Nature for the laboratory: Dr. Robert Velten uses a chromatograph to purify insecticidal active substances. The inspiration for these substances comes from natural substances which research colleagues track down in Asia, for example (small photo).

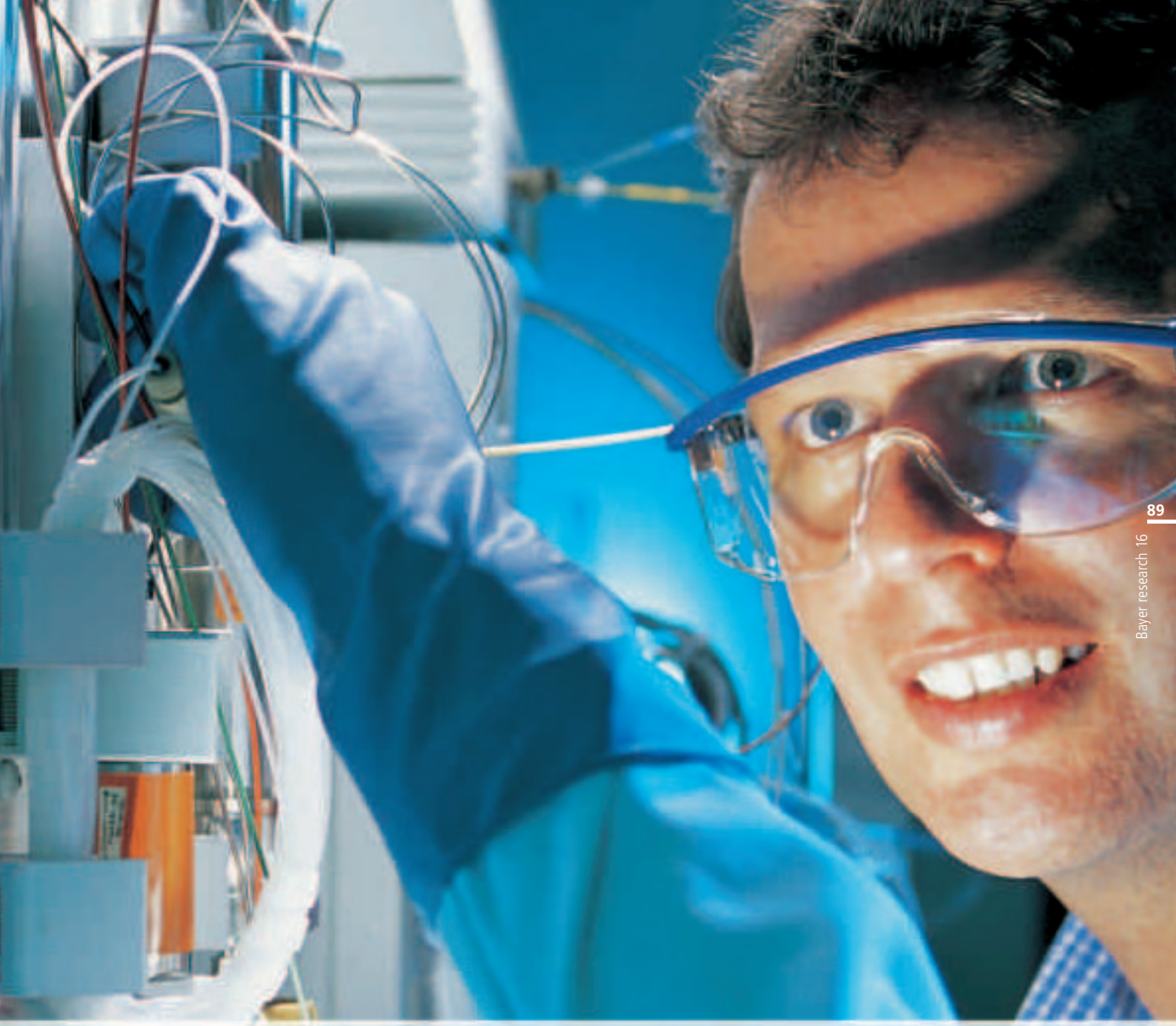
Crop protection enriched by the use of natural substances

Learning from evolution

Modern pesticides need to control pests selectively yet must also be environmentally compatible. That's why researchers are on the look-out for previously unknown substances. A team of specialists from Bayer CropScience is working together with colleagues from Bayer HealthCare's Natural Substance Research department to identify natural substances as lead structures for new active ingredients.

Life on earth first began three and a half billion years ago with tiny, simple bacteria. Since then, nature has been in a constant state of flux, with organisms reproducing, changing randomly or winning the battle against competitors, with whole species dying out and new ones being born. Today there is an incalculable variety of creatures and just as many successful survival strategies. It has been clear for a long time that evolution is nature's almost perfect optimization process. Time and again, biologists' enthusiasm is fired by new insights into the wonders of nature – for example when they unravel the secrets of a tricky physiological mechanism which an organism uses to gain advantage.

And what about the active substance chemists? They are constantly searching for new sources of attractive lead structures. These are substances which already have a desired biological effect, but lack certain characteristics for "practical" use as active substances. The enormous variety in nature offers broad scope for new ideas here. "After all, the organisms which exist today have had to hold their own against others during their evolution, and in doing so have produced different sub-



stances and developed refined strategies," explains Dr. Robert Velten of Bayer CropScience's Global Chemistry Insecticides Research Department in Monheim. Roots have always had to protect themselves against fungi, leaves have always needed a suitable defense mechanism against caterpillars and bacteria have used a wide variety of substances to get rid of their competitors. The natural substance researchers are trying to coax as many of these well-hidden secrets as possible out of mother nature. In doing so, it is not uncommon for them to stumble across as yet unknown modes of action. This is especially important as pests can become resistant to active ingredients and control strategies.

"Evolution has provided natural substances with numerous structural variations which have already proved their efficacy against pests," explains Velten. A good example of this is the pyrethroids, which block an ion channel in the nerves of insects and arachnids. These highly effective insecticides, including Decis® which is currently one of Bayer's successful products, can be traced back to pyrethrum extract, a substance that was derived from chrysanthemum flowers in Iran more than one hundred years ago and exported as a household pesticide.

Many pesticides are based on natural substances

A great many other well-established pesticides are also natural substances or have at least been developed on the basis of these. The active ingredient in the Bayer herbicide Basta®, for example, is the chemically easily available active constituent of an ingredient from Streptomyces bacteria. One of the most modern fungicides from Monheim, the antifungal agent Fandango®,

Thanks to new methods, natural substance research has become even more attractive to Dr. Peter Jeschke, an expert in the field.

Inspiration from flora: Bayer researchers also use fungi on bunches of grapes (top) as well as lilies (right) as the basis for new fungicides.

also contains an active ingredient developed using nature as a model: HEC®. Like fungicides made by other companies, the substance is based on essential structural fragments of strobilurin, a substance isolated from fungi.

The chemists in Monheim can look back on decades of experience in the search for new ideas from nature, and the selective processing of these lead structures. "Natural substances are often highly effective and difficult to improve on," says Dr. Peter Jeschke, Group Leader of Global Chemistry Insecticides Research Department 2, who is responsible for coordinating natural substance activities at Bayer CropScience. "But sometimes further structural modifications are needed before a suitable product can be obtained from the natural substance and produced on a large scale – perhaps enabling it to act on the seed itself or to more easily reach the target site of action." According to Jeschke, modern methods of analysis, purification and processing, together with the use of robots for automated screening of large substance libraries, mean that "natural substance research has become very attractive again."

CropScience and HealthCare researchers work closely together

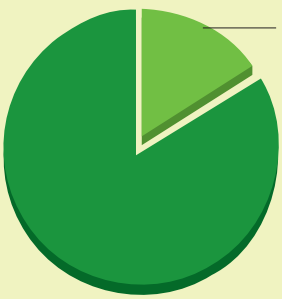
Organisms that reveal their refined strategies as openly as the source of strobilurin or the fungus which causes "pink root disease" in onions are very rare, however. The former betrayed its fungicidal action by strongly inhibiting the growth of other fungi in its environment while the latter was considered as a potential herbicide because of its role in causing a plant disease.

Today's chemists discover new active substances from nature by mass screening, and because it is very difficult to predict before these tests whether a substance can ultimately be used as a medicine or a pesticide, researchers at Bayer HealthCare are cooperating closely with their colleagues at Bayer CropScience. Explains Jeschke: "Our common base is above all the extensive collection of microorganism strains in Wuppertal-Elberfeld – it creates great synergistic effects." Dr. Matthias Gehling of Pharma research at Bayer HealthCare in Wuppertal is responsible for a goldmine of countless natural products.

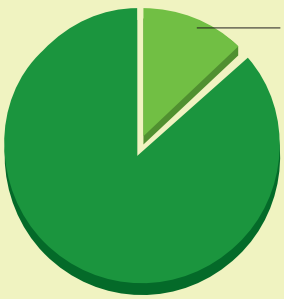
Important inspiration for crop protection products

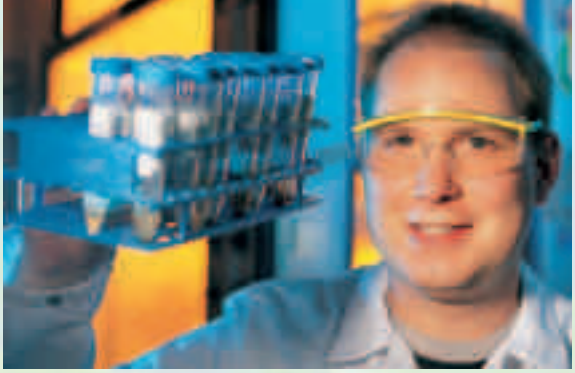
As lead structures, natural substances have a significant influence on the total pesticides market. The natural substances pyrethrin and strobilurin are two good examples.

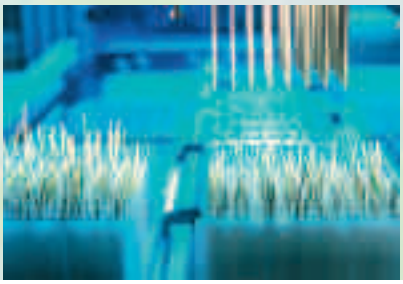
Total insecticides market



Total fungicides market







Ultra-high-throughput in vivo screening is used to test the effects of new substances on plants.

Natural cocktails: Dr. Torsten Grothe with fungal extracts prepared for the search for new medicines.

Dr. Torsten Grothe, also of Pharma Research, prepares the substances in Monheim. He squeezes juice out of roots, extracts solutions from cultures of fungi and physically separates the enormous number of constituents using modern methods of chromatography so that only a manageable number of natural substances is actually tested. The natural substance extracts are then automatically tested by ultra-high-throughput in vivo screening (UHTVS), which is performed in Frankfurt by a team headed by Dr. Mark Drewes from Bayer CropScience, for appropriate insecticidal, fungicidal and herbicidal efficacy. If the robots discover that a sample has the desired biological effect, it goes through further stages of isolation before being tested for its suitability as a possible pesticide.

This is where the work of Velten and his colleagues begins. Using the previously identified chemical structure of the successfully tested natural substances, they then develop ideas as to whether and how the lead structure can be processed to give a new pesticide. The researchers employ molecular modeling – using information from the spatial structure of a molecule – to analyze the natural substance and create related substances by computer simulation. They use chemical processing – a technique known as microderivatizing – to alter the structural parts of the natural substance molecule and test whether these are still biologically active. Once they have identified structural characteristics that are crucial for the effect, they devise simpler molecular structures which ideally have the same or even an improved effect.

Bayer researchers have already identified a large number of natural substances and are now successfully setting their sights on them as lead structures for new pesticides: annonin, an extract of the seeds of the sugar apple, kills insects by inhibiting an important enzyme in cell respiration. Cripowellin, from the bulb of a type of lily (Crinum powelli) has a similar effect on insect pests as natural pyrethroids. Enniatins are cyclical macromolecules of hyphomycetes which prevent strawberry rot, for example.

The Bayer CropScience natural substance team is also looking forward to a promising future. Says Jeschke: "In a few months we are expecting the first new lead structures, known as leads, based on the screening concept."

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The Kunming Institute of Botany in China offers a virtual tour of 4,000 medicinal plants.

Precious cargo from the Far East

Many of the natural substances analyzed by Bayer come from the Far East. Thanks to traditional Chinese medicine, which goes back about 4,500 years, people in that part of the world are especially knowledgeable about essences from nature. For example, in the Yunnan province, where the famous Kunming Institute of Botany is located, 4,000 different medicinal plants grow, some of which have already stimulated Bayer research. The company's experts have been working together with the institute for a long time now in accordance with the United Nations Convention on Biological Diversity (see *research* 13, pages 92-97).

The crop protection scientists in Monheim are already experimenting with a root extract of Vietnamese Tacca plants to control tapeworms. The raw material was particularly difficult to obtain: it took 750 grams of roots for the researchers to first of all produce 84 grams of crude extract, from which they then extracted 234 milligrams of active substance using complicated technology. Once its potency had been demonstrated, a ton of roots was harvested in a plantation in Vietnam from which ultimately 30 grams of active substance were extracted. No wonder that the chemists' ambition is to process the natural substances in order to make it possible to produce them synthetically.