing plants and new industries have originated to satisfy the needs for herbicides.

The knowledge that chemicals could kill plants or render soils sterile has existed since ancient times. The use of selective herbicides that could kill weeds without damage to crops growing in the same cultivated area is a twentieth-century development that has brought about major changes in agriculture and agricultural communities.

Sulfuric acid, sodium chlorate, arsenic compounds, copper sulfate, and other inorganic compounds have been used as weed killers since the early twentieth century. Until the introduction of synthetic organic chemicals, weed control in fields and turf depended on inorganic compounds and various combinations of surface tillage, mowing, chopping, hand weeding, scorching, and burning of unwanted plants. Those time-honored but highly inefficient and labor-intensive methods were essential to agriculture because weeds successfully compete with crop plants for water, sunlight, and nutrients. Early in the twentieth century, sodium chlorate was used to control deep-rooted perennial weeds in noncrop areas. Borates also found use for control of weeds in specific locations. The introduction of synthetic organic herbicides that acted selectively against broadleaved weeds changed the situation irreversibly. The first organic chemical herbicide to be introduced was 4,6-dinitro-*o*-cresol *[534-52-1]* (DNOC) in 1932.

DNOC was used initially as an insecticide, and the selective herbicidal properties of this and related compounds were discovered later. This was followed by the introduction in the 1940s of the substituted phenoxy acids, and in 1951 of the substituted ureas and uracils. The triazine family of herbicides appeared in 1955, and the bipyridiniums in 1960. Chemicals of many other classes rapidly entered the herbicide market and their usage in major crops expanded rapidly. Herbicides represented about 62.5% of the U.S. pesticide market (about $17.28 million during the period 1986–1989). By 1982, almost 95% of the corn, cotton, and soybean acreage was being treated with pesticides by U.S. farmers.

2. Development of Herbicides

As knowledge of biochemical targets has increased through studies of metabolism and mode of action of pesticides, screening techniques have been improved, making it possible to identify candidate compounds that are effective at specific receptor sites. The introduction of newer synthetic techniques, such as combinatorial chemistry, which can generate large numbers of new compounds, made it

is possible to increase the throughput of compounds. Although there is a constant flow of new compounds through the developmental stages, industrial resources dedicated to the search for improved chemical controls are currently shifting to biotechnological approaches. One application of biotechnology is to increase herbicide tolerance in existing crops by genetic modification. Seeds of crop plants that are resistant to environmentally safe herbicides have been produced by genetic manipulation. Weeds can then be eliminated by conventional herbicides without damage to the growing crop. This favors the use of currently registered chemicals that have been shown to be environmentally acceptable. Other approaches involve the genetic manipulation of crops to introduce genes responsible for generating insecticidal *Bacillus thuringiensis* toxins, resistance to diseases or plant-parasitic nematodes.

2.1. Selective Herbicides. The development of selective herbicides followed early investigations of the biochemical factors affecting plant growth. The hypotheses that growth substances were present in plants and played an important role in regulating their growth and development led to the isolation and identification of plant growth regulators. F. W. Went who recognized their role and isolated the first growth substance in 1926 postulated the existence of naturally occurring plant growth regulators. The term "auxin" (coined from the Greek "auxein," to increase) was used initially to describe these substances that were later termed "phytohormones." F. Kögl later identified the first naturally occurring phytohormone as indo-3-lyl acetic acid in 1934. This was isolated from urine and shown to be identical with Went's growth substance. Subsequently, its presence in plants was confirmed.

Indo-3-lyl acetic acid promotes longitudinal growth by cell elongation and stimulates cell division in the cambium and roots. It is used to stimulate rooting of cuttings of herbaceous and woody ornamentals. The auxins stimulate growth at low doses, but at higher doses, the growth-regulating effect results in lethally abnormal growth and becomes an herbicidal effect. In the course of attempts to synthesize auxin analogs, it was found that a variety of compounds elicited auxin-like responses. Some were subsequently developed as herbicides, and a number were shown to control weeds selectively in grass crops.

The discovery in 1934 that indoleacetic acids promoted cell elongation in plants was followed by the synthesis and evaluation of many structurally related compounds. These studies revealed the extremely high activity of indoleacetic acids and halogenated aryloxyacetic acids. However, it was not until the 1940s that these compounds were applied to weed control. Description of the growth regulating activity of 2,4-D (2,4-dichlorophenoxyacetic acid) in 1942 was followed by field trials in which it was shown to kill weeds selectively. Subsequently, 2,4-D was developed for use as a major herbicide for control of weeds in corn and other cereals. It was widely used to control annual and perennial broadleaf weeds in tolerant crops and on noncrop areas. The discovery of the phenoxyalkanoic acids as weed killers and their successful development and commercial application provided a stimulus for further search for new synthetic herbicides. Although dinitrophenols had been used in the 1930s, the scale of herbicide use in agriculture expanded after the introduction of 2,4-D, and this was followed by the introduction of atrazine, the first of the triazine herbicides, in 1958. Since then, many new herbicides representing a wide variety of chemical classes

have been commercialized to improve environmental safety, selectivity, and control of weeds at low rates of application.

2.2. Constraints on Herbicide Development. Considerable time and capital investment are required for the development of a new herbicide. As a consequence, about 10 companies that had sufficient resources to develop, register, bring new compounds to the market, and maintain registration dominated the market globally. In the search for profitability in the agrochemical market, the number of companies involved in the discovery and development of new herbicides continues to diminish. This is in part due to the impact of biotechnology, which has directed resources to the crop plant as the key to pest management.

Traditionally, promising new leads to compounds possessing pesticidal activity were discovered by random screening, but currently, many more constraints affect the selection of a candidate for development, such as patent status, ease of manufacture, environmental implications, toxicology, and so on. In 1950, a successful marketable pesticide resulted from examination of 1800 compounds on the average. The estimated number has increased greatly as constraints have multiplied. As additional criteria had to be taken into account in selecting suitable candidates for development, the process became more difficult. Success rates obtained by screening new chemical compounds fell yearly. Although in 1970–1973 the number of chemicals screened per new compound was 8,500, it rose to about 21,600 during 1986 and 1987. Much higher rates of throughput are now the goal of industry, and in recent years, technological progress has made it more practicable to generate large libraries of compounds for screening and accelerate the rate of submissions.

Considerable costs of development are consumed by safety tests prescribed by regulatory authorities, and the costs of new long term and short-term safety tests continually add to the developer's costs and delay the introduction of the product to the market. In 1967, two new chemical herbicides were registered in the United States under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The number of new registrations increased to 11 in 1975 and subsequently dropped to 3 in 1990 and 2 in 1991.

With the establishment of the U.S. Environmental Protection Agency (EPA) in 1970, the EPA became responsible for registration of pesticides in the United States. Measures to safeguard the environment were introduced, and environmental regulations continued to grow in complexity. As one outcome, new pesticides were targeted primarily for major markets in the United States and overseas, ie, to control major pests on major crop-producing areas. In the United States, only four crops are considered major ones based on area planted, and these are corn, soybean, wheat, and cotton. The continuing registration of pesticides for use on minor crops in the United States has required a cooperative program (IR-4) among government agencies, industry, and growers to obtain data and maintain registration of needed pesticides to ensure their continued availability to growers.

The herbicide market matured during the 1980s, and by 1982, about 95% of the corn, cotton, and soybean acreage was being treated with herbicides. Although the markets have expanded globally, the introduction of new compounds has reduced total quantities of pesticides applied, because new compounds are effective at rates many times lower than the insecticides and

herbicides introduced in the 1950s. The decrease also results from the more effective use of pesticides and the adoption of integrated pest management (IPM) programs in which greater use is made of pest threshold information. The decrease in the United States through these two mechanisms has amounted to 51% less active ingredient in 1991 than in 1979.

Preliminary screening in the laboratory or greenhouse indicates the type of activity a chemical might exhibit, followed by larger scale field tests. A suitable formulation must then be developed. Large-scale trials are required to study efficacy over a wide range of conditions, including soil types, climate, cropping methods, and many other factors.

3. Modes of Herbicide Action

Photosynthesis is the light-driven, membrane-localized electron/proton transport system by which plants, algae, and some bacteria convert the energy of a quanta of light into the phosphoryl group transfer potential of adenosine triphosphate (ATP) and the redox potential of nicotinamide adenine dinucleotide phosphate (NADPH) while oxidizing water to produce oxygen (1–3). In higher plants, the photosynthetic light energy conversion processes are localized in the thylakoid membranes of the grana of chloroplasts and the carbon-fixing processes occur in the stroma. Chloroplasts are chlorophyll-bearing, double membrane-bound organelles within photosynthetic plant cells; grana consist of stacks of thylakoids, vesicle-like structures that have internal spaces defined by a membrane and that are connected by unstacked stromal thylakoids. The thylakoid membranes contain the light-harvesting pigments and the electron- and proton-translocating components of both Photosystem I (PSI) and Photosystem II (PSII) of photosynthesis.

Traditionally, the electron and proton transport pathways of photosynthetic membranes (4) have been represented as a "Z" rotated 90° to the left with noncyclic electron flow from left to right and PSII on the left-most and PSI on the right-most vertical in that orientation (5,6). Other orientations and more complex graphical representations have been used to depict electron transport (7) or the sequence and redox midpoint potentials of the electron carriers. As elucidation of photosynthetic membrane architecture and electron pathways has progressed, PSI has come to be placed on the left as the "Z" convention is being abandoned. Figure 1 describes the orientation in the thylakoid membrane of the components of PSI and PSII with noncyclic electron flow from right to left.

Both PSI and PSII are necessary for photosynthesis, but the systems do not operate in the implied temporal sequence. There is also considerable pooling of electrons in intermediates between the two photosystems, and the indicated photoacts seldom occur in unison. The terms PSI and PSII have come to represent two distinct, but interacting reaction centers in photosynthetic membranes (9,10); the two centers are considered in combination with the proteins and electron-transfer processes specific to the separate centers.

3.1. Photosystem I Inhibitors. Photosystem I is the reaction center or site in photosynthetic membranes of oxygen-evolving organisms at which light-activated electron transfers lead to reduction of the iron–sulfur, FeS^{-}, centers of

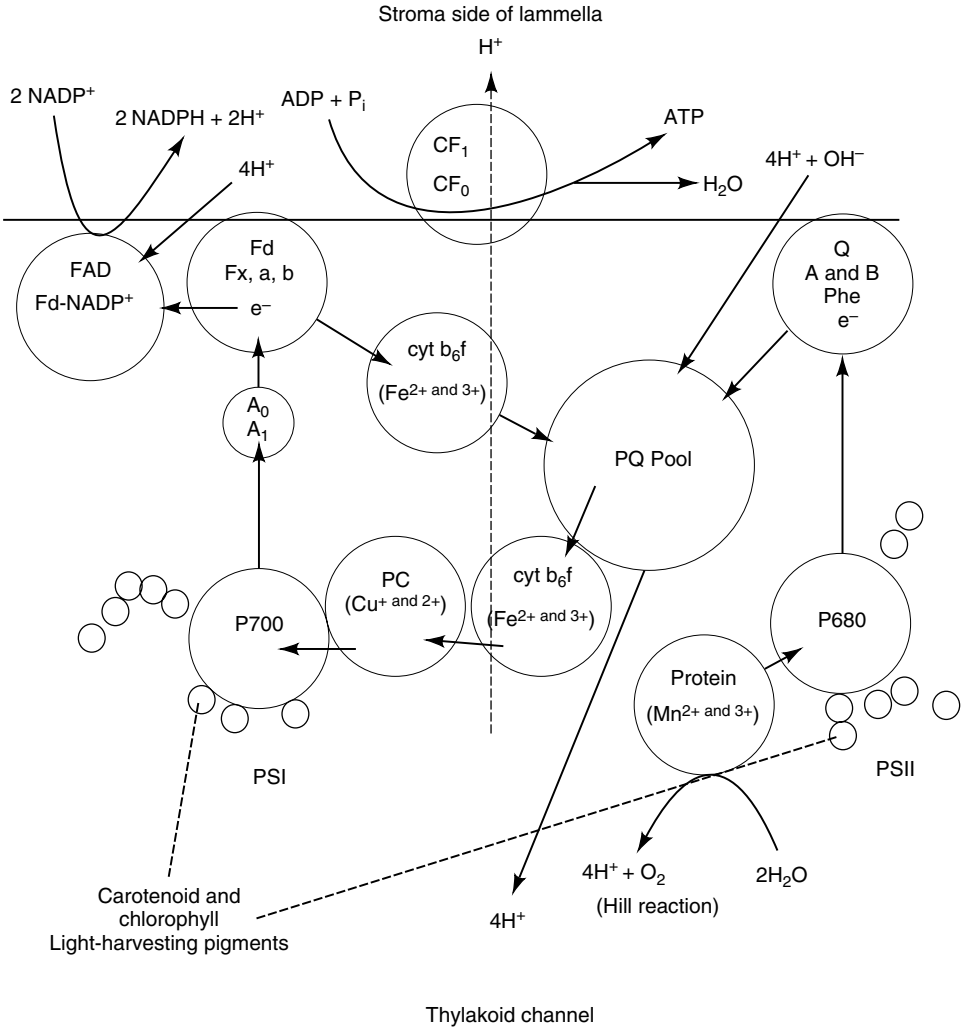

Fig. 1. An abbreviated schematic representation of photosynthetic electron flow in chloroplasts where PSII is photosystem II; PSI, photosystem I; Protein, Mn-containing oxygen evolving enzyme complex; P680, PSII reaction center chlorophyll; Phe, pheophytin a PSII e acceptor, Q_A, a bound PSII single e acceptor plastoquinone; Q_B, a bound PSII double e acceptor plastiquinone; PQ, membrane mobile reduced and oxidized plastoquinone; cyt, Fe-containing cytochrome e acceptor/donor; PC, copper-containing plastocyanin; P700, PSI reaction chlorophyll; A_0 and A_1, uncharacterized PSI e acceptors; Fx, a, b, FeS containing PSI e acceptors; Fd, ferredoxin; FAD, flavin adenine dinucleotide; Fd – $NADP^+$, nicotinamide adenine dinucleotide phosphate-reducing enzyme that contains ferredoxin; $NADP^+$ and NADPH, oxidized and reduced nicotinamide adenine dinucleotide phosphate, respectively; P_i, inorganic phosphate; ADP, adenine diphosphate; ATP, adenine triphosphate; and CF_1 and CF_0 ATP-synthesizing coupling factors. Light-harvesting pigments (smallest circles) transfer energy to reaction center chlorophyll molecules initiating a series of redox reactions that result in an electrochemical gradient across the thylakoid membrane. These reactions produce the reduced nucleotide and ATP required for anabolic metabolism in the plant. Solid arrows indicate the flow of H^+ and/or e among acceptor-donor compartments (larger circles). The dotted arrow indicates the flow of H^+ through the ATP synthetic coupling factors 8.

ferredoxin (9) indicated as Fd in Figure 1. PSI cycling is ensured by electrons transferred from PSII or the cytochrome b_6/f complex via the copper-containing plastocyanin (PC) which is the primary electron donor to P700, the specialized chlorophyll *a* molecule associated with PSI (5). From P700, electrons are transferred singly to FeS^- and thence to soluble ferredoxin. Ferredoxin nicotinamide adenine dinucleotide phosphate reductase transfers electrons to $NADP^+$ from soluble ferredoxin.

PSI transport processes include both this directional electron transfer to produce NADPH and a cyclic electron transfer that pumps protons into the stroma, resulting in the synthesis of ATP (9). Production of ATP by photophosphorylation can be inhibited (Table 1) by either uncouplers, eg, phenylhydrazones, carbanilates, diphenylamines, and ethane diamines (which dissipate the proton gradient necessary to drive ATP synthesis), or by inhibitors at ATP synthase, ie, coupling factor CF_1, nitrofen, and other chlorinated *p*-nitrodiphenyl ethers (10). Since ATP synthesis is not specific to oxygen-producing organisms, PSI inhibitors of the latter type are toxic to both plants and animals. Other herbicides, eg, oxyflurofen and other bipyridylium salts of *p*-nitro- or *p*-chlorodiphenyl ethers which act on PSI, have been reported to act by causing general destruction of the chloroplasts through membrane component peroxidation (10). Studies indicate that the diphenyl ethers, acifluorfen and oxyfluorfen, inhibit protoporphyrinogen oxidase, the penultimate enzyme in heme synthesis (11,12).

3.2. Electron Transport Between Photosystem I and Photosystem II Inhibitors. The interaction between PSI and PSII reaction centers (Fig. 1) depends on the thermodynamically favored transfer of electrons from low redox potential carriers to carriers of higher redox potential. This process serves to communicate reducing equivalents between the two photosystem complexes. Photosynthetic and respiratory membranes of both eukaryotes and prokaryotes contain structures that serve to oxidize low potential quinols while reducing high potential metalloproteins (13). In plant thylakoid membranes, this complex is usually referred to as the cytochrome b_6/f complex, or plastoquinol:plastocyanin oxidoreductase, which oxidizes plastoquinol reduced in PSII and reduces plastocyanin oxidized in PSI (5,14). Some diphenyl ethers, eg, 2,4-dinitrophenyl 2′-iodo-3′-methyl-4′-nitro-6′-isopropylphenyl ether [69311-70-2] (DNP-INT), and the quinone analogues, 2,5-dibromo-3-methyl-6-isopropyl-*p*-benzoquinone [29096-93-3] (DB-MIB) and 5-*n*-undecyl-6-hydroxy-4,7-dioxobenzothiazole [43152-58-5] (UHDBT) are presumed to interfere with the cytochrome b_6f complex by altering the Rieske Fe-S center (13,15). The high potential Fe-S protein with its characteristic epr spectrum was first discovered in the mitochondrial cytochrome bc_1 complex and is present in animal and plant cytochrome complexes that are active in quinol–cytochrome *c* oxidoreduction (13).

3.3. Photosystem II Inhibitors. The PSII complex usually is assumed to be that structural entity capable of light absorption, water oxidation, plastoquinone reduction, and generation of transmembrane charge asymmetry and the chemical potential of hydrogen ions (14). The typical PSII complex contains approximately a dozen different polypeptides; 200 chlorophyll *a* molecules; 100 chlorophyll *b* molecules; 50 carotenoid molecules; at least three different plastoquinones, ie, PQ, QA, and Q_B in Figure 1; one iron; two pheophytin *a* (Phe) mole-

Table 1. **Modes of Herbicide Action**

Common name	CAS Registry number	Chemical name	Molecular formula
		Photosystem I inhibitors	
acifluorfen	[50594-66-6]	5-[2-chloro-4-(trifluormethyl)phenoxy]-2-nitrobenzoic acid	$C_{14}H_{17}ClF_3NO_5$
nitrofen	[1836-75-5]	2,4-dichloro-1-(4-nitrophenoxy)benzene	$C_{12}H_7Cl_2NO_3$
oxyflurofen	[42874-03-3]	2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene	$C_{15}H_{11}ClF_3NO_4$
		Photosystem II inhibitors	
atrazine	[1912-24-9]	6-chloro-*N*-ethyl-*N*′-isopropyl-1,3,5-triazine-2,4-diamine	$C_8H_{14}ClN_5$
metribuzin	[21087-64-9]	4-(amino-6-*t*-butyl-3-methylthio)-1,2,4-triazin-5(4*H*)-one	$C_8H_{14}N_4O_5$
diuron	[330-54-1]	*N*′-(3,4-dichlorophenyl)-*N,N*-dimethylurea	$C_9H_{10}Cl_2N_2O$
bromacil	[314-40-9]	5-bromo-6-methyl-3-*sec*-butyl-2,4(1*H,*3*H*)pyrimidinedione	$C_9H_{13}BrN_2O_2$
ioxynil	[132-66-1]	4-hydroxy-3,5-diiodobenzonitrile	$C_7H_3I_2NO$
dinoseb	[88-85-7]	2-*sec*-butyl-4,6-dinitrophenol	$C_{10}H_{12}N_2O_5$
bromoxynil	[1689-84-5]	3,5-dibromo-4-hydroxybenzonitrile	$C_7H_3Br_2NO$
dinitrocresol	[534-52-1]	2-methyl-4,6-dinitrophenol	$C_7H_6N_2O_5$
		Bleaching herbicides	
fluridone	[59756-60-4]	1-methyl-3-phenyl-5-(3-trifluoromethylphenyl)-4(1*H*)-pyridinone	$C_{19}H_{14}F_3NO$
flurochloridone	[61213-25-0]	3-chloro-4-(chloromethyl)-1-(3-trifluoromethylphenyl)-2-pyrrolidinone	$C_{12}H_{10}Cl_2F_3NO$
flurtamone	[96525-24-4]	5-(methyl)amino-2-phenyl-4-(3-trifluoromethylphenyl)-3(2*H*)-furanone	
S3442	[65261-98-5]	3-(2,5-dimethylphenoxy)-*N*-ethylbenzamide	$C_{17}H_{19}NO_2$
diflufenican	[83164-33-4]	*N*-(2,4-difluorophenyl)-2-(3-trifluoromethylphenoxy) nicotinamide	$C_{19}H_{11}F_5N_2O_2$
difunon	[7703-36-8]	5-(dimethylaminomethylene)-2-oxo-4-phenyl-2,5-dihydrofurane-carbonitrile	$C_{14}H_{12}N_2O_2$
norflurazon[a]	[27314-13-2]	4-chloro-5-(methylamino)-2-(3-trifluoromethylphenyl)-3(2*H*)-pyridazione	$C_{12}H_9ClF_3N_3O$
amitrole[b]	[61-82-5]	1*H*-1,2,4-triazol-3-amine	$C_2H_4N_4$
fluometuron	[2164-17-2]	*N,N*-dimethyl-*N*′-(3-trifluoromethylphenyl)urea	$C_{10}H_{11}F_3N_2O$
fomesafen	[72178-02-0]	5-[2-chloro-4-(trifluoromethyl)phenoxy]-*N*-(methylsulfonyl)-2-nitrobenzamide	$C_{15}H_{10}ClF_3N_2O_6S$
		Chlorophyll biosynthesis inhibitors	
oxadiazon	[19666-30-9]	3-[2,4-dichloro-5-(1-methoxyethoxy)-phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2-(3*H*)-one	$C_{15}H_{18}Cl_2N_2O_3$
DTP	[58010-98-3]	1,3-dimethyl-4-(2,4-dichlorobenzoyl)-5-hydroxypyrazole	
MK-616	[39985-63-2]	*N*-(4-chlorophenyl)3,4,5,6-tetra-hydrophthalimide	$C_{14}H_{12}ClNO_2$

Table 1 (*Continued*)

Common name	CAS Registry number	Chemical name	Molecular formula
		Lipid and wax synthesis inhibitors	
clethodim	[99129-21-2]	(*E,E*)-(±)-2-[1-[[3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio) propyl]-3-hydroxy-2-cyclohexen-1-one	$C_{17}H_{26}ClNO_3S$
sethoxydim	[74051-80-2]	2-[1-(ethoxyimino)butyl]-5-[2-(ethylthio)propyl-3-hydroxy-2-cyclohexen-1-one	$C_{17}H_{29}NO_3S$
haloxyfop, methyl	[69806-40-2]	2-[4-[[3-chloro-5-trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propanoic acid, methyl ether	$C_{16}H_{13}ClF_3NO_4$
tralkoxydim	[87820-88-0]		
fenoxaprop, ethyl	[82110-72-3]	ethyl (±)-2-[4-[(6-chloro-2-benzoxazolyl]oxy]phenoxy]propanoate	$C_{18}H_{16}ClNO_5$
fluazifop, butyl	[69806-50-4]	butyl (±)-2-[4-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propanoic acid	$C_{19}H_{20}F_3NO_4$
	[79241-46-6][c]		
alachlor[d]	[15972-60-8]	2-chloro-*N*-(methoxymethyl)acetamide	$C_{14}H_{20}ClNO_2$
metolachlor[d]	[51218-45-2]	2-chloro-*N*-(2-ethyl-6-methyphenyl)-*N*-(methoxy-1-methyethyl)acetamide	$C_{15}H_{22}ClNO_2$
diclofop, methyl	[51338-27-3]	methyl (±)-2-[4-(2,4-dichlorophenoxy)-phenoxyl] propanoic acid	$C_{16}H_{14}Cl_2O_4$
CDEC	[95-06-7]	2-dichloroallyldiethyldithiocarbamate	$C_8H_{14}ClNS_2$
diallate	[2303-16-4]	*S*-(2,3-dichloro-2-propenyl)bis(1-methylethyl)carbamothioate	$C_{10}H_{17}Cl_2NOS$
EPTC	[759-94-4]	*S*-ethyl dipropyl carbamothioate	$C_9H_{19}NOS$
triallate	[2303-17-5]	*S*-(2,3,3-trichloro-2-propenyl)bis(1-methylethyl)carbamothioate	$C_{10}H_{16}Cl_3NOS$
metflurazon	[23576-23-0]	2-(3-trifluoromethylphenyl)-4-chloro-5-dimethylamino-3(2*H*)-pyridazinone	$C_{13}H_{11}ClF_3N_3O$
		Inducers of damage to antioxidative systems	
paraquat	[4685-14-7]	1,1′-dimethyl-4,4′-bipyridinium ion	$C_{12}H_{14}N_2$
diquatop	[2764-72-9]	6,7-dihydrodipyridol[1,2-α:2′,1′-c]pyrazinedium ion	$C_{12}H_{12}N_2$
tridiphane	[58138-08-2]	2-(3,5-dichlorophenyl)-2-(2,2,2-trichloroethyl)oxirane	$C_{10}H_7Cl_5O$
		Herbicidal inhibition of enzymes	
MAA	[124-58-3]	methylarsonic acid	CH_5AsO_3
MSMA	[2163-80-6]	monosodium salt of methylarsonic acid	$CH_5AsO_3{\cdot}Na$
DSMA	[144-21-8]	disodium salt of methylarsonic acid	$CH_5AsO_3{\cdot}2Na$
AMA		ammonium methylarsonic acid	
cacodylic acid	[75-60-5]	dimethyl arsinic acid	$C_2H_7AsO_2$
glufosinate	[51276-47-2]	2-amino-4-(hydroxymethylphosphinyl)-butanoic acid	$C_5H_{12}NO_4P$
glufosinate, ammonium	[77182-82-2]	ammonium-2-amino-4-(hydroxymethyl-phosphinyl)butanoic acid	$C_5H_{12}NO_4P{\cdot}H_3N$
		Amino acid and nucleotide biosynthesis inhibitors	
phaseolotoxin	[62249-77-8]	L-lysine, N^6-(aminoiminomethyl)-N^2-[*N*-[N^5-[[(amino sulfonyl)oxy]hydroxyphosphinyl]-L-ornithyl]-L-alanyl]	$C_{15}H_{33}N_8O_9PS$
glyphosate	[1071-83-6]	*N*-(phosphonomethyl)glycine	$C_3H_8NO_5P$

Table 1 (*Continued*)

Common name	CAS Registry number	Chemical name	Molecular formula
rhizobitoxine	[37658-95-0]	2-amino-4-(2-amino-3-hydroxypropoxy)-*trans*-3-butanoic acid	$C_7H_{14}N_2O_4$
chlorsulfuron	[64902-72-3]	2-chloro-*N*-[[4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino][carbonyl]benzenesulfonamide	$C_{12}H_{12}ClN_5O_4S$
chlorimuron, ethyl	[90982-32-4]	2-[[[[4-chloro-6-methoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]benzoic acid, ethyl ester	$C_{15}H_{15}ClN_4O_6S$
sulfometuron	[74222-97-2]	2-[[[[(4,6-dimethyl-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]benzoic acid, methyl ester	$C_{15}H_{16}N_4O_5S$
bensulfuron, methyl	[83055-99-6]	methyl-2-[[[[4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-benzoic acid, methyl ester	$C_{16}H_{18}N_4O_7S$
imazaquin	[81335-37-7]	2-(4,5-dihydro-4-methyl-4-isopropyl-5-oxo-1*H*-imidazol-2-yl)-3-quinolinecarboxylic acid	$C_{17}H_{17}N_3O_3$
imazapyr	[81334-34-1]	(±)-2-(4,5-dihydro-4-methyl-4-isopropyl-5-oxo-1*H*-imadazol-2-yl)-3-pyridinecarboxylic acid	$C_{13}H_{15}N_3O_3$
imazethapyr	[81335-77-5]	2-(4,5-dihydro-4-methyl-4-isopropyl-5-oxo-1*H*-imadazol-2-yl)-5-ethyl-3-pyridinecarboxylic acid	$C_{15}H_{19}N_3O_3$
imazamethabenz	[81405-85-8]	(±)-2-(4,5-dihydro-4-methyl-4-isopropyl-5-oxo-1*H*-imadazol-2-yl)-4 (and 5)-methylbenzoic acid, methyl ester	$C_6H_{20}N_2O_3$
		Cell division inhibitors	
trifluralin	[1582-09-8]	2,6-dinitro-*N,N*-dipropyl-4-(trifluoromethyl)benzenamine	$C_{13}H_{16}F_3N_3O_4$
oryzalin	[19044-88-3]	4-(dipropylamino)-3,5-dinitrobenzenesulfonamide	$C_{12}H_{18}N_4O_6S$
pendimethalin	[40487-42-1]	*N*-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzenamide	$C_{13}H_{19}N_3O_4$
nitralin	[4726-14-1]		
dinitramine	[29091-05-2]	N^3N^3-diethyl-2,4-dinitro-6-(trifluormethyl)-1,3-benzenediamine	$C_{11}H_{13}F_3N_4O_4$
asulam	[3337-71-1]	methyl 4-aminophenylsulfonylcarbamate	$C_8H_{10}N_2O_4S$
propham	[122-42-9]	isopropyl phenylcarbamate	$C_{10}H_{13}NO_2$
chloropropham	[101-21-3]	isopropyl 3-chlorphenylcarbamate	$C_{10}H_{12}ClNO_2$
barban	[101-27-9]	4-chloro-2-butynyl 3-chlorophenylcarbamate	$C_{11}H_9Cl_2NO_2$
butylate	[2008-41-5]	*S*-ethyl bis(2-isobutyl)carbamothioate	$C_{11}H_{23}NOS$
cycloate	[1134-23-2]	*S*-ethyl cyclohexylethylcarbamothioate	$C_{11}H_{21}NOS$
propachlor	[1918-16-7]	2-chloro-*N*-isopropyl-*N*-phenylacetamide	$C_{11}H_{14}ClNO$
DCPA	[709-98-9]	dimethyl 2,3,5,6-tetrachloro-1,4-benzenedicarboxylate	$C_9H_9Cl_2NO$
pronamide	[23950-58-5]	3,5-dichloro-(*N*-*t*-butyl-2-propynyl) benzamide	$C_{12}H_{11}Cl_2NO$
bensulfide	[741-58-2]	*O,O*-bis(isopropyl)-*S*-[2-[(phenyl sulfonyl)amino]ethyl]phosphorodithoate	$C_{11}H_{24}NO_4PS_3$

Table 1 (*Continued*)

Common name	CAS Registry number	Chemical name	Molecular formula
cinmethylin	[87818-31-3]	*exo*-1-methyl-4-isopropyl-2-[(2-methylphenyl)methoxy]-7-oxabicyclo [2.2.1]heptane	$C_{18}H_{26}O_2$
		Plant growth regulator synthesis and function inhibitors	
naphthalene acetic acid	[86-87-3]	1-naphthaleneacetic acid	$C_{12}H_{10}O_2$
indolebutyric acid	[133-32-4]	1*H*-indole-3-butanoic acid	$C_{12}H_{13}NO_2$
2,4-D	[94-75-7]	2,4-dichlorophenoxyacetic acid	$C_8H_6Cl_2O_3$
2,4,5-T	[93-76-5]	2,4,5-trichlorophenoxyacetic acid	$C_8H_5Cl_3O_3$
MCPA	[94-74-6]	(4-chloro-2-methylphenoxy)acetic acid	$C_9H_9ClO_3$
dicamba	[1918-00-9]	3,6-dichloro-2-methoxybenzoic acid	$C_8H_6Cl_2O_3$
chloramben	[133-90-4]	3-amino-2,5-dichlorobenzoic acid	$C_7H_5Cl_2NO_2$
picloram	[1918-02-1]	4-amino-3,5,6-trichloro-2-pyridinecarboxylic acid	$C_6H_3Cl_3N_2O_2$
naptalam	[132-66-1]	*N*-napthylphthalamide	$C_{18}H_{13}NO_3$
TIBA	[88-82-4]	2,3,5-triiodobenzoic acid	$C_7H_3I_3O_2$
diclofop	[40843-25-2]	(±)-2-[4-(2,4-dichlorophenoxy)phenoxy] propanoic acid	$C_{15}H_{12}Cl_2O_4$
ethephon	[16672-87-0]	(2-chloroethyl) phosphonic acid	$C_2H_{16}ClO_3P$
tetcyclacis	[65245-23-0]	1-(4-chlorophenyl)-3a,4,4a,6a,7,7a-hexahydro-4,7-methano-1-*H*-[1,2]diazeto[3,4-f]benzotriazole	$C_{13}H_{12}ClN_5$
AMO-1618	[2438-53-1]	2-isopropyl-5-methyl-4-(trimethylammonium chloride)-phenyl-1-piperidiniumcarboxylate	$C_{19}H_{31}N_2O_2 \cdot Cl$
chlormequat chloride	[999-81-5]	(2-chloroethyl)-trimethylammonium chloride	$C_5H_{13}ClN \cdot Cl$
mepiquat chloride	[24307-26-4]	*N*,*N*-dimethylpiperdinium chloride	$C_7H_{16}N \cdot Cl$
ancymidol	[12771-68-5]	α-cyclopropyl-α-(4-methoxyphenyl)-5-pyrimidine methanol	$C_{15}H_{16}N_2O_2$
uniconazole	[83657-22-1]	(*E*)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)-penten-3-ol	$C_{15}H_{18}ClN_3O$
paclobutrazol	[76738-62-0]	1-(4-chlorophenyl-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)-pentan-3-ol	$C_{15}H_{20}ClN_3O$
BAS 11100W	[80553-79-3]	1-phenoxy-3-(1*H*-1,2,4-triazol-1-yl)-4-hydroxy-5,5 dimethylhexane	$C_{16}H_{23}N_3O_2$

[a] Also effective as an inhibitor of lipid and wax synthesis.
[b] Primary mode of action is inhibition of amino acid synthesis.
[c] (*R*) isomer, commonly called fluazifop-P-butyl.
[d] Also general cell growth inhibitors.

cules; one or more cytochrome b_6/f molecules; four manganese ions; and varying numbers of chloride and calcium ions. The reaction center of PSII is more narrowly defined (16) as consisting of P680, a photo-oxidizable chlorophyll *a* which transfers an electron to the primary acceptor; pheophytin *a*; and, thence to the first quinone acceptor (Q_A), a plastoquinone. The so-called core of PSII is a set of five hydrophobic polypeptides (14), two of which form the reaction center that

performs the primary photochemical charge separation of PSII, ie, the 47 and 43 kDa polypeptides (43–45). Since polypeptide molecular weights are only estimates and species-specific variations in molecular weights exist, this pair of polypeptides has been reported as 51 and 45 kDa (19). Evidence favors the association of P680 with the larger polypeptide of this pair; the smaller polypeptide serving primarily as a light harvesting antenna for the reaction center. The plastoquinone Q_A is tightly bound to a PSII reaction center polypeptide, most likely the larger of the pair under discussion here (14,16).

The PSII complex contains two distinct plastoquinones that act in series. The first is the Q_A mentioned above; the second, Q_B, is reversibly associated with a 30–34 kDa polypeptide in the PSII core. This secondary quinone acceptor polypeptide is the most rapidly turned-over protein in thylakoid membranes (14,19). It serves as a two-electron gate and connects the single-electron transfer events of the reaction center with the pool of free plastoquinone in the membrane (5,14,19). The Q_B is probably the most studied protein in thylakoid membranes (46) since it is the binding site of many, if not most, PSII-inhibiting herbicides (19).

Many commercial herbicides inhibit electron flow on the reducing side of PSII (10,14,19). Compounds as chemically different as atrazine, metribuzin, diuron, bromacil, ioxynil, and dinoseb (see Table 1) all block electron transfer from Q_A to Q_B (19). Herbicidal PSII inhibitors, such as these and other triazines, ureas, pyrimidines, nitriles, and phenols, all appear to have the same site and mode of action; differences in activity are determined by the lipophilicity of the various side chains (19). These herbicides prevent electron transfer from Q_A to Q_B by displacing Q_B from its binding site on the Q_B polypeptide (19). This displacement from the proteinaceous receptor is competitive in the case of the phenylureas, triazines, pyridazinones, and biscarbamates (5). The herbicides cannot be reduced by Q_A, and electron transfer is blocked. The herbicides are competitive with plastoquinone which accepts electrons from Q_B (19), and schemes visualizing binding sites of herbicides to the Q_B protein have been presented (20,21). An allosteric action has been suggested for these herbicides (22,23). Conformational alterations of the Q_B protein through herbicide binding would affect both electron transport and binding of Q_B, plastoquinone, and additional herbicide molecules (19).

Polypeptide conformational changes through herbicide binding also have been suggested as the mode of action of the phenol PSII inhibitors, eg, dinitrocresol (DNOC), dinoseb, bromoxynil, and ioxynil (5) (Table 1). These phenolic herbicides also uncouple oxidative phosphorylation in PSI at high concentrations and have been classed as inhibitory uncouplers (24). Phenolic herbicides inhibit at the same site as ureas and triazines, but there is no common basic chemical structure, and the interactions at the thylakoid membrane receptor site are different (5). Structure–activity relationship studies of halogenated nitro- and dinitrophenols suggest that phenolic herbicidal activity is determined by steric parameters. Additional phenol analogues, eg, benzoquinones, napthoquinones, pyridones, quinolones, pyrones, dioxobenzthiazoles, and cyanoacrylates are potent inhibitors of PSII (5,20).

The extensive research effort that has increased understanding of PSII and the binding of herbicides to the various polypeptides in photosynthetic

membranes has initiated molecular modeling studies aimed at new inhibitors and herbicides (25). QSAR techniques have been applied, usually *a posteriori,* in investigations of various chemical classes, ie, ureas, carbamates, and anilides; triazines; triazinones; pyridazinones, uracils, and pyrimidones; imidazoles and pyrazolones; cyanoacrylates; pyrrolones and pyridones; phenols and quinones; and phenylureas (26).

From the beginning, herbicide developmental research has been focused on PSII and, more recently, the different modes of inhibitor binding that confer specificity and efficacy (20,27). The characteristics and level of understanding of the water-oxidation and donor-side reactions in photosynthesis encourage this emphasis on the PSII plastoquinone–polypeptide complexes (14,18). Decreasing tolerance for herbicides which persist in the soil is a contributing factor in this lessening use and acceptability. Other modes of action, particularly those relevant to membrane function or enzymatic activity, now show greater potential for producing new herbicides with desirably low application rates.

3.4. Bleaching Herbicides. Membrane-based modes of herbicidal action relevant to photosynthesis (10) include those of inhibitors of carotenoid biosynthesis, eg, norflurazon, difunon, *m*-phenoxybenzamines; inhibitors of chlorophyll biosynthesis, eg, oxadiazon, DTP or 1,3-dimethyl-4-(2,4-dichlorobenzoyl)-5-hydroxypyrazole [19666-30-9], MK-616 or *N*-(4-chlorophenyl)-3,4,5,6-tetrahydrophthalimide; and promoters of peroxidative destruction of membrane lipids, eg, bipyridyliums and diphenyl ethers. Bleaching herbicides can act at multiple sites in lipid metabolism and are reported to affect chloroplast pigments, ie, carotenoids and chlorophylls, by interfering with phytoene desaturation. This interference usually results in the accumulation of phytoene, a tetraterpene formed by the condensation of two molecules of geranylgeranyl pyrophosphate and the first carotene precursor of the carotenoid auxiliary pigments of photosynthesis.

There are three distinct groups of phytoene desaturase (dehydrogenase) inhibitors. The norflurazon class includes fluridone, flurochloridone, flurtamone, S3442, diflufenican, and difunon (Table 1). These compounds directly inhibit the conversion of phytoene to the colorless α- and β-carotenes which are the substrates for phytoene desaturase (PD), the enzyme which produces the colored carotenoid, ζ-carotene (10). Norflurazon (28) and fluridone (29) act as reversible noncompetitive PD inhibitors in cell-free systems.

A second class of herbicides primarily affects ζ-carotene desaturase. These herbicides are apparent feedback inhibitors of PD as well. This class of compounds includes dihydropyrones like LS 80707 [90936-96-2] (30) and 6-methylpyridines (31,32). The third class consists of the benzoylcyclohexane-diones, eg, 2-(4-chloro-2-nitrobenzoyl)-5,5-dimethyl-cyclohexane-1,3-dione. This class of atypical bleaching herbicides induces phytoene accumulation when applied either pre- or post-emergence. However, it does not inhibit phytoene desaturase activity *in vitro* (33). Amitrole also has been considered a bleaching herbicide, though its main mode of action is inhibition of amino acid synthesis.

Quantitative structure–activity studies of the typical PD inhibitors from the norflurazon group have been used to elucidate the influence of various substituents of herbicidal activity (34). Some herbicides known to inhibit PD interact with other targets, eg, fluometuron and fomesafen (10) also inhibit elec-

tron transport. Fluometuron is more potent as an inhibitor of electron flow *in vitro* through PSII than as an inhibitor of carotenoid formation. The action of fomesafen occurs more through initiation of peroxidative destruction of membranes than through inhibition of carotogenesis. Some phenylpyridazinones interfere with desaturation of linoleic acid to linolenic acid (7,10), probably through interaction with other lipid desaturase enzymes, specifically δ-15-desaturase (7,35). The bleaching herbicide fluorochloridone inhibits PD *in vivo* and *in vitro* and also inhibits linolenic acid formation (10,36).

Structure-activity studies of the seven herbicide classes that inhibit PD suggest that all classes target the same enzyme (10). Chemically, these classes are phenoxybenzamides, phenoxynicotinamides, phenylpyridazinones, phenylpyrrolidinones, phenylfuranones, phenylpyridinones, and phenyltetrahydropyrimidones. Cross-resistance studies of Synechococcus mutants (37) indicate that inhibitors of PD bind to the enzyme in the same general region but not to the same amino acid residues. Computer modeling techniques have been used to define and compare four regions in PD-inhibitor molecules (38). Two to four of these regions were present in the different PD-inhibitors examined. The first steps have also been made toward employing QSAR in the construction of a model describing the general features of PD-inhibitors and in the characterization of PD through determination of PD enzymology, amino-acid composition, and genetic markers (39,40).

3.5. Chlorophyll Biosynthesis Inhibitors. Chemically, the chlorophylls are magnesium-porphyrin complexes in which the four central nitrogen atoms of the pyrrole rings are coordinated with a Mg^{2+} ion to form an extremely stable planar complex. Chlorophyll also has a long hydrophobic terpenoid side chain consisting of phytol [150-86-7], an alcohol which is esterified to a propionic acid residue in ring IV. Several herbicides are reported to inhibit chlorophyll biosynthesis, eg, oxadiazon, DTP, and MK-616 (see Table 1), but the target or targets of these compounds is unknown (10). Along with similar compounds, amitrole has been reported to induce accumulation of ζ-carotene and also to induce chlorophyll bleaching and inactivation of enzymes other than PD (41).

3.6. Lipid and Wax Synthesis Inhibitors. Lipids, primarily in the form of acyl lipids derived from long-chain fatty acids, are present in all plant organs and on leaf surfaces (42–44). In plant roots and shoots, acyl lipids such as phospho- or glycolipids are structural components of the essential biological membranes of cell compartmentation, enzymology, and bioenergetics. Acyl lipids are constituents of a large variety of different structures with different functions and are, therefore, promising potential target sites for herbicide action. The effects of herbicides on lipid metabolism have been reviewed (45–47).

Fatty acid synthesis in plants has been reviewed (43,48). The reactions that lead to the formation of fatty acids are roughly divided into three classes, ie, initial reactions, biosynthesis of 16:0 and 18:0 saturated fatty acids by fatty acid synthetase (FAS), and biosynthesis of 18:1, 18:2, and 18:3 unsaturated acids. The initial steps in fatty acid biosynthesis are those which produce acetyl-CoA and malonyl-CoA. The key enzyme in these steps is acetyl-CoA carboxylase (ACC), a multifunctional protein located in the chloroplasts (45). Clethodim is reported to inhibit ACC (2), as are sethoxydim, haloxyfop, and tralkoxydim (49,50) (Table 1). Fenoxaprop; fluazifop, butyl; and fluazifop-P-

butyl also act through inhibition of fatty acid biosynthesis in sensitive plant species (51,52) (Table 1). These oxyphenoxy propionic acids and the analogous diclofop–methyl; clofop–isobutyl [51337-71-4]; haloxyfop–methyl; and fenthiaprop–ethyl [93921-16-5] all inhibit fatty acid synthesis *de novo* (53,54). Sethoxydim and alloxydim [55634-91-8], also inhibitors of fatty acid synthesis, are cyclohexanedione derivatives (17,55). The herbicidal activity of the cyclohexanediones is similar to the oxyphenoxy propionic acids, but alloxydim and sethoxydim also cause necrosis in meristematic regions and leaf chlorosis. These herbicides are selective against grasses (17,56). With some exceptions (56), cyclohexandiones do not inhibit incorporation of ^{14}C-acetate into chloroplast lipids of tolerant monocotyledonous, eg, *Poaannua*, *Festuca longifolia*, *F. rubra*, and *F. myuros* (50), and dicotyledonous, eg, pea, spinach, and tobacco, species (57).

Incorporation inhibition of ^{14}C-acetate into lipids is also the most rapid and pronounced effect of the α-chloracetamides, alachlor, metazachlor, and metolachlor (58) (Table 1), suggesting that the acetate-incorporating steps of lipid synthesis are the site of action for these herbicides. The thiocarbamate, EPTC, inhibits three enzymes that produce acetyl-CoA, ie, chloroplastic acetyl-CoA synthetase and both the chloroplastic and mitochondrial pyruvate dehydrogenase complexes (59). These two classes of herbicides have somewhat parallel properties and modes of action, possibly through reaction with sulfhydryl groups of proteins and low molecular weight thiols such as glutathione (60). Further, both the α-chloracetamides and the thiocarbamates have been reported to inhibit the lipid metabolic pathways that lead to the formation of the very long-chain epicuticular waxes of leaves (7,42,61). Reductions in leaf cuticular waxes increase leaf wetability by decreasing water surface tension, thus increasing plant sensitivity to subsequently applied herbicides (7,61). It has been reported that dithiocarbamates, eg, diallate, CDEC, EPTC, and triallate, alter the structure, composition, or amount of wax (62,63). The alkanes and secondary alcohol components of the waxes were reported to be significantly affected by CDEC and EPTC (62). EPTC, diallate, and triallate also inhibit suberin formation (64). Suberin consists of relatively high amounts of dicarboxylic acids, phenolics, very long-chain fatty acids, and very long-chain alcohols (7).

Pyridazinone herbicidal activity depends on inhibition of multiple target sites in plants, eg, PSII, the Hill-reaction, and carotenoid biosynthesis, as well as changes in fatty acid composition (7,43). Pyridazinone-induced changes in fatty acid composition include increases in the 18:2/18:3 fatty acid ratios, suggesting inhibition of δ-15-desaturase (7,35). The 5-dimethylamino-substituted pyridazinones, eg, BAS 13 338 [3707-98-0] and metflurazon, have strong effects on the 18:2/18:3 ratio; some monomethylamino derivatives, eg, norflurazon, and structurally analogous phenylpyridazinones are also effective (65). Metflurazon and norflurazon increase the 18:2/18:3 ratio in galactolipids and phospholipids (7) in sensitive species. Metflurazon affects primarily the saturation of C-16:0, but it also inhibits desaturation of 18:2 to 18:3 when it is applied in the right concentrations to sensitive species (66).

The oxyphenoxypropionic acids and the cyclohexadiones are phytotoxic because they inhibit synthesis *de novo* of fatty acids (7,53,56). Inhibition of lipid synthesis could also produce the other physiological effects attributed to these herbicides, ie, membrane disruption (7) and chloroplast damage with

accompanying decreases in chlorophyll, CO_2 fixation, and ATP production (7,67), and the disruption of mitochondrial function (7,56). However, the phenoxy propionic acids, cyclohexadiones, thiocarbamates, and chloroacetamides, classes of herbicides reported to affect lipid synthesis, also have been shown to have significant effects on the production and activity of plant growth regulators such as auxin (68,69) and gibberellins (70).

3.7. Radical Damage to Antioxidative Systems and Cellular Components Inducers. The herbicidal activities of many of the inhibitors of PSII are enhanced by light, eg, metflurazon, norflurazon, and fluridone (51,71), possibly through the mechanism of photooxidative destruction (72,73). Excitation of chlorophyll pigments leads initially to a singlet state chlorophyll, ^{1}Chl. If electron transport is inhibited and the excitation is unquenched, a lower energy triplet state, ^{3}Chl, is generated. This triplet state chlorophyll interacts with oxygen to produce $^1O_2$. If ^{3}Chl and $^1O_2$ are formed during normal photosynthesis, quenching occurs through the agency of carotenoids, membrane-bound α-tocopherol, and stromal radical scavengers like ascorbate, glutathione, polyamines, and flavanols (71). Herbicides that enhance the production and/or activity of toxic free radicals and singlet oxygen include the bipyridiniums, paraquat and diquat (72). The *p*-nitro- or *p*-chlorodiphenyl ethers (DPEs), acifluorfen–methyl, and oxyfluorfen (10,72) have been reported to be involved in the initiation of free-radical chain reactions with polyunsaturated fatty acid moieties of phospholipid molecules intrinsic to cell membranes. More recent reports indicate that the phytotoxic mechanism of DPE herbicides depends on inactivation of protoporphyrinogen oxidase and the subsequent accumulation of Protoporphyrinogen IX (Proto IX), a potent photosensitizer (74). Proto IX accumulates, and illumination then leads to the formation of singlet oxygen and lipid peroxides which result in loss of membrane integrity and cell death. The herbicidal activity of the bipyridiniums is also enhanced by both light and oxygen (72). The dicationic nature of the bipyridiniums allows easy reduction to a cation radical through electron donation from the terminal end of PSI. This diverts electrons from ferredoxin, the natural PSI acceptor, and leads to inhibition of $NADP^+$ reduction and CO_2 fixation. Electron flow from water with the photosynthetically driven release of O_2 in the chloroplasts permits reoxidation of the bipyridinium radical and formation of superoxide (72). Superoxide, $O_2^{\bullet}$, is generated as a normal part of chloroplast electron transport, and the radical is scavenged by superoxide dismutase (SOD) enzymes, ie, metalloproteins which catalyze the conversion of two superoxide radicals and two protons to hydrogen peroxide and water. Leaves of paraquat-tolerant plants are reported to have higher levels of SOD than do the leaves of sensitive species (10,75). The hydrogen peroxide produced by SOD is further converted to very active hydroxy radicals, probably by a metal-catalyzed Fenton-type reaction.

Light and photosynthetic electron transport convert DPEs into free radicals of undetermined structure. The radicals produced in the presence of the bipyridinium and DPE herbicides decrease leaf chlorophyll and carotenoid content and initiate general destruction of chloroplasts with concomitant formation of short-chain hydrocarbons from polyunsaturated fatty acids (10,72).

The effectiveness of herbicides that induce lipid peroxidation depends on the activity of the natural protective mechanisms which are based on antioxidants

and radical scavengers, ie, α-tocopherol, the carotenoids, ascorbate, glutathione, polyamines, and the flavanols (10,72,76). Plant defenses against radical-inducing compounds include an antioxidative system consisting of ascorbate, α-tocopherol, and reduced glutathione (GSH), closely associated with SOD and catalase. Peroxidation by oxyfluorfen is counteracted by the appropriate ratio of ascorbate and α-tocopherol. Increased radical formation leads to higher production of antioxidants. For example, acifluorfen–sodium induces increased glutathione reductase activity, elevated levels of glutathione and ascorbate, and simultaneous increases in galactonolactone oxidase activity. Conjugation of metabolites and xenobiotics with GSH is catalyzed by GSH-transferase(s), the activity of which can be increased by low concentrations of chloroacetamides and other safeners, compounds which can protect selected crops from some herbicides. Tridiphane inhibits GSH transferases and may prevent conjugation of atrazine in some species (51,76).

The chemical mechanism of other herbicides also involves peroxidative destruction of polyunsaturated fatty acids by starter radicals (10). Fenton reactions produce alkoxy radicals which can split into alkyl radicals leading to hydrocarbon gases (77) or can initiate further radical destruction of other chloroplast components (10,72). Potent peroxy and alkoxy radicals and lipid hydroperoxides are formed (78). Lipid hydroperoxides also decompose to form cytotoxic malondialdehye [542-78-9] (MDA), a compound often used as an index of lipid peroxidation (72,78). MDA, a significant 2-thiobarbituric reactant, can cause intra- and intermolecular cross-linking of sulfhydryl-containing proteins (72). Proteins can also be fragmented or modified by hydrogen peroxide in the presence of transition metals (72,79). The resulting hydroxyl radicals and the alkoxy radical intermediates from lipid peroxidation also attack proteins and individual amino acids (79), particularly histidine, cysteine/cystine, methionine, lysine, tyrosine, and tryptophan (72,78,80).

3.8. Herbicidal Inhibition of Enzymes. The list of known enzyme inhibitors contains five principal categories: group-specific reagents; substrate or ground-state analogues, ie, rapidly reversible inhibitors; affinity and photoaffinity labels; suicide substrate, or k_{cat}, inhibitors; and transition-state, or reaction-intermediate, analogues, ie, slowly reversible inhibitors (81).

The radical-generating herbicides, described above, that attack specific amino acid residues are examples of group-specific enzyme inhibitors. Substrate analogue enzyme inhibitors include the organoarsenicals, MAA and MSMA (see Table 1). Arsenical pesticides, known since the time of Aristotle, have been widely used as herbicides since 1951 (82). Arsenite (As^{3+}) reacts with sulfhydryl groups in enzymes and other thiol groups (83). Arsenate (As^{5+}) replaces phosphate in essential metabolic phosphorylation reactions, eg, glyceraldehyde-3-phosphate dehydrogenase, and oxidative phosphorylation (85). The arsonic acid herbicides, MAA, MSMA, DSMA, and AMA, are not technically plant growth regulators since they act through enzyme systems to inhibit growth (82) and thus kill plants relatively slowly. Cacodylic acid and its sodium salt are used extensively as selective post-emergence herbicides in cotton and noncrop areas and orchards. Cacodylate is reported to be a nonspecific competitive inhibitor of adenine nucleotide deaminase (86) and may inhibit other enzymes as well (82).

Suicide substrate and reaction intermediate inhibitors promise the highest degree of specificity and have drawn increased attention (81). Heteroatom or radical replacement in reaction–intermediate analogues is a simple pesticide development strategy that offers potential for achieving extremely potent inhibition without high chemical reactivity. This simple design strategy may produce effective intermediate inhibitors for families of mechanistically related enzymes. For instance, substitution of a phosphorous for a carbon has produced potent inhibitors of metalloproteases, cytidine deaminase, and glutamine synthase (81,87–89).

In the formation of glutamine by glutamine synthase, ammonia attacks the carbonyl of a glutamate phosphate intermediate (81). In the potent herbicide glufosinate ie, phosphinothricin, the tetrahedral carbon of the enzymatic intermediate is replaced by phosphorus and the attacking ammonia is replaced by a methyl group (81). Primary ammonium assimilation is a plant-specific process (89–91), although glutamine synthase plays a role in recycling catabolically produced ammonia in both plants and animals. In plants, ammonium ions can be taken up by the plant or can originate through turnover of endogenous *N*-containing cell components. Elevated concentrations of ammonia are cytotoxic (92), and ammonium ions are usually reassimilated through the action of glutamine synthase which binds ammonium to glutamate (93).

Glutamine synthase is inhibited by glufosinate (89,93), methionine sulfoximine [15985-39-4] (MSX) (95), bialaphos [35597-43-4] (31), hydroxylysine [28902-93-4] (89), and tabtoxin [40957-90-2] (31). Bialaphos is a tripeptide, from Streptomyces hydroscopicus, that can split into two alanine molecules and glufosinate (96). Glufosinate is activated by light and conditions that promote photorespiration; it blocks photosynthesis while inducing high accumulations of ammonia (92,94,97,98). Depletion of glutamine in the presence of glufosinate leads to a shutdown of the oxidative C_2-carbon cycle. Intermediates of that cycle, phosphoglycolate and possibly glyoxylate, accumulate, shutting down photosynthesis (94). Tabtoxin is a dipeptide composed of threonine or serine and tabtoxinine (31); it is excreted by *Pseudomonas syringae spp*. Tabtoxinine [40957-88-8] also causes ammonia accumulation (100) through noncompetitive and irreversible binding to glutamine synthase (101). Other biologically derived inhibitors of glutamine synthase have been reported (102).

A carbonyl reagent, aminooxyacetate, inhibits pyridoxalphosphate-dependent enzymes such as decarboxylases and transaminases. This reagent is the basis for the herbicides benzadox [5251-93-4], benzamidooxyacetic acid [5251-93-4], and other lipophilic analogues (103). Benzadox decreases photosynthesis and inhibits both alanine and aspartate aminotransferase (104). Isonicotinic hydrazide [54-85-3] affects glycine–serine aminotransferase (105), and aminoacetonitrile [540-61-4] inhibits glycine decarboxylation in a manner similar to that of gulfosinate (106).

When ATP-synthase, specifically the plastidic coupling factor CF_0–CF_1, is inhibited, ATP formation by photophosphorylation is blocked. Inhibitors of this energy-transfer process prevent conversion into ATP of the electrochemical potential formed by electron transport during photosynthesis. One such inhibitor, dicyclohexylcarbodiimide [538-75-0] (DCCD), binds irreversibly to the F_0 part of the synthase, preventing transfer of protons to the F_1 portion (31). Two

allelochemicals, phlorizin [60-81-1] and quercetin [117-39-5], inhibit ATP-synthase by competing with phosphate; chlorinated *p*-nitrodiphenyl ethers compete with adenosine diphosphate (ADP) (107). One of the most studied inhibitors of the plastidic coupling factor is tentoxin [28540-82-1], a cyclic tetrapeptide produced by *Alternaria alternata f. tenuis* (108). Tentoxin is plant-specific, able to pass through membranes, and highly active, binding to the catalytic site of the CF_1. Its mode of action may also include interference with transport through the plastid envelope and with transport polypeptides (31). Tentoxin is an example of a naturally occurring compound with potential as a model for synthetic analogues with herbicidal activity.

3.9. Amino Acid and Nucleotide Biosynthesis Inhibitors. The metabolism of amino acids is affected by both chemical herbicides and biogenic inhibitors, eg, bialaphos, phaseolotoxin, and rhizobitoxine (31). Phaseolotoxin, a tripeptide from Pseudomonas syringae pv. phaseolicola, causes increased ornithine accumulations through inhibition of ornithine carbamoyltransferase, an enzyme in the pathway from ornithine to citrulline, the precursor of arginine. Peptidase activity cleaves phaseolotoxin to form a sulfodiaminophosphinyl-L-ornithine (109) that binds irreversibly and covalently to ornithine carbamoyltransferase like a natural affinity label. Rhizobitoxine, formed by *Rhizobium japonicum spp*., inhibits β-cystathionase which cleaves β-cystathionine to produce homocysteine, the precursor in the pathway to methionine (110,111).

Herbicides also inhibit 5-*enol*-pyruvylshikimate synthase, a susceptible enzyme in the pathway to the aromatic amino acids, phenylalanine, tyrosine and tryptophan, and to the phenylpropanes. Acetolactate synthase, or acetohydroxy acid synthase, a key enzyme in the synthesis of the branched-chain amino acids isoleucine and valine, is also sensitive to some herbicides. Glyphosate (12), the sulfonylureas (113), and the imidazoles (114) all inhibit specific enzymes in amino acid synthesis pathways.

In plants and microorganisms, synthesis of aromatic amino acids, ie, *p*-aminobenzoic acid, and ubiquinone, proceeds by the shikimate pathway (112,115). In plants, this pathway also provides the precursors for indoleacetic acid [87-51-4] (IAA), a plant growth regulator, alkaloids, lignin, the flavonoids, and a wide variety of secondary metabolites (116). Some 20 enzyme-catalyzed reactions are involved in the production of the aromatic amino acids. However, herbicide mode of action studies have focused on the three enzymatic steps that convert shikimic acid to chorismic acid, the branch intermediate for a variety of metabolites. In the first step (117–119), shikimic acid is phosphorylated by shikimic kinase to form shikimate-5-phosphate which condenses with phosphoenolpyruvate (PEP) to form 3-phospho-5-*enol*-pyruvylshikimic acid (EPSP). This reaction is catalyzed by 3-phospho-5-*enol*-pyruvylshikimic synthase (EPSP synthase), the target site of glyphosate. The EPSP ring is oxidized with the loss of a phosphate group to give chorismic acid. Nanomolar levels of glyphosate inhibit only EPSP synthase. Glyphosate shows competitive inhibition with respect to PEP and noncompetitive inhibition with respect to shikimate-3-phosphate (119,120). Inhibition of aromatic amino acid synthesis by glyphosate exerts early effects on a broad range of plant processes, ie, ion uptake and transport, chlorophyll synthesis, photosynthetic CO_2 uptake, and protein and nucleic acid synthesis (121).

Two relatively new classes of herbicides, the sulfonylureas, eg, chlorsulfuron, sulfometuron, bensulfuron methyl, and chlorimuron ethyl; and the imidazolinones, eg, imazaquin, imazapyr, imazethapyr, and imazamethabenz, have totally different chemical structures but remarkably similar modes of action in plants (26,51,122) (Table 1). Both types of herbicides inhibit the same key enzyme acetolactate synthase, in the biosynthetic pathway to branched-chain amino acids. The branched-chain amino acids, ie, valine, leucine, and isoleucine, are essential amino acids produced by microorganisms and plants only. Their synthesis proceeds from threonine and pyruvate through a common series of reactions (89,123). The first common reaction in the branched-chain pathway is the formation of acetohydroxy acids by acetolactate synthase, and alternatively, acetolactate synthase (ALS) or acetohydroxyacid synthase (AHAS) (89) and imidazolinone herbicides. ALS, a nonoxidative thiamine pyrophosphate-dependent decarboxylase, is found in a wide variety of plant species; compartmentation studies indicate that it is localized in the chloroplasts (124). Unlike bacteria, plants contain a single form of ALS, and resistance to sulfonylureas is inherited as a single Mendelian trait (89,125). Sulfonylurea herbicidal activity is very potent and rapid (89,126). Sulfonylureas inhibit ALS at levels in the nanomolar range (122). These compounds appear to bind tightly to FAD (flavin adenine dinucleotide; hydroxyethylthiamine pyrophosphate) in the ALS complex. Sulfonylureas interfere with the binding of pyruvate in the case of valine synthesis and 2-oxobutyrate in isoleucine and leucine synthesis (89,127). In addition to inhibiting ALS, sulfonylureas also indirectly inhibit plant-cell division and DNA synthesis (89,126). The α-ketobutyrate accumulating when ALS is inhibited may also be cytotoxic (128). QSAR techniques applied to sulfonylurea herbicides have elucidated the physicochemical factors that determine activities *in vivo* and *in vitro,* allowing modeling of the sulfonylurea binding site (122).

The imidazolinone herbicides selectively block branched-chain amino acid synthesis through inhibition of ALS (89,129). The structures of these compounds, however, are very different from those of the sulfonylureas that block the same enzyme. Based on the extraordinary activity of the pyridyl imidazolinones (26,130), the QSAR approach was used to examine imidazolinones (26) with the goal of identifying novel synthesis candidates of high predicted activity. Initial reports (131) indicated that inhibition of maize suspension cell cultures and seedlings by imazapyr was reversed by the addition of valine, leucine, and isoleucine and that these compounds are uncompetitive (132) or simple noncompetitive (134) inhibitors of ALS. Treatment with imidazolinones inhibited plant cell division and reduced root-soluble protein, without significant effect on protein synthesis (129). Genetic evidence strengthens the hypothesis that ALS is the site of action of both the imidazolinones and the sulfonylureas (133,134).

Amitrole (3-amino-*s*-triazole) blocks histidine synthesis in bacteria by inhibiting imidazole glycerol phosphate dehydrase (134). In higher plants the active site is not known (135). In light-grown plants, amitrole increases free amino acids and decreases protein (136). The effect on protein synthesis may be indirectly caused by interferences with purine metabolism (137) and/or glycine–serine interconversion (136). Amitrole may also interfere with purine synthesis

at the step in which formylglycineamidine ribotide is cyclized to form 4-aminoimidazole (138). Amitrole also inhibits catalase (139). Plastids from amitrole-treated plants grown in light are highly aberrant, containing few 70 S ribosomes and reduced amounts of protein and plastid DNA (140). Amitrole also inhibits ζ-desaturase activity (10).

3.10. Cell Division Inhibitors. The most common mode of action of soil-applied herbicides is growth inhibition, primarily through direct or indirect interference with cell division (141). Such growth inhibitory activity is the basis for most pre- or post-emergent herbicides intended to control germinating weed seeds. In germinating seeds, cell division occurs in the meristems of the root and the shoot. Meristematic cells go through a cycle (141,142) consisting of four discrete periods: G_1, gap 1; S, DNA synthesis; G_2, gap 2; and M, mitosis. The time to complete this cell cycle is species dependent and ranges from 12 to 17 h (143). The G_1 is sometimes called the pre-DNA synthesis period and the G_2 the post-DNA synthesis period. The period of DNA transcription is represented by S, and the G_1, S, and G_2 stages constitute the interphase of the cell cycle. Many interrelated biochemical reactions occur during these stages, and interruption of any of the metabolic events in the cell cycle halts DNA synthesis, as well as RNA, protein, and essential metabolite syntheses (144).

Mitosis, the physical division of individual G_2 cells into two complete cells, is the most studied stage of the cell cycle. Mitosis itself is divided into four stages: prophase, metaphase, anaphase, and telophase (141). The two key processes of mitosis are the physical movement of chromosomes from one cellular location to another during the metaphase and anaphase and the shuttling of Golgi vesicles into the cell plate region during cell wall formation during telophase. Chromosome movement requires the attachment of several hundred microtubules to the kinetochore of each chromosome. Other microtubules extend from one end of the cell to the other to complete the mitotic spindle apparatus. Microtubules may also provide the cell skeletal framework needed for orientation and movement of Golgi vesicles during formation of the new cell wall between the two daughter cells resulting from mitosis (141).

The influences of herbicides on cell division fall into two classes, ie, disruption of the mitotic sequence and inhibition of mitotic entry from interphase (G_1, S, G_2). If cell-cycle analyses indicate increases in abnormal mitotic figures, combined with decreases in one or more of the normal mitotic stages, the effect is upon mitosis. Mitotic effects usually involve the microtubules of the spindle apparatus in the form of spindle depolymerization, blocked tubulin synthesis, or inhibited microtubule polymerization (141). Alkaloids such as colchicine [64-86-8], vinblastine [865-21-4], and vincristine [57-22-7] disrupt microtubule function (142). Colchicine prevents microtubule formation and promotes disassembly of those already present. Vinblastine and vincristine also bind to free tubulin molecules, precipitating crystalline tubulin in the cytoplasm. The capacities of these drugs to interfere with mitotic spindles, blocking cell division, makes them useful in cancer treatment.

Those herbicides that block mitotic entry decrease or prevent the formation of mitotic figures in meristems. Amino acid, protein, RNA, DNA, and ATP synthesis and/or utilization can all arrest cell growth (141,144). Although not registered as herbicides, cycloheximide [66-81-9] inhibits mitotic entry by inhibiting

protein synthesis (145); hydroxyurea [127-07-1] inhibits DNA synthesis (146); and actinomycin D [50-76-0] inhibits RNA synthesis (145).

The best understood of those herbicides inhibiting cell division are the dinitroanilines (see Table 1). Micromolar levels of these herbicides, eg, trifluralin, oryzalin, pendimethalin, nitralin, and dinitramine, act by disrupting mitosis (147–149) and producing aberrant mitotic figures in which there is no chromosome movement due to the absence or dysfunction of the spindle apparatus (150). Dinitroanilines are reported to bind to higher plant tubulin (151) and to prevent, in a concentration-dependent manner, the polymerization of higher plant tubulin in microtubles (151,152). Characteristically, dinitroaniline treatment induces swelling of the cell-elongation zone of the root-tip area (153). This hypertrophy is isotropic, suggesting that the microtubule orientation skeleton necessary for cell wall formation is absent or functioning improperly (154). Phosphorothioamidates, although not developed commercially as herbicides, also disrupt tubulin function and the mitotic sequence (155).

Various compounds in the *N*-phenylcarbamate class of herbicides, eg, propham, chloropropham, asulam, barban, and carbetamide [16118-49-3], act through disruption of mitosis (156–158), inhibition of PSII electron transport, or uncoupling of oxidative phosphorylation and photophosphorylation (141). These compounds affect the microtubule organizing center, causing the formation of multipolar spindle configurations (159). The *N*-phenylcarbamates also cause root-tip swelling (160) and branching of the cell plate during cell-wall formation during telophase (158,160), and chromosome abnormalities like bridging between daughter chromosomes (156,157,160).

The growth inhibitory mechanism of the thiocarbamate herbicides, eg, EPTC, butylate, cycloate, diallate, and triallate, is not well defined. Cell elongation, rather than cell division, appears to be inhibited (161), although mitotic entry may be inhibited by diallate (162). Thiocarbamates have a greater effect on shoot than root tissue (141,162). The well-documented inhibition of lipid synthesis by thiocarbamates certainly contributes to the observed inhibitions of cell division and elongation. These compounds may also inhibit gibberellic acid synthesis (163).

Chloroacetamide herbicides, such as alachlor, allidochlor [93-71-0], metolachlor, and propachlor, are general growth inhibitors that inhibit both cell enlargement and mitotic entry (141,164). The mechanisms by which mitotic entry is prevented are not known nor are the biochemical causes of cell-enlargement inhibition. Chloroacetamide herbicides are alkylating agents that could inhibit the cell cycle at interphase through alkylation of essential enzymes (165).

The inhibitors of amino acid synthesis, sulfonylureas, imidazolinones, and glyphosate, were first recognized as general growth inhibitors that prevent mitotic entry (166,167). Whatever the mode of action, herbicides that inhibit amino acid synthesis also cause a rapid inhibition of cell growth, usually through inhibition of mitotic entry.

DCPA inhibits the growth of grass species by disrupting the mitotic sequence, probably at entry (168). DCPA influences spindle formation and function (159) and causes root-tip swelling (160) and brittle shoot tissue (169). It has been reported that DCPA, like colchicine and vinblastine, arrests mitosis at prometaphase and is associated with formation of polymorphic nuclei after mitotic

arrest (170). Pronamide also inhibits root growth by disrupting the mitotic sequence in a manner similar to the effect of colchicine and the dinitroanilines (171,172). Cinmethylin and bensulide prevent mitotic entry by unknown mechanisms (172).

Before the germination process has begun, quiescent or dormant seeds are not sensitive to chemical herbicides, and many noxious weeds owe their persistence to seed dormancy survival strategies (173,174). Weed seeds lie dormant in the soil until specific conditions of environment and time since dispersal are met, and a portion of the seeds in the soil seed bank germinate. These germinated seedlings then become susceptible to herbicides. Other dormant seeds, with different germination requirements, remain in the soil and eventually germinate after earlier herbicide applications are no longer effective. Programs to control weed species, eg, *Avena fatua L.*, or wild oats, surviving through seed dormancy and parasitic weeds, eg, *Striga spp*. or witchweed, that germinate only in the presence of host roots frequently include development of germination stimulants that break seed dormancy (174,175). The nonparasitic weed seedlings are then susceptible to pre-emergence herbicides such as those described as inhibiting cell division, an essential process in seed germination. Further, suicide germination in the absence of an obligate host kills the parasitic weed seedlings by starvation (174–176).

3.11. Plant Growth Regulator Synthesis and Function Inhibitors. In a broad sense, herbicides are exogenous plant growth regulators, ie, plant growth inhibitors (21). Endogenous plant growth regulators, which can both stimulate and retard growth, fall into five categories, ie, auxins, gibberellins, cytokinins, abscisic acid, and ethylene (177). In the past, these compounds have been called plant hormones or phytohormones because of similarities with animal hormones, ie, defined as organic compounds synthesized in one part of an organism and translocated to another part where, in very low concentrations, they cause a physiological response. However, significant differences between plant and animal physiology have led to the use of plant growth regulator (PGR) as the preferred descriptor for these compounds which are common to all higher plants and also for the synthetic compounds which are analogues, competitors, or antagonists of the natural PGR compounds.

The auxins include the first natural PGR recognized, indoleacetic acid (IAA). In plants, IAA is the chemical signal responsible for the first identified auxin-response, phototropism (177). Auxin mediation is observed in stem and root elongation, as well as in control of lateral bud development and fruit set. Auxin also stimulates intracellular ethylene production. Similar synthetic compounds that induce the physiological responses associated with IAA include naphthalene acetic acid, indolebutyric acid, 2,4-D, 2,4,5-T, and MCPA (see Table 1). The last three compounds belong to the chlorophenoxy acid class of herbicides (51,177). Development of 2,4-D and its phenoxyalkanoic acid analogues occurred during World War II, and use of these herbicides in food production was readily accepted as a consequence of increased labor costs in the industrialized countries after that war (177,178). The structure–activity studies of the phenoxyacetic acids were the basis of the initial QSAR papers (179,180). Trace levels of 2,4-D stimulate elongation growth, as does IAA. Higher concentrations

are needed to produce the inhibitory effects associated with these herbicides (46,181).

Other auxin-like herbicides (21,51) include the chlorobenzoic acids, eg, dicamba and chloramben, and miscellaneous compounds such as picloram, a substituted picolinic acid, and naptalam (see Table 1). Naptalam is not halogenated and is reported to function as an antiauxin, competitively blocking IAA action (177). TIBA is an antiauxin used in receptor site and other plant growth studies at the molecular level (182). Diclofop-methyl and diclofop are also potent, rapid inhibitors of auxin-stimulated response in monocots (68,69). Diclofop is reported to act as a proton ionophore, dissipating cell membrane potential and perturbing membrane functions.

All auxins, both natural IAA and the synthetics, stimulate ethylene production, and some reports have suggested that auxin effects may be due to increased ethylene concentration (177,183). Auxin-induced tissue elongation is apparently not directly affected by ethylene, but leaf epinasty, inhibition of stem, root, and leaf elongation, and floral senescence may involve ethylene to some degree. Lateral expansion or swelling is a rapid, easily recognizable physiological response to ethylene (183). This ethylene-induced change from elongation to isodiametric expansion is often accompanied by changes in basic cell wall structure, hormone balance, water relationships, metabolic pool sizes, intercellular localization of enzyme activities, and wall extensibility. Ethylene exposure frequently increases enzyme synthesis (177) and inhibits auxin-induction of enzymes in cell wall metabolism (184). Plant responses to ethylene are the basis for the growth-inhibiting uses of ethephon (Ethrel) which is applied to promote fruit ripening and abscission, and boll opening and defoliation in cotton (51). It has been suggested that an antagonism or buffering effect exists between ethylene and auxin (184–187), as well as between ethylene and gibberellic acid (188).

Abscisic acid [21293-29-8] (ABA), a sesquiterpenoid, is a natural plant growth inhibitor found in all higher plants (189). The three principal activities of ABA are inhibition of auxin-induced growth through plasmalemma charge alteration, inhibition of RNA synthesis, and inhibition of protein synthesis (177). ABA also interacts with other PGRs to control bud dormancy and induce flower, leaf, and fruit abscission (177). The biosynthetic pathway from farnesyl pyrophosphate to ABA is similar to those which produce sterols, carotenoids, and gibberellins. Several fungicides, eg, triadimefon [43121-43-3], and plant growth retardants, eg, tetcyclacis, that block sterol metabolism also block ABA biosynthesis (190,191).

The gibberellins (GAs), which constitute a large PGR class, occur in all higher plants and influence many plant growth processes, eg, induction of hydrolytic enzymes during seed germination, induction of flowering in some plants, stimulation of cell elongation and, to some degree, cell division (177). The history, occurrence, and chemistry of the GAs have been reviewed (192–194). Like the other natural PGRs, GAs are theoretically susceptible to influence by xenobiotics at the biosynthesis stage, during catabolism, during transport of the GAs or precursors, by alteration of the number and activity of GA receptors, and through modifications of the reactions induced by GAs.

Since GAs as diterpenes share many intermediates in the biosynthetic steps leading to other terpenoids, eg, cytokinins, ABA, sterols, and carotenoids, inhibitors of the mevalonate (MVA) pathway of terpene synthesis also inhibit GA synthesis (31). Biosynthesis of GAs progresses in three stages, ie, formation of *ent*-kaurene from MVA, oxidation of *ent*-kaurene to GA_{12}-aldehyde, and further oxidation of the GA_{12}-aldehyde to form the different GAs; more than 70 different GAs have been identified.

Compounds that slow cell division and shoot elongation without causing malformation are defined as growth retardants rather than herbicides (195,196). Growth retardants have value in the horticultural industry where short, compact flowering plants are desired and in cereal grain production where they serve as antilodging agents. Grain and fruit yields may also be increased when vegetative growth is retarded (192). Most commercial growth retardants act on GA biosynthesis. The onium growth retardants containing positively charged ammonium, phosphonium, or sulfonium moieties (51,197, 198) interfere directly with the biosynthetic steps leading to *ent*-kaurene. AMO-1618, chlormequat chloride (CCC), mepiquat chloride, chlorphonium chloride, and some trimethyl iodides inhibit *ent*-kaurene synthetase. A in several species and standard assay systems. However, CCC does not seem to lower GA contents of some higher plants (199,200). The dwarfing effects of these compounds can be reversed in some cases by exogenously applied GA, suggesting that other factors beyond inhibition of GA biosynthesis are involved in the action of these onium compounds. CCC, AMO 1618, and chlorphonium chloride also restrict synthesis of sterols and other terpenoids (201).

Ancymidol, a pyrimidine derivative, has found some commercial application since pyrimidines inhibit the oxidative reactions that produce *ent*-kaurenoic acid from *ent*-kaurene in the GA synthetic pathway (202,203). Other related pyrimidines and cytokinins have also been described as inhibiting GA synthesis (204). A second class of growth retardants, the norbornenodiazetine derivatives, eg, tetcyclacis, also inhibit the first three steps of *ent*-kaurene synthesis in higher plants (195). After the triazole fungicides, triadimefon [43121-43-3] and tridimenol [55219-65-3], were reported to inhibit shoot elongation (205), other triazoles were developed as growth retardants, eg, uniconazole (206), paclobutrazol (207), and BAS 11100W (208). The site of action of these triazole fungicides and plant growth retardants appears to involve the cytochrome P-450–containing monooxygenase(s) that catalyze the oxidation of *ent*-kaurene to *ent*-kaurenoic acid (209,210). This hypothesized mechanism may also extend to imidazoles, eg, 1-*n*-decylimidazole [53529-02-1] (211) and 4-pyridines which also retard plant growth (212). The nobornenodiazetine and triazole growth retardants are translocated in the xylem and are more active when applied via the roots or stems than when sprayed on the leaves (192,213).

Cytochrome P-450 is frequently the oxygenase which detoxifies xenobiotics, including herbicides. Blocking the metabolism of a herbicide increases the activity or delays the inactivation, thus increasing the effectiveness of such herbicides as chlortoluron [15545-48-9] and bentazon [25057-89-0] (214–216). Most of the GA-synthesis inhibitors characterized so far affect two segments of the complicated pathway from MVA to the many different GAs identified. The cyclization reactions that produce *ent*-kaurene are inhibited by the onium growth retar-

dants, and the oxidations of *ent*-kaurene to *ent*-kaurenoic acid are sensitive to heterocyclic triazoles such as paclobutrazol and similar compounds. Other enzymes in the pathway are points for pathway disruption by as yet undeveloped GA biosynthesis inhibitors (217).

Cytokinins, first recognized as inducers of cell division, also evoke a diversity of other responses in plants (218). Root-produced cytokinins move to the shoot, interacting with other PGRs and factors to control both development and senescence. The biosynthesis and metabolism of cytokinins are quite complex, and the effects of herbicides on cytokinins are not well understood. Cytokinins also occur as component nucleosides in tRNA in plants, as well as animals and microorganisms. The lack of plant-specificity has made cytokinins less interesting than other PGRs to developers of herbicides. Some exogenous chemicals, including ABA, significantly modify cytokin in metabolism in plants.

4. Environmental Fate of Herbicides

4.1. Herbicide Fates in Plants. Beyond modes of action and structure–activity relationships, developers of new herbicides must also consider uptake by plants, translocation within the plant, and possible deactivation of herbicides by contact with soil. Some of these problematic factors can be addressed as part of the QSAR studies and during the screening process. Considerable attention is also being paid to the use of safeners (51,76) which protect the crop from herbicides that specifically target the weeds usually associated with that crop. Environmental protection and pesticide regulation concerns are the driving forces in the current efforts toward minimizing application rates, optimizing delivery through improved formulations and application equipment, and increasing target specificity. These research and development efforts include other important and related areas of interest to chemists, eg, the fate and detection of herbicides in the soil and ground and surface water.

4.2. Factors Affecting Environmental Fate. The fate of herbicides in the environment is influenced by many chemical, biological, and physical factors. The principal transport and dissipation pathways include sorption to organic and mineral soil and sediment constituents; transport to groundwater in the solution phase by mass flow and/or diffusion; transport to surface water in either the solution or sorbed phases; loss to the atmosphere through volatilization, with redeposition at a later time and location; transformation or mineralization by biological, chemical, or photochemical processes; and uptake by plant or animal species. These processes do not operate as isolated systems, but occur simultaneously and involve significant interaction and feedback. Although the environmental fates of most herbicides are controlled primarily by one or two of the outlined processes, all of these factors influence the fate to some extent. Each of the processes are discussed briefly to provide a basis for understanding their relative importance to an individual herbicide's environmental fate.

Sorption. The retention or sorption of a herbicide by soil, sediment, or aquifer material is one of the most important factors in deciding a particular chemical's environmental fate. The degree to which a herbicide is retained determines its concentration in the soil solution and thus the amount that is

available to be leached. Sorption of a herbicide is dependent on the sum of the attractive and repulsive forces between the solid and solution (or vapor) phases. The majority of the interactions between the herbicide and the soil are electrostatic in nature and are therefore influenced by factors that affect the charge status of the system. Proposed sorption mechanisms would include cation and anion exchange, hydrogen bonding, ligand exchange, hydrophobic bonding, and nonpolar van der Waals interactions. Herbicide sorption is most often quantified through the use of a soil sorption, ie, distribution, coefficient (K_d), which is the ratio of the herbicide in the solid, or sorbed phase, to that in the solution phase (219,220).

The amount of herbicide sorbed by a given soil is influenced by properties of both the soil and the herbicide. Important properties related to the soil's retention ability include clay mineralogy, organic matter content, soil pH, and iron and aluminum oxide content. These properties, in turn, affect the soil's cation- and anion-exchange capacities (220). Important properties of a herbicide include charge, polarity, size, and flexibility (219). The charge of the herbicide is frequently influenced by the soil pH because many herbicides are ionizable. Sorption theory as it relates to herbicides and other organics has been reviewed (221,222).

Leaching. Leaching can be loosely defined as the transport of chemicals in the soil profile, as a result of the action of percolating water (223). Strictly speaking, this occurs through two distinct mechanisms, diffusion and mass flow. Diffusion results from random molecular motion and occurs from areas of high to low concentration. Movement of a herbicide through dispersion, which results from the effects of differential mixing and pore water velocities in the soil matrix, is usually included with the effects of diffusion. Transport by mass flow occurs through the movement of water in which the herbicide is dissolved or by the movement of suspended soil or sediment to which the herbicide is sorbed. Thus the total amount of a herbicide leached is the sum of that transported by diffusion, dispersion, and mass flow processes (224,225).

As previously stated, the degree to which a given herbicide is leached is significantly influenced by its sorption to soils and sediments. Therefore, factors of the soil and herbicide that affect sorption also have an influence on the degree to which the herbicide is leached. However, other factors related to the movement of water through the soil can influence this process. Important contributing factors include the amount and intensity of precipitation or irrigation, the soil texture, the tillage system, and the soil topography. Reviews are available on the theory and modeling of herbicide leaching (221,226–228) and on experimental techniques (222,223).

Runoff. Runoff can be defined as water and any dissolved or suspended matter it contains that leaves a plot, field, or small-cover watershed in surface drainage (225). Processes that influence herbicide leaching also influence the degree to which a herbicide is subject to runoff loss. Those factors that encourage the leaching of a herbicide generally reduce its loss in runoff and vice versa. Specific factors known to influence the amount of herbicide lost to runoff include rainfall timing and intensity with respect to herbicide application time, herbicide application rate, herbicide solubility in water, terrain slope, vegetative cover, and soil texture (225,229). Factors relating to the herbicide's sorption, mobility,

and persistence also influence its runoff susceptibility. The practical and theoretical aspects of herbicide runoff have been reviewed (230).

Volatilization. The susceptibility of a herbicide to loss through volatilization has received much attention, due in part to the realization that herbicides in the vapor phase may be transported large distances from the point of application. Volatilization losses can be as high as 80–90% of the total applied herbicide within several days of application. The processes that control the amount of herbicide volatilized are the evaporation of the herbicide from the solution or solid phase into the air, and dispersal and dilution of the resulting vapor into the atmosphere (231). These processes are influenced by many factors including herbicide application rate, wind velocity, temperature, soil moisture content, and the compound's sorption to soil organic and mineral surfaces. Properties of the herbicide that influence volatility include vapor pressure, water solubility, and chemical structure (232).

Degradation or Transformation. Degradation or transformation of a herbicide by soil microbes or by abiotic means has a significant influence not only on the herbicide's fate in the environment but also on the compound's efficacy. Herbicides that are readily degraded by soil microbes or other means may have a reduced environmental impact but may not be efficacious. Consider the phenomenon of herbicide-resistant soils. In these cases, repeated application of a given herbicide has led to a microbial population with an enhanced ability to degrade that herbicide (233,234). This results in a decrease or total loss of the ability of the herbicide to control the weed species in question in a cost-effective manner.

The degradation of a herbicide by soil microbes is primarily an enzymatic process in which cellular or extracellular enzymes break down the herbicide into smaller molecules that may be used by the organism as an energy or nutrient source. If the herbicide is used by the organism, the process is called catabolism. If the herbicide is degraded incidentally and not used by the organism, the process is called co-metabolism (235). Microbes also may influence the degradation of a herbicide through changes in soil pH or other soil properties. The degradation of herbicides by soil microbes is an extremely active area of research, and reviews have been published (235,236).

Degradation of a herbicide by abiotic means may be divided into chemical and photochemical pathways. Herbicides are subject to a wide array of chemical hydrolysis reactions with sorption often playing a key role in the process. Chloro-*s*-triazines are readily degraded by hydrolysis (237). The degradation of many other herbicide classes has been reviewed (238,239).

The photochemical degradation of herbicides is dependent on the ability of the herbicide to absorb light at a wavelength between 285 and 400 nm (240,241). Light below these wavelengths is generally absorbed by the earth's ozone layer and does not reach the surface. Light above 400 nm does not have sufficient energy to alter chemical bonds and thus does not photodegrade herbicides. Considerable work is being conducted to investigate the possibility of utilizing photochemical reactions to degrade waste herbicides. Examples of these approaches would include photocatalytic systems, eg, ultraviolet (uv) light plus a photocatalyst; ozonation/uv light systems; and free-radical generating systems, eg, $Fe_2^{2+}O_2$ or Fe^{3+}/H_2O_2 with or without uv light. Specific examples of these systems are discussed in the sections on individual herbicide classes.

Plant or Animal Uptake. Uptake and accumulation of a herbicide by a plant species is an important dissipation pathway for some herbicides. Indeed, for the target weed species, uptake of the herbicide is the desired outcome. The principal point of entry for soil-applied herbicides in seedling and adult plants is usually the root system, although this may be complicated by volatilization of the herbicide and subsequent absorption of the herbicide through aboveground plant organs (226). Foliage-applied herbicides must enter the plant through the leaf cuticle or the stomata. Successful penetration through the cuticle requires several complex steps and is significantly more involved than uptake through the plant root system (242). Distribution of the herbicide throughout the plant after uptake is primarily dictated by the mode of action of the herbicide. Some plants have the ability to detoxify a herbicide after uptake, eg, corn (Zea mays) cultivars which can hydrolyze atrazine or propazine to their nonphytotoxic hydroxy metabolites (243).

The extent to which a herbicide is accumulated in living organisms is defined as bioaccumulation. If a compound is transferred in the food chain, with a concurrent increase in concentration, it is called biomagnification (244). Uptake and accumulation of a herbicide by a living organism is controlled largely by the compound's solubility in water (245). Herbicides that tend to bioaccumulate and biomagnify are those compounds that are not readily soluble in water. Other properties that give an indication of a herbicide's tendency to bioaccumulate or biomagnify include the octanol–water partition coefficient (K_{ow}) and the soil sorption coefficient (K_d). The octanol–water partition coefficient indicates a herbicide's lipophilic nature and thus its tendency to accumulate in fatty tissue. The soil sorption coefficient relates the extent to which a compound will be retained by the soil and thus potentially be removed from the food chain. It should be noted, however, that even a herbicide which is strongly bound to the soil may be transported to an aquatic system by runoff and become available to bottom-feeding fish or benthic organisms (245). Individuals interested in the study of bioaccumulation and biomagnification indicators are referred to References 245 and 246.

4.3. Measurement of Environmental Fate. *Water Quality Risk.* Continued concern is expressed over the potential contamination of surface and groundwaters by agricultural chemicals. Herbicides have received much of this attention, due to their widespread use and the large total volume applied. However, this perceived threat to groundwater resources appears to be largely unfounded. A survey of private wells and public water well supplies in the United States has revealed that <1% contain herbicides at levels that would affect human or animal health (247). In addition, those sources that are contaminated can usually be attributed to point rather than nonpoint sources. A point source of contamination is readily located and thus more easily controlled and remediated, and is generally associated with industrial sources or municipal wastewater plants, although agricultural sources such as herbicide equipment rinsing stations also could be point sources. A nonpoint contamination source is one in which the exact source is unknown. They are typically diffuse, often of large areal extent (248), and are generally of agricultural origin. Nonpoint sources are generally treated by modifications in agricultural management practices. Typical modifications would include the use of alternative herbicide formula-

tions, the splitting of the herbicide application in time, or the installation of vegetative buffer strips to trap runoff.

A re-evaluation of the water quality problem has revealed that surface water resources, rather than groundwater resources, are at higher risk of contamination from agricultural chemicals. It has been demonstrated that 94% of the herbicides reaching the Cedar River Basin in Iowa were transported in runoff, compared to 6% through groundwater flow (249). In addition, runoff had a higher herbicide concentration than groundwater sources. Additional information on the effects of herbicides on drinking water quality (250) and groundwater hydrology or remediation are available (251–253).

Carcinogenicity. The public health implications of drinking water contamination by herbicides are unclear. The levels that have been detected in groundwater are generally in the part per billion (ppb) or part per trillion (ppt) range and are below estimated acute toxicity levels. However, the long-term health effects of this exposure are generally unknown. Several studies have demonstrated that the mortality from some types of cancer is significantly higher in rural residents of many corn belt states (254). This trend is particularly evident in a study from Kansas involving 2,4-D exposure; however, factors other than 2,4-D exposure are also being considered. The U.S. Environmental Protection Agency (EPA) developed a classification scheme in an attempt to further evaluate the carcinogenic potential of herbicides and pesticides (250). In this system, chemicals are placed in one of five groups, A–E, according to their carcinogenic potential, ranging from definite (A) human carcinogens to no evidence of carcinogenicity for humans (E). The principal difference between these groups is the amount of accumulated evidence demonstrating carcinogenic potential. There is sufficient evidence of a causal association between Group A compounds and cancer, but this is not the case with the other groups. Group B has been further divided into B1, for which a limited amount of epidemiological evidence indicating carcinogenicity is present, and B2, for which adequate evidence from animal studies is present. For those compounds in Group C, limited animal data suggesting carcinogenicity is present, but inadequate or no human data exist. There is inadequate animal and human data for Group D compounds. Finally, for Group E compounds, there is no evidence of carcinogenicity in at least two animal tests or in adequate animal and human studies (250).

This classification scheme is used in part in the determination and calculation of health advisory (HA) drinking water levels or carcinogenic risk estimates. The majority of herbicides in use in the United States for which HAs have been issued fall into Group D, with a smaller percentage falling into Group C (250). This would indicate that there are insufficient data to classify the carcinogenic potential of many herbicides. This does not imply that chemical companies are not adequately testing herbicides. To the contrary, exhaustive toxicological testing of a potential herbicide is required by the U.S. EPA before registration. Thelack of data does indicate, however, that further testing will be required before the carcinogenic potential of many herbicides is known. Based on available HAs and the U.S. EPA classification scheme, acifluorfen, alachlor, amitrole, haloxyfop–methyl, lactofen, and oxadiazon have been listed as B2 carcinogens (255). Further information on carcinogenic risk assessment is available (256).

Analytical Methods. Since 1984, dramatic technical advances have been made in the analysis of trace organic chemicals in the environment. Indeed, these advances have been largely responsible for the increased public and governmental awareness of the wide distribution of herbicides in the environment. The ability to detect herbicides at ppb and ppt levels has resulted in the discovery of trace herbicide residues in many unexpected and unwanted areas. The realization that herbicides are being transported throughout the environment, albeit at extremely low levels, has caused much public and governmental concern. However, the public health implications remain unclear.

Numerous collections of herbicide analysis methods have been published (257–260). An increased emphasis has been placed on the first step in the environmental sampling process, that of obtaining a representative, uncontaminated sample. If this is to be accomplished, consideration must be made of such factors as sample size and location (261–264). After the sample has been obtained, it must be stored in such a way as to minimize degradation. This generally consists of refrigeration, possibly preceded by some type of drying (265).

Preparation of soil–sediment of water samples for herbicide analysis generally has consisted of solvent extraction of the sample, followed by cleanup of the extract through liquid–liquid or column chromatography, and finally, concentration through evaporation (266). This complex but necessary series of procedures is time-consuming and is responsible for the high cost of herbicide analyses. The advent of solid-phase extraction techniques in which the sample is simultaneously cleaned up and concentrated has condensed these steps and thus greatly simplified sample preparation.

Traditionally, herbicides have been analyzed by gas chromatography (gc) or spectrophotometric methods. The method of choice when accuracy and sensitivity are of the utmost importance is gc, especially when combined with mass spectrometry (268). However, several other methods are used for routine monitoring or screening purposes. High pressure liquid chromatography (hplc) provides detection limits that nearly rival gc and require significantly less sample preparation and cleanup (266,269). Advances in the 1980s have made thin-layer chromatography (tlc) a valuable tool in herbicide analysis (266,270). The combination of high performance tlc plates and scanning densitometers allows quantitative results to be obtained at detection limits that nearly rival hplc. Significant advances have been made in stationary phases for both hplc and tlc systems, including reverse-phase options. These have proven to be invaluable for herbicide analysis. Another analytical tool that has received much attention and shows great promise for routine analysis is enzyme immunoassay (eia) (271–273). This technique offers the advantages of a low cost analysis, few interferences, high specificity and sensitivity, and a minimal amount of sample preparation.

A mobility ranking based on soil thin-layer chromatography (stlc) is used to classify the herbicide leaching potential of various herbicides (274,275). The rankings range from I (immobile) to V (very mobile) with intermediate categories of II (low mobility), III (intermediate), and IV (mobile). This method is widely used and has been accepted for submission of leaching data for herbicide registration purposes by the U.S. EPA (223).

A comprehensive search (276) of the STORET water quality database, maintained by the U.S. EPA Office of Water, is used to evaluate the potential water quality implications of various herbicides. This database contains information on contamination of surface water (SW) and groundwater (GW) supplies. The data are provided to give a general impression of the occurrence of a given herbicide in SW and GW (250). The U.S. EPA scheme for categorizing a chemical's carcinogenic potential is used for herbicides for which healthy advisory information (HA) is available. The U.S. EPA is continually issuing HAs for various environmental contaminants; HAs available in Reference 250 were used in preparation of this article.

5. Classification of Herbicides

There is no general agreement as to the best system of herbicide classification. However, the classification based on mode of action is most useful for weed management purposes. This method of classification is supported by the Weed Science Society and the Herbicide Resistance Action Committee.

Herbicides may be selective or nonselective in action; ie, nonselective herbicides are generally toxic to all vegetation, although selectivity may be achieved by varying dosage or method of application. Glyphosate is an example of a nonselective herbicide used for total vegetation control.

Herbicides may be used before the emergence of a particular crop or weed (preemergence) or postemergence, that is, after the particular crop or weed has emerged. Herbicides may be applied to the leaves of plants (foliar application), to the soil surface, or incorporated in soil or injected into the soil prior to seeding or transplanting. Herbicides absorbed by the root or leaf may be moved by translocation within the plant. By contrast, contact herbicides kill plant tissue directly on contact.

For the chemist, classification may be based on the structural formula. However, allocation to a particular class may be somewhat arbitrary when a variety of substituents and linkages are contained in a complex molecule. The structural diversity of organic herbicides continues to increase. The chlorinated aryloxy acids that dominated the United States market following their introduction as plant growth regulators in 1942 were replaced by chemicals of many distinct chemical classes, including triazines, amides (haloacetanilides), benzonitriles, carbamates, thiocarbamates, dinitroanilines, ureas, phenoxy acids, diphenyl ethers, pyridazinones, bipyridinium compounds, ureas and uracils, sulfonylureas, imidazolinones, halogenated carboxylic acids, inorganics, organometallics, and many compounds that are the sole representative of their class.

6. Herbicide Groups

Herbicides can be grouped according to common structural features. Sometimes the assignment is arbitrary when there are a multitude of functional groups, eg,

acifluorfen which is a diphenyl ether (phenoxy compound) as well as a trifluoromethyl compound.

6.1. Phenoxyalkanoics. The phenoxyalkanoic herbicide grouping is composed of two subgroups, the phenoxyacetic acids and the phenoxypropionic acids. The phenoxyacetic acid herbicides include some of the first commercially successful herbicides, eg, 2,4-D. They continue to be widely used for foliar control of broadleaf weeds. The more heavily functionalized phenoxypropionic acid herbicides are relatively new herbicides compared to the phenoxyacetic acids and are used primarily for selective control of grassy weeds in broadleaf crops (15,227,278).

The phenoxyalkanoic herbicides are acidic in nature and thus subject to some degree of ionization. The extent to which the herbicide ionizes is controlled by the acid dissociation constant (K_a) of the herbicide in question and the soil solution pH (219). The leaching potential is significantly influenced by these reactions.

The sorptive behavior of the phenoxyacetic acid herbicides has been investigated. Both the free acid and amine salt formulations of 2,4-D are minimally sorbed to the soil (279) and would be classified as mobile by stlc techniques (274). Some increase in sorption is expected in soils containing significant quantities of organic matter (51). The salt formulations of 2,4-D, 2,4-DB [94-82-6] (4-(2,4-dichlorophenoxy)-butanoic acid) and 2,4-DP [120-36-5] (2-(2,4-dichlorophenoxy)-propanoic acid), tend to be slightly more mobile than the free acids (280). No difference was noted in the runoff potentials of an amine salt and ester formulation of 2,4-D; however, the ester formulation resulted in significant volatilization losses (281). MCPA is weakly retained by soil and is also classified as mobile. The phenoxybenzenes, nitrofen and oxyfluorfen, were found to be strongly sorbed to organic soils and were only minimally leached (282).

Considerable research has been conducted on the breakdown of phenoxyacetic acids in soil. The decomposition of 2,4-D appears to be primarily a microbial process that occurs rapidly in surface soils under aerobic conditions and decreases with depth (283). MCPA is also degraded by microbial means although at a slower rate than 2,4-D (284). MCPA has also been shown to photodecompose rapidly, losing $>80\%$ of the initial herbicide application in six days of exposure (285). 2,4-D has been shown to be completely degraded in aerated solutions of hydrogen peroxide containing Fe^{3+}. This reaction can be further accelerated by irradiation with visible light containing a small ultraviolet (uv) component (286). Other related materials include bifenox [42576-02-3] and (4-(4-chloro-2-methylphenoxy)-butanic acid) MCPB [94-81-5].

The phenoxypropionic acids, eg, haloxyfop–methyl and fluazifop–butyl (Table 1) bear a variety of other functional groups and are not strongly sorbed to soils of widely varying constituents (278). Thus the leaching potential of these compounds is significant. Both compounds are rapidly hydrolyzed to the parent free acids in soil and gradually decomposed by microbial means (278,287). Diclofop–methyl (Table 1) is hydrolyzed in hydroalcoholic solutions in the presence of montmorillonite (288). Finally, mecoprop [7085-19-0] was degraded by several microbial communities (289) but not by the individual members, indicating a co-metabolic relationship. Other phenoxypropionic acid herbicides include dichlorprop [120-36-5] and quizalofop–ethyl [76578-14-8].

Considerable concern has been raised over the carcinogenic potential of 2,4-D. However, the World Health Organization (WHO) has evaluated the environmental health aspects of this chemical and concluded that 2,4-D posed an insignificant threat to the environment. They did indicate, however, that only limited data on toxicology in humans are available (290). An HA has been issued (250) for MCPA. It was found in 4 of 18 SW samples analyzed and in none of 118 GW samples (276), and has been placed in Group D for carcinogenic potential (250). EPA has published two gc methods for the analysis of the phenoxyalkanoic herbicides (258).

6.2. Bipyridiniums. The bipyridinium herbicides (Table 2), paraquat and diquat, are nonselective contact herbicides and crop desiccants. Diquat is also used as a general aquatic herbicide (51,277). Bipyridinium herbicides are organic cations and are retained in the soil complex via cation exchange. They are strongly sorbed to most soils and are not readily desorbed (313). Both paraquat and diquat are not readily leached (274).

Paraquat and diquat can both be degraded by photochemical means, and degrade quite rapidly under natural sunlight (314). Paraquat can be degraded by microbial means (315), and rapidly degraded by uv-ozonation (316); this process can be accelerated by the addition of a photosensitizer such as acetone. Finally, both paraquat and diquat have been demonstrated to dissipate rapidly in aquatic systems, paraquat taking a slightly longer time (317). Paraquat and diquat are much more toxic than most herbicides and ingestion of sufficient quantities can result in death if prompt medical treatment is not obtained (51).

6.3. Benzonitrile, Acetic Acid, and Phthalic Compounds. Benzonitrile herbicides (Table 2) are generally used for pre-emergence and post-emergence control of broadleaf weeds. Dichlobenil [1194-65-6] also controls grass weeds (280) and dichlobenil, endothall [145-73-3], and fenac [85-34-7] are used as aquatic herbicides (51). Most benzonitriles are selective in their control (277). Benzonitrile herbicides are acidic in nature, thus their environmental fate is influenced by changes in soil pH. Sorption of these herbicides is expected to increase with decreasing pH (318). This is the case with dicamba, which is minimally sorbed at near neutral pH but demonstrates a dramatic increase in sorption as the soil pH decreases (319). Endothall is also only minimally sorbed at a near neutral pH (320).

Benzonitrile herbicides tend to possess a high leaching potential; dichlobenil is an exception, due to its stronger sorption. The benzonitrile herbicides are also prone to volatilization losses (321) and off-site deposition (322).

Benzonitrile herbicides are readily degraded by soil microbes. Dicamba is rapidly degraded in soil (323) and water samples (324) by microbial means, and is metabolized by several species of soil bacteria (325). DCPA degrades very rapidly under optimum conditions (25°C) and slower at lower temperatures (326). Bromoxynil can be degraded by microbial (327) or photochemical means. The photodegradation of bromoxynil is highly pH-dependent, a decrease in degradation occurring at lower pH values (328). Endothall, which is widely used as an aquatic herbicide, is rapidly dissipated in water (329) and dissipates only slightly slower in soil (330). Dichlobenil is apparently degraded by a combination of microbial and photochemical processes (331). Finally, fenac is slowly degraded in water and soil by microbial processes (332).

Table 2. **Environmental Health Advisories for Herbicides**

Herbicide	Health advisories[a] SW	GW	Mobility[d]	Carcinogenic potential group[b]	Analytical methods[c]
		Bipyridinium compounds			
diquatop			immobile		hplc
paraquat		0/843	immobile	E	hplc
		Benzonitrile, acetic acid, and phthalic compounds			
chloramben	13/34	1/566	very mobile	D	gc[e]
DCPA	386/1995	12/982		D	gc[e]
dicamba	262/806	2/230	very mobile	D	gc[e]
dichlobenil			low		
endothall	0/3	0/604		D	gc
naptalam					uv
		Dinitroaniline and derivatives			
benefin					gc
dinitramine					gc
dinoseb	1/89	0/1270		D	
fluchloralin					gc
oryzalin					uv
pendimethalin					gc
trifluralin	172/2047	1/507	immobile	C	ir
		Acid amides			
alachlor					gc
bensulide			immobile[f]		hplc
diphenamide	0/3	0/678	intermediate	D	gc
metolachlor	2091/4161	13/596		C	gc
napropamide					
pronamide	20/391			C	gc[g]
propachlor	34/1690	2/99	intermediate	D	gc[h]
propanil			low		
		Phenyl carbamates			
chloropropham			low		
karbutilate					hplc
propham	1/392	0/583	intermediate	D	hplc[i]
		Thiocarbamates			
asulam					uv
butylate	91/836	2/152		D	gc, glc
EPTC					hplc
thiobencarb			relatively immobile		gc, glc
triallate					gc, glc
vernolate					hplc
		Triazines			
ametryn	2/1190	24/560	intermediate	D	general[j]
atrazine	4123/10,942	343/3208	intermediate	C	gc
cyanazine	1708/5297	21/1821	intermediate[k]	D	ir
hexazinone			relatively immobile[l]	D	gc
metribuzin	938/4651	0/416		D	general[j]
prometon	386/1419	36/746	intermediate	D	gc
prometryn			low		
propazine	33/1097	15/906	intermediate	C	general[j]
simazine	922/5873	202/2654	intermediate	C	gc
terbutryn					general[j]

Table 2 (*Continued*)

Herbicide	Health advisories[a] SW	GW	Mobility[d]	Carcinogenic potential group[b]	Analytical methods[c]
			Pyridines		
clopyralid			minimal[m]		
fluroxypyr			varied		
picloram	420/744	3/64	mobile[n]	D	general[n]
triclopyr			intermediate[o]		hplc
			Pyridazinones		
norflurazon			low		
pyrazon					uv
			Sulfonylureas		
chlorimuron, ethyl			mobile[p]		
chlorsulfuron			intermediate to very mobile[q]		hplc, gc[r]
metsulfuron, methyl					gc[r]
sulfometuron			mobile to very mobile[s]		
			Imidazole compounds		
buthidazole					eia[t]
imazamethabenz					eia[t]
imazapyr					eia[t]
imazaquin			mobile to very mobile[u]		eia[t]
imazethapyr			immobile to mobile[u]		eia[t]
			Other heterocyclic nitrogen derivatives		
amitrole			mobile		vis
bentazon			very mobile[v]	D	hplc
isoxaben			immobile[w]		
			Ureas and uracils		
bromacil	0/3	0/841	mobile	C	glc
chloroxuron			immobile		glc
diuron	0/25	0/1337	low	D	ir
fluometuron	0/14	0/156	intermediate	D	uv
linuron					uv
tebuthiuron			intermediate to very mobile[x]	D	uv
terbacil				E	uv
			Aliphatic-carboxylic		
dalapon	0/14	0/14	very mobile	D	ir
TCA			very mobile		
			Inorganics and metal organics		
AMS				D	titration
			Miscellaneous trifluoromethyl compounds		
acifluorfen				B_2	hplc
fluridone					gc[y]
lactofen					hplc
			Amino acid analogues		
glufosinate, glyphosate	0/6	0/98	intermediate[z] immobile to low mobility[a']	D	hplc

Table 2 (*Continued*)

Herbicide	Health advisories[a] SW	GW	Mobility[d]	Carcinogenic potential group[b]	Analytical methods[c]
		Other miscellaneous compounds			
cinmethylin					gc
ethofumesate					gc
tridiphane					

[a] Ref. 276 unless otherwise noted. SW = surface water; GW = ground water. Positive results/number of tests.
[b] Ref. 250. Group A, human carcinogen; Group B, probable human carcinogen; Group C, possible human carcinogen; Group D, not classifiable; Group E, no evidence of carcinogenicity for humans.
[c] Ref. 258 unless otherwise noted: gc = gas chromatography; hplc = high pressure liquid chromatography; ir = infrared spectroscopy; uv = ultraviolet spectroscopy; glc = gas*liquid* chromatography; eia = enzyme immunoassay; vis = visible spectroscopy.
[d] Refs. 274 and 275. Mobility ranking based on soil thin-layer chromatography (stlc).
[e] Ref. 291. Gc for chlorinated pesticides can be used.
[f] Ref. 292.
[g] Ref. 293.
[h] Ref. 294.
[i] Ref. 295.
[j] General draft method for nitrogen- and phosphorus-containing pesticides.
[k] Ref. 296.
[l] Ref. 297.
[m] Mobility has been reported to be mobile (Refs. 274 and) and minimal in different studies.
[n] General draft method for determination of chlorinated acids in water .
[o] Ref. 298.
[p] Ref. 300.
[q] Ref. 301.
[r] Ref. 302.
[s] Ref. 303.
[t] Ref. 304.
[u] Ref. 305. Mobility is a function of soil pH 306.
[v] Ref. 307.
[w] Ref. 308.
[x] Ref. 309.
[y] Ref. 310.
[z] Ref. 311.
[aa] Ref. 312.

Development of resistance to these herbicides is rare (333).

HAs have been issued for chloramben, DCPA, dicamba, and endothall (250); health advisories have not been issued for the remaining benzonitrile herbicides (258).

6.4. Dinitroanilines and Derivatives. Dinitroaniline herbicides are used principally for the selective, pre-emergence control of annual grasses and broadleaved weeds. They have little or no post-emergence activity. Oryzalin is used for selective weed control in flooded rice culture. In general, dinitroaniline herbicides are extremely prone to volatilization losses (280). For this reason, they should always be incorporated in the soil immediately after application; oryzalin

and pendimethalin are exceptions to this statement. Dinitroaniline herbicides are nonionic and retained in soil primarily by hydrogen bonding to soil organic matter, or possibly through hydrophobic or van der Waals forces. The uptake of nonionic herbicides has been described as a chemical partition of the herbicide into soil organic matter (334,335). The reactions are governed, to a large extent, by the herbicide's polarity.

Considerable research has been conducted to investigate the soil sorption and mobility of dinitroaniline herbicides. In general, these herbicides are strongly sorbed by soil (336), and sorption has been correlated to both soil organic matter and clay content (337). Dinitroaniline herbicides are not readily leached in most soils (338), although leaching of trifluralin is enhanced by addition of surfactants (339).

Degradation of dinitroaniline herbicides has also been extensively investigated. Trifluralin undergoes rapid initial dissipation, primarily by volatilization, and then steady, but slower, dissipation through a combination of volatilization and degradation pathways (340,341). A similar dissipation pattern was noted for dinitramine and fluchloralin [33245-39-5] (342). Oryzalin and isopropalin [33820-53-0] also degrade and do not accumulate in field soils, even after repeated applications (343) Benefin [1861-40-1] shows a similar two-stage degradation pattern consisting of a rapid initial decomposition followed by a slower first-order breakdown (344). The degradation of benefin also proceeds faster in turf thatch than in soil (345) and under anaerobic, compared to aerobic, conditions (346). Pendimethalin has been rapidly degraded in grass clippings and compost (347), as well as under anaerobic conditions (348). The breakdown of pendimethalin in soil increases with temperature and, to a lesser extent, with moisture (349). Finally, several species of soil fungi have been isolated that can effectively degrade pendimethalin (350).

Health advisories have been issued for the phenol dinoseb and trifluralin; health advisories have not been issued for the remaining dinitroaniline herbicides, eg, profluralin [26399-36-0].

6.5. Acid Amides. The principal use of acid amide herbicides is the selective control of seedling grass and certain broadleaved weeds (280). The majority of acid amide herbicides are applied pre-emergence or pre-plant incorporated, except for propanil which is applied post-emergence (52). In general, the acid amide herbicides are not considered subject to large volatilization losses (52). However, under ideal conditions, eg, high soil moisture and low soil sorption, volatilization may be significant (231).

Acid amide herbicides are nonionic and moderately retained by soils. The sorption of several acid amide herbicides has been investigated (351). Acetochlor [34256-82-1] is sorbed more than either alachlor or metolachlor, which are similarly sorbed by a variety of soils. Sorption of all the herbicides is well correlated to soil organic matter content. In a field lysimeter study, metolachlor has been found to be more mobile and persistent than alachlor (352); diphenamid [957-51-7] and napropamide [15299-99-2] have been found to be more readily leached (338).

The breakdown of acid amide herbicides in soil has been extensively investigated. They do not appear to be persistent in the soil and most are readily metabolized by soil microbes. Alachlor degradation is well correlated with microbial

biomass and respiration (353) although breakdown is slower in subsoils. Pretreatment of alachlor samples with uv light has been shown to accelerate the microbial breakdown process (354). The pretreatment process results in the dechlorination of the alachlor parent molecule and the formation of several intermediates. Pronamide is readily transformed in the soil via hydrolysis (355). Breakdown of metolachlor is also microbial in nature, though it is significantly longer lived in soil than alachlor, with a half life as long as 50 days. Preacclimation of the soil with metolachlor results in an enhanced rate of degradation (356). The isolation of soil microbes capable of degrading various acid amide herbicides has been reported, ie, several species that could transform, but not mineralize, metolachlor (357); microbial communities capable of metabolizing propachlor (358); one species that could metabolize propanil [709-98-8] (359); and finally, a microbial community which degraded diphenamid (360). The degradation process was accelerated when the microbes were preacclimated with the herbicide.

Health advisories have been issued (250) for diphenamid, metolachlor, pronamide, and propachlor. Other acid amide herbicides include butachlor [23184-66-9] and ethalfluralin [55283-68-6].

6.6. Phenylcarbamates. Phenylcarbamate herbicides represent one of two subgroups of carbamate herbicides, the phenylcarbamates and the thiocarbamates (280). Both groups are prone to volatilization losses; the thiocarbamates are particularly susceptible and should be soil-incorporated immediately after application (52). The carbamate herbicides are used, in general, for the selective pre-emergence control of grass and broadleaved weeds (280). Exceptions would include barban, desmedipham, and phenmedipham which are applied post-emergence.

Phenylcarbamate herbicides are nonionic and, in general, readily leached in soils (280). One notable exception is chlorpropham which is strongly sorbed to soils (361). Movement of karbutilate [4849-32-5] has been studied in several Texas rangeland soils and found to be greater in a loamy sand soil than in a clay loam soil (362), but more persistent in the clay loam soil. The phosphonate fosamine–ammonium [25954-13-6] readily degrades in soils, having a half-life of one week in the field and 10 days in the laboratory (363); applications of fosamine–ammonium to the soil do not adversely affect soil microbial populations (364). Finally, a bacterial strain has been isolated that can utilize chlorpropham as a sole carbon source (365). Other phenylcarbamate herbicides include desmedipham [13684-56-5] and phenmedipham [13684-63-4].

6.7. Thiocarbamates. Thiocarbamate herbicides are also nonionic. Diallate and triallate were strongly sorbed to both cation- and anion-exchange resins, but minimally to kaolinite or montmorillonite (336). This behavior suggests a physical rather than an ionic mechanism of attraction. The mobility of the thiocarbamate herbicides increases with increasing water solubility. The ranking of five thiocarbamate herbicides, in terms of leaching depth, is molinate [2212-67-1] > EPTC > vernolate [1929-77-7] > pebulate [1114-71-2] > cycloate (366). Thiobencarb [408-27-5] has been found to be relatively immobile in soil columns under saturated flow conditions (367).

The degradation of thiocarbamate herbicides has been extensively studied. Cycloate and EPTC are readily degraded in the air by reaction with OH and NO_3 radicals (368). This is an important observation, considering the volatile nature

of the thiocarbamates. Thiobencarb is rapidly degraded in three Florida soils, exhibiting half-lives from 16–33 days (369). An increased breakdown of many of the thiocarbamate herbicides has been linked to previous application of thiocarbamates. This has generally been attributed to high enzymatic activity, resulting from an adaptation and acclimization of the microbial community to the herbicide in question. Accelerated breakdown of vernolate, EPTC, and butylate, but not of cycloate, was reported in vernolate-history soils (334). This trend also has been reported for butylate-history soils that exhibited accelerated breakdown of EPTC, but not of vernolate, pebulate, or cycloate (370). Finally, a strain of bacteria that degraded EPTC also degraded diallate (371). Metham–sodium [137-42-8] also is a thiocarbamate herbicide. A health advisory (HA) has been issued for butylate (250).

6.8. Triazines. Triazine herbicides are one of several herbicide groups that are heterocyclic nitrogen derivatives. Triazine herbicides include the chloro-, methylthio-, and methoxytriazines. They are used for the selective preemergence control and early post-emergence control of seedling grass and broadleaved weeds in cropland (280). In addition, some of the triazines, particularly atrazine, prometon [1610-18-0], and simazine [122-34-9], are used for the nonselective control of vegetation in noncropland (51). Simazine may be used for selective control of aquatic weeds (51).

The environmental fate of the triazines, particularly atrazine, has been extensively studied. The intensive use of triazine herbicides has led to the first observation of weed resistance (372). This is due, in part, to their widespread use and the regularity with which they are found in GW and SW. Triazine herbicides are weak bases and can be protonated to form cationic species depending on the herbicide pK_a and the soil pH (318). Sorption of the triazines has been positively correlated with soil organic matter content, clay content, and soil cation-exchange capacity (CEC) (373,374). When five triazines were evaluated on 25 Missouri soils, prometryn [7287-19-6] was the most strongly sorbed, followed by prometon, simazine, atrazine, and propazine [139-40-2] (373).

Triazine herbicides are not readily volatilized. However, given ideal circumstances, volatilization losses may be significant. The tendency to volatilize varies among herbicides and is highly dependent on soil type and moisture conditions. A study of the volatilization potential of seven triazines reported the following ranking of decreasing volatilization losses: prometon $\geq$ trietazine $>$ atrazine $\geq$ ametryn[834-12-8] $\geq$ prometryn $>$ propazine $\geq$ simazine (375).

Triazine herbicides are subject to degradation by a wide variety of mechanisms, eg, the photocatalytic degradation of atrazine, simazine, trietazine, prometon, and prometryn (376). Degradation of all herbicides is rapid, although complete mineralization does not occur. Atrazine is also subject to degradation through chemical hydrolysis reactions (237). In general, the chlorotriazines appear to be more readily degraded through chemical hydrolysis reactions and the methoxy- and methylthiotriazines are more susceptible to microbial processes (280).

The microbiological degradation of the triazine herbicides has been thoroughly investigated. Although atrazine is thought to degrade primarily by abiotic means, several papers have demonstrated degradation of atrazine by soil bacteria (377) and soil fungi (378). Cyanazine [21725-46-2] has been found to

degrade significantly faster than atrazine in soils by a combination of chemical and microbiological processes (379). Metribuzin degraded significantly faster in surface soils than in subsoils (380). The retarded breakdown of metribuzin in subsoils was attributed to lower microbial populations and activity. Finally, terbutryn [886-50-0] degradation has been found to be particularly sensitive to soil moisture content, degradation decreasing with increasing soil moisture content (381). Other triazine herbicides include dipropetryn [4147-51-7] and hexazinone [51235-04-2]. Use is now restricted because they leach into groundwater (372). Health advisories have been issued for most of the triazine herbicides (250).

6.9. Pyridines and Pyridazinones. Pyridine herbicides are auxin-type herbicides generally used for selective control of broadleaved weeds in cropland, rangelands, and noncroplands (51,277). The pyridazinones are used primarily for the selective pre- and post-emergence control of seedling grass and broadleaved weeds in cotton and sugarbeets (280). The pyridines are slightly acidic in nature and the pyridazinones, slightly basic.

Pyridine herbicides are not strongly sorbed to soils and are readily leached. The mobility of fluroxypyr [69377-81-7] has been found to decrease with increasing incubation time (382); this is attributed to entrapment of the herbicide within the soil organic matter.

A study investigating the breakdown of clopyralid [1702-17-6] reported half-lives on different soils of approximately 2–7 weeks in a laboratory incubation (383); it was indicated that carryover was likely to occur in field soil. Picloram degrades and does not accumulate in field soil although low residue levels do persist for several years (384). The half-life for triclopyr [55335-06-3] is reported to be two weeks in two Canadian soils (385), and it has been shown to be rapidly degraded by aqueous photolysis (386).

Pyridazinone herbicides tend to be strongly sorbed in soils and do not leach readily. Norflurazon sorption increases as organic matter and clay contents increase (387), and it is subject to degradation through photolysis but only minimally through volatilization processes (387). Pyrazon [1698-60-8] sorption also has been shown to increase, and mobility to decrease, with increasing soil organic matter contents (388). The degradation of pyrazon appears to be a microbially mediated process directly related to soil organic matter content (389). Difenzoquat [43222-43-6] also is a pyridazinone herbicide.

6.10. Sulfonylureas. Sulfonylurea herbicides are a relatively new class of herbicides generally used for selective pre- and post-emergence control of broadleaved weeds in croplands (2,296). In general, the sulfonylureas are applied in significantly lower amounts than most herbicides, and they tend to be more active against broadleaved species than grasses. Sulfometuron–methyl [74222-97-2] is used for broad-spectrum selective or nonselective weed control in noncroplands (277).

Sulfonylurea herbicides are weak acids and, in general, are not strongly sorbed to soils. Sorption of chlorsulfuron and metsulfuron–methyl is inversely related to soil pH (390) and is positively correlated to soil organic matter (391).

The degradation of sulfonylurea herbicides in soils appears to occur by two processes. The first pathway involves the acid-catalyzed hydrolysis of the urea function (392,393). This process is highly pH dependent, the rate increasing as pH decreases. Several herbicidally inactive fragments formed by this process

may then be degraded by microbial means. A second pathway involves the direct microbial degradation of the sulfonylurea herbicide. This process generally occurs in conjunction with breakdown by chemical hydrolysis (394,395). Microbial degradation may be the dominant mechanism in neutral or alkaline soils where hydrolysis is minimal (394).

The EPA has not issued HAs for any of the sulfonylurea herbicides (250) and data on the occurrence of the sulfonylurea herbicides in SW or GW are not available. Additional sulfonylurea herbicides include bensulfuron [99283-01-9] and metsulfuron, methyl [74223-64-6].

6.11. Imidazoles. Imidazole herbicides are generally used for selective pre- and post-emergence control of grass and broadleaved weeds in croplands. Buthidazole [55511-98-6] and imazapyr are used for broad-spectrum, nonselective weed control in noncroplands (51,277). Imidazole herbicides are amphoteric, possessing both acidic and basic functional groups (396). A notable exception is buthidazole which is nonionic in nature (51). At typical soil pH values, most of the imidazole herbicides exist as anions (305).

Sorption of imidazole herbicides has been shown to increase with decreasing pH. This is most likely due to protonation of the basic functional groups. Imazethapyr is more strongly sorbed to soils, and thus less mobile, than imazaquin (306). The classifications for imazethapyr range from immobile on a silty clay soil (pH 5) to mobile on a sandy loam soil (pH 7); the classifications for imazaquin range from low mobility to mobile for the same soils. Similar amounts of buthidazole leached in four soil columns of varying texture (396); however, the distribution of the herbicide within the columns was different. In the fine textured soils, a greater amount of the herbicide has been detected in the surface layers than in lower layers. In the sandy soils, the herbicide is uniformly distributed throughout the column.

The persistence of imidazole herbicides varies significantly with soil pH. Imazaquin persistence increases with decreasing soil pH (396). The increase is attributed to increased sorption and thus decreased availability for microbial degradation. Imazaquin and imazethapyr have both been shown to degrade primarily by microbial or enzymatic means (397). Degradation is faster in warm, moist soils than in cool, dry soils. Finally, imazaquin also undergoes significant photodecomposition when exposed to artificial uv light or sunlight (398).

No HAs have been issued for any of the imidazole herbicides (250) and data on the occurrence of the imidazole herbicides in SW or GW are not available.

6.12. Other Heterocyclic Nitrogen Derivative Herbicides. The herbicides in this group are heterocyclic nitrogen derivatives that do not readily fall into one of the previously discussed groups. They have a wide range of uses and properties. Most of these herbicides are used for selective, pre- and/or post-emergence weed control. Amitrole is used for post-emergence, nonselective weed control in non-croplands and also as an aquatic herbicide (51,277).

Bentazon [25057-89-0] is anionic in nature and is not significantly sorbed to any of 11 Illinois soils; its half-lives have been determined to range from 11 to 32 days in water and 5 days in soil (399). Isoxaben [8255-50-7] is a nonionic compound with low water solubility (400) which degrades in aqueous systems by photolysis (400). Amitrole is degraded by free-radical generating systems (401). Finally, methazole [20354-26-1] is strongly sorbed to soils, has a low leaching

potential, and rapidly degrades in soils (402). A health advisory (HA) (250) has been issued for bentazon, though it was not found in sampling performed at two water supply stations (276).

6.13. Ureas and Uracils. Urea herbicides are generally used for selective pre-emergence and early post-emergence control of seedling grass and broadleaved weeds. Uracil herbicides are generally used for selective control of annual and perennial weed control in certain crops and for general weed control in noncrop areas. Bromacil, linuron [330-55-2], and tebuthiuron [34014-18-1] are used for the nonselective control of weeds in noncropland (51,277,280). Bromacil is also used in citrus crops, and linuron is used in sorghum and corn crops. Urea herbicides are nonionic and generally of low water solubility. The uracils are ionic herbicides that are not strongly sorbed to soils and readily leach (280).

The sorption of diuron and bromacil has been investigated on two Florida soils (403). Diuron is strongly sorbed to both soils, while bromacil was only weakly retained. Bromacil has been found to be very mobile in a related field study (404). Fenuron [101-41-8] and linuron are strongly sorbed to several Hawaiian soils, and the degree of sorption has been related to soil organic matter contents (405). The mobilities of the urea herbicides are directly related to herbicide water solubilities with mobility increasing with solubility. The mobility rankings for tebuthiuron and fluometuron may range from intermediate on a silt loam soil to very mobile on a sandy soil (309).

Urea and uracil herbicides tend to be persistent in soils and may carry over from one season to the next (280). However, there is significant variation between compounds. Bromacil is debrominated under anaerobic conditions but does not undergo further transformation (406), linuron is degraded in a field soil and does not accumulate or cause carryover problems (407), and terbacil [5902-51-2] is slowly degraded in a Russian soil by microbial means (408). The half-lives for this breakdown range from 76 to 2,475 days and are affected by several factors including moisture and temperature. Finally, tebuthiuron applied to rangeland has been shown to be phytotoxic after 615 days, and the estimated time for total dissipation of the herbicide is from 2.9 to 7.2 years (409).

HAs have been issued for bromacil, diuron, and fluometuron; no occurrence data are available for tebuthiuron or terbacil (276). Chloroxuron [1982-47-4], fenuron TCA [4482-55-7], and norea [18530-56-8] also are urea herbicides.

6.14. Aliphatic-Carboxylics. There are only two herbicides present in this class, trichloroacetate [76-03-9] (TCA) and dalapon [75-99-0]. These are used primarily for the selective control of annual and perennial grass weeds in cropland and noncropland (51,280). Dalapon is also used as a selective aquatic herbicide (410). Dalapon and TCA are acidic in nature and are not strongly sorbed by soils. They are reported to be rapidly degraded in both soil and water by microbial processes (51,410). However, the breakdown of TCA occurs very slowly when incubated at 14–15°C in acidic soils (411). Liming not only accelerates this degradation but also increases the numbers of TCA-degrading bacteria. An HA has been issued for dalapon, but not TCA (250).

6.15. Metal Organics and Inorganics. The metal organic herbicides are arsenicals used for the selective, post-emergence control of grass and broadleaved weeds in cropland and noncroplands. These herbicides are particularly useful for weed control in cotton and turf crops (51,275,277). Cacodylic acid is

a contact herbicide used for nonselective weed control in cropland and noncropland (280). Ammonium sulfamate [7773-06-0] (AMS) is an inorganic herbicide used for control of woody plants and herbaceous perennials (51).

Arsenical herbicides are salts of methylarsonic acid, eg, calcium salt of methylarsonic acid [5902-95-4] (CMA), and are thus freely soluble in water (280). They are strongly sorbed to soils and not readily leached (51). The sorption of DSMA is greater on clay soils than on sandy soils (412). In addition, the amount sorbed is greater on kaolinite than on montmorillonite or vermiculite, indicating possible retention by exposed hydroxyl groups. Sorption of MSMA is also significantly higher on clay soils than on sandy soils (413), and MSMA is essentially immobile in field studies and not expected to leach. AMS is not retained in soils and is susceptible to leaching losses (414). Cacodylic acid and MSMA are both degraded in field soils and do not accumulate with repeated application (415). MSMA is degraded at a faster rate under flooded soil conditions than in soils at a moisture content less than field capacity (416). Finally, MSMA appears to be degraded, at least partially, by soil microbes (417). An HA has been issued for AMS, but not for any of the arsenical herbicides. A method for the analysis of the arsenicals by hplc is also available (418).

6.16. Miscellaneous Trifluoromethyl Compounds. The herbicides in this group are used for a wide variety of weed-control purposes. Acifluorfen, lactofen [77501-63-4], and oxyfluorfen are used for selective, pre-, and post-emergence weed control in croplands. Fluorochloridone is used for selective, pre-emergence weed control in cropland, and fluridone, fomesafen, and mefluidide [53780-34-0] are used for post-emergence control (277). Fluridone is also used as an aquatic herbicide (51).

Fluridone is a weak base with low water solubility. Sorption of fluridone increases with decreasing pH (419). Leaching of fluridone was not significant in field study, and the persistence has been determined to be less than 365 days. The degradation of fluridone appears to be microbial in nature, and accelerated breakdown of the herbicide occurs upon repeated applications (420). Fluorochloridone is shown to degrade by hydrolysis at pH 7 and 9, but not at lower pH. The half-lives for this reaction are 190 and 140 days for pH 7 and 9, respectively. Breakdown by photolysis occurs rapidly with a half-life of 4.3 days at pH 7 (421). An HA is available for acifluorfen.

6.17. Amino Acid Analogues. Amino acid analogue herbicides also control a large variety of weeds. Glyphosate and glufosinate are used for the broad-spectrum, nonselective control of grass and broadleaved weeds. Diethatyl [38725-95-0] is used for selective, pre-emergence control of grass and broadleaved weeds. Flamprop [58667-63-3] is used to control the growth of wild oats in wheat (51,277).

Glyphosate is zwitterionic and thus can be sorbed as an anion, cation, or zwitterion (226). Although the amount of glyphosate sorbed decreases with increasing soil pH (422), at the pH of typical agricultural soils glyphosate is strongly sorbed relatively immobile (423). The mobility classification varies from immobile on an acidic sandy clay loam soil to low mobility on an alkaline clay loam soil. The increase in mobility with increasing pH arises from a decrease in sorption (312).

Glyphosate is readily degraded by microbial means in most soils (312). A species of bacteria (*Pseudomonas sp.*) capable of degrading glyphosate has been isolated (424). Flamprop–methyl [52756-25-9] is transformed by a combination of chemical and microbial processes when incubated under aerobic conditions (425). The degree of transformation increases when the herbicide is incubated under flooded conditions. Finally, glufosinate is rapidly degraded by microbial means with half-lives ranging from 3 to 7 days (311). An HA is available for glyphosate. Diethatyl–ethyl [38727-55-8], and sulfosate [81591-81-3] are additional amino acid analogue herbicides.

6.18. Miscellaneous Other Herbicides. The herbicides in this group are not readily included in any of the preceding groups. Acrolein [107-02-8] (2-propenal) is used as a contact, aquatic herbicide. Sethoxydim, clethodim, and tridiphane are used for selective, post-emergence weed control. Cinmethylin and clomazone [81777-89-1] are used for selective pre-emergence control and etholumesate [26225-79-6] for selective pre- and post-emergence weed control (51,277).

Cinmethylin has been found to resist leaching in several soils and is less mobile than metolachlor (426). Cinmethylin is of interest because this class of chemical bridges classic synthetic herbicides and the area of natural product-based herbicides (427). Clomazone is a nonionic herbicide that is sorbed primarily to soil organic matter (428); it is rapidly dissipated in soil with half-lives ranging from 33 to 37 days (429). Clethodim is degraded by chemical hydrolysis and photolysis (430). Half-lives for these reactions range from 2.4 to 3.2 hours in aqueous solution, the rate increasing with decreasing pH. Finally, ethofumesate is strongly sorbed to soils and is subject to degradation via chemical hydrolysis (431). The sorption of ethofumesate is greater on dry soils. Cycloxydim [101205-02-1] also is a herbicide. Health advisories have not been issued for any of the aforementioned herbicides (250), and data on the occurrence of these herbicides in SW or GW are not available.

7. Economic Aspects

The world agricultural and noncrop herbicide market had annual sales of \$14–17×10^9 in 2001. Noncrop herbicides refer to use in the home and garden markets. The United States accounted for $\$6 \times 10^9$ of the market. Consumption of herbicides in recent years has risen slightly because of increased planting. However, herbicide use is expected to decline through 2006 because of the introduction of newer herbicides with more highly active ingredients. In 2001, the global market for agricultural use surpassed $\$14 \times 10^9$ and the noncrop market accounted for about $\$3 \times 10^9$ (432).

There were about 120 herbicides in use in the United States in 2001. By the end of 2006, herbicide end-user sales are expected to be $\$6.3 \times 10^9$ or an expected average growth rate of 1.0%/yr.

The United States accounts for the use of 35% of the value of the world market and 25% of the world volume market for agricultural and noncrop herbicides. Herbicide use in the U.S. is mainly for corn and soybeans.

Herbicide production has decreased steadily in Western Europe since 1989. About 50 major herbicides are used in this area of the world. Most are produced by European-based companies. The largest markets in dollar terms in Western Europe are France, Germany, the UK, Spain, and Italy. They account for about 78% of the Western Europe market (432).

Japan's consumption of herbicides has been declining at the rate of 2.6%/yr and the market is not expected to grow. Less rice is being planted and rice farmers are using herbicides that offer more residual weed control. About 18 major herbicides are used in Japan and most of these are imported or manufactured by non-Japanese companies (432).

8. Registration of Herbicides

A herbicide that promises to be commercially successful must be officially approved or registered with the EPA before it can be used or sold in the United States. Labeling and marketing of pesticides in interstate commerce are regulated in the United States by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, which is administered by the U.S. EPA. The most significant changes to FIFRA took place with the passage of the Food Quality Protection Act (FQPA) of 1996 (see entry: Food Quality Protection Act of 1996). Most states have similar laws. Federal registration does not remove the requirement for a state registration. Safety tests evaluate hazards to human, the environment, and nontarget species, and acute and chronic toxicity data are obtained. Methods of residue analysis must be devised and validated. If residues might occur on foodstuffs, a tolerance or exemption therefrom must be obtained. Tolerance has been defined as the maximum concentration of pesticide residue that is permitted in or on food at a specified stage in the harvesting, storage, transport marketing, or preparation of the food, up to a final point of consumption, and the concentration is expressed in parts by weight of the pesticide residue per million parts of the food (ppm) (see also LC/MS, Pesticide Residue Analysis).

At the present time, many governments mandate reductions in pesticide usage. This may be achieved to some degree by using more effective chemicals (lower rates of application) and by improved application technology (formulation and precision agriculture). It was suggested that reductions in application rates were driven by discovery rather than by regulation. The combination of selectivity with improved efficacy helps to meet environmental objectives, as exemplified by the steady decrease in application rates of new classes of herbicides introduced between 1954 and 1981 (atrazine 1959, alachlor 1967, acifluorfen 1975, chlorsulfuron 1979, imazaquin 1981, as representative members of the classes of triazine, chloracetanilide, phenoxy acid, and imidazolinone, respectively).

Another factor in reduction of pesticide use is the adoption of integrated pest management practices. The federal government of the United States is committed to the concept of IPM, and compatibility of new pest control chemicals or technologies with IPM is an important factor in regulatory approval. In Europe, integrated crop management (ICM), a similar concept, has developed.

9. Formulation and Application

Because many newly introduced herbicides show biological activity at application rates that are many times lower than compounds that have been in use for several decades, environmental considerations are very important. Development of formulations continues to aim, not only at improving efficacy, but also at increasing safety by minimizing exposure of both the environment and those applying the pesticide. Controlled release formulations, water-soluble packaging, and premeasured doses have been available for some time, but a variety of new concepts have been introduced.

Application technology is undergoing many changes. The concept of precision agriculture in which pesticide applications are directed more efficiently to specified targets is gaining ground. Computer-based systems make it possible to improve efficiency of application by varying the applied dose of nutrients or pesticides using spray booms with variable outlets programmed to deliver precise amounts. Global positioning systems and geographic information systems may be employed to map terrain and its variability (nutrient status, pH, composition, etc) to determine the required outputs of pesticides of nutrients. Site-specific application based on imaging analysis for identification of weed species and recycling sprayers are among newer technologies that will be instrumental in changing herbicide application systems of the past.

10. Other Weed Management Agents and Techniques

Chemical, cultural, and mechanical weed control practices have been relatively successful in reducing yield losses from weeds (433). However, herbicide-resistant weed populations, soil erosion, pesticide persistence in the environment, and other problems associated with technologies used to control weeds have raised concerns for the long-term efficacy and sustainability of herbicide-dependent crop production practices (434). These concerns, coupled with ever-increasing demands for food and fiber, contribute to the need for innovative weed management strategies (435).

Adoption by the agricultural community requires that an innovative weed management agent must be an effective control of the target species, be cost-effective, and be practical to employ. It must not interfere with crop production practices such as crop rotation or the use of other pesticides. Additionally, new weed-control agents cannot pose a significant threat to human health or the environment. Considerable costs are incurred in the development, registration, production, and marketing of weed control agents. These costs require that an herbicide have sufficient long-term market viability and market niche potential to justify these costs in time and money. The need for safe and effective methods of crop production in an environment that contains competitive weeds is becoming increasingly critical (See also the article, Herbicides, Biotechnology).

10.1. Weed Management Strategies. The paradigm that all noncrop plant populations in a field should be controlled, regardless of the actual impact on crop yield and quality, is not justifiable. The objective determination *a priori* of which plant populations require control and which do not, directly reduces the

economic, environmental, and social costs associated with weed control and can be considered an innovative approach to weed management. For example, some noncrop plant populations do not significantly hinder production. In some developing areas of the world, producers have found uses for noncrop plants that would otherwise be considered weeds (436), and many weeds are both edible and nutritious (437). In aquaculture systems, certain highly problematic algal and bacterial weeds are also essential to the overall stability and productivity of the production system (438).

The immediate and total removal of weeds is often recommended. However, this recommendation may be based more on when control methods can most easily be applied, rather than on considerations of the optimal time for effective weed control (439). Controlling plants that are not actually problems or that are present at noncritical times is costly and may not truly benefit the producer. However, weeds that are present initially in very low numbers may require subsequent eradication if introduction of a new noxious species is to be prevented.

Managers of agroecosystems are being encouraged to manage weed populations at levels that are below their economic optimum thresholds (440), rather than attempting to eliminate or control all noncrop plants, regardless of their actual impact. Decisions concerning management of weed populations should be governed by both agroecological principles and site-specific considerations in the context of an overall integrated pest management program (436,441). However, the practical implementation of integrated pest management (IPM) programs can be difficult (442).

Nonchemical or traditional practices, such as weed seed removal, optimal crop seeding rates, crop selection, enhanced crop competitiveness, crop rotation, and mechanical weed control are all important components of an effective weed management program (443,444). In the context of modern intensive chemical herbicide application, nonchemical practices may even represent an innovative approach to weed management and should receive careful consideration.

10.2. Natural Products and Allelopathic Compounds as Herbicides. Approximately 60% of the registered herbicides are halogenated hydrocarbons. These compounds were discovered primarily by screening large numbers of chemically synthesized compounds for phytotoxic activity (445). The chemical synthesis *de novo* and bioscreening of large numbers of complex organic compounds are extremely costly and time consuming. In terms of yielding new chemical control agents, this approach is considered by many to have reached a point of diminishing returns (446). Additionally, there is growing concern that compounds that do not occur in nature may produce unanticipated health and environmental problems. However, plants, fungi, marine organisms, and certain bacteria produce a vast array of organic compounds, and many of these natural products exhibit biological activity (447–449). In nature, these compounds are produced in minute quantities and present interesting chemical problems in detection, identification, quantification, and production of active and stable analogues of these natural products. Although these compounds appear to be ecologically safe in naturally occurring amounts, the large quantities required for agricultural applications may cause environmental problems similar to those associated with chemical herbicides.

Natural products have exerted evolutionary pressure that has led ecological and biological systems to develop mechanisms that efficiently degrade or metabolize such organic compounds. Therefore, natural products may be less likely to accumulate in the environment than would metabolically resistant synthetic compounds. Although some natural products can be highly toxic, eg, aflatoxin in grains and cottonseed, and their safety cannot be assumed, there is great interest in the development potential of environmentally safe natural products and natural product derivatives that could control specific weeds and other pests.

Approximately 7000 naturally occurring secondary metabolites have been reported. Many of these compounds are difficult or impossible to synthesize chemically (450). If sufficient quantities of these natural products can be obtained, possibly through fermentation technology, their efficacy as commercial pest control agents can be evaluated more fully (445,451). Although there are difficulties associated with the direct commercialization of natural products as herbicides, the chemical alteration and optimization of natural products can still yield patentable and marketable control agents (452–454). A primary benefit of investigations of the biological activity of natural products may be the provision of leads to new classes of weed control agents (445).

Investigations of natural product chemistries have aided in the development of bialaphos, cinmethylin, picloram, glufosinate, and other important herbicides (433). Additional compounds may be found through investigations of natural products that cause plants and other organisms to undergo rapid physiological change, such as plant hormones and phytotoxins (108). Many plant hormones and phytotoxins are also produced by microorganisms. For example, it has been reported that the plant hormones, indole-3-acetic acid, gibberellins, ethylene, abscisic acid, and cytokinins, are produced by various microorganisms. Additionally, microorganisms have been reported to contain novel natural products that could provide basic structural templates for the development of new herbicides (455).

One route to the discovery of innovative control agents involves the search for compounds that affect interactions among plants and other organisms. The negative connotation of the term allelopathy refers to chemical interactions among plants that result in the suppression of other plant species (456). Although allelopathic compounds are often affected by microbial activity (457) and nonchemical interactions and competition among plants can complicate investigations of allelopathic interactions (456,458), identification of the causative suppressive compounds may lead to the discovery of novel control agents. In addition, new crop varieties that directly suppress weed growth with endogenous natural products could be developed (457,459).

Advances in biotechnology and fermentation technology, coupled with a desire for naturally derived compounds, show promise for the utilization of microorganisms in the commercial manufacture of natural products. A primary constraint in this approach is the limited availability of microbial strains to produce commercially exploitable amounts of the desired compounds. Such strains often require mutagenesis and extensive selection before they can be used on a commercial scale. Although this is a costly and primarily random process that may not yield a useful result, enhanced understanding of microbial physiology and genetics can greatly expedite the development of useful strains (460).

Biological systems produce an extremely wide variety of natural products. This ecological and genetic diversity offers researchers a vast index of compounds to search for innovative weed management agents.

10.3. Plant Pathogens and Insects as Control Agents. Concerns about accumulations of chemical control agents in the environmental and food resources have also increased interest in microbial weed control agents (461). Controlling weeds with carefully screened plant pathogens offers several benefits, including a high degree of specificity for a given target weed, low potential for negative human health and environmental impact, inability to accumulate in the food chain, and other advantages (462,463). The high degree of host specificity may limit the market size for some biological control agents (462,464), but these bio-control agents can be combined with chemical herbicides and other pathogens to increase the spectrum of weeds controlled (462). The marketing of biological control agents may also be constrained by slow expression of phytotoxicity, pathogen dependence on optimum environmental conditions, potential resistance of the weed toward the pathogen, and lack of formulation stability under field conditions and during preuse storage (465). These constraints can be addressed by genetic manipulation of selected pathogenic strains to produce more effective control agents (465,466) and by the investigation of the mechanisms of disease resistance in plants (467).

There are two principal approaches to the biological control of weeds (468–470). The first approach is referred to as classical or inoculative biological weed control. Plants that have been introduced to areas outside of their natural range often encounter fewer growth and seed dissemination constraints. This release from constraining factors can stimulate such migrant plants to become highly competitive and problematic weeds. The intent of classical biological weed control approaches is to manage introduced weed populations by introducing host-specific pathogens from the weed's native range, thus moderating the growth of weed populations by the reestablishment of an old association between host and pathogen populations in the expanded range (468,471). Just as a release from constraining factors can stimulate weed growth, release from hyperparasites, antagonists, fungivores, and other constraining factors in the newly expanded range of a plant pathogen can improve its effectiveness on target weeds in that expanded range (470). If an association can be established, the pathogen may become epiphytotic and require no further manipulations or repeated inoculations (472). This approach may be of particular benefit in developing nations where periodic reapplications of control agents may be difficult. The rich biodiversity in developing nations also provides a potential source for pathogen strains appropriate for biocontrol applications (473).

The long association of pathogen and host-plant in the host's native range, however, can contribute to the coevolution of polygenic resistance to the pathogen. This resistance can sometimes be overcome by the use of several and perhaps novel pathogens to form a new association in the expanded range of the weed. This approach takes full advantage of available biodiversity to overcome any polygenic resistance to biological control agents (474).

An additional approach to biological weed control is referred to as the inundative or augment approach to biological weed management. This approach utilizes pathogenic propagules formulated as a weed control agent, eg, mycoherbicides. The mass-inoculation of pathogenic propagules in an effective

formulation can enhance the dissemination and survival of the pathogens, overwhelm target weed resistance, and produce results similar to those achieved with chemical herbicides. Mycoherbicides often contain native pathogens that are active against native weeds and are thus highly selective against the target weed species (468,469,475).

Typically, mycoherbicides are developed by isolating useful pathogens from the environment, followed by the mass production of large quantities of pathogenic propagules. Once large amounts of propagules, ie, spores, are obtained, they are then combined with formulation components that increase the viability and longevity of the propagules in the formulation, as well as the ability of the propagules to withstand desiccation after application; these are all requirements for an overall increase in efficacy. Mycoherbicides may be applied using methods similar to those used to apply chemical herbicides and often require application on a repeated, periodic basis, as do many chemical herbicides. Difficulties maintaining pathogen virulence until application, limitations in formulation and application technology, and various marketing factors have so far limited the commercial life of many mycoherbicides.

The isolation of potentially useful pathogens with appropriate host-specificity is a critical first step in the development of biological control agents. However, full commercialization requires that effective pathogenic propagules be mass-produced and that effective formulations be developed that enhance the stability, ease of application, and overall efficacy of mycoherbicides. If these constraints can be overcome, the use of biological weed management agents can expand more rapidly.

10.4. Control of Weed Seeds. Efforts to control parasites often focus on the most vulnerable stage in the life-cycle of the parasite, such as when the parasite is present and the host is absent. If weeds can be considered a type of parasite in cropping systems, then a point of vulnerability for weeds occurs after harvest and prior to the next crop planting. However, during this period weeds are usually present as seeds and/or other over-wintering storage structures. With the exception of a few soil fumigants that cannot be used over large areas, there have been no agents available for elimination of weed seed populations in the soil, ie, the soil seed bank. If agents that control weed seed germination could be applied prior to planting, interference from weeds would be prevented until reintroduction of weed propagules. Additionally, if a very large portion of the weed seed bank could be stimulated to germinate prior to planting, weeds could be controlled by a single cultivation or application of nonselective herbicide (476,477).

Efforts toward developing agents which destroy weed seeds in the soil are hindered by several factors. The soil seed bank can be very large with estimates ranging as high as 70,000–90,000 weed seeds per m^2 of the upper 15–25 cm of the soil (478). Seeds and other over-wintering propagules typically exhibit reduced metabolic activity, compared to growing plants. This lack of metabolic activity makes it difficult to render seeds nonviable with chemical agents that rely on the inhibition of metabolic pathways to produce a lethal effect, eg, most commercially available herbicides.

The soil seed bank consists of both dormant and nondormant seeds. Dormant seeds can remain viable in the soil for several years and in some cases

as long as 50–100 years (476–478). These factors, as well as the technical difficulties associated with preventing seed production and distribution and removing seeds from the soil, limit the effectiveness of strategies to deplete the seed bank (477). Control efforts have focused on investigating factors, such as moisture, light, temperature, oxygen, and chemical germination stimulants, that effect dormancy and control weed seed germination (476,477). In addition, increased seed predation by insects and rodents has been considered a weed control strategy (479).

10.5. Biotechnology. Genetic modification may provide plants resistant to disease, nematodes, or insects. Plants resistant to herbicides are being marketed, but their acceptance in some areas is a controversial issue. Internationally, there is no agreement on safety protocols. Introduction of viable organisms produced by genetic modification has generated a number of unanswered questions, and there still remains a need for readily applicable techniques to assess the environmental impact of the new technology. The rapid expansion of this field of science opens many questions of application, ownership, and exploitation of its novel discoveries.

Transgenic crops resistant to glyphosate, glufosinate, and bromoxynil herbicides have been commercialized, and their impact may be to increase herbicide sales. Transgenic crops now represent a substantial portion of major crops globally (12% of cotton, 58% of soybeans, and 23% of corn planted in 1998). Most of the acreage in transgenic crops is in the United States (68%), Argentina (23%), and Canada (7%), and almost all of it is planted in herbicide-resistant crops (74%). Modification of the plant genome may be used to achieve a variety of objectives: resistance to insects, drought tolerance, and so on, which have long been pursued by "classical" plant breeding approaches, but the combination of genetic modification techniques, rapid throughput screening, and combinatorial chemistry has made it more opportune for major companies to strengthen and diversify their investment in pest control. To enter the new markets, major companies have acquired seed companies, and have entered into alliances and research agreements with biotechnology-based companies, universities, and companies with expertise in drug discovery.

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