Natural Products from Microorganisms and Plants as Alternatives to Synthetic Chemical Pesticides

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ABSTRACT

$30 billion of synthetic chemical pesticides are used annually to control pests, weeds and plant diseases on crops and in homes and gardens. While chemical pesticides are often inexpensive and highly effective, there are issues of ground water contamination, acute toxicity, non-target effects, residues, and resistance development. This talk will provide an overview of the global pesticide market and discuss the potential for utilization of natural products as green chemistry alternatives to chemical pesticides, following the discovery, development, and marketing of biopesticides based on microorganisms and plant extracts and their associated natural product compounds.

Keywords: natural products, green chemistry, biopesticides

THE PESTICIDE MARKET

The global chemical market is $46.2B, comprised of crop ($31.2 billion) and non-crop ($15 billion). The crop market is mature and flat in real dollars – projected to grow to $36.6 billion in 2010 or 0.9% annually – less than inflation. This slow growth is due to removal and restriction of chemicals by regulatory bodies and governments, the rise of genetically engineered crops, global movement of food requiring a reduction of chemical residues, and public demand for pesticide reductions and organic food.

Table 1. World Crop Protection Sales by Region ($ million)

Region	2006	% change	2007	Real % chge[1]
Europe	9,217	+13.1	10,420	+ 2.8
NAFTA	7,379	+ 1.5	7,490	- 1.7
Asia	7,405	+ 5.1	7,780	+ 0.2
Latin America	5,203	+18.6	6,170	+14.0
Rest of world	1,221	+ 8.9	1,330	na
Total	30,425	+ 9.1	33,190	+ 3.0

1 excluding currency effects and inflation; na = not available.
Source: Phillips McDougall AgriService.

Table 2. 2005 Global Pesticide Market by Segment (Source: Cropnosis)

Fungicides	$ 7.7 Billion
Herbicide	$15.4 Billion
Insecticides	$ 8.8 Billion
Total	$31.9 Billion

DEFINITION OF BIOPESTICIDE

According to the Biopesticide, Pollution, Prevention Division (BPPD) at the U.S. Environmental Protection Agency (EPA), which registers biological pesticides for sale, biological pesticides or biopesticides are derived from such natural materials as animals, plants, bacteria, and certain minerals. Biopesticides fall into three major classes: (1) Microbial pesticides consist of a microorganism (e.g., a bacterium, fungus, virus or protozoan) as the active ingredient. The most widely used microbial pesticides are *Bacillus thuringiensis*, or Bt. (2) Biochemical pesticides are naturally occurring substances that control pests by non-toxic mechanisms. Biochemical pesticides include substances, such as insect sex pheromones, that interfere with mating, as well as various scented plant extracts that attract insect pests to traps. (http://www.epa.gov/pesticides/biopesticides/whatarebiopesticides.htm).

THE BIOPESTICIDE MARKET

The biopesticide market is rapidly growing and expected to reach more than a billion dollars in the next three years. Global Industry Analysts, Inc. (GIA) estimate that the biopesticides market is likely to reach $1 billion by 2010, as stated in a recent report (http://www.strategyr.com/MCP-1573.asp). Biopesticides represented about 2.4% of the overall pesticides market ($512 million in 2006), and are expected to grow to about 4.2% by 2010. Orchard crops hold the largest share of biopesticides use at 55%. (From BCC Research Corporation, Jan 2006) (http://www.bccresearch.com/chm/CHM029B.asp).

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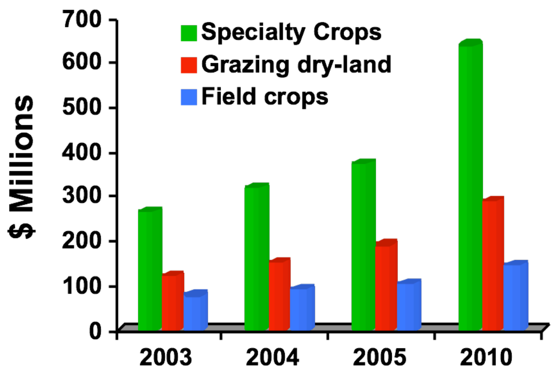
Figure 1. The Biopesticide Market (BCC Research)



The demand for natural biopesticides is rising steadily in all parts of the world. This is because of increased public awareness of the environment, and the pollution potential and health hazards related to many conventional pesticides (worker safety, bird toxicity, air pollution, and surface and ground water contamination). The issues are most acute at the interface of urban/housing and agriculture, where the rapid growth of housing into rural areas creates clashes of farmers, environmental groups and residents.

Bt-based bioinsecticides (sold by Valent Biosciences, Certis USA and several generic companies) comprise most of the microbial pesticides' segment and they are mainstays of forestry, fruit and vegetable production, used on millions of acres for caterpillar control and worldwide for mosquito larvae control.

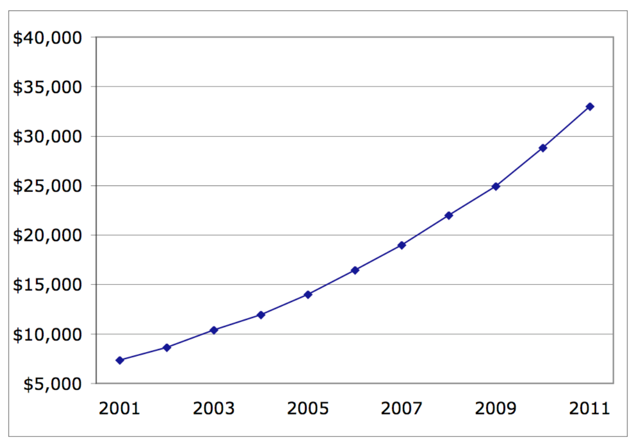
A National Academy of Sciences report sparked a public debate on the soundness of pesticide regulations regarding tests relevant to children's diets. As a result, pesticide legislation (Food Quality Protection Act) passed by Congress in 1996 required companies to assess the effects of synthetic pesticides on infants and children. Since that time, the uses of organophosphates and Class B and C carcinogens have been limited or eliminated, especially on high value specialty crops (fruit, vegetable and ornamentals) and for home and garden use. In addition, the number of insects and plant pathogens that are becoming resistant to chemical pesticides continues to grow (now more than 510).

In March 2004, the Department of Health and Human Services announced the results of a study of two organophosphate insecticides before and after regulatory action of FQPA. There was a dramatic increase in birth weight of newborns after the EPA enacted restrictions of these chemicals. The effect was likened to the effect of not smoking during pregnancy. A recent CDC study found certain heavily used chemical pesticides (i.e., synthetic pyrethroids) widespread in the human population and in stream sediments. These results are likely to lead to more restrictions and studies, especially on the health and environmental effects of multiple chemical combinations.

THE RISE OF ORGANIC FOOD

Organic food is produced without synthetic chemicals (pesticides and fertilizers) and genetically engineered crops. Organic food has been growing at 20% per year for the past ten years and is projected to grow 13-20% per year worldwide for the next ten years. The global organic food market in 2006 is estimated at more than $40 billion of which $16.9 billion is in the US. Worldwide there are 24 million hectares under organic management (IFOAM, Ecology and Farming, January 2004 page 12) and approximately 3.5 million in the US (2005, ERS, USDA). The establishment of national organic standards by the USDA in 2003, which eliminated the confusing patchwork of state standards, has fueled growth of organic foods in the US. At the end of 2003, the EU announced that organic and sustainable farming should be the basis for the Common Agriculture Policy.

Figure 2. Organic Food and Beverage Sales in the U.S., 2000-2011



ADVANTAGES OF BIOPESTICIDES

Because steady advances were made in the 1990s and 2000s in microbial and biochemical research and in formulation technology, today's biopesticides are much improved than biopesticides from earlier eras. The advantages of biopesticides are driving the increase in usage in farming, landscaping and home gardening:

- When used in integrated pest management (IPM) systems, biopesticides' efficacy can be equal to or better than conventional products, especially for crops like fruits, vegetables, nuts and flowers.

- Biopesticides provide greater margins of safety for applicators, farm workers and rural neighbors and have much shorter field restricted-entry intervals (REI), which makes it easier for farmers to complete essential agronomic practices on a timely basis and schedule harvest operations.
- Biopesticides generally affect only the target pest and closely related species. They pose little or no risk to many if not all non-target organisms including birds, fish, beneficial insects and mammals.
- Many of today's biopesticides are biodegradable, resulting in essential no risk to surface and groundwater. Biopesticides also generally have low VOC (volatile organic chemicals) content and can be used to reduce the air pollution caused by high-VOC chemicals (e.g., by fumigants in the San Joaquin Valley in California).
- Biopesticides typically have a lower chance for the development of resistance to pests than single-site chemicals because of their complex mode of action. Biopesticides are excellent resistance-management tools when used alone or in combinations with chemicals as tank mixes and rotations.
- They typically have no pre-harvest interval and very short re-entry intervals (REIs), allowing the grower to harvest the crop immediately after spraying the biopesticide. This is particularly important for export crops now that produce is shipped globally and is subject to international maximum residue levels (MRLs).
- Biopesticides are produced by environmentally friendly and sustainable production processes. Microbial biopesticides are produced by fermentation using readily available biomass (agricultural raw materials) such as soy flour and corn starch. Waste from fermentation processes is often applied back to farms as fertilizer.
- Biopesticides can be and many are approved for use in organic farming, the fastest growing segment of the food industry.

THE NEED FOR NEW PRODUCTS

The following chart shows the acceleration of costs for discovery and development of a new chemical pesticide, now estimated an average of $185 million over a 10-year time line (Crop Life America). The increasing costs are due to the increased requirements for safety and toxicology and the increasing difficulty in discovering truly unique new chemical products. In addition, the pests and diseases are increasingly becoming resistant to chemical products because the newest chemicals have single site of action (work in only one way) and the pest can mutate easily to overcome the chemical.

Figure 3. The Cost of Development of a New Chemical Pesticide (Source: CropLife America)

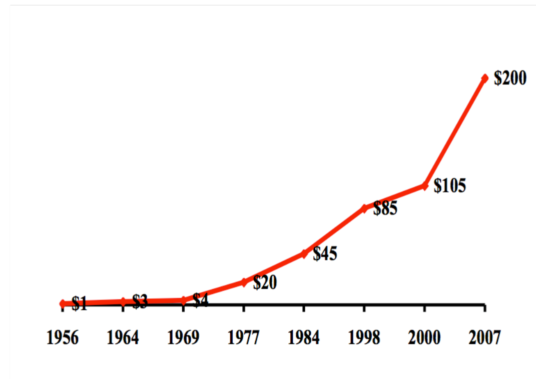


Figure 4. The Launch of New Chemical Pesticides and the Discovery of New Lead Chemicals (Source: Ag Chem New Compound Review (Vol 25) 2007)

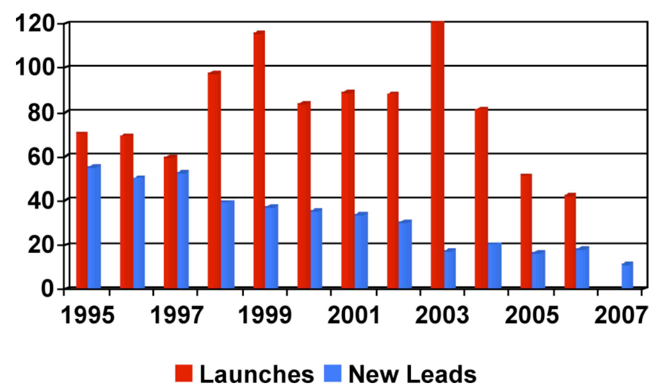


Figure 4 illustrates the current dilemma faced by agrichemical companies. There were many new products launched in the 1998-2004 timeframe from new leads discovered 7-10 years earlier. Because of the decline of new leads, there will be many fewer new launches from here on out.

DISCOVERY OF BIOPESTICIDES

These are the steps we undergo to discover a new biopesticide from microorganisms.

1) Collection and isolation. With our years of expertise, we target selected habitats and niches to collect soil, compost, insect, flowers, etc. from which we isolate our proprietary microorganisms on proprietary media.

2) Fermentation. We grow the selected microorganisms in proprietary media, which maximizes their pesticidal

properties. In addition, we use proprietary fermentation processes that are designed to replicate those that would be required for large-scale fermentation and commercial production, therefore we avoid the time and expense of an unsuccessful scale-up.

3) Primary screening. We use automated, miniaturized biological assays to test the selected microorganism's effectiveness against several weed, insect and nematode pests and plant pathogens. We compare those results to synthetic chemical pesticide standards. When a microorganism shows a high level of pesticidal activity, we conduct further tests to determine the spectrum of activity, mode of action, stability and activity on plants.

4) Natural product chemistry. Using HPLC with diode array detection technology, we compare the natural product compounds produced by each of the selected microorganisms with known compounds. This allows us to eliminate those microorganisms that produce known toxins and select those that we believe are novel and safe. From the selected microorganisms, we identify and characterize the natural product compounds responsible for their pesticidal activity by using HPLC, LCMS and NMR equipment.

5) Patents. When we find a microbial product in our screen that kills/inhibits one or more pest or pathogen, we file a patent claiming any one or more of the following:

- The microbe (and mutants, derivatives etc.)
- The use of the microbe for pest management
- Novel natural product compounds and unique mixtures of compounds produced by the microbe
- The new use of known natural product compounds for pest management
- Formulations of the microbe/compounds
- Synergistic mixtures of the microbe and/or compounds with chemical or other pesticides.

DEVELOPMENT PROCESS

Based on our preliminary assessment of the commercial potential of a natural product, determined through laboratory, greenhouse and initial field tests, we select product candidates for further development. Key aspects of our product development include:

- *Development of the manufacturing process that maximizes the pesticidal natural product compounds.* We develop proprietary processes that increase the yield of both the microorganism and the natural product compounds produced by the microorganism during fermentation. This process development allows us to produce products that have superior performance. We then scale up these proprietary processes in progressively larger fermentation tanks. We develop quality control methods based on the active natural products.

- *Formulation.* We are able to develop proprietary wettable powder, liquid and granule formulations that allow us to tailor our products to our customers' needs. This allows us to develop product formulations with enhanced performance characteristics, such as effectiveness, value, shelf life, suitability for organic agriculture, dispersibility, wettability, rainfastness, compatibility with other pesticides and ease of use.

- *Field testing.* We conduct hundreds of field trials for each product candidate that we develop. These field trials are conducted in small plots on commercial farms or research to determine large-scale effectiveness, use rates, spray timing and crop safety. As the product candidate nears commercialization, we conduct demonstration trials on the farm. These trials are conducted with distributors, influential growers and food processors on larger acreages.

NEW PRODUCTS IN OUR PIPELINE

Marrone Organic Innovations, founded in 2006 by the author, is discovering, developing and marketing natural products for pest, weed and plant disease management. The company in-licenses pesticidal extracts from plants and microbial natural products for development into products. We have our own microbial natural product screening as described earlier.

Besides the organic herbicide we have launched into the market, additional products we have in development include:

1) A broad spectrum insecticide from Chinese medicinal plant extracts
2) A strain of *Pseudomonas fluorescens* for killing invasive zebra and quagga mussels
3) A fungicide extracted from giant knotweed
4) A fungicide/bactericide extracted from Japanese fir trees
5) A marine microbe that selectively kills weeds in rice
6) A new species of bacterium that kills a broad spectrum of insects

REFERENCES

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[2] Willer and Youseffi (eds), 2007. The World of Organic Agriculture, Statistics and Emerging Trends 2007. 9th edition. International Federation of Organic Agriculture Movements, IFOAM, Bonn, Germany and Research Institute of Organic Agriculture, FiBL, Frick, Switzerland. 260 pages.