PESTICIDE INNOVATION: TRENDS IN RESEARCH AND DEVELOPMENT

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CHEMISTRY IN AGRICULTURE - HOW IT CAME ABOUT

Jonathan Swift writes in Gulliver's Travels about the King of Brobdingnag:

> *"He explained, that whosoever allows two corn cobs or two blades of grass to grow on a piece of ground where previously only one grew, would do more for mankind, and his country a greater service, than all the politicians together."*

Men such as the American, Norman E. Borlaug, or the Briton, George Douglas Bell, have achieved even more with the cultivation of high-yielding wheat and barley varieties, but are nevertheless virtually unknown to the general public.

Without the sensational increase in crop yield, neither the growing prosperity in the industrialized countries nor the satisfactory feeding of the remainder of the world's rapidly increasing population would have been possible.

As well as the aforementioned cultivation methods and mechanization, chemistry has also made a considerable contribution to the advancement of agriculture.

The first pesticides such as the legendary Bordeaux mixture were serendipitous, to a certain extent "off the shelf", chemicals and were the first modest weapons in the fight against epidemics in potato and wine cultivation. These first useful pesticides were mostly inorganics, which were nonselective, only active in high application rates and rather toxic (Fig. 1).

Carefully planned and targeted industrial research with the aim of discovering new, selective, organic, and biologically active substances for use as pesticides dates from the period just before and during the Second World War. Easily prepared compounds such as E 605, DDT, or the phenoxyacetic acids mark the first successes (Fig. 2) . The tremendous and beneficial effect that, for example, DDT has had in the control of malaria requires no further comment.

This short excursion into the history of pest control is intentionally placed at the beginning of this article. Without prior knowledge of the starting point it would be difficult to comprehend the impressive growth of this new branch of the chemical industry, the agrochemical industry, which today has attained a world market value of 26 billion dollars. In the beginning there was

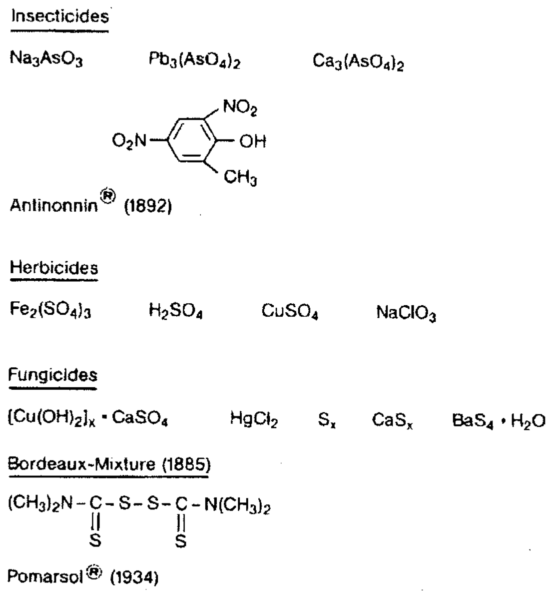


Fig. 1
First Generation of Agrochemicals (1800-1930)

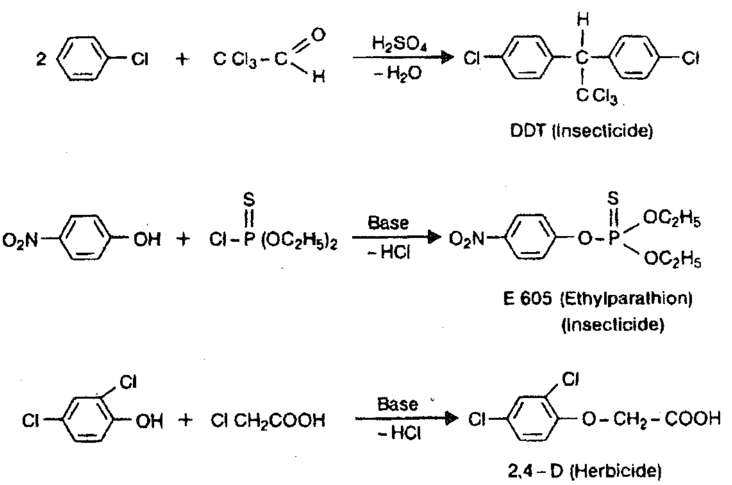


Fig. 2
Second Generation of Agrochemicals (1940-1950)

a tremendous requirement to secure the agricultural advances which had been attained through improved crop varieties, fertilizers, and mechanization against the influence of pests. The acceptance of pesticides by the farmer was extremely high, not in the least because of the accompanying humanization of his life and the reduced economic risks. The use of pesticides meant a considerable return on investment.

A perfect world, a happy partnership, or so it appeared.

THE PRESENT SITUATION

Highlighted by the publication of R. Carson's Silent Spring, the relationship between chemistry and agriculture, at least in the eyes of the general public, has considerably worsened.

Severals years ago a survey from a German university demonstrated that 81 % of those questioned see more disadvantages than advantages in the use of fertilizers and agrochemicals in modern agriculture. This result takes on a greater significance in the light that only 51 % see more disadvantages in the use of nuclear power.

One could discuss the reasons for this lack of acceptance for hours on end. Of course, in the past the occasional noncritical use of large amounts of pesticides has contributed to the previously cited disapproval. Due to the high efficiency of chemical pesticides the traditional agricultural knowledge about plant hygiene as preventative measure against pests, which had been accumulated over hundred's of years, was sometimes overshadowed.

At this point, only two reasons for the lack of acceptance are more precisely illuminated. First, the general "chemophobia" of modern society which is irrationally directed toward synthetic chemicals. In reality, in terms of frequency and abundance these are completely dominated by natural "environmental chemicals", whose properties are completely misjudged as being "soft and kind" and quasi-"God-given".

To illustrate the naiveté of this impression substances found in normal "everyday" foods are listed in Fig. 3. Mother Nature has armed herself with an inexhaustible arsenal of chemicals, which for the most part are nothing more than chemical weapons for defence against hostile organisms and can therefore be viewed as natural pesticides.

One often hears in discussion the improper use of a so-called omnipresent equilibrium, which can be negatively influenced by even the minute traces of man-made substances. Even a single molecule of a substance recognized as carcinogenic, mutagenic, or teratogenic in high dosage in animal experiments is suspected by the general public to induce these undesirable effects.

How many people in modern industrial society are still confronted with the problems encountered by the farmer in defence of his crops? In the corner supermarket, the consumer finds a variety of reasonably priced, highquality goods in abundance, and at the same time reads about surpluses that are destroyed to maintain price levels. Therefore, it should be of no surprise that there is little understanding for the use of pesticides. The immeasurable benefits derived from the use of pesticides remain unseen. The high efficiency of modern agricultural production is seen as an integral part of our modern society, but the necessary contribution made by chemistry is continually ignored.

	Substance	Effect
Carrots	Carotoxin	Nerve toxin
Pepper	Piperine	Mutagenic
Parsley, Celery	Psoralen	DNA-damage, Cancer
Radish, Onion, Broccoli	Thiols	Thyroid gland, inhibition of Thyroxin synthesis
Coffee	Catechols	DNA-damage, Skin irritation
Mushrooms	Agaritine	Stomach ulcers
Apple	Phloridzin	Glycosuria
Mustard, Horseradish	Allylisothiocyanate	Chromosome damage, Cancer
Rasberry	Coumarin	Liver, Blood clotting

If the same safety regulations covering synthetic pest control agents and food additives were applied to "natural" substances,

the consumption of foodstuffs would be forbidden.

Fig. 3
A "very healthy" Meal

However, the situation should be examined in more sober light. To moan about the unscientific, emotional attitude toward chemistry, about the vehement criticism of ficticious residual risks, and about the reluctance to see the huge benefits brought by chemistry, provides no constructive help. The facts and arguments must be presented in layman's terms and the trust in the use of agrochemicals must be strengthened by continuously developing and improving the technology.

Zero limit values - without risk evaluation - do not bring additional security, but provoke fears and insecurity. Exceeding such a limit value is in the eyes of the general public mistakenly the transition from good to evil. The observance of such senseless limit values ties up funds which are urgently needed for other areas of research such as prognosis models, resistance research, and discovery of new active substances.

WHERE DOES THE AGROCHEMICAL INDUSTRY STAND TODAY?

Almost unnoticed by the general public, agrochemistry has changed itself into a high-tech industry. In the eyes of an expert there is at present practically no difference in the highly scientific approach to research and development in the pesticide and pharmaceutical areas. Both now als have comparable average development time spans of 8 - 10 years which reinforces the point.

Pesticides, along with pharmaceuticals, belong to the most extensively tested chemicals with which man comes into contact. This is a fact that nobody would contradict. There is not only an impressive arsenal of products available worldwide, but these products are being ever more rigorously tested.

The time when the information about a pesticide was limited to its structure and observed activity belongs to the distant past (Fig. 4).

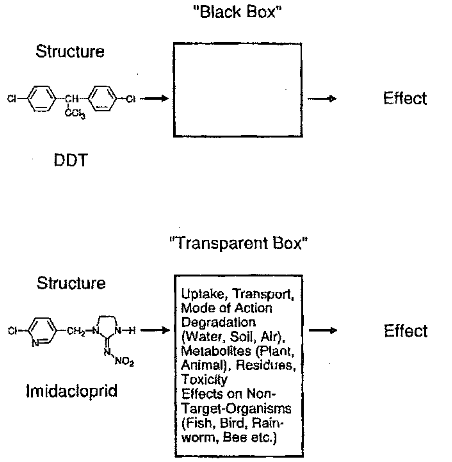


Fig. 4.
Deadly Risks

The earlier "black box" is at present transparent, filled to bursting with information gathered from scientists who are absolute experts in their fields. As in the pharmaceutical sector, the clarification of the mechanism of action of a substance at the target enzyme or receptor is a part of basic research in the early stages of development. With the aid of biochemical and microbiological techniques, this kind of research has been considerably boosted. These methods also allow the possibility of recognizing possible resistance or toxicologicial risks at an early stage in the discovery process.

The transparent active substance, whose relevant properties, environmental fate, and impact on the ecosystem are to be clarified, presents an interesting challenge for researchers from various disciplines. An array of problems, such as how do absorption and transport function, what is the effect on the target organism, and what is the mechanism of action, how is the active substance degraded in the plant, animal, water, soil, and air, what are the side effects in nontarget organisms, and what sort of toxicological profile has the substance, is addressed by a multitude of committed scientists.

Unfortunately, there is a bitter pill that all of us in the enthusiastic quest for new scientific territory must swallow, and that is the limitation placed on available money.

With a background of worldwide stagnating markets, and above all rapidly increasing registration requirements which imply growing expenditure for research and development, industry must question the future profitability of its innovatory activities. Put in simple terms, research and development costs are running away from us. As opposed to the world pharmaceutical market, where for example, the market for antiinfectives alone has a volume of approximately 3/4 of the total agrochemical market, the individual market sectors for agrochemicals are considerably smaller and consequently the dramatic increase in research and development costs must be curtailed.

The development costs for a new product have increased by a factor of five between 1975 and 1990 and at present lie at approximately 250 - 300 million DM. The lion's share of this increase is devoted to the detection of residues in the environment and the influence of the active substance on target and nontarget organisms (Fig. 5).

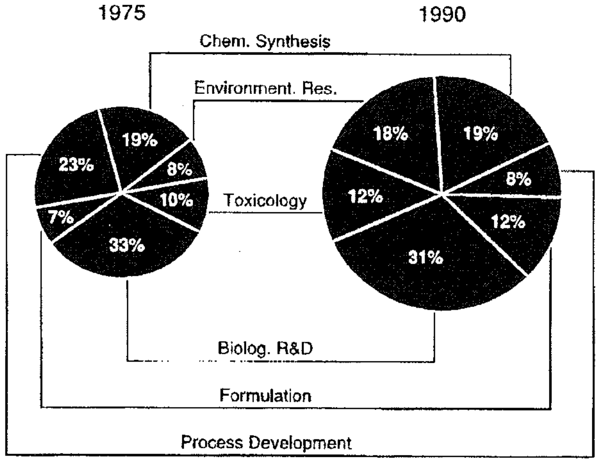


Fig. 5
Increase of Research and Development Costs - Bayer Crop Protection (World)

It is not so long ago that Bayer was proud of the broad spectrum of products and formulations it had to offer its customers, the farmers. With increasing costs, in particular for product reregistration, this variety has proved to be a considerable burden. An additional painful blow, particularly for researchers, came with the "thinning out" of the product pipeline, because the expected turnover from many of the products no longer justified their development costs.

For certain minor uses the farmer no longer has a registered product available. Products with a greater market potential are being sought after, therefore a concentration of resources on the larger markets has taken place. It could be argued that the registration requirements are already extreme and unjustified if good and practical products are lost to the market, even though their application involves only minute risks.

WHAT DOES THE FUTURE HOLD?

One thing is certain and no sensible person can deny it: in future the protection of cultivated plants will be needed more than ever in order to secure the yields from our planet.

With the background of a population explosion the safeguarding of the world's present and future food supplies is a major problem facing mankind.

In the year 2000 the population of the world will be 6.5 billion and could reach 10-12 billion by the year 2100 (Fig. 6). Up to now there is no sign of a reversal in this trend.

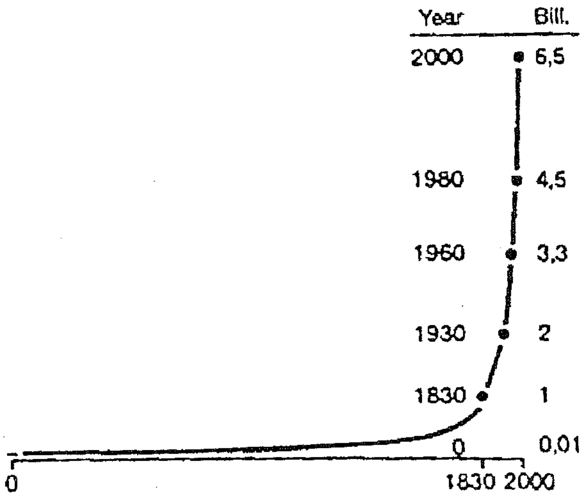


Fig. 6
Increase of World Population

The above-mentioned was to elucidate the general conditions that current and future innovations in plant protection are submitted to. The agrochemical companies have already focussed their R&D-strategies accordingly. The magic words are: take the offensive in innovation and improve efficiency.

Some of the present rules and regulations are from a scientific point of view senseless and strangle the possibility for further innovations. If this trend can be halted and if management continues to make the necessary money available for research and development, it will still be possible to make innovative contributions to the next generation of pest control agents.

Due to continuous scientific advancement in all disciplines, the above-mentioned progress in innovative agrochemistry can be guaranteed.

Conditions are such that in the not too distant future level-headed risk-benefit considerations will overcome pure emotion and research efforts will be socially accepted.

Allow me to introduce a few theses concerning the key-note of innovation and actual trends in R&D. I will discuss them in detail and give some examples later on.

- Chemical methods will play a dominating role well into the 21st century.
- Revolutionary changes will not occur, but the existing technology will undergo a continuous evolutionary development.
- The innovation and development process of new drugs will become considerably more efficient. Especially by minimalizing, automatizing and computerizing essential procedures.

- Fewer and successively safer made-to-measure active substances will be developed into commercial products.
- Improved formulation and application techniques will let drugs act more specifically resulting in higher efficiency but also in improved safety for the user, the consumer and for the environment.
- Nonchemical measures will increasingly support chemical measures in an integrated pest control strategy.
- The introduction of transgenic plants with incorporated herbicide and insect resistance will produce medium-term shifts within the corresponding markets.
- Diagnosis and prognosis methods will be considerably further developed (economic threshold concept)
- Applicator education and training will play an increasingly important role in the future.

CHEMICAL METHODOLOGY

A clear definition of what is meant by chemical methods is first required. These include the use of active substances from synthetic or natural origin, which can be clearly defined single compounds or mixtures of substances and which can function by lethal or modulating principles. This means that the use of pheromones, tobacco, and stinging nettle extract are nothing more than chemical pest control!

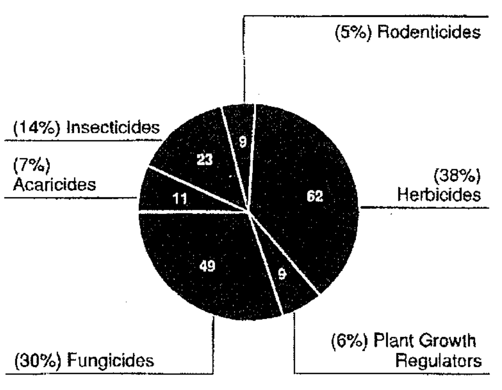


Fig. 7
The 164 Substance Classes are Represented in the 590 Registered Agrochemicals (1989)

Synthetic chemistry has far from shot its bolt. Up to now there is no end in sight to the flow of new promising lead structures, a fact which is supported by a glance into the patent literature. Figure 7 shows that of the 590 active substances listed since 1930 at least 164 substance classes are represented.

One can estimate that for every successful substance class there are three to five more which have not led to commercial products. Since 1930 this amounts to a sum total of new lead structures with a commercial potential of at least 600 - 700.

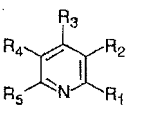
In Fig. 8 are listed interesting structural classes of the 1970s and 1980s which have provided answers to important problems.

Class	Indication	Mode of Action
Azoles	Fungicides PGR's	Ergosterol Biosynthesis Inhibitors
Glyphosate	Herbicide	Aromatic Aminoacids Biosysnthesis Inhibitor
Triazinones	Herbicides	Photosynthesis Inhibitors
Acylanilides	Fungicides	Nucleic Acids Synthesis Inhibitors
Pyrethroids	Insecticides	Na-Channel Effectors
Acylureas	Insect Growth Regulators	Chitine Biosynthesis Inhibitors
Sulfonylureas	Herbicides	ALS-Inhibitors
Imidazolinones	Herbicides	ALS-Inhibitors
Diphenylether	Herbicides	PPG-Oxidase Inhibitors
Nitroguanidines	Insecticides	n-AChR-Agonists
Phenoxypropionic Acids	Herbicides	ACC-ase Inhibitors

Fig. 8

Important New Classes of the 1970s and 1980s

In the foreseeable future, people should not worry that this flow of valuable new classes of active substances and lead structures will dry up. The possibilities for variation within modern synthetic chemistry are simply too diverse.



$Z \approx 1/2\ N^5$

Z: Number of possible individual compounds

N: Number of different substituents for positions R_1-R_5

N	Z
10	50 000
20	1 600 000
30	12 150 000
.	.
.	.
.	.

Fig. 9

Structural Variability

Let us take a look at the example of a pyridine ring which has five possible positions for substitution (Fig. 9). With 10 different substituents, 50,000 new compounds are possible; with 30 substituents the number is more than 12 million. In particular, the number of new types of substituents has considerably increased in modern crop protection chemistry. The already available and almost daily increasing arsenal of substituents is remarkable.

Examination of interesting active substances from the last decade reveals a multitude of compounds containing a pyridine rings. Interestingly, they have differing mechanisms of action and are active in different indications (Fig. 10).

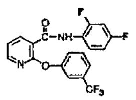
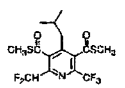
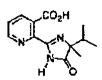
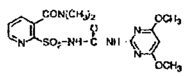
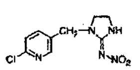
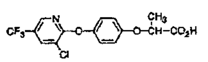
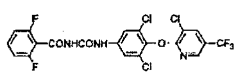
	Diflufenican	Herbicide Inhibitor of carotenoid biosynthesis
	Dithiopyr	Herbicide Inhibitor of mitosis
	Imazapyr	Herbicide Inhibitor of branched-chain amino acid biosynthesis
	Nicosulfuron	Herbicide Inhibitor of branched-chain aminoacid biosynthesis
	Imidacloprid	Insecticide Agonist of the nicotinic acetylcholine-receptor
	Haloxyfop	Inhibitor of acetyl-CoA-carboxylase
	Chlorfluazuron	Insect growth regulator Inhibitor of chitine biosynthesis

Fig. 10
New Pyridine based Commercial Products of the 1980s.

The decisive factor for biological effect is not the basic chemical element but rather a specific substituent in a clearly defined position in the molecule. Due to a continuously growing number of tools at the chemists disposal, people can await the discovery of still more interesting classes of active compounds.

An important limitation must certainly be made. The actual success rate, that is to say the number of marketable products in relation to the number of compounds tested, will increasingly decline. This relationship is illustrated in Fig. 11 for Bayer and is also typical for other companies.

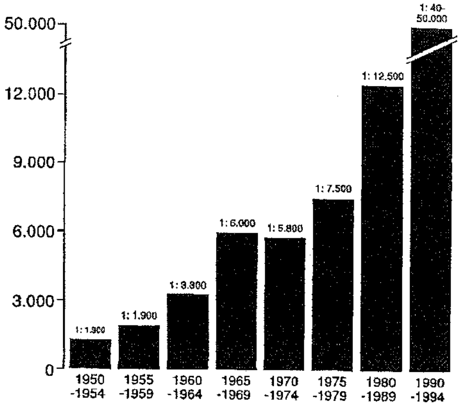


Fig. 11
Success ratio

A new predevelopment product must, on the one hand, measure up against the already available highly active economic commercial products and, on the other, must satisfy the ever-increasing registration requirements in the areas of selectivity, toxicity, environmental impact, and market potential. It is true that biological activity has always been a necessary requirement, but this alone is by far not sufficient.

INNOVATIONS IN SCREENING AND SYNTHESIS - HIGH TROUGHPUT SCREENING AND COMBINATORIAL CHEMISTRY

In the meantime, all companies engaged in research have taken the more stringent guidelines into account. Key words here are more efficient, more rational discovery of lead structures and targeted optimization of all development-relevant parameters as soon as possible in an integrated approach. This requires very early information about possible problems with toxicity and environmental impact. The introduction and evaluation of relevant highly efficient early test systems is well underway.

Only when the necessary certainty is found can the actual development with the worldwide field tests, process development, intensive animal experiments, metabolism studies, and residue analysis be justified. Fig. 12 makes clear how only through the interlocking efforts of synthetic chemistry, natural product isolation, intelligent biochemical and biological test systems, mechanism studies, target identification, and computer-assisted design, etc. this early certainty and high efficiency can be obtained.

In the beginning there was the lead these are the first words from the credo of the drug hunters. A lead structure is a defined chemical compound derived from synthetic or natural pools. It exhibits a considerable activity in relevant biochemical or biological assays.The nearer the assay is to practice the more relevant the test result and therefor the more worth it is to pursue the detected hit.

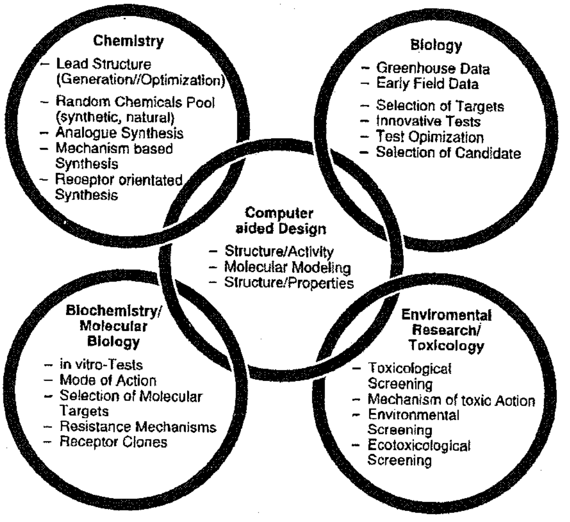


Fig. 12.
The Integrated Discovery and Optimization Process

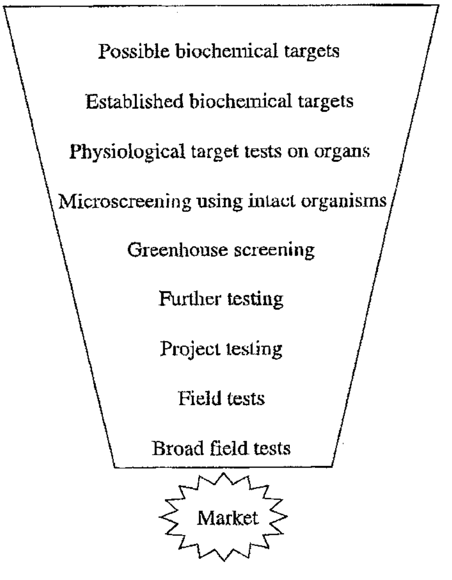


Fig. 13
Screening Cascade

Naturally, to screen compounds with the complete target organism (insect, plant or fungus) is nearer to practice than a biochemical assay. Influences by resorption, transport and metabolism on the overall effect of the drug are already included in the test result. In addition, one can screen all potential targets within the organism even without knowing them. Target-screening can only reveal compounds acting on the tested target.

This relationship is reversed if one compares the number of compounds that can be tested at reasonable costs.

Therefor one will try to use the appropriate assay depending on number and quality of the compounds.

As already mentioned, the lead stands only at the very beginning. Normally, hundreds, maybe thousands of more compounds will have to be synthesized during an SAR-optimization in order to identify a predevelopment product and bring it into the market.

Considerable intuition is required by the chemist when confronted with extremely important strategic decisions. Is it worth the effort to proceed with a lead structure possessing weak activity? Do the scientists find themselves already on an "activity plateau" where no further increase is possible? It requires the healthy optimism of creative chemists and biologists to pursue exactly this lead and not another.

How to generate a lead structure? During the past decades drug scientists repeatedly had to change their views substantially in answering this question (Fig. 14).

Pesticide Innovation

It all starts from a valid lead structure.
From random to design and back to random

< 1960 **The Past**	**The Vision of the Eigthies**	> 1990 **The Future**
• costly greenhouse testing	• known biological targets	• all possible targets
• g-amounts of test compounds	• receptor-inhibitor-modelling (lock-and-key model)	• high throughput testing (in vitro, in vivo)
• practically no automation	• de novo design	• automation
⇩	⇩	⇩
• limited testing of natural compound pool	• testing only for designed compounds necessary	• bottle neck: chemistry
• random chemistry from different sources ⇩	⇩ but	• the solution:
• bottle neck: greenhouse testing	• lack of information about relevant targets	- automated synthesis - combinatorial chemistr - molecular diversity
	• only in vitro lead structures	

Fig. 14
Lead Structure

In the early phase of crop protection research, labour-intensive greenhouse tests formed the bottleneck in finding new leads. These tests afforded high dosage of the active ingredients and in order to test the compounds in all indications extensively several grams were needed. Thus, broad testing of compounds from various sources (especially natural products and academics) was severely limited. Automatization was used neither in synthesis nor in testing.

Progress in biochemistry, molecular biology and computer technology brought up a vision of the 80s. The new magic words were: Rational design and molecular modelling.

Based on the knowledge of the three-dimensional target structure it should be possible to design the optimal effectors by molecular modelling just like fitting a key into a lock.

In this vision, synthesis was just the tool for providing a hand full of tailor-made structures. One can then select the predevelopment product from these few compounds by biological testing.

The experienced drug scientists knew that this wouldn't work. The necessary information of the relevant targets for a de novo design was missing. Furthermore, having found an in vitro activity on an isolated enzyme or receptor doesn't necessarily implicate an in vivo activity of a drug at the target organisms: plants, insects or fungi. To put it brief, de novo design to generate a lead hasn't worked out yet.

Nevertheless, molecular modelling is undoubtedly a method for lead optimization. By the so called "Active Analogue Approach" it is possible nowadays to correlate the structure of molecules with their biological activities in the same biochemical assay using special software. One can identify essential structural features, the so called "Pharmacophores", forming a matrix for the synthesis of new drugs.

Since a few years the strategy for lead finding has switched back once more to the random search. Prerequisite was the generation of "High-Throughput-Test-Systems". Today, robots are available, that can test more than 100.000 compounds in a biochemical assay in only a few weeks.

This technology offers completely new perspectives to pharmaceutical as well as to agrochemical research. Nevertheless, there is a major difference between finding and evaluating a pharmaceutical and an agrochemical lead.

Whereas pharmaceutical research depends on biochemical and molecular biological assays, agrochemical research has the alternative option to use medium throughput micro-tests in vivo on a few selected organisms next to the above mentioned high-throughput systems. Today these in vivo tests afford only a few mgs of the test compound.

Now chemistry has evolved to be the bottleneck. How to generate a broad diversity of chemicals in order to feed the hungry test systems?

Classical chemical synthesis with an average output of 200-300 compounds a year cannot keep up with this new situation (Fig. 15).

The solution could be a completely new innovative technology: the combinatorial automated synthesis.

This technology evolved in a very short time as a counterpoint to the automated high-throughput screening and still is further developing rapidly.

The basic principle of combinatorial synthesis is to successively combine "chemical building blocks" to large ensembles of defined compounds with a sufficient diversity. These

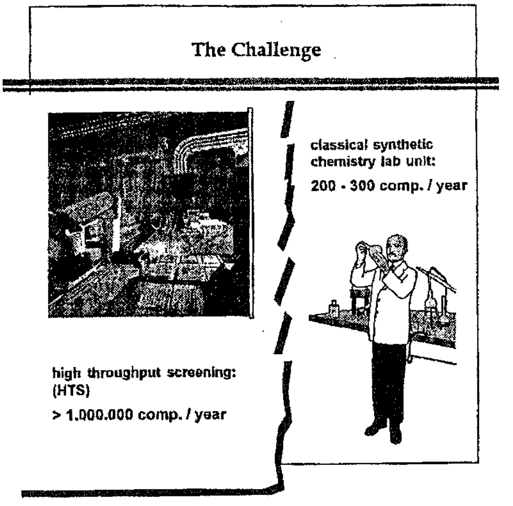

The Challenge
classical synthetic chemistry lab unit:
200 - 300 comp. / year
high throughput screening: (HTS)
> 1.000.000 comp. / year

Fig. 15

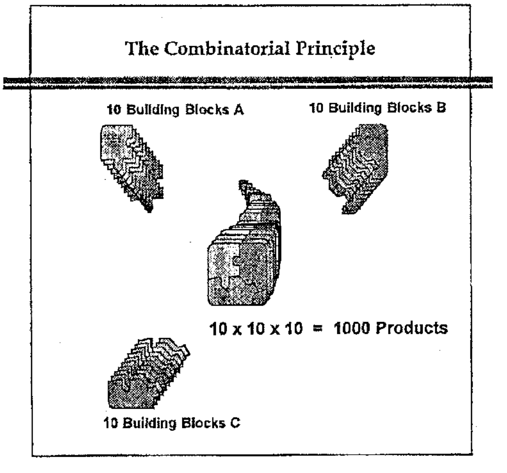

The Combinatorial Principle
10 Building Blocks A
10 Building Blocks B
10 x 10 x 10 = 1000 Products
10 Building Blocks C

Fig. 16

ensembles are the so called "chemical libraries". For example, the combination of A, B and C containing 10 building blocks each according to the pattern shown in Fig. 16 will lead to a library of 1000 compounds.

The realization of such a combinatorial principle naturally should be performed on an automatized system. Herefor, solid-phase synthesis turned out to be a useful tool.

The procedure for synthesizing such libraries is schematically depicted in Fig. 17.

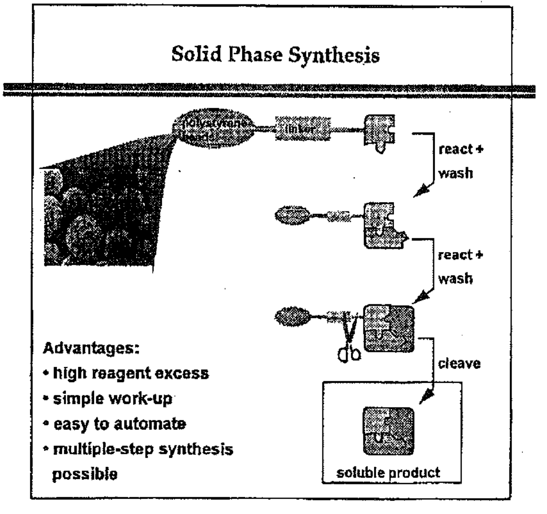


Fig. 17

A normal synthetic lab still demands a considerable manual effort with multi-step reactions and tedious upworks in order to gain maximum purity each step. On the other hand, nowadays solid-phase synthesis allows the chemist to perform a continuously growing variety of steps without having to isolate and purify the intermediates. By cleaving off the products from the solid carrier one can isolate mg amounts of compounds in a broad diversity and a highly efficient manner. These amounts are sufficient for the above mentioned high-throughput-systems.

Solid-phase synthesis has already been used in peptide synthesis for decades. By combining amino acids to peptides in the above shown manner one can expect the following peptide library (Fig. 18).

But peptides normally aren't very good agrochemicals for several reasons. Other libraries with heterocyclic moieties are more attractive. But also in these cases it is possible to achieve a high diversity of chemical individuals by applying the above mentioned strategies. So one can offer to the hitherto unknown lock a high number of keys for fitting, hereby increasing the probability of at least finding a close fit.

Combinatorial chemistry and high-throughput screening have initiated a revolutionary change in the search and generation of new lead structures. Since these technologies have only recently been established and are being evolving further, no success has been achieved with this technique yet.

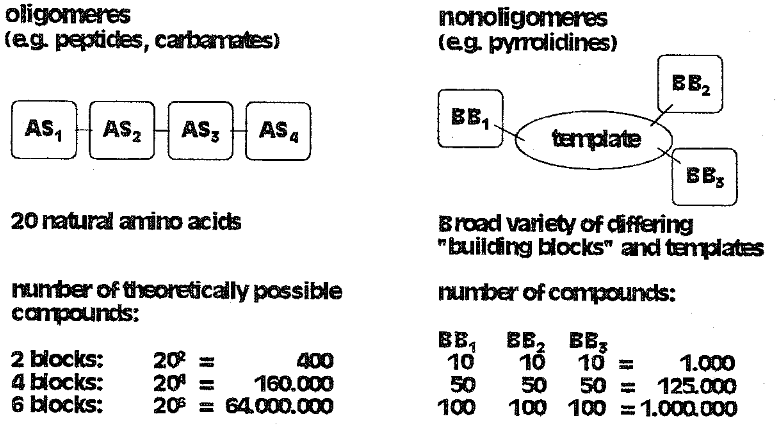


Fig. 18
Compound Libraries

The future will tell us, if the game with random chance can really be won by entering it with a high number of compounds. More active hits from primary screening will have to result in more innovative solutions to the problems of agrochemistry.

The innovative classes of compounds I will refer to now were still discovered by the "classical" method. Either by random screening of chemicals resulting from chemistry driven programs as in the case of the sulfonyl ureas and the chloronicotinyls or by screening of natural products as in the case of the methoxyacrylates.

OPTIMIZATION OF LEAD STRUCTURES

A completely new class of herbicides, which in terms of activity leave all previous ones in the shade, are the sulfonylureas (Fig. 19). The prototype, which resulted from an originally chemically driven program, was only moderately active (ca. 2 kg/ha).

Optimization led to a new class of herbicides with an application rate which up until then had never been seen before and with a selective mechanism of action, nontoxic to warm-blooded animals, acting by inhibition of the biosynthesis of branched-chain aliphatic amino acids.

Through systematic structure-activity optimization of the originally only cerealselective active substances, a wide array of products with selectivity for almost all important crops was found and developed (Fig. 20). Today 20 different sulfonylureas have entered the market.

Throughout the world there has been an enormous increase in effort from numerous companies to gain a foothold in this area. This has led to new highly active substances which are no longer sulfonylureas, but nevertheless inhibit the same target enzyme (Fig. 21).

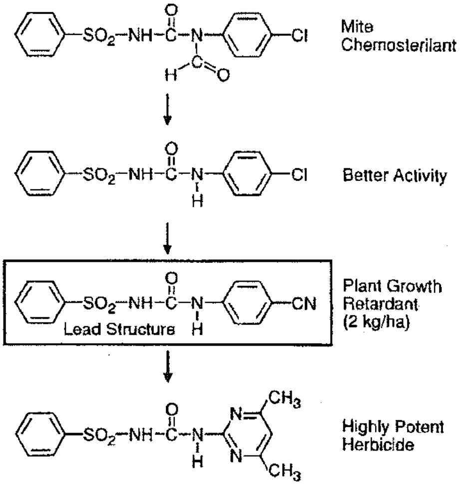


Fig. 19
Discovery of the Sulfonylurea Herbicides (G. Levitt, Dupont)

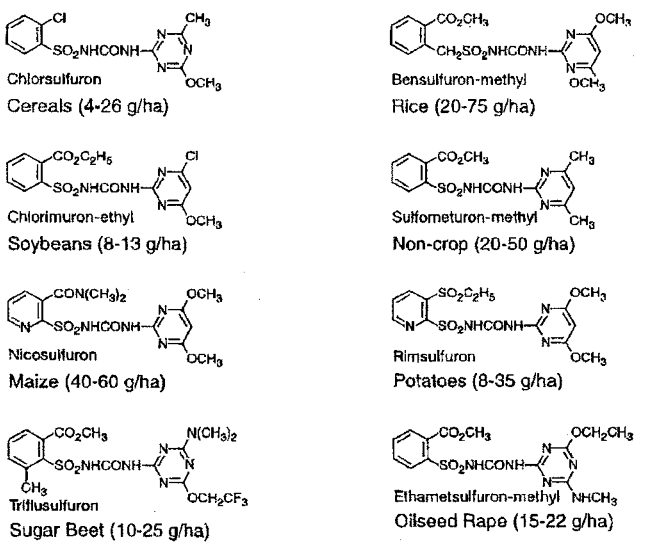


Fig. 20
From Cereals to Sugar Beet Herbicidal Sulfonylureas

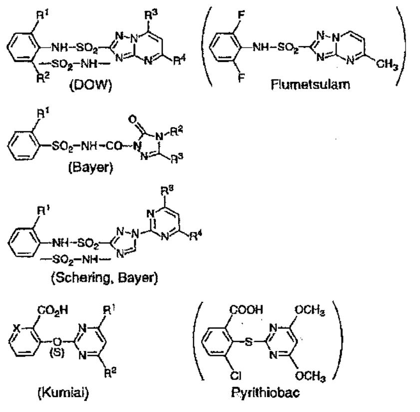


Fig. 21
Newer ALS-Structures

The belief in the ability to optimize a class of substances, which due to lack of success had been abandoned at the end of the 1970s, originated in the discovery of a new insecticide for Bayer. This product has become a blockbuster insecticide within a few years.

In the 1970s Shell worked on the nitromethylenes as potential insecticides. A commercial product could not be found. A few years later chemists at a Bayer subsidiary in Japan began a synthesis program around the nitromethylene lead structure (Fig. 22).

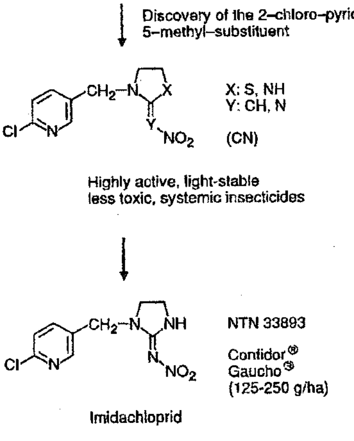


Fig. 22
Beginning of the 1980's New Research in the Area of the Nitromethylenes by Bayer (Japan)

By introduction of a special pyridine substituent in the nitromethylene and nitroguanidine framework new highly active, only slightly toxic, broadly applicable, systemic insecticides were found and the most interesting candidate, imidacloprid, was developed. During development this substance revealed more and more favorable properties (Fig. 23).

NTN 33893: General Characteristics

- Low acute toxicity
- Leaf- and soil insecticide
- Toxic through contact and feeding
- Root-systemic
- Good plant tolerance
- New mode of action
- No cross-resistance
- Low fish toxicity

Fig. 23

Seed Treatment with NTN 33893

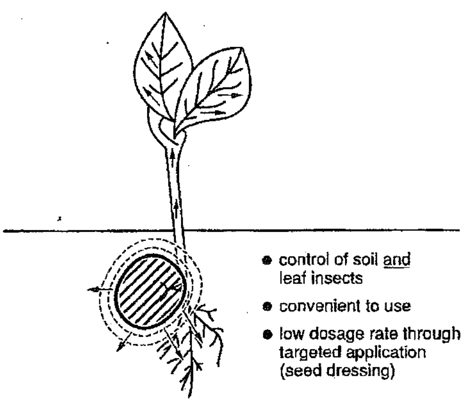


Fig. 24

Through its distinctive systemic properties, imidacloprid can be applied in its most environmentally acceptable form as seed dressing with excellent results (Fig. 24).

Imidacloprid is for Bayer an example of the previously discussed multidisciplinary approach, by which from the very beginning it became possible to identify and develop the most interesting candidate of the group in record time.

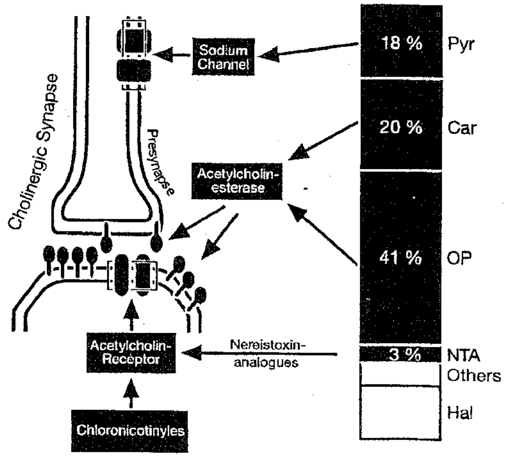


Fig.25
The cholinergic synapse

Imidacloprid also has a very interesting mechanism of action.The following scheme gives you a rough description of a cholinergic synapse in the CNS. This is the location of most of the active sites of the major insecticides known in the market. Pyrethroids are effectors of the presynaptic sodium channels and carbamates and phosphorous esters are inhibitors of cholinesterase. The chloronicotinyl insecticides such as imidacloprid act as agonists of the nicotinic acetylcholine receptor similar to the commercially available small group of Nereis-toxin analogues (Fig. 26).

These analogues are - as the name already implicates - derived from Nereis-toxin, an insecticidal natural product isolated from a marine organism. Whereas the structures of imidacloprid and the Nereis-toxin analogues differ completely, the historic insecticide and receptor agonist nicotine and imidacloprid display similar structural elements.

With full right one can say that imidacloprid really is the first broadly applicable insecticide product with the mechanism described above. Pests that are resistent to conventional insecticides therefor react highly sensitive towards imidacloprid.

An additional benefit is the selective toxicity of imidacloprid. Today the reason herefor is believed to be the sensitivity of the insect nicotinic receptors to chloronicotinyls being more than a 1000 fold higher than the sensitivity of mammalian receptors.

The chloronicotinyl group is a very important structural element of imidacloprid and related insecticides (Fig 27). At the first glance it appears to be a typical synthetical chlorohydrocarbon. Therefor scientists were surprised to discover a chloronicotinyl group in a natural product, thus being "invented" millions of years ago. In 1992 a compound called epibatidine was isolated from

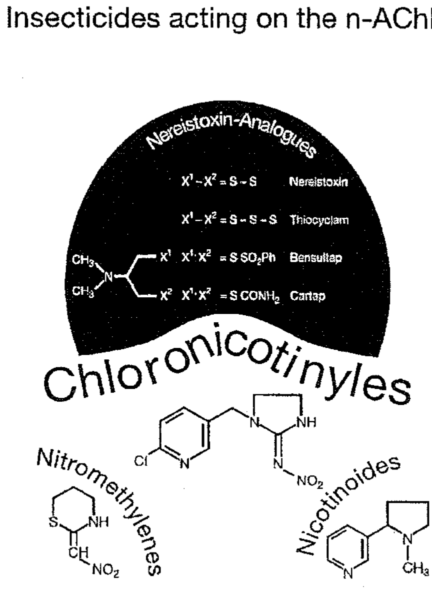


Fig. 26
Chloronicotinyles

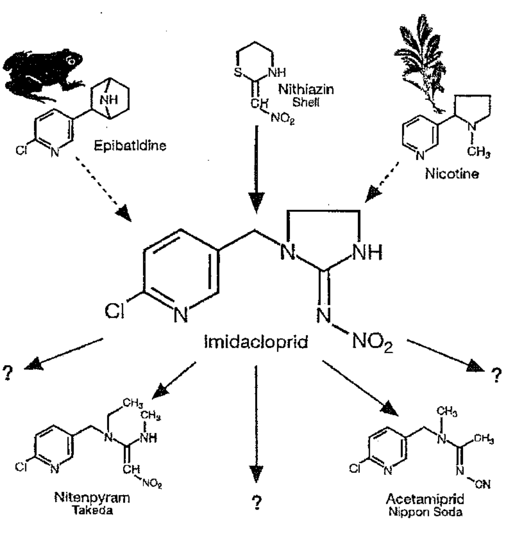


Fig. 27
Epibatidin etc.

a south american frog. Astonishingly, the structure of this frog venom featured the imidacloprid moiety. It is a strong analgesic and a highly potent agonist of the nicotinic receptor. So the interesting connection between the two natural products nicotine and epibatidine together with their knowledge on nitromethylenes could have brought Shell to the synthesis of imidacloprid much earlier. Products such as Nitenpyram and Acetamiprid are analogues of imidacloprid clearly demonstrating that our competitors are not sleeping. There are good prospects that the chloropyridyls will be established as a new insecticide class in the future market.

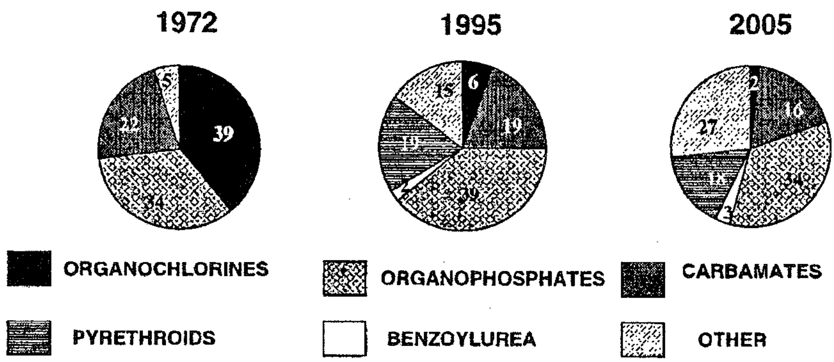


Fig. 28
Agrochemicals Groups

In the early 70s three groups dominated the market: the chlorocarbons, the organophosphates and the carbamates. Later on the pyrethroids came into business. They have already reached their zenith in the world market with a share of 20 %. Benzoyl ureas always have only played a subordinate role. New classes of insecticides will have to grow on cost of the established ones in the next 10 years (Fig. 28.). Probably one of the most important classes will be the chloronicotinyls.

Screening of worldwide available pools of natural products especially isolated from plants, marine organisms and microbes have repeatedly delivered new interesting leads not only in the pharmaceutical research but also in the agrochemical area. As already indicated above, the new opportunity of medium and high throughput screening will offer even more chances in the future. The Pyrethroids are definitely the most prominent example being derived from the naturally insecticidal pyrethrum-extract.

A new similar story of success is evolving as agrochemical scientists currently are pursuing a fungicidal lead derived from natural products, synthetic analogues of the strobilurines. Meanwhile, more than 30 of these strobilurines and related oudemansines and myxothiazoles have been isolated and characterized.

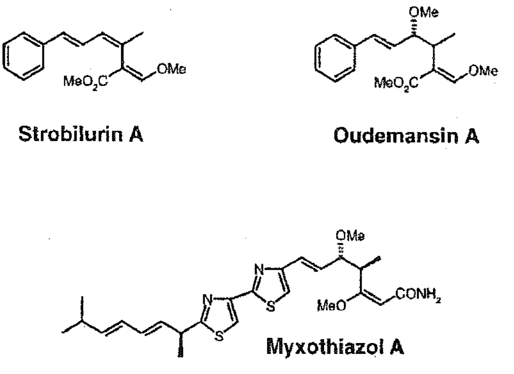


Fig. 29
Natural Fungicidal Derivatives Of ß-Methoxyacrylic Acid

Chemically speaking, these compounds are derivatives of the ß-methoxyacrylic acid. The strobilurines and oudemansines are ingredients of different species of small fungi, e.g. Oudemansiella Mucida, typically growing on beeches (Fig. 30).

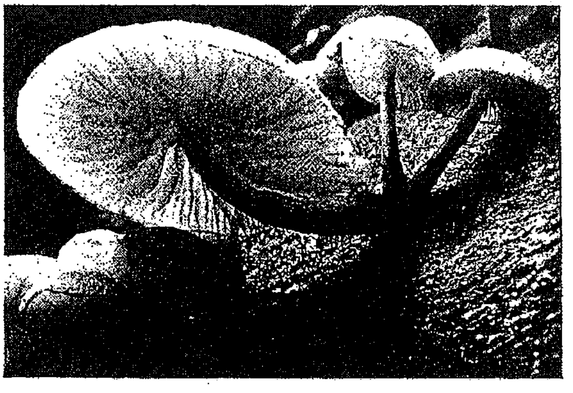
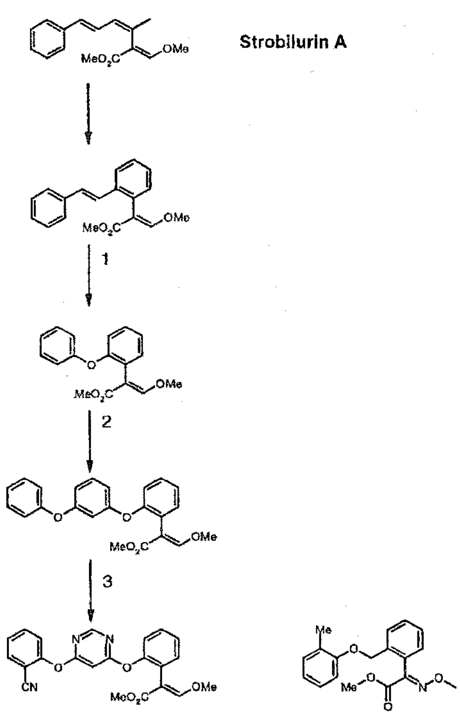


Fig. 30
Oudemansielle Mucida

The fungicidal mechanism of action is based upon the inhibition of the mitochondrial electron transfer by blocking a specific binding site on cytochrome b. No other commercially available fungicide acts in this manner and therefor one cannot observe any cross-resistance.

Although the mechanism of action principally is toxic to warm-blooded animals the methoxyacrylates stand out because of an excellent safety profile. The natural products themselves cannot be used as agrochemicals because of their low photostability, high volatility and finally their low availability from natural sources.



Strobilurin A

Azoxystrobin ICI A5504 Amistar

BAS 490 F Strobee

Fig. 31
Evolution of Ideas From Strobilurin A to Azoxystrobin

On the way to optimizing the lead structure of strobilurine A important milestones had to be discovered (Fig. 31). Step by step photostability, intrinsic and systemic activities were increased by substitution. The result was Azoxystrobine, a broadly applicable fungicide in cultivations like grains, rice, wine, fruit and vegetables. It acts protective, curative and eradicative against a large number of fungi. Similar interesting properties have been described for Strobee from the BASF baring the methoxy-imino acetate moiety bioisosteric to the natural methoxyacrylate group.

A highly promising new fungicide class standing at the very beginning. After the year 2000 it may become just as important as the azoles have been in the last two decades.

The herbicidal sulfony ureas, the chloronicotinyls and the methoxyacrylates are examples for a number of other new developments in the agrochemical area.

These representative examples should show how dominating a role chance can play in the discovery and development of an innovative active substance. However, a concentrated scientific effort can hugely promote the process of optimization in the direction of the ideal solution. At present, all participating scientific disciplines are at the forefront of the innovation and development processes.

NONLETHAL PRINCIPLES OF PEST CONTROL

Up to now, only the expected future progress in the area of classical chemical principles has been discussed. For her part, Mother Nature possessses a rich treasury of compounds which promote communication between organisms, such as insects, of the same or different species. Figure 32 shows the classification of the so-called semiochemicals, according to function and effect.

Semiochemicals

"Language of the insects"

A. Pheromones
(intraspecific)

Sexual-P. Aggregation-P. Marker-P. Alarm-P.

B. Allelochemicals
(interspecific)

Kairomones Allomones Synomones Apneumones

Differentiated according to the response produced:

Attracting	Repelling	Stimulating	Arresting
Attractant Lure	Repellent Deterrrent Antifeedant	Stimulant	Arrestant

Fig. 32

The idea of using such substances for the control of pests is not new. Considerable scientific effort into researching this area has been exerted worldwide. Pheromones, antifeedants, and deterrents were the targets of most research projects. Up to now, however, they have only captured a minor market share, primarily in the use of sexual and aggregation pheromones in traps for monitoring insect populations or for trapping en masse or to cause mating disruption in insect populations. The use of semiochemicals as part of an integrated pest management system and in pest control generally will undoubtedly become more and more important. Presented here are a few advantages: high species selectivity and conservation of beneficial organisms, lower toxicity, lower application rates, reduced persistence, no residue problems, the possiblitiy of partial surface area treatment, and the combination of semiochemicals with reduced amounts of insecticides as a synergistic measure with reduced resistance problems.

Here is a clear example in order to demonstrate how small an amount of substance is required to produce a pheromone effect: 1 kg bombykol evenly evaporated in the airspace over the whole of Germany would be sufficient to gain the attention of a single male silkmoth.

The volatility of semiochemicals requires in practice significantly larger quantities and, more importantly, sophisticated release systems. The sexual attractant of the grape berry moth *Eupoecilia ambiguella*, commercialized as RAK 1 by BASF, is used to disrupt insect mating in vineyards and is applied at 50 g/hectare.

Most importantly, the development of semiochemicals requires the extrapolation of laboratory results into the field and will be no easy task, but the necessary technology is noticeably improving. Above all, advances in molecular biology, behavioural biology, electrophysiology, and last but not least synthetic chemistry will play a decisive role in the future.

A particularly intelligent strategy, the Attract and Kill-strategy, which brings the insect to the poison and not the other way round, should be discussed here (Fig. 33)

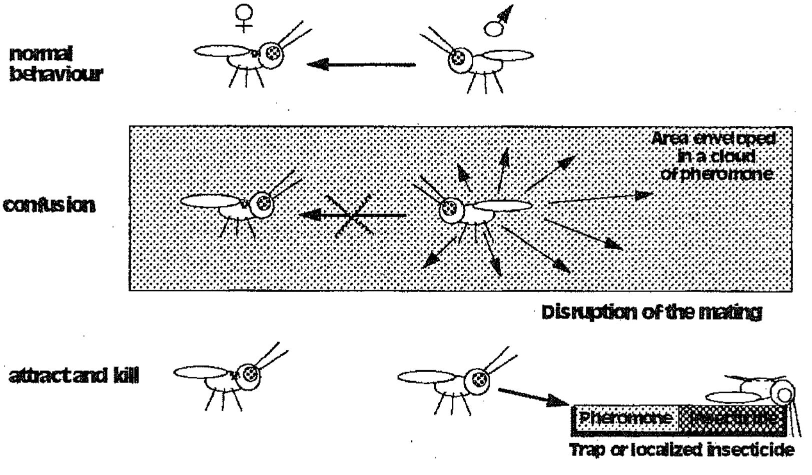


Fig. 33
Attract and Kill Strategy

Until now the method relevant to practice for the application of pheromones to fight pests is the confusion-technique. The cultivation to be protected is wrapped into a cloud of pheromones by controlled release systems. Female and male insects aren't able to find each other; consequently the chance of copulation is largely decreased.

The attract and kill strategy seems more promising, since - as already mentioned - the insect is guided to its poison. Pheromone and insecticide are worked into a highly viscous formulation. The formulation can then be applied e.g. in a fruit plantation by mounting it only to a few single locations, maybe a tree.

The advantage of this method is obvious: only a small amount of pheromone is needed and also the insecticide can be applied in much lower doses than in conventional spraying. The method is highly selective, only the main pests responding to the pheromone will be killed. An excellent method for use in scope of an integrated plant protection. The results with a typical formulation (Fig. 34) sound promising.

The use of so-called hatching factors in the control of plant-parasitic nematodes appears to be highly attractive. Inducing nematode egg hatching at a time when the host plant is unavailable or in combination with a nonpersistent nematocide could provide an excellent alternative to classical methods of nematode control.

Combination of Insecticide and Pheromone in a Highly Viscose Formulation

- **Improved Reliability**
- **Reduction in the Amount of Insecticide**
- **Greater Selectivity**

Example: ***Cydia pomonella*** **(Codling moth)**

- **A&K-Formulation:**
  - **0.16% pheromone (codlemone; E8,E10-12OH)**
  - **6% insecticide (permethrin)**
  - **>50% UV-absorber (Tinuvin)**
- **3-5 Spots (50-100 mg) per Tree**
- **Period of Activity Approxemately 8 Weeks**
- **1 or 2 Treatments per Season**

Results:

- **Very Good Results with Low to Moderate Pest Pressure (< 10%)**
- **Economic Damage Threshold (1-2% Infestation of Apples) is not Surpassed**

Fig. 34
Attract and Kill - Strategy

On the border between chemical and biological pest control are substances which stimulate the natural immune defenses of the plant against pathogens and can help in the reduction of fungicides. Under the influence of so-called elicitors, which are commonly cell-wall fragments of a pathogen, the synthesis of defense substances via a signal cascade is initiated. These so-called phytoalexins are employed to ward off infections. In the meantime an array of purely synthetic substances have been discovered which are able to function as resistance inducers. The Novartis resistance inducer Bion™ has been introduced to the market just recently.

The larger field of allelopathic substances, which are excreted from plants to improve their immediate environment, can only be mentioned here, but will not be discussed further. The whole area on the border between chemistry and biology is scientifically very interesting and future surprises are expected.

BIOLOGICAL PEST CONTROL

In the media, at least, the expectations concerning biological pest control are very high and have reached a point where the needs for chemical measures are no longer seen. This point of view is unrealistic wishful thinking. A study carried out by a group comprising people from universities, government research institutes, and industry, concerning biological crop protection in Germany, contains the following synopsis: "Only in a few cases could an extrapolation of basic knowledge into practical crop protection processes be realized. Besides economic hurdles, for instance limited market potentials, there are specific problems, such as unreliable biological effects, which inhibit rapid market-relevant development.

The major share of today's products, which are sold as bioinsecticides, are derived for Bacillus thuringiensis (Bt). Bt products will become more important in the future and work is already being carried out to broaden their usage through genetically modified bacteria. In the meantime, the number of insect species wich can be controlled by Bt products has already considerably increased.

The Bt-preparations known today are listed in Fig. 35; they are sold not only by biotechnological companies but also by the leaders in the agrochemical industry.

Pest	Market	Strain or Producer	Products	Company
Lepidoptera	Vegetables Fruits Cotton Maize Forest	B. t. k. (kurstaki)	Bactospeine Biobit Condor Cutlass Dipel Forey Javelin	Novo Novo Ecogen Ecogen Abbott Novo Sandoz
		Pseudomonas fluorescens	MVP	Mycogen
	Plutella xylostella	B. t. aizawai	Cen Tari Florbac	Abbott Novo
		Transconjugant (kurstaki/aizawai)	Agree	Ciba
Coleoptera	Potatoes Vegetables Forest	B. t. (tenebrionis)	M-One Trident Novodor	Mycogen Sandoz Novo
		Transconjugant (kurstaki/aizawai)	Foil	Ecogen
		Pseudomonas fluorescens	M-Trak	Mycogen
Diptera	Mosquito Blackfly	B. t. (israelensis)	Acrobe Bactimos Skeetal Teknar Vectobac	ACC Novo Novo Sandoz Abbott

Fig. 35
Commercial Bt Products

Meanwhile their spectrum of activity exceeds the lepidopteran market and includes the coleopteran and dipteran, too.

Although R&D of Bt-preparations has been going on for some 50 years their market share has been estimated at only 1.5 - 2 %, corresponding to 110-140 mio. $. Experts have predicted that the share will double to the year 2000.

Independently of the undoubtable success of the Bt-products they are restricted only to special high-grade markets, e.g. fresh vegetables, control of vectors and forests. The reasons can be found in the biology of bacillus thuringiensis and its crystal toxins:

- the highly selective activity of Bt restricted to only a few species.
- the lack of sustained activity on leaves, because of UV-instability or degradation by other components.
- the inactivity towards pests growing on roots in soil or in stems of plants; areas inaccessable to non-systemically acting spraying agents.
- the lack of sustained action in soil because of microbial degradation.
- the short activity in water because of rapid sedimentation of spores and crystals and because of absorption on organic particles.

These properties contribute to the often cited disadvantages of Bt-preparations, e.g. having to apply too frequently, the necessity to buy special equipment and the necessity to intensively observe and control the plant stock in order to determine the optimal time point of application. In other words: cost and time spent for a Bt-preparation are much higher than for a chemical insecticide. For these reasons Bt is still rarely used by farmers growing the most important cultivations such as corn, grains, cotton or oil seeds.

In order to enter these markets the properties of Bt have to be optimized, e.g. by better formulations, new application technologies, or maybe by modifying the biology of the Bt-preparation itself. The most promising approach could be the recombinant DNA-technology (rDNA) applied in transgenic microorganisms and plants expressing Bt-endotoxins. More will be said to this subject under the topic transgenic plants.

However, the spray application of Bt toxins formulated in dead bacteria is nothing more than chemical pest control with a specific, rather nontoxic substance. The question of whether or not this low toxicity remains guaranteed, if genetically modified bacteria are used to produce toxins, will have to be examined in more depth. In the meantime, resistance to Bt products has already been reported.

The real world of biological pest control is that of living bacteria, viruses, fungi, nematodes, and predatory insects which parasitize the pests and kill them. The intelligent use of these principles is a stimulation challenge. These methods are particulary attractive when combined with pesticides or semiochemicals in the form of an integrated pest management strategy.

However, in the application of biological pest control agents their limitations should be recognized:

- small spectrum of activity due to high host specificity,
- effective activity only under controlled conditions,
- effective only up to a certain level of infestation

The conclusions that schould be drawn are as follows:

- the application of biological pest control agents alone cannot cover all indications;
- biological products cannot tolerate extreme weather conditions;
- at high infestation levels effectiveness cannot be guaranteed.

In cases where these limitations can be accepted, for example, under controlled conditions in a greenhouse or in the relatively stable microclimate in the soil, biological products are an interesting alternative.

Fungus	Product and company	Indication	Formulation
Aschersonia aleurodis	Koppert/ Netherlands	Trialeurodes vaporariorum Bemisia tabaci (White flies)	Wettable powder
Beauveria bassiana	Naturalis™/Troy Bioscience/USA	White flies, Thrips, White grubs	Liquid formulation
Beauveria bassiana	Conidia™/AgrEvo/Germany, Columbia	Hypothenemus hampei (Coffee berry beetle)	Suspendible granules
Beauveria bassiana	Mycontrol-WP/Mycotech Corp. /USA	Trialeurodes vaporariorum Bemisia tabaci (White flies)	Wettable powder
Beauveria bassiana	Ostrinil/Natural Plant Protection/France	Ostrinia nubilalis (European corn borer)	Microgranules of mycelium
Beauveria brongniartii	Betel/Natural Plant Protection/France	Hopochelus marginalis (no englisch name was found)	Microgranules of mycelium
Metarhizium anisopliae	Bio-Path™/EcoScience/USA	Blattella germanica (German cockroach)	Conidia on a medium placed in trap/chamber
Metarhizium anisopliae	Biogreen/Biocare Technology Pty. Ltd/Australia	Adoryphorus couloni (Redheaded cockchafer)	Conidia produced on grain
Metarhizium anisopliae	Bilogic® Bio1020/Bayer AG/Germany	Otiorhynchus sulcatus (Black vine weevil)	Granules of mycelium
Verticillium lecanii	Mycotal/Koppert/Netherlands	Trialeurodes vaporariorum Bemisia tabaci (White flies) F. occidentalis (WFT)	Wettable powder
Verticillium lecanii	Vertalec/Koppert/Netherlands	Aphidus sp. (Aphids)	Wettable powder

Fig. 36

Examples for Entomopathogenic Fungi Commercialized or in Development

Several companies have developed bioinsecticides based on entomopathogenic fungi of the genus Beauveria, Metarrhizium and Verticillium (Fig. 36).

Bayer for instance has developed a mycelium-granulate (Bilogic™) based upon the fungus *Metharrhizium anisopliae* which can be applied to control pests in ornamental plants and tree nurseries with excellent results. At a certain temperature spores develop which represent the infective agent. Growth and reproduction follow in the insect and death results.

A very important point in the development of biopesticides and biological products is the question of registration. As the markets here are relatively small, development is only profitable when the registration costs are significantly less than with synthetic pest control agents. As yet, there is still no consistent legislation.

TRANSGENIC PLANTS

Genetically altered crop plants with favourable properties have always been a target for classical breeding research. The advances in molecular biology are opening more and more possibilities to build in these properties in crop plants. Herbicide resistance, pest resistance, drought resistance, tolerance of poor sites, and nitrogen fixation are a few key words in this context.

The agrochemical industry adopted this topic a long time ago and promotes its development through in-house research and in cooperation with external research institutes and seed companies.

The major activities are focussed on insecticide and herbicide resistance. In both cases cultivated resistant species have already entered the market.

The idea not to apply the Bt-toxin from outside the plant but to let it be produced by a transgenic plant as a secondary metabolite seems to be impressive, naturally. Some of the limitations of classical Bt-preparations, such as lack of sustained activity, lack of UV-stability and the small spectrum of application could be compensated.

Field experiments have demonstrated a resistance against the European corn borer in the case of transgenic corn.

In 1996, Monsanto introduced Bt-cotton with a resistance against Heliothis and Bt-potatoes with a resistance against potatoe beetles in the US-market.

The critical issue of cultivating transgenic plants baring Bt-genes will be if the toxins are invalidated by development of resistance. Should it be possible to overcome this problem there will be no cultivated species unprotected by resistance genes in foreseeable time.

One can expect an even greater influence on the market by the introduction of cultivations baring a herbicide resistance. Especially preparations such as Round up™ (Glyphosate) and Basta™ (Glufosinate) could massively profit. Recently the first cultivations were introduced: Round up Ready™ with glyphosate resistant Soybeans and cotton types; and Liberty Link™, the first glufosinate resistant rape.

The following table describes the herbicide resistant cultivations to be expected until the year 2002 (Fig. 37).

Resistance	Company	Crop	Technique
RoundupReady (Glyphosate)	Monsanto	Soybeans Cotton	Gene Technology
Liberty Link, BastaR	Agrevo/(PGS)	Oilseed Rape Maize Soybeans	Gene Technology
Imidazolinones	ACC	Maize	Cell Culture
Sulfonylureas	DuPont	Soybeans	Cell Culture
Bromoxynil	Calgene (Monsanto)	Cotton	Gene Technology
Sethoxydim	BASF	Maize	Cell Culture
RoundupReady (Glyphosate)	Monsanto	Oilseed Rape Maize Rice	Gene Technology
RoundupReady (Glyphosate)	Monsanto	Sugar Beet Rice	Gene Technology
Imidazolinones	ACC	Maize Soybeans Oilseed Rape	Gene Technology
Sulfonylureas	DuPont	Maize Soybeans Oilseed Rape	Gene Technology

Fig. 37
Crop with Herbicide Resistance (Market or Development 1996-2002)

Naturally one cannot expect the above-mentioned approach to solve the problems of plant protection in an overall manner.

Despite all the impressive prospects that gene technology offers in plants, there is one thing that it cannot produce: a plant which combines all positive properties including high yield potential and at the same time is resistant against all imaginable pests. The fight against pests is endless and in principle cannot be won.

TRENDS IN FORMULATION TECHNOLOGY

Up to now, this article has only been concerned with the effort-intensive search for new active substances and with approaches to improved biological and environmental properties. As well as the actual active substance with its intrinsic properties, the form of application, the formulation, is of extreme importance. The attainable effect on the target organism and the environmental impact are to a large extent dependent on this technology. However, scientists must accept that the large bioavailability found in oral and intravenous application of pharmaceuticals can never be achieved with crop protection agents.

Under the aspects of improved bioavailability, less risk for the applicator, and reduced environmental impact, the agrochemical industry has put a lot of effort into improving rational formulation. The aim is to move away from a purely empirical approach to optimizing formulations.

The future trends can be summarized under the following key words: better bioavailability, reduced applicator risk, and reduced environmental impact:

- Electrostatic charging of spray droplets
- Influence of the spray droplet size on specific applications (avoidance of drift)
- Enclosed spray system (e.g., tunnel spraying)
- Formulation with reduced or no solvent content
- Dust-free formulations
- Suspension concentrates and water-dispersable granules instead of emulsion concentrates and water-dispersable powders
- More seed dressing
- Slow-release formulation (microcapsules, etc.)
- Recyclabel containers
- Water-soluble packaging

Under the heading of lower applicator risk, the trend in formulation type is moving away from emulsion concentrates and water-dispersable powders to suspension concentrates, water-dispersable granules, and even tablets.

The advantages for the applicator are obvious: Avoidance of dust contact and reduced impact of solvents on the environment.

Another type of formulation which will become more important is seed dressing. Here, also, advantages are evident: The active substance is located only where its effect is desired; the seed treatment is carried out by professionals under controlled conditions; and, consequently, the applicator does not come into contact with the active substance.

Application	Formulation type	Area treated
Seed treatment	Seed dressing	ca. 58 m^2
Furrow treatment	Granule	ca. 500 m^2
Complete surface-spraying	Spray	10.000 m^2

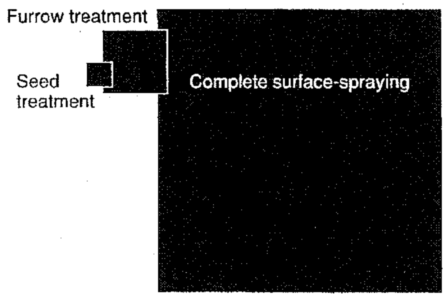


Fig. 38
Surface Area Treated as a Function of Application Procedure using NTN 33893 as an Example

Fig. 38 shows the differences in surface coverage of a hectare between complete-surface spraying, band spraying, and seed dressing. Additionally to the aforementioned trends in formulation, important future advances will be made in the areas of machinery and packaging. Conclusion: As well as improved active substances, the development of better formulations and delivery systems will prepare the way for increasingly environmentally safe crop protection.

DIAGNOSIS AND PROGNOSIS

The methods of diagnosis and prognosis of pest infestation have considerably improved in recent years. By means of powerful computers a large amount of different data can be directly translated into useful information. Time, intensity and the type of measure, adapted to the environment and culture, can be chosen in the best way. From the point of view of the economic damage threshold the motto is: As much as necessary, as little as possible! By means of applicator training, this idea which is also supported by industry will become increasingly the center of focus in the agrochemical business.

CONCLUSION

So far as to the topic "pesticide innovation: trends in research and development". This review was to give you a current survey; it couldn't deal with the topic in detail. The examples given during the presentation were chosen as according to the background of the author.

In agricultural practice all available technologies for fighting pests will further develop in an evolutionary manner in future. Revolutionary changes are not to be expected. These words will not even be undermined by the increasing cultivation of transgenic plants.

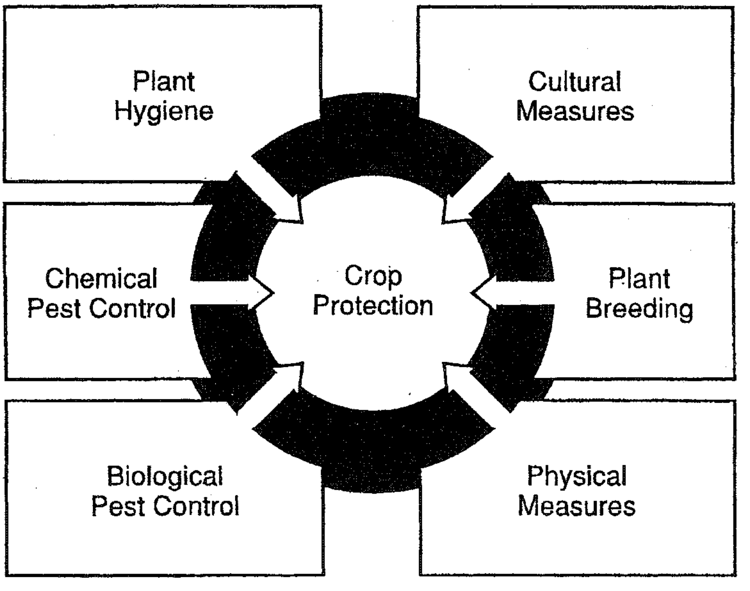


Fig. 39
Integrated Crop/Pest - Management

A concept that all agrochemical companies support is that of integrated crop/pest management (Fig. 39), that is to say the inclusion and use of all relevant measures which are required for the preservation of a productive agriculture, protecting resources, and environment. Chemical pest management is only one of the possible measures of doing this. It will be increasingly assisted by cultural techniques, breeding (gene technology), biological and physical measures. The participating disciplines are well prepared for this development.

One thing, however, must be considered: specific application of the available methods requires increasingly better trained applicators. This is becoming more and more apparent in government institutions and industry. But, at the same time, an ever increasing gap is opening between the industrialized and developing countries. They will not be able to carry out this step into the high-tech world of crop protection without huge support from the industrialized countries.

A last remark too: All future research efforts will only be useful if the social environment is receptive the results.