Historical Development of Pesticides in Japan

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■ Abstract

This paper aims to provide an overview of the history and development of pesticides in Japan, following a study by the author on the role of pesticides, their impact on society and the establishment and development of the pesticide industry in Japan.

Pesticides in Japan can be traced back to 1600. A document from this era, entitled *Family Traditions on the Killing of Insects*, records that noxious insects can be exterminated using a mixture of five types of ingredients. Researchers have also discovered that in 1670, whale oil was poured onto fields as a method of exterminating leafhoppers. These examples indicate the beginning of pest control in Japan. Up until the mid-19th century, these primitive types of pest control were the only methods used in Japan; they were accompanied by *mushi-oi* – prayers to ward off insects.

An industry eventually started to develop in the late 19th century, when various products began to be introduced from overseas, such as lime sulphur, Bordeaux mixture and other copper agents as well as pyrethrum insect powder, nicotine and other natural products. Arsenic compounds and chlorpicrin became industrialised in the early 20th century; by the 1930s, a good foundation had been laid for the pesticide industry. However, the outbreak of war interrupted the progress of technology in Japan.

Research and development continued in the West on new synthetic pesticides, even in wartime. While Japan lagged behind in its technological developments, it was not long after the introduction of DDT, BHC, parathion and other synthetic pesticides that it started producing similar products domestically. By the 1950s, an industry had developed, with synthetic pesticides not only being produced by dedicated pesticide manufacturers, but also by specialised chemical companies. Agricultural production improved greatly as a result of the superior performance of these synthetic pesticides. In the late 19th century, paddy rice typically yielded around 250 kg per 10 ares; by the 1960s, this figure had increased to more than 400 kg. The current figure is more than 500 kg.

By the 1960s, Japanese companies were already competent enough to develop their own new pesticides. MAS, the first domestically-produced fungicide, hit the markets in 1959, followed by MAF, an improved version, two years later and then MEP, an insecticide. Other major pesticides also emerged, such as cartap, an insecticide, blasticidin, an antibiotic, IBP, benthiocarb, a herbicide, and giberellin, a plant growth regulator. However, a number of social problems arose during this time, as parathion and other chemicals were highly toxic to mammals, organomercury compounds were highly residual and other chemicals such as PCP were highly toxic to fish.

By the 1970s, Japan's period of rapid economic growth had come to an end and the country was experiencing a time of stable growth. While the pesticide industry also continued to grow during this time, it underwent dramatic changes. The Agricultural Chemicals Regulation Act was amended in 1971, adding "protecting human health and conservation of living environment" as considerations to ensure "safety of use". Long-term toxicity testing and environmental impact evaluation became required practice for registering pesticides. Testing methods became stricter with the introduction of good laboratory practice (GLP) for pesticides. These changes meant that the socially-problematic pesticides of the past were phased out and replaced. Japanese companies continued to develop new chemicals, resulting in the emergence of insecticides fenvalerate, buprofezin and hexythiazox, fungicides thiofanate-methyl, isoprothiolane and probenazole, and herbicides pyrazolate, sethoxydim and fluazifop-butyl. While the next two decades saw a major paradigm shift in the pesticide industry, it grew to the point where it was turning over more than ¥400 billion in a year.

The following is an overview of events from the 1990s to the present day. With the bubble bursting in 1991, the Japanese economy went into a long recession, which continues to this day. This also had a major impact on the pesticide industry, which has had a steady decrease in sales since turning over ¥440 billion in 1996. By 2011, this figure had dropped by around 20% to ¥350 billion. Major overseas players repeatedly ended up in mergers and acquisitions due to the rising cost of research and development and the decreasing success rate. Japan lagged a little behind in this

trend as well, but by the early 21st century, Japanese companies were consolidating as well. However, even during this time and since, Japanese companies have continued to work on new chemicals. One of the key points of note of this time has been the emergence of ultra-high-performance pesticides. One typical example is the insecticide imidacloprid, a ground-breaking chemical modelled on nicotine, a natural product. Japanese companies also invented a number of compounds similar to the sulfonylurea herbicide produced by Du Pont, which is effective with an ultra-low dosage of several grams to several tens of grams per hectare.

Japanese companies have thus continued to create new chemicals with a number of advantages. This report discusses the relevant course of events, the reasons why relatively small-scale Japanese companies have achieved such results, and the future of the industry.

Japanese agriculture will never fail while it is surrounded by high-income consumers who make their purchases assured of freshness and high quality. Pesticides are a huge part of this. The hope is that Japanese companies will continue to produce new, world-class chemicals.

This study focuses on synthetic pesticides rather than biopesticides, which have been the subject of recent attention.

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1969 Graduated from The University of Tokyo Faculty of Agriculture, Department of Agricultural Chemistry (Organic Chemistry)
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1. Introduction

Ever since the dawn of agriculture in Japan during the Jōmon period, people have had to battle with crop pests. Agriculture is the act of artificially cultivating large amounts of a single crop to harvest a large volume of produce – it is an act that is contrary to nature, so to speak. In response, nature tries to restore the original ecosystem by sending in pests that feed on the produce. In 1732, one million people died of starvation in the Kyōhō Famine, caused by cold-weather damage and an outbreak of leafhoppers in western Japan.

This study discusses the history and significance of the development of agricultural chemicals or pesticides, a major weapon in the war between agriculture and the pests sent by nature. Many pesticides have now been developed that are far more safe and effective than they were in the past, with no danger of environmental pollution. The quality of produce has improved, so that general consumers no longer have to see worm-eaten fruits and vegetables. The pesticides used in Japan have been the result of the hard work and discovery by our forefathers before the war, during the turbulent times after the war and in the age of restoration that followed. However, a number of social problems arose in the past because some of the early chemicals developed were highly toxic to mammals, others were highly residual on crops and soil, while yet others were highly toxic to fish.

In 1947, during the turbulent times following the war, Professor Sankichi Takei (1896-1982) of the Kyoto Imperial University Department of Agricultural Chemistry contributed an article on the future of organic pesticides to the first number issue of the journal *Pesticides*, published by the newly-established Agricultural Chemicals Association, later the Japan Plant Protection Association. While the main pesticides used in Japan at the time were natural products such as pyrethrum insect powder, derris and nicotine, this article made the following comparison with synthetic insecticide DDT, which had just been introduced.

"While the best DDT is far better than natural insecticides pyrethrum insect powder and derris in many ways, it has the following shortcomings. Natural products are unstable compounds; after they have waged war on the insects, they quickly break down again. They do not residually remain on plants and soil and so have no long-term side effects; such is the wonder of nature. This vital property is lacking in inorganic compounds such as arsenicals; even outstanding synthetic chemicals such as DDT fall far short of natural products in this regard. At present, we have to say that 'nature is far wiser and smarter at chemosynthesis than humans.' [abridged] It is not just a dream to say that in the future we could have a synthetic insecticide that is better than pyrethrum or rotenone in that regard."

Large quantities of highly-residual pesticides, such as DDT, BHC and organomercury compounds, were used to boost food supplies after the war. This opinion expressed by Takei demonstrated a keen insight into the darker side of pesticide practices, namely, poisoning, crop contamination and environmental pollution. Subsequent technological developments were carried out in light of this consideration. The aim of this research and development was to achieve what Takei insisted was "not just a dream" – replacing these pesticides with the gentler, non-residual pesticides we have today.

What is worthy of note here is that around half of the latest, high-performance pesticides used in Japan today were developed by Japanese companies. They are used as important and key pesticides not only in Japan, but overseas as well. This study not only traces the history of the Japanese pesticide industry, but also outlines Japan's experience in developing new, world-class chemicals. This study also examines the reasons why Japan has done so well and achieved so many success stories in pesticide development. Finally, this study attempts to illustrate the future of the industry.

This report is structured as follows. Chapter 2 provides an overview of pesticides, including definitions, names, classifications, production status, improvement to agricultural production, laws and regulations, development processes and contributing technology.

Chapter 3 outlines the history of pesticides from the 17th century onwards, referring where possible to the social conditions and agricultural environment at the time.

Chapter 4 lists 20 new pesticides from Japan, attempting, where possible, to explain their history of development and the impact they had. While there are numerous other Japanese pesticides, the author has had to select a limited number due to space constraints.

Chapter 5 presents a discussion and considers the future prospects of the industry, including looking at how pesticides are perceived in society and the current awareness of the agricultural environment, as well as examining the strength and future of the ties between

the pesticide industry and agriculture.

A technology flow diagram is provided to show an outline of the pesticide industry, to be referred to where necessary.

Due to the nature of the technology, the author cannot avoid using technical terms and chemical structural formulas in this report. While it is the intention of the author to make explanations as plain as possible, the reader is invited to skim-read any parts that are difficult to understand. Conversely, readers with specialist knowledge of pesticide science may find the technical explanations not detailed enough. These readers are invited to refer to the reference literature cited where possible.

With respect to names of companies, the author has made every effort to use the contemporary name of the company at the time the invention was made. However, companies often change due to mergers and acquisitions and the like, so it has not always been possible to maintain consistency. The author asks for understanding on this point.

The following reference works are cited throughout.

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2. Overview of Pesticides

This chapter discusses the definitions, names, classifications and role of pesticides, as well as relevant laws and regulations, development process and contributing technology. Many general consumers take the view that while pesticides may be necessary, they should be avoided if possible. These consumers are concerned about the effects of residual pesticide in food. However, let us objectively examine what the pesticides used today are like, what role they play and what processes they go through to become commercial products.

If we look back through history, the "bright" side of pesticides in service to humanity is undeniable: increases in food production, improved quality, economizing of labor and so on. Conversely, the "dark" side of pesticides was magnified a decade or so after the war when, once a stable food supply was secured, concerns arose over ensuring the safety of farmers, food safety for general consumers and environmental problems. In some instances, pesticides actually caused problems, such as poisoning from parathion; in other instances, such as cases of residual mercury in rice, problems were averted before any harm could be done.

Let us examine the current situation. Lessons have been learned from the past; modern pesticides are backed by the latest science and technology. While pesticides are chemical treatments that have the potential to do both harm and good, the food that people eat is a chemical substance in itself. People actually place themselves at considerable risk from food poisoning or from toxic chemicals already found in food (poisonous mushrooms, blowfish poison and countless others). Provided pesticides are used appropriately, the risk of residual pesticide in food is negligible compared to the risk of food poisoning or the risks from chemical substances naturally occurring in food. The results of large-scale investigations into residual pesticides in food show that this is a negligible issue in terms of both the frequency of residual pesticide detection and the amounts detected.

Since pesticides are artificially manufactured chemicals, people seem to have focused on the "dark" images from the past. Mass media reports also seem to be focused on this "dark" side, with hardly any coverage given to the "bright" side.

2.1. Pesticide Definition

Pesticides, or agricultural chemicals, are defined as follows in Article 1 of the *Agricultural Chemicals Regulation Act*, enacted in 1948. While this is a rather old law, it covers all of the agricultural chemicals presently used.

(Purpose)
Article 1:
The purpose of this Act is to improve the quality of agricultural chemicals and to ensure their safe and proper use by introducing an agricultural chemical registration system to regulate their sale and use, thus contributing to the conservation of our living environment as well as the protection of human health and stable agricultural production.

(Definition)
Article 1-2:
[1.] For the purpose of this law, the term "Agricultural chemicals" shall mean fungicides, insecticides, and other substances used to control fungi, nematodes, mites, insects, and rodents or other plants and animals, or viruses (hereinafter generically called "diseases and insect pests") that may damage crops (including trees and agricultural and forestry products, and hereinafter called "Crops, etc."), and also refers to other substances (including those, specified by government ordinances, that are used as raw materials or materials to control the diseases and insect pests) and agents such as growth accelerators and germination suppressors, etc. used to promote or suppress the physiological functions of crops, etc.

2. Under this Act, natural enemies used as a means of the biological pest control referred to in the previous Paragraph shall also be regarded as "agricultural chemicals."

3. For the purpose of this law, "Manufacturers" shall mean those who manufacture or process agricultural chemicals, "Importers" shall mean those who import agricultural chemicals, and "Dealers" shall mean those who sell agricultural chemicals (including presenting them other than selling them. The same applies hereinafter).

4. For the purpose of this law, "persistency" shall mean the characteristics of any agricultural chemical (including the characteristics produced by chemical changes of the substance involved) that resides in crops etc. or soil due to the use of the agricultural chemical.

We can sum up this definition by saying that "agricultural chemicals", or pesticides, are "fungicides, insecticides and other substances used to control fungi, nematodes, mites, insects and rodents or other plants and animals, or viruses that may damage crops, etc., as well as other substances and agents such as growth accelerators and germination suppressors, etc. used to promote or suppress the physiological functions of crops, etc."

Pesticides also include rodenticides, natural enemies, insect attractants such as pheromones, repellents, biopesticides such as effective microorganisms to combat plant pathogens and spreaders used to boost the effects of any active ingredients.
"Crops, etc." is a general term for plants cultivated by humans and can include rice plants, vegetables, fruit trees, mushrooms, bamboo shoots and so on. It also includes golf courses, park lawns and roadside trees.
"Fungi" includes any filamentous fungi harmful to crops etc., such as molds, as well as any bacterial pathogenic microbes.
"Diseases and insect pests" include fungi, nematodes, mites, insects, rodents and viruses, as well as birds, slugs and crayfish that may damage crops, etc. While this definition makes no specific mention of "herbicides" that control weeds that cause major damage to crops, etc., weeds are included in "other plants and animals" and herbicides are included in "other substances and agents".
As shown above, anything that is defined as an "agricultural chemical" in the *Agricultural Chemicals Regulation Act* is treated as a pesticide and subject to regulation. However, remedies for insects that are sanitary hazards (fleas, mosquitos, cockroaches, etc.) are not covered by the *Agricultural Chemicals Regulation Act* even if they contain the same active ingredients as pesticides; they are subject to the *Pharmaceutical Affairs Act* and other regulations.
Agents used to preserve crops after they have been harvested (post-harvest agents) are treated as food additives and are subject to the *Food Sanitation Act*. There are maximum residue limits in place for these agents. Some fumigants used to preserve grain are treated as pesticides.

2.2. Names of Pesticides

Pesticides sold on the market must be sold in labelled containers. These labels usually include information such as the common name of the product, the chemical name, the brand name and the category. The example below is taken from a label for thiophanate-methyl. This study primarily uses common names that clearly identify the active ingredient.
This study also uses code number "test names" when discussing stages of development.
Common name: thiophanate-methyl (name of the active ingredient determined by the pesticide division of the International Organisation for Standardization ISO)
Chemical name: dimethyl [1,2-phenylenebis (iminocarbonothioyl)] bis [carbamate] (CAS) or dimethyl 4,4'-(O-phenylene) bis (3-thioallophanate) (IUPAC)
Brand name: Topsin-M, Top Grass
Category: thiophanate-methyl wettable powder (when registering pesticides in Japan, the common name of the active ingredient is usually given, along with the type of agent)
Test name: NF-44

There are many types of pesticides and various ways to classify them. This chapter discusses classification by use, classification by type of active ingredient, classification by formulation and classification by toxicity.

2.3. Pesticide Classification

2.3.1. Classification by Use

Table 2.1 shows a classification of pesticides by their use.

Table 2.1. Classification of Pesticides by Use

Type	Use
Insecticides	Controlling pest insects that damage crops
Miticides	Controlling mites that damage crops
Nematicides	Controlling nematodes that damage crop roots and tissue
Fungicides	Controlling diseases that damage crops
Insecticide fungicides	Controlling pest insects and crop diseases at the same time
Herbicides	Controlling weeds
Rodenticides	Controlling rodents that damage crops
Plant growth regulators	Promoting/suppressing crop growth
Attractants	Mainly for attracting pest insects through scent or other means
Repellents	Using particular scents or tastes disliked by birds or wild animals
Spreaders	Added to make the agent adhere more readily to the pest insect or crop
Natural enemies	Natural enemies of pest insects that damage crops
Microbial agents	Using microbes to control diseases and pest insects that damage crops

Partially modified from *Nōyaku Q & A [Pesticide Q & A]*, revised edition, Japan Crop Protection Association (ed.), 2011, p. 36.

2.3.2. Classification by Type of Active Ingredient

The majority of pesticides used today are chemical pesticides with active ingredients (the chemical content of the pesticide), while the remainder are biopesticides or other types. Tables 2.2, 2.3 and 2.4 classify pesticides according to the chemical composition of their active ingredients or by their mode of action. It is very important to know the chemical class of each pesticide, because if pesticides from the same chemical class or with the same mode of action are used in succession, this may sometimes reduce the effectiveness of the agent.

Table 2.2. Classification of Pesticides by Active Ingredients (Insecticides, Miticides)

Classification					Typical Pesticides
Insecticides/Miticides	Chemical Pesticides	Acts on the nervous system	Organophosphates		acephate, dimethoate, diazinon, malathion, DDVP, DMTP, MEP, MPP
			Carbamates		alanycarb, oxamyl, carbosulfan, thiodicarb, benfuracarb, methomyl, BPMC, NAC
			Synthetic pyrethroids		etofenprox, cyhalothrin, cyfluthrin, cypermethrin, silafluofen, bifenthrin, pyrethrin, fenvalerate, fenpropathrin, flucythrinate, fluvalinate, permethrin
			Nereistoxins		cartap, thiocyclam, bensultap
			Neonicotinoids		acetamiprid, imidacloprid, clothianidin, dinotefuran, thiacloprid, thiamethoxam, nitenpyram
			Macrolides	Avermectins	emamectin benzoate
				Milbemycins	milbemectin
				Spinosyns	spinosads
			Phenylpyrazoles		fipronil, ethiprole
			Sodium channel blockers		indoxacarb, metaflumizone
			Other		pymetrozine, flonicamid
		Intracellular respiration inhibitor	Electron transport inhibitors I		tebufenpyrad, pyridaben, fenpyroximate, tolfenpyrad
			Electron transport inhibitors II		cyflumetofen
			Electron transport inhibitors III		acequinocyl, fluacrypyrim
			Uncouplers		chlorfenapyr
		Insect growth regulator (IGR)	Chitin synthesis inhibitors		chlorfluazuron, diflubenzuron, teflubenzuron, flufenoxuron, lufenuron, hexythiazox, etoxazole
			Metabolic moulting hormone inhibitors		buprofezin
			Juvenile hormone active substance		pyriproxyfen
			Other		cyromazine
		Metabolic inhibitor	Tetronic acid		spirodiclofen, spiromesifen
			Dihalopropenes		pyridalyl
		Acts on the sarcoplasmic reticulum	Diamides		flubendiamide chlorantraniliprole
	(Other)	Blocks spiracles			starch, reduced-starch saccharified product, machine oil, sodium oleate
	Biopesticides		Microbes		*Pasteuria penetrans, Bacillus thuringiensis (BT), Monacrosporium phymatopagum, Paecilomyces tenuipes, Beauveria brongniartii, Beauveria bassiana*
			Natural enemies of insects, mites and nematodes		*Steinernema carpocapsae, Phytoseiulus persimilis, Amblyseius cucumeris, Aphidoletes aphidimyza, Orius sauteri, Orius strigicollis Poppius, Encarsia formosa Gahan, Diglyphus isaea, Aphidius colemani, Dacnusa sibirica, Neochrysocharis formosa*

Nōyaku Q & A [Pesticide Q & A], revised edition, Japan Crop Protection Association (ed.), 2011, p. 37.

Table 2.3. Classification of Pesticides by Active Ingredients (Fungicides)

Classification				Typical Pesticides
Fungicides	Chemical Pesticides	Multi-site contact activity	Inorganic compounds	Bordeaux mixture, lime sulphur (copper, sulphur)
			Dithiocarbamates	thiram, ziram, polycarbamate, manzeb, maneb, propineb
			Other	chlorothalonil (TPN), captan, folpet, fluoromide, dithianon, iminoctadine
		Nucleic acid synthesis	Phenylamides	metalaxyl
			Carboxylic acids, other	oxolinic acid, hydroxy-isoxazole
		Mitosis	Benzimidazoles	benomyl, thiofanate-methyl
			Other	diethofencarb, pencycuron
		Respiration	Acid amides (complex II inhibitors)	mepronil, flutolanil, furametpyr, thifluzamide, boscalid
			QoI (complex III inhibitors)	azoxystrobin, kresoxim methyl, metominostrobin, trifloxystrobin, orysastrobin, pyraclostrobin, famoxadone
			QiI (complex III inhibitors)	cyazofamid, amisulbrom
			Other	fluazinam, ferimzone
		Amino acid synthesis and protein synthesis	Anilinopyrimidines	mepanipyrim, cyprodinil
		Signal transduction	Phenylpyrroles	fludioxonil
			Dicarboximides	iprodione, procymidone
		Lipid and cell membrane synthesis	Organophosphates	EDDP, IBP
			Carboxylic acid amides	dimethomorph, benthiavalicarb isopropyl, mandipropamid
			Other	isoprothiolane, tolclofos-methyl, propamocarb
		Cell membrane sterol synthesis	Sterol biosynthesis inhibitors	oxpoconazole, pefurazoate, prochloraz, triflumizole, triforine, fenarimol, bitertanol, cyproconazole, difenoconazole, fenbuconazole, hexaconazole, imibenconazole, ipconazole, metconazole, myclobutanil, propiconazole, simeconazole, tebuconazole, tetraconazole, triadimefon, fenhexamid
		Cell membrane melanin synthesis	MBI-R	tricyclazole, pyroquilon, fthalide
			MBI-D	carpropamid, diclocymet, fenoxanil
		Unclear	Other	cymoxanil, fosetyl, flusulfamide, diclomezine, cyflufenamid
		Plant resistance inducers		probenazole, thiazinyl
		Soil fungicides		dazomet, chlorpicrin
	Antibacterial agents			kasugamycin, validamycin, polyoxin
	Biopesticides			*Bacillus subtilis, Agrobacterium radiobacter,* non-pathogenic *Erwinia carotovora, Trichoderma atroviride, Talaromyces flavus*

Nōyaku Q & A [Pesticide Q & A], revised edition, Japan Crop Protection Association (ed.), 2011, p. 37.

Table 2.4. Classification of Pesticides by Active Ingredients (Herbicides)

Classification			Typical Pesticides
Herbicides	Inorganic compounds		chlorate, cyanate
	Synthetic organic pesticides	Synthetic auxins	2,4-PA, MCPB ethyl, dicamba, triclopyr, quinmerac
		ACCase inhibitors	sethoxydim, fluazifop-butyl
		ALS inhibitors	imazosulfuron, thifensulfuron methyl, nicosulfuron, pyrazosulfuron-ethyl, bensulfuron methyl, imazapyr, flumetsulam, penoxsulam, bispyribac-sodium, pyriminobac-methyl, flucarbazone-sodium
		Photosynthesis inhibitors	atrazine, simetryn, linuron, DCMU, bromacil, phenmedipham, bentazone, ioxynil
		PPO inhibitors	oxadiazon, pentoxazone, oxyfluorfen, pyraflufen ethyl, flumioxazin, fluthiacet-methyl, carfentrazone-ethyl, pyraclonil
		Carotenoid synthesis inhibitors	norflurazon, diflufenican, clomazone
		4-HPPD inhibitors	pyrazolate, benzofenap, mesotrione, isoxaflutole
		Cell division inhibitors	trifluralin, pendimethalin, dithiopyr
		Very long chain fatty acid biosynthesis inhibitors	alachlor, butachlor, pretilachlor, propachlor, dimethenamid, mefenacet, cafenstrole, indanofan, anilofos, fentrazamide
		Fatty acid synthesis inhibitors	benthiocarb, molinate, EPTC, benfuresate
		Cellulose synthesis inhibitors	dichlobenil, flupoxam, isoxaben
		EPSP synthase inhibitors	glyphosate
		Glutamine synthetase inhibitors	glufosinate, bialaphos
		Bipyridiniums	paraquat, diquat
		Other	dymuron, oxaziclomefone, etobenzamid, cinmethylin, bromobutide, MSMA
	Biopesticides		*Xanthomonas campestris*

Nōyaku Q & A [Pesticide Q & A], revised edition, Japan Crop Protection Association (ed.), 2011, p. 39.

2.3.3. Classification by Formulation

The active ingredients in pesticides are not usually used on their own, but rather processed into products that are easier to use, safer to store and maximize their effectiveness. Pesticides are designed and produced with various adjuvants in them, taking into consideration the physical and chemical properties of the active ingredients as well as their application and manner of use. Let us outline some typical formulations.

(1) Dust

The pesticide in its primary form (the manufactured active ingredient) is dispersed into a mineral carrier such as clay, processed into a dust (45μm or less) and usually applied on fields in this form. To prevent it scattering, the quantity of particles less than 10μm is reduced to make it driftless (DL), the currently popular dusts having particles with an average size of at least 20μm. Flowdust (FD) is an ultra-fine dust with an average particle size of 5μm or less. This is a labor-saving product for horticultural use, such as in greenhouses, and is effective at small doses (300-500g/10a).

(2) Granules

Loose grains of 1.7mm or less are generally called granules. These are usually dispensed on fields in this form by hand or with a dispensing machine. There are three types of granules, categorized by grain size: fine

granules (710μm or less), microgranules (300μm or less) and fine microgranules (210μm or less).

A labor-saving product has been developed for rice cultivation and has reduced the required volume of product used from 3kg/10a to 1kg/10a. This product has been increasingly popular in recent years.

(3) Wettable Powders
Technical grade active ingredient is mixed or absorbed into a mineral carrier such as clay with a grain size of around 5μm, together with a dispersant, a wetting agent and other substances. This product is sprayed on fields as a dilute suspension in water.
Wettable powders also come in granular dry flowable (DF) and water-dispersible granule (WG, WDG) forms to prevent scattering of the powder when it is being diluted.

Liquid formulations are also used, such as water suspensions (flowable or suspension concentrates (SC) or suspoemulsions (SE)).

(4) Emulsion concentrates
These are clear liquids made by adding organic solvents and emulsifiers to the technical grade active ingredient. This product is dispensed, having been diluted and emulsified in water. Recently, emulsions of oil in water (EW) and clear/translucent micro emulsions (ME) of fine emulsion particles have also been developed.

(5) Other
Microcapsules for rice seedling boxes have also been developed to provide long-term residual effects.

Water-soluble packs of around 50g provide jumbo formulation for direct use on paddy fields. There are also bean-sized granules that can be scattered onto the water in the rice field; these reduce the amount needing to be applied to 250-500g/10a, less than the traditional 1kg dosages.

2.3.4. Classification by Toxicity

(1) Classification by Acute Toxicity
The *Poisonous and Deleterious Substances Control Act* designates pesticides with active ingredients that are highly toxic to animals (mice, rats) as poisons or deleterious substances and regulates the handling, manufacture and sale of them. Other less toxic pesticides are classified as ordinary substances (a general term for anything that is not a hazardous substance). Highly toxic poisons with a significant risk of injury are designated as "specific poisonous substances".

Some formulations may be less toxic even if their active ingredient has been designated as a deleterious substance. In many cases, reducing the amount of the active ingredient reduces the toxicity of the product. These formulations may be treated as ordinary substances if they are certified as "exemptions from the deleterious substance designation".
Table 2.5 shows the evaluation criteria for toxicity.

Table 2.5. Criteria for Poisonous and Deleterious Substances

Toxicity Test		Determination	
Oral Toxicity (LD_{50})		Poison	50mg/kg or less
		Deleterious substance	Over 50mg/kg but less than 300mg/kg
Dermal Toxicity (LD_{50})		Poison	200mg/kg or less
		Deleterious substance	Over 200mg/kg but less than 1,000mg/kg
Inhalation Toxicity	Gas (LC_{50})	Poison	500ppm (4hr) or less
		Deleterious substance	Over 500ppm (4hr) but less than 2,500ppm (4hr)
	Vapor (LC_{50})	Poison	2.0mg/l(4hr) or less
		Deleterious substance	Over 2.0mg/l (4hr) but less than 10mg/l (4hr)
	Dust / Mist (LC_{50})	Poison	0.5mg/l (4hr) or less
		Deleterious substance	Over 0.5mgl/L (4hr) but less than 1.0mg/l (4hr)

LD_{50}: the dose required to kill 50% of the members of a tested population. Shown as milligrams of substance per kilogram of test subject body mass.
LC_{50}: the dose required to kill 50% of the members of a tested population through inhalation. Shown as parts per milligram (ppm) or milligrams of substance per kilogram of test subject body mass.
Tabulated from the Internal Regulations of the Pharmaceutical Affairs and Food Sanitation Council, Ministry of Health, Labour and Welfare (March 2007).

(2) Classification by Fish Toxicity
Pesticides are classified as follows according to their degree of impact on fish and shellfish when used near water systems such as rivers. All pesticides except those in Category A must display a fish and shellfish warning label. These evaluations used 50% lethal concentrations LC_{50} for carp and daphnia.

Category A: Carp LC_{50} (48hr)>10ppm
Daphnia LC_{50} (3hr)>0.5ppm
Category B: Carp LC_{50} (48hr)≤10ppm - >0.5ppm
Daphnia LC_{50} (3hr) ≤0.5ppm
Category Bs: Any in Category B needing special attention
Category C: Carp LC_{50} (48hr)≤0.5ppm

2.4. Status of the Pesticide Industry and Productivity Improvement

2.4.1. Status of the Pesticide Industry

A simple summary of the market situation and business activities will provide a better understanding of the pesticide industry. Pesticides hold a dominant position in the fine chemicals industry, with domestic sales

amounting to ¥300 billion per year. This equates to around 9% of the world market. Japan is the third largest market after the United States and Brazil.

As synthetic pesticides developed in the years after the war, the scope of business for pesticides expanded significantly, both in Japan and across the world. A study by Wood Mackenzie showed rapid growth in the world pesticide market, from $850 million in 1960 to $11.6 billion in 1980 and then to $26.4 billion in 1990 [(1)]. While it plateaued in 1995 due to low produce prices and increased cultivation of genetically modified crops, it began to grow again in the 2000s, reaching $38 billion in 2008 [(2)].

The Japanese market initially showed roughly the same rapid growth as the world market, peaking in 1994 at ¥445 billion. However, a prolonged economic downturn and a set-aside for rice cultivation and other crops meant that by 2011 the market had dropped by 20% to ¥355 billion. For changes in the value of domestic pesticide shipments, please refer to Section 3.4.4. (1) and an accompanying graph. The rising value of the yen during this period meant almost no change in the value of overseas sales when converted into dollars.

Let us examine the main business activities in the pesticide industry. For more details, please refer to the Shibuya Index = II [(3)], published in 2009. In summary, the current oligopoly in the worldwide pesticide industry is the result of repeated, relentless mergers and acquisitions. This is particularly evident overseas.

With the advent of the 1980s, developing new pesticides meant having to clear tests on their biological effects, their safety in large quantities and their impact on the environment. This caused a dramatic decline in the success rate of new products and markedly increased development costs. This is very similar to the difficulties arising in recent years in developing new pharmaceutical products. While medicines are only given to patients with a prescription from a doctor, general consumers eat produce treated with pesticide whether they like it or not (and may be exposed to the pesticide if there are any residual traces). Since pesticides contend with nature through agriculture, they must also undergo environmental impact testing. Despite these differences, pesticides and medicine are similar in terms of the difficulties faced in developing them. Many companies opted for mergers and acquisitions as a way to beat this difficulty and survive.

This trend started overseas. Currently, there are three companies in the United States that deal with pesticides from the research and development stage right through to manufacture and sale: Dow, DuPont and Monsanto. In Europe, the three main companies are Swiss company Syngenta and German companies BASF and Bayer. While there are other specialized pesticide companies, they are mainly involved in selling generic, off-patent products. In terms of sales volume, these six surviving companies are all corporate giants worth well over ¥200 billion each, with Syngenta taking the lead at ¥800 billion. These companies can invest proportionately large sums into research and development and are engaged in fierce competition over invention and development.

Let us examine the situation in Japan. While many chemicals companies engaged in pesticide research and development from the 1980s onwards with the intention of breaking into the fine chemicals market, they had difficulty staying in business amid the economic downturn and declining success rate in pesticide development. Since 2000, there has been a trend to sell off pesticide operations in the name of "selection and concentration". In 2002, Takeda Pharmaceutical sold its pesticide operations to Sumitomo Chemical, despite having been a long-standing player in the pesticide industry. Also in 2002, Mitsubishi Chemical sold its pesticide operations to Nihon Nohyaku. In 2004, Dainippon Ink & Chemicals sold its pesticide operations to Nippon Soda. In 2009, Sankyo sold its pesticide operations to Mitsui Chemicals.

While Japanese companies have followed the merger and acquisition trends of the major overseas companies, they are still nowhere near the same size in terms of scale. The largest, Sumitomo Chemical, is worth ¥130 billion, followed by Ishihara Sangyo, Kumiai Chemical, Mitsui Chemicals Agro, Nippon Soda and Nissan Chemical, each worth around ¥40 billion. Nevertheless, Japanese manufacturers have continued to produce new pesticide products to rival the major overseas players and have produced many of the best products currently available. How is it that they have been able to compete with the major players who have invested far more heavily into research and development? This is discussed in Chapter 6: "Discussion and Future Prospects".

Cited References

(1) Takayama. *Shin Nōyaku no Kaihatsu Tenbō [Prospects for the Development of New Pesticides]*, Ikura, Katsuyata (supervising editor), CMC, 1997, p. 243.
(2) Takayama. *Shin Nōyaku Kaihatsu no Saizensen [The Forefront of New Pesticide Development]*, Yamamoto, Izuru (supervising editor), CMC, 2003, p. 322.
(3) Shibuya. *Shibuya Index – II : 2009*, Shibuya, Shigeyoshi, 2009.

2.4.2. The Role of Pesticides

Synthetic organic pesticides appeared in Japan after the war. Highly effective at controlling pest insects and weeds, they rapidly improved agricultural productivity

and acted as a kind of trump card to beat the food crisis. However, in those days, little consideration was given to toxicity to mammals, residual toxicity or environmental impact. Problems arose with lasting residues of organic mercury on produce and in soil, DDT, BHC and highly acutely toxic pesticides such as parathion, as well as problems with highly ichthyotoxic pesticides such as PCP.

This prompted several law changes and the problematic pesticides all disappeared, replaced by highly effective yet highly safe pesticides. Currently, farmers and their produce are guaranteed to be safe as long as the pesticides are used appropriately (on the right crops in the right quantity at the right time, etc.) as specified by the law.
Let us examine the role played by modern pesticides in terms of yield size, produce quality and economy of labor.

(1) Yield Size
The Japan Plant Protection Association has worked with agricultural experiment stations in various regions to compare the yield loss and profit loss rates between areas in which traditional agriculture is practiced and areas in which pesticide-free agriculture is practiced.(1) In principle, no pesticides at all were used in the pesticide-free areas, although, a minimal amount was used where the experiment was not working. The results are shown in Fig. 2.6.

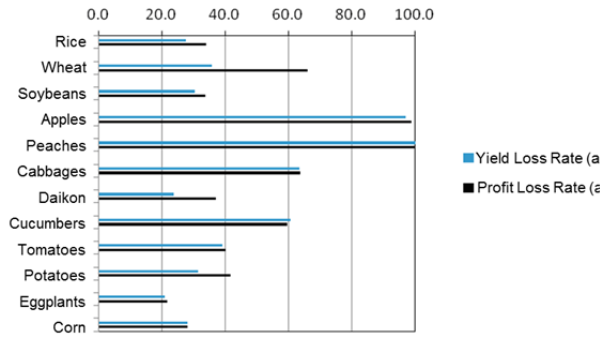


Fig. 2.6. Yield Loss and Sales Profit Loss due to Pests etc. where Pesticides are not used in Cultivation (1)

The results show that rice suffered an average yield loss of 27.5%, while the loss in monetary profit was even higher at 34%. For rice, anything more than a 10% yield loss is classed as "very bad" on the Crop Situation Index, equivalent to a major disaster. While some savings can be made by not using pesticides, these results show that the loss of income from such a yield loss would cost farmers far more dearly. The results also show yield losses of almost 100% in apples and peaches.

Accordingly, this report concludes that, under the current circumstances, agricultural production would be difficult without the use of pesticides.

(2) Produce Quality
Not using pesticides results in a drop in produce quality. One example is the damage caused to rice by the stink bug. Rice that has been sucked on by stink bugs appears speckled, reducing it to a lower grade produce and significantly lowering its commercial value. From this perspective, stink bugs are a major pest.

Plants are known to spontaneously produce phytoalexins when attacked by external enemies (pest insects, etc.). In some cases, a plant attacked by a pathogen produces an antibacterial substance, which can trigger effects such as food allergies.

When plants are attacked by a mold, the mold can also produce a mycotoxin. One example of this is Deoxynivalenol (DON), produced by fusarium scab in wheat. The Ministry of Health, Labour and Welfare established residue limits for DON in wheat and promoted the eradication of fusarium scab. Mold can also produce aflatoxin B1, a mycotoxin, in grains, peanuts, corn and other crops. Aflatoxin is known to be highly carcinogenic and the *Food Sanitation Act* stipulates that no food product may contain any Aflatoxin.(2)

(3) Labor Saving
Studies show an average 41% yield loss in rice cultivation with no weed control.(3) While this was once prevented by weeding by hand, this practice became a thing of the past as herbicides became more popular. Manual weeding bent over in the hot sun is hard work. In 1949, it took 50.6 hours per 10 ares; by 2004, this had been reduced to 1.6 hours (4)(5).

Fruit trees such as apples or mandarin oranges also need to have their blossoms or fruit thinned. In the past, this was done by manual labor. This used to be a hard task concentrated into a short period of time, but now the use of chemical fruit thinners has reduced the amount of work by 30-50%. (6).

As discussed above, pesticides are vital agricultural materials in terms of yield size, produce quality and labor saving. According to the *Statistics of the Ministry of Agriculture, Forestry and Fisheries*, pesticide costs accounted for 6.2% (¥7,409) of the rice production costs for 2011 (¥119,355/10a). The total number of working hours per 10 ares was 26.11 hours, around one-eighth of the 200.7 hours spent per 10 ares in 1951. Of course, rice planting machines, combine harvesters and other machinery account for a large part of this reduction in working hours, but pesticides have also made a significant contribution.

While there has been a recent demand from general consumers for pesticide-free produce, the price of pesticide-free produce has risen about 20%. Although the amount of organic produce (JAS) is increasing year by year, in 2010 it still only accounted for 0.23% of the total agricultural production.

Japanese produce is expected to be consistent in taste, size and shape, of good quality, with no bruises or other imperfections. While this may seem excessive at times, it raises the question of how the use of pesticides can be reduced while maintaining product quality. This would require comprehensive technology developments, such as producing pest-resistant varieties of crops, crop rotation, rootstock (grafted) cultivation and weather-protected cultivation of crops such as tomatoes.

Cited References

(1) Japan Plant Protection Association (ed.). *Nōyaku o Shiyō shinaide Saibai shita baai no Byōgaichū no Higai ni Kansuru Chōsa Hōkoku [Survey Report on Pest Damage where Pesticides are not used in Cultivation]*, Japan Plant Protection Association, 1993, p. 38.
(2) Ministry of Agriculture, Forestry and Fisheries. *Shokuhin no Kabi Doku ni Kansuru Jōhō [Information on Mycotoxins in Food Products]*, accessed 13 December 2012. http://www.maff.go.jp/j/syouan/seisaku/risk_analysis/priority/kabidoku/kabi_iroiro.html
(3) Japan Plant Protection Association. *Nōyaku Gaisetsu [Pesticide Overview]*, 2011.
(4) Chisaka. "Zassō Bōjo Gijutsu no Genjō to Kadai ni Tsuite. [Current Status and Issues with Weed Control Technology.]" *Nōgyō [Agriculture]*, Dai Nippon Farmers' Association, 1995, p. 4.
(5) Takeshita. *Journal of Weed Science and Technology*, Vol. 49, No. 3, 2004, p. 220.
(6) *Nōyaku Q & A [Pesticide Q & A]*, 2011, p. 28.

2.5. Pesticide Regulations

Pesticides are regulated by various laws. While regulation was more lenient in the pre-war era, legislation was put into place after the war. The goal at the time was to protect users of pesticides, that is, farmers. However, later issues with residual pesticides and environmental impact issues triggered a review of the laws to consider not only the safety of users (farmers), but also the safety of consumers and the environment as well, resulting in the legislation we have today.

2.5.1. Enacting the Agricultural Chemicals Regulation Act (MAFF)

The *Agricultural Chemicals Regulation Act*, first announced in July 1948, and a number of other laws regulate the production, importation, circulation, sale and use of pesticides. Let us examine the course of events leading up to the present situation.

Although pesticide production bloomed from the late 1920s onwards, the government had no particular policies in place regarding production methods or product quality and offered only a moderate degree of guidance in this area. A rapid increase in pesticide imports at this time saw the government set up an Association for Regulating Pesticide Imports in 1938 and begin to regulate the import and distribution of four products: nicotine sulfate, derris, lead and pine resin. In 1940, the government started regulating the distribution of agricultural agents; this practice continued until 1950.

Turbulent times during and after the war saw a shortage of all goods, not least of all an extreme shortage of pesticides needed to boost food production. This resulted in overproduction of inferior products and many ineffective pesticides appeared on the market. To put an end to this, the government enacted the *Provisions of the Ministry of Agriculture and Forestry on the Inspection and Certification of Agricultural Agents* in 1947. Shipments of pesticides were inspected by the Pesticide Association, established the previous year, with the aim to facilitate the spread of superior pesticides.

The following year in August 1948, the more binding *Agricultural Chemicals Regulation Act* was enacted. This law made it mandatory to register and label pesticides. The government established the new Ministry of Agriculture and Forestry Pesticide Inspection Center (now the Food and Agricultural Materials Inspection Center (FAMIC)). Manufacturers could not sell any pesticides that had not been inspected here and registered by the Minister of Agriculture and Forestry.

Thus, the focus of the *Agricultural Chemicals Regulation Act* was to ensure that high quality pesticides were manufactured safely and provided to farmers in order to boost food production. From that time on, a succession of high-quality, synthetic organic pesticides began to appear at a rate that has not been replicated since. These products made a huge contribution to increasing agricultural productivity and saving labor.

As Japan entered a time of rapid economic growth, a number of social problems emerged, such as the effluence of chemicals into the ecosystem and the residual impact of this, as well as concerns for general consumer safety, or, more specifically, concerns about residual pesticide in produce. The *Agricultural Chemicals Regulation Act* was amended several times and several related regulations were enacted, resulting

in the stricter regulatory conditions of the present day. Sections 3.4.4. (2) and 3.4.5. (1) touch on the main amendments in more detail.

2.5.2. The *Poisonous and Deleterious Substances Control Act* (Ministry of Health, Labour and Welfare)

The *Poisonous and Deleterious Substances Control Act* was enacted in 1950 to prevent injuries from highly toxic chemical substances such as pesticides (except for pharmaceutical products or quasi-pharmaceutical products). The classification criteria are given in Table 2.5.

This law stipulates matters relating to the manufacture, import, sale, labelling, storage and disposal of poisonous and deleterious substances. Any substance that is not categorized as a poisonous or deleterious substance is treated as an "ordinary substance" and this law does not apply. Highly toxic pesticides have been phased out and replaced since this law was enacted, thanks to tighter regulation as well as efforts by developers. In the late 1950s, poisons and specific poisonous substances accounted for around half of all pesticides; by 2011, this figure had dropped to 0.8%. This shall be discussed in detail in Section 3.4.4. (1).

2.5.3. The *Food Safety Basic Act* (Cabinet Office)

The *Food Safety Basic Act* was enacted in 2003 to ensure food safety for the protection of public health. This law saw the establishment of the Food Safety Commission and played a part in establishing the criteria for evaluating pesticide safety and determining the acceptable daily intake (ADI) of residual pesticides in food.

2.5.4. The *Food Sanitation Act* (Ministry of Health, Labour and Welfare) et al.

The *Food Sanitation Act* is an old law enacted in 1947. Let us discuss residue limits in relation to this law.

The *Agricultural Chemicals Regulation Act* stipulates criteria for suspending registration for each pesticide. This means that if a pesticide fails to satisfy certain criteria, its registration can be suspended. Meanwhile, the *Food Sanitation Act* specifies the residue limits. These are the standard criteria for ensuring food safety. If the amount of pesticide detected in a food commodity exceeds the amount permitted in the residue limits, the distribution and sale of that food commodity is restricted. The total pesticide intake is calculated from the amount of pesticides residual in food and the amount of food consumed by the average Japanese person. This intake must not exceed 80% of the ADI, based on animal experiments and other research.

The Positive List System for Agricultural Chemical Residues in Foods was implemented in 2003 to set maximum residue limits for all pesticides. This is discussed in detail in Section 3.4.5. (2).

Several other laws not mentioned above also relate to pesticides. Their names and jurisdictive agencies are given here.

Ministry of the Environment: *Basic Environment Act*, *Water Pollution Control Act*, *Water Supply Act*, *Waste Management and Public Cleansing Act*
Ministry of Internal Affairs and Communications: *Fire Services Act*
Ministry of Economy, Trade and Industry: *Law concerning Pollutant Release and Transfer Register*, *Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc.*

While some treatments used to control sanitary pests such as mosquitoes, flies or cockroaches have some of the same ingredients as pesticides, their use against sanitary pests means that they are classed as pharmaceutical products or quasi-pharmaceutical products and are regulated by the *Pharmaceutical Affairs Act*. Treatments targeting nuisance insects such as termites, wasps, gnats, caterpillars, centipedes and spiders are subject to the *Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc.* or the *Autonomous Standards of the Council for the Extermination of Health Pests*.

2.6. Process of Pesticide Development and Key Technology

This section provides an overview of the development process and contributing technology that go into the creation of new pesticides. It takes around ten years to develop a pesticide and costs more than ¥3 billion to produce it domestically and up to ¥10 billion to produce it overseas. The chances of success are also extremely low; it takes a synthesis of tens of thousands of compounds to finally produce a successful agent. The most difficult part of it is that there is no guarantee that such a huge investment of time and money will actually succeed. It takes a continuous flow of resources (people, goods, money) into research and development to sustain a pesticide business and continually produce new products. This is one of the reasons for the repeated amalgamation of businesses in the pesticide industry.

The pesticide development process is shown in Fig. 2.7. The process from research and development through to successful registration and going on the market requires a number of contributing technologies, each requiring its own cutting-edge research and development. The

following is an outline of the development steps.

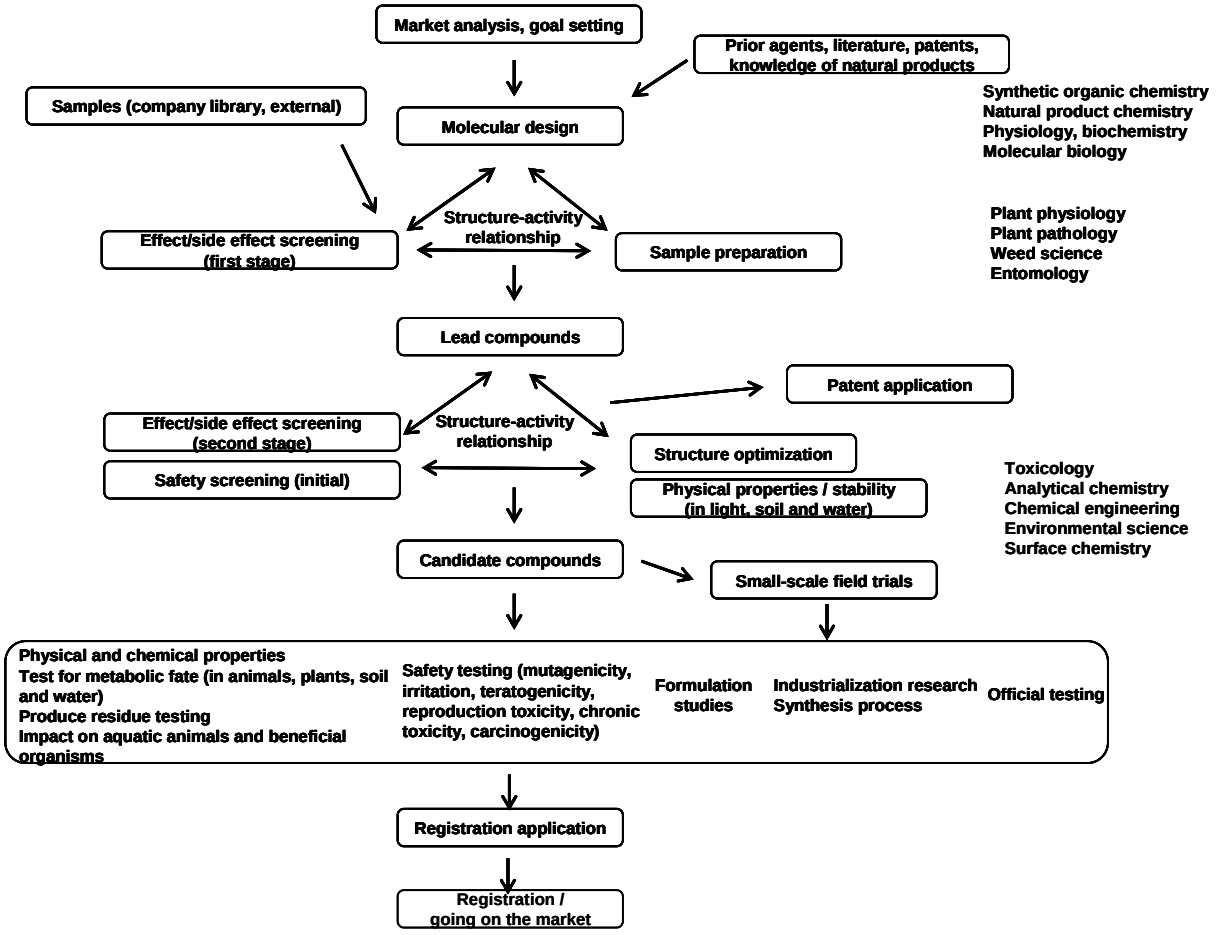
(1) Exploratory stage (the stage ending with the discovery of the lead compounds)
This stage is also called Phase Zero, in which the research goes from zero to the first stage. Molecular design is carried out to create a compound that will achieve the development aims. Repeated activity evaluations (biological screening) are carried out to come up with a basic structure that is worth taking on to the next step. There is a diverse range of ways in which research can progress and there are advantages and disadvantages to each of them. They can be summarized as follows.

- Random Screening: A means of evaluating the activity of compounds held by the company or synthesized by an intermediary or external organization such as a university. Predictably low chance of detecting activity.

- Bio-rational approach: A method of molecular design based on mode of action, metabolism studies, or knowledge of natural products combined with physiological/biochemical expertise. The source of the idea is important, and many successful cases have been achieved this way in the past. Advances in 3-D structural analysis techniques for protein and other high molecular compounds as well as advances in computer-aided technology have enabled spatial structure analyses of protein at the site of action, making it easier to design chemical structures that will interact there.

- Chemical approach: A method of molecular design in which researchers have a good knowledge of specific chemical reactions or companies have their own intermediates with good knowledge of chemistry. Since synthetic organic chemistry is a key technology, a good idea of production costs can be ascertained quite early on.

- Approach of altering existing chemicals: A method of molecular design by taking chemical structures known to be effective pesticides and altering them so that they do not infringe existing patents. While this is quite effective at the research level, the product must be better than the existing products, have competitive manufacturing costs and not be limited by existing patents.



Partially modified from *Nōyaku Q & A [Pesticide Q & A]*, revised edition, Japan Crop Protection Association (ed.), 2011, p. 179.

Fig. 2.7. Pesticide Development Process

In reality, research is often done using a combination of these methods. There are no royal roads when it comes to exploratory research. It is largely dependent on individual skills. The important thing is collaboration between those responsible for synthesizing compounds and the researchers who will conduct biological testing. This stage requires unique creativity. Researchers need to have knowledge of past research, be able to come up with ideas that are unrestrained by common sense and have a tenacity of purpose so as not to be discouraged by low chances of success. This could be likened to mountain climbing. The route up the mountain differs according to the individual: one person might take a detour to climb safely, while others might climb up an overhang with no thought for the risk of falling. Research management is very difficult at this stage.

(2) Lead Compound Optimization Stage (deciding on lead compounds to develop)

This stage of development involves maximizing the activity of the lead compound to make it more competitive. It is about optimizing chemical structure and specifying candidate compounds. The research theme is confirmed at this stage and researchers from a number of different fields take part in the planning. Each company has its own development phases and specifies items to be clarified in each phase.

Synthesis researchers are requested to provide a number of analogues and also establish a broad-ranging patent ahead of competitors. They must also prepare samples of kilogram scale for various tests. Biological researchers have to cover a wide area, from ascertaining product performance and whether or not there are any adverse effects on crops, to confirming effectiveness through field trials. Researchers also carry out preliminary studies on formulation, perform initial safety evaluations (mutagenicity, acute toxicity, fish toxicity, etc.) and ascertain the physicochemical properties of the compound (light stability, dynamic state in soil, analytical methods, etc.).

(3) Final Stage of Development (compliance for pesticide registration)

This stage is where the project goes into full swing and concerted efforts are put into it. Each company has its own development phases and specifies items to be clarified in order to move on to the next phase. Management has to decide whether or not to make a large-scale investment into the project.

Table 2.8 shows the tests required for pesticide registration. Most of these tests must be carried out by a certified testing agency in accordance with the Ministry of Agriculture, Forestry and Fisheries Good Laboratory Practice (GLP) standards for toxicity tests and residue. To complete the package, it takes more than two years and costs around ¥1 billion in direct expenses. If there is a problem with the toxicity results, development will be stopped.

Table 2.8. Test Scores Required for Pesticide Registration (tabulated from *Notice of the Director of the Ministry of Agriculture, Forestry and Fisheries Agricultural Production Bureau No. 12-8147* dated 24 November 2000)

Efficacy	Pest Insects and Diseases to Which Applied
Side effects	Crop to Which Applied
	Surrounding Crops
	Subsequent Crops
Toxicity	Acute Oral Toxicity
	Acute Dermal Toxicity
	Acute Inhalation Toxicity
	Dermal Irritation
	Ocular Irritation
	Dermal Sensitization
	Acute Neurotoxicity
	Acute Delayed Neurotoxicity
	Oral Toxicity Test Repeated for 90 Days
	Dermal Toxicity Test Repeated for 21 Days
	Inhalation Toxicity Test Repeated for 90 Days
	Neurotoxicity Test with Repeated Oral Administration
	Delayed Neurotoxicity with Repeated Administration for 28 Days
	Oral Toxicity Repeated for One Year
	Carcinogenicity
	Reproduction Toxicity
	Teratogenicity
	Mutagenicity
	Impact on Biological Functions
	Metabolic Fate in Animals
	Plant Metabolism
	Soil Metabolism
	Water Metabolism
	Impact on Aquatic Animals and Plants
	Impact on Beneficial Organisms other than Aquatic Organisms
	Properties, Stability, Degradation, etc. of Active Ingredient
	Water Pollution
	Derivation of Predicted Environmental Concentration
Residues	Residues in Crops
	Residues in Soil

(4) Pesticide Registration System

An application for pesticide registration is presented to the Ministry of Agriculture, Forestry and Fisheries with the above test results included. The Ministry examines the application with assistance from the Ministry of Health, Labour and Welfare, the Ministry of the Environment, the Cabinet Office Food Safety

Commission and other government agencies. If the product is deemed suitable, registration is granted and permission is given to put the product on the market. There are three sets of criteria to determine the suitability of a pesticide: the criteria for suspending registration (if these criteria are not met, registration is cancelled and the product cannot be sold), the residue criteria (if the amount of pesticide in a crop exceeds the criteria, sale of the crop is banned and the crop is recalled) and the pesticide use criteria (standards to be adhered to by users in relation to usage period, usage times, etc.).

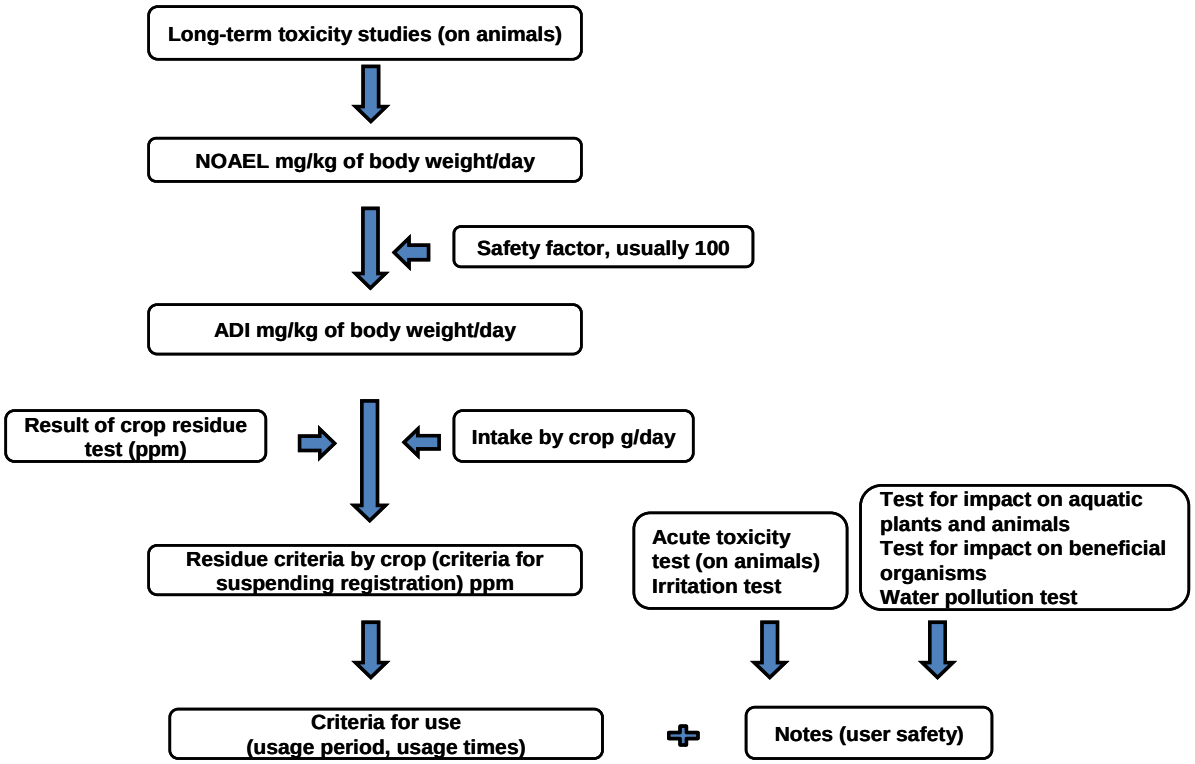
While there are sometimes mass media reports of pesticides detected in crops in excess of the maximum residue limits, the opinion is often expressed that "there are no immediate health effects". This is due to the manner in which the maximum residue limits are set. Fig. 2.9 below provides details on the criteria for safety evaluation and residue on crops.[1]

The No Observed Adverse Effect Level (NOAEL) is determined by the toxicity tests given in Table 2.8. This level is measured in milligrams per kilogram of body weight per day. Since the NOAEL is derived from animal testing, the Acceptable Daily Intake (ADI) can be determined by multiplying the NOAEL by a safety factor (usually 1/100) that takes into account differences between species and differences between individuals.

The ADI is the amount of a certain substance a person can habitually consume over a lifetime with no adverse health effects. This is the maximum permissible amount an individual can ingest based on the average Japanese body weight of 53.5kg.

The amount of residual pesticide in crops is determined by residue analyses. For instance, crop samples are taken 1, 3, 7 and 14 days after a pesticide treatment and the amount of residue measured. The estimated intake of residue can be calculated by multiplying the amount of residue (the volume measured plus an additional placeholder for safety) by the average amount of the produce consumed by Japanese (e.g. 185g of rice per person per day). The maximum residue limits are set so that the estimated intake does not exceed 80% of the ADI multiplied by the body weight (in parts per million). If a particular pesticide is used on multiple crops, the sum of the respective estimated intakes is used. The reason that the maximum residue limits are no higher than 80% of the ADI is because consumers may also ingest the same pesticide from sources other than crops, such as water, air or fish.

While setting the residue criteria is a rather complex process and somewhat difficult to understand, the main points are as follows.



Partially modified from *Nōyaku Q & A [Pesticide Q & A]*, revised edition, Japan Crop Protection Association (ed.), 2011, p. 179.

Fig. 2.9. Pesticide Safety Assessment Flowchart

Firstly, the criteria are set to ensure that the food that we eat every day "will have no adverse health effects even if we eat that food every day for the rest of our lives". Conversely, we can also be assured that if we were to eat any food that exceeds the maximum residue limits, "there would be no immediate adverse health effects". To put it another way, the maximum residue limit is a regulatory standard rather than a safety standard. The limits are determined by the results of the numerous toxicity tests given in Table 2.8 multiplied by further safety factors. Thus, the maximum residue limits for pesticides are determined based on a whole range of long-term toxicity studies. Other than pharmaceutical products, nothing else undergoes such extensive safety testing.

The second point relates to acute toxicity. General consumers seem to believe that if they were to ingest a food product containing a higher amount of residue than the maximum residue limit, this would present a health hazard or a case of acute toxicity. This understanding is based on repeated cases of poisoning as a result of the use of large volumes of highly toxic synthetic pesticides such as parathion after the war. However, around 60 years later, only a very small proportion (0.8%) of pesticides is classed as poisonous substances and the safety of farmers is now guaranteed. Meanwhile, the residue criteria are standards relating to the safety of the food consumed by general consumers. It is highly unlikely that there would be any cases of acute adverse effects from this level of exposure to pesticides.

Humans have a long history of learning and distinguishing what we can eat and what we cannot eat (toxic substances). However, we have never studied the safety of the natural chemical substances found in the food we eat to the same level of detail as we have done for pesticides. We know about poisonous blowfish and poisonous mushrooms and we understand that alcohol is carcinogenic; there have also been past cases of poisoning in livestock that have eaten large amounts of bracken (which contains carcinogenic ptaquiloside). The point is that natural food products are not necessarily safe. We need to be aware that chemical substances, whether natural products or compounds, can be harmful or beneficial, depending on the amount of exposure to them.

Above, we have discussed the process of pesticide development, the contributing technologies and the final stage, the pesticide registration system. The reason it has become increasingly more difficult to develop pesticides is that new pesticides have to undergo detailed checks to ensure their safety, including user safety checks, safety checks for consumers ingesting produce on which pesticides have been used and environmental impact checks. Chapter 5 discusses how Japanese companies, despite not being major global players in the industry, have continually been able to produce pesticides that rival those of the major Western corporations and also discusses the future prospects for Japanese companies in the industry.

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3. The History of Pesticides

This chapter provides an overview of the history of pesticides in Japan. The discussion will be divided by era: early (Jōmon period through to the 17th century), early modern (17th to late 19th century), modern (late 19th century to pre-WWII) and present (post-WWII). The reason for this categorization is that the pesticide industry began to develop in the present period as advances were made in science and technology, especially chemistry. Although there were only a handful of pesticide varieties of limited effectiveness before that time, the roots of the highly effective pesticides popular today can be traced back to the late 19th century. This chapter also touches on the agricultural and social environments surrounding the use of pesticides.

3.1. Prayer and the Beginning of Agriculture (Jōmon period through to the 16th century)

Cultivation of crops such as foxtail millet and barnyard millet to supplement hunting and fishing began in what is known as the Jōmon period (around 10,000 BC to the 3rd century BC). Paddy rice cultivation was later introduced to Japan from the Asian continent around the end of the Jōmon period or early Yayoi period. The remains of paddy fields have been uncovered at several sites from this era [(1)].

Around this time, a battle would have commenced against disease and pest insects that damage crops. Agriculture is an unnatural task: humans working against nature to extensively cultivate a single crop in order to survive and thrive. With a single crop, the fields are simpler than in their natural state; life also becomes simpler for the insects (pests) that live there, being provided with an abundance of suitable food. The crops are more vulnerable to disease and pest insects than wild plants are, with yields dropping after an outbreak. Cold and drought led to starvation; the human population declined due to countless deaths from starvation. The population at the start of the early modern period (c. 1600) is estimated to have been around 10-12 million, with around 1.6 million hectares of arable land [(2)].

Farmers in those days had no means to control pest insects. To prevent crop damage, they looked to fields as the object of their faith and developed agricultural rituals such as prayers. There is an entry on pest insects in *Gleanings from Ancient Stories* [(2)], written 1200 years ago in 807 by Inbe Hironari of Awa Province (Tokushima). This was an age in which people literally entreated deities through ceremonies called *mushi-oi* to ward off insects. They would place beef or phallic-shaped ritual equipment in the water inlets in the field to ward off insect pests, or wave fans with crows depicted on them to drive off rice pests (pest insects that damage rice plants, such as armyworms and leafhoppers). Vestiges of these prayers have continued as traditions down to the present day, despite the development of highly effective pesticides.

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3.2. *Mushi-Oi* and the Roots of Modern Pesticides (early modern; 17th to late 19th century)

There was a major increase in arable land from the 17th century onwards. In 1600, Japan had around 1.64 million hectares of arable land; by around 1720, this had risen to 2.97 million hectares. There was no major increase in arable land for a long time after that; by the late 19th century this figure had only risen to 3.05 million hectares [(1)]. The population also continued to grow. The population of around 12 million in 1600 had grown to around 31 million by 1721, reaching a peak at 33 million around the time of the Meiji Restoration in 1868 [(2)].

3.2.1. Family Traditions on the Killing of Insects

In 1600, the year of the Battle of Sekigahara, Matsuda Naiki of Izumo Province (present-day Shimane prefecture) wrote a document addressed to Namba Jinemon, entitled *Family Traditions on the Killing of Insects*. This document records family remedies for killing insects using a combination of five types of ingredients and comments on their effectiveness. Okamoto made the existence of this document known in 1953 [(3)] and discussed it in more detail 1992 [(4),(5),(6)]. A recent survey reaffirmed the existence of this document with the help of the Iinan Town Board of Education in Iishi District, Shimane. The findings are outlined here.

There are two extant variants of the document. The original was written in 1600. One manuscript was transcribed in 1776; this is held by the Namba family in the form of a record entitled *Kokumin Hōjō-ki [Record*

of the Nation's Fertility] (Fig. 3.1). The other manuscript is the *Family Traditions on the Killing of Insects*, copied in 1845 and passed down by the Kurahashi family of Akanahachimangū Shrine (Fig 3.2). While the content of the two documents is more or less the same, only the latter has an entry detailing the following prescription.

The document records that a compound of five ingredients: morning glory seeds, aconitum root, amber (fossilized resin used as a fragrance), camphor and alum can be made into a smoke as is, or boiled and the liquid dispensed where desired to eradicate cutworms, earthworms, insects on spring grasses and radishes, leafhoppers, wild boar and deer. There are precise descriptions of its method of application, the mode of life of leafhoppers and other details. However, judging from the ingredients, it would have had rather limited effectiveness.

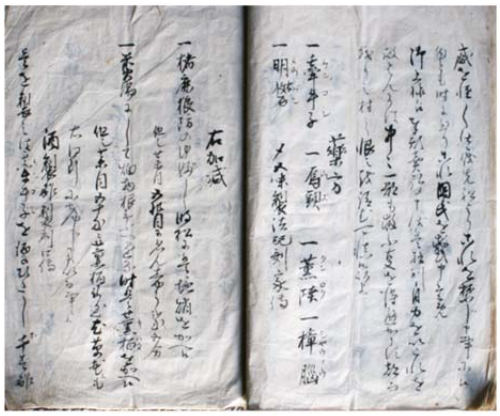
Family Traditions on the Killing of Insects is the oldest extant record of pesticide in Japan and could be hailed as the root of modern Japanese pesticides.

難波家に伝わる「国民豊饒記」と保存されている蔵

Fig. 3.1. *Record of the Nation's Fertility* Namba Family

赤穴八幡宮倉橋家に伝わる「家伝殺虫散」と資料館

Fig. 3.2. *Family Traditions on the Killing of Insects* Kurahashi family of Akanahachimangū Shrine



「家伝殺虫散」の薬方

Fig. 3.3. Prescription from *Family Traditions on the Killing of Insects*

3.2.2. Control by Oiling and the Introduction of the Agricultural Book

In 1670, Kuratomi Kichiemon, a village headman from Chikuzen Province (Fukuoka) discovered a method of eradicating leafhoppers by pouring whale oil onto paddy fields [7], [8]. The history of Yatsurugi Temple in Mizumaki, Onga District, Fukuoka, records that "this is held to be the beginning of pest insect control in Japanese agriculture" (Fig. 3.4) [9]. From a practical point of view, this method discovered by Kuratomi of using whale oil to control leafhoppers was indeed the beginning of effective pest insect eradication in Japan.

福岡県遠賀郡水巻町にある八剱神社の由緒

Fig. 3.4. The History of Yatsurugi Temple in Mizumaki, Onga District, Fukuoka (provided by Mr. Kitake [9])

In 1697, Miyazaki Yasusada of Chikuzen Province wrote the ten-volume *Compendium of Agriculture* [10]. This became very popular as the most systematic guidebook to agriculture in 18th century Japan. It records methods for eradicating pest insects, such as making broth from agarwood or chinaberry powder, sophora root, Japanese andromeda leaves and tobacco stems, as well as making smoke from sulfur or wormwood [11].

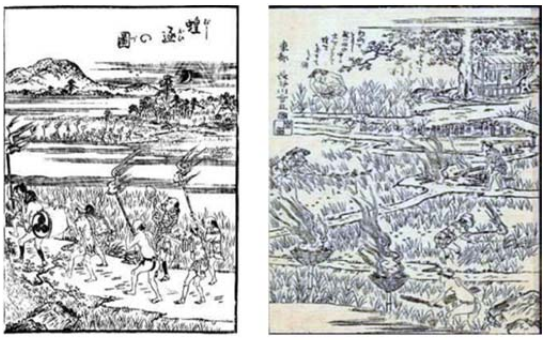
In 1731, Sugimoto Shōbei of the Tosa domain (Kochi) compiled *Rich Treasury of Records*, another guidebook

for eradicating pest insects [11], [12]. This work listed grassleaf sweetflag, chinaberry, sweet autumn clematis, sophora, Japanese andromeda, tobacco, St. John's wort, Japanese mugwort, rheum, pagoda tree, gingko biloba, pine needles and cereals as plants that could be used to eradicate pest insects. Animal products that could also be used included whale oil and fish broth.

All of the plants listed in the *Compendium of Agriculture* and *Rich Treasury of Records* are types of medicinal plants. Each of these is now known to have insecticidal or insect repelling components to it: chinaberry contains azadirachtin; Japanese andromeda contains grayanotoxin; tobacco contains nicotine. Presumably, these would have had some degree of effectiveness.

In 1788, Nagaki Shichizaemon of Ushu (Akita) compiled the *Methods for Eradicating Rice Pests in Ushu Akita* [13]. This document records the use of perilla oil, blowfish oil and shark oil to eradicate pest insects on fields.

In 1826, Okura Nagatsune of Bungo (Oita) wrote *Eradicating Rice Pests*, using diagrams to explain methods of extermination, mainly the use of whale oil. In 1844, he wrote *Eradicating Rice Pests, Part Two*, summarizing other methods of eradication besides whale oil, such as using mustard oil, canola oil, tung oil and Japanese andromeda [14]. This was Japan's first systematic compilation of pest control methods using pesticides. It seems to have been widely popular throughout the entire country, as there is evidence of the shogunate notifying prefectural governors to use these methods in the event of a pest outbreak. This book also has a number of illustrations showing specifically how to apply the oil. There are also images of *mushi-oi*, a method of pest eradication by incantation, practiced at the time. It involved marching around the fields burning pine torches, blowing horagai (conch shells) and beating drums and bells in the hope of burning the insects. Putting oil on the paddy fields and shaking off the pest insects into it apparently had the effect of suffocating the insects (Fig. 3.5). The late early modern period saw a famine in 1732 due to a major outbreak of leafhoppers, the Tenmei Famine in 1783 and the Tenpo Famine in 1833, caused by cold weather damage. The damage from the Tenpo Famine in particular was severe across western Japan, with one million people dying of starvation. This triggered the widespread practice of using oil on fields. In certain regions, the *mushi-oi* or *mushi-okuri* ceremony is still practiced as a traditional event in much the same way as it always was. Fig. 3.6 shows a *mushi-okuri* ceremony being held in Muroushimokasama in Uda, Nara [15].



虫追いの図

Fig. 3.5. *Mushi-Oi* Illustration from *Eradicating Rice Pests* [14]

As discussed above, up until the late 19th century, the only way farmers could keep pest insects from their fields was through the use of oils such as whale oil, or by using medicinal plants – the efficacy and popularity of which are unclear – or by prayer in the form of *mushi-oi*. During this era, there were repeated major famines caused by unseasonable weather, leafhoppers and other factors, and many people starved to death. Agricultural production was nowhere near what it is today. Since the population plateaued at around 30 million from the late 1700s, we can presume that the country was only capable of feeding around this number of people.

奈良県宇陀市室生下笠間の虫送り（2004）

Fig. 3.6. *Mushi-Okuri* Ceremony in Murou shimokasama in Uda, Nara (reprinted from *Yamatoji Photo Album* [15])

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3.3. The Emergence of Modern Pesticides (late 19th century to pre-WWII): the Appearance of the 'Long-Lived Pesticides'

Japan opened its country to the world in the late 19th century and began to adopt various goods and technologies from overseas in many fields, including agriculture. While there were negative aspects to this, such as an increasing number of non-native insect pests (such as scale insects) as seeds and seedlings were introduced, Western agricultural techniques, such as selective breeding and using fertilizer, were also introduced to Japan.

The population rapidly increased from 30 million in the late 19th century to 80 million before the Second World War. Meanwhile, the advancement of modern industrialization saw a steady decline in the number of farmers from 14.6 million around 1880 to 13.74 million in the 1930s. Conversely, the amount of arable land grew from 4.7 million hectares in the 1870s to 6.04 million hectares by the 1930s. Advances in agricultural technology meant that rice production multiplied by 1.8 times, while the yield increased from 200kg to 300kg per 10 ares [(1), (2)].

However, as we shall mention later, there were only a limited number of pesticides at the time. In modern terms, organic farming was mainstream, which meant limited productivity. The present-day rice yield is around 500kg per 10 ares.

This chapter discusses early pesticides including oil, inorganic compounds (such as lime sulfur, Bordeaux mixture, copper agents and arsenicals) and natural products (such as pyrethrum insect powder, nicotine and derris), as well as early synthetic organic pesticides and their development, such as organomercury compounds and chloropicrin. It is worth mentioning here that industrial pesticide production began during this time and four pesticides emerged: machine oil, lime sulfur, Bordeaux mixture and chloropicrin. These four pesticides are still listed on the pesticide register and hold a very important place as key pesticides. Although many highly effective pesticides have been developed since the 1930s, this time period is historically significant, as it was when industrial production began on these four major long-lived pesticides.

3.3.1. Oil

Using whale oil on fields to eradicate pest insects dates back to the 17th century. This practice became popular in the late 19th century and it continued into the 1930s, although there was a transition taking place from animal oil to mineral oil. Synthetic insecticides such as BHC introduced to Japan after the war replaced whale oil as a leafhopper eradicator.

Machine oil works as an insecticide by physically covering insects with a hydrocarbon coating and suffocating them to death. This means that the insects can never become resistant to the treatment. Oil emulsion concentrates were produced and sold from the late 1920s onwards as a means of controlling spider mites in particular. It is still in popular use today, with 5,000 tons of it being sold to eradicate scale insects and leaf mites on fruit trees and vines, such as mandarins, pears and grapes.

3.3.2. Inorganic Compounds

(1) Lime Sulfur

Lime sulfur was first produced in 1851 by a Frenchman named Grison [(3)]. It was introduced to Japan in the late 19th century and became widely used after an experimental field test was conducted on scale insects on fruit trees in 1907 [(4)]. It was later used to control wheat leaf rust. Lime sulfur production started in Japan in 1910 by Nippon Seimi Seizo (now Nissan Chemical Industries) under the name of "liquid sodium sulfate" and in 1912 by Kanto Sanso (now also Nissan Chemical Industries) under the name of "Sanso liquid". This marked the beginning of industrial production of

pesticides in Japan [5]. As the product was tested on a wide range of applications, it rapidly expanded as a pesticide for wheat and an insecticide-fungicide for fruit trees. By 1939, the market had grown to 22,500 tons [6]. It inevitably declined in use due to its strong alkalinity and sulfurous odor, as well as the emergence of other highly effective pesticides after the war. Despite this decline, however, 5,000 tons of it were produced in 2008.

The main ingredient in lime sulfur is calcium polysulfide (CaS_x x=4-5) made by boiling lime and sulfur together in water. It works as an insecticide or fungicide by producing free sulfur from oxygen and carbon dioxide in the air. The sulfur released has a SH inhibiting effect on the electron transport chain in the metabolic energy system [7]. The 2012 Mode of Action Classification of the Fungicide Resistance Action Committee (FRAC), a sub-branch of CropLife International, classified the mode of action of sulfur and other inorganic substances such as copper as "Multi-site contact activity" M1-M9, with the comment that they are "generally considered as a low risk group without any signs of resistance developing to the fungicide" [8]. This is one of the main reasons it has continued to be used for the past 100 years.

(2) Bordeaux Mixture and Other Copper Formulations

In 1885, Pierre-Marie-Alexis Millardet, a professor at the University of Bordeaux in France, discovered by chance that a mixture of copper sulfate, lime and water (what became known as "Bordeaux mixture") was effective against diseases in grapes. The mixture was first used in Japan in 1897 at a vineyard in Ibaraki [9]. It was later used to control disease damage in fruit trees, such as pears, apples and mandarins, fruits and vegetables, such as melons, tomatoes and cabbages, and other crops such as cereals and konjac.

The chemical composition of Bordeaux mixture is calcium copper sulfate ($CuSO_4$, $_zCu(OH)_2$, $_yCa(OH)_2$, $2H_20$), and several different varieties can be made using the ingredients in different proportions. For instance, Bordeaux mixture type 4-4 is a mixture of 400g copper sulfate, 400g caustic lime and 100L water. The mixture achieves its effect by means of the well-known bactericidal properties of copper ions, which have a SH inhibiting effect on the electron transport chain in the respiratory system. Bordeaux mixture became popular because it could be prepared by farmers as the need arose (so-called mixing in the garden), although it has some drawbacks in that it is tedious to prepare and cannot be stored. A number of other copper formulations were produced as improved versions of this product, such as dusts, wettable powders and chelating agents. After the war, organocopper formulations were also developed. Fig. 3.7 shows these copper fungicides.

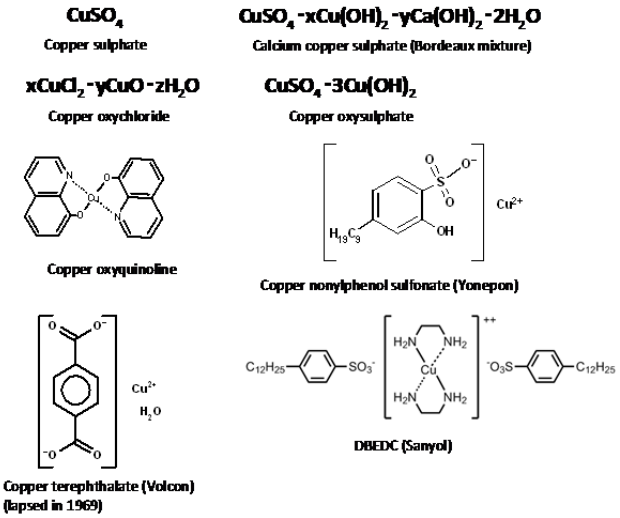


Fig. 3.7. Copper Fungicides

Production of copper fungicides started in the 1910s with companies such as Furukawa, Nissan Chemicals and Sankyo [10]. The pre-war production volume of 1,000 tons per year increased after the war; by 1957, this figure had grown to 5,000 tons. Despite a later downward trend, there were still 4,000 tons of orders placed in 2010.

Recently, opinions changed regarding organic agriculture and products appeared on the market claiming to be organic produce. However, production methods were vague and there was concern that this would cause confusion in the market. Accordingly, the *Japan Agricultural Standards (JAS) for Organic Produce* were defined in 2000. These standards stipulated the basic criteria for production methods, in principle prohibiting the use of chemically synthesized fertilizers, pesticides and recombinant DNA technology and giving details on materials that can be used in exceptional cases [11]. Permissible pesticides include machine oil, lime sulfur and the copper formulations mentioned above. For further details, see Section 3.4.5. (1).

(3) Arsenicals

Inorganic arsenicals have long been known for their insecticidal effect. Paris Green (copper (II) acetoarsenite) and London Purple (a mixture of lime arsenate and calcium arsenate) were pigments known to have an insecticidal effect [12]. In 1892, lead hydrogen arsenate ($PbHAsO_4$) was found to be effective against gypsy moth larvae; this was first imported to Japan in 1908 by Yokohama Ueki (later Toa Agricultural Chemical). In 1921, an experimental station in Hokkaido used calcium arsenate ($Ca_3(AsO_4)2$) to control rice leaf beetles. In 1922, Furukawa (later Nihon Nohyaku) and Yokohama Ueki started industrial production of lead hydrogen arsenate. In 1932, Nihon

Nohyaku started manufacturing calcium arsenate; in 1935, Nihon Jinzo Hiryo (later Nissan Chemical) started manufacturing ferric arsenate ($FeAsO_4$). Japanese companies also started exporting pesticides around this time and production drastically increased. In 1941, Japanese companies produced 4,500 tons of lead hydrogen arsenate, calcium arsenate and ferric arsenate [13]. At the time, lead hydrogen arsenate was labeled as a "toxic agent". Fig. 3.8 shows posters from the time encouraging its use.

Arsenicals release arsenic into the digestive system of the insect and are toxic; they are also highly toxic to animals. They are designated as poisons, having an acute oral toxicity of 80mg/kg in rats. Many cases of acute poisoning have been from inorganic arsenic compounds. Inorganic arsenic compounds are generally highly toxic, while organic arsenic compounds are less toxic. Trivalent arsenic is more toxic than pentavalent arsenic. Arsenic works as a poison by bonding with and inhibiting enzymes such as SH-group myocardial lactate dehydrogenase. The Ministry of the Environment has made detailed reports on the health impacts of arsenic and its compounds [14].

Lead hydrogen arsenate and other arsenicals became popular from the 1910s onwards as key pesticides. Lead hydrogen arsenate was the first pesticide to be registered when the post-war pesticide registration system began.

By around 1959, 3,000 tons of lead hydrogen arsenate was being produced every year. Fig. 3.9 shows a registration form and a product label from that time. However, production later gradually decreased. It was designated as a residual pesticide on crops in 1971 and its registration was revoked in 1978, bringing its half-century of service to an end.

Left: Using Toxic Agent to Eradicate Pests from Sweet Potatoes (Iwate)
Right: Controlling Pests on Potatoes (Hokkaido)

Fig. 3.8. Posters Encouraging the Use of Toxic Agent (Lead Hydrogen Arsenate) (poster on the left from 1925, poster on the right from 1930) (provided by the Japan Plant Protection Association Plant Protection Museum)

Left: Registration Form for Lead Hydrogen Arsenate (the first pesticide registered)
Right: Product Package for Sale

Fig. 3.9. Lead Hydrogen Arsenate Registration Form and Product Package (provided by Nihon Nohyaku, Inc.)

3.3.3. Organomercury Compounds

Mercuric chloride ($HgCl_2$), an inorganic mercury, was used to disinfect seeds and sterilize soil since the late 19th century. While formalin and copper formulations such as Bordeaux mixture were used as sprays and seed treatments for rice and wheat, they were not very popular as they were not sufficiently effective and there were concerns about harmful side effects. Organomercury compounds were introduced and their efficacy against rice blast and other crop diseases made them very popular.

In 1914, German company Bayer, part of IG Farben, the world's largest chemical group at the time, invented Uspulun (methoxyethylmercury chloride $CH_3OCH_2CH_2HgCl$) and confirmed its efficacy against wheat smut by seed treatment. The product went to market the following year and was introduced to Japan in 1921 [15], [16]. By 1935, it was evident that using Uspulun to disinfect seeds was very effective against a wide range of diseases, such as rice blast and wheat smut, and the product became widely popular (Fig. 3.10).

Japanese manufacturer Sankyo started marketing Mercuron (phenylmercury acetate $C_6H_5HgOCOCH_3$) in 1937.

Sanei Shoten (later Nihon Tokushu Noyaku Seizo) introduced Bayer Ceresan (phenylmercury acetate $C_6H_5HgOCOCH_3$) to Japan in 1938. This product gained a lot of attention in Manchuria, where it proved to be effective against seedling blight in cotton [17]. However, wartime conditions soon made it extremely difficult to import anything from Germany. Sanei

Shoten had imported and marketed Uspulun and Ceresan and managed to secure a technology licensing contract for both products from IG Farben. The decision for an importer/distributor to take on the technology licensing for the world's largest chemical company shows something of the resourcefulness of those company managers. Sanei Shoten took this opportunity to establish Nihon Tokushu Noyaku Seizo, Inc. in 1941 and rushed to complete its Hachioji factory the following year, with the intention of producing 100 tons of Uspulun and 200 tons of Ceresan per year. Even during wartime, this factory continued manufacturing at full capacity until it was destroyed in an air raid in August 1945.

Organomercury compounds thus became popular against a wide range of diseases in rice, wheat and other crops. This trend continued until the 1950s and 1960s, when problems started arising from mercury pollution in industrial wastewater, such as Minamata disease and Niigata Minamata disease, and organic mercury rice blast treatments were found to be leaving residual traces on rice. In 1966, the decision was made to replace these products with non-mercurial pesticides, under the instruction of the Ministry of Agriculture and Forestry. By 1973, registration had lapsed for all organomercury pesticides. This is discussed in the next section.

Uspulun Mercury Seed Treatment Product Package

Fig. 3.10. Uspulun Product Package [2]

3.3.4. Pyrethrum (Pyrethrins)

The (dried) flowers (ovaries) of *Chrysanthemum cinerariifolium*, a type of pyrethrum (Fig. 3.11) [18], contain 1.2-1.5% pyrethrins, which have insecticidal properties. This section discusses the rapid development of pyrethrins in Japan from the late 19th century to the pre-war era, as well as the history of pyrethrum cultivation and its industrial use.

Pyrethrum Flowers (Innoshima, Hiroshima)

Fig. 3.11. Pyrethrum Flowers, from *100 Years at Kincho* [18]

Natural pyrethrins and their derivatives are called pyrethroids. As advances were made in organic synthesis technology, many synthetic pyrethroids also developed from the late 1960s onwards. These new developments were used not only for home gardening and disease control, but also for agricultural pesticides. The production of natural pyrethrum gradually declined as the number of synthetic products increased.

(1) Origins and Production of Pyrethrum

In the early 19th century, an Armenian named Jumtikoff discovered that powdered Caucasian chrysanthemums had insecticidal properties [19]. By the mid-19th century, use of the Dalmatian chrysanthemum from the Dalmatian region (later Croatia) as an insecticide had spread throughout Europe. While the three following types of chrysanthemums are pyrethrums, the Dalmatian chrysanthemum has the highest pyrethrin content and is the most commonly used for insecticides [20], [21].

Dalmatian chrysanthemum (*Chrysanthemum cineraliaefolium*)
Persian chrysanthemum (*Chrysanthemum roseum*)
Armenian chrysanthemum (*Chrysanthemum Marshalli Ascherson*)

While there is a record of pyrethrum (powder) being first introduced to Japan around 1860 [22], this is not definitive, as another record states it was first introduced by Keirindo in 1881 as a flea powder, while yet another record states pyrethrum was introduced to Japan in 1884 by Austrian Georg Hütterot [23], [24]. In any case, it seems safe to say that pyrethrum was introduced to Japan in the late 19th century.

Another record states that Kizo Tamari introduced an American variety of pyrethrum to Japan in 1885 and grew them on a field at Tokyo Agricultural and Forestry

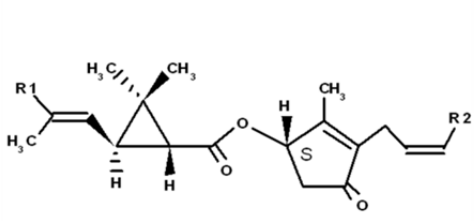
School, while still another record states that Nagayoshi Nagai (1845-1929), the so-called father of pharmacology (and discoverer of ephedrine), planted and cultivated a German variety in the Medical Herb Garden in Meguro, Tokyo [23], [25].

Pyrethrum cultivation was popularized by Eiichiro Ueyama, the owner of a mandarin plantation in Wakayama. Ueyama established Ueyama Shoten (now Kincho) in 1885 at the same time as he obtained pyrethrum seeds from H.E. Amoore, the manager of a plant company in San Francisco. The following year, Ueyama began full-scale pyrethrum cultivation in Wakayama. He then set about promoting pyrethrum cultivation across the entire country. To popularize pyrethrum cultivation, Ueyama wrote and published *Guide to Pyrethrum Cultivation* in 1890 and worked hard in Hokkaido and Inland Sea coastal regions such as Okayama to promote the effectiveness of pyrethrum as a pesticide as well as ways to cultivate and dry it [26], [27]. Hokkaido became the center of pyrethrum production from the 1910s; by the mid-1930s, the cultivation area had increased to 20,000 hectares in Hokkaido alone (and 29,000 hectares nationwide). Dried flower yields rose to 13,000 tons, 70% of the world's production. Two-thirds of this was exported, making Japan the top pyrethrum producer in the world. These exports decreased in the early 1940s because of the war; production also decreased as food production became a more pressing need. After the war, domestic cultivation of pyrethrum dropped off due to the emergence of synthetic organic pesticides such as DDT and BHC, as well as synthetic pyrethroids allethrin. Currently, pyrethrum is not produced at all in Japan. It is still grown in Kenya, Tanzania, Rwanda, Tasmania and China, with around 10,000 tons of dried flowers produced in 2010.

(2) Pyrethrin Chemistry

Dried pyrethrum flowers contain 1-1.5% pyrethrin; the pyrethrin content starts to increase from when the flower buds, reaching its maximum level at full bloom [28], [29]. When extracted with petroleum-based solvents, the products can contain around 20% pyrethrin. Fig. 3.12 shows six mixtures of homologues. There are two carboxylate moieties: chrysanthemic acid and pyrethric acid and three alcohol moieties: pyrethrolone, cinerolone and jasmorolone. Combinations of these are called Pyrethrin I and II, Cinerin I and II and Jasmolin I and II. Fujitani et al. [30] isolated the pyrethrins; Yamamoto et al. [31] estimated the chemical structure from the structure of the degradation product, Staudinger et al. performed further research on the planar structures [32], while La Forge et al. [33] made the final clarifications in this respect. The carboxylate moieties have a cyclopropane skeleton structure, while the alcohol moieties have a cyclopentenolone skeleton structure.

Crombie determined in 1954 that the carboxylate moieties have a three-dimensional structure of (+) 1R, 3R-trans [34], while Katsuda et al. determined in 1958 that the alcohol moieties have a three-dimensional structure of (+) S cis [35].



	R1	R2
Pyrethrin I	$-CH_3$	$-CH=CH_2$
Pyrethrin II	$-CO_2CH_3$	$-CH=CH_2$
Cinerin I	$-CH_3$	$-CH_3$
Cinerin II	$-CO_2CH_3$	$-CH_3$
Jasmolin I	$-CH_3$	$-CH_2CH_3$
Jasmolin II	$-CO_2CH_3$	$-CH_2CH_3$

Fig. 3.12 Natural Pyrethrin Chemical Structures

With the planar and steric structures having been clarified, major developments were made in synthetic pyrethroid research from the late 1950s onwards. Many pyrethroids were invented and further developed for use in the home or against sanitary pests, as well as for agriculture. Japanese researchers played a major role in these developments.

(3) The Insecticidal Effects of Pyrethrins and their Uses

Pyrethrins have an immediate (knock-down) effect on many pest insects at low doses. They are far less toxic and far more selective than other pesticides when it comes to their effect on mammals. While they have a highly effective median lethal dose LD_{50} for insects at 0.2mg/kg, the lethal dose is 4,500 times more selective for mammals (rats) at 900mg. They are quite highly toxic to fish [36].

Pyrethrins are effective against agricultural pests such as caterpillars, cabbageworms, aphids, brassica leaf beetles and leafhoppers, as well as sanitary pests such as flies, mosquitoes, lice and cockroaches. While they have a knock-down effect in agricultural use, they have a drawback in that they are less stable than nicotine or derris when exposed to ultraviolet rays, oxidation or heat. Accordingly, their effects are less consistent and less durable (residual). As a result, extracts, pyrethrum soaps and other solutions are used to control leafhoppers, aphids and caterpillars. While these were used as a substitute for derris during the war when it became difficult to import, they did not become very popular, due to the appearance of arsenicals. However, pyrethrins became popular insecticides for household use or on livestock due to their knock-down effect. 1935 saw more than 10,000 tons produced, including exports. The industry had grown to meet the demands

of the world.

(4) Invention of Mosquito-Repelling Incense

While pyrethrum was initially popular as a flea powder, Ueyama found that it worked to repel mosquitoes when mixed with sawdust and smoked in an incense burner. Ueyama developed this further and invented mosquito-repelling incense in 1890 [18]. This was made by mixing pyrethrum powder with a flour paste or other binder and forming it into sticks, using the conventional Japanese production method for making incense sticks for Buddhist altars. Thus, the world's first mosquito-repelling incense sticks came into being (Fig. 3.13).

However, these thin sticks would only last for about 40 minutes and it would take two or three of them burning at once to kill any mosquitoes. In 1895, Ueyama's wife, Yuki, suggested the idea of improving these sticks by making them into coils. A wooden prototype from this time has survived to this day (Fig. 3.14). Ueyama finally achieved a method of manufacturing by coiling a thick incense stick. The product went to market in 1902 [37]. Products, wooden extruders and commercially-made extruders from this time still exist today (Figs. 3.15, 3.16, 3.17). The manufacturing method improved from the late 1920s onwards, progressing from hand-wound to punched-out. Modern coils can burn for around seven and a half hours. The method of burning pyrethrum as mosquito-repellent incense was a ground-breaking invention, using smoke and vaporization to achieve a wide range of effects. The mosquito coil is well-known and used not only in Japan but overseas as well. Fig. 3.18 shows posters used overseas at the time.

The World's First Mosquito-Repelling Incense Sticks

Fig. 3.13. The World's First Mosquito-Repelling Incense Sticks (provided by Kincho)

Wooden Mosquito Coil Prototype from 1895

Fig. 3.14. Wooden Prototype of the World's First Mosquito Coil (provided by Kincho)

Hand-Wound Mosquito Coil c. 1919

Fig. 3.15. Early (1919) Hand-Wound Mosquito Coil (provided by Kincho)

Wooden Mosquito Coil Extruder (Incense Stick Pipe)

Fig. 3.16. Wooden Mosquito Coil Extruder (provided by Sanda Mosquito Fumigation Archives)

Early 20th-Century Mosquito Coil Extruder

Fig. 3.17. Mosquito Coil Extruder (provided by Kincho)

Fig. 3.18. Pre-War Overseas Mosquito Coil Posters (provided by Kincho)

As discussed above, Japanese pyrethrum technology led the world from the time pyrethrum was introduced to Japan in the late 19th century through to post-war chemical research. Specifically, Japanese researchers were instrumental in isolating its active ingredients, determining its molecular structure, cultivating it and also developing new uses for it. Based on this groundwork, many synthetic pyrethroid pesticides have been developed for agriculture since the 1960s. While details will be given in a later section, for now we can say that Japanese technological development is leading the world in this area.

3.3.5. Nicotine: Origins of the Modern Synthetic Organic Pesticides

Nicotine and pyrethrum, discussed in Section 3.3.4, are matchless as far as the origins of modern synthetic organic pesticides go. This section traces the history of nicotine from its introduction to Japan in the late 19th century through to the pre-war and post-war eras and attempts to highlight the important role that it has played.

Nicotine is an alkaloid found in plants of the *Nicotiana* genus of the *Solanaceae* family. It exists in the form of citric or malic acid salts (Fig. 3.19). In practical use, it is generally found in tobacco powder or nicotine sulfate.

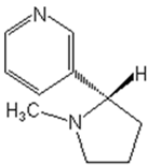


Fig. 3.19. Nicotine

Tobacco was introduced to the French elite as a medicinal plant by Frenchman Jean Nicot in 1560. In 1828, Germans Reimann and Posselt isolated a chemical substance from a tobacco leaf by steam distillation and named it nicotine, after Jean Nicot [38]. Nicotine was first synthesized by Craig in 1902, followed by Speath (1928) and Craig (1933). In practice, there are two varieties of *Nicotiana*: tobacco (*Nicotiana tabacum*), with 2-5% nicotine content, and mapacho (*Nicotiana rustica*), with 5-14% nicotine content [39].

The oldest record of the insecticidal properties of tobacco is in a document from 1690 stating that it was used to exterminate lace bugs. In 1746, Collinson discovered that it was effective against the plum weevil[40]. In 1910, Gillette used nicotine sulfate to control codling moths in pears and peaches [41].

In Japan, tobacco extract was produced by the Monopoly Bureau in 1908, while Yokohama Ueki started importing nicotine sulfate from the United States in 1910 [42], [43]. It was found to be effective against all kinds of pest insects, such as aphids, thrips, rice borers and moths in rice, vegetables and fruit trees, and became widely popular during the 1910s and 1920s. Before the war, Japan was using 100 tons of nicotine sulfate and 2,000 tons of tobacco powder; in the late 1950s, even after synthetic pesticides such as DDT and BHC appeared, Japan was still using 300 tons of nicotine pesticides. However, the role of nicotine pesticides all but died out once other high-performance pesticides appeared. The biggest drawback with nicotine is that it is highly toxic to mammals and has been designated as a poison. The median lethal dosage LD_{50} for nicotine sulfate in rats is 75-83mg/kg [44].

The mode of action of nicotine produces an insecticidal effect by bonding to the nicotinic acetylcholine receptors (nAChR) in the synaptic membrane and causing antagonistic stimulation [45].

Although nicotine thus poses a problem of acute toxicity to mammals, it was used as a highly effective pesticide from the late 19th century through to the post-war era of increased food production. Many researchers worked hard to develop new nicotine analogues, but they went for a long time without any success. However, in the 1990s, nearly 50 years after the war, a number of so-called neonicotinoids began to appear, as shall be mentioned later in Section 4.20: Imidacloprid. These pesticides were modeled on the composition of natural pesticides and are highly effective without being toxic to mammals. Who at the time could have predicted such an amazing development?

3.3.6. Derris (Rotenone): South Asian Leguminous Plant Root

Derris (rotenone) (Fig. 3.20) is a pesticide compound found in the root of the derris plant (*Derris elliptica*) from South Asia.

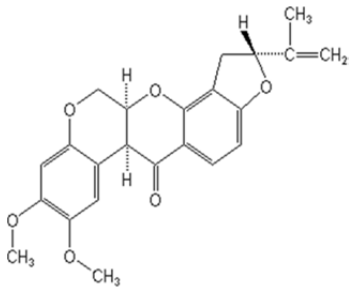


Fig. 3.20. Derris (Rotenone)

Derris has long been known to have insecticidal and fish toxic properties. People would grind up the roots and use them as poison for arrows or for putting in waterways to catch fish [46]. The first documented references to it are Rumphius in 1747 as a fish poison [47] and Oxley in 1848 as a pesticide [48]. In terms of chemistry, Nagai isolated its chemical composition in 1902 and called it rotenone [49]. In 1932, Takei et al., Butenandt et al. and La Forge et al. each independently determined and published its chemical structure. Miyano of the University of Tokyo accomplished its total synthesis in 1958 [50], [51]. Chemical research on rotenone has thus been spearheaded by Japanese researchers.

Derris was one of the top three natural pesticides in pre-war Japan, along with pyrethrum and nicotine. First imported to Japan from Singapore in 1912, it was soon found to be very effective. Factory production began in 1923, with a number of different formulations, such as derris powder, derris emulsion concentrate and derris soap. While it was not as fast-acting as pyrethrum, it was reliably lethal against pest insects such as aphids, lace bugs and various leaf beetles. While it had the disadvantage of being highly toxic to fish it had the advantages of being relatively harmless to mammals and not residual on crops, as it would break down and dissipate quite early on after application.

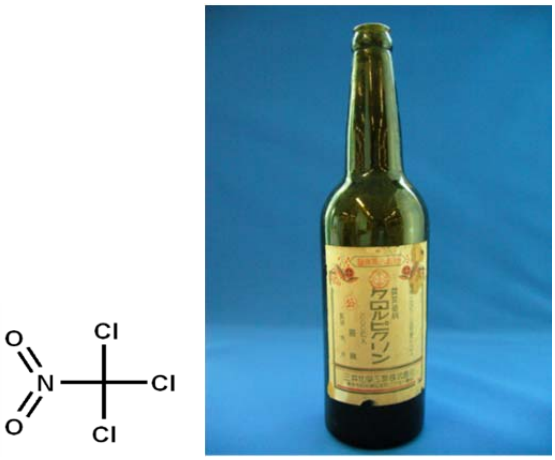
Later studies have shown that the mode of action of rotenone achieves an inhibitory effect on the electron transport chain in the respiratory system that governs energy metabolism. It is known to work as an insecticide by inhibiting electron transfer in NADH-ubiquinone oxidoreductase Complex I in the mitochondrial respiratory chain [52], [53], [54].

Production of rotenone increased greatly from the late 1920s onwards, mainly by Nihon Nohyaku, which had taken over Derris Seizai, the main manufacturer of derris products. It became one of the leading pesticides in Japan, along with pyrethrum and nicotine, with 250 tons used in 1942. However, imports from South Asia were suspended during the war and there was a dramatic decline in the amount of derris used. While it made a brief comeback after the war, it was designated as a water pollutant due to its high fish toxicity. It declined in use from the late 1950s onwards and its registration finally lapsed in 2006.

3.3.7. Chloropicrin: the First Synthetic Organic Pesticide

Chloropicrin (Fig. 3.21) has a long history. Scottish chemist John Stenhouse discovered it by chlorinating picric acid in 1848 [55]. It is a volatile liquid with a very high vapor pressure of 2.7kPa/20ºC at its boiling point of 112ºC. Being highly lachrymal, it was used as tear gas in the First World War.

W. Moore discovered the effectiveness of chloropicrin against maize weevils in 1917 and this discovery was published by Bertrand. Ryo Yamamoto of RIKEN accordingly synthesized the first chloropicrin compound in Japan in 1918 and validated the effect the following year. At the time, carbon disulfide (CS_2) or hydrocyanic acid gas was used for fumigating warehouses; the former was potentially explosive and could lower the quality of stored grain, while the latter was highly toxic to humans. Chloropicrin grew in popularity because of these drawbacks with the existing products. However, chloropicrin has its own drawback in that it is highly lachrymatory, although this is a transient symptom. This disadvantage led to the appearance of methyl bromide (CH_3Br) in 1950, which kept up a steady 1,000-ton shipment volume until around 1985.



Left: Chloropicrin
Right: Chloropicrin Product from the Late 1940s

Fig. 3.21. Chloropicrin and a Chloropicrin Product from the Late 1940s (provided by Mitsui Chemicals)

Around the same time it was being used for warehouse fumigation, chloropicrin also became known for its effectiveness as a soil sterilizer and insecticide when used to fumigate soil. Its efficacy against soil diseases and nematodes, such as the various insect pests on lettuce, mulberries, ginger, burdock, potatoes and sweet potatoes, was confirmed during the 1910s and 1920s. However, it did not become widely popular until after the war, as it was difficult to handle because of its strong irritativeness and highly priced for the time [56].

Chloropicrin was the first synthetic organic pesticide in Japan, produced by the following companies as shown below. Fig. 3.22 shows a chloropicrin product from the late 1940s.

1921: Sankyo (Mukojima factory)
1928: Hodogaya Soda
1930: Mitsui Chemicals
1934: Nippon Soda (Nihongi factory), Nippon Kayaku (Ogura factory)
1946: Mitsubishi Kasei

After the war, chloropicrin became a key chemical agent, with its use in soil fumigation becoming an established countermeasure against Granville wilt in tobacco and root-knot nematodes. The chloropicrin use steadily increased as it became more widely adopted as a countermeasure against damage from continuous cropping – not only for tobacco, but also for fruit and vegetable plants such as potatoes, sweet potatoes, cabbage, Chinese cabbage, daikon radish and eggplants. Chloropicrin shipments reached 5,000 tons in the late 1970s; by 2009, this figure had grown to 9,000 tons and was worth ¥9 billion.

As mentioned above, chloropicrin was first manufactured 90 years ago and remains a major long-lived pesticide with a wide range of uses. However, chloropicrin is an acutely toxic deleterious and highly irritant substance. Farmers have to take extra care, as it is very awkward to handle. Nevertheless, it is still being sold in high volumes for the following reasons.

(1) Effective insecticide-fungicide
(2) No observed residue on crops
(3) Localized production of fruit and vegetables; facilitated large-scale agriculture of fewer varieties
(4) The Japan Chloropicrin Manufacturers' Association has developed and promoted application methods and dedicated application equipment to ensure safety for users and avoid harm to workers or surroundings
(5) Methyl bromide, which has the same effects as chloropicrin, was designated as an "ozone-depleting substance" in 1992 and has been restricted in use except where absolutely necessary [57]

In the future, the hope is that we will not simply rely on treatments such as chloropicrin to control soil diseases, but instead develop various other pest control technologies from a holistic approach that incorporates other methods, such as using water or steam to sterilize soil, crop rotation or developing new cultivation methods.

3.3.8. Summary of the late 19th Century to the Pre-War Era

Above, we have given an overview of pesticides in Japan from the late 19th century through to the pre-war era. This period saw the development of new agricultural technology and the emergence of new pesticides that could not have previously been imagined. This was a time of vastly improved agricultural

productivity. However, the war dealt a serious blow to this productivity; Japan's defeat was catastrophic to the growing pesticide industry. Agricultural production dropped dramatically due to wartime shortages. Fig. 3.22 shows posters promoting food security in wartime.

Wartime Posters for Increased Food Production (Hokkaido, Ibaraki)

Fig. 3.22. Wartime Posters for Increased Food Production (provided by the Japan Plant Protection Association Plant Protection Museum)

Some of the pesticides that appeared during this time – machine oil, lime sulfur, copper agents and chloropicrin – are truly long-lived pesticides, as they are still used today. Pyrethrum and nicotine are also important, as they were the sources for the synthetic pyrethroids and neonicotinoids that have appeared since the 1980s. Table 3.23 shows the volumes and values of the main pesticides produced before and during the war [1].

There are several distinguishing characteristics about this table. Firstly, there is a major increase in overall pesticide production from the late 1920s onwards. Usage increased by nearly four times from just under ¥6 million around 1935 to a peak figure of ¥21 million in 1941. This figure plummeted due to disruptions and shortages until the end of the war.

The main insecticides were inorganic arsenicals, the natural products pyrethrum, nicotine and derris, and chloropicrin, used for fumigation. While machine oil was used from the 1910s to the 1930s, it dropped out of use due to the war. The only fungicides used during this time were copper agents and lime sulfur. Mercury compounds were recommended as a countermeasure to boost food production during the war and began to increase in use from around 1939. They started to become popular from around the late 1940s due to their effectiveness at disinfecting seeds.

While many synthetic organic pesticides appeared during and after the post-war rebuilding of Japan, given the level of science and technology at the time, there is no way anyone could have foreseen the current state of Japan's pesticide industry.

Table 3.23. Volumes and Values of Pesticides Produced Before and During the War [58]

Volume unit: tons　　Value unit: ¥1,000

	1934		1939		1941		1942		1945	
Item	vol.	val.	vol.	val.	vol.	val.	vol.	val.	vol.	val.
Lead arsenate	821	481	2,043	2,025	1,168	1,168	911	911	250	240
Calcium arsenate	8	4	817	378	3,213	1,317	2,403	985	1,200	640
Ferric arsenate	-	-	-	-	170	87	145	72	42	25
Derris	131	340	231	817	105	399	252	958	24	912
Pyrethrum	214	366	656	1,889	2,400	6,600	2,100	5,775	640	1,613
Nicotine sulfate	88	571	112	1,059	80	665	37	307	10	24
Tobacco powder	726	79	1,990	197	2,000	220	2,131	234	1,000	110
Machine oil emulsion	1,405	84	2,070	805	-	-	-	-	-	-
Soda compound	-	-	-	-	1,170	269	637	147	50	12
Pine resin compound	415	48	-	184	-	-	-	-	-	-
Pine resin	303	74	40	18	-	-	-	-	-	-
Caustic soda	20	52	524	157	-	-	-	-	-	-
Chloropicrin	99	268	227	710	550	1,529	500	1,390	45	158
Formalin	233	169	1,400	910	1,200	804	1,130	757	500	335
Sodium cyanide	21	50	300	810	300	372	200	248	100	124
Copper sulfate	1,526	1,049	4,500	2,250	5,427	2,876	4,300	2,279	2,700	1,782
Quicklime	4,380	207	15,000	370	15,000	345	10,000	230	4,000	92
Mercury	-	-	20	250	18	162	51	459	35	415
Copper agents	58	29	-	-	-	-	-	-	750	960
Lime sulfur	9,367	774	22,500	3,000	9,000	810	8,500	765	6,000	540
Other (spreading agents, etc.)	819	963	11	1,834	2,977	3,871	3,100	3,416	970	1,367
Total	-	5,608	-	17,663	-	21,494	-	18,933	-	9,349

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3.4. Advancement of Modern Synthetic Pesticides since the War

3.4.1. Overview

This section discusses the dramatic development of synthetic pesticides from the turbulent times during and after the war to the present day, presenting this 70-year period in four stages.

To begin, Section 3.4.2 discusses the rebuilding period (1945-1960), in which integrated chemical manufacturers and other companies used overseas technology licensing to start full-scale manufacture of synthetic organic pesticides. Next, Section 3.4.3 outlines the emergence of new domestically-invented pesticides (1960-1970), when rising Japanese manufacturers started developing their own products. Section 3.4.4 discusses the tightening of regulations for problematic pesticides and the emergence of substitute products (1970-1990), as well as the problems occurring with toxicity and residues and how they were dealt with. Section 3.4.5 traces the time from when the industry reached its full growth to when it had to downsize (1990-present) and discusses how challenges were faced and the emergence of ultra-high-performance pesticides.

Compared with the crawling pace of technological developments during Japan's period of national seclusion and the slow progress that was made on inorganic compounds and natural pesticides in the late 19th and early 20th century, the 70-year period since the war has been a time of accelerated technological development. Agricultural productivity has increased and the food situation has improved significantly. While the rise in productivity can of course be partly attributed to selective breeding, better cultivation techniques and the widespread use of agricultural machinery, another major contributing factor is the development of new, highly effective pesticides. Let us consider rice cultivation, for example. Disease control over rice blast and other diseases, pest control over insects such as rice borers and leafhoppers and the herbicides that were developed after the war doubled the previously unstable crop yield to a steady 500kg/10a. The advent of mechanization and the on-going development of effective herbicides reduced the labor hours per unit area to almost one-sixth of what it was previously and made the back-breaking task of weeding under the blazing sun a thing of the past. Table 3.24 shows a time trend of rice yield and labor hours per 10a of paddy rice.

While the above is the "lighter" side of pesticides, there is also a "darker" side. This has been an age of problems: safety issues resulting from pesticides that are highly toxic to mammals, issues with residual pesticides in produce, soil and waterways, as well as the issue of environmental impact on beneficial organisms and fish. The post-war rebuild period saw the import of DDT, BHC and Drins, as well as mass industrial production of organophosphates and PCP. These were all released into crop fields. These early pesticides were ground-breaking inventions for the science and technology of the time and their superior pest control properties ensured their widespread popularity. However, the science and technology of the day was unable to keep track of the risks involved with these products. Many farmers suffered acute poisoning from failing to take appropriate care when handling these pesticides in the field.

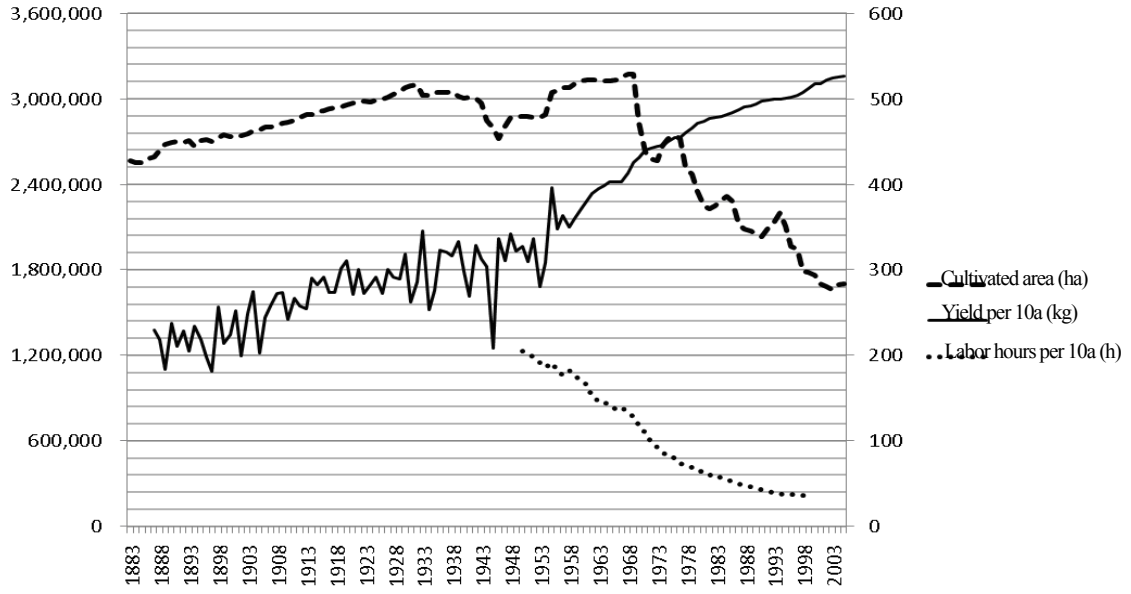

Fig. 3.24 Trends in Rice Yield and Labor Hours over Time [(1), (2)]

Table 3.25 compares the instances of pesticide poisoning between this period and the present day. The table shows that 40-45 deaths and 700 cases of non-fatal poisoning occurred due to the widespread use of highly acutely toxic pesticides such as parathion from the late 1950s to the early 1970s.

As mentioned in the notes, this table does not include applications other than the intended use (such as suicide/homicide). Although parathion was designated as a specific toxic substance in 1955 and major restrictions were put on its usage, it actually grew in usage because it was a wonder drug for rice and fruit trees and it was quite inexpensive. Eventually, a law change in 1971 banned its use for the sake of safety and it was replaced by less toxic pesticides. As a result, the number of accidents gradually decreased; from the 1990s, the number of deaths and poisonings from spraying pesticides dropped by more than 90%.

There were also problems of residual pesticides on crops and soils from using large amounts of pesticides with long-lasting effects, as well as issues with water pollution and negative impacts on fish and other beneficial organisms. We cannot deny that society at the time could not have expected these consequences and that the appropriate legislation came a little too late. The level of science and technology at the time was also unable to keep up with the widespread popularity of these new pesticides.

Successive steps were made to rectify these negative aspects: problematic pesticides were restricted and the regulations were tightened. Businesses shifted the aim of their research to developing pesticides that were safer and less environmentally impacting. This was achieved from the 1970s onwards with a succession of highly effective, less toxic, less residual pesticides to replace the existing products.

From the 1990s onwards, a number of new, highly effective pesticides were developed to fulfill these criteria. Many of these became world-famous Japanese products. Typical examples are the neonicotinoids, using nicotine as a lead compound, and new, effective miticides with novel modes of action.

This era has seen a shift towards developing safer, more environmentally-conscious agricultural technology based on the idea of "sustainable agriculture." Pesticides released into the environment must now have a lower environmental impact than ever before. While agriculture in itself is an act contrary to nature in that it involves cultivating a large amount of a single crop, this is an age in which sustainable agriculture must preserve the environment as much as possible. We need to increase our food production, but we can no longer expect an increase in arable land. The role of pesticides has now become all the more crucial. To a certain extent, there has to be a trade-off between this and the difficult task of environmental protection and harmony. In the future, we will need to integrate all areas of science and technology such as cultivation methods and breeding; we cannot rely on pesticides alone.

Table 3.25. Instances of Pesticide Poisoning [3]

(individual persons)

Year (average)	Deaths (no. while spraying)	Poisoning (no. while spraying)	Total (no. while spraying)
1957-1960	45	681	726
1961-1965	38(20)	322(296)	360(316)
1966-1970	39(15)	276(252)	315(267)
1971-1975	21(4)	233(216)	254(220)
1976-1980	17(6)	158(147)	175(153)
1981-1985	12(2)	68(59)	80(61)
1986-1990	6(2)	54(45)	60(47)
1991-1995	3(1)	20(13)	24(14)
1996-2000	2(0)	52(41)	54(41)
2001-2005	4(1)	64(54)	68(55)
2006-2010	3(0)	50(28)	53(28)

Cited References: Partially modified from *Nōyaku Gaisetsu [Pesticide Overview]*, Japan Plant Protection Association, 2011.
Notes:
Figures for 1957-1975 are taken from a survey by the Ministry of Health and Welfare Pharmaceutical Affairs Bureau
Figures for 1976-2000 are taken from a survey by the Ministry of Agriculture, Forestry and Fisheries Development and Promotion Bureau Plant Protection Division
Later figures are taken from a survey carried out on all the administrative divisions of Japan through collaboration between the Ministry of Agriculture, Forestry and Fisheries and the Ministry of Health, Labour and Welfare
http://www.maff.go.jp/j/nouyaku/n_topics/h20higai_zyokyo.html (accessed 29 July 2012)
These statistics do not include suicides/homicides
Accidents that do not occur while spraying are the result of misuse or accidental ingestion

Cited References

(1) Table created from the Ministry of Agriculture, Forestry and Fisheries crop statistics http://www.maff.go.jp/j/tokei/kouhyou/sakumotu/sakkyou_kome/index.html#r (accessed 5 November 2012).
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3.4.2. The Rebuilding Period (1945-1960): Technology Licensing

Rebuilding Japan after the war was a major challenge. The agricultural environment was a serious issue. Agricultural productivity had dropped significantly – 65% of that of the 1930s – due to a shortage of labor and fertilizer. Overseas food imports had been suspended and supply to the government by farmers had dropped off, while the consumer population had increased as five million overseas Japanese were repatriated. Japan entered an unprecedented food crisis. A rationing system was established and food assistance was provided by the United States. The land reform in 1946 set tenant farmers free. The government took measures such as enacting the *Agricultural Cooperatives Act* in 1947 [(1)]. The outbreak of the Korean War in 1950 brought about a special procurements boom which hastened the rebuilding of Japan. The rebuild was so quick that Japan was "no longer in the post-war period" by 1956.

The pesticide industry was also seriously damaged. Worth ¥21.5 million in 1941, this figure had dropped to ¥9.3 million by 1945. The revival of the pesticide industry started with the surviving pre-war pesticide companies and major chemical companies such as alkali industries beginning to manufacture pesticides using overseas technology licenses. The government was also active in passing legislation and taking other measures to prevent the mass production of inferior goods.

(1) Enacting of the *Agricultural Chemicals Control Act*

Although pesticide production bloomed from the late 1920s onwards, the government had no particular policies in place regarding production methods or product quality and offered only a moderate degree of guidance in this area. A rapid increase in pesticide imports at this time saw the government set up an Association for Regulating Pesticide Imports in 1938 and begin to regulate the import and distribution of four products: nicotine, derris, lead and pine resin. In 1940, the government started regulating the distribution of agricultural agents; this practice continued until 1950.

Turbulent times during and after the war saw a shortage of all goods, not least of all an extreme shortage of pesticides. This resulted in overproduction of inferior products and many ineffective pesticides appeared on the market. While there was a movement towards tighter control over pesticides from the late 1920s, the legislation was delayed because of the war. The government finally enacted the *Provisions of the Ministry of Agriculture and Forestry on the Inspection and Certification of Agricultural Agents* in 1947. Shipments of pesticides were inspected by the Pesticide Association, established the previous year, with the aim to facilitate the spread of high quality pesticides that had been granted certificates of inspection.

The following year, in August 1948, the more binding *Agricultural Chemicals Control Act* was enacted. This law made it mandatory to register and label pesticides. The government established the new Ministry of Agriculture and Forestry Pesticide Inspection Center (now the Food and Agricultural Materials Inspection Center (FAMIC)). Manufacturers could not sell any pesticides that had not been inspected here and registered by the Minister of Agriculture and Forestry. There were 449 pesticide registrations in 1948.

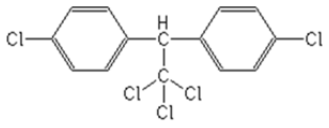
Thus, the focus of the *Agricultural Chemicals Control Act* was to ensure that the manufacture of high quality pesticides was stable and that they were provided to farmers in order to boost food production, the urgent issue of the day. From that time on, high-quality, synthetic organic pesticides began to appear at a rate that has not been replicated since. These products made a huge contribution to increasing agricultural productivity and saving labor.

The *Poisonous and Deleterious Substances Control Act* was enacted in 1950 to prevent injuries from highly toxic chemical substances such as pesticides (except for pharmaceutical products or quasi-pharmaceutical products). For more details on the classification of poisons and deleterious substances, see Section 2.3.4. This law stipulates matters relating to the manufacture, import, sale, labeling, storage and disposal of poisonous and deleterious substances. Any substance that is not categorized as a poisonous or deleterious substance is treated as an "ordinary substance" and this law does not apply. In 1955, a high proportion of pesticides produced were toxic, with 27.7% designated as specific toxic substances, 20.2% as poisons and 9.4% as deleterious substances. Given the state of society and the level of science and technology at the time, there was little choice but to use pesticides that were effective yet highly toxic.

(2) The Emergence of Organochlorine Pesticides (DDT, BHC, Drins, D-D)

The ground-breakingly effective organochlorine pesticide DDT (abbreviation of dichloro-diphenyl-trichloroethane) was introduced to

Japan during this period (Fig. 3.26). Austrian chemist Othmar Zeidler first synthesized DDT from chlorobenzene and chloral in 1874. DDT became the focus of much attention once Paul Müller (1899-1965) from Swiss company J.R. Geigy discovered its insecticidal properties in 1938 [3], [4], [5]. Müller was awarded a Nobel Prize in Physiology or Medicine in 1948 for his findings.

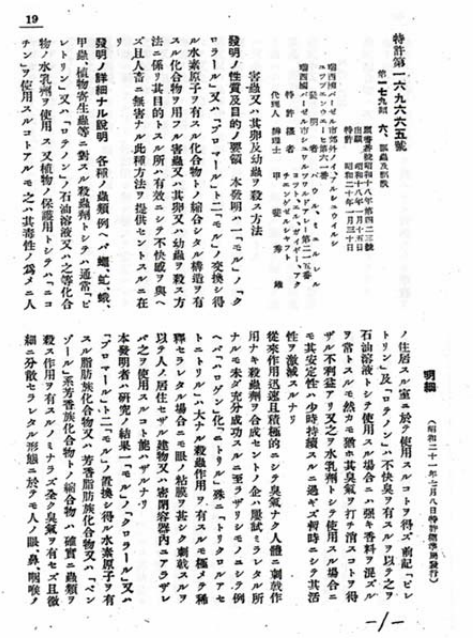


DDT

Fig. 3.26. DDT

DDT was introduced to Japan by the GHQ right after the war. It was put out in large quantities to control communicable diseases by eradicating fleas, lice and flies. Further investigations were carried out on its use as an agricultural pesticide and it was soon shown to be effective against rice borers and other vegetable pests, such as cutworms and caterpillars. Later studies showed the mode of action for DDT as affecting insect nerve axons, like pyrethrins, causing abnormal stimulation by preventing sodium ion channels from closing [6]. It has relatively low toxicity to mammals.

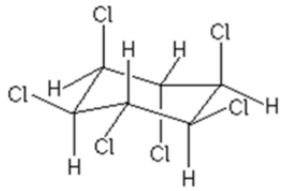
As Nichizui Trading had a patent license from J.R. Geigy, Nippon Soda and other alkali companies sublicensed the patent and started industrial production of DDT in 1947. In 1951, production reached 1,600 tons.



J. R. Geigy DDT Patent

Fig. 3.27. J. R. Geigy DDT Patent (Japan Patent No. 169665)

However, the use of large quantity of DDT brought the buildup of DDT resistance in insects, so its efficacy became less consistent. In agriculture, DDT was not adequate from the start against aphids, scale insects and leafhoppers and was gradually replaced by BHC (benzene hexachloride) (Fig. 3.28).



γ-BHC

Fig. 3.28. γ-BHC

BHC was first synthesized by English scientist Michael Faraday (1791-18967). Slade et al., of British company ICI, and Frenchman Dupire discovered in 1941-1942 that its gamma isomer (called Lindane) had highly insecticidal properties [7].

BHC was introduced to Japan a little later than DDT. It became widely used in agriculture as it was effective against a wide range of pest insects, especially leafhoppers, a major pest in rice cultivation. The existing pest control method of using whale oil or machine oil on rice fields fell out of use as BHC appeared on the scene.

As luck would have it, BHC had no patent restrictions. In 1947, Asahi Glass and Kanegafuchi Chemical started manufacturing the technical product, while Nippon Soda, Toyo Soda, Mitsubishi Kasei and other alkali companies also started manufacturing the chemical. By 1950, there were 15 companies producing it; by 1954, there were 17. By 1958, these companies were producing more than 2,000 tons a month [8]. Production of the gamma isomer Lindane started in 1952.

The effects of BHC differ from those of DDT. BHC suppresses the effects of gamma-aminobutyric acid (GABA), which controls the release of acetylcholine from the cholinergic presynaptic membrane in the central nervous system, thereby releasing acetylcholine and causing abnormal stimulation [9].

Drins are organic chlorine compounds with cyclic diene structures. Three of them, Aldrin, Endrin and Dieldrin, were introduced to Japan in 1955 by Shell USA. In 1957, Velsicol introduced Heptachlor, and they started growing in popularity across Japan. They received a lot of attention as they were generally more effective than DDT and BHC; in 1959, Japan had imported more than 1000 tons of active ingredients. However, usage of these products was later restricted as they were highly

acutely toxic and highly toxic to fish; this restriction dropped their usage dramatically.

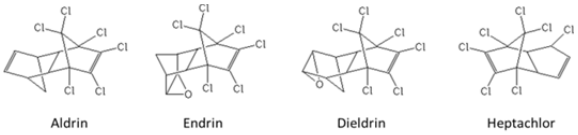


Fig. 3.29. Drins

Shell also developed soil fumigant D-D to eradicate root-knot nematodes, a soil pest harmful to fruit and vegetable plants. This product was used in Japan from 1950 onwards. The main ingredient in D-D is 1,3-dichloropropene. Its mode of action is achieved by reactive chlorine reacting to and inhibiting SH enzymes. This product is still in production, with about 9,000 tons being produced per year, worth around ¥5 billion.

(3) Introduction of Organophosphate insecticides (Parathion, Malathion, Diazinon, Dipterex, EPN, etc.): Ground-Breakingly Effective, yet Highly Toxic…

Gerhard Schrader (1903-1990), of Bayer under IG Farben, researched organophosphate compounds with the aim of developing new insecticides. In 1944, he discovered parathion [10], [11]. While Schrader was also famous for inventing Sarin and other nerve gases, the aim of most of his research was agricultural applications. There are two types of parathion: ethyl ester (parathion) and methyl ester (methyl parathion) (Fig. 3.30). With patent rights going to the Allies at the end of the war, American Cyanamid (ACC) obtained the patent in the United States and gained the Japanese patent as well [12].

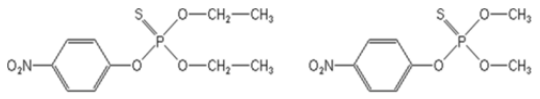


Fig. 3.30. Parathion and Methyl Parathion (Folidol)

Parathion was introduced to Japan in 1951 by Bayer under the name "Folidol E605." It became the immediate focus of attention, as it was more effective than BHC and DDT against the rice borers that would eat their way into the pith of the plant. Registered on the pesticide register in 1952 and subsidized by the Ministry of Agriculture and Forestry's Increased Food Production Plan, it became wildly popular. To meet the demand, Nihon Tokushu Noyaku started importing it from Bayer, while Sumitomo Chemical started importing it from ACC. The volume of imports skyrocketed from 8,200 tons in 1953 to 240,000 tons the following year [13].

Parathion works as an insecticide by blocking neurotransmission with an inhibitory effect on acetylcholinesterase (AChE), a catabolic enzyme for acetylcholine, which is responsible for neurotransmission. Since mammals also have this neurotransmission mechanism, it is highly acutely toxic to humans and animals to varying degrees. The acute toxicity of parathion and methyl parathion in rats is 10mg/kg and 30mg/kg respectively, equal to that of potassium cyanide. As parathion is also permeable through skin, care must be taken by those who spray it and anyone entering fields on which it has been sprayed. Consequently, it was designated as a "specific toxic substance" in 1953. People had been aware of this safety issue from the outset, but they knew it was a very effective pesticide, so it remained highly popular after 1953. Fig. 3.31 shows posters of products at the time [10].

Posters for Folidol from Germany

Fig. 3.31. Parathion Emulsion (Folidol) [10]

Domestic production of parathion was a natural consequence of the following circumstances. While Sumitomo Chemical, Nippon Soda, Ihara Agricultural Chemicals, Nissan Chemical, Mitsui Chemicals and other companies bid for the technology import license, it was Sumitomo Chemical that won sole manufacturing rights from ACC in October 1954. The following year, Sumitomo also gained a technology import license from Bayer for methyl parathion and started producing 100 tons per month.

Thus, parathion made a major contribution to boosting Japan's food production, hailed as a wonder chemical for its ground-breaking efficacy against the rice borer. Before then, farmers had no means of avoiding the rice borer other than delaying their planting and growing; however, this sometimes resulted in a lower yield due to typhoon damage. Parathion solved this problem, enabling earlier rice planting. A field trial at the agricultural experiment station in Shikoku showed 99% control of rice borers in the parathion test area compared to the control, with a 45-55% yield increase and a better quality product [14].

Given the popularity of parathion, Sumitomo Chemical

promptly set about researching and developing new organophosphate compounds and had soon successfully developed MEP (Fenitrothion, Sumithion), a less toxic substitute for parathion. This is discussed in Section 4.3.

A number of other organophosphate insecticides besides parathion have been developed in the West and introduced to Japan (Fig. 3.32). The relatively low-toxic ones are still used today. The numbers in parentheses indicate the year registered (or when the registration lapsed).

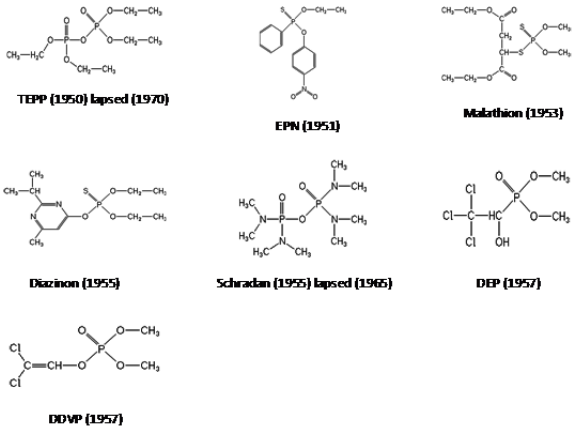


Fig. 3.32. Organophosphate Insecticides

(4) The Emergence of Rice Blast Mercury Dust (Ceresan Lime)

As discussed in Section 3.3.3, organomercury formulations such as Uspulun and Ceresan were introduced to Japan in the late 1930s and were mainly used for seed treatment. They became widely popular for controlling various diseases such as rice blast and wheat smut. Until then, the only available treatments were Bordeaux mixture and lime sulfur, so the appearance of mercurial seed disinfectants was ground-breaking in terms of side effects and ease of use.

There was a major outbreak of rice blast in Kochi and Hiroshima in 1949. While applying Ceresan directly to fields did have some side effects on crops, researchers discovered a method of mixing it with five parts quicklime and dispensing it on fields in powder form, thus producing the uniquely-Japanese Ceresan lime [(15)]. The results were outstanding and the formulation was registered on the pesticide register in 1952. It was the main fungicide product used in Japan until 1965. Given the success of Ceresan lime, developers worked on a number of other organomercury formulations. In 1965, 130 dusts, 31 wettable powders and 29 emulsifiable concentrates from 17 active ingredients were registered. By 1966, usage had increased to 11.6 tons of dusts, 2,600 tons of wettable powder and 779 kl of emulsifiable concentrates [(16)]. While rice blast was known to be often caused by heavy manuring culture, it was eradicated with this formulation, meaning that heavy fertilizing now resulted in higher crop yields. Although Ceresan was a Bayer product, Ceresan lime was a Japanese invention and thus worthy of special mention here.

Organomercury pollution became a social and political issue with the outbreak of Minamata disease in the late 1950s caused by wastewater containing methylmercury and Niigata Minamata disease in the Agano River region in the late 1960s. It was then discovered that using mercuric pesticides containing phenylmercuric acetate, such as Ceresan (although it had a different chemical structure from the problematic methylmercury), resulted in microscopic mercury residues on rice and that Japanese people's hair contained three times more mercury than non-Japanese. In light of these findings, the Ministry of Agriculture and Forestry finally issued a notice "on the promotion of non-mercuric pesticides" in 1966. In 1968, organomercury compounds stopped being used on rice blast; in 1970, registration was cancelled for all mercurial pesticides used on fruit and vegetable plants; in 1973, registration was finally cancelled for seed disinfecting as well, and organomercury pesticides disappeared off the market.

Organomercury formulations played a major part in eradicating rice blast and other diseases and, although they were highly residual, it took a long time for people to finally stop using them, as there were very few alternative pesticides. It is fortunate that no specific harm was caused as a result of this residual mercury.

(5) The Popularity of Herbicides such as 2,4-PA(2,4-D), 2,4,5-T, MCPA and PCP

2,4-PA(2,4-D), 2,4,5-T and MCPA are herbicides with plant-hormone-like auxin activity. They were introduced to Japan soon after the war (Fig. 3.33).

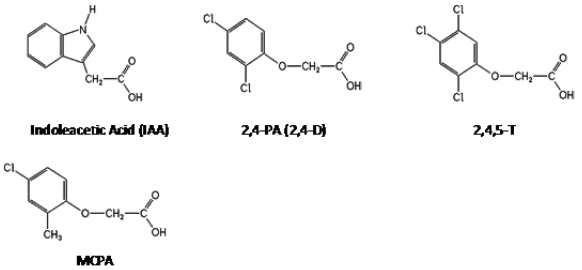


Fig. 3.33. Indoleacetic Acid and Phenoxyacetic Acid Herbicides

The history of indoleacetic acid can be traced back to the 19th century, when Charles Darwin (1809-1882) discovered phototropism in gramineous coleoptiles [(17)]. Later, Kögl et al. showed that phototropism is the result of a growth promotion activated by plant hormones. In 1934, they discovered that this growth promotion is activated by indoleacetic acid (IAA) [(18),(19)]. Kögl et al.

also discovered that using high concentrations of IAA acts as a growth suppressant [20]. This group of plant hormones later came to be called auxins.

A number of researchers discovered substituted phenoxyacetic acids with auxin activity in the early 1940s. For details on these discoveries, see J. Troyer [18] and Orvin C. Burnside [21]. We shall provide a simple history of this invention here.

William Templeman of ICI in the United Kingdom discovered that substituted phenoxyacetic acid derivatives were effective against weeds among grain crops and applied for a patent in 1941 [22]. Separately, FD Jones of ACP in the United States discovered the pesticidal properties of 2,4-PA and applied for a US patent [23].

Another group from Rothamsted Experimental Station in the United Kingdom and a group at Chicago University in the United States also confirmed the same herbicidal properties around the same time. Due to wartime restrictions on the disclosure of patents and literature, nobody knew until after the war that four completely independent research institutions had made almost identical inventions at almost the same time.

These chemicals were introduced to Japan right after the war. The Japanese confirmed their effectiveness, with 2,4-PA (2,4-D, sodium salt) being registered in Japan in 1950. In 1951, Nissan Chemical and Ishihara Sangyo obtained a patent license for 2,4-PA from ACP (later Amchem), followed by Mitsui Chemicals in 1955 with a patent license from ICI for 2,4-D, 2,4,5-T and MCP. Companies started manufacturing their own sodium salts, amine salts and esters. During this time, there were disputes between ICI and ACP over the scope of the patents, but they eventually reached a settlement and each company started manufacturing their own product.

The various salts and esters in 2,4-PA and MCPA quickly became popular for their effectiveness on broad-leaf weeds in rice and other crops. They played a major role in economizing labor. While they initially could not be used without draining the rice fields, it was soon discovered that 2,4-D and MCPA ethyl ester granules could work directly on submerged fields. These products became widely popular from around 1954.

PCP (Pentachlorophenol) (Fig. 3.34) was originally used as a preservative for timber. PCP sodium salt was first developed for agricultural use as a fungicide for fruit trees and registered as such in 1955.

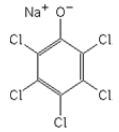


Fig. 3.34. PCP

PCP is very effective against echinochloa species of weeds that are not easily controlled with 2,4-PA and MCPA. It quickly became popular after it was registered as a herbicide in 1956. It was later developed into a granule formulation and was widely used against barnyard grass, a major rice weed. By late 1955, it was being used on around one third of Japan's rice cultivation areas.

PCP's mode of action works by inhibiting ATP production through the uncoupling of oxidative phosphorylation in the energy metabolism system [24]. PCP barium salt has received much attention as a substitute for mercurials, as it is also effective against rice blast. It was registered as a fungicide in 1963.

However, it was always known that PCP is highly toxic to fish. The Ministry of Agriculture and Forestry issued some administrative guidance at the end of 1960 as a counter-measure to prevent any harm, but fish were affected nonetheless. Major social and political issues arose in the Ariake Sea and Lake Biwa regions in 1962 when the fishing industry was badly affected by PCP effluence from a severe rainfall after PCP had been used. The damage to the fishing industry caused by PCP that year was as high as ¥2.6 billion in the currency of the day [25]. The *Agricultural Chemicals Control Act* was amended the following year as a result, to legally regulate the use of pesticides harmful to aquatic plants and animals. In 1971, PCP was designated as a water polluting pesticide, with major restrictions placed on its use. Other herbicides emerged and its registration was finally revoked in 1990.

(6) Summary and Introduction to Other Pesticides

As mentioned above, the fifteen-year period after the war was a time of rebuilding. It was a time in which a number of highly effective, synthetic organic pesticides were introduced to Japan from the West. It was a time in which Japanese pesticide companies used technology licensing to build up their own development capabilities and lay a foundation for later pesticide development. Pesticide shipments were worth a mere ¥15 million in 1946, just after the war (or ¥21.5 million in terms of the value of the yen in 1958); by 1959, this figure had grown to over ¥90 billion. Licensed technology and imported goods accounted for around 50% of this market [26]. This truly shows how dependent Japan was on other countries during this time.

However, this was also a time of magnified issues

stemming from the overuse of pesticides such as parathion that were highly toxic to mammals and highly residual pesticides such as DDT, BHC and mercurials. A fixed negative image of pesticides as being poisonous took hold among ordinary consumers. It took a lot of time and the successive appearance of improved pesticides to rectify this.

The other pesticides introduced to Japan during this time are given below (Fig. 3.35) without any additional details.

Tokyo Organic Chemical brought in dithiocarbamate fungicides Zineb (Dithane) and Ambam (Dithane Stainless) from Rohm and Haas. Nippon Soda introduced miticide CPCBS (Sappiran) from Dow, while Nippon Kayaku brought in Chlorobenzilate (Akar) from J.R. Geigy. Nippon Soda also brought in fungicide Triazine from Pittsburgh Coke & Chemical.

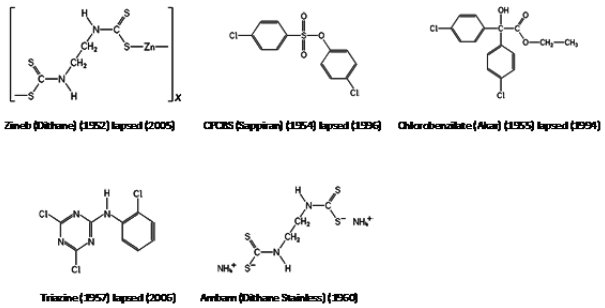


Fig. 3.35. Pesticides Introduced in the Post-War Period

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3.4.3. The Emergence of New, Domestically-Invented Pesticides (1960-1970)

Following the special procurements boom for the Korean War in 1950, Japan experienced an economic boom from 1954, followed in turn by another boom in 1958 and the Izanagi boom of 1965-1970. Dramatic changes in the agricultural environment went hand in hand with this period of rapid economic growth. The farming population dropped significantly in the 1960s as people transitioned into non-agricultural occupations. This move was undergirded by the mechanization of agriculture and an economizing of labor due to

pesticides. Agricultural productivity also improved; it was an age of excess rice, with the total area of paddy rice fields reaching a peak of 3.17 million hectares in 1969. This later decreased as consumers shifted away from rice consumption, dropping to just over 1.5 million hectares by 2011.

The economic recovery was also linked to the pesticide industry, with synthetic organic pesticides introduced after the war playing a huge part in the rapid growth. Pesticide shipments were worth ¥28 billion in 1960; ten years later, they had almost tripled to ¥83 billion. Ninety per cent of the pesticides during this period were synthetic, while the remaining 10% were natural and inorganic products. From 1955 onwards, mass synthetic pesticide manufacturers were divided into two categories: active ingredient manufacturers (the so-called integrated manufacturers) and formulation manufacturers (the traditional type of specialized pesticide manufacturers).

Japanese companies built up some expertise during this time. Proficient at synthesis technology thanks to their experience with licensing, they embarked on their own research and development with the aim of producing new pesticides for themselves. This was a period of time fraught with problems: mammalian toxicity problems, such as with parathion; fish toxicity problems, such as with PCP; residue problems, such as with DDT, BHC and mercurials. There were high hopes for a safer substitute to be developed.

(1) Publication of *Silent Spring*

American scientist Rachel Carson (1907-1964) published *Silent Spring* in 1962. It was translated into Japanese and released by Shinchosha as *Sei to Shi no Myōyaku [Elixir of Life and Death]* in 1964. This book had a major impact on society, sounding the alarm against DDT, BHC and organochlorine pesticides such as the drins as causing environmental pollution and the destruction of ecosystems. This book made people aware of the seriousness of the impact of pesticides on the environment. Pesticide manufacturers were required to perform environment and ecosystem impact assessments when developing pesticides. In this regard, this book was hugely significant. However, the book draws attention to the proper use of pesticides and does not say that pesticide use should be abolished altogether. It was later pointed out that many human lives were lost because of a ban on DDT, which was used to control malaria-carrying mosquitoes. For instance, the number of malaria cases in Sri Lanka in the 1960s dropped from 2.5 million per year to almost zero due to the use of DDT; when DDT was later banned, this figure reverted to what it had been before. According to the World Health Organization (WHO), DDT has saved 5 million lives and prevented 100 million cases of disease [(1)]. This raises the difficult question of whether environmental destruction takes precedence over human lives. We must also give level-headed consideration to the good that has been achieved by DDT.

(2) Insecticides

Low-toxic organophosphate MEP (Sumithion) was developed and registered on the Japanese pesticide register in 1961. It was a radical improvement on parathion and other highly acutely mammalian toxic pesticides and became a world-renowned product. This is discussed in more detail in Section 4.3. Many other highly safe organophosphates were developed. Typical compounds still used today include PAP (Elsan, registered in 1963), developed by Bayer, and CYAP (Cyanox, registered in 1966), developed by Sumitomo.

Many carbamate insecticides that appeared during this period were a new chemical structure. These originated from physostigmine (eserine), a toxic alkaloid found in calabar seeds (*Physostigma venenosum*) from West Africa (Fig. 3.36). It has a strong cholinesterase inhibiting effect and is used in medicine as a pupil contractant, but has no insecticidal effects. Metcalf et al. from the University of California carried out research modeled on this compound and later discovered insecticides with carbamate groups [(2),(3),(4),(5)]. Fig. 3.37 shows some typical carbamate insecticides and their year of registration/cancellation on the Japanese pesticide register.

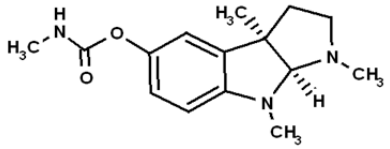


Fig. 3.36. Physostigmine

NAC (Denapon) was discovered by Union Carbide Corporation (UCC) in the United States. It was first registered in Japan in 1959, followed by a number of other carbamates. Each of these was very effective against leafhoppers on rice plants. While the organophosphate Malathion was often used at the time, a problem arose around 1962, when green rice leafhoppers started becoming resistant to Malathion. Since carbamates were also effective against these Malathion-resistant green rice leafhoppers, they became widely popular and are now viewed as one of the representative rice insecticides of that time. However, they were not so effective against the rice borer.

During this time, Japanese companies had been working on pesticides to rival NAC, PHC and APC. Many products that had dropped due to resistance problems had their registration lapse when these competing products appeared, but NAC, MIPC and BPMC are still worth several hundred million yen in

sales.

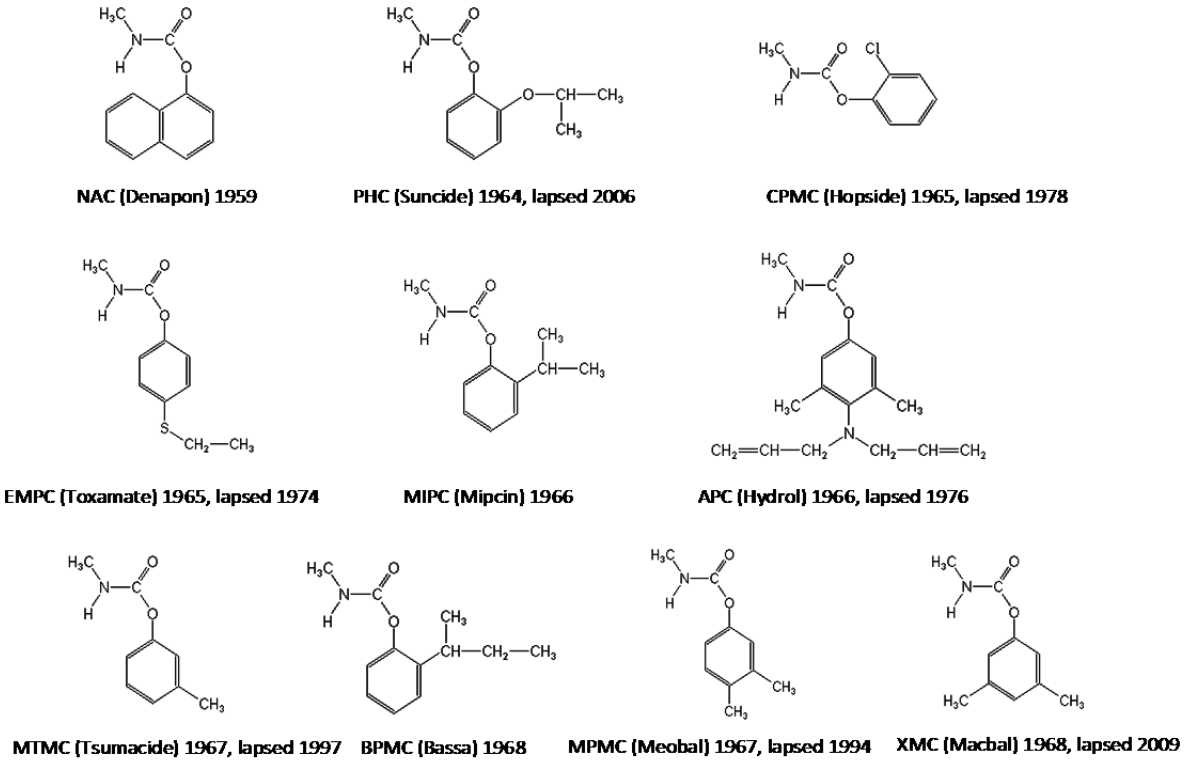


Fig. 3.37. Carbamate Insecticides

Like organophosphates, the mode of action for carbamates works by inhibiting acetylcholinestrase (AChE) in the neurotransmission system. They block neurotransmission by the carbamoylation of the AChE hydroxyl group. While some carbamate compounds are highly toxic to mammals, the ones registered in Japan are relatively safe (deleterious substances).

Some time later, DuPont discovered oxime carbamates, which have no benzene ring in their chemical structure. Methomyl (Lannate) was registered in Japan in 1970; a little later, Oxamyl (Vydate) was registered in 1981 (Fig. 3.38). While these work as AChE inhibitors as with the compounds above, they have the drawback of being quite highly toxic to mammals. However, they have the advantage of being very effective against chewing insects on fruit and vegetable plants and are still used today.

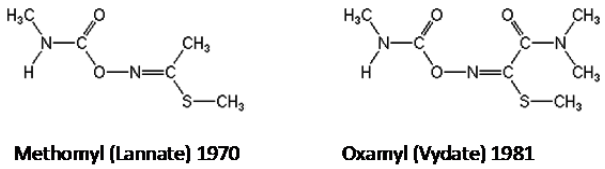


Fig. 3.38. Oxime Carbamate Insecticides

Carbamate insecticides appeared in the middle of this period and became so popular they were second only to organophosphates as the main insecticides for rice cultivation. Later, further research was devoted to making them less toxic to mammals, which was their main drawback. This research resulted in the so-called second generation carbamates that appeared from the late 1980s to the early 1990s. These results are discussed in Section 4.16.

In 1967, Takeda Pharmaceutical invented and marketed Cartap (Padan), an insecticide with a unique chemical structure. Modeled on nereistoxin found in marine animals, this compound became widely popular as it was effective against a wide variety of pest insects. The outstanding academic research was also a good achievement for Japan. This is outlined in Section 4.6.

(3) Fungicides

A succession of long-awaited domestically invented fungicides began to appear during this time. Ihara Agrochemical developed and marketed MAS (Asozin), a fungicide for rice sheath blight and Japan's first domestically-produced pesticide, in 1959, followed by MAF (Neoasozin). Post-war Japan had depended on licensed technology imports for its synthetic pesticides, but now production of its own pesticides had begun. This is discussed in detail in Section 4.1.

Blasticidin S is the world's first agricultural antibiotic, discovered by the University of Tokyo in 1961 and jointly developed by Kaken Chemical, Toa Agricultural

Chemical and Nihon Nohyaku. It became widely used, having come at a time when there was a demand for non-mercurial fungicides, as problems had developed with the organomercury fungicides that were used in large quantities after the war. In 1965, Hokko Chemical developed Kasugamycin, an antibiotic for rice blast. These two products held much academic value. This is explained in further detail in Section 4.2.

In 1965, Ihara Agrochemical (now Kumiai Chemical) brought out EBP (Kitazin), followed by IBP (Kitazin P). Together with Blasticidin, these organophosphate rice blast treatments became wildly popular as a non-mercurial secret weapon in the war against crop diseases. They could penetrate into the plant, which meant they could be of practical use in the rice field. Section 4.7 discusses these products in more detail.

Polyoxin is an agricultural antibiotic that is very effective against diseases such as rice sheath blight, powdery mildew on fruit and vegetable plants, *Alternaria alternata* in pears and *Alternaria mali* in apples. It was discovered in 1967 by RIKEN researchers and developed by Kaken Chemical [6], [7]. Other agricultural antibiotics include Validamycin (Validacin), effective against rice sheath blight, developed by Takeda Pharmaceutical registered as a pesticide in 1972 [8], [9]. Takeda Pharmaceutical also marketed Mildiomycin (Milanecin), very effective against powdery mildew, in 1983 [10]. Thus, this period saw a succession of agricultural antibiotic fungicides developed by Japanese companies. A major advantage of antibiotic fungicides is that they are effective at low concentrations and therefore safe to mammals and non-residual on crops. Japan leads the world in technology development in this field. Fig. 3.39 shows the structures of Polyoxin, Validamycin and Mildiomycin.

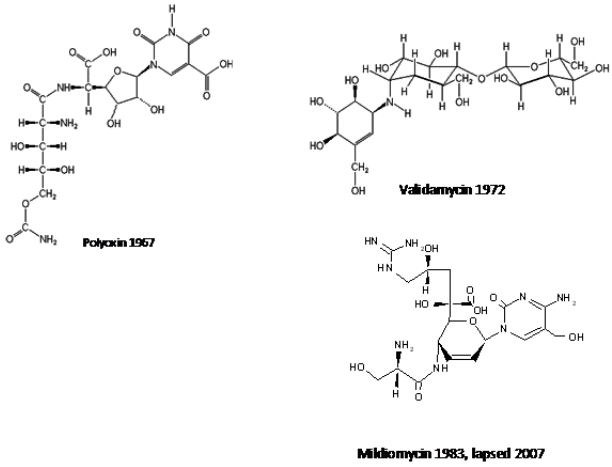
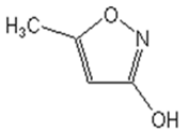


Fig. 3.39. Agricultural Antibiotic Fungicides

In 1969, Sankyo developed and marketed Hydoroxyisoxazole (Tachigaren), shown to be effective against soilborne diseases such as seedling wilt, brown spot disease and sheath blight (Fig. 3.40). With a chemical structure similar to isoxazole, this fungicide is made up only of carbon, oxygen and hydrogen. It has also become widely used in seed raising, as it is effective for promoting rooting and growth as well as growing healthy seedlings. It is also used as a fungicide on rice, vegetables, sugar beets and other produce in Japan and at least another 30 countries around the world [11], [12], [13].



Hydroxy isoxazole (Tachigaren)

Fig. 3.40. Hydroxy isoxazole (Tachigaren)

(4) Herbicides and Plant Growth Regulators

While the herbicide PCP mentioned above was registered in 1956, it rapidly grew in popularity for rice cultivation after it was developed into granules in 1960. However, the early conception that it was toxic to fish proved to be true. When the *Agricultural Chemicals Control Act* was amended in 1963, PCP usage was regulated and the use of substitute formulations was encouraged.

Two major Japanese herbicides appeared during this time. One was CNP (MO), developed by Mitsui Chemicals and registered in 1965 (See Section 5.5 for details); the other was Benthiocarb (Saturn), developed by Kumiai Chemical and registered in 1969. Benthiocarb is effective on perennial weeds and has become one of the top herbicide products for rice cultivation, recognized as a superior herbicide formulation.

A number of other herbicides were registered during this time as well. Photosynthesis-inhibiting traizine herbicides on the market included CAT (Simazine), Prometryn (Gesagard), Atrazine (Gesaprim) and Simetryn (Gibon). Urea pesticides included DCMU (Carmex), Linuron (Lorox) and Siduron (Tupersan), while DCPA (Stam) was a typical amide pesticide. Dinitroaniline herbicide Trifluralin (Trefanocide) was used on a variety of crops including rice, wheat and vegetables and was particularly effective against rice weeds. Trifluralin is still widely used today and has a market worth ¥2 billion.

Let us now mention plant growth regulators. Giberellin, developed by Kyowa Hakko, was officially registered on the pesticide register as a plant growth regulator in 1964. While it is mainly used on seedless grapes, it has a number of other applications as well. Giberellin is definitely worth a special mention, as the entire process from its discovery in the early 20th century to the determination of its structure and its development as a

pesticide has been spearheaded by Japanese technology. This is discussed in Section 4.4. Other products were developed and marketed during this time, including rooting promoter 1-Naphthyl-acetamide (Rootone), fruit accelerator 4-CPA (Tomato-tone) and growth retardant Daminozide (B-nine). These are still in use today.

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3.4.4. Tighter Regulation of Problematic Pesticides and the Emergence of Substitute Pesticides (1970-1990)

(1) Overview

The 1970s saw the end of Japan's period of rapid economic growth and a transition to a period of slow growth. Although Japan had already become the world's second largest economic superpower in the late 1960s, the dollar shock took place in 1971 and a Japanese archipelago remodeling plan was issued the following year. This was followed by the oil shock in 1973 as well as rampant inflation, known to the Japanese as *kyōran bukka*, or price frenzy.

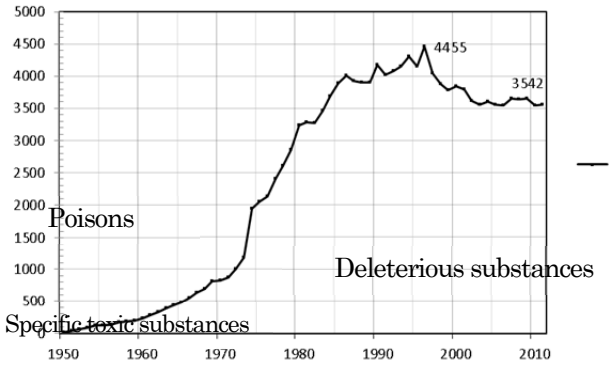
Japan's Four Big Pollution Diseases (Minamata Disease, Niigata Minamata Disease, Yokkaichi Asthma, Itai-itai Disease) occurred as side effects of the rapid economic growth. This became a social issue during this period, with the Environment Agency (later the Ministry of the Environment) created in 1971 and a flurry of activity in the area of environmental improvement during this time as well.

Manufacturing and shipping in the pesticide industry continued as it had during the rapid economic growth period, despite reductions in rice field land due to a set-aside policy enacted in 1971. Pesticide shipments multiplied 3.7 times in ten years, from ¥83 billion in 1970 to ¥320 billion in 1980. A number of highly effective new pesticides appeared during this time, meaning a stable, high yield of good quality produce, despite a drop in the working population engaged in agriculture. Once the increase in food production had been achieved, views changed about pesticides. This change in viewpoint started being reflected in the government during this time. The "negative aspects" of pesticides came to be viewed as problematic – namely, toxicity to mammals and marine life, lasting residues on crops and soil and the risk of long-term toxicity from exposure to or ingestion of these residues, as well as the impact on the environment and on beneficial organisms such as natural enemies. In other words, the existing regulations to ensure "user safety" and protect against acute toxicity were tightened to ensure "end consumer safety" as well as to minimize the impact of pesticides on the environment, such as water and soil. During this period, stricter pesticide regulations were placed on new and existing products alike.

Let us now move forward to the 1980s. The economy continued to slump due to the second oil shock in 1979, while a high-yen recession followed the Plaza Accord in 1985. While later ultra-low interest policies sparked the bubble economy boom, this did not last long and the economy dropped once more when the bubble burst in 1991.

Agricultural mechanization, such as the introduction of rice planters and combine harvesters, compensated for the decline in the agricultural work force; combined with the growing use of pesticides, this made for a favorable agricultural environment with increased productivity. Most of the government's agricultural measures were to do with rice prices, and most farming continued as side-line businesses with no major changes such as large-scale restructuring.

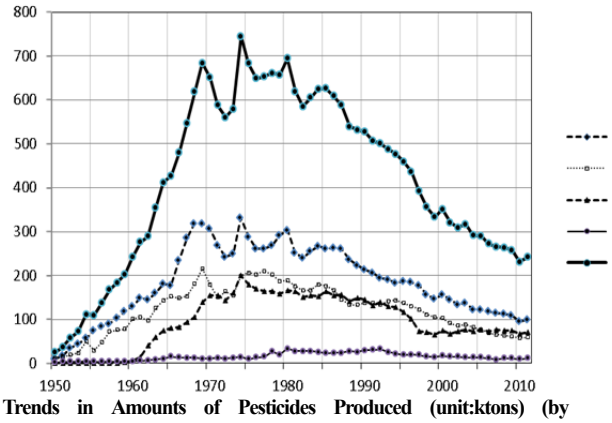
The pesticide industry transitioned from a period of rapid growth to a period of moderate growth due to the recession and the reduction in acreage; this was also a time of excessive competition in the industry. The growth in shipments of the past decade peaked at ¥400 billion, 1.3 times what it had reached in the 1970s. After peaking in 1986, shipments have continued to gradually decline to the present day. Fig. 3.41(a) shows the trends in pesticide shipments.



Annual Trends in Pesticide Shipments (units: ¥10^7) tabulated from *Pesticide Manual*

Fig. 3.41(a) Annual Trends in Pesticide Shipments (tabulated from *Pesticide Manual*)

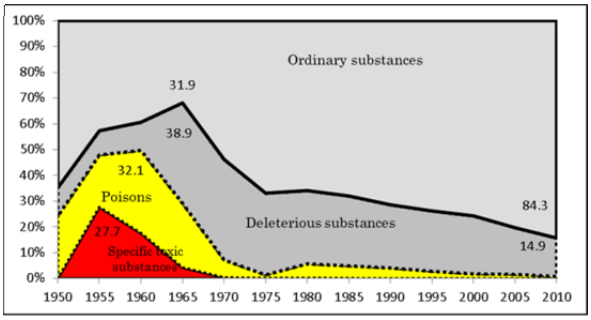
Fig. 3.41(b) shows the amount of pesticides produced (t, kl) per application. While the trends shown do not differ from those shown in Fig. 3.41(a), based on the value of shipments, we see that pesticide usage peaked in the 1970s and then dropped significantly. This is because there was less demand for pesticides due to reductions in planted areas, as well as a reduction in the amount needed per unit area. This was made possible by the development of improved pesticide formulations with highly effective active ingredients. To use an analogy, it was like being able to achieve with a spoonful of household detergent what used to require a cupful.



Trends in Amounts of Pesticides Produced (unit:ktons) (by Application) tabulated from *Pesticide Manual*

Fig. 3.41(b) Trends in Amounts of Pesticides Produced (by Application) (tabulated from *Pesticide Manual*)

Fig. 3.42 shows how pesticide safety improved after the war. The initial post-war period, when synthetic organic pesticides came to the fore, has the highest proportion of highly toxic chemicals such as parathion. More than 50% of all pesticides were designated as poisons or specific toxic substances during this period. While there were a number of social problems during this time, such as a rising number of accidents among farmers, the conditions significantly improved with tighter regulations and the appearance of new, safer pesticides. By 1970s, the proportion of specific toxic substances had dropped to 0.4% and poisons to 0.8%. These figures have continued to drop; by 2010, specific toxic substances accounted for 0.0%, poisons 0.8% and deleterious substances 14.9%. The remaining 84.3% are classed as ordinary substances, indicating a significant increase in pesticide safety.



Trends in Pesticide Production by Toxicity (value ratio) tabulated from *Pesticide Manual*

Fig. 3.42 Trends in Pesticide Production by Toxicity (value ratio) tabulated from *Pesticide Manual*

As mentioned above, pesticide regulations tightened during this period. All pesticides, whether new or existing, had to undergo various tests, especially safety tests, based on the new standards and a number of existing pesticides were weeded out. The increased number of test criteria and the increased cost of development presented a high hurdle for new pesticides. As a result, the success rate for new inventions dropped. However, despite this, Japanese companies continued to place huge amounts of effort and investment into developing their own pesticides and came up with a number of world-renowned products.

(2) Stricter Regulations and Amendments to the *Agricultural Chemicals Control Act*

The sale of organomercury compounds (sprays) was banned in 1970 [(1)]. The following year, the sale of DDT, BHC, Aldrin and Dieldrin was banned and the *Agricultural Chemicals Control Act* was amended significantly [(2)]. As discussed in Section 3.4.2 (1), the *Agricultural Chemicals Control Act* enacted in 1948 focused on ensuring that high quality pesticides were manufactured safely and provided to farmers in order to boost food production, the urgent issue of the day. The aim was to ensure the safety of farmers, the users of pesticides. The amendment incorporated a strong focus on making farmers safer through appropriate use of pesticides, ensuring public health and protecting living environments.

The directive [(3)] from the Ministry in light of this amendment specifically stipulated that: (1) acute toxicity tests, chronic toxicity tests and residue tests on crops and soil had to be carried out; (2) the criteria for

suspending registration included crop-residual pesticides (lead arsenate, Endrin), soil-residual pesticides (Dieldrin, Aldrin) and water-polluting pesticides (Telodrin, Endrin, Benzoepin and PCP); (3) even registered pesticides could have their registration suspended (or revoked) if they were considered to be seriously hazardous.

The *Good Laboratory Practice Standards for Pesticide Toxicity Tests (METI GLP)* were enacted in 1984. GLP is a system originally used in the field of medicine. GLP for medicine was put in place in the United States in the 1970s after it was found that fraudulent data was being used in drug applications. The requirements for pesticide registration include 32 toxicity tests, 4 metabolism tests, 15 physiochemical properties tests, 10 environmental impact on aquatic animals tests and a crop residue test. Each of these tests has strictly regulated GLP compliance criteria for the testing institution, including its organizational structure, a clear indication of its responsibility system, its adherence to uniform Standard Operation Procedure (SOP), its testing carried out in accordance with protocol and operating procedures, its recording of experiments, its storing of related materials and independent quality assurance system. All new pesticides must meet these criteria, as does all toxicity data required for re-registering existing pesticides every three years.

(3) Insecticides

While the main insecticides during this period were organophosphates, a number of new ones appeared that were comparatively low-toxic. However, many of these disappeared off the market with the appearance of high-performance pesticides. The following are typical examples of these pesticides still in use today. Dow registered Chlorpyrifos (Dursban) in 1971. Sankyo developed and registered Isoxathion (Karphos) in 1972. Even today, this product is widely used because of its effectiveness against a wide range of pest insects on fruit and vegetable plants. Chevron developed Acephate (Orthene) and put it on the market in 1973. This product is highly systemic and can be used in the planting hole as well as sprayed; it still has a ¥7 billion market. Bayer Japan developed Prothiofos (Tokuthion) in 1975. This pesticide is still widely used on fruit and vegetable plants because of its delayed but durable effects and its effectiveness against a wide range of insect pests, including soil pests. ICI marketed Pirimiphos-methyl (Actellic) in 1976. Thus, a number of organophosphate insecticides were developed and although they are still used today, the competition to develop new ones all but came to an end during this period. Fig. 3.43 shows the structures of these chemicals.

The next insecticides to appear on the scene were the second generation carbamates in the 1980s; these were far less toxic to mammals. The first on the market was Carbosulfan (Advantage) in 1983. This was followed by Benfuracarb, registered by Otsuka Chemical in 1986. The next to appear was Alanycarb (Orion), developed by Otsuka Chemical in 1991. For details on these, refer to Section 4.16.

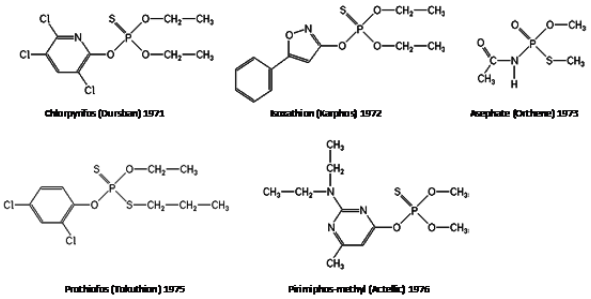


Fig. 3. 43. Organophosphate Insecticides Developed in the 1970s

With the advent of the 1980s, a number of new major insecticides appeared with completely different chemical structures from the existing products. In 1983, Sumitomo Chemical put Fenvalerate (Sumicidin) on the market – the world's first pyrethroid for agricultural use. With this, a number of other synthetic pyrethroids were developed for agriculture. For details on this product, refer to Sections 4.14 and 4.18. Fierce competition ensued with each company furiously developing their own version of these new-generation synthetic pyrethroids; by 1995, a great number of new pesticides had emerged. However, it is very interesting to note that no more of these have been produced since then.

In 1983, Nihon Nohyaku put out Buprofezin (Applaud). This was the first insect growth regulator (IGR) produced in Japan. For details, refer to Section 4.13.

Nippon Soda registered Hexythiazox (Nissorun) in 1985, the forerunner of the high-performance miticides. Between 7 and 80 times more active than existing miticides, it was wildly popular and was also used overseas. For details, refer to Section 4.15.

As mentioned above, these two decades were a time of weeding out the old pesticides with safety issues and other problems and replacing them with a number of products that were far safer to mammals. Many of these new products were from Japan: Japanese companies were starting to see the fruits of their concentrated research and development efforts during the post-war rebuilding period.

(4) Fungicides

Several world-renowned Japanese fungicides were developed in the 1960s. Nippon Soda first brought out Thiophanate (Topsin) in 1969, followed by the more effective Thiophanate-methyl (Topsin M) in 1971.

These new fungicides had unprecedented chemical structures; they had systemic activity and were highly effective against a number of diseases in fruit and vegetable plants and other crops. This pesticide became popular in Japan and a renowned product throughout the world. Refer to Section 4.9 for details.

Fthalide (Rabcide) was invented by Kureha and registered in 1970 as a fungicide for rice blast (Fig. 3.44) [4]. Fthalide strongly inhibits hyphal penetration after appressorium formation in Pyricularia oryzae. Its mode of action is known to work by inhibiting Melanin Biosynthesis Inhibitors Reductase (MBI-R) in Pyricularia oryzae [5]. Soon after Fthalide appeared, overseas manufacturers developed two rice blast fungicides with the same effect. One was Tricyclazole (Beam), marketed by Dow in 1981; the other was Pyroquilone (Coratop), marketed by Ciba-Geigy in 1985. Fig. 3.44 shows their chemical structure .

Fig. 3.44. Rice Blast Fungicides (MBI-R Inhibitors)

Two more major rice blast fungicides appeared during this period, both invented by Japanese manufacturers. One is Isoprothiolane (Fuji-one), invented by Nihon Noyaku and registered in 1974; the other is Probenazole (Oryzemate), invented by Meiji Seika and also registered in 1974. These became major pesticides and very popular due to the fact that rice blast was of frequent occurrence, the fact that both products had systemic activity and the fact that they were highly effective both for submerged applications and seedling box treatment. For details, refer to Sections 4.10 and 4.11.

As discussed above, in the fifty years following the war, fungicides transitioned from being mainly inorganic compounds such as copper, mercury and arsenic to synthetic organic compounds. Remarkable improvements were also made in terms of their performance. Competition to develop new products continued and a succession of new pesticides are being developed with new modes of action. Many of the new fungicides work by inhibiting particular enzymes pinpointed in the metabolic pathway. However, continued use of such fungicides will result in a mutation in the part that is being inhibited, meaning that the fungicidal effect can easily be weakened if there is a build-up of resistance to it. There is a need to prevent resistance building up by avoiding continuous use of the same product.

(5) Herbicides

A number of major herbicides were developed during this period and since. We shall first discuss herbicides for paddy rice agriculture – the main Japanese market – followed by herbicides for upland field agriculture.

CNP (MO), a herbicide for controlling barnyard grass in paddy rice fields, was developed and marketed by Mitsui Chemicals in 1965, as discussed in Section 3.4.3 (4). For more details, refer to Section 4.5.

Benthiocarb (Saturn) was developed and marketed by Kumiai in 1969. This is discussed in Section 4.8.

Stauffer brought out Molinate (Ordram) in 1971. The following year, Rhône-Poulenc registered and marketed Oxadiazon (Ronstar), while Monsanto did the same with Butachlor (Machete). The emergence of these barnyard grass killers enabled a so-called "sequential application" involving multiple applications of products: a combination of pretreatments during the early rice growth phase and foliar-soil treatments during the medium growth phase. By 1974, this system was being used on 6.2 million hectares of land, 2.3 times the total area of paddy rice fields [6], [7], [8].

Other barnyard grass killers were developed. Ciba-Geigy developed Pretilachlor (Solnet) in 1984, followed by Bayer Japan with Mefenacet (Hinochloa) in 1986. Mitsubishi Yuka started selling Dimepiperate (Yukamate) in the same year. Stauffer went to market with Esprocarb (Fujigrass) in 1988, while Tosoh started marketing Pyributicarb (Eigen) the following year. Thus, a large number of superior-performing herbicides (able to eradicate barnyard grass through to the mature leaf stage) appeared during this period, with fierce competition between companies to develop and market new products.

Fig. 3.45 shows the chemical structures of the above barnyard grass killer.

Next, we shall discuss *Cyperaceae* herbicides and broadleaf (including perennials) herbicides used in conjunction with barnyard grass treatments. While hormone herbicides such as 2,4-PA (2,4-D) and MCPB and triazine herbicides such as Prometryn and Simetryn were used for this purpose, a number of more effective herbicides were developed.

In 1979, Mitsui Chemicals developed and marketed Naproanilide (Uribest), highly effective against perennial weed *Sagittaria pygmae* Miq. (Urikawa) and annual broadleaf weeds [9], [10]. Its mode of action works by the same hormonal effect as 2,4-PA. This formulation won the company the 33rd Okochi Memorial Grand Production Prize in 1986 for "development of the paddy rice herbicide Naproanilide."

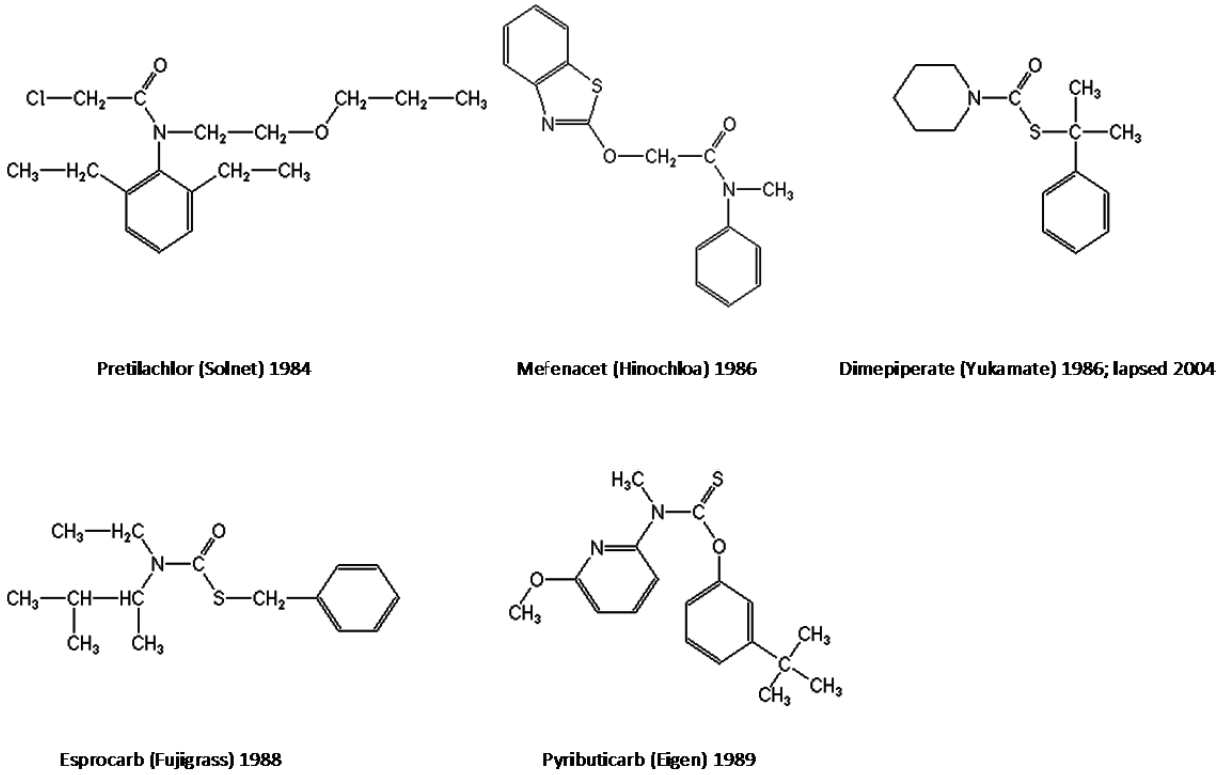


Fig. 3.45. Barnyard Grass Herbicides from the 1980s

In 1974, Showa Denko (now SDS Biotech) registered Dymron (Shoron), highly effective against Cyperaceae weeds, particularly *Scirpus juncoides*. This product is still widely used today in combination formulations.

Sumitomo Chemical started selling Bromobutide (Sumiherb) in 1986. This is a N-benzyl-butanamide with intentionally bulky substituents in the amide structure and is effective at low doses against perennial weeds such as *Scirpus juncoides*, needle spikerush (*Eleocharis acicularis*) and flatsedge (*Cyperus serotinus*) [(11)]. Sales of this product grew rapidly in the mid-2000s due to its effectiveness against weeds resistant to Sulfonylurea herbicides, which have become a problem in recent years.

Mitsubishi Yuka developed the similarly-effective Clomeprop (Yukahope) and started marketing it in 1988 [(12)]. Fig. 3.46 shows the chemical structure of these herbicides.

Let us now discuss Pyrazolate (Sanbird), a herbicide with a completely new chemical structure developed by Sankyo and registered in 1979 [(13), (14), (15)]. Pyrazolate immediately gained popularity due to its superior efficacy against annual broadleaf weeds and perennial weeds such as *Sagittaria pygmae* Miq.(Urikawa) – considered difficult to eradicate in those days, waterplantains (*Alisma canaliculatum*) and flatsedge (*Cyperus serotinus*). This herbicide enabled a transition from the existing sequential application to a so-called "one-shot application," which reduced the number of applications, thereby saving labor. Later, a number of new one-shot herbicides came on the scene and began to become very popular from around 1983, replacing the existing sequential herbicides. Pyrazolate was arguably one of the first one-shot herbicide formulations.

Pyrazolate kills weeds by inhibiting biosynthesis of carotenoids, which are pigments found in the chloroplasts of plants. After a variety of investigations, its mode of action has been found to inhibit 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) that helps to produce plastoquinone, which governs the electron transport chain in photosynthesis. Several 4-HPPD inhibitors have been discovered, as a number of companies started working on research and development in this area once Pyrazolate appeared on the scene. Typical herbicides include Pyrazoxyfen, marketed by Ishihara Sangyo in 1985, and Benzofenap, developed by Mitsubishi Yuka in 1987. Other herbicides with the same mode of action but completely different chemical structures include isoxazole and triketone compounds, which have been actively developed since 1995. For more details, refer to Hirai et al. [(16)]. Thus, Pyrazolate sparked the development of a new division of paddy rice herbicides. As a result, it won the company the 32nd Okochi Memorial Grand Production Prize in 1985. Fig. 3.47 shows the chemical

structure of the 4-HPPD inhibitors.

A super-herbicide for paddy-field broadleaf weeds appeared in 1987: Bensulfuron methyl, developed by DuPont. This super-herbicide brought the amount of active ingredient per hectare down into the double digits: 50-75g, far less than the existing products. The sulfonylurea (SU) chemical structure was completely unprecedented; it came to be called SU (ALS inhibitor) as its mode of action worked in a new way by inhibiting acetolactate synthase (ALS). SU first appeared in 1982 in the United States in the form of Chlorsulfuron for broadleaf weeds in wheat; Bensulfuron methyl was a modified version of this developed for use on paddy-rice fields. As this type of herbicide became known, many companies set out on research and development in the footsteps of DuPont. This resulted in the development and marketing of Pyrazosulfuron by Nissan Chemical in 1989, Imazosulfuron by Takeda Pharmaceutical in 1990 and Halosulfuron by Nissan Chemical in 1993. The ensuing competition to develop SU herbicides has continued to this day. For details, see Section 4.19.

As mentioned above, this period saw the successive development of paddy rice herbicides with markedly improved effectiveness against barnyard grass, *Cyperaceae* and broadleaf weeds. As a number of different combinations of these paddy rice herbicides were developed, they gradually replaced the existing formulations, thereby causing a transition from the existing method of sequential application to that of one-shot application. The subsequent advances in one-shot herbicides shall be mentioned later.

Finally, let us discuss herbicides in a non-rice context (fruit trees, vegetables, non-agricultural land, etc.). Glyphosate (Roundup), developed by Monsanto, was registered in Japan in 1980. It is a non-selective foliage-applied herbicide with a delayed effect that works by moving down to the roots and killing the plant. Its mode of action is known to work by inhibiting the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSP) in the biosynthesis of aromatic amino acids (phenylalanine, tyrosine and tryptophan) [17]. As it quickly loses its effectiveness in soil, it has no effect on succeeding crop, so it is widely popular for undergrowth in orchards, furrows between vegetable plants and on non-crop land. It soon became a world-renowned product, with shipments in Japan worth over ¥20 billion – the highest-selling pesticide in Japan. In the United States, the introduction of Glysophate-resistant crops such as soy and corn has meant that this originally non-selective herbicide can be used without affecting the quality of the produce. Businesses have sprung up selling seeds and herbicides as a pair. This product is still widely used today.

Meiji Seika developed and registered the non-selective herbicide Bialaphos (Herbiace) in 1984 [18], [19]. This product is a metabolite produced by *Streptomyces hygroscopicus* bacteria and was the first herbicide in the world produced by fermentation. It has a tripetide chemical structure with a unique carbon- phosphorus bond. Its mode of action is known to build up toxic levels of ammonia by inhibiting the biosynthesis of glutamine, one of the amino acids [20]. Bialaphos won the company the 35th Okochi Memorial Grand Production Prize in 1988 for agrochemical production and also for the high academic value of the research. In the same year, Hoechst registered Glufosinate (Basta), which has a similar chemical structure and the same mode of action as Bialaphos. Fig. 3.48 shows these chemical structures.

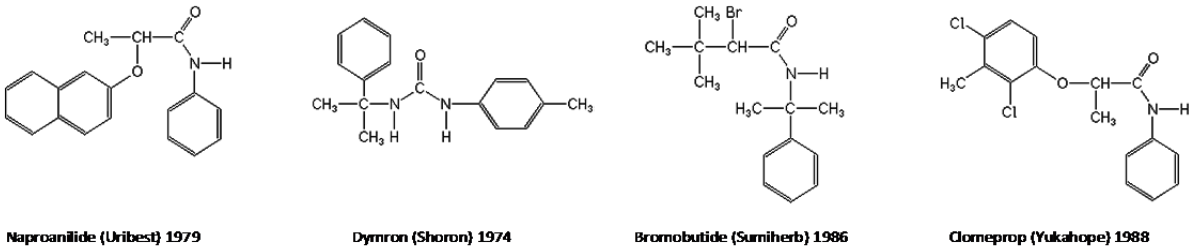


Fig. 3.46. Naproanilide, Dymron, Bromobutide, Clomeprop

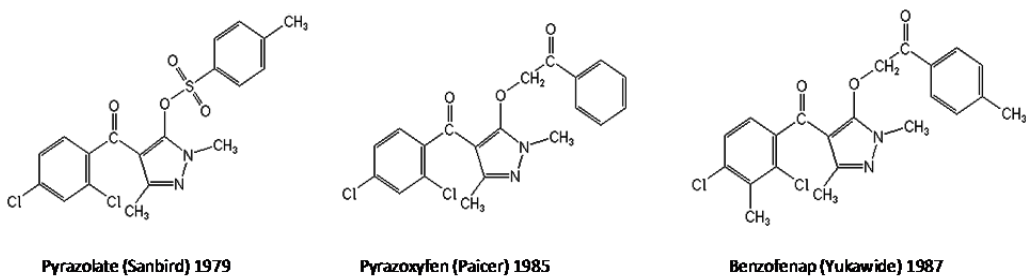


Fig. 3.47. 4-HPPD Inhibiting Herbicides

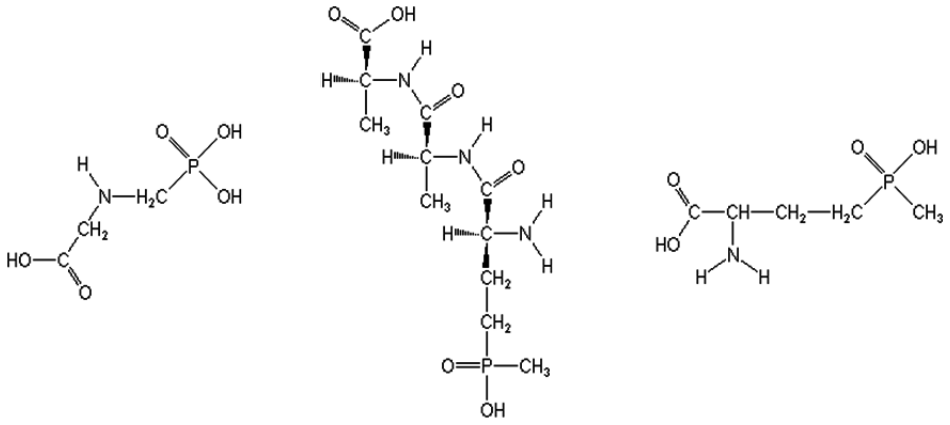


Fig. 3.48. Non-Selective Herbicides

Nippon Soda developed and registered grass-weed herbicide Alloxydim (Kusagard) in 1980, followed by Sethoxydim (Nabu) in 1985. With a completely unprecedented cyclohexanedione chemical structure, these were major world-renowned products developed for the sugar-beet, rapeseed, cotton and soybean markets. Significant modifications were later added to this chemical skeleton to develop several related herbicides. Details are given in Section 4.12.

Ishihara Sangyo developed and registered Fluazifop-butyl (Onecide) in 1986. This product had the same effect as Sethoxydim, mentioned above; that is, it is selective against grass weeds. In 1989, Nissan Chemical developed and marketed Quizalofop-ethyl (Targa), which has a similar chemical structure. Since the main market for these two formulations is overseas, they were promoted with overseas development in mind from the beginning. For details, see Section 4.17.

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3.4.5. Full Growth to Downsizing: Successive Emergence of Ultra-Performing Pesticides as Regulations Tighten (1990-present)

Japan's bubble economy burst in 1991, although it was later followed by a period of economic expansion. However, the poor economic recovery was made worse by the so-called "Lehman Shock" in September 2008; the unfavorable conditions have continued to the present day. This recession has continued for so long that it became known as the lost ten years, then as the lost twenty years.

The agricultural environment has also slumped during this time. Japanese agricultural production has steadily slowed since import liberalization of beef, oranges and other products in 1991. Japan's food self-sufficiency

has fallen year by year: in 1965, Japan's food self-sufficiency rate was 73% on a calorie basis and 86% on a production volume basis. By 2011, these figures had dropped to 39% and 66% respectively. Viewing this product by product provides a better perspective on food productivity. Japan's degree of food self-sufficiency (2011) on a quantity basis by product is shown below. The figures for meat, eggs and dairy products shown below do not account for self-sufficiency in animal feed. Otherwise, Japan's self-sufficiency ratio is over 50% in most areas except for wheat and beans.

Rice	95	%
Wheat	11	
Tubers	76	
Beans	9	
Vegetables	71	
Fruit	38	
Meat	54	
Beef	43	
Pork	52	
Chicken	66	
Eggs	95	
Dairy products	65	
Fish	52	

Japan's absolute food consumption volume has also dropped. In particular, rice consumption has steadily dropped since peaking at 118.3kg/person/year in 1962, falling to 57.8kg/person/year by 2011 [(1)]. The farming population peaked in 1960 at 14.54 million; by 2012, this had dropped to 2.51 million, with the average age also rising to 65.9 years [(2)].

The pesticide industry has also entered a time of stagnation and decline in keeping with the agricultural climate. As shown in Fig. 3.41(a) above, the value of shipments reached a peak of ¥445.5 billion in 1996 and continued to drop thereafter, falling 20% to ¥355.2 billion by 2011. Meanwhile, increasing concern over consumer food safety led to the enactment of the *Food Safety Basic Act* in 2003; the *Food Sanitation Act* was also amended accordingly.

Amidst these circumstances, the hurdles became increasingly higher for developing new pesticides and the success rate dropped each year. Major amalgamations took place overseas in an attempt to avoid the risks of the industry, and Japan eventually became caught up in the aftereffects as well, with several Japanese companies disposing of their pesticide operations. However, even in the midst of these harsh conditions, Japanese companies have carried on putting out new pesticides. This is testament to the level of technology infrastructure for pesticide development that Japanese companies have managed to build up over a long period of time.

(1) Regulatory Trends

In 1990, the Ministry for the Environment formulated the *Provisional Guidelines on the Prevention of Water Pollution from Pesticides used on Golf Courses* with the aim of preventing water pollution from pesticides used on golf courses. While pesticides were necessary for maintaining golf courses, this became a social issue that attracted media attention as the government had fallen behind in its regulation of these pesticides. These regulations were intended to ensure proper use of pesticides. Each year since, the Ministry for the Environment has continued to measure the concentration of pesticides in water draining from golf courses. A survey in 1990 examined 46,000 samples from 1,455 golf courses and found 10 cases (0.02%) of readings over the indicated limit. Later studies tested over 100,000 samples each year, with the number of samples over the limit remaining steady (around 0.002% of all samples); since 2001, there have been no samples over the limit [(3),(4)]. While this can be attributed to the enforced proper use of pesticides, we also see that this problem was not always there.

In 2000, the Ministry of Agriculture, Forestry and Fisheries set out the *Japan Agricultural Standards (JAS) for Organic Produce* [(4)] due to confusion in the market from vague definitions of organic cultivation, as society tried to produce crops while protecting the ecosystem by reviving and using traditional natural organic fertilizers and pesticides rather than chemical fertilizers and synthetic pesticides. These standards strictly stipulated that only produce that had had no chemically synthesized fertilizers or pesticides used on it and no genetic modification done to it could be sold as "organic produce." The standards also regulated the permissible fertilizers and soil ameliorating products and stipulated that where pesticide use could not be avoided, then only pyrethrum, machine oil, lime sulfur, copper formulations, antibiotics such as Milbemectin, natural enemies and sex pheromone agents could be used. However, the organic produce yield in Japan has remained low, accounting for 0.23% of the total amount of produce produced in 2010 [(5)].

In 2003, other standards were formulated to allow the sale of produce labeled as "specially cultivated agricultural products," or produce cultivated where the nitrogen content of the chemical fertilizer used and the amount of synthetic pesticides used is 50% or less than the normal level [(6)].

Let us now mention "Specified Pesticides." Products that are not registered as pesticides, but clearly work as such without any damage to people, animals or marine

life, are designated as "Specified Pesticides" (or "Specified Pest Control Agents") and may be used as pesticides [7],[8]. Currently, sodium bicarbonate, vinegar and local natural enemies (such as ladybirds, *Coccinella septempunctata*) have been designated as such.

Finally, let us discuss the "positive list system" introduced in 2006 by the Ministry of Health, Labour and Welfare [9],[10]. This system sets maximum residue limits (including uniform standard values) for all pesticides, feed additives and veterinary drugs (collectively referred to as pesticides, etc.) and residual in food products (all food products, including produce, processed food, meat, eggs, dairy products and fish) as well as prohibits the sale and distribution of any product with any pesticide residues over the maximum limits. The existing system became known as the "negative list system," as it simply listed the regulated pesticides and regulated those pesticides only, with no regulatory principles in place. As a result, there were cases of the Japanese authorities being unable to regulate certain imported pesticides used overseas as there were no residue standards in place for those particular pesticides. The positive list system has meant that all pesticides can be regulated; any pesticides with no defined maximum residue limit must conform to the uniform standard value of 0.01ppm (1/100,000,000) - the designated "amount at which there is no fear of harm to human health."

When used properly in accordance with usage standards, pesticides will not leave any residue in food products over the maximum residue limits. If residues are within the standard limits, they are harmless to human health. Even if food products containing amounts over the maximum residue limit were to be ingested from time to time, it would not cause any immediate health damage. This is because these maximum limits are based on the maximum residue amount able to be continually ingested throughout a lifetime with no health damage. The maximum residue limits, particularly the uniform standard values, are a regulatory yardstick (to indicate whether or not pesticides are being used properly) rather than a safety standard.

How much residual pesticide do we actually ingest in the food we eat? The Ministry of Agriculture, Forestry and Fisheries, the Ministry of Health and Welfare and other government departments have conducted nationwide studies to address this question. Here we shall outline the official totals taken from tests carried out by the Ministry of Health and Welfare at local public bodies and quarantine stations [11]. The results show an extremely low detection rate for pesticide residues and an extremely low rate of instances of residues exceeding the maximum residue limits. This shows that the guidance on the proper use of pesticides has been effective.

	Produce		Processed Foods	
No. Tested	3,455,719		463,330	
Pesticides detected	9,804	(0.28%)	954	(0.21%)
Domestic products	2,314	(0.36%)	29	(0.27%)
Imported products	7,490	(0.27%)	925	(0.20%)
Residue in excess of limit	417	(0.012%)	84	(0.03%)
Domestic products	21	(0.003%)	0	(0.00%)
Imported products	396	(0.014%)	84	(0.03%)

Thus, pesticide legislation has been developed with the main aims of preventing environmental pollution and ensuring the safety of the food eaten by end consumers. An extensive follow-up survey has raised no points of issue on this point; thus, it is safe to say that the guidance on proper pesticide usage has produced positive results.

(2) Insecticides

A number of highly effective insecticides have been developed since 1990, leading a transition from the age of organophosphates and carbamates to an era of new insecticides with new modes of action. Of the 61 newly registered active ingredients for insecticides (excluding pesticides with lapsed registrations and biopesticides such as natural enemies) registered by 2011, 34 (55.7%) were invented by Japanese companies. This is a good example of the strong research and development capabilities of Japanese companies. Let us now outline some of the main Japan-made insecticides.

There are three organophosphate formulas developed for use against soil pests. Ishihara Sangyo registered Fosthiazate (Nematorin) in 1992 [12]. FMC brought out Cadusafos (Rugby) in 2001, while Agro-Kanesho registered Imicyafos (Nemakick) in 2010 [13],[14]. While the active ingredient in Cadusafos is a poison and highly toxic to mammals, it has been downgraded to a deleterious substance by preparing it in microcapsules (Note 1). Both of the other two formulations are low-toxic to mammals, but selectively effective against root-lesion nematodes, root-knot nematodes and other green vegetable pests. Safety issues such as frequent irritation while fumigating against soil pests and the issue of methyl bromide depleting the ozone layer mean that there is scope for other means of chemical control to be developed in place of these formulations. Fosthiazate has become widely popular since going on the market and is currently worth ¥3 billion in shipments. Fig. 3.49 shows the chemical structures of

these formulations.

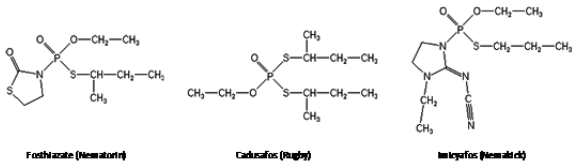


Fig. 3.49. Fosthiazate, Cadusafos, Imicyafos

Section 3.4.4 (3) mentions synthetic pyrethroid insecticides, typified by Fenvalerate (Sumicidin), which appeared in 1983. Five such pyrethroids had been developed by 1995 and continued to be popular as key insecticides. For details, see Sections 4.14 and 4.18.

Shinzo Kagabu, of Nihon Tokushu Noyaku (now Bayer Japan), invented Imidacloprid (Admire) and registered it in 1992. Called a neonicotinoid, as its mode of action is similar to the natural insecticide nicotine, it became the best-selling insecticide in the world, reaching ¥100 billion in sales. It truly is a super-pesticide. This insecticide sparked intensive research and development by various companies over the next decade, resulting in another seven neonicotinoids by 2002, each with different characteristics. These are discussed in Section 4.20.

There was a flurry of research on insect growth regulators (IGRs) - named for their insecticidal effect caused by a new mode of action - during this time, with a significant number of IGRs produced. Buprofezin (Applaud), with a thiadiazine structure, was the first IGR to be produced in Japan, brought out by Nihon Nohyaku in 1983. For details, see Section 4.13.

IGRs work as insecticides by disrupting particular biological functions in insects, namely ecdysis and metamorphosis. Since this is species-specific, it has the advantage of being highly safe to mammals and also safe to beneficial insects such as bees. However, IGRs also has the disadvantages of being slow-acting, as they are effective as a stomach poison, as well as having a significant impact on crustaceans.

Duphar brought out the benzoylphenylurea (BPU) compound Diflubenzuron (Dimilin) in 1981. This caught the attention of other companies, who then worked on BPUs, resulting in another seven products by the present day. These products, shown in Fig. 3.50, inhibit the biosynthesis of chitin, a component in insect exoskeletons, thereby hindering ecdysis. The numbers indicate the year of registration (or lapse thereof).

During this period, companies also developed IGRs modeled on the insect hormone ecdysone (a steroidal prohormone that governs ecdysis and metamorphosis, also called molting hormone or prothoracic gland hormone). These have a dibenzoyl hydrazine structure and are very effective against Lepidoptera larvae on fruit and vegetable plants. They have the advantage of being highly selective and so have little effect on natural enemies and pollinators. The first of these was Tebufenozide (Romudan), registered and marketed by Rohm and Hass in 1994. This was followed by Chromafenozide (Matric) in 1999, jointly developed by Nippon Kayaku and Sankyo. In 2001, Rohm and Hass developed and marketed Methoxyfenozide (Falcon) [15]. These products work as insecticides by disrupting feeding behavior and promoting ecdysis within a few hours of being eaten by insects. Their chemical structures are shown in Fig. 3.51.

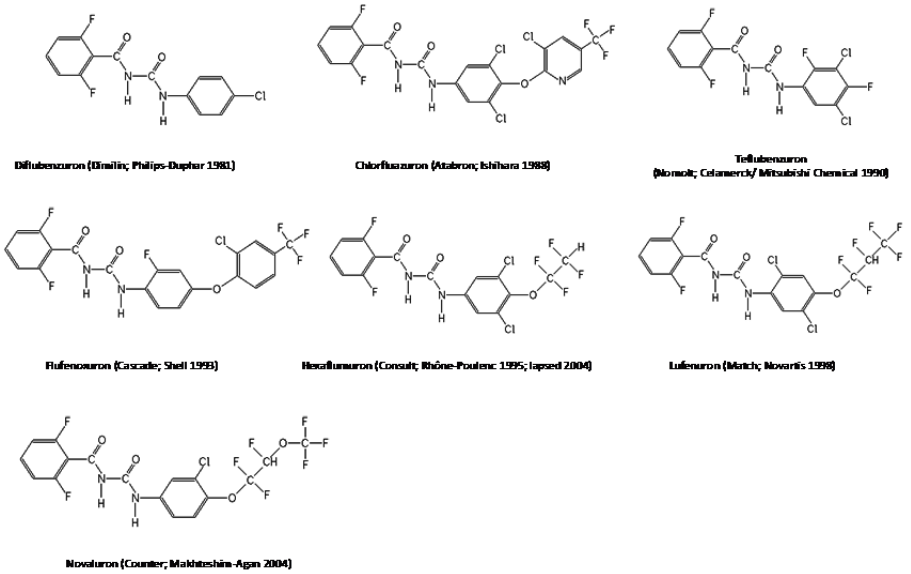
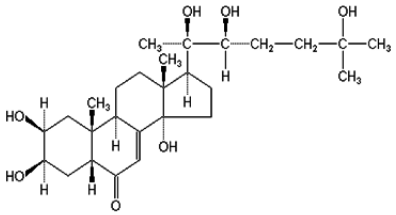
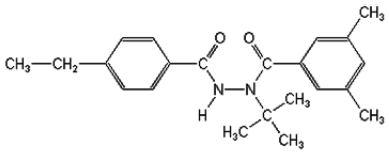


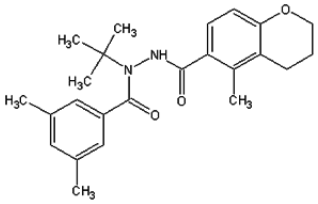
Fig. 3.50. Benzoylphenylurea Insecticides



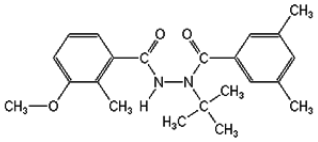
20-Hydroxyecdysone



Tebufenozide (Romudan; Rohm and Hass 1994)



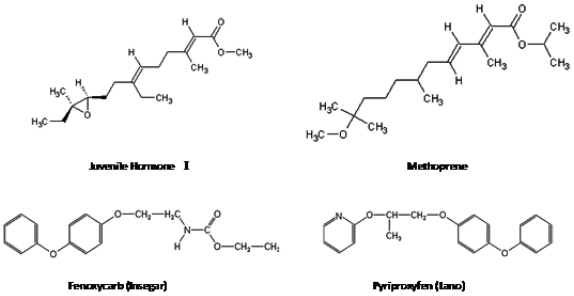
Chromafenozide (Matric; Nippon Kayaku/Sankyo 1999)



Methoxyfenozide (Falcon; Rohm and Hass 2001)

Fig. 3.51. Dibenzoyl Hydrazine Insecticides

Sumitomo Chemical developed and marketed Pyriproxyfen (Lano) in 1995. This IGR works as an insecticide by promoting larva growth and preventing metamorphosis in the same manner as a juvenile hormone (JH). Similarly-acting insecticides include Methoprene, used for disease control against flies and mosquitoes, and Fenoxycarb (Insegar), registered by Maag in 1990 as an insecticide for Lepidopterae (registration lapsed in 2004). Pyriproxyfen is quite stable in light and is very effective against hard-to-kill insects such as whiteflies, thrips and scale insects. It has a number of different effects on insects at the juvenile stages, such as inhibiting metamorphosis in larvae, inhibiting adult eclosion and preventing eggs from hatching, but it has no effect on adult insects [16]. Fig. 3.52 shows the chemical structures of these IGRs.



Juvenile Hormone I

Methoprene

Fenoxycarb (Insegar)

Pyriproxyfen (Lano)

Fig. 3.52. JH-Emulating IGRs

Let us now discuss the miticides that emerged during this period, which were unprecedented both in terms of chemical structure and mode of action. Fifteen of these miticides have now been registered since the appearance of Hexythiazox (Nissorun) in 1985, mentioned previously. Five of these are inventions by overseas manufacturers, while the remaining ten were all invented and developed by Japanese manufacturers. Miticides have a relatively small global market as well as quite a short product lifespan. Accordingly, it is quite difficult to recoup any research and development costs and, as a result, major overseas corporations have tended to put less effort into developing miticides than Japanese companies have.

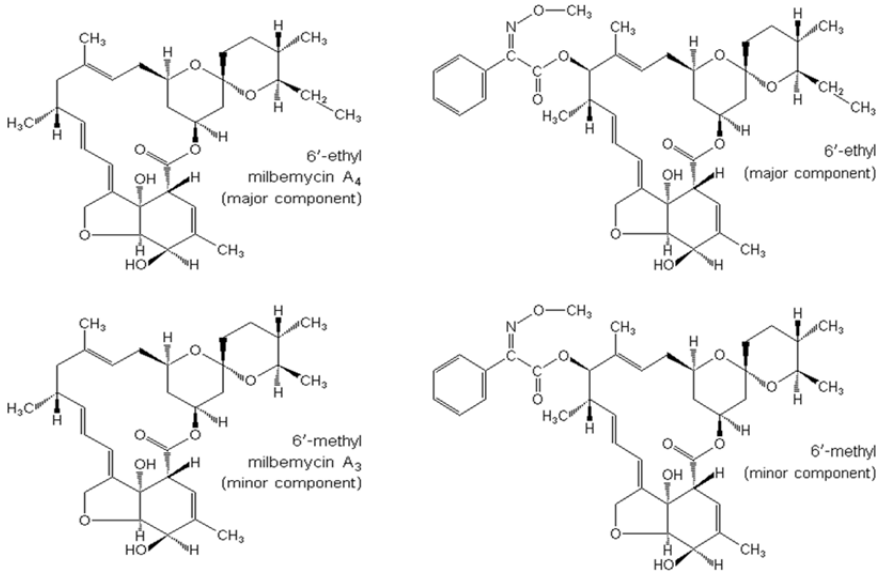
Milbemectin (Milbenock, Koromite) is a miticidal antibiotic produced by actinomycetes found in the soil in Hokkaido and isolated by Sankyo. This was developed into a mixture of Milbemycin A_3 and A_4 and put on the market in 1990. Highly effective against a broad range of mites, it is widely used on fruit and vegetable plants as there has been no observed cross-resistance as seen in existing miticides. Its mode of action is achieved by functioning as an agonist (Note 2) in the Cl-channel for gamma-aminobutyric acid (GABA) in the nervous system, fatally activating the channel. It is worth noting that of the numerous miticides, this is the only formulation to which no resistance has developed. One probable reason for this is that Milbemycin quickly dissipates after application [17]. This distinguishing characteristic has meant that this product is still widely used today. For further details, refer to Ide et al. [18].

While Lepimectin (Aniki) is not a miticide, we shall mention it here as it has a similar chemical composition to Milbemectin. Registered as a pesticide in 2010 by Sankyo (now Mitsui Chemicals Agro), it was discovered by altering the structure of Milbemectin (ester structure added at the 13-position) to give it an insecticidal effect. It works rapidly on insects such as Lepidopterae, Hemipterae and thrips and is particularly effective against butterflies [19]. Fig. 3.53. shows the structure of these two formulations.

Our discussion now turns to the miticides from this

period in the mitochondrial electron transport inhibitor (METI) category. Nissan Chemical developed and marketed Pyridaben (Sanmite) in 1991, while Nihon Nohyaku did the same for Fenpyroximate (Danitron) the same year [21]. This was followed by the development and sale of Tebufenpyrad (Pyranica) by Mitsubishi Chemical in 1993 [22] and Pyrimidifen (Miteclean) by Ube Industries/Sankyo in 1995 [23]. These high-performance miticides started to dominate the industry from the late 1980s onwards, when the afore-mentioned Hexythiazox was in its heyday. These formulations rapidly gained popularity in the early 1990s, accounting for half of the miticide market. They were all effective at low doses, fast-acting and worked at all stages in the spider-mite life cycle. They are all known to inhibit Complex I in the mitochondrial electron transport chain in the respiratory system. While various different companies worked on their own versions of these miticides, they all had the same mode of action. Sale of these formulations gradually decreased as some cross-resistance was observed a few years after these products first went on sale.

Another compound with the same mode of action is Tolfenpyrad (Hachihachi), developed as an insecticide. This product was jointly developed by Mitsubishi Chemical and Otsuka Chemical and registered in 2002. It is widely popular due to its superior effectiveness against a wide range of insects, including Lepidopterae, Hemipterae and thrips. It is also effective against powdery mildew on eggplants, watermelons and other plants. Fig. 3.54 shows the chemical structures of these formulations.



Milbemectin (Milbenock) Lepimectin (Aniki)

Fig. 3.53. Milbemectin and Lepimectin

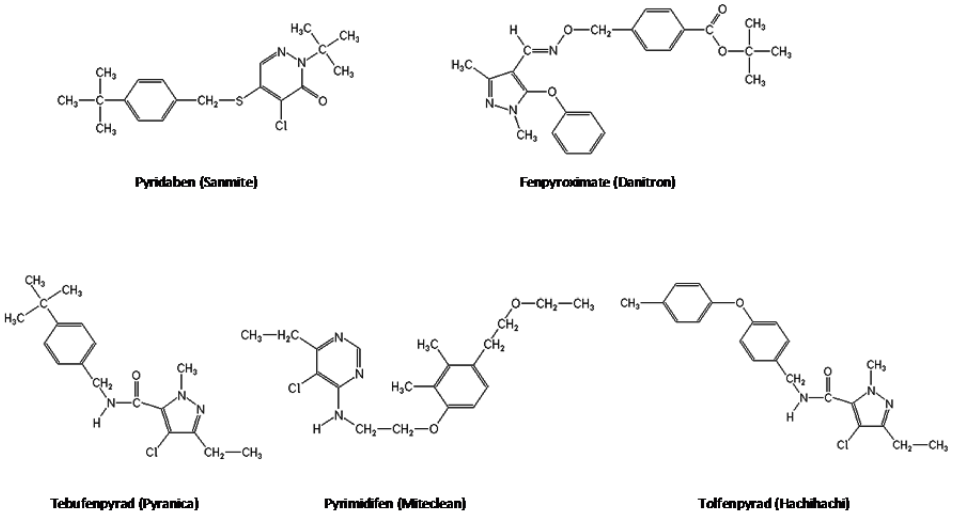


Fig. 3.54. METI Inhibitors

Etoxazole (Baroque) is a new miticide invented by Yashima Chemical and registered in 1998. Yashima Chemical came up with Etoxazole through research on oxazoline chemistry. While it is not very effective on mature spider-mites, it is incredibly effective against insect eggs and nymphs. In terms of its ppb level, it is 100 times more powerful than other miticides such as Hexythiazox. Its mode of action is not yet clearly known, although it is presumed to work like Hexythiazox by inhibiting ecdysis [24].

Otsuka Chemical invented Cyflumetofen (Danisaraba), a miticide with a completely new benzoylacetonitrile structure and put it on the market in 2007. It is fast-acting and is specific to spider-mites while having no effect on beneficial insects. Its mode of action is conjectured to work by inhibiting Complex II in the mitochondrial electron transport chain [25].

Nissan Chemical invented acrylonitrile miticide Cyenopyrafen (Starmite) and registered it in 2008. Cyenopyrafen has strong ovicidal activity for all kinds of spider-mites and has none of the cross-resistance issues seen in existing miticides. Like Cyflumetofen, mentioned above, it works by inhibiting Complex II in the mitochondrial electron transport chain [26], [27], [28].

Nihon Nohyaku presented a report on the powerful miticide Pyflubumide (NNI-0711) at a conference in 2012 (Fig. 5.52). It also works by inhibiting Complex II in the mitochondrial electron transport chain, although it is still in development and has not yet been put on the market [29], [30].

Fig. 3.55 shows the chemical structures of the miticides mentioned above that have been recently developed or are still in development.

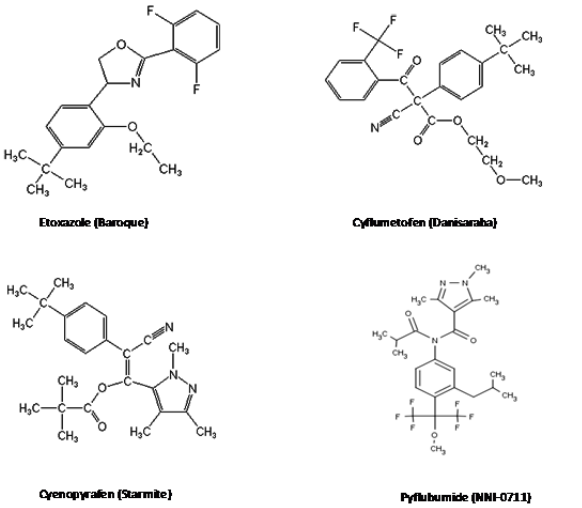


Fig. 3.55. Japanese Miticides Developed since 1998

Thus, previously unimaginably highly effective miticides were successively developed. The Japanese miticide market is worth over ¥12 billion, shared between these highly effective formulations. While overseas manufacturers developed other miticides during this time, these have all been domestically-developed products pioneered by Japanese manufacturers (such as Acequinocyl, Bifenazate and Fluacrypyrim). The overwhelming majority of miticides are developed by Japanese manufacturers. Resistance to a product is an on-going battle and new miticides are in constant demand. Our future hope lies in the development of formulations with new modes of action, or softer formulations that are safer for natural enemies and other environmental factors.

Finally, let us return to insecticides. There have been a great number of insecticides developed recently with unprecedented chemical structures and unprecedented modes of action. Several of these were invented and developed by Japanese companies; we shall examine these here.

Sumitomo Chemical invented Pyridalyl (Pleo) and put it to market in 2004. Highly effective against Lepidopterae and thrips, it is also effective against pest insects that have become resistant to existing pesticides, such as organophosphates, synthetic pyrethroids and IGRs. While its mode of action is not yet clearly known, it is thought to work through a completely unprecedented mechanism [31], [32], [33].

Ishihara Sangyo developed a fluorine-containing pyridine insecticide, Flonicamid (Ulala), and registered it in 2006. While it has no effect on Lepidopterae, it is selectively effective against aphids and thrips on fruit and vegetable plants and has systemic activity. Its mode of action is unknown, but it does not fit into any of the existing categories [34].

In 2007, Nihon Nohyaku developed and marketed Flubendiamide (Phoenix), with an unprecedented phthalic acid diamide structure and a completely new effect [35]. This formulation drew attention for its specific effectiveness against Lepidopterae, such as leafrollers on fruit trees and armyworms, diamondback moths, etc. on vegetable plants. It works as a stomach poison with residual effectiveness. While its effects are slightly delayed, it causes the body of the insect to fatally crumple up on itself [36]. Its mode of action is achieved by acting on the ryanodine receptors (RyRs) that govern the contractions of the insect's muscles. Flubendiamide activates the RyRs, releasing calcium ions into the muscles of the insect and causing the insect to fatally crumple up. Hatano provides more details on this mode of action [37]. The appearance of Flubendiamide piqued the attention of pesticide manufacturers worldwide and a development competition ensued. DuPont won out with the

development of Chlorantraniliprole (Acelepryn), which has similar effects, registering it in 2009. A number of manufacturers are currently focusing on this area of pesticides and future developments are promising.

Nihon Nohyaku developed Metaflumizone (Accel), an insecticide with a semicarbazone structure, and registered it in 2009. It is very effective against Lepidopterae on vegetable and tea plants. Reports show that its mode of action works in the sodium channel in the nervous system [38]. While synthetic pyrethroids are known to work in the sodium channel, Metaflumizone is thought to have a different mode of action, as it also works on insects that have built up a resistance to synthetic pyrethroids. Indoxacarb (Tornado), registered by DuPont in 2001, also has a similar mode of action [39]. Metaflumizone also can be regarded as having the ring-opened structure of Indoxacarb.

Nihon Nohyaku registered quinazolinone-structured Pyrifluquinazon (Colt) in 2010. This formulation is highly effective against aphids, stink bugs, thrips and scale insects on fruit and vegetable plants. It is categorized as an insect behavior regulator (IBR), as it prevents insects from feeding and sucking and causes them to immediately drop off plants [40],[41],[42]. While its mode of action is not clearly known, it is similar to Pymetrozine (Novartis), which went on the market in 1998. There is also a partial chemical resemblance between them.. The research team at Nihon Nohyaku started investigating methoxyacrylate fungicides in the late 1980s. They discovered that the aminoquinazoline derivative they had synthesized as an intermediate had insecticidal properties, so they researched it further. They introduced the perfluoroalkylated aniline structure, the intermediate in Flubendiamide, resulting in Pyrifluquinazon.
Fig. 3.56 shows the chemical structures of these compounds.

As mentioned above, a number of pesticides that have emerged during this period are highly effective, safe to mammals and have little impact on the environment. A succession of new products is being developed with unprecedented chemical structures, new pesticidal characteristics and new modes of action. Although there are high hurdles to surmount in development, it is worth noting that many of the new products have been discovered by Japanese companies and many of these have become world-renowned products. As insects have begun to build up resistance to existing insecticides, there is a continuous need for new insecticides with new modes of action and further development is expected.

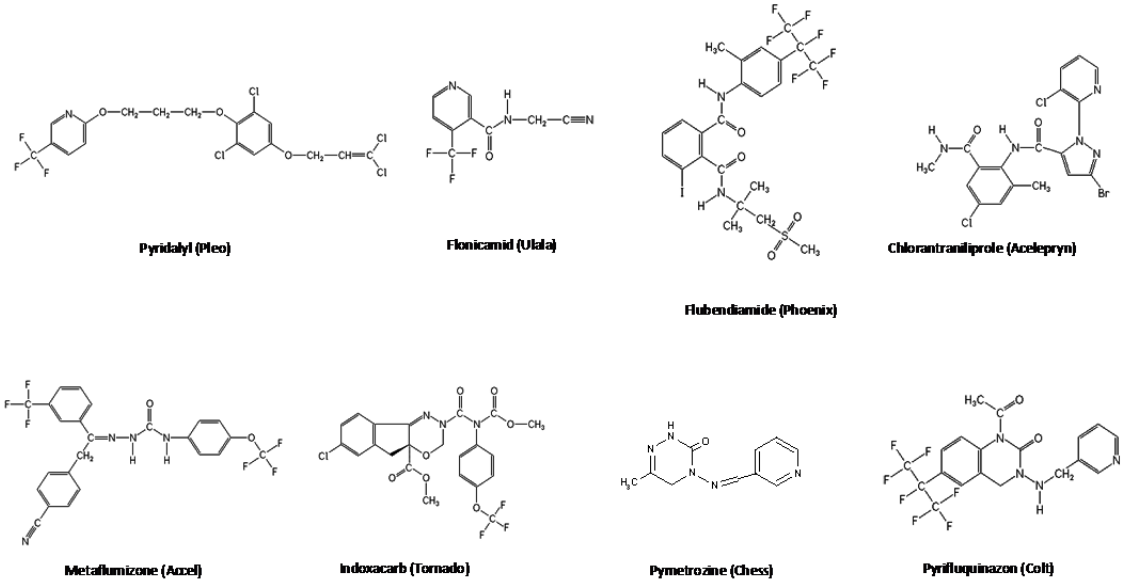


Fig. 3.56. New-Effect Insecticides developed since the 2000s

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Note 1: Microcapsule formulations are made from a slurry coated in a polymeric membrane for the purpose of controlled release. This has the effects of reducing unwanted toxicity, durability of effect (residual activity) and reducing any harmful side effects on crops.

Note 2: An agonist is a substance that acts on (stimulates) the receptor (point of action) in the same way as a naturally occurring substance (in this case, GABA).

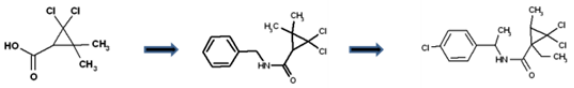
(3) Fungicides

Let us now discuss the main fungicides developed during the 1990s and since, with particular focus on those developed in Japan. A number of rice blast fungicides with various different characteristics were developed after the war, such as mercurials, organochlorides, organophosphates and antibiotics. During this period, some fungicides emerged with unprecedented effects and modes of action.

First, let us mention the rice blast fungicides that work by inhibiting biosynthesis of melanin. Kureha developed and marketed Fthalide (Rabcide) in 1970. As discussed in Section 3.4.4 (4), this is classified as a MBI-R, a second-generation MBI. Other MBI formulations with new chemical structures different from Fthalide were developed in the late 1990s. As shall be mentioned later, these formulations are third-generation MBIs, called MBI-Ds, because they act at a different step in the rice blast melanin biosynthesis process from Fthalide, inhibiting the scytalone dehydrogenase [(1)].

Bayer Japan developed and marketed Carpropamid (Win) in 1997. Inventor Shinzo Kagabu had been focusing on substituted cyclopropane-carboxylic acid derivatives and examining related compounds after reading a published paper on momilactone as an inducer (resistance inducer) of rice phytoalexin(Note 1). Meanwhile, while investigating herbicides, Kagabu discovered that amides derived from substituted phenethylamine and bulky carboxylic acid derivatives worked as a fungicide against rice blast. Combining these two areas of research resulted in Carpropamid (Fig. 3.57). The initial aim for this research was to develop fungicides that were active in inducing resistance and although it was indeed proven to induce resistance, it became known more for its effect of inhibiting melanin biosynthesis [(2),(3)]. This success was the result of the attention paid to a number of research papers, the idea of developing that work into a lead compound and the tenacity to overcome a string of failures. Kagabu also invented world-renowned Imidacloprid, and thiacloprid (see Section 4.20) around

the same time. While Kagabu attributes these inventions as a gift from God [3], the true reason for his success was not a gift. It was the result of the wealth of knowledge and experience at his disposal, the way in which he brought out those ideas and, most importantly, his tireless hard work and his good fortune (serendipity, the power to bring about success).

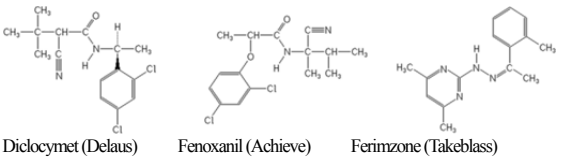


Lead Compound 1 Lead Compound 2 Carpropamid (Win)

Fig. 3.57. Carpropamid and its Lead Compounds

Following the appearance of Carpropamid, Sumitomo Chemical developed and marketed Diclocymet (Delaus) in 2000 [4], while ACC and Nihon Nohyaku did the same for Fenoxanil (Achieve) the same year.

Takeda Pharmaceutical developed and marketed Ferimzone (Take-blass) in 1991. Reports indicate that, unlike the MBIs, this fungicide acts on the cellular membrane to prevent hyphal growth [5]. Fig. 3.58 shows the chemical structures of these products.



Diclocymet (Delaus) Fenoxanil (Achieve) Ferimzone (Takeblass)

Fig. 3.58. Rice Blast Pesticides developed since the 1990s (other than Melanin Synthesis Inhibitors)

Next, we shall discuss ergosterol biosynthesis inhibitors (EBIs), which are fungicides that work by inhibiting the biosynthesis of ergosterol (a lipid component that makes up the cellular membrane in molds and biosynthesized from squalene, equivalent to cholesterol in animal cells). Since the appearance of this type of fungicide in the 1970s, companies have been working on developing them. They are widely popular as they have systemicity, working as prevention and a cure, and are also very effective on a wide range of diseases on wheat, soybeans, vegetables and fruit plants. From the 1990s onwards, these have been the most significant fungicides for agriculture. Resistance to EBIs is slow to develop and there is little risk of the effect weakening, although there is a growing resistance to many of these pesticides because of long-term use. Little research has been done on these pesticides since 2000.

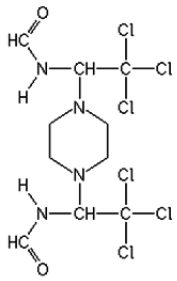
The first EBI developed in Japan was Triforine (Saprol), invented by Celamerck and registered in 1977. In 1983, Bayer marketed Triadimefon (Bayleton). This triggered other companies to start their own development and a number of other EBIs emerged. The EBI development rush lasted 20 years from the late 1980s. There are more than 20 EBIs currently registered in Japan. Seven of these are Japanese inventions, each with their own distinguishing characteristics. Fig. 3.59 shows the chemical structures of these formulations and lists their manufacturers. All of them have nitrogen-containing hetero-cyclic ring structures, such as imidazole and triazole.

Just as the development competition over EBIs ebbed a little into the 1990s, a new fungicide emerged with a new mode of action: strobilurin fungicides, modeled on natural strobilurin, a fungicidal substance found in *Strobilurus tenacellus*, a type of basidiomycete [6]. This has a distinctive methoxyacrylate structure. The first strobilurin fungicide registered in Japan was Kresoxim-Methyl (Stroby), developed by BASF and registered in 1997. This was followed by Azoxystrobin (Amistar), developed by Zeneca and registered in 1998. Later, more than 20 companies competed to develop the next strobilurins, ushering in the age of the strobilurin fungicide. Currently, there are 10 such products on the pesticide register. Two of these were developed by Japanese companies and are shown in Fig. 3.60.

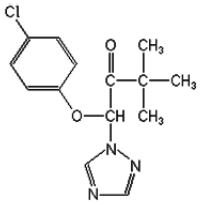
Shionogi invented Metominostrobin (Oribright) and put it to market in 1998. This product proved to be effective against rice blast and a wide range of other rice diseases such as sheath blight and leaf blight. While the research team at Shionogi was developing isoxazole derivatives as herbicides, they also noted that these had some minor fungicidal effects. They developed this into a ring opened heterocyclic structure, resulting in Metominostrobin [7].

Kumiai Chemical registered Pyribencarb (Fantasista) very recently, in 2012. This formulation is distinctive for its suitability for a wide range of diseases on fruit and vegetable plants as well as its effectiveness against fungi that have grown resistant to strobilurin [8],[9]. It has only just been registered, but it is expected to grow in popularity in future.

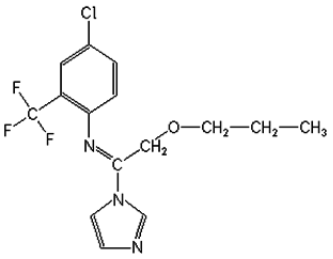
The mode of action of the strobilurins mentioned above is known to work by inhibiting respiration in fungi by inhibiting Complex III (Qo) in the mitochondrial electron transport chain (Note 2).
This effect is achieved by strobilurins, mentioned above as being produced by molds; however, this does not mean that strobilurins inhibit respiration in molds. Reports indicate that these fungi have various defense mechanisms in place, such as low susceptibility at the point of action. The growing resistance to these types of fungicides in powdery mildew in wheat and downy mildew in cucumbers could have something to do with these defense mechanisms.



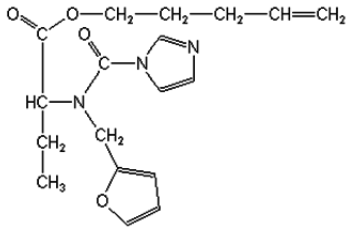
Triforine (Saprol; Celamerck, 1977)



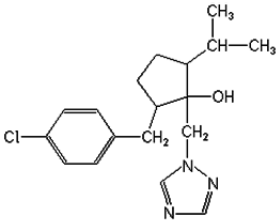
Triadimefon (Bayleton; Bayer, 1983)



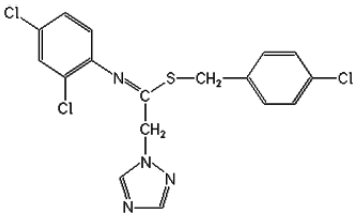
Triflumizol (Trifmine; Nippon Soda, 1986)



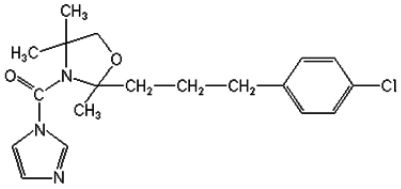
Pefurazoate (Healthid; Hokko Chemical, 1989)



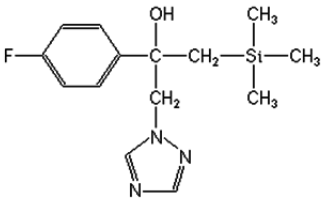
Ipconazole (Techlead; Kureha, 1993)



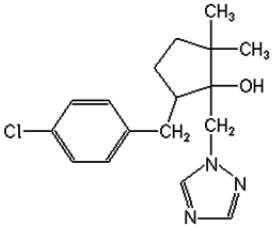
Imibenconazole (Manage; Hokko, 1994)



Oxpoconazole (Oshin; Ube, 2000)

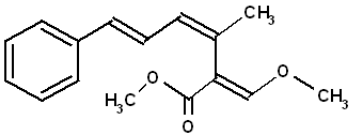


Simeconazole (Patchcolon; Sankyo, 2001)

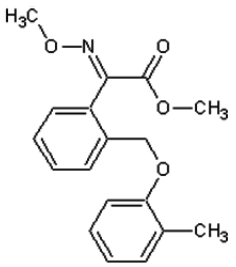


Metconazole (Workup; Kureha, 2006)

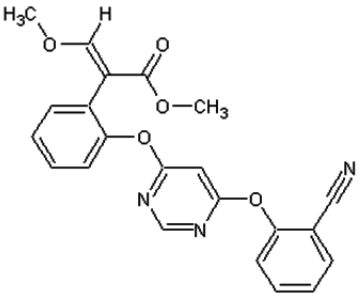
Fig. 3.59. Ergosterol Biosynthesis Inhibitors (EBIs)



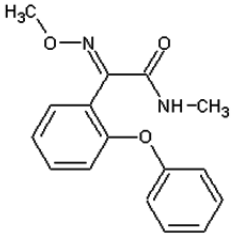
Strobilurin A (natural product)



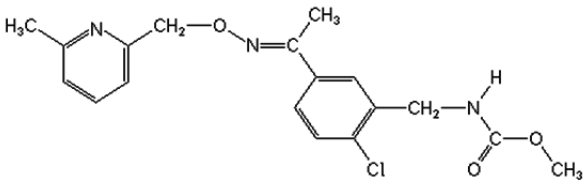
Kresoxim-Methyl (Stroby; BASF, 1997)



Azoxystrobin (Amistar; Zeneca, 1998)



Metominostrobin (Oribright; Shionogi, 1998)



Pyribencarb (Fantasista; Kumiai Chemical, 2012)

Fig. 3.60. Typical Strobilurin Fungicides

Japanese companies have invented a number of other fungicides besides EBIs and strobilurins since 2000. Each of these has a different mode of action from the two mentioned above and is effective against fungi that are resistant to existing formulations.

Ishihara Sangyo registered Cyazofamid (Ranman) in 2001 and put it on the market. It is effective against late blight in potatoes and downy mildew in grapes (both oomycetes). Initially sold in Japan, it later spread throughout 16 countries. It was discovered as a result of further developments on cyanoimidazole and benzimidazole structures, known through patents to have fungicidal properties. While its mode of action is achieved by inhibiting respiration, like the strobilurins, it is known to act in a different position (electron transport chain Complex III (Qi)) [(10)].

Nippon Soda developed and registered oxime-ether-structured Cyflufenamid (Pancho) in 2002. This fungicide is distinctive for its broad ranging effects on powdery mildew on wheat, vegetables and fruit plants, as well as its effectiveness against diseases showing signs of resistance to existing fungicides. Nippon Soda already had experience with oxime-ether compounds from having developed the herbicide Alloxydim and presumably applied this knowledge to existing fungicides to produce Cyflufenamid. While its mode of action is completely different from any existing formulations, the details of it are not yet clearly known [(11)].

Kumiai Chemical developed and marketed Benthiavalicarb isopropyl (Mamolot) in 2007. This fungicide has an amino acid valine amide carbamate structure and works as both prevention against and cure for blight and downy mildew. Kumiai worked on developing structures based on the fungicidal properties of valine derivatives patented by Bayer, resulting in this benzothiazole skeletal structure. Reports indicate that its mode of action is achieved by inhibiting biosynthesis of cell walls [(12), (13)].

Nissan Chemical developed sulfamoyltriazole-structured Amisulbrom (Leimay) and put it to market in 2008. This product is highly effective against blight and downy mildew, penetrating quickly into plants to produce a high preventive effect [(14), (15)]. While its mode of action is presumed to work by inhibiting respiration like the aforementioned Cyazofamid, no detailed reports have been made. The two are similar in chemical structure, both having a sulfamoyl-based azole skeleton.

Mitsui Chemicals developed and marketed carboxylic acid-amide-structured Penthiopyrad (Affet) in 2008. This product shows superior effectiveness against a wide range of diseases, such as grey mold, powdery mildew, leaf mold, scab and monilia blossom blight. It is also highly effective against fungi that have developed resistance to existing fungicides. Its mode of action works by inhibiting succinate dehydrogenase in the respiratory electron transport chain Complex II [(16), (17)]. While other carboxylic acid-amide fungicides have been developed with this mode of action, such as Mepronil (Basitac; registered by Kumiai Chemical in 1981), Flutolanil (Moncut; registered by Nippon Soda in 1985) and Furametpyr (Limber; registered by Sumitomo Chemical in 1996), Penthiopyrad is highly effective against diseases that these other fungicides have failed to beat. It is also effective against newly problematic diseases that have developed resistance to EBIs and strobilurins.

Ishihara Sangyo started marketing Pyriofenone (Property) in the United Kingdom. This fungicide has a benzoylpyridine structure and is very effective against powdery mildew in wheat, cucumbers and other crops [(18), (19)]. The fungicidal action of this fungicide is achieved by inhibiting the formation of haustoria and conidia in the parasitic fungus and interfering with the morphology of secondary appressoria and hyphae. The chemical structure of this product was developed by replacing the benzene ring in Metrafenone, developed by BASF, with a pyridine ring – the result of Ishihara's wealth of experience with pyridine. This product has not yet been registered in Japan. Fig. 3.61 shows the new fungicides developed by Japanese companies in the 2000s discussed above.

As discussed above, there have been major developments in fungicides since the 1990s. This era has seen the successive appearance of MBI-D, a new type of melanin biosynthesis inhibitor, ergosterol biosynthesis inhibitors (EBIs), effective against a broad range of fungi, and strobilurin fungicides. A number of other fungicides have also emerged, with new modes of action and new chemical structures. It is worth noting that many of these were developed by Japanese companies. Given the intrinsic problem of fungi developing resistance to products, there are limitations to fungicides, in that the continuous use of products with the same mode of action should be avoided or the doses should be reduced, etc. in order to delay the build-up of resistance to some extent. From the developers' perspective, there is an on-going demand to develop new pesticides with new modes of action, but the hurdles to clear are getting increasingly higher, such as having to create highly effective pesticides while ensuring their safety and assessing their impact on the environment.

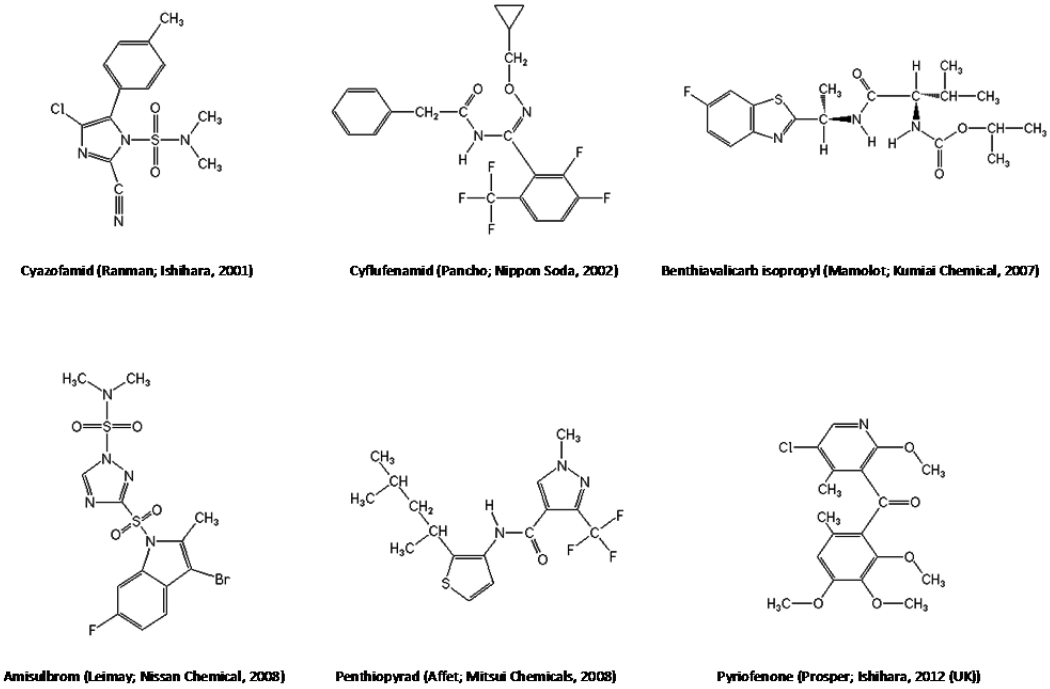


Fig. 3.61. New Fungicides developed since 2000

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(13) Sakai et al. *Journal of Pesticide Science*, Vol. 35, No. 4, 2010, p. 501.
(14) Takahashi et al. *Abstracts from the 32nd Annual Convention of the Pesticide Science Society of Japan*, 2007, SI3.
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(16) Sakurai et al. *Journal of Pesticide Science*, Vol. 36, No. 4, 2011, p. 520.
(17) Katsuta. *Abstracts from the 32nd Annual Convention of the Pesticide Science Society of Japan*, 2007, SI9, p. 33.
(18) Patent No. 2004-168757 (Ishihara Sangyo)
(19) *Fine Chemicals*, Vol. 39, No. 10, 2010, p. 43.

(Note 1) Phytoalexins are antimicrobial secondary metabolites produced in plants under stress when infected by a fungus or similar. "Phyto" means "plant;" "alexin" means "defensive substance."
(Note 2) Mitochondria are organelles within a cell; these have complexes (enzymes) in their membranes that govern the electron transport chain that produces energy during respiration.

(4) Herbicides

Let us examine the developments in herbicides from the 1990s onwards. Besides the paddy rice barnyard grass killers discussed in Section 3.4.4 (5), a number of other effective herbicides appeared during this time.

Researchers in the late 1990s worked on modes of action and clarified that chloroacetamide herbicides (such as Butachlor and Pretilachlor), which had previously been thought to work by inhibiting protein synthesis, actually worked by inhibiting Very-Long-Chain Fatty Acid Elongase (VLCFAE) in fatty acid synthesis [(1), (2)]. This prompted the development of a number of herbicides having this mode of action.

Tokuyama Soda (now Tokuyama) started pesticide research and development in 1980, working jointly with Utsunomiya University. A study involving adding various heterocycles to chloroacetamide herbicides resulted in Thenylchlor (Alherb) with a thiophene heterocycle, registered in 1993. Multiple times more active than existing chloroacetamide herbicides, it was very effective not only against barnyard grass, but also against *Cyperaceae* and *Monochoria vaginalis* [(3), (4)].

Hodogaya Chemical developed and marketed Etobenzanide (Kickby) in 1995. Selectively effective against barnyard grass, this was used in combination formulations [5].

Chugai Pharmaceutical invented Cafenstrole (Himeadow) and put it on the market in 1996. Effective against barnyard grass until the 2.5 leaf stage and long-lasting, it is very popular as a base substance for combination formulations. By 1998, it was a major herbicide, being used on more than 450,000 hectares. It is also suitable for use on turf. Its carbamoyl triazole structure is unprecedented among herbicides [6], [7].

Indanofan (Trebiace) is a new herbicide combining an oxirane ring with an indandione structure. Inspired by the oxirane-structured maize herbicide Tridiphane (no longer in use), Mitsubishi Chemical worked on developing its own compound, resulting in Indanofan, with a new chemical structure previously unseen in a herbicide, and registered it in 1999. This product is very effective against barnyard grass at the 2.5 leaf stage and broad-leaf weeds at a low dosage of 120-150g per hectare [8], [9].

Fentrazamide (Innova) is a paddy rice herbicide invented by Bayer Japan. Registered in 2000, this product became very popular, marketed as the main ingredient in a combination formulation, making a name for itself as a key barnyard grass killer. While Uniroyal was the first to identify the herbicidal properties of the tetrazolinone structure, the herbicidal effect on barnyard grass significantly increased with improvements to the structure [10].

Kumiai Chemical developed Fenoxasulfone, very effective against barnyard grass and also annual weeds, and applied for registration in 2012. It is expected to become a popular formulation. With a sulfonyl-substituted isoxazoline structure, it should be very effective at low doses of 100-250g. Kumiai Chemical also developed the similarly-structured Pyroxasulfone, which is very safe on major crops such as wheat, maize and soybeans, very effective against broadleaf weeds such as *Chenopodium album* (Common lambsquarters) and *Abutilon theophrasti* (velvetleaf) and also effective on glyphosate-resistant weeds, which have become a problem in recent times. Pyroxasulfone was registered in 2011 in Australia and in 2012 in the United States [11], [12], [13].

All of the herbicides discussed here work by inhibiting VLCFAE, mentioned above. While these represent a wide range of different chemical structures, there is still potential for a completely new compound to be discovered that works in the same way, and there is much promise for future development. This is a good example showing the importance of researching the target mode of action when inventing new pesticides. Fig. 3.62 shows these VLCFAE inhibitors.

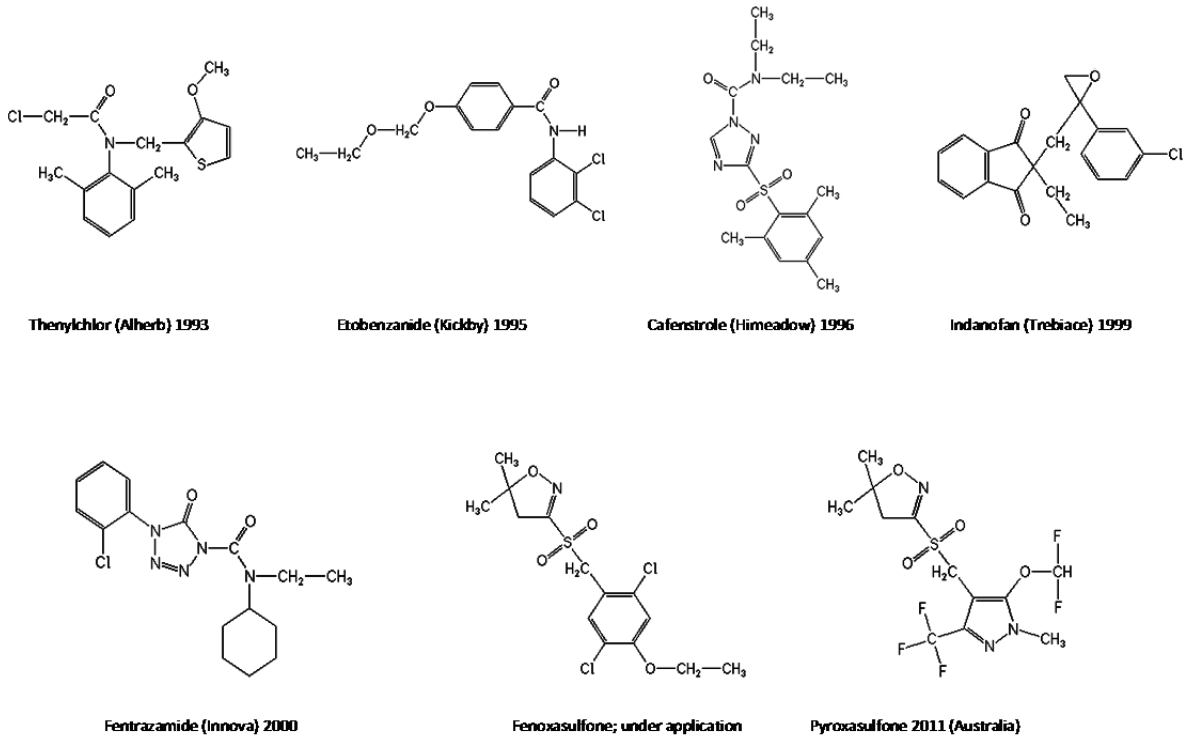

Fig. 3.62. VLCFAE Inhibitors developed since 1990

Next, we shall discuss carotenoid synthesis (4-HPPD) inhibitors, which have been actively researched since the late 1990s. Section 3.4.4 (5) touched on 4-HPPD; the forerunner of these formulations was Pyrazolate (Sanbird), developed by Sankyo in 1979. Once Japanese companies started developing pyrazole-structured herbicides in the late 1980s, no further development was done on pyrazole derivatives. SDS Biotech later discovered the triketone derivative Benzobicyclon (Show Ace) and registered it in 2001. While it had been known since the 1980s that triketone-structured compounds had herbicidal effects, SDS started developing it for use on paddy rice fields. After a number of modifications to the structure, Benzobicyclon became the first such herbicide highly suited for use in paddy rice cultivation. It proved to be very effective against annual broadleaf weeds and perennial weeds at doses of 200-300g per hectare [14), (15), (16)]. It rapidly became popular due to its effectiveness on weeds such as *Scirpus juncoides* and *Monochoria vaginalis* that had become resistant to SU herbicides; by 2009, it was being used on 500,000 hectares. Other herbicides in this category include Tefuryltrione (Mighty One), developed and marketed by Bayer Japan in 2010, and Mesotrione (Callisto), developed and marketed by Syngenta.

Much research has gone into the area of 4-HPPD inhibitors since the appearance of the triketone structure and future developments are expected.

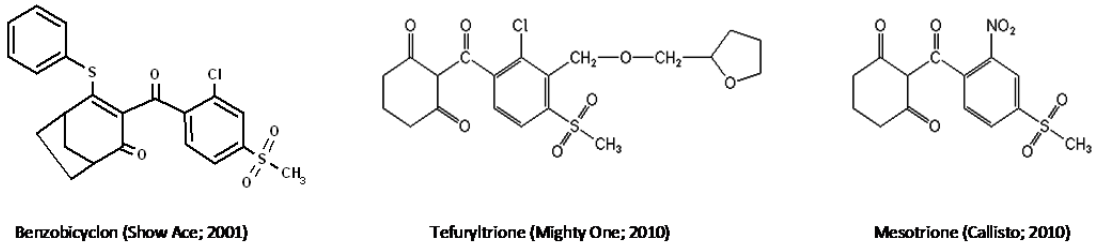

Fig. 3.63. Triketone 4-HPPD Inhibitors developed since 2000

Finally, let us discuss the significant development that has taken place during this period on herbicides that work by inhibiting chlorophyll biosynthesis. Compounds with this effect have a long history dating back to diphenyl ether herbicides. While we shall discuss this in more detail in Section 4.5, let us mention here that NIP (registered in 1963), CNP (registered in 1965) and Chlomethoxynil (X-52) require light in order to work as herbicides and were thus initially called light dependent or photobleaching herbicides. Later, Rhône-Poulenc developed Oxadiazon (Ronstar), with a completely different chemical structure. This formulation is still used as a paddy rice herbicide. Mitsubishi Chemical developed and marketed cyclic-imide-structured Chlorphthalim in 1981. This formulation is still used today as a herbicide for turf. While these products have completely different chemical structures, they are light-dependent herbicides, like the diphenyl ether products (Fig. 3.64).

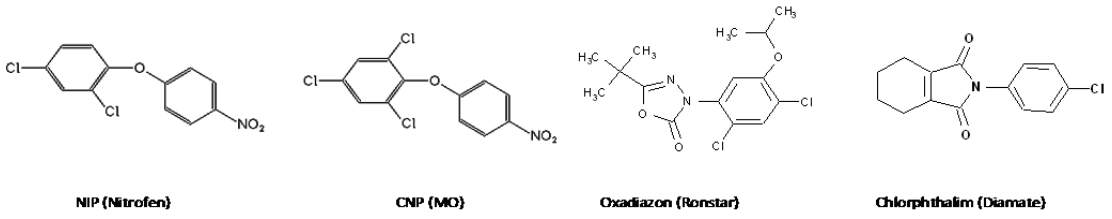

Fig. 3.64. Early Light-Dependent Herbicides (PPO Inhibitors)

In the late 1980s, research showed that these formulations killed plants by means of reactive oxygen produced during photosynthesis as a result of inhibiting protoporphyrinogen-IX oxidase (PPO), a synthase for protoporphyrin IX in the chlorophyll biosynthesis process [17), (18), (19)]. Development competition ensued and a number of these PPO inhibitors were produced by various different companies.

Sumitomo Chemical developed Flumiclorac pentyl (Resource) in 1994 as a herbicide for use on soybeans [20)] and also registered Flumioxazin (Sumisoya) in

Japan in 2000. It then registered this product in the United States in 2001 for use on soybeans and peanuts [21].

Kaken Pharmaceutical developed Pentoxazone (Vexor) for use on barnyard grass and broadleaf weeds and put it to market in 1997. Effective against annual weeds in general, this product is also very effective on common false pimpernel and *Monochoria korsakowii* (mizuaoi) that have become resistant to sulfonylurea pesticides [22]. Currently, more than 40 combination formulations include this product and it is very popular as a paddy rice herbicide.

Nihon Nohyaku developed and marketed Pyraflufen ethyl (Ecopart) in 1999. This formulation is highly effective on broadleaf weeds (such as *Galium spurium*) in wheat at low doses comparable with sulfonylurea pesticides (6-12g/hectare). It has also been registered overseas in Europe. Unlike the existing PPO inhibitors, this formulation has a unique chemical structure, with a benzene ring bonded to hetero ring carbon atoms (C-C bond) [23], [24].

Kumiai Chemical developed and marketed Fluthiacet methyl (Velvecut) in 2002. This product is very effective on *Abutilon theophrasti* (velvetleaf), a noxious weed on maize crops, at doses of 3-10g/hectare [25]. It was registered in the United States in 1991 for use on soybeans and maize.

While we have discussed the PPO inhibitors developed by Japanese companies, there has been intense competition among overseas companies in this field as well. Herbicides produced by overseas companies and registered in Japan for use on the Japanese rice market include Carfentrazone ethyl (Hardy), registered by FMC in 1999, Oxadiargyl (Fenax), registered by Rhône-Poulenc (now Bayer) in 2001, and Pyraclonil (Pyraclon), registered by Schelling (now Bayer) in 2007. Fig. 3.65 shows the chemical structures of these PPO inhibitors.

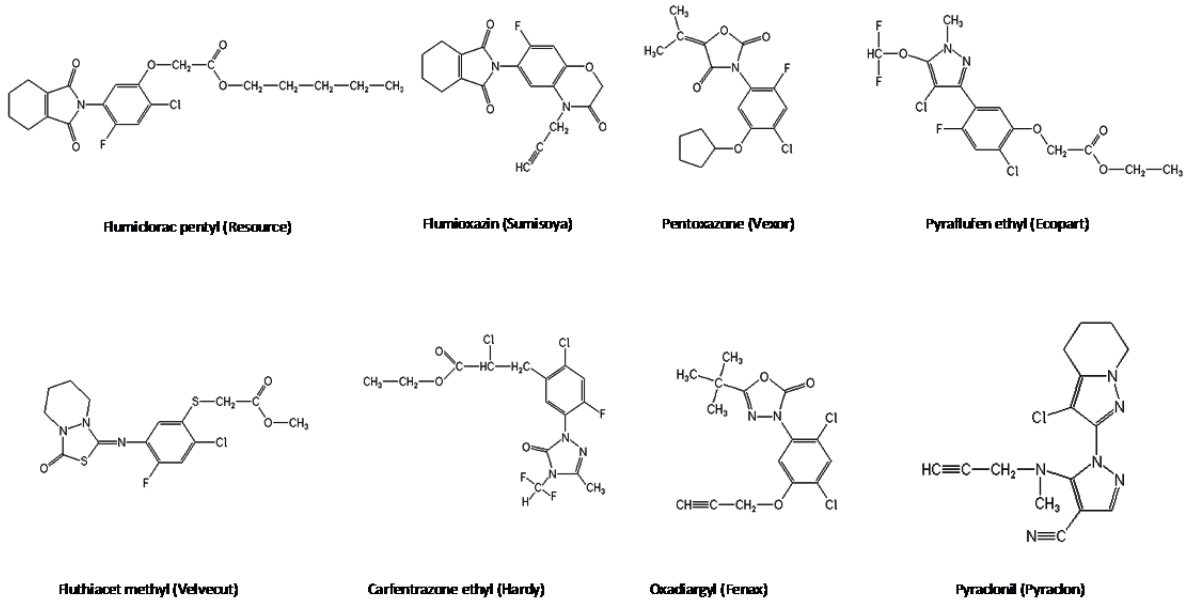

Fig. 3.65. PPO Herbicides

As discussed above, a number of high-performance herbicides have emerged since 1990. In terms of mode of action, there has been much research and development on ALS inhibitors, VLCFAE inhibitors, 4-HPPD inhibitors and PPO inhibitors. However, there also have been two significant issues. One is the issue of reduced effectiveness due to a build-up of resistance, as seen with the ALS inhibitors. The other issue is that of Roundup tolerance in upland crops such as soybeans. Herbicides are no longer thought to have far less problems with resistance than insecticides or fungicides and no longer have a long lifespan. While continuous development of new herbicides with new effects is the most-cited way to solve this, there needs to be a better way of preventing the build-up of resistance, regardless of whether a new or existing product is used. While the emergence of genetically-modified crops such as Roundup-tolerant soybeans has made it possible to efficiently produce a stable yield, we are now seeing a backlash against the use of a single herbicide to solve all problems. Further research on herbicides is needed to solve this issue.

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4. New Pesticides Invented in Japan

This section discusses new Japanese pesticides that have become world-renowned products. We shall begin by outlining the current status of the Japanese pesticide register (as of June 2012). The figures below indicate the number of registered so-called organic compounds. Inorganic compounds, ordinary low-molecular-weight compounds, adjuvants, rodenticides, natural enemies and other biopesticides are excluded, as are the number of such pesticides developed by Japanese companies [(1), (2)].

Insecticides: 122 registered; 54 of Japanese origin (44.3%)
Fungicides: 98 registered; 43 of Japanese origin (43.9%)
Herbicides: 138 registered formulations; 51 of Japanese origin (44.0%)
Plant growth regulators: 25 registered formulations; 11 of Japanese origin (41.5%)
Total: 383 registered formulations; 159 of Japanese origin (41.5%)

Thus we see that over 40% of pesticides were made and developed in Japan. Mergers among major companies in the West have meant that overseas companies far outweigh Japanese companies in terms of scale; overseas research and development investments are also far greater. Nevertheless, the comparatively small-scale Japanese companies have demonstrated an ability to create pesticides more efficiently and have discovered a number of pesticides that have either become world-class products or proved to be of immense scientific value.

This section discusses the development history and significance of the more impacting of these pesticides and also examines why so many successful Japanese pesticides have emerged. It must be noted that there are many other Japanese pesticides that could not be mentioned here due to space constraints.

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4.1. The Invention of Fungicides MAS (Asozin) and Neoasozin (MAF), the First Pesticides Discovered in Japan

MAS (Asozin) and MAF (Neoasozin) are organic arsenic fungicides invented by Ihara Noyaku (later Kumiai Chemical Industry Co., Ltd.) for use on rice sheath blight and *Glomerella cingulata* (ripe rot) in grapes (Fig. 4.1).

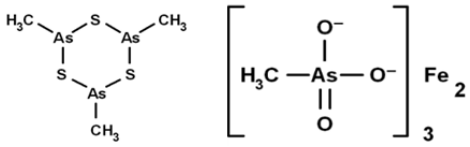

Fig. 4.1. MAS Asozin and MAF Neoasozin

Methyl arsine sulfide (MAS; Asozin) was first registered in 1959, while ferric methanearsonate (MAF; Neoasozin), which had less side effects on crops, was registered in 1961. These were very effective and MAF in particular was used in the development of a number of combination formulations. These were the first synthetic pesticides originally developed in Japan.

While early trans-planting, dense planting and heavy fertilizing were popular methods used in rice cultivation at the time, this resulted in repeated occurrences of sheath blight, one of the two worst rice diseases along with rice blast [(1)]. In 1968, this disease is said to have affected 2 million hectares of land. Accordingly, MAF became very popular due to its efficacy against rice sheath blight. Ihara Noyaku allowed other companies to sell this product and it reached an 80% market share in 1968, with 300 tons of active ingredients and 40,000 tons of formulated product sold [(2)].

Later, these figures dropped as other subsequent fungicides appeared, such as the polyoxins and Validamycin. Registration for MAF finally lapsed in 1998 and its role in the industry came to a close. Let us now outline the history of its development.

Ihara Noyaku was a pesticide manufacturer established in 1949 out of what had been a citrus growers' association in Shizuoka that had started making machine oil and lime sulfur in the late 1920s. Having had experience making parathion and malathion formulations and working on research and development, the company was keen to develop its own products and break into the industry as an active ingredient manufacturer (Note 1). In 1953, it sent two researchers to the Tokyo Institute of Technology and started investigating synthetic pesticides in earnest. Focusing on arsenic, in the same group, 5, as same as phosphorus,

these researchers discovered its fungicidal properties and successfully developed MAS. In 1959, the company put a synthesis plant into operation and started its journey as a fully-fledged active ingredient manufacturer.

Originally a formulation manufacturer, Ihara Noyaku began focusing on research and development soon after the war, when organic pesticides were brought in from overseas. In 1959, it went one step further, establishing an integrated research and development institute dealing with chemistry, entomology, formulations, plant pathology and toxicology, with all systems in place as a fully-fledged agrochemical company (Fig. 4.2). Its serious research and development focus – an executive decision by management – was exceptional for the times, but this laid the foundation for its later development of a number of major proprietary pesticides such as IBP and Benthiocarb.

Fig. 4.2. Ihara Integrated Research and Development Institute, completed in 1959 [(3)]

The invention of Asozin won the company the 7th Okochi Memorial Grand Technology Prize (1960) [(4)] and the 3rd Synthetic Organic Chemistry Award (Technology) (1963) [(5)]. It was the first time that either prize had been awarded to anyone in the pesticide industry, showing the significance of this invention that became the forerunner of Japanese pesticides.

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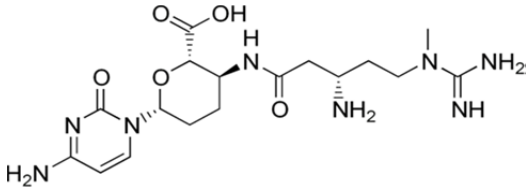
(Note 1) Active ingredient manufacturers are companies that exclusively make and sell technical products (active ingredients as industrial chemical products). By contrast, formulation manufacturers are companies that process technical products into formulations (pesticide products) such as wettable powders or emulsifiable concentrates. Some technical product manufacturers also make and sell their own formulations.

4.2. The Discovery of Blasticidin S (Bla-S), the World's First Agricultural Antibiotic and the Subsequent Appearance of Kasugamycin (Kasmin)

Blasticidin S is an antibiotic produced by *Streptomyces glyseochromogenes* that is effective against filamentous fungi such as rice blast. Discovered and developed in Japan, it is the world's first agricultural antibiotic. Lauryl sulfate was registered on the pesticide register in 1961, while benzylamino benzenesulfonate, with fewer side effects on crops, was registered the following year, both for use on rice blast (Fig. 4.3).



Blasticidin S (Bla-S)

Fig. 4.3 Blasticidin S (Bla-S)

While organomercury fungicides had been used to treat rice blast, these were largely replaced by Blasticidin S. Although its registration eventually lapsed in 2004 (Note 1) due to the emergence of some resistant fungi and the development of higher performance pesticides, this fungicide played a significant role in the Japanese pesticide industry [(1)].

As discussed in Section 3.4.2 (4), rice blast mercury dust was developed in 1953 and became very popular due to its superior efficacy. However, as social issues began to emerge, such as Minamata disease, Niigata Minamata disease and mercury pollution in industrial wastewater in the late 1950s and early 1960s, and as it also became evident that rice blast mercury dust left trace residues on rice, there was an increasing demand for highly effective, non-mercurial pesticides.

A group from the University of Tokyo led by Sumiki, Yonehara et al. joined with Fukunaga, Misato et al. from the Ministry of Agriculture and Forestry Agricultural Technology Research Institute started investigating the rice blast effects of

antibiotic-producing actinomycetes collected from soil from around Japan. This study began in 1950 and screened 10,000 samples. This resulted in the discovery of Blasticidin S (meaning "blast killer") in soil from Saikazaki in Wakayama. This was jointly developed by Toa Agricultural Chemical (now Kumiai Chemical), Nihon Nohyaku and Kaken Chemical (now Kaken Pharmaceutical) [2),(3)].

The mode of action is to inhibit protein biosynthesis. It works as a prevention and a cure due to its systemic properties [(4)].

However, as this formulation became more popular, there were issues with eye irritation while spraying dust formulation. Various additives were investigated to alleviate this problem with the eyes; researchers eventually discovered that adding calcium acetate reduced this problem dramatically. From 1974 onwards, this was no longer an issue.

Thus, Blasticidin S became an established non-mercurial rice blast fungicide, reaching an equivalent of 70 tons of technical product in shipments in 1964. It later dropped in usage as new rice blast fungicides were developed, but it is still worth special mention as the world's first agricultural antibiotic. It won the company the 11th Okochi Memorial Grand Production Prize in 1964 [(5)].

In 1965, four years after Blasticidin S went on the market, Hokko Chemical developed a new rice blast antibiotic, Kasugamycin (product name Kasmin) [(6),(7)]. Kasugamycin is an amino-sugar antibiotic produced by *Streptomyces kasugaensis* found in soil from Kasuga Shrine in Nara as a result of joint research by Hokko Chemical and Hamao Umezawa from the Institute of Microbial Chemistry (Fig. 4.4).

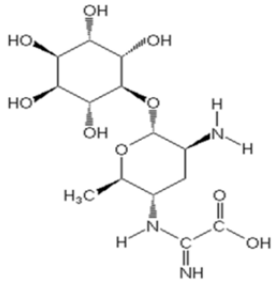


Fig. 4.4. Kasugamycin (Kasmin)

While Kasugamycin showed no direct effect on rice blast fungus in a petri dish experiment, it demonstrated powerful antimicrobial properties in acidic environments inside rice plants, with a distinctive curative effect. Like Blasticidin S, its mode of action works by inhibiting protein synthesis, inhibiting the formation of mRNA and tRNA ribosomes that trigger this synthesis. Kasugamycin is very safe to use, as it is very low-toxic to mammals and aquatic organisms. However, its effectiveness may decrease with continuous use, as resistance can build up. In 1971, the effectiveness of this fungicide was confirmed to have decreased in the Shonai region of Yamagata due to continuous use. Meanwhile, it has also been confirmed that its effectiveness returns after several years of not using it [(8)]. Accordingly, Kasugamycin is still being produced to the scale of 150 tons of active ingredients (2011), as it is highly effective against rice blast and very safe to use. There are more than 35 different formulations of it, as a standalone product or in combination formulations, and it holds an important place in the industry as one of the main rice blast treatments.

As mentioned above, organomercury compounds were replaced by Blasticidin S, followed by Kasugamycin. A succession of other effective rice blast formulations appeared, starting with PCP sodium salt (Chlon), developed in 1955, followed by PCP barium salt (Gobe), PCBA (Blastin), PCMN (Oryzon) and CBA (Minocol) between 1963 and 1968. However, these fungicides were not widely used and soon disappeared off the market for various reasons, including inconsistent effects, residues on paddy straw affecting later crops and toxicity to fish. Later, Japanese manufacturers developed better rice blast treatments, such as IBP (Kitazin), Isoprothiolane (Fuji One) and Probenazole (Oryzemate), as we shall discuss later.

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(Note 1) Lapsing of registration means the cancellation of the registration of a pesticide if the triennial re-registration

application has not been made due to product adjustment or economic reasons. Registration may also lapse if it has been revoked due to safety concerns or other issues. In such cases, measures are taken such as recalling the product or banning it from being used or sold.

4.3. The Emergence of Low-Toxic Organophosphate Insecticides (MEP, Fenitrothion) Sumithion

As mentioned in Section 3.4.2 (3), the appearance of organophosphate pesticides soon after the war, such as parathion and methyl parathion, was revolutionarily beneficial and made a huge contribution to increasing food production, a pressing need in post-war Japan. This section discusses the post-parathion era: the invention, development and spread of MEP (Sumithion), discovered by Sumitomo Chemical. MEP is the forerunner of the major international pesticides produced in Japan; 50 years after it was developed, it is still a dominant Japanese pesticide used throughout the world (Fig. 4.5).

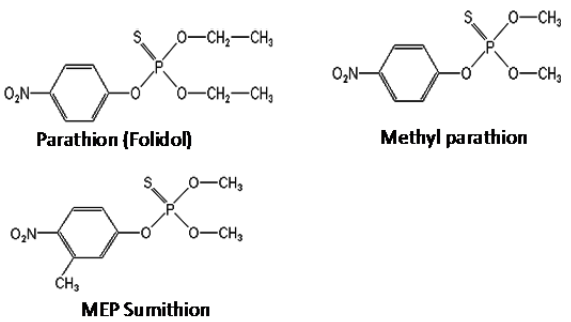


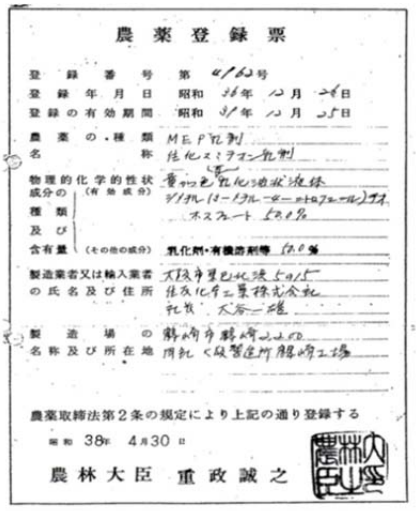
Fig. 4.5. Organophosphate Insecticides

G. Shrader of the German company Bayer invented parathion and methyl parathion in 1944. These were introduced to Japan in 1951 and became wildly popular due to their superior effectiveness, with imports starting the following year. Sumitomo Chemical initially imported these products from the American Cyanamid Company (ACC) and marketed them in Japan, but later decided to produce them domestically due to their outstanding performance. In 1953, Sumitomo obtained a technology license from Japanese patent-holders ACC and Bayer and began production.

While parathion is quite highly acutely toxic to mammals, with a median lethal dose in rats of 2-22mg/kg, it is highly effective against rice stem borers. Conversely, while other organophosphate compounds with lower toxicity to mammals (such as DEP and malathion) were later introduced to Japan, they were less effective against rice stem borers; consequently, parathion and methyl parathion held the monopoly.

Nishizawa et al. of Sumitomo Chemical held concerns about this toxicity to mammals from the outset and in 1956 set about exploring low-toxic organophosphate pesticides to replace parathion. This started out as a series of trial-and-error experiments by three or four researchers. Their method of evaluating insecticidal activity and mammalian toxicity at the initial exploration stage was unprecedented in the West [(1)]. These efforts paid off, meeting the initial target with MEP in 1959, the fourth year of research, and they immediately applied for a patent. As luck would have it, they later found out [(1)] that they had secured this patent only weeks before Bayer applied for the same patent [(2), (3)].

Two years later, with a good supply of valid data accumulated through practical development tests, MEP was registered as Pesticide No. 4962 on the Japanese pesticide register on 26 December 1961 and put on the market the following year (Fig. 4.6). While early sales were slow due to the popularity of parathion, it eventually became a popular insecticide due to its capacity to be used on fruit and vegetable plants as well as rice and also for its efficacy against sanitary pests such as mosquitoes and flies.


農 薬 登 録 票

農薬取締法第2条の規定により上記の通り登録する

農林大臣 重政誠之

MEP Emulsion Concentrate Registration Certificate (Sumithion Emulsion, Sumitomo Chemical)

Fig. 4.6. Registration Certificate for MEP Emulsion Concentrate (Sumithion Emulsion, Sumitomo Chemical)

Domestic production continued to increase, with more than 10,000 tons of technical product manufactured in 1999 and 6,000 tons of this being exported. As of 2010, more than 15 different standalone formulations on the pesticide register contained MEP, with a shipment value of ¥2.97 billion. Another 49 combination formulations also contain MEP; if we calculate the MEP proportion of these shipments, the total comes to ¥5.4 billion. It has a wide range of applications, including rice, wheat,

beans, deciduous fruit trees, citrus, vegetables, tea, ornamental flower, household disease control, forestry and termites.

Sumitomo pushed into the overseas market from the beginning; in the early 1960s, it started exporting to Kenya, Korea, Taiwan and other countries. Long-term efforts to promote the product have paid off, with MEP now being used in 60 countries around the world on crops such as rice, wheat and maize, as well as fruit trees, vegetables, coffee, cacao, rapeseed, cotton, grain storage pest control and forestry. It is also used against malaria-bearing mosquitoes, locust outbreaks in desert regions and termites. In recognition of the contribution this product has made in Japan and overseas, the company was awarded the 9th Okochi Memorial Grand Technology Prize in 1962 [4].

As shall be discussed below, the insecticidal activity of MEP is equal to or greater than that of parathion. It is also far less toxic to mammals and therefore around 90 times safer than parathion. In terms of toxicity classification, it is treated as an ordinary substance [5], [6].

	LD_{50} in rice stem borers (μg/larva) [5]	LD_{50} in mice (mg/kg) [6]	LD_{50} in rats (mg/kg) [1]
MEP	0.092	870	800
Parathion	0.223	9.8	2-22
Methyl parathion		26.0	20-62

Thus, MEP has very selective toxicity. The reason for this has been debated to be one of the following: (1) the differences in acetylcholinesterase (AChE) between mammals and insects at the point of action; (2) the differences in absorption and translocation to the point of action; (3) the substrate specificity of the counteracting enzymes. However, it is still not clearly known why there is such a difference in toxicity when the only difference is whether or not there is a methyl group at meta position in the benzene ring; this has come to be known as magic methyl [7], [8].

Let us now discuss the manufacture of MEP. While it can be manufactured by condensing the intermediates 0,0-dimethyl-chlorthiophosphate (DMCT) and 4-nitrometacresol (NMC), Sumitomo developed a efficient chemical process for these key intermediates and established a consistent production system [1]. The company now uses this system to produce 10,000 tons per year, making pricing competitive enough to dominate the world market (Fig. 4.7).

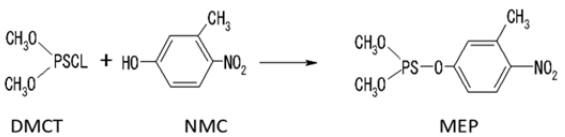


Fig. 4.7. Method of Manufacturing MEP

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4.4. Gibberellins: Miracle Plant Hormones

We shall now discuss the history of the technology development behind the seedless grapes such as Delaware that are commonly eaten these days. Let us disclose the secret to seedless grapes. It has been more than 50 years since seedless grapes appeared on the world market in 1960 and it has now become commonplace to have grapes without seeds. The core of this technology is a plant hormone called gibberellin (Fig. 4.8). This was discovered in Japan, where a Japanese scientist isolated and identified its structure, which was then put to practical use by Kyowa Hakko. This is a prime example of Japan's world-class science and technology. For details on gibberellin research, see the cited work [1].

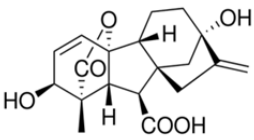


Fig. 4.8. Gibberellin A_3

4.4.1. From Discovery to Structure Determination and Synthesis

The discovery of gibberellin can be traced back to 1898. Shotaro Hori from the Agricultural Experiment Station of the Ministry of Agriculture discovered that *bakanae* – a disease that makes rice seedlings etiolated and the stem elongated – was caused by a filamentous fungus and published his exposition on the existence of *bakanae* (Fig. 4.9) [(2)]. This was the first paper written on *bakanae*.

Fig. 4.9. [(2)] Paper from 1898

Bakanae was also rampant in Taiwan at the time. Eiichi Kurosawa, actively researching this disease at the Agricultural Experiment Station of the Government-General of Taiwan, noted that affected seedlings would grow remarkably long and discovered in 1926 that a kind of "toxin" produced by the *bakanae* fungus significantly promoted growth in the rice seedlings [(3)]. This was an age in which there was no concept of "microbes producing biologically active substances," so demonstrating this for the first time was a major achievement in itself. A number of researchers were inspired by Kurosawa's work and started studying the growth promoting substance produced by the *bakanae* fungus.

In 1935, Teijiro Yabuta of Tokyo Imperial University (Fig. 4.10) isolated the active ingredient from a *bakanae* fungus culture medium and named it gibberellin after the scientific name of the fungus, *Gibberella fujikuroi*. This was the first use of the name gibberellin (at the time, it was pronounced according to the German reading of the word) [(4)].

Fig. 4.10. Prof. Teijiro Yabuta of Tokyo Imperial University [(1)]

Three years later, Yabuta and Sumiki successfully crystallized Gibberellin A and B [(5)]. However, their work was interrupted for a long period of time as Japan went to war. This research was attracting attention overseas as well. While research had drawn to a halt in Japan, it was carried on in the United Kingdom and the United States and gained a lot of ground, particularly with mass culture techniques for *Gibberella fujikuroi*.

Research in Japan eventually revitalized after the war and a study by Takahashi in 1955 showed that the active substance Gibberellin A was a mixture of three substances and named them GA_1, GA_2 and GA_3, respectively [(6)]. British researcher Cross was the first to identify the chemical structure of Gibberellin A_3 in 1959. While total synthesis of the compound was very difficult due to the complex chemical structure, Mori achieved total synthesis of GA_2, GA_4, GA_9 and GA_{10} in 1968 (using bridging) [(7)]. Corey achieved total synthesis of GA_3, the main component of gibberellin [(8),(9)].

Around 136 varieties of gibberellins have been found in plants, molds and bacteria; these have all been numbered in order of their discovery [(10)]. The type currently used as a pesticide is the most popular: GA_3.

Industrial production of gibberellin started overseas; by 1950, US company Merck and UK company ICA had already established the technology for mass culture. Kyowa Hakko started researching the production and practical application of gibberellin in 1956; after validating its results, it licensed the production technology from Merck and started marketing it as "agricultural material." Fig. 4.11 shows an early sample production tank.

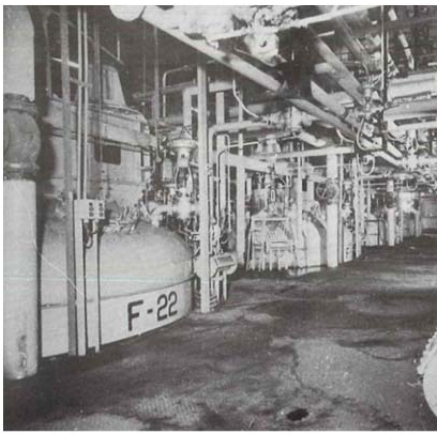


Fig. 4.11. Deep Stirrer Culture Tank [(11)]

It was officially registered as a "plant growth regulator" in 1964 to comply with the 1963 amendment of the Agricultural Chemicals Control Act. Its registration is still current.

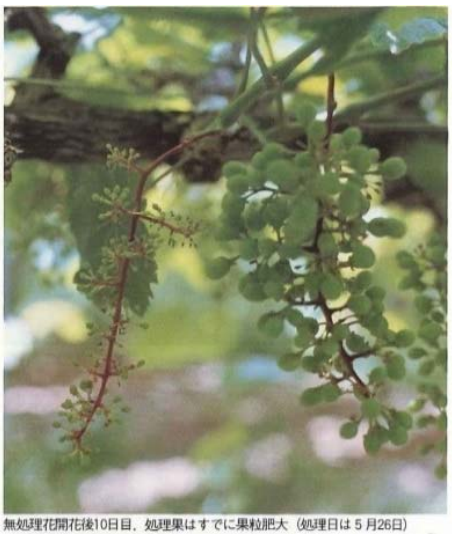
Thus, gibberellin has the longest history of all plant growth regulators. While almost 60 years have passed

since it was registered as a plant growth regulator, its registration number 6001 is the oldest one still on the register and it still has the highest number of shipments of all plant growth regulators. There are six different formulations of gibberellin on the market according to the application, as a solution in water, liquid formulations, pastes, etc.) sold by Kyowa Hakko Bio, Meiji Seika and Sumitomo Chemical. While order volumes peaked at ¥2.4 billion in 1994, this dropped due to a decline in grape production, its primary use. Recent figures have held steady at just over ¥1.1 billion [11].

4.4.2. The Effects of Gibberellin and its Use as a Pesticide

The physiological actions of gibberellin are wide-ranging, as shown below. A number of studies have been carried out in this area, as the effects differ significantly according to the amount used, the crop and variety targeted and the stage of growth. Some examples are given below.

(1) Seedless Grapes: Promoting Parthenocarpy (Note 1) and Later Fruit Enlarging Effect (Fig. 4.12)
Grapes are treated (poured on each bunch with a cup) with a 100ppm dilution of gibberellin 14 days before full bloom to promote parthenocarpy, followed by another treatment with a 100ppm dilution 10 days after full bloom to enlarge the fruit. This enables the grapes to grow without seeds and also allows them to be harvested early. The amount used and time of application varies according to the variety of grape.



Untreated fruit on the 10th day after full bloom; the treated fruit is already enlarged (treated on 26 May) (1)

Fig. 4.12. Seedless Grapes (untreated at left, treated at right) [1]

(2) Citrus Trees: Suppressing Budding, Preventing Fruit Abscission, etc.
Spraying citrus trees with a 0.5-50ppm dilution of gibberellin can suppress budding, prevent fruit from dropping and help sudachi and other fruit to stay green. It is also used on persimmons to prevent fruit dropping and on pears to promote ripening.

(3) Vegetables: Promoting Germination and Growth, Increasing Produce Yield
Gibberellin can promote germination and growth in vegetables and enlarge the yielded produce. For instance, it can increase the fruit yield and promote ripening and runner growth in strawberries. Fig. 4.13 shows an example of promoted growth in a cabbage plant.


American researchers are amazed at the growth of a cabbage plant treated with gibberellin.

Fig. 4.13. Cabbage Growth Promotion [1]

(4) Flowering Plants: Promoting Budding, Growth and Blooming
Gibberellin promotes budding and growth in flowering plants such as cyclamen and chrysanthemum, as well as breaking dormancy.

(5) Cedar, Cypress
Promoting floral differentiation for timber trees and improves seedling productivity.

As mentioned above, research on gibberellin began in the 19th century and Japanese technological developments have led the world in discovering it, determining its structure, chemically synthesizing it and applying it as a pesticide. Seedless grapes, which are now commonplace, are the visible result of the technological developments achieved by the researchers of years long past.

Researchers have recently made progress on its mode of action, while recent X-ray analyses have identified the three-dimensional structure of the receptor protein

complexes that bind to gibberellin. Future progress on this technology will hopefully enable the molecular design of new compounds with gibberellin-like activity and also in future enable the production of new plants by controlling the responses of this plant hormone [12].

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(12) Saka et al. *Nihon no Nōyaku Kaihatsu [Japanese Pesticide Development]*, 2003, p. 365.
(13) K. Murase, Y. Hirano, T. Sun, and T. Hakoshima, Nature 456, (7221) p520 (2008)

(Note 1) Parthenocarpy is the production of fruit without seeds by developing the ovaries of flowering plants without pollination or fertilization. It is also called parthenogenesis and occurs naturally in some plants such as bananas and pineapples.

4.5. Post-PCP Paddy rice Herbicide CNP (MO), Followed by Chlomethoxynil

CNP (Chlornitrofen, MO) is a diphenyl ether paddy rice barnyard grass herbicide invented by Mitsui Chemicals and was registered in 1965. As mentioned in Section 3.4.2 (5), the emergence of the PCP granule around 1960 meant a means of soil treatment against barnyard grass before and after transplanting rice. PCP was a ground-breaking formulation that provided relief from the hard task of hand weeding that had long plagued farmers. However, a lower-toxic formulation was in great demand, as PCP was highly toxic to fish. Although Mitsui Chemicals was the leading manufacturer of PCP, it promptly set about exploring other less ichthyotoxic herbicides, focusing on diphenyl ether compounds, and came up with CNP, a low-ichthyotoxic replacement for PCP (Fig. 4.14) [1].

Rohm and Haas had developed and registered a similar compound, NIP (Nitrofen) (Fig. 4.15), slightly earlier in 1963, so CNP had to settle for second place. However, CNP proved to be a safe, long-lasting barnyard grass killer with little side effects on rice, even in young seedlings for transplanting and it soon outstripped its predecessor NIP in popularity. While rice field acreage peaked in 1969 at 3.17 million hectares, CNP was used on 1 million hectares the following year. By 1974, it had become a large-scale commodity, being used on more than 2 million hectares [2], [3]. In 1968, Mitsui Chemicals won the 15th Okochi Memorial Grand Technology Prize for the "development and commercialization of rice herbicide MO-338."

Another barnyard grass herbicide in the same category is Chlomethoxynil (X-52) (Fig. 4.16), registered in 1973. Chlomethoxynil was invented by Nihon Nohyaku and jointly developed with Ishihara Sangyo. Despite its late start, it had more consistent efficacy and by 1978 had become a major product to rival CNP, used on 600,000 hectares [4].

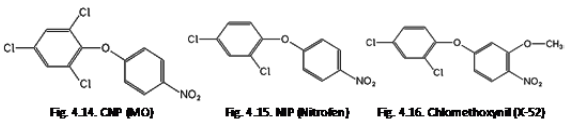

Fig. 4.14 CNP(MO) Fig. 4.15 NIP Fig. 4.16 Chlomethoxynil(X-52)

These diphenyl ether compounds came to be called light-dependent herbicides, as they required light in order to be effective. However, later research showed that this chemical structure works by inhibiting protoporphyrinogen IX oxidase in the chlorophyll biosynthesis process, achieving a herbicide effect as the built-up protoporphyrinogen IX photosynthesizes, releasing reactive oxygen, which destroys cellular membranes [5], [6], [7].

Usage of diphenyl ether herbicides decreased from the late 1970s onwards with the appearance of higher-performing rival herbicides such as Benthiocarb and their role eventually came to an end. Registration for NIP lapsed in 1982, followed by CNP in 1996 and Chlomethoxynil in 1997. In the case of CNP, the cancellation of registration was triggered by trace amounts of dioxins in it. There was also some question

as to whether an outbreak of gall bladder cancer in Niigata was caused by trace residues of CNP in tap water. While there was no clear causal relationship epidemiologically, it was difficult to prove its "safety" to counteract these "misgivings," so its registration had to be withdrawn. In any case, CNP demonstrated unprecedented superiority as an initial soil treatment agent for rice cultivation and made a significant contribution to rice production.

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4.6. Cartap (Padan), the Only Insecticide Derived from Bioactive Substances Produced by Animals

Cartap (Padan) (Fig. 4.17) is a uniquely-structure insecticide invented by Takeda Pharmaceutical (pesticide division now taken over by Sumitomo Chemical) and registered in 1967. Highly effective against a wide range of pest insects, including Lepidopterae such as rice stem borers, Hemipterae such as aphids, and thrips, it is widely used in Japan and across the world.

The invention of this compound was modeled on nereistoxin (Fig. 4.18), a natural toxin with a sulfur-containing dithiolane structure, found in eunicids, which are used as fishing bait. The method of discovering new pesticides by modeling naturally bioactive substances is currently widely used, with a number of examples including antibiotics produced by actinomycetes and synthetic pyrethroids, modeled on pyrethrins found in plants (pyrethrum). However, this nereistoxin-related compound is the only pesticide to be derived from bioactive ingredients produced by animals. Another very interesting point is that the entire research and development process, from the discovery of nereistoxin to its synthesis and the invention of Cartap, has been the result of Japanese work.

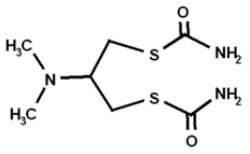

Fig. 4.17. Cartap (Padan)

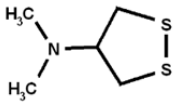

Fig. 4.18. Nereistoxin

The discovery of nereistoxin dates back to the 1920s, when it was observed that flies coming into contact with dead eunicids (a family of polychaetes in the annelid phylum) used for fishing bait would become paralyzed and die. Having examined cases of headaches, vomiting and breathing difficulties among people dealing with eucinids, in 1922 Dr. Masahiro Nitta, a medical doctor, started researching if this was caused by a toxin. In 1930, he named this toxic ingredient nereistoxin. In 1934, he isolated it, hypothesized on its chemical structure and confirmed its toxicity to mammals [(1)]. Completely independent from Nitta's work, another researcher named Inagawa isolated nereistoxin and published its molecular formula as $C_5H_{11}NS_2$ [(2)]. There was no further progress on this area of research until Hashimoto and Okaichi of the University of Tokyo confirmed its molecular structure to be 4-N,N-dimethylamino-1,2-dithiolane in 1962 [(3)].

Sakai from Takeda Pharmaceutical embarked on a joint research project with Hashimoto of the University of Tokyo in 1960, focusing on the unique chemical structure and biological activity of nereistoxin. This study confirmed the efficacy of neriestoxin against rice stem borers, a major pest [(4)]. They also achieved total synthesis of it, which enabled them to define its chemical structure as well as to produce large quantities of it for research samples, which sped up the research [(5), (6), (7)]. Uneme provides a detailed review of the structure-activity relationship of related compounds [(8)]. Of these related compounds, 1,3-Bis(carbamoylthio)-2-(N,N-dimethylamino) propane hydrochloride (product name Cartap) was selected for production and went on the market in 1967. Cartap had an unprecedented chemical structure for an insecticide; its distinguishing characteristics are outlined below.

(1) It has the same mode of action as nereistoxin. Studies have shown that when it is absorbed into the body of the insect, it kills the insect by blocking the cholinergic synaptic acetylcholine receptors, which govern stimulus transmission in the central nervous system [(9), (10)]. Since this effect differs from existing compounds that work on the nervous system, such as organophosphates, carbamates and pyrethroids, there is little chance of cross-resistance. Further, since the actual effect activates once the nereistoxin is inside the body of the insect, Cartap is considered to work as a so-called pro-drug (Note 1).

(2) It is highly effective against a wide range of pest insects, such as rice stem borers and other Lepidopterae, leafhoppers, aphids and other Hemipterae, and rice water weevil and other beetles. It is suitable for fruit and vegetable plants as well as rice.

(3) It is systemic and therefore effective throughout the entire plant as it is absorbed through the roots or leaves. This allows it to be used in rice nursery boxes.

As mentioned above, the invention of Cartap was the result of a long process involving the isolation and structure determination of eunicid toxins, which started in the 1920s. It has been the result of Japanese academic research and the sharp minds of company researchers, as well as the later high-level research and development capabilities in examining its biological effect and achieving total synthesis of it. While it has been 45 years since Cartap first went on the market, it is still a major product worth almost ¥2 billion in domestic shipments due to its superior efficacy. It has also been actively marketed overseas, with 3,800 of the 4,500 tons produced in 1999 being exported to 40 countries around the world, to be used on a wide range of plants, including rice, vegetables and grain crops [8]. This won the company the Okochi Memorial Grand Technology Prize in 1971 for the "invention and commercialization of rice stem borer formulation."

Once Cartap went on the market, other companies started developing nereistoxin analogue pesticides. One of these is Thiocyclam (Evisect), developed by Sandoz (now Syngenta) (Fig. 4.19) and registered in 1981 by Sankyo and Nippon Kayaku. Another is low-mammalian-toxic Bensultap (Ruban), developed by Takeda Pharmaceutical in 1986 (Fig. 4.20).

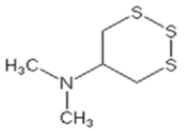

Fig. 4.19. Thiocyclam (Evisect)

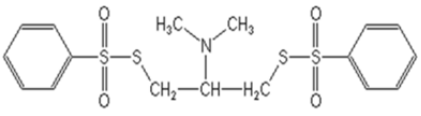

Fig. 4.20. Bensultap (Ruban)

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(Note 1) Pro-drugs are pharmaceutical products that have in-vivo drug metabolism mechanisms; while the compounds themselves are not pharmaceutically active, they activate once they metabolize. This is a medical term also used for pesticides. They are also called pro-pesticides.

4.7. The Emergence of Non-Mercurial Organic Rice Blast Fungicides (EBP, Kitazin and IBP, Kitazin P)

EBP (Kitazin) (Fig. 4.21) and IBP (Kitazin P) (Fig. 4.22) are organophosphate rice blast fungicides invented by Ihara Chemical (now Kumiai Chemical). While EBP went on the market first in 1965, it was superseded by the more consistent, less odorous IBP (Iprobenfos, Kitazin P), which hit the market two years later in 1967.

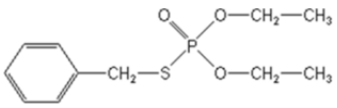

Fig. 4.21. EBP (Kitazin)

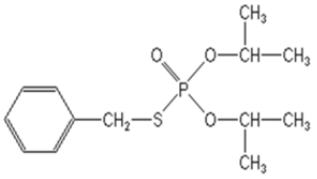

Fig. 4.22. IBP (Kitazin P)

While Blasticidn S appeared in 1962 and Kasugamycin in 1965 in response to the demand for non-mercurial rice blast treatments discussed in Section 5.2, EBP and IBP were the world's first organophosphate fungicides.

The focus of research at Ihara Chemical had been to explore new pesticide possibilities; as part of this, the company had also been researching organophosphate compounds. While the initial aim was to discover an

insecticide, the fungicide research group found that organophosphates were effective against rice blast, resulting in EBP and IBP. Another cause for success was the use of the bio-assay method of examining rice inoculated with rice blast.

IBP is highly systemic and is absorbed by the roots or leaves and is translocated throughout the entire rice plant. Its effects are long-lasting and highly curative. Developers produced a granule formulation to take advantage of these strengths, which in turn has popularized a new method of application by applying the granules to the surface of the water in the rice field. While existing formulations were commonly sprayed directly onto the plants in dust or liquid form, the method of sprinkling granules onto the water has the advantage of only needing to be applied once.

The mode of action of IBP is known to have a fungicidal effect by inhibiting the lipogenesis of phospholipids such as the phosphatidylcholines that make up the biomembrane of the fungus [1].

IBP has also been confirmed to be effective against stem rot and sheath blight as well as rice blast and to turn lower internodes into dwarf plants. It reduces lodging, which then produces the secondary effect of higher yields [2],[3].

Thus, IBP appeared at a time when non-mercurials were in demand and played a major role as a key fungicide against rice blast. Shipments in 1977 totaled 27,000 tons of standalone formulations and 23,000 tons of combination formulations, while production of technical product exceeded 4,000 tons [4]. While these figures later dropped due to the emergence of more effective fungicides, it is still selling to the tune of hundreds of millions. These results won the company the Okochi Memorial Grand Technology Prize in 1967 and the Synthetic Organic Chemistry Award in 1970, definite proof of the superiority of this invention.

Let us now discuss the industrial manufacture of IBP. For practical application, IBP requires a concentration of around 500ppm, quite a substantial amount compared to the 30ppm required for the existing organomercury compounds and the 10-20ppm for Blasticidin S. To make the product more competitive, production of the technical product had to cost as little as possible. Following a manufacturing feasibility study, the company decided to take the efficient route of synthesizing IBP by first making diisopropyl phosphite from phosphorus trichloride and isopropyl alcohol, then turning this into diisopropyl phosphorothiolate through sulfurization in an alkali environment, then reacting this with benzyl chloride [4].

$PCl_3 + i\text{-}C_3H_7OH \rightarrow (i\text{-}C_3H_7O)_2POH$

$(i\text{-}C_3H_7O)_2POH + S \rightarrow (i\text{-}C_3H_7O)_2POSNa$

$(i\text{-}C_3H_7O)_2POSNa + ClCH_2Ph \rightarrow IBP$

Other organophosphate rice blast fungicides like IBP have been developed by a number of other companies. While EDDP (Hinozan), developed by Bayer, is still in use, ESBP (Inezin) and BEBP (Conen) had their registrations lapse due to issues such as residual odor in rice (Fig. 4.23), (Fig. 4.24), (Fig. 4.25).

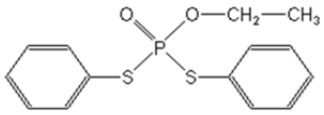

Fig. 4.23. EDDP (Hinozan)

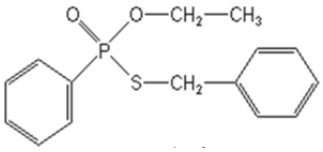

Fig. 4.24. ESBP (Inezin)

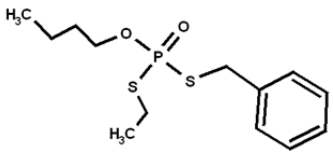

Fig. 4.25. BEBP (Conen)

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4.8. The Emergence of Benthiocarb (Saturn), the Super-Herbicide for Rice

Benthiocarb (Saturn) (Fig. 4.26) is a pre-, and early-post application rice herbicide invented by Kumiai Chemical and registered in 1969. While the appearance of CNP as discussed in Section 4.5 enabled near-total control over major rice weed barnyard grass as well as

broadleaf weeds, there was a demand for an even better pesticide that would target needle spikerush and other perennial weeds on which CNP had insufficient effect. Since Benthiocarb was equally effective against annual weeds and perennial weeds alike, it came to dominate the market as a super-herbicide. The product name Saturn comes from the name of the Roman god of agriculture.

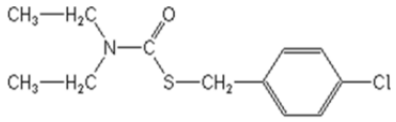

Fig. 4.26. Benthiocarb (Saturn)

Kumiai Chemical started exploratory research on new rice herbicides in three directions: an easy-to-use treatment with a broad time window for application; efficacy against not only annual weeds such as barnyard grass, but also perennial weeds without causing any side effects in rice; and low toxicity for mammals and aquatic organisms [(1)]. As Kumiai Chemical had developed the rice blast fungicide IBP, the company could overlap this research with particular focus on S-benzyl-thiolcarbamic acid ester-related compounds, to which it could apply the same technology. The result was Benthiocarb. This is a good example of extremely well-executed collaboration between biological researchers, who made improvements to the biological assay, and synthesis researchers, who performed the structural development.

Benthiocarb is thought to act mainly as a leaf sheath growth inhibitor at the germination stage by inhibiting protein and lipid biosynthesis, but the details are not clearly known [(2), (3), (4)].

Benthiocarb is intergenerically selective between rice and barnyard grass. While it is safe on transplanted rice at realistic concentrations, it is effective against barnyard grass until the 2-leaf stage. It is also highly effective against *Cyperaceae*, *Monocholia vaginalis* and needle spikerush. It has been marketed as a standalone product and also developed into several combination formulations to give it a wider window of application as well as better efficacy against a wider range of weeds. Several of these formulations are given below. Using this product in combination compound formulations has given it a wider range of uses, not only as an initial soil treatment agent around planting time, but also as a foliar and soil treatment agent at the later leaf stage.

Saturn S granules (Benthiocard + Simetryn)
Saturn M granules (Benthiocard + CNP)
Kumi-Lead SM granules (Benthiocarb + Simetryn + MCPB)
Kumi-Shot SM1K granules (Benthiocarb + Mefenacet + Bensulfuron methyl + MCPB)
Wolf Ace 1K51 granules (Benthiocarb + Mefenacet + Bensulfuron methyl)

As discussed above, Benthiocarb is a key sequential treatment herbicide in the paddy rice production. Its popularity spread wildly from 1970 onwards; by 1974, it had become a super-herbicide used on 1.7 million hectares, or 65% of Japan's rice lands [(5)]. These figures later dropped with the emergence of a number of other new, high-performance herbicides (such as Butachlor, Pretilachlor and Mefenacet). Later, another onset of new, high-performance pesticides appeared from 1993 onwards (such as Pyributicarb, Cafenstrole, Thenylchlor and Oxaziclomefone) and the ensuing competition spelled the end of Benthiocarb's role in Japan.

However, it was actively promoted overseas for rice and other crops and most of its present use takes place overseas, mainly in the United States, Russia, Korea, Cuba, Egypt, Taiwan and Thailand. It continued to grow as a major world product, with over 90,000 tons being exported across 55 countries until 1997. While the amount of exports has dropped since peaking at 9,000 tons in 1978, it is a long-lived product, with more than 2,000 tons still being exported in 2008 [(6)].

Consequently, this product has won the company a number of awards, including the 19th Okochi Memorial Grand Technology Prize in 1972 for "development and commercialization of the new herbicide Saturn," the 21st Chemical Society of Japan Award for Technical Development in 1972 for "development of the herbicide Saturn and establishing a manufacturing system for it" and the 15th Synthetic Organic Chemistry Award in 1973 for "development of the new herbicide Saturn." This shows how outstanding this invention is.

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4.9. Thiophanate (Topsin) and Thiophanate-Methyl (Topsin M),

World-Class, Broad-Range Fungicides

Thiophanate (Topsin) (Fig. 4.27) and Thiophanate-methyl (Topsin M) (Fig. 4.28) are thioallophanate structured fungicides invented by Nippon Soda and effective against a broad range of diseases. Ethyl ester Thiophanate (Topsin) was the first of the two to be registered, in 1969, while the more effective methyl ester Thiophanate-methyl (Topsin M) was registered two years later in 1971.

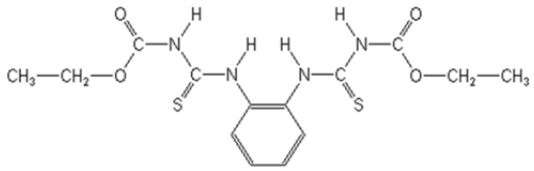

Fig. 4.27. Thiophanate (Topsin)

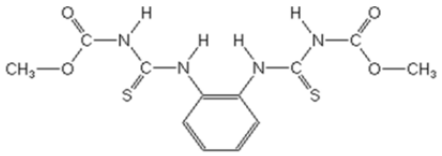

Fig. 4.28. Thiophanate-Methyl (Topsin M)

Nippon Soda started working on a new fungicide around 1965 and came up with Thiophanate and Thiophanate-methyl, both with completely unprecedented chemical structures, after researching the structure of thioallophanic acid, an organic sulfur compound. Thiophanate was gradually replaced by Thiophanate-methyl; only the latter is in use today.

Thiophanate-methyl is fast-acting and long-lasting against a broad range of diseases at low concentrations. When applied to leaves, it is systemic throughout the entire plant, passing through the cuticle and translocating within the plant, acting as a prevention and cure and stopping the spread of any infection. It is safe to use and has no side effects on crops.

This fungicide is a powerful inhibitor at all stages in the life cycle of pathogenic fungi except spore germination [(1), (2)]. This means it can be used against diseases on a broad range of plants, including fruit trees and vines, such as citrus, apples, pears and grapes, vegetables, root crops, wheat and other grains, beans, tea, specialty crops such as tobacco, and ornamental plants [(3), (4)]. Around 1000 tons were sold in 1975. While this figure later dropped, it has stood the test of time, still being widely used as a key pesticide in 2008, registered for use on 86 types of crops and 186 diseases. An overseas market for this product also developed very early on for use on grains, fruit and vegetables; it has become a world-class product registered in 80 countries around the world [(5)].

The mode of action of Thiophanate-methyl is mainly achieved by inhibiting karyokinesis in cells [(1)]. As Nippon Soda was developing Thiophanate-methyl, DuPont was independently working on Benomyl (Benlate), a benzimidazole compound, which it marketed in Japan in 1971, and Carbendazol (Sanmate), which followed two years later. Later research showed that Thiophanate-methyl metabolizes into Carbendazol, a Benomyl metabolite, in vivo [(1), (5)] (Fig. 4.29). This is a good example of a pro-drug. It is very interesting that different formulations developed by different organizations at the same time happen to metabolize into the same compound. For this reason, Thiophanate-methyl is also classified as a benzimidazole compound. However, there is a point of issue in that these fungicides have the same mode of action, which could lead to a build-up of resistance with continued use. In fact, resistance has already been observed in grey mold, black spot and powdery mildew.

As discussed above, Thiophanate-methyl was ground-breaking at the time, as it worked as a prevention and a cure. This turned it into a world-class product, used on a wide range of diseases on vegetables, fruit and other plants. While the later emergence of other high-performance pesticides has meant a decline in its usage, it is still a major world-class pesticide. This achievement won the company the International Plant Protection Award from the International Plant Protection Convention in 1970, the Okochi Memorial Prize in 1975 for "research and development of the fungicide Thiophanate (Topsin)" and the Prime Minister's Invention Award, one of the National Commendations for Invention, in 1976.

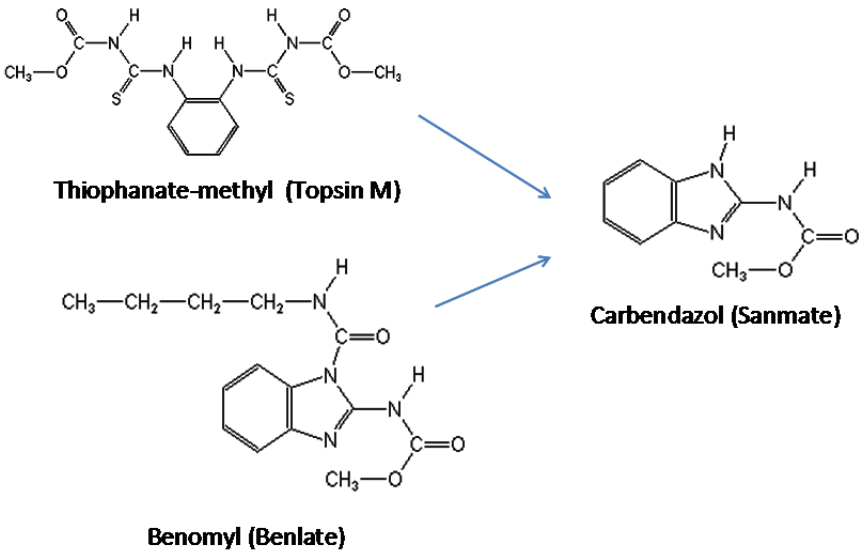

Fig. 4.29. Active Substance of Thiophanate-Methyl and Benomyl

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4.10. The Invention of Isoprothiolane (Fuji One), a Rice Blast Fungicide with a New Organosulfur Structure and Diverse Secondary Effects

Isoprothiolane (Fuji One) (Fig. 4.30) is a rice blast fungicide with a new chemical structure invented and developed by Nihon Nohyaku. Registered in 1974, this fungicide is widely popular due to its consistent efficacy.

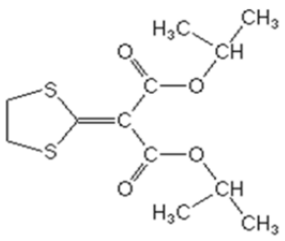

Fig. 4.30. Isoprothiolane (Fuji One)

Treatments for rice blast, a major rice disease, were in great demand in the late 1960s and early 1970s. Since there was such a large market for it, every pesticide manufacturer devoted its attention to researching and developing its own fungicides. Nihon Nohyaku developed the organochlorine rice blast treatment PCMN (Oryzon) and put it on the market in 1966. However, it was later found that residues of this formulation formed a degradation product in rice straw, which caused unwanted side effects in any secondary fruit and vegetable crops on which this straw was used. It had to be withdrawn from sale, creating a demand for a new rice blast fungicide. Nihon Nohyaku had started exploratory research on new rice blast formulations in the early 1960s, focusing on organosulfur compounds rather than organophosphates or organochlorine. While there were already organosulfur compounds on the market in the form of dithiocarbamate ester compounds sold as fruit and vegetable fungicides, they had little effect on rice diseases. The company developed this further, resulting in Isoprothiolane, with a ketene dithioacetal structure previously unseen in a fungicide, in 1968 [(1)]. For details on the optimization of the chemical structure during this process, see Taninaka et al. [(2),(3),(4)].

Various ingenious methods of testing had to be employed to test its biological effects [(5)]. In others words, methods had to be developed that would not only test its preventive effect (preventing disease by administering treatment to inoculate seedlings against rice blast fungi) – a common test at the time – and its curative effect (stopping the spread of disease by administering the treatment to seedlings already under attack), but also test its systemic effect (secondary effects on developing leaves that have not been treated). Researchers also investigated its submerged application effect to examine its efficacy in being absorbed through

the roots when irrigated onto rice seedling pots [2]. A large-scale field experiment commenced in 1968, confirming its expected systemicity when applied in water; these effects were also long-lasting. It also proved to be excellent in nursery box application with no side effects in the rice seedlings, thus becoming widely popular.

Researchers investigated which part of the rice blast fungus life cycle this formulation was effective in. Fig. 4.31 shows the propagation cycle of rice blast fungus once a flying spore attaches to the leaf of a rice plant, namely: spore germination → appressorium formation → infection peg formation → mycelial growth → lesion formation → spore formulation. Isoprothiolane has hardly any effect at the spore germination stage, but strongly inhibits the development of infection pegs following appressorium formation [6]. Researchers also investigated the mode of action and confirmed that it inhibits the lipogenesis of phospholipids such as the phosphatidylcholines that make up the biomembrane of the fungus, similar to IBP. While some IBP-resistant fungi selected in the laboratory showed some cross-resistance to Isoprothiolane, Isoprothiolane is effective against the moderate field-level resistance to IBP. Accordingly, there are subtle differences between the two [6],[7].

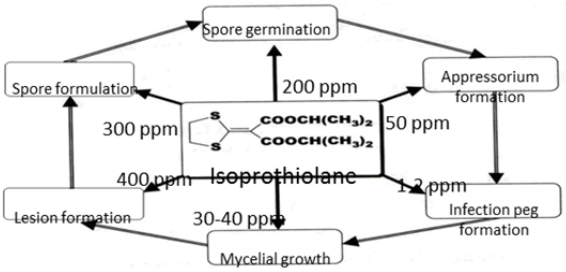

Fig. 4.31. The Isoprothiolane-Sites of Action in the Rice Blast Fungus Life Cycle [6]

Let us now mention the diverse secondary effects of Isoprothiolane. Besides achieving its main target of preventing rice blast, Isoprothiolane is also confirmed to work against stem rot, control leafhoppers, prevent seedling blight, nurture good seedlings, improve ripening in rice, prevent white root rot in pears and other fruit trees, and stimulate growth in carnations, strawberries and fruit tree saplings [6]. Isoprothiolane is worth special mention as it is rare to have so many biological effects, not only as a fungicide, but as an insect repellent and a plant growth regulator.

As mentioned above, Isoprothiolane went on the market in 1974 and became widely popular due to its superior efficacy. By 1984, it had become a large-scale pesticide selling 9,400 tons in granular form and in combination formulations to the value of ¥5.6 billion. The market had also expanded into Northeast Asia, including Korea, Taiwan and China, bringing the total to 13,900 tons in shipments and a value of ¥10.4 billion. This outcome won the company the 22nd Okochi Memorial Grand Technology Prize in 1975 for "development of systemic crop protectant Isoprothiolane (Fuji One)," proving how ground-breaking this invention was.

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4.11. The Invention of Probenazole (Oryzemate), a World-Class Induced Resistance Fungicide

Probenazole (Fig. 4.32) is the world's first induced resistance fungicide (also called a plant defense activator) invented by Meiji Seika (now Meiji Seika Pharma). Registered in 1974, this formulation soon became very popular due to its superior, long-lasting efficacy against rice blast. While a lot of higher eating quality rice is grown, such as Koshihikari, it is susceptible to lodging and rice blast. Probenazole has played a major role in helping to solve these issues.

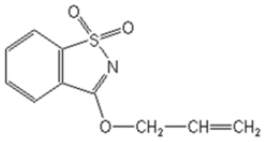

Fig. 4.32. Probenazole (Oryzemate)

Meiji Seika had been exploring fungicides for rice diseases since around 1960 and in the process discovered Probenazole, a saccharin derivative. The key to the success of this research was using in vivo testing to check the inoculation of rice seedlings against rice blast fungus rather than petri dish tests. While

Probenazole showed hardly any antibacterial properties in itself, when applied to an infected plant, it prevented disease by inducing and activating the plant's resistance to the disease. This was the first such ground-breaking fungicide in the world. Probenazole's product name Oryzemate means "friend (mate) of rice (*Oryzae sativa L.*)." [1]

In 1993 there was a major onslaught of abnormal weather (low temperatures, heavy rain, typhoons), resulting in repeated outbreaks of rice blast, with 45% of Japan's 2.13 million hectares of paddy rice fields affected by leaf blast and 43% by panicle blast. Consequently, the national Crop Situation Index dropped to "Very Bad" – 74% of the average year – and 3 million tons of emergency rice imports were made. Given these circumstances, Oryzemate granules grew increasingly popular as they produced good results [2].

Since Probenazole was readily absorbed through the roots, it was first developed into a granule form for submerged application. Less labor-intensive and longer lasting formulations were later developed, such as controlled release formulations for nursery boxes, throwing formulations, inter-row formulations and combination formulation with insecticides. The total combined shipments for these formulations since 1974 is worth ¥292.3 billion (to 2011) (Fig. 4.33).

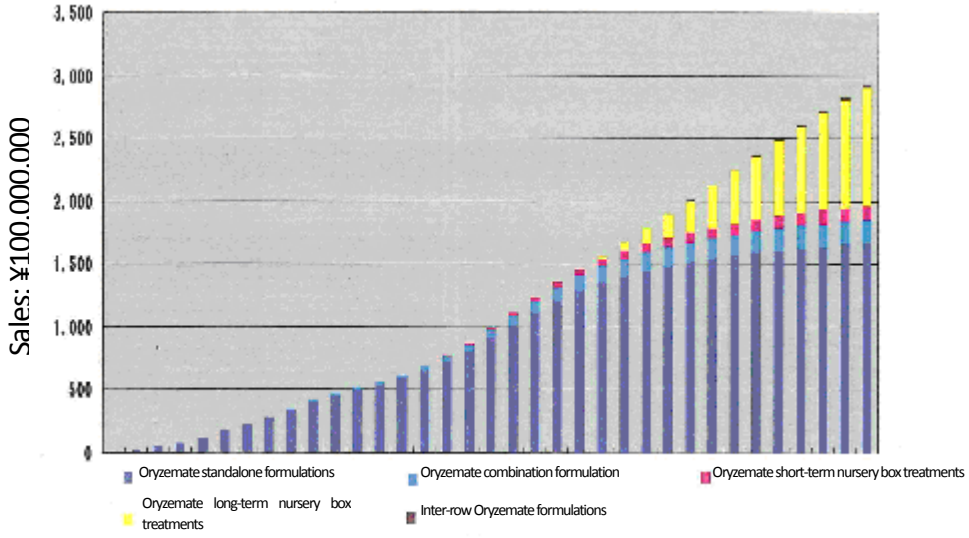

Fig. 4.33. Cumulative Trends in Oryzemate Formulation Shipments (formulated by Meiji Seika from the Pesticide Handbook)

Probenazole shows outstanding efficacy against rice blast, rice leaf blight and grain rot, as well as other bacterial diseases such as bacterial spot in cucumbers and soft rot in cabbages. However, it works only as a preventive measure rather than a cure.

Despite Probenazole having no direct antibacterial properties in itself, as mentioned above, it prevents rice penetration, mycelial growth, lesion expansion, spore formation and spore germination in rice blast fungus [3], [4], [5]. While its mode of action has no clearly-defined point of action, current genetic-level research indicates that Probenazole induces resistivity, that is, it activates the signal transduction pathway for systemic acquired resistance (SAR) [1], [2], [6]. Specifically, it kills host cells with reactive oxygen such as superoxide, then produces antibacterial substances such as oxidized fatty acids, phytoalexins and PR proteins, and then activates the phenylpropanoid system that governs lignin synthesis in the cell walls to contain the rice blast fungus. At this point, infection-specific PR genes are expressed and salicylic acid is stored as a transmitter. Since it does not act directly on the fungus, but on the resistance-inducing signal pathway, there is little risk of resistance developing to this fungicide.

As well as being a scientifically-outstanding invention, Probenazole also played a large part in disease control in crops, especially rice. This won the company the Okochi Memorial Grand Technology Prize in 1978 for "development and commercialization of Probenazole."

As mentioned above, Probenazole appeared in 1974 as the world's first induced resistance fungicide. It was a

long time before any other similarly effective fungicides appeared. Finally, after more than 20 years, several other fungicides appeared with similar modes of action, listed below. Novartis (now Syngenta) released Acibenzolar-S-methyl (Fig. 4.34) in 1998; registration for this lapsed in 2006. This was followed by Tiadinil (Fig. 4.35), put out by Nihon Nohyaku in 2003, and Isotianil (Fig. 4.36), jointly developed by Bayer and Sumitomo Chemical and put to market in 2010. Since each of these is mainly used on rice blast, it is conceivable that they were modeled on the mode of action of Probenazole.

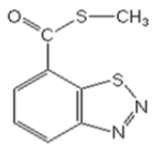

Fig. 4.34. Acibenzolar-S-methyl (Bion)

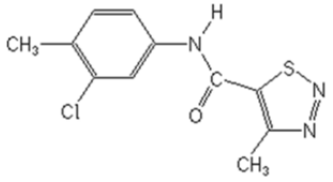

Fig. 4.35. Tiadinil (V-GET)

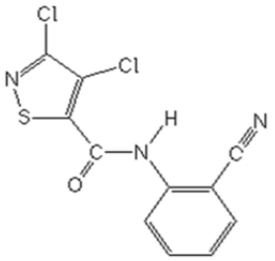

Fig. 4.36. Isotianil (Routine)

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4.12. Dedicated Graminicides Alloxydim and Sethoxydim: Trailblazing World-Class Products

Alloxydim (Kusagard) (Fig. 4.37) and Sethoxydim (Nabu) (Fig. 4.38) are grass killers invented by Nippon Soda with a new cyclohexanedione structure. Registered in Japan in 1980 and 1985 respectively, they first expanded into the overseas market, with Alloxydim marketed in Europe in 1978 for use on sugar beet and rapeseed. Sethoxydim was registered in 1983 in the United States and was marketed there for use on soybeans, cotton and onions. While both formulations have the same effect, Sethoxydim has higher activity, a broader herbicidal spectrum and is safer on crops than Alloxydim, and eventually became more popular [(1), (2), (3), (4)].

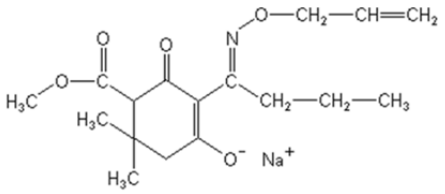

Fig. 4.37. Alloxydim (Kusagard)

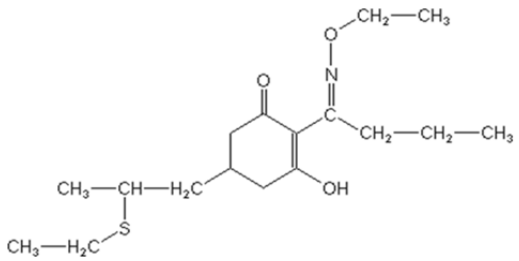

Fig. 4.38. Sethoxydim (Nabu)

Nippon Soda successfully developed the miticide Benzoximate (Citrazon) after researching various hydroxamic acid derivatives in the late 1960s and early 1970s. In the process of modifying the structure further, Nippon Soda discovered a series of chemical classes with selective herbicidal properties against grassy weeds. Further investigation resulted in Alloxydim, followed by the more effective and less phytotoxic Sethoxydim. This was a long-awaited major invention

for Nippon Soda in the herbicide field. Development continued on Alloxydim in Europe and on Sethoxydim in the United States [5], [6].

Both herbicides have the same unprecedented effect, being highly selective against annual and perennial grassy weeds at doses of 200g/hectare, while having no effect on broadleaf crops (such as soybeans, sugar beets, cotton, sunflowers, rapeseed and vegetables). Moreover, while most existing herbicides worked by soil application either pre- or early post-germination treatment, these were unprecedented highly systemic foliar treatments that were quickly absorbed into the plant. Conversely, they had little effect in soil applications, as they would quickly break down in soil.

Their mode of action is known to work by competitive inhibition of acetyl-CoA carboxylase (ACCase) in lipid biosynthesis. This is the first case of this mode of action in a herbicide.

As mentioned above, Alloxydim and Sethoxydim are effective foliar treatments for the main grassy weeds, which made them popular overseas. By 1991, they were registered in 65 countries. Since grassy weeds take up a large portion of the herbicide market, these herbicides drew the attention of overseas manufacturers, resulting in the development of the related compounds shown below (Fig. 4.39).

Clethodim (Select; Valent 1998)
Tralkoxydim (Grasp; ICI 1986 (France))
Cycloxydim (Focus; BASF 1989 (France))
Butroxydim (Falcon; Zeneca 1996 (EU))
Profoxydim (Aura; BASF 1998 (Spain))
Tepraloxydim (Honest; BASF 2000)

It is worth noting that this cyclohexanedione structure discovered by a Japanese manufacturer went on to occupy a large portion of the global herbicide market. This achievement won Nippon Soda the 31st Okochi Memorial Grand Prize in 1984 for "research and development of cyclohexanedione pesticides."

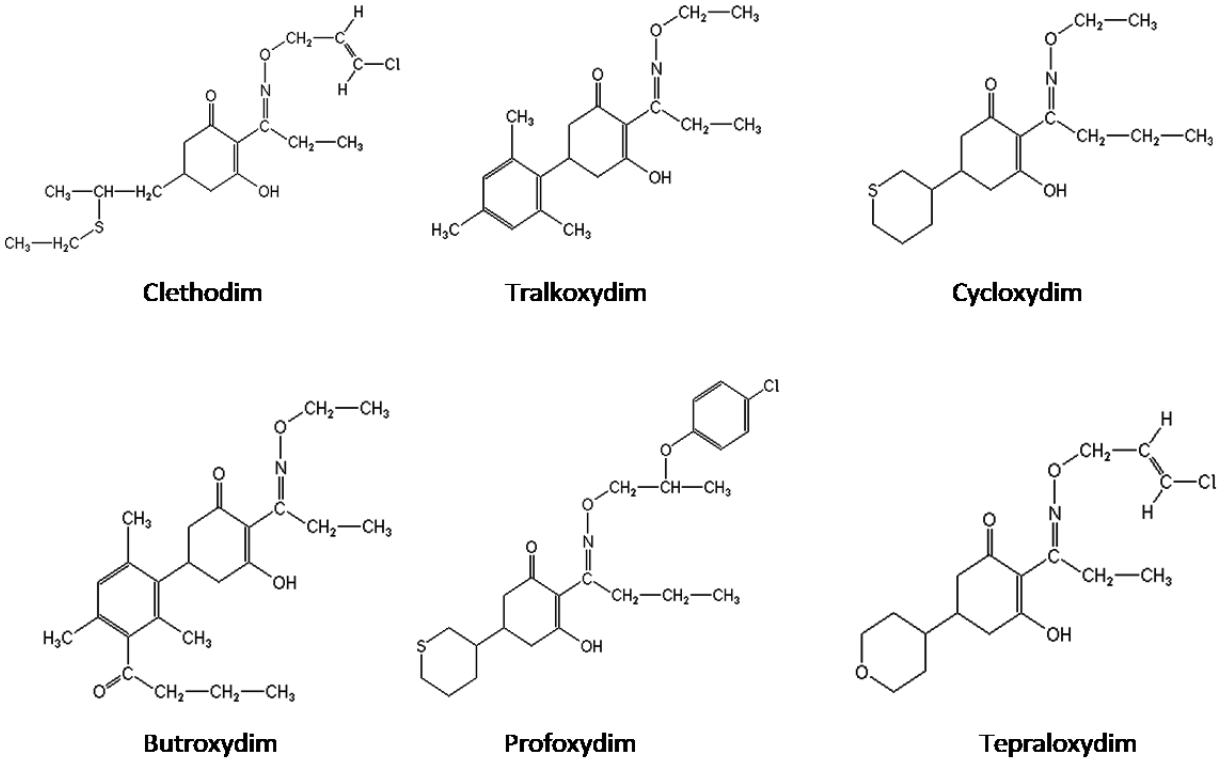

Fig. 4.39. Cyclohexanedione Herbicides

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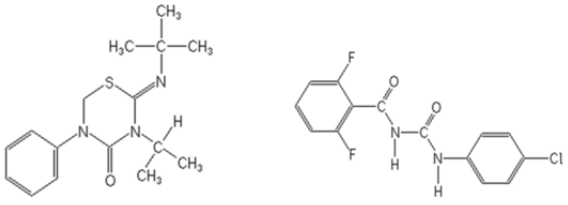
4.13. Buprofezin (Applaud): An Insect Growth Regulator (IGR) with a New Chemical Structure

Buprofezin (Applaud) is an insecticide with a new chemical structure, invented by Nihon Nohyaku and registered in 1983. It is highly effective against Hemipterae such as leafhoppers, whitefly and scale insects. It has a completely new thiadiazine chemical structure. Although it has no effect on adult insects, it acts specifically at particular stages of the insect life cycle, namely ecdysis, egg-laying and hatching. It is thus more of an insect growth regulator (IGR) than an insecticide. It is the first pesticide produced in Japan to have this effect.

Nihon Nohyaku put the fungicide Isoprothiolane on the market in 1974, as mentioned in Section 4.13. This fungicide was found to have a density inhibitory effect on leafhoppers in addition to its fungicidal activity. The company started working on exploratory research on synthesizing related compounds with the idea that there would be good future prospects for pesticides that not only killed insects but also acted at particular stages in the insect life cycle, such as ecdysis, egg-laying and hatching. This was around the same time that Dutch company Philips-Duphar invented Diflubenzuron (Dimilin), a benzoylurea chitin biosynthesis inhibitor (ecdysis inhibitor) (registered in Japan in 1981) and much attention was being drawn to the fact that this was highly effective against insects resistant to organophosphates and other chemicals. This exploratory research took the form of screening for chemicals that acted as quickly as existing organophosphates as well as longer-term observations to check the delayed ecdysis-inhibiting effect [(1)].

Tireless synthesis experiments resulted in Buprofezin, with a perhydro-1,3,5-thiadiazine skeleton formed by reacting N-chloromethyl carbamoyl chloride with substituted thiourea [(2), (3)]. This is a completely new chemical structure, although it looks similar in parts to having used a diflubenzuron cyclic structure, which has the same ecdysis-inhibiting effect (Fig. 4.40).



Buprofezin (Applaud) **Diflubenzuron (Dimilin)**

Fig. 4.40. Buprofezin (Applaud) and Diflubenzuron (Dimilin)

Buprofezin is a relatively narrow-spectrum insecticide with the specific effect of inhibiting ecdysis in the larvae of Hemipterae such as leafhoppers, whitefly and scale insects. This selectiveness is an advantage, as it means it has little impact on beneficial insects such as natural enemies and bees.

It has a very powerful effect on insect larvae, with a lethal median dose of 1 ppm or less, far more powerful than organophosphate and carbamate insecticides. While it does not kill adult insects, its confirmed secondary effects of shortening their life span as well as inhibiting egg-laying and hatching are of great interest. Like Dimilin, its mode of action is achieved by inhibiting biosynthesis of chitin, a component in the cuticle layer of the epidermis of the insect. The inhibition of egg-laying and hatching in adult insects is confirmed to be due to the inhibition of prostaglandin E_2, an oviposition stimulant [(4), (5)].

As mentioned above, Buprofezin became widely used due to the new IGR effect and its efficacy. It became a hit formulation, with ¥22.8 billion in shipments within four years. With resistance to existing insecticides becoming problematic, this was a highly valuable formulation, since it had no issue with cross-resistance (Note 1). The market for it expanded overseas for use on various grains, fruit trees and vegetables; by 2007, it had been registered and widely used in 88 countries [(6)].

This outcome won the company the Okochi Memorial Grand Technology Prize for "research and development of the insect growth regulator Buprofezin" in 1988 and the Japan Science and Technology Agency Presidential Award in 1990.

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(3) Ikeda et al. "Satchū-zai Bupurofejin no Kaihatsu [Development of the Insecticide Buprofezin]," *Journal of Pesticide Science*, Vol. 11, 1986, pp. 287-295.

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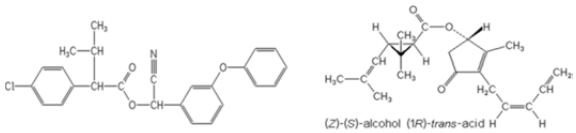
(Note 1) Cross-resistance here means resistance to one pesticide (lowering its efficacy) resulting in resistance developing to other pesticides. Also called cross-tolerance.

4.14. New-Generation Agricultural Synthetic Pyrethroid Fenvalerate (Sumicidin)

Fenvalerate (Sumicidin) is a synthetic pyrethroid insecticide for agriculture, invented by Sumitomo Chemical and developed into a world-renowned product. Registered in Japan in 1983, this global product had already been on the market in the United States as an insecticide for cotton since 1979. While its chemical structure is a modified version of natural pyrethrins, if the two were compared side by side, they differ to the point of questioning whether or not one is an analogue of the other (Fig. 4.41). It took a lot of research to come up with this product.

As mentioned in Section 3.3.4, pyrethroids have a long history. It has been nearly 130 years since pyrethrum was introduced to Japan in 1885. The first 50 years were spent researching the chemical structure of the insecticidal component of pyrethrum, with the chemical structure finally being elucidated in the 1950s. With developments in synthetic organic chemistry, researchers then worked on clarifying the structure-activity relationship, which resulted in the invention of a number of highly effective synthetic pyrethroids.



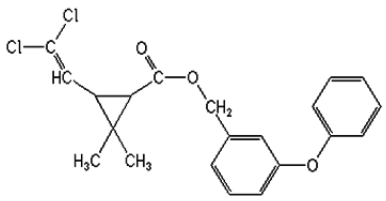
Fenvalerate (Sumicidin) Pyrethrin

Fig. 4.41. Fenvalerate and Pyrethrin

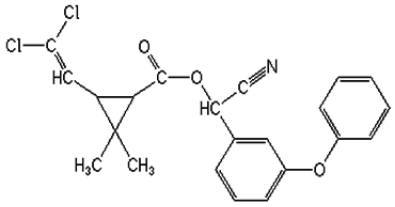
Sumitomo Chemical continued actively researching synthetic pyrethroids, resulting in the development of a number of insecticides, mainly for household use and for disease prevention. This paper cannot discuss these household and disease-prevention formulations in detail due to space constraints.

While pyrethrins, a component of pyrethrum, had been used in agriculture before the war and synthetic pyrethroids allethrins [(1)] had been on the market since 1967, these did not become very popular, as they were highly priced and were not very effective as insecticides on outdoor fields. This was because they had poor photostability and poor durability (residual activity) as they were susceptible to heat and oxidization and easily broke down in the environment. When the more competitively priced and more effective DDT, BHC and organophosphates appeared after the war, pyrethrins and allrethrins were hardly used for agriculture any longer.

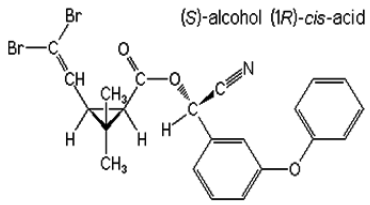
This problem was solved by Permethrin, Cypermethrin and Deltamethrin [(2)], invented by British researcher Michael Elliott, as well as Fenpropathrin [(3)], discovered by Sumitomo Chemical (Fig. 4.42). These inventions all appeared around the same time, from the late 1960s to the early 1970s.



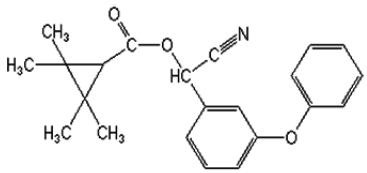
Permethrin (Adion)



Cypermethrin (Agrothrin)



Deltamethrin



Fenpropathrin (Rody)

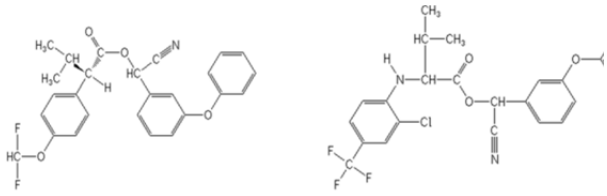
Fig. 4.42. Agricultural Pyrethroids (3-membered rings)

Sumitomo Chemical discovered the alcohol component of pyrethrins to comprise a stable 3-Phenoxybenzyl alcohol and its cyano substitute, α-cyano-3-phenoxy-benzyl alcohol [4]. Meanwhile, Elliott identified its acid component as dihalovinyl chrysanthemic acid to protect a light-sensitive double bond. Permethrin, Cypermethrin and Deltamethrin are combinations of these. Sumitomo Chemical also invented Fenpropathrin on discovering that tetramethyl cyclopropane carboxylic acid [5] is very stable. These inventions enabled a long-awaited expansion into agriculture.

Around the same time, Sumitomo Chemical discovered that α-substituted phenylacetic acids without the cyclopropanecarboxylic acid 3-membered ring structure – previously thought necessary in pyrethroid compounds – had highly effective insecticidal properties. This resulted in Fenvalerate, with the results presented at a conference in 1974 [6].

Fenvalerate was around ten times more active than existing organophosphate insecticides. Effective against a wide range of pest insects, including Lepidopterae such as the common cutworm and diamondback moth, Dipterae such as houseflies, Dictyopterae such as cockroaches and Hemipterae such as aphids, it became a major global product used on a broad range of applications, including cotton, grains, fruit trees and vegetables. Sumitomo Chemical completed manufacturing equipment capable of producing 1200 tons per year and used this technology to start producing 1500 tons per year in the United States from 1982 onwards. These achievements won the company the 27th Okochi Memorial Prize in 1982 for "development of Fenvalerate." [7]

Following the appearance of Fenvalerate, another two pyrethroids appeared with a non-3-membered ring structure. One was Flucythrinate, invented by ACC and registered in 1986. The other was Fluvalinate, invented by Katsuda and registered in 1987. Their chemical structures are shown in Fig. 4.43.



Flucythrinate (Payoff) **Fluvalinate (Mavrik)**

Fig. 4.43. Agricultural Pyrethroids (without 3-membered rings)

Given the aforementioned long history of pyrethroids, the invention and development of Fenvalerate had a major impact on the world by paving the way to expansion into agricultural applications. Accordingly, overseas manufacturers followed suit in the 1970s, with competition ensuing over research and development. This resulted in the development and sale of a total of 19 different synthetic pyrethroids in Japan by 1995. There were also more than nine new insecticides for household use or disease prevention. It is worth noting here that of the 19 formulations, eight were Japanese inventions, while eight of the nine new household or disease prevention formulations were Japanese inventions. We can truly say that Japan has beaten the major overseas players in this field.

Although synthetic pyrethroids have the advantage of being very safe for mammals, there are several problems with them. Firstly, they are unable to be used on rice fields in Japan, as they are highly toxic to fish and other aquatic organisms. Secondly, there are concerns that flies and mosquitoes may develop resistance to them. Thirdly, they affect phytoseiidae, the natural enemies of spider mites, which could result in a resurgence of spider mites in greater numbers than before pyrethroid use. As shall be discussed later, later insecticides such as Etofenprox are less ichthyotoxic and there is hope that they will be able to be used on rice fields.

Finally, Yoshio Katsuda has written some excellent reviews and articles on the development and prospects of pyrethroid chemistry, cited below [8], [9], [10].

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4.15. High-Performance Miticide Hexythiazox (Nissorun)

Hexythiazox (Nissorun) is a major agricultural miticide invented by Nippon Soda and registered and marketed in 1985 (Fig. 4.44). It has an unprecedented chemical structure and distinctive effects. It is selectively effective against parasitic spider mites on fruit trees, vegetables, tea, cotton and other crops. While other miticides were developed in Japan after this invention, Hexythiazox was the forerunner of the Japanese miticides.

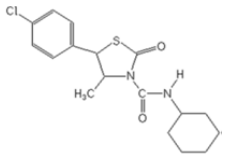

Fig. 4.44. Hexythiazox (Nissorun)

Spider mites belong to the spider family rather than the insect family. They are a type of plant parasite and are a major parasitic pest on leaves and fruit. They multiply quickly and once an outbreak occurs, the damage can be devastating. Miticides are in great demand, as regular insecticides have no effect on these pests. As highly effective insecticides such as DDT became popular after the war, there was a decline in natural spider mite enemies such as phytoseiidae, resulting in more apparent damage from spider mites. Since spider mites reproduce quickly, they quickly acquire resistance, meaning that any existing miticides soon lose their efficacy. Consequently, new miticides are in great demand.

Nippon Soda developed and marketed CPCBS (Sappiran, licensed from Dow) in 1954, followed by CPAS/DDDS (Mikazin, Milbex) in 1962 and MNFA (Nissol) in 1965. It then developed Benzomate (Citrazon) in 1971, occupying a large share of the market as "Miticidal Nippon Soda." However, registration for each of these formulations has lapsed due to resistance problems.

Nippon Soda continued to work on developing new formulations and discovered a thiazolotriazine compound with miticidal properties while investigating fungicides. The researchers altered this compound and this resulted in Hexythiazox [(1),(2),(3),(4)].

The effects of Hexythiazox are 7-80 times more powerful than existing miticides, such as those for two-spotted spider mites, Kanzawa spider mites, citrus red mites and European red mites. While it has no effect on adult mites, it is highly effective at all other stages of growth and sufficiently residual. It does not affect phytoseiidae, the natural enemy of spider mites. Its mode of action is not yet known in detail.

Thus, Hexythiazox emerged as a far more effective miticide than existing formulations and became wildly popular. Within three years of going on the market in 1986, it had become a major product, gaining a nearly 40% share of the domestic market, thanks to the timing of its appearance, at a time when there was a shortage of effective miticides due to resistance problems. However, as previously mentioned, when miticides are used in such large quantities, resistance to them will quickly build up. Hexythiadox also developed its own resistance problems across the country and usage of it declined. Global discussions began around this time on countermeasures to resistance and an international agreement was made to avoid the build-up of resistance as much as possible by using miticides with different modes of action in rotation where possible.

Since the appearance of Hexythiazox, Japanese companies have led the development of miticides. There is always a demand for new miticides with new chemistry and new effects to avoid cross resistance. The development capabilities of Japanese companies have provided the main means to meet this challenge [(5)]. For details on these new miticides, see Section 3.4.5 (2).

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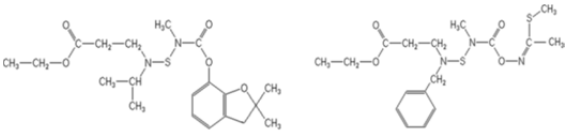
4.16. Low-Toxic, Second-Generation Carbamate Insecticides Benfuracarb (Oncol) and Alanycarb (Orion)

Benfuracarb (Oncol) is a carbamate insecticide for use on rice and vegetable plants, discovered by Otsuka Chemical and registered in 1986. Alanycarb (Orion) is an insecticide for use on fruit and vegetable plants, developed by Otsuka Chemical and registered in 1991 (Fig. 4.45).



Benfuracarb (Oncol) **Alanycarb (Orion)**

Fig. 4.45. Benfuracarb and Alanycarb

Both of these insecticides have been designed to be selectively toxic: for insects and not for mammals, in order to reduce the acute mammalian toxicity of their active ingredients [1], [2], [3]. The active ingredient in Benfuracarb is Carbofuran (Furadan), developed by FMC (Fig. 4.46), while the active ingredient in Alanycarb is oxime carbamate Methomyl (Labin), developed by DuPont (Fig. 4.47). These two active ingredients were developed between the late 1960s and early 1970s and both have an acetylcholinestrase (AChE) inhibitory effect as their mode of action. However, since mammals also have this enzyme, both have the drawback of being highly acutely toxic to mammals as well. Consequently, Carbofuran was never registered in Japan, while certain preparations of Methomyl were exempted and registered on the pesticide register as deleterious substances.

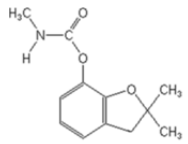


Fig. 4.46. Carbofuran

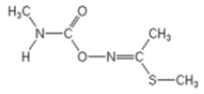


Fig. 4.47. Methomyl

Dr. Roy Fukuto of the University of California pointed out that the mammalian toxicity of carbamate insecticides could be reduced while preserving their insecticidal properties by substituting the nitrogen atom of the carbamyl group. During the 1980s, a number of companies used this method of reducing toxicity [4]. Otsuka Chemical came up with these insecticides as part of this process. These formulations take advantage of the differences in metabolic capacity between insects and mammals, transforming into active carbamates in insects, but breaking down and metabolizing into phenolic compounds with no effect on AChE in mammals, thereby reducing their mammalian toxicity. In pharmaceutical terms, they work as pro-drugs. Their toxicity to insects (houseflies) and mammals (mice) is shown below, indicating no loss of insecticidal properties but over 90% reduction in mammalian toxicity [1], [2], [3], [5], [6], [7].

	LD_{50} on topical application to insects (μg/g)	LD_{50} oral toxicity in mice (mg/kg)
Carbofuran	6.7 (houseflies)	5.6
Benfuracarb	9 (houseflies)	106
Methomyl	0.45 (common cutworm)	16
Alanycarb	3.9 (common cutworm)	412

Benfuracarb became widely popular in nursery box applications due to its efficacy against problematic rice water weevils and its residual effects. It was also popular due to its superior efficacy in soil applications for vegetables against a wide range of pests, including Lepidopterae, Hemipterae and thrips.

Benfuracarb was also marketed in Europe in 1983 and is used in 50 countries around the world to control major pest insects such as hairworms and aphids on maize, sugar beets, potatoes and other crops.

Alanycarb is effective against larger Lepidopterae, leaf rollers and worms on fruit trees and aphids and other pests on vegetable plants.

As mentioned above, Benfuracarb and Alanycarb are widely popular as second-generation carbamates; that is, carbamate insecticides with reduced toxicity to mammals. This invention is very significant, not only in terms of safety, but also in terms of improved biological efficacy in the field. Interestingly, while the compound has around twice the weight, the effectiveness is equivalent to the parent compound. The use of a pro-drug to solve the issues with existing highly active substances is a good example of superior science and technology.

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4.17. Fluazifop-butyl (Onecide) and Quizalofop-ethyl (Targa): the Graminicides that Followed after Sethoxydim

Fluazifop-butyl (Onecide) is an aryloxy phenoxypropionic acid grass killer invented by Ishihara Sangyo and registered in Japan in 1986. It was widely popular overseas, beginning with its registration in Argentina in 1982.

Quizalofop-ethyl (Targa) is a herbicide in the same chemical group, invented by Nissan Chemical and registered in 1989. Since it is mainly used overseas, it

was developed first for the overseas market, registered in the United Kingdom in 1983, France in 1984 and the United States in 1988. It is a major product worth over ¥5 billion and registered in more than 60 countries worldwide. Both of these formulations have the same mode of action as Sethoxydim, discussed in Section 4.12, and so have similar effects and applications.

In the early 1970s, Hoechst discovered Diclofop-methyl, another product in the same chemical compound group [1], [2].

Ishihara Sangyo had carried out exploratory research on new herbicides such as Chlomethoxynil by altering the diphenyl ether structure,. and later came up with Fluazifop, with a substituted pyridyloxyphenoxy chemical skeleton [3], [4], [5].

Nissan Chemical started researching this chemical skeleton in the late 1970s, noting that the aryloxy phenoxypropionic acid structure was selective against grassy weeds. Developers then expanded the phenoxy structure to a nitrogen-containing aromatic ring, resulting in Quizalofop-ethyl with a fused-ring quinoxaline skeleton [6], [7], [8], [9]. This was Nissan Chemical's first world-class product.

While compounds in this series have aryloxypropionic acid structures, it is interesting to note that they demonstrate no auxin-like activity, but are selective against grassy weeds. This effect is similar to the cyclohexanedione-structured Sethoxydim; later research has shown that its mode of action works by inhibiting lipogenesis through non-competitive inhibition of ACCase [10], [11], [12]. Thus, they interestingly have completely different chemical structures, but are treated the same way by plants. Only the R isomer of this phenoxypropionic acid shows activity; the S isomer shows no substantial activity. Both herbicides currently on the market have been switched to the optically-active (R isomer) form.

These have become widely known as a group that is highly active against grassy weeds. They have caught the attention of many manufacturers, with the following herbicides later developed and emerging on the Japanese market. Cyhalofop butyl is highly selective and good for rice cultivation; accordingly, a number of standalone and combination formulations of it have been developed to control barnyard grass in its later stage of growth. A number of other related compounds have been developed for the overseas market as well [13], [14], but have been omitted here.

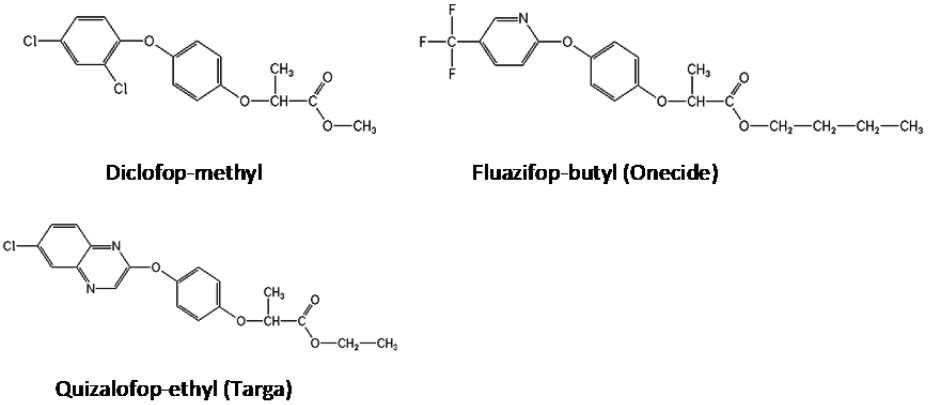

Fig. 4.48. Diclofop-methyl, Fluazifop-butyl and Quizalofop-ethyl

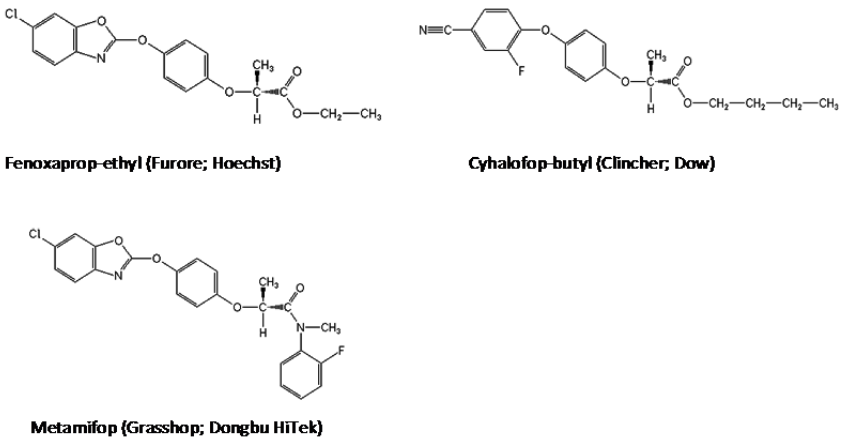

Fig. 4.49. Aryloxy Phenoxypropionic Acid Herbicides

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4.18. Etofenprox (Torebon): Achieving Low-Ichthyotoxicity with Synthetic Pyrethroids

Etofenprox (Torebon) is a synthetic pyrethroid insecticide invented and developed by Mitsui Chemicals. It is characterized by being the first pyrethroid in the world to be low-ichthyotoxic, a problem in existing pyrethroids, meaning it could be used not only on fruit and vegetable plants, but also on rice, Japan's most important crop. It was registered in Japan in 1987 (Fig. 4.50).

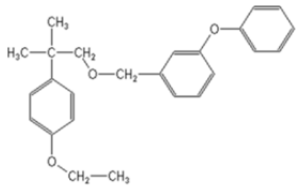


Fig. 4.50. Etofenprox (Torebon)

With the appearance of Fenvalerate (Sumicidin), discussed in Section 4.14, synthetic pyrethroids reached the level of usability in agriculture and expanded into a wide range of applications, including fruit and vegetable plants, cotton and grains. This sparked a battle among a number of companies in the late 1970s to develop new synthetic pyrethroids. Mitsui Chemicals started working on developing a new product that would rival Fenvalerate and Permethrin – with known chemical structures – as an insecticide with low-toxic for fish.

During the course of this research, researchers at Mitsui Chemicals tried modifying the ester portion – the only thing that had not been tried. They swapped the ester bond for an ether bond and this resulted in Etofenprox. The ester portion had been viewed as an essential moiety for any activity to show, but it turned out that the radical idea of replacing this moiety was the key to the invention of Etofenprox. This compound remains highly insecticidal, but is stable in both acid and alkali environments, due to the ether bond. It was also found to be significantly less toxic to fish and therefore able to be used on rice fields [(1), (2), (3), (4)].

Another noteworthy characteristic is that its chemical structure comprises only carbon, oxygen and hydrogen, with no nitrogen or halogen atoms. This radical structural change was the most significant achievement in pyrethroid history since Fenvalerate. The structure has evolved so much that it is difficult to imagine that it is a structural analogue of natural pyrethrins and has the same effect.

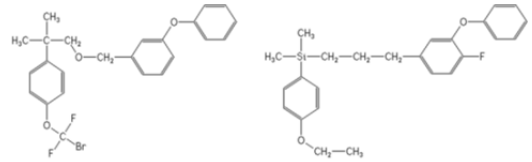
Highly effective against a broad spectrum of insect pests, including Lepidopterae, Hemipterae, Coleopterae, Dipterae and Orthopterae, it is also effective against insects that have developed resistance to organophosphates and carbamates, such as leafhoppers.

Based on the above, Etofenprox took over from Fenvalerate as the number one synthetic pyrethroid. As at 2006, it was included in 157 standalone and combination formulations on the pesticide register and used on 58 types of crops, including rice. Since it also has little impact on the environment, it is widely used in aerial spraying. It is truly a super-product, with total shipments reaching ¥170 billion in the 20 years since it went on the market. It is also popular for its efficacy in household use and in disease prevention (flies, mosquitoes and termites).

Etofenprox has become a world-renowned product, continuing to be used to this day in more than 50 countries around the world, including the United States, to control malaria-carrying mosquitoes and other insect pests.

These achievements won the company the Nikkei Superior Products Award in 1988, the Pesticide Science Society of Japan Achievement Award in 1990, the Synthetic Organic Chemistry Award in 1991 and the Okochi Memorial Grand Technology Prize in 1992.

Other related compounds were developed after Etofenprox went on the market, including the miticide Halfenprox [5], developed and registered by Mitsui Toatsu Chemicals in 1994, the registration for which lapsed in 2006. Yoshio Katsuda of Kincho also developed the silicon-containing Silafluofen [6], registered in 1995. Silafluofen is an ether-bonded, carbon-chain compound that is safer for fish than Etofenprox.



Halfenprox (Annivers) Silafluofen (Mr Joker)

Fig. 4.51. Non-Three-Ringed Pyrethroids

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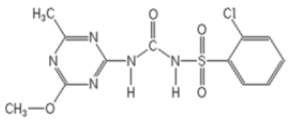
4.19. Acetolactate Synthase (ALS) Inhibitors: the Rise of Sulfonylurea (SU) Herbicides and Various Later Developments

In 1977, G. Levitt et al. of DuPont applied for a patent for a ground-breaking sulfonylurea (SU) herbicide with a new chemical structure [1]. The compound they presented on at a conference in 1981 made a striking entrance with herbicidal properties at low doses of several grams to several tens of grams per hectare, an amount more than two digits less than for of existing herbicides [2]. The first such product to be developed was Chlorsulfuron (Glean), marketed in the United States in 1982 for use on broadleaf weeds in wheat and barley (Fig. 4.52). It became a super-product, with usage in the United States reaching 72,000 lb. (32.7t) of active ingredient per year on 5.5 million acres (around 2.2 million hectares) from 1988 to 1999, mainly for winter wheat cropping [3].



Chlorsulfuron DuPont

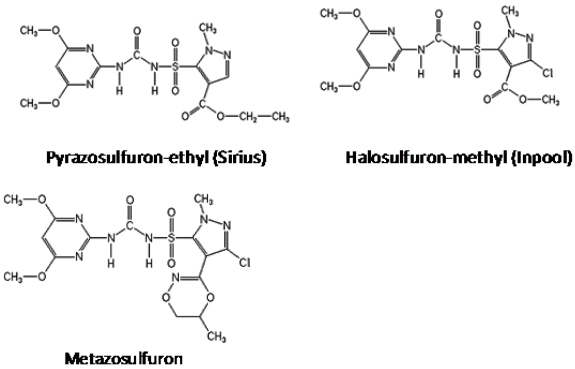
Fig. 4.52. Chlorsulfuron

While DuPont started out with Chlorsulfuron, other pesticide manufacturers started developing their own SU herbicides, resulting in the development of more than 50 herbicides, each with its own distinguishing characteristics. Refer to the Cited References for details on the course of these developments [4], [5], [6].

The mode of action of SU formulations is known to be achieved by inhibiting acetolactate synthase (ALS) at the early stage of biosynthesis of branched-chain amino acids such as leucine, valine and isoleucine, essential amino acids in plants.

Following the development of these SU herbicides, several other series have been developed with different chemical classes but the same mode of action. These include the imidazolinones developed by ACC, the triazolinones developed primarily by Bayer, the triazolopyrimidines developed by Dow and the pyrimidinyl carboxy herbicides developed primarily by Kumiai Chemical. Japanese manufacturers developed a number of ALS inhibitors to rival the companies in the West. Below, we shall outline the main herbicides developed by Japanese manufacturers.

(1) Pyrazosulfuron-ethyl (Sirius) and Halosulfuron-methyl (Inpool) (Fig. 4.53)



Pyrazosulfuron-ethyl (Sirius) Halosulfuron-methyl (Inpool)

Metazosulfuron

Fig. 4.53. Pyrazosulfuron-ethyl, Halosulfuron-methyl and Metazosulfuron

Pyrazosulfuron-ethyl (Sirius) is an SU formulation invented and developed by Nissan Chemical; the aryl portion of the structure is converted to a pyrazole ring. It is effective at controlling stubborn rice weeds such as *Eleocharis kuroguwai* and *Sagittaria trifolia* at very low doses of 21g/ha and is also very safe on rice. It was

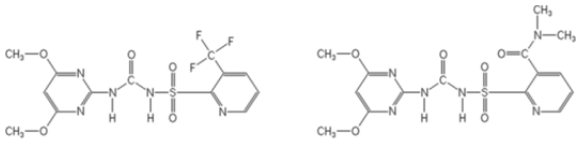
registered in Japan in 1989. Its distinguishing characteristics have made it just as popular a pre- and early-post one-shot herbicide as Bensulfuron methyl. It has become a major herbicide, currently sold in 20 of the main rice-growing countries around the world [7],[8].

Nissan Chemical then developed Halosulfuron-methyl (Inpool) [9]. This formulation is distinctive for its efficacy against *Cyperaceae*, its safety and its selectivity on maize, turf and rice. It was first marketed in the United States in 1994 for use on maize, and then registered in Japan in 1995 for use on rice and turf. It is a major product, currently used in 38 countries around the world.

Nissan Chemical also discovered Metazosulfuron, its third SU with a pyrazole structure [6],[10]. It is said to be safe to use on rice. It was first marketed in Korea in 2010, with an application in progress for registration in Japan. This formulation is highly effective against annual weeds, including barnyard grass, and stubborn perennial weeds such as *Eleocharis kuroguwai*, *Scirpus planicumis* and *Scirpus nipponicus*.

Nissan Chemical started exploring SU formulations quite early on. Its development of a method of de novo synthesis for pyrazole derivatives led to the development of these three SUs. This achievement won the company the 34th Synthetic Organic Chemistry Award in 1992 for "development and commercialization of the new herbicide pyrazosulfuron-ethyl."

(2) Flazasulfuron (Shibagen) and Nicosulfuron (Onehope) (Fig. 4.54)



Flazasulfuron (Shibagen) **Nicosulfuron (Onehope)**

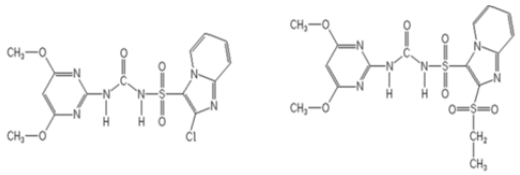
Fig. 4.54. Flazasulfuron and Nicosulfuron

Ishihara Sangyo developed Flazasulfuron (Shibagen), a SU herbicide that is selective on turf, and registered it in 1989. Unlike existing grass herbicides, it is effective against annual weeds, perennial weeds and broadleaf weeds at low doses of 50g/ha in a foliar application and is characteristically safe on turf [11]. This was followed by the development of the structurally-analogous Nicosulfuron (Onehope), developed for use on maize. This was registered in 1994 and had the distinguishing characteristic of being effective at low doses of 40-60g/ha in foliar applications against stubborn maize weeds such as couch grass and Johnson grass. Its safety to maize has been verified as being due to the rapid degradation in maize, rather than differences in sensitivity at enzyme level. It has become popular for use on maize, registered and sold in Japan as well as another 38 countries [12],[13].

These two formulations have their aryl structure replaced by substituted pyridines. Researchers at Ishihara Sangyo had been working on substituted pyridines and tested many derivatives, finally resulting in the invention of these. Following up all options in exploratory research on new pesticides by adding a fluorine atom to a pyridine ring is a classic case of a successful method of molecular design led by synthetic organic chemistry. There are now a total of seven independently-developed substituted pyridine derivatives on the market, beginning with Fluazifop-butyl, discussed in Section 4.17. While the details are omitted, the following shows these pesticides by year of development.

Herbicide Fluazifop-butyl (Onecide 1986)
Insecticide Chlorfluazuron (Atabron 1989)
Herbicide Flazasulfuron (Shibagen 1989)
Fungicide Fluazinam (Frownicide 1990)
Herbicide Nicosulfuron (Onehope 1994)
Insecticide Flonicamid (Ulala 2006)
Fungicide Pyriofenone (Property 2012)

(3) Imazosulfuron and Sulfosulfuron (Fig. 4.55)



Imazosulfuron (Takeoff) **Sulfosulfuron (Monitor)**

Fig. 4.55. Imazosulfuron and Sulfosulfuron

(4) Propyrisulfuron (Zeta-One) (Fig. 4.56)

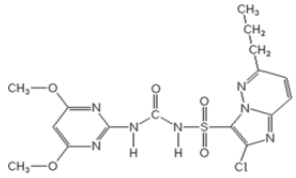


Fig. 4.56. Propyrisulfuron

Propyrisulfuron (Zeta-One) is a SU herbicide for rice developed by Sumitomo Chemical and registered in Japan in 2010. Its chemical structure is a condensed imidazopyridazine ring similar to Imazosulfuron, mentioned above. Its two main distinguishing characteristics are its capacity to control barnyard grass up to the 3-leaf stage at doses of 90g/ha and its efficacy against SU-tolerant common falsepimpernel and *Scirpus juncoides* [19],[20].

The main rice herbicides in use today are one-shot herbicides used in the pre-to early post treatment to save labor. Combination formulations of three to five different herbicides including SU formulations have been developed to control multiple weeds in one application. However, Propyrisulfuron achieves the same effect as a standalone formulation, as it targets a broad spectrum of weeds. This has the major advantage of reducing the number of active ingredients used on fields; it is expected to become widely popular in future.

(5) Pyrimidinyl carboxy (PC) Herbicides

Pyrimidinyl carboxy (PC) herbicides are a group of compounds developed by Kumiai Chemical. To date, herbicides in this group include cotton herbicide Pyrithiobac-sodium salt (Staple) and rice herbicides Pyriminobac-methyl (Hieclean), Bispyribac-sodium salt (Nominee) and Pyrimisulfan (Best Partner) (Fig. 4.57). Since each of these acts as a herbicide by inhibiting ALS like the aforementioned SU herbicides, they are classified as a group in the ALS inhibitor.

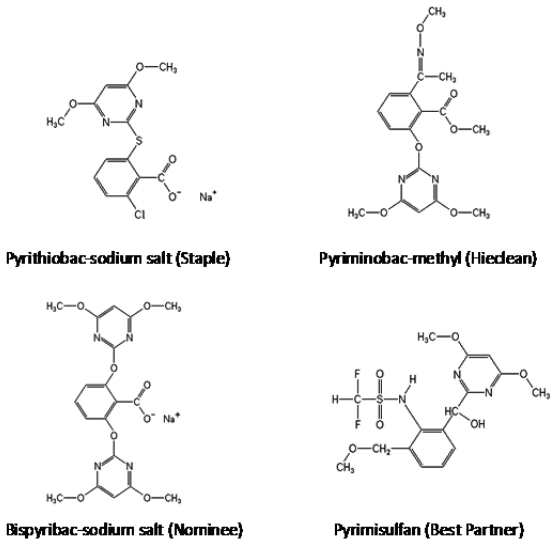


Fig. 4.57. PC Herbicides

Pyrithiobac-sodium salt is characterized by having carboxylic acid substituted at ortho position in the benzene ring, with the sulfonylurea portion of a SU compound replaced with thioether. This structure was the result of experience with SU herbicides and diphenyl ether herbicides [(21)]. This compound is specifically selective on cotton and is highly effective against the main cotton weeds (Ipomea indica, spotted spurge, prickly sida and velvetleaf) at doses of 35-70g/ha. It was registered in the United States in 1996 and later came to be used in Brazil and other countries all over the world [(22), (23), (24)].

Pyriminobac-methyl (Hieclean) is a compound that came about as a result of modifying the aforementioned PC compounds to achieve selectivity for rice. This aim was achieved by introducing oxime ether at sixth position in the pyrimidinyl salicylic acid structure. It is characterized by being specifically effective against early water grass, a major rice weed, at low doses of 30g/ha until the 3-leaf stage. Registered in 1996, it is now mainly used as a mixture base for barnyard grass formulations [(25), (26), (27)].

Bispyribac-sodium salt (Nominee) is the third PC herbicide developed by Kumiai Chemical to be registered on the pesticide register. Used as a foliar treatment during transplanting or directly planting in rice fields, it is highly effective against a broad range of weeds, including mature barnyard grass, at low doses of 20-45g/ha. It is also used to suppress weeds on ridges between rice fields. Registered in Japan in 1997, it is very safe to use on rice, with clear selectivity between rice and barnyard grass. It has also been registered in 34 countries around the world, including the United States, mainly for direct planting use on rice fields. In 2002, its estimated area of use was 1.6 million hectares [(28), (29), (30), (31)].

Pyrimisulfan (Best Partner) is a new formulation registered in 2010. It is a rice herbicide structurally modified from PC herbicides.

Kumiai Chemical aimed to produce a herbicide that would control as many weeds as possible and also be effective against the once-problematic SU-tolerant *Monocholia vaginalis* and *Scirpus hotarui*. Developers replaced the ether bridge structure between benzene and pyrimidyl ring with a carbon bridge and then made the radical structural change of replacing the carboxylic acid moiety with a sulfonamide structure, thus creating the company's fourth ALS inhibitor [(32), (33), (34), (35)].

The so-called one-shot herbicide that combine multiple active ingredients in order to save labor replaced the previous sequential applications and is currently used on most rice fields today. However, although one-shot herbicides reduce the number of applications necessary, they also contain two to five types of active ingredients, so there is high demand among rice producers for formulations that use fewer ingredients to suppress weeds. Another major problem is that 90% of one-shot formulations contain SU, repeated use of which has resulted in a build-up of resistance to it since around 1995.

Pyrimisulfan is highly effective against annual weeds such as barnyard grass (3-leaf stage) and perennial weeds at dosages of 67g/ha. It is ground-breaking in that it can achieve in a standalone ingredient what used to take a combination of two to five existing ingredients. It is also consistently effective against weeds that have become resistant to SU, such as *Monocholia vaginalis*,

Monochoria korsakowii, *Scirpus juncoides* and *Sagittaria trifolia*. While it is effective in submerged applications, its solubility in water is relatively high (114mg/L), so an improved formulation was developed to ensure a more residual effect. Since it is very effective in rice fields at ultra-low concentrations of 10ppb, making it into a controlled-release formulation has helped to make the best use of this product [36].

As mentioned above, the SU herbicides discovered by Levitt of DuPont created a market for ALS inhibitors, which have undergone tremendous development over the past 30 years. ALS inhibitors are the ideal herbicide: they are very safe to mammals, as mammals do not have the target enzyme, they also perform far better than existing formulations at a dosage of more than two digits less, amount, and they can be used on a diverse range of crops. As mentioned, a number of non-SU ALS inhibitors were developed and gained a firm foothold among modern pesticides. Japanese companies played a huge role in this.

However, their popularity spread too quickly. From around 1995, there were major problems with resistant weeds in areas where SU formulations were used. Much research has been done to show that this resistance was due to gene mutations in multiple places [37], [38]. Fortunately, some ALS inhibitors such as Propyrisulfuron and Pyrimisulfan were also effective against resistant weeds. In any case, appropriate measures must be taken to avoid resistance building up where formulations are used, such as not using the same formulation continuously. Future research and development is expected to produce new formulations that will resolve this issue.

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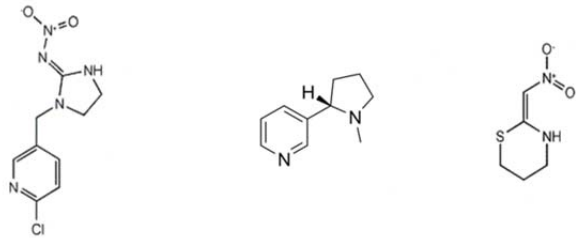
4.20. Major Neonicotinoid Insecticide Imidacloprid (Admire) and Subsequent New Japanese Insecticides

Imidacloprid (Admire) is an insecticide invented and developed by Nihon Tokushu Noyaku (now Bayer Crop Science). It is currently the best-selling pesticide in the world. Developed first for overseas markets, it was registered in Japan in 1992. It is called a neonicotinoid as it is based on and has the same mode of action as nicotine, a natural pesticide.

As discussed in Section 3.3.5, nicotine was used as an insecticide before the war in the form of nicotine sulfate. This was toxic to mammals and dropped in usage with the appearance of more effective synthetic pesticides after the war. By the 1990s, it had dropped to several hundred tons in shipments and registration for it finally lapsed in 2006. While there was little exploratory research on new substances modeled on nicotine for a long time, from around 1972, Shell started actively focusing on this field of research, announcing its discovery of Nithiazine, a nitromethylene compound, in 1978 [(1)]. This compound was effective against green rice leafhoppers that had become resistant to existing insecticides and was also safe for mammals, but its development was not successful as it had poor light stability. Kagabu et al. of Nihon Tokushu Noyaku started exploratory research on related compounds in 1979, focusing on the nitromethylene structure of Nithiazine. After a series of structural modifications, they discovered a highly active compound group that included the 6-chloro-pyridylmethyl group, resulting in Imidacloprid in 1985 [(2),(3),(4)] (Fig. 4.58).



Imidacloprid (Admire) Nicotine Nithiazine

Fig. 4.58. Imidacloprid, Nicotine and Nithiazine

With insecticidal effects on green rice leafhoppers at low concentrations of 0.32ppm, Imidacloprid is more than 125 times more active than Nithiazine [(5)].

Imidacloprid is effective against a broad range of pest insects, including Hemipterae, Coleopterae, some Lepidopterae, Dipterae, thrips and termites, at 80-90% lower concentrations than existing formulations. It is also systemic in plants and has no side effects on crops, meaning it can be used in granular form. It is also safe to use, with low mammalian toxicity and ichthyotoxicity.

Imidacloprid is used on a wide range of crops, including rice, fruit trees, vegetables, wheat, soybeans, potatoes, cotton and maize. It can also be used to control fleas on pets and to eradicate termites.

Like nicotine, its mode of action produces an insecticidal effect by binding to the nicotinic acetylcholine receptors (nAChRs) on the postsynaptic side of the neuromuscular junction, causing antagonistic stimulation [(6),(7),(8)].

Imidacloprid is currently the best-selling insecticide in the world. Registered in 131 countries, this blockbuster (Note 1) dominates the insecticide market with sales worth more than ¥100 billion. This achievement won the company the Okochi Memorial Grand Product Prize in 1998 for "development of the new chloronicotinyl insecticide Imidacloprid."

The appearance of Imidacloprid opened the way for the neonicotinoids, the next major branch of insecticides after the organophosphates and the carbamates. Once Nihon Tokushu Noyaku disclosed its patent, other companies set to work exploring analogues. The following distinctive formulations appeared as the result of fierce patent competition (Fig. 4.59).

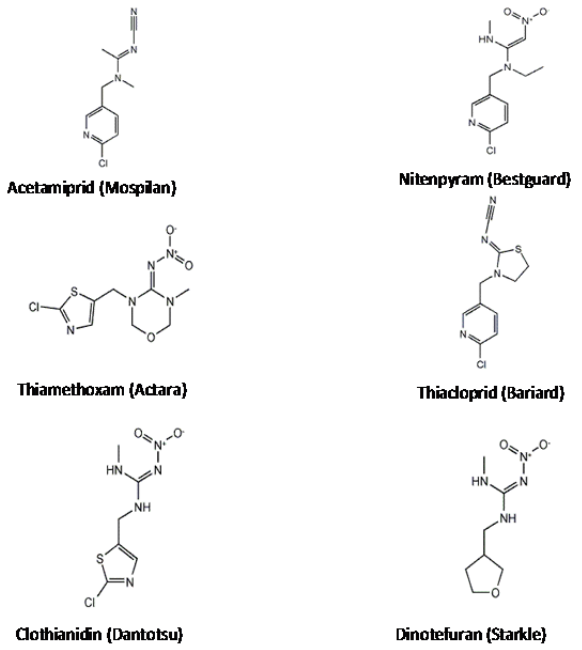


Fig. 4.59. Neonicotinoid Insecticides

Acetamiprid (Mospilan; Nippon Soda, 1995)
Nitenpyram (Bestguard; Takeda Pharmaceutical, 1995)
Thiamethoxam (Actara; Chiba Geigy, 2000)
Thiacloprid (Bariard; Bayer Japan, 2001)
Clothianidin (Dantotsu; Takeda Pharmaceutical, 2001)
Dinotefuran (Starkle; Mitsui Chemicals, 2002)

Acetamiprid is highly effective against Lepidopterae and also safe for bees. Dinotefuran is the only one to have no halogen atom in its structure; it is widely used on rice, fruit and vegetable plants and is effective against a broad range of pest insects such as stink bugs and silverleaf whiteflies. Thiacloprid is relatively safe for bees.

As mentioned above, neonicotinoid insecticides began 20 years ago with the invention of Imidacloprid by Kagabu. They followed on from the synthetic pyrethroids and are more effective than any other insecticide, becoming a mainstay among modern pesticides. It is worth noting that all of these neonicotinoids except Thiamethoxam were invented in Japan, a world-class achievement rivaling the major corporations in the West.

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(Note 1) Blockbuster originally meant a large bomb (that could destroy a city block). In medicine, it refers to a product that is worth more than ¥100 billion in annual sales.

5. Discussion and Future Prospects

While pesticides in Japan date back to the 17th century, the greatest change has been since the appearance of a large number of synthetic pesticides after the war. Social awareness of pesticides has also changed with the times. This section discusses society's awareness of pesticides, the current state of the pesticide industry and the competitive power of Japanese companies. While there are many industries in which Japanese companies hold their own against the major corporations in the West, this section considers whether this competitive power will continue in the future.

5.1. Social Awareness: Safety and Security

The mass media often portrays negative responses to pesticides. Consumers seem to think that "pesticides are poisons; therefore, it is concerning to have pesticide residues in food and preferable to have pesticide-free produce". Along with food additives, pesticides are becoming a source of concern to consumers.

As stated throughout this paper, the safety of pesticides in use today is sufficiently guaranteed, both for the farmers who handle them and for the consumers who eat crops that have been treated with them. In fact, the results of several million tests performed each year on pesticide residues in food are conclusive that there is negligible problem. However, like other chemical substances, pesticides are medicinal as well as toxic. Even medicines come with instructions: taking too many sleeping pills could be fatal or taking certain cold remedies can cause allergies (for example, Stevens-Johnson syndrome). Pesticides are the same: they can be medicinal or they can be toxic, depending on the amount. However, there is one major difference that is cause for concern: while people take cold medicine of their own volition, they have no choice over whether or not they ingest any pesticide residues in the food they eat. To solve this issue, it must be carefully explained that the degree of risk is so small that it is not a problem.

Another cause for concern about pesticides is a sense of fear or anxiety about events that actually took place in the past. The use of highly-toxic parathion to increase food production after the war, Minamata disease, arsenic milk poisoning and the Kanemi rice oil disease were social problems which caused a kind of social allergic reaction to all chemical substances.

Misunderstanding about chemical substances is another reason for this concern. While the food products we eat every day are considered to be safe (including various chemical substances such as vitamins and spices), the idea persists that any additives not originally in the food and any residual pesticides are toxic, irrespective of the amount. However, chemical substances, whether natural or synthetic, are both poisons and also medicines.

Let us take ethanol as an example. Let us suppose that ethanol has a particular effect against pest insects and estimate an acceptable daily intake of it.

- A rat reproduction test result shows the no-observed-adverse-effect level (NOAEL) to be 2,000mg/kg/day [(1)]
- Taking into account the differences between species and the differences between individuals multiplied by a safety factor of 1/100, the acceptable daily intake (ADI) is 20mg/kg/day.

Multiplying this by the average Japanese body weight (53.5kg) gives an ADI of 1,070mg/day. This is equivalent to 8.6g of Japanese sake (which contains 12.5w/w% ethanol), meaning that drinking one cup of sake per day is equivalent to ingesting around five times the ADI.

The WHO International Agency for Research on Cancer (IARC) has already categorised ethanol in Group 1 (carcinogenic to humans), meaning it would not be allowed to be registered as a pesticide. This gives us a sense of just how strict pesticide regulation is.

Many natural chemical substances are far more toxic than pesticides. Conversely, there are countless substances that are not subject to the same level of safety testing as pesticides are. Buying organic produce is a personal preference. It is not the intention of this paper to stop people believing the "myth" that natural products are safe, but it seems that there is little realisation that these vegetables are made up of pesticide-like substances at 10,000 times the volume of any possible pesticide residues.

Another reason for concern about pesticides is the issue of how they are handled by the mass media or in schools. The mass media mainly report stories that arouse interest in people; that is, credible stories that disturb the peace and make people feel concerned. Viewers are not interested in hearing that all is well; if something does not raise the ratings, it will not be reported. There is no media coverage of the aforementioned misunderstanding about pesticides.

Even the NHK often uses expressions indicating that a particular food product is safe because pesticides were not used on it. Once a misunderstanding about pesticides has been evoked, it is very difficult and time-consuming to dispel it, because the sense of unease is a personal sentiment. Schools do not provide accurate education on safety risks and even contribute to this sense of unease about the dangers of chemical substances. There is a pressing need to dispel this sense of unease with frank, scientific explanations.

5.2. Agricultural Environment: Poor in Structural Reforms; Future Prospects

The pesticide industry is inseparably linked to agriculture. Before the war, agriculture was a fight against starvation. While Japan managed to overcome its food crisis as synthetic pesticides emerged after the war, there were other issues to deal with, such as environmental pollution. At least Japan has long since left its food issues behind and entered a so-called age of excess. Consumers demand produce that looks and tastes good, and farmers have responded to this demand.

However, faced with a reduction in agricultural land, an aging workforce and an increase in food imports, we cannot deny that agriculture structural reform is overdue. Pressure by the WTO, FTA and TPP to free up international trade will only increase. The Ministry of Agriculture, Forestry and Fisheries enacted the *Sixth-Order Industrialization Act*, albeit belatedly, and started initiatives to unite and strengthen production, processing and distribution/sales, as well as backing up other activities such as direct selling of local products, providing school lunches, promoting farm stays and exporting specialty products. The hope is that other initiatives will also increase in future, such as enlarging areas of high-quality farmland, encouraging larger-scale operations, such as community farming, and increasing horticultural establishments, such as plant factories.

Although organic farming is widely accepted by society, it is not as popular in Japan as it is overseas. This is probably because Japan's hot and humid climatic conditions make it very difficult to grow crops without pesticides or with fewer pesticides. According to MAFF statistics, organic farming accounted for 8,500 hectares or 0.18% of Japan's total agricultural land in 2011.

Thus, the reality is that Japan's agricultural environment is fraught with difficulties, but there is a way for it to survive: high-income-earning, domestic-production-minded consumers who will purchase fresh, safe and tasty food products even if they are a little expensive. Meeting this demand will require structural reform in the agriculture industry. Produce of such high quality is competitive enough for exporting, creating a "made in Japan" branding for agricultural products. Japan will need to expand this area and promote dynamic restructuring to bring in a level of income that is attractive to farmers.

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5.3. The Japanese Pesticide Industry: Present and Future

As mentioned previously, the pesticide industry has developed hand in hand with agricultural trends. Licenced technology imports boomed during the post-war period of increased food production, while investments into research and development during the period of rapid economic growth paid off with results at least rivalling those of the major corporations in the West. Even with rising concerns over safety and social problems arising from environmental impact, the pesticide industry managed to surmount these issues and survive to the present day. Reduced acreage and a slump in the economy resulting from oil shocks and a high yen has meant a gradual decline in pesticide shipments since the late 1990s, but the market is still stable.

This section outlines the author's own opinion on structural changes in the pesticide industry and why Japanese companies are equally or more competitive than the major corporations in the West.

5.3.1. Structural Transformation in the Pesticide Industry

The development success rate of new pesticides is decreasing every year. There are two reasons: it is becoming more difficult to invent potential new pesticides and the development costs required for safety and environmental impact evaluations have increased. Only one compound in several tens of thousands synthesized becomes a commercial product, meaning that it costs ¥3-5 billion to develop a new pesticide. This requires a scale of operation large enough to sustain this cost. It is difficult to cover a wide range of research alone, so companies have collaborated with universities or other companies, or outsourced some of the work, a trend that is likely to continue.

Although this study has not covered biopesticides, let us mention here that biopesticides are on the rise. As at 2010, there were 60 types of biopesticides listed on the pesticide register. While organic and reduced-pesticide farming are expected to expand, at present, biopesticide shipments only amount to ¥2.2 billion, no more than 0.6% of the market. Although there are advantages to biopesticides, such as little environmental impact, no concerns over residual toxicity and low chances of resistance developing, the reality is that they are not very popular because they are not very good for controlling multiple simultaneous pest insect outbreaks as has been seen in Japan, they do not offer a consistent effect, they are expensive and they do not last.

Another structural change has been the appearance of genetically-modified organisms (GMOs). While only a few of these have been permitted in Japan (such as blue roses), in the United States, nearly all soybeans and maize has been genetically modified. Farmers cultivate (Roundup Ready) crops resistant to non-selective herbicides such as Glyphosate (Roundup) or Glufosinate (Basta) and use only Glysophate to control weeds on their fields. This has quickly become popular due to benefits such as increasing yield size while enabling no-till farming, thus spelling the end of soil-treatment herbicides. The trouble with GMOs is that the only benefits are to the farmers. Consumers perceive no benefit from GMOs; instead, they have a sense of uneasiness about them. The current situation in Japan is that GMOs are undergoing safety evaluations, but are not accepted by consumers.

Recently there has been a problem with Roundup-resistant weeds. This problem was largely magnified when GMOs were developed in 1996. Future measures to counteract this will involve using multiple herbicides with different modes of action so as to avoid relying on one single formulation.

While there have been some major changes in the pesticide industry, as mentioned above, new, high-performance pesticides have always been in demand.

5.3.2. Survival of Japanese Companies: Dependent on Continuous Creation of New Formulations

How have Japanese companies managed to fare to well thus far despite far smaller in scale than the major corporations in the West? Will this competitive power continue? The following is the personal opinion of the author, but it may be of use as a reference despite being an abstract explanation.

(1) Advantageous Position

Japanese companies know Japanese agriculture. Consequently, they have an overwhelming advantage in effective and efficient development. Overseas companies are handicapped by the fact that although they might have a conceptual understanding, when they develop potential compounds for new formulations on their own, they are influenced by policies in their own country.

It is very important to set goals at the exploratory stage and incorporate biological screening methods that incorporate these goals. For instance, when conducting exploratory research on rice blast fungicides, it is vital to test the actual effect on rice plants actually infected with the disease, as some compounds are effective against the disease in the field despite showing no antibacterial effects in petri dish experiments. The key to success is having a meticulous screening system in place. There are also differences in climatic conditions, pest insects and weed outbreaks between the East and the West, so it is necessary to develop appropriate formulations, combination product formulations and methods of application in accordance with regional differences during the development stage. Rice blast control is a classic example that requires mastery of a range of treatment methods, such as seed treatment, spraying and submerged treatments. This requires combination formulations for one-shot application as well as jumbo formulations to save labor. Japanese companies are very good at this kind of development.

(2) Developing Small-Scale Pesticides

Japanese companies are characteristically able to develop pesticides they have discovered even if there is only a small market for them. When major overseas corporations decide whether or not to invest further into developing a formulation, they conduct strict market research, calculate the net present value of the formulation and determine whether future recovery is possible. The more countries that are involved, the greater the development costs. It can cost as much as ¥10 billion, which is higher than development carried out in Japan alone. Meanwhile, Japanese companies take only the domestic market into consideration and develop formulations even if the expected proceeds are small. At a rough estimate, it costs around ¥1.5 billion (direct expenses) to develop a pesticide from the time a particular candidate compound is identified. One example is miticides. Compared with insecticides, miticides are more prone to resistance developing and therefore there is constant demand for new formulations. Accordingly, formulations have a very short life span and there is little chance of recovering any investment. This is reason that Japanese companies have been able to develop so many miticides.

There are even instances of candidate formulations

abandoned by overseas corporations being acquired and developed for the Japanese market; in a sense, this creates a kind of dichotomy.

(3) Making One Development into Two

All pesticide companies, whether Japanese or from overseas, need an array of products in development (a product pipeline). Since development takes a long time, like medicine, the contents of the pipeline are a major indicator of the company's future business situation and also have an effect on stock prices.

In some cases, Japanese companies have discovered a promising potential formulation for development and, using that formulation as leverage, granted overseas development rights to an overseas manufacturer in exchange for the development rights in Japan for a formulation held by that company. This is a win-win relationship, in which each company benefits from the strengths of the other. Of course, companies sometimes make a bid for the world market on their own, but this requires a huge investment into development as well as facing a number of difficulties with overseas development. Japanese companies often use consultants or work on developments together with overseas companies.

In any case, Japanese companies must keep on coming up with promising potential candidates.

(4) Manoeuvrability and Teamwork in Small Organisations

Japanese companies are smaller in scale than their overseas counterparts, but there must be benefits to carrying out research and development on a smaller scale. If we ask if the abilities of individual researchers are any better than those in overseas corporations, or if Japanese are inherently more intelligent, the answer would have to be that "they are not inferior to their rivals, who are also good at what they do, but their rivals have the advantage both in the number of researchers and in the budget for research and development." However, the teamwork and manoeuvrability found in Japanese companies is able to compensate for any differences in scale.

Historically, Japanese research on organic synthesis has been first-rate. Japan can be proud that out of seven Japanese Nobel laureates in Chemistry, four of them have been specialists in synthetic organic chemistry; namely, Kenichi Fukui, Ryoji Noyori, Akira Suzuki and Eiichi Negishi. This tradition of outstanding work in synthetic organic chemistry has evidently been put to use in the development of pesticides.

From the 1990s onwards, the major overseas corporations combined combinatorial solid-phase synthesis with high throughput screening (HTS) to create an efficient system of synthesizing and evaluating large amounts (hundreds of thousands) of test samples in a short period of time (several months). This was an attempt to use robots to explore lead compounds more efficiently. First used in research and development of medicines, this method drew much attention for its suitability for pesticides. Further details on this technology are given in the cited work [(1)]. While this was initially said to have caused a paradigm shift in exploratory research, this method has not become universal due to other issues with it, such as not having enough diversity in its library of compounds for future development. While the major overseas corporations have the financial resources, they are focusing on HTS and building up their library of compounds and have not made any dramatic increase in their development of new formulations. Japanese companies have adopted this system but refined it to match their scale of business, putting some "soul" into their test samples. To put it another way, rather than engaging in inefficient, brute-force carpet bombing, they are shooting with a highly precise rifle with pinpoint accuracy.

Japanese companies focus on teamwork. A major weapon in their arsenal is their attitude towards research. Successful pesticide development requires the ability to integrate a range of key technologies. The key to success is being able to bring a range of experts together and unite their focus. The difference with the major overseas manufacturers is that they are huge companies and therefore have a greater division of labor. A typical example is patent applications. Patent applications by Japanese companies often have a large number of patent applicants listed, while applications by overseas companies often have only a few applicants listed, even if there were more in practice. While there may only be one or two actual inventors, being listed on the patent application is a major motivation incentive for all researchers involved.

(5) Serendipity

Serendipity is often cited as the reason for success in exploratory research, not only in the area of pesticides. However, if we look at the 20 Japanese formulations outlined in Section 4, we see that they were not discovered by chance, but by determination (tenacity) and a firm belief that "we are going to discover this by all means." While the modest expression "discovered by chance" often appears in academic presentations outlining the details of an invention, surely this serendipity is the result of persistent concentration and hard work.

(6) Future Prospects

Will Japanese companies continue to be competitive in the future? The answer is yes. The reason is that there is a very good Japanese market. Despite rising pressure for free trade, expected future increases in produce imports from overseas and an overdue structural reformation, Japanese agriculture will not fade out altogether. Fresh, good quality produce with the added value of security cannot be replaced by imports. Given the state of the market and the major damage from pest insects as a result of climatic conditions, pesticides will continue to be necessary.

However, although pesticides will remain an important resource for production, no significant future growth can be expected in terms of the scale of the market, given the development of organic farming, the emergence of biopesticides and the preference for reduced amounts of pesticides. New pesticides will always be in demand, although the hurdles to development are getting higher, both in safety assessments and environmental impact assessments. Sumithion and a number of other Japanese formulations have become world-class products. The hope is that other major formulations will continue to appear and follow in their footsteps.

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6. Afterword and Acknowledgements

Afterword

Despite having been involved in pesticide research and development, the author's study of the related history had only been fragmentary. The opportunity provided by this study was a chance to formally put together a complete picture of the history of the pesticide industry. I was reminded of how I used to engage in working on real challenges and seeking solutions for future issues rather than looking back on the past and learning from pioneers in the industry. Despite having a conceptual understanding of the importance of learning from history, too often the foolish choice has been made to simply learn from experience. This study has provided, albeit belatedly, a fresh sense of the importance of history.

Several major paradigm shifts have taken place throughout the history of the pesticide industry.

Until the late 19th century, the only means of controlling pest insects in agriculture was the rather inconsistent and inefficient use of whale oil on fields to eradicate leafhoppers; the only other means was by prayer. However, overseas technology arrived in the late 19th century and agricultural productivity rapidly improved. The pesticide industry started to develop with inorganic substances such as sulphur and copper as well as natural pyrethrum and nicotine, followed by organic mercurials. The population had hovered around 30 million from the 17th century to the mid-19th century, but rapidly increased in the late 19th century, reaching a peak 140 years later in 2008 at 128 million, more than 3.8 times higher. One reason for this has been the growth in agricultural productivity. This was the first paradigm shift.

After the war, pesticides played a role in averting a food crisis. Their popularity spread quickly with the appearance of synthetic organic pesticides such as DDT, BHC and parathion. The pesticide industry then experienced significant growth as Japan entered a period of rapid economic growth. This was the second paradigm shift. The pesticide industry became an established chemical industry.

The third paradigm shift had a major impact on the pesticide industry. Repeated cases of poisoning from highly-mammalian-toxic pesticides and long-term residual impact on the environment turned pesticides into a social issue. Laws and regulations were tightened, with safety assessments and environmental impact assessments becoming mandatory, resulting in the weeding out of a number of older, problematic pesticides. It was during this time that society branded pesticides as a threat to food safety; this stigma and the resultant sense of unease has been hard to shift and still lingers today, despite the problems having been resolved.

The final paradigm shift is still under way: the appearance of ultra-high-performance pesticides. A number of formulations have been developed that achieve the same effect as existing formulations at only a few grams or a few tens of grams per hectare, such as the sulfonylurea herbicides that appeared in the 1980s. Of course, these have no safety of environmental impact issues.

What will the next paradigm shift be? There have been changes in the industry as a result of the development of organic pesticides, the appearance of non-chemical pesticides such as biopesticides, the issue of reduced effectiveness due to a build-up of resistance and the impact of the rising spread of genetically modified produce. However, regardless of what changes may take place in the future, the hope is that Japanese companies will draw on their past successes and keep on contributing to society through the development of new technologies.

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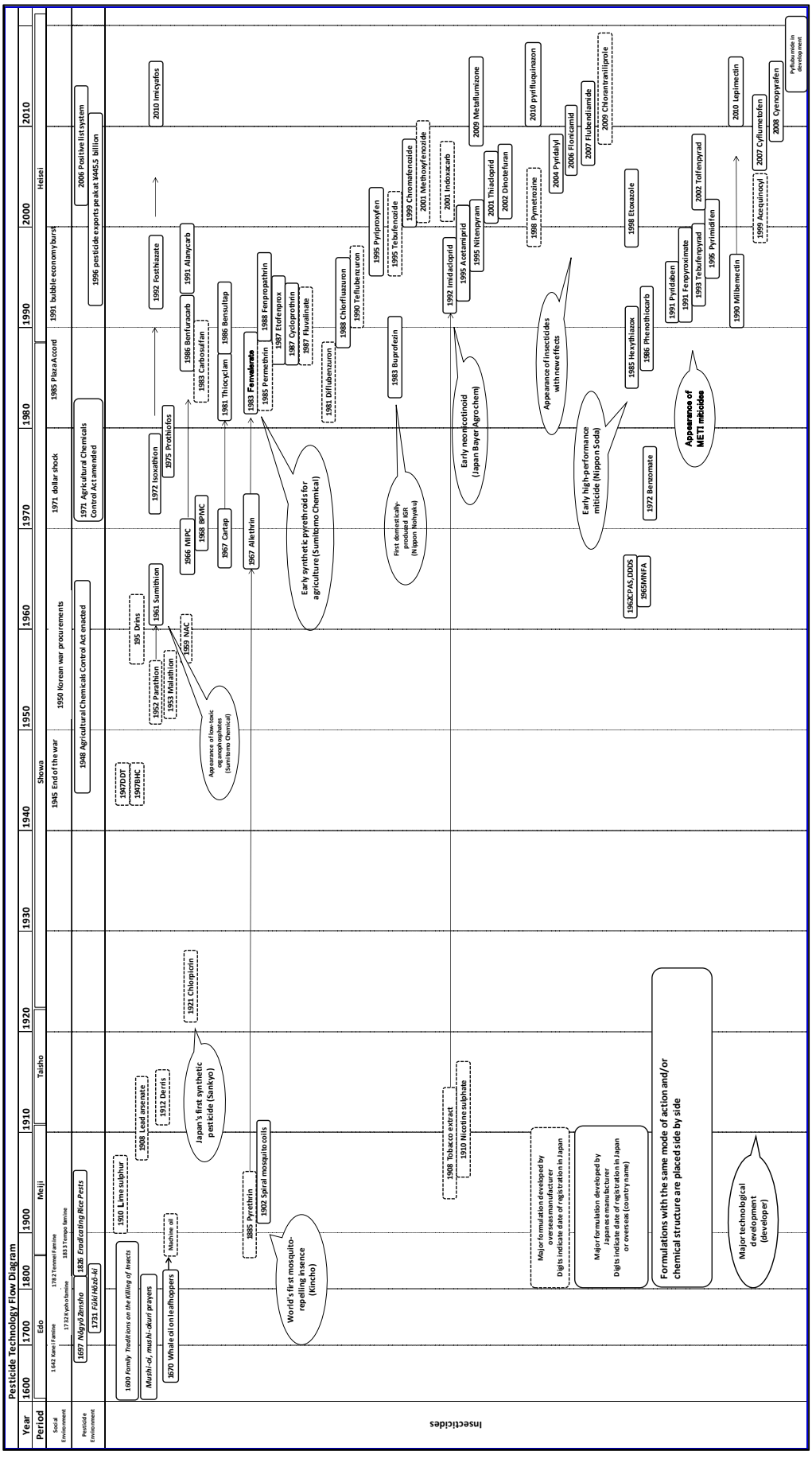
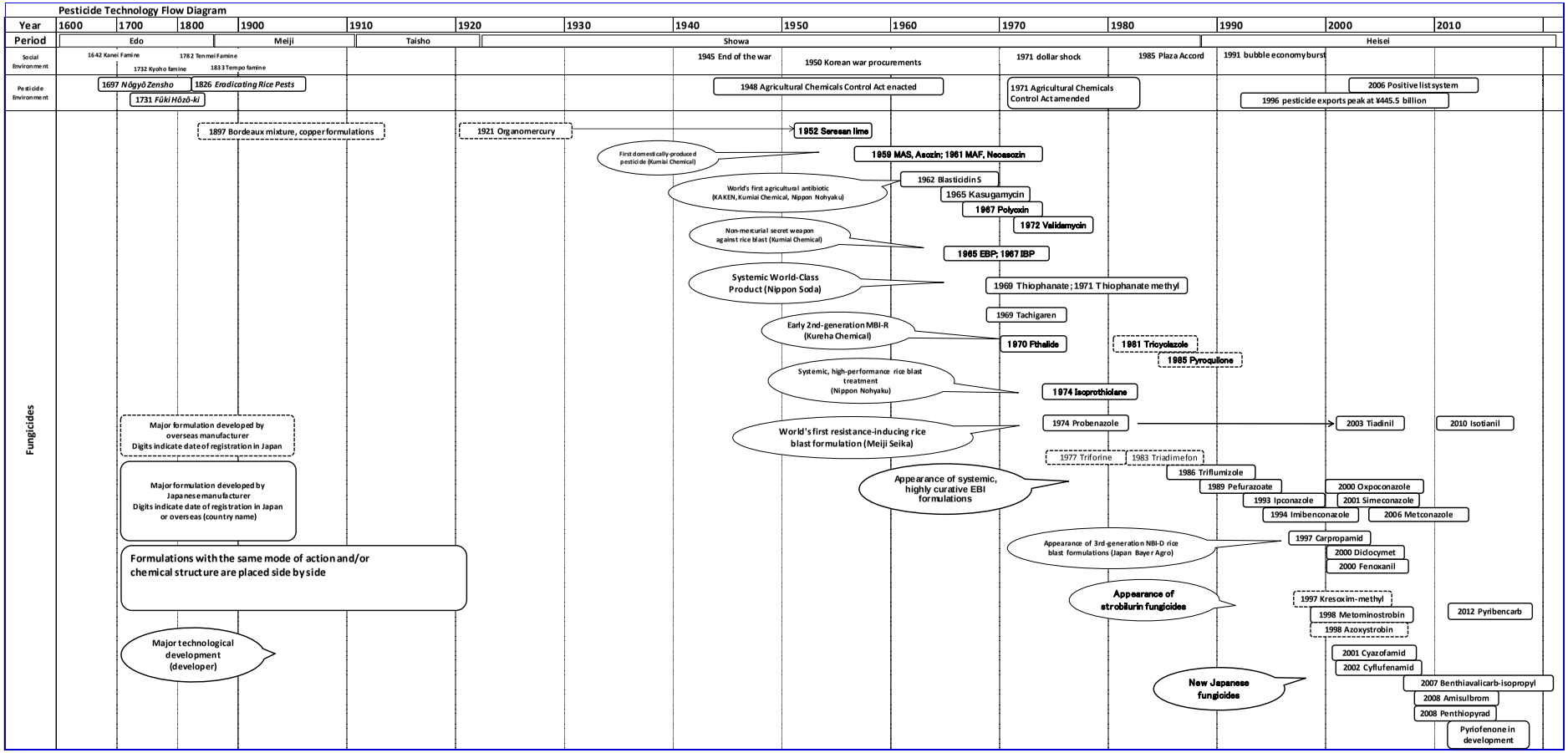
Pesticide Technology Flow Diagram




Pesticide Technology Flow Diagram
Year
1600
1700
1800
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
Period
Edo
Meiji
Taisho
Showa
Heisei
Social Environment
1642 Kanei Famine
1732 Kyoho famine
1782 Tenmei Famine
1833 Tempo famine
1945 End of the war
1950 Korean war procurements
1971 dollar shock
1985 Plaza Accord
1991 bubble economyburst
Pesticide Environment
1697 Nōgyō Zensho
1731 Fūki Hōzō-ki
1826 Eradicating Rice Pests
1948 Agricultural Chemicals Control Act enacted
1971 Agricultural Chemicals Control Act amended
2006 Positive list system
1996 pesticide exports peak at ¥445.5 billion
Fungicides
1897 Bordeaux mixture, copper formulations
1921 Organomercury
1952 Seresan lime
First domestically-produced pesticide (Kumiai Chemical)
1959 MAS, Asczin; 1961 MAF, Neoasozin
1962 Blasticidin S
World's first agricultural antibiotic (KAKEN, Kumiai Chemical, Nippon Nohyaku)
1965 Kasugamycin
1967 Polyoxin
1972 Validamycin
Non-mercurial secret weapon against rice blast (Kumiai Chemical)
1965 EBP; 1967 IBP
Systemic World-Class Product (Nippon Soda)
1969 Thiophanate; 1971 Thiophanate methyl
1969 Tachigaren
Early 2nd-generation MBI-R (Kureha Chemical)
1970 Fthalide
1981 Tricyclazole
1985 Pyroquilone
Systemic, high-performance rice blast treatment (Nippon Nohyaku)
1974 Isoprothiolane
1974 Probenazole
2003 Tiadinil
2010 Isotianil
World's first resistance-inducing rice blast formulation (Meiji Seika)
1977 Triforine
1983 Triadimefon
1986 Triflumizole
1989 Pefurazoate
2000 Oxpoconazole
1993 Ipconazole
2001 Simeconazole
1994 Imibenconazole
2006 Metconazole
Appearance of systemic, highly curative EBI formulations
Appearance of 3rd-generation NBI-D rice blast formulations (Japan Bayer Agro)
1997 Carpropamid
2000 Diclocymet
2000 Fenoxanil
Appearance of strobilurin fungicides
1997 Kresoxim-methyl
1998 Metominostrobin
1998 Azoxystrobin
2012 Pyribencarb
2001 Cyazofamid
2002 Cyflufenamid
New Japanese fungicides
2007 Benthiavalicarb-isopropyl
2008 Amisulbrom
2008 Penthiopyrad
Pyriofenone in development
Major formulation developed by overseas manufacturer
Digits indicate date of registration in Japan
Major formulation developed by Japanese manufacturer
Digits indicate date of registration in Japan or overseas (country name)
Formulations with the same mode of action and/or chemical structure are placed side by side
Major technological development (developer)

Pesticide Technology Flow Diagram
Year
Period
Social Environment
Pesticide Environment
1600
1700
1800
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
Edo
Meiji
Taisho
Showa
Heisei
1642 Kanei Famine
1732 Kyoho famine
1782 Tenmei Famine
1833 Tempo famine
1697 Nogyo Zensho
1731 Fuki Hozo-ki
1835 Eradicating Rice Pests
1945 End of the war
1948 Agricultural Chemicals Control Act enacted
1950 Korean war procurements
1971 dollar shock
1971 Agricultural Chemicals Control Act amended
1985 Plaza Accord
1991 bubble economy burst
1996 pesticide exports peaked at ¥446.5 billion
2006 Positive list system
Herbicides and Plant Growth Regulators
1950 2,4-PA
1953 MCPA
1959 MCPB
1956 PCP
1963 NIP
1965 CNP
1963 Gibberellin
1969 Benthiocarb
1971 Molinate
1972 Butachlor
1973 Chlomethoxynil
1972 Oxadiazon
1981 Chlorphthalim
1979 Naproanilide
1988 Clomeprop
1986 Dimepiperate
1989 Pyributicarb
1984 Pretilachlor
1984 Mefenacet
1986 Bromobutide
1993 Thenylchlor
1995 Etobenzanide
1996 Cafenstrole
1999 Indanofan
2000 Fentrazamide
1997 Pentoxazone
1999 Pyraflufen-ethyl
1999 Carfentrazone-ethyl
2000 Flumioxazin
2001 Oxadiargyl
2002 Fluthiacet-methyl
2007 Pyraclonil
Fenoxasulfone in development
Pyroxasulfone in development
1974 Daimuron
1979 Pyrazolate
1985 Pyrazoxyfen
1987 Benzofenap
1996 Cumyluron
2000 Oxaziclomefone
2001 Benzobicyclon
2010 Tefuryltrione
2010 Mesotrione
1980 Glyphosate
1984 Bialaphos
1984 Glufosinate
1980 Alloxydim
1985 Sethoxydim
1986 Fluazifop-butyl
1989 Quizalofop-ethyl
1996 Cyhalofop-butyl
1998 Clethodim
1982 Chlorsulfuron
1987 Bensulfuron methyl
1989 Pyrazosulfuron-ethyl
1989 Flazasulfuron
1993 Imazosulfuron
1994 Nicosulfuron
1995 Halosulfuron
1997 Eastern Europe: Sulfosulfuron
2010 Korea: Metazosulfuron
2010 Propyrisulfuron
1996 USA: Pyrithiobacsodium
1996 Pyriminobac-methyl
1997 Bispyribac-sodium
2002 Pyriftalid
2007 Penoxsulam
2010 Pyrimisulfan
First broadleaf herbicide for rice cultivation
First grassy-weed herbicide for rice cultivation
Early PPO inhibitor (Mitsui Chemicals)
World-class technology with diverse effects such as seedless grapes (Kyowa Hakko)
Key pesticide for sequential application on rice (fatty acid biosynthesis inhibitor) (Kumiai Chemical)
Major VLCFAE-inhibiting herbicide (Japan Bayer Agro)
Cell division inhibitor (SDS)
Early 4-HPPD inhibitor (Sankyo)
World's first herbicide produced by fermentation (Meiji Seika)
ACCase inhibitor for grassy weeds (Nippon Soda)
Appearance of high-performance SU herbicides (ALS inhibitors)
Appearance of high-performance PC herbicides (ALS inhibitor) (Kumiai Chemical)
Major formulation developed by overseas manufacturer
Digits indicate date of registration in Japan
Major formulation developed by Japanese manufacturer
Digits indicate date of registration in Japan or overseas (country name)
Formulations with the same mode of action and/or chemical structure are placed side by side
Major technological development (developer)

List of Candidates for Registration as Pesticide Industry Technology

No.	Name	Year of manufacture	Manufacturer	Format	Location	Reason for selection
1	Documents *Kokumin Hōjō-ki* and *Family Traditions on the Killing of Insects*	1600	Naiki Matsuda	in storage	Namba family; Kurahashi family; Akanahachimangū Shrine	Valuable documents containing Japan's oldest extant recorded pesticide preparation (of five ingredients including morning glory seeds and aconitum root) and its use; hailed as the origin of modern pesticides in Japan.
2	Spiral mosquito coil wooden prototype	1895	Kincho	in storage	Kishu Factory, Kincho	The world's first prototype wooden mould for mosquito-repelling incense, forming the pyrethrum into a spiral shape for a longer burning time. Subsequent versions are still commercially available.
3	Mechanical hand-wound incense extruder	Used late 19th century to 1957	Kincho	in storage	Kishu Factory, Kincho	Meiji-era hydraulic machine used to extrude incense into a noodle shape to be wound into a coil. The oldest and most valuable of its type in existence.
4	Pre-war mosquito coil posters for overseas	1930-1940	Kantaro Ueyama	in storage	Kincho	Valuable Showa-era posters used for exporting pyrethrum products such as mosquito coils around the world. Languages vary by country, including English, Chinese, Russian and Portuguese.
5	Guide to Pyrethrum Cultivation; *Japanese Pyrethrum*	1896	Eiichiro Ueyama	in storage	Kincho	The earliest manual written to promote pyrethrum cultivation; it played a part in Japan becoming the top pyrethrum producer in the world. 24 editions were published, but only 9 have been kept.
6	'KINCHO' mosquito repelling rods	1911-1914	as above	in storage	Kincho	The oldest extant resource of its kind; the world's first pyrethrum-containing mosquito repellent. 20cm in length with a 40-minute burn time.
7	'KINCHO Coil' mosquito coils	1919-1925	as above	in storage	Kincho	The world's first mosquito-repelling incense, made into a spiral shape for a longer burning time. Exported all over the world, these are widely used today. This is the oldest extant product of its kind.
8	Wooden incense extruders	c. 1902	unknown	on display	Sanda Mosquito Fumigation Archives	Altar incense sticks made into mosquito repellent; a valuable prototype prior to Taisho-era hydraulic mechanization. Initially machine-extruded and then coiled by hand.
9	Bottled chloropicrin fumigant	c. 1948	Mitsui Chemicals	on display	Japan Plant Protection Association Museum	Chloropicrin is the first synthetic organic pesticide industrially produced in Japan in 1921 and is still widely used today. These oldest product bottles in existence are highly valuable.