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Biopesticides: State of the Art and Future Opportunities

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Abstract
The use of biopesticides and related alternative management products is increasing. New tools, including semiochemicals and plant-incorporated protectants (PIPs), as well as botanical and microbially derived chemicals, are playing an increasing role in pest management, along with plant and animal genetics, biological control, cultural methods, and newer synthetics. The goal of this Perspective is to highlight promising new biopesticide research and development (R&D), based upon recently published work and that presented in the American Chemical Society (ACS) symposium "Biopesticides: State of the Art and Future Opportunities," as well as the authors' own perspectives. Although the focus is on biopesticides, included in this Perspective is progress with products exhibiting similar characteristics, namely those naturally occurring or derived from natural products. These are target specific, of low toxicity to nontarget organisms, reduced in persistence in the environment, and potentially usable in organic agriculture. Progress is being made, illustrated by the number of biopesticides and related products in the registration pipeline, yet major commercial opportunities exist for new bioherbicides and bionematicides, in part occasioned by the emergence of weeds resistant to glyphosate and the phase-out of methyl bromide. The emergence of entrepreneurial start-up companies, the U.S. Environmental Protection Agency (EPA) fast track for biopesticides, and the availability of funding for registration-related R&D for biorational pesticides through the U.S. IR-4 program provide incentives for biopesticide development, but an expanded effort is warranted both in the United States and worldwide to support this relatively nascent industry.

Keywords
biopesticides, semiochemicals, plant-incorporated protectants, bioherbicides, bionematicides

Disciplines
Entomology

Comments
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Perspective

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Biopesticides: State of the Art and Future Opportunities

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Supporting Information

ABSTRACT: The use of biopesticides and related alternative management products is increasing. New tools, including semiochemicals and plant-incorporated protectants (PIPs), as well as botanical and microbially derived chemicals, are playing an increasing role in pest management, along with plant and animal genetics, biological control, cultural methods, and newer synthetics. The goal of this Perspective is to highlight promising new biopesticide research and development (R&D), based upon recently published work and that presented in the American Chemical Society (ACS) symposium "Biopesticides: State of the Art and Future Opportunities," as well as the authors' own perspectives. Although the focus is on biopesticides, included in this Perspective is progress with products exhibiting similar characteristics, namely those naturally occurring or derived from natural products. These are target specific, of low toxicity to nontarget organisms, reduced in persistence in the environment, and potentially usable in organic agriculture. Progress is being made, illustrated by the number of biopesticides and related products in the registration pipeline, yet major commercial opportunities exist for new bioherbicides and bionematicides, in part occasioned by the emergence of weeds resistant to glyphosate and the phase-out of methyl bromide. The emergence of entrepreneurial start-up companies, the U.S. Environmental Protection Agency (EPA) fast track for biopesticides, and the availability of funding for registration-related R&D for biorational pesticides through the U.S. IR-4 program provide incentives for biopesticide development, but an expanded effort is warranted both in the United States and worldwide to support this relatively nascent industry.

KEYWORDS: *biopesticides, semiochemicals, plant-incorporated protectants, bioherbicides, bionematicides*

■ INTRODUCTION

This Perspective will provide an overview of the current status of biopesticides based in part on the symposium "Biopesticides: State of the Art and Future Opportunities", as well as the authors' own perspectives on the field of biopesticides. The symposium was held at the Fall 2013 National Meeting of the American Chemical Society (ACS), in the Agrochemical Division of ACS, with cosponsorship from the Agricultural Biotechnology Stewardship Technical Committee. An ACS book based upon a compilation of 18 chapters from the symposium has been published.[1]

Biopesticide use is rapidly expanding after a long period of gestation following much pioneering work, such as that of Zoecon in the 1960s and 1970s and earlier. Altosid ((*S*)-methoprene), patterned after insect juvenile hormone, was an early example of a pesticide inspired by a natural compound. The premise of the symposium was that new tools, now including RNA interference (RNAi) technology, would play an increasingly major role in future pest management, along with synthetic chemicals, biological control, and cultural methods.

■ BACKGROUND AND DEFINITIONS

The U.S. Environmental Protection Agency (EPA) recognizes three categories of biopesticides: (1) biochemical biopesticides (e.g., certain natural compounds used for pest management); (2) plant-incorporated protectants (PIPs), which are the result of transgenes that impart the synthesis of natural pest management compounds in crops (e.g., transgenic Bt toxin); and (3) biocontrol organisms (e.g., microbial fungi). The regulatory authorities of most other countries do not include PIPs in their definition of biopesticides. A recent review summarized biochemical biopesticides approved for use by the U.S. EPA during 1997−2010.[2]

The ACS symposium focused on the biochemical category of biopesticides. Synthetic pest management chemicals based on natural compounds were also discussed, although these are not considered biopesticides by the U.S. EPA. Desirable qualities of most biochemical biopesticides include target specificity, low environmental persistence, and low nontarget organism toxicity. They can range from small molecules to larger complicated structures such as *Bt* toxins, spinosyns, and avermectins and are usually made by microbial or plant biosynthesis. The term biopesticide would benefit from a more complete, broadly agreed upon definition and consistency of use between those groups that support and refer to them. For example, Google lists 10 definitions of "biopesticides" that are quite broad, including the U.S. EPA definition, that is, "biopesticides are certain types of pesticides derived from

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such natural materials as animals, plants, bacteria, and certain minerals".[3]

Biopesticides would be those things included in the definition of pesticide,[4] but with several modifications as noted above, in particular, "naturally occurring". Some people include synthetic pesticides derived from natural compounds as biopesticides. Third-generation pest control agents, reduced-risk pesticides, and biobased pesticides are other terms sometimes used interchangeably with biopesticides. Whatever the definition, the desirable qualities are

- Naturally occurring chemicals or their derivatives
- Reduced toxicity to nontarget organisms
- Reduced persistence in the environment
- Usable in organic agriculture
- Low mammalian toxicity
- Safe for farmworkers and nearby residents
- "Green" technology
- Nonrestricted use

Few products would fit all of these criteria. For example, no natural product-inspired or -derived synthetic compounds are approved for organic agriculture, nor would they be considered a biochemical biopesticide by the U.S. EPA.

■ TRENDS

The market is growing, but still no biopesticides appear on the list of top 10 chemicals used in California. Some biopesticides are effective at low doses and would not be expected to appear on the list of pesticides used in largest quantities (Figure 1).[5] A reflection of the growing use of biopesticides may be found in trends in pesticide use, in California and worldwide, with compounds of nonconventional, bioderived structures such as spinosad and avermectins finding steadily increasing usage.

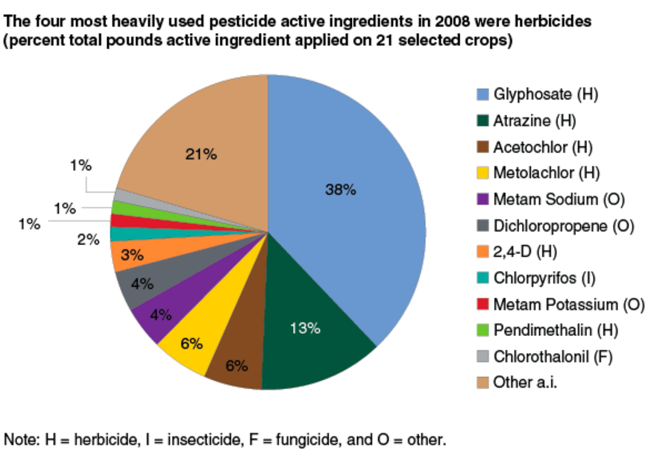


Figure 1. Most heavily used pesticides on 21 selected crops in the United States.[5]

The trend both worldwide and in the United States is to reduce the amounts of pesticides since the peak in usage in the 1980s (Figure 2).[5] This trend reflects the phase-out of many high-dose chemicals such as toxaphene, DDT, and methyl bromide because of their environmental persistence and/or mammalian toxicity. More attention has been given to application methods that reduce drift and otherwise more precisely deliver the chemical to the target, thus reducing the amount of pesticide applied. The introduction of transgenic corn, soybeans, and cotton that are protected from insects by means of transgenes encoding *Bt* toxins (a PIP biopesticide) in the host plant has greatly decreased insecticide use in these crops. Integrated pest management tools, such as intercropping, cover crops, crop rotation, and use of hedgerows, have reduced pest populations without the use of external chemical application. The introduction of reduced risk pesticides such as spinosad that are effective at generally lower doses than conventional pesticides has furthered the reductions of amounts of pesticide applied.

Mechanical control, cover crops, solarization, and cultural methods can play a role in reducing the overall need for herbicides, as well as for other classes of pesticides. Agriculture is ripe for innovative approaches. Acquisitions and mergers may play into this as well as a society's desire for "green" technologies in helping with market development. In some cases the major retailers may favor organic or biopesticide approaches in products they market.

Smaller, specialty companies such as AgraQuest, Trécé, and Marrone Bio Innovations are leading the biopesticide technology as did Zoecon in the past, but larger companies such as Dow, DuPont, Monsanto, Syngenta, Merck, BASF, and Bayer are developing or marketing biopesticides along with the conventional chemicals that are their mainstays. The EPA has helped to catalyze the introduction of biopesticides by offering some regulatory relief for their registration. They include insect repellants and attractants, biochemical insecticides, fungicides, herbicides, nematicides, and others that were topics during this symposium. Figure 3 provides some examples of biochemical biopesticides approved by the EPA under their biopesticide program. The California Department of Pesticide Regulation (CDPR) does not offer a "fast track" for pesticide products involving biopesticides. However, if the biopesticide contains a new active ingredient, the applicant for registration can submit its application to CDPR concurrently with the application for federal registration with EPA. In addition, data requirements for biopesticides are reduced as compared to conventional chemicals, so the evaluation time period for a biopesticide may be shorter than for a conventional chemical.[6]

The trend toward reduced-risk pesticides, or toward little or no pesticide chemical at all, will likely continue and thus continue to lessen the load of xenobiotic chemicals in the environment. This said, it will be critical that practical levels of pest control be maintained, or even increased, so that agriculture can meet its challenge of providing more food within existing resources of land, water, and other resources to a world population expected to exceed 9 billion by 2050.

■ NEEDS, OPPORTUNITIES, AND ALTERNATIVES

The case for new bioherbicides is particularly compelling in that the introduction of biochemical bioherbicides is lagging far behind those for pests other than weeds. Furthermore, there are strong needs for any new weed management technology because of the rapid evolution and spread of herbicide resistance.[7] Due to the widespread adoption of transgenic glyphosate-resistant (GR) crops, glyphosate has been overused, resulting in evolution of extremely problematic GR weeds.[8,9] New herbicides with new modes of action are badly needed to combat GR weeds, as well as weeds with resistance to other herbicides, but no new herbicide mode of action has been introduced for well over 20 years.[10] Many natural phytotoxins that might be considered biochemical bioherbicides have novel modes of action that might fill this need.[11,12]

Weed management is the most costly pest management problem in organic agriculture.[13] In comparison to crop disease

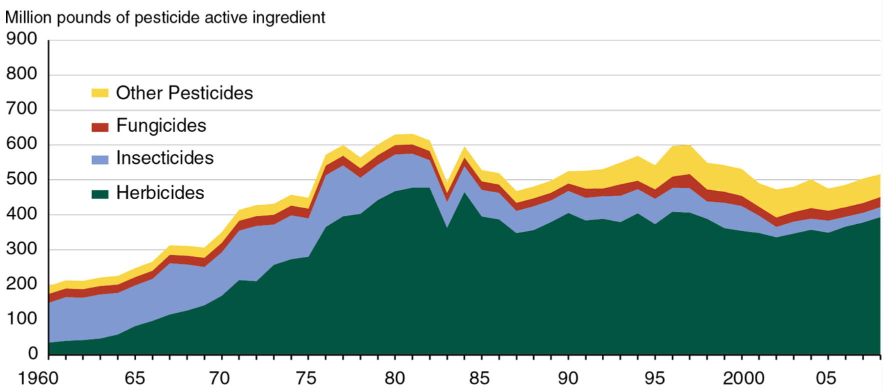


Figure 2. Pesticide use in U.S. agriculture, 21 selected crops, 1960–2008.[5]

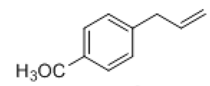
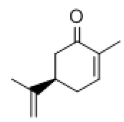
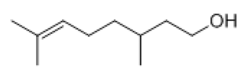
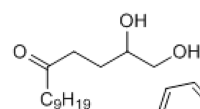
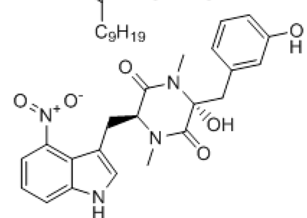
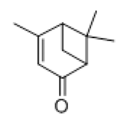
Compound	Source	Use	Structure
4-allyanisol	basil oil	insecticide	
L-carvone	caraway seed oil	insecticide	
citronellol	plant essential oil	insecticide	
glycerol monocarpate	animal or veg. fat	miticide, fungicide	
thaxtomin A	*Streptomyces* spp.	herbicide	
verbenone	essential oil of several plants	insecticide	

Figure 3. Examples of active ingredients for biochemical biopesticides registered by the U.S. EPA.

and insect management tools, organic farmers have relatively ineffective weed control products. Products such as corn gluten-based herbicides and vinegar require high dosage rates for control, and even then their performance is generally poor compared to that of synthetic herbicides. Furthermore, weed management with such tools is usually much more expensive than with conventional herbicides.[14] There are effective new bioherbicides in the pipeline (e.g., thaxtomin[15] from Marrone Bio Innovations), but some hurdles need to be surmounted before they are available for widespread use.

Similarly, new bionematicides for soil application and for use in stored products are critically needed. This is due to the mandated (Montreal Protocol) phase-out of methyl bromide and off-target movement and exposure issues with other fumigants such as methyl isothiocyanate (MITC) and chloropicrin.[16]

Semiochemicals, or sensing/communication chemicals, are another promising class of biopesticides that are far along in development including use in crop protection and related pest control needs. They include pheromones, allomones, kairomones, and other attractants and repellants for both monitoring and population control of pests. Some of the promising tools for orchard pest management come from the use of plant-biosynthesized pheromone mimics, such as the pheromone alternative found in pear leaves that can aid in control of the codling moth, a worldwide pest of apple, pear, walnut, almond, and other crops that is the reason for extensive pesticide-based control.[17] Controlling this damaging pest, and other boring insects that affect cotton seed and peanuts, is a critical element in controlling invasion of *Aspergillus* fungi, which can affect pome fruits, tree and ground nuts, and seeds, producing aflatoxins, a group of carcinogens, and other toxic mold metabolites. The use of semiochemicals to monitor insect pests in pistachio orchards was described by Beck et al.[18] in a presentation during the "Biopesticides: State of the Art and Future Opportunities" symposium.

Microbially produced biopesticides have been very successful in the past, with such products as bialaphos (bilanafos), spinosyns, blasticidin, abamectins, validamycin, streptomycin, and milbemectin being sold as pesticides.[19] Semisynthetic modification of microbial products has also had some success in the generation of products such as emamectin from avermectin, lepimectin from milbemectin, and spinetoram from spinosyns. The impact of natural product-inspired pesticides (not biopesticides) has been tremendous, with such products as the strobilurin-based fungicides (e.g., azoxystrobin), and the synthetic version (glufosinate) of the natural herbicide phosphinothricin. Furthermore, there is an almost U.S. $1 billion market in live microbes as biocontrol agents, with or without natural product active ingredients. These include *Bacillus thuringiensis*, *Bacillus subtilis*, *Thichoderma* spp., and many others. New biopesticide products from microbes are being or may be introduced, such as the herbicides thaxatomin and mevalocidin. Microbial bioinsecticide products, such as formulations of *Chromobacterium subtsugae*, have been introduced into the marketplace. This product should be highly sustainable, in that it has a complex mode of action that causes repellency, oral toxicity, reduced egg hatch, and reduced fecundity.[20]

Pest management products from plants are also an important segment of the biopesticide market, including such products as pyrethrum and neem for insect control and many essential oil formulations for a range of pest management options. Isman[21] discussed botanical insecticides from a global perspective, noting that in 1980 <2% of all journal papers on insecticides dealt with botanicals, but the number exceeded 21% in 2011. There has been an explosive growth in reported studies of the insecticidal activity of plant essential oils, but this activity has not been reflected in increased commercialization of botanical insecticides, at least not in the major North American and European markets. Much of the interest in botanical insecticides has come from China and other Asian nations, Latin America, and Africa, perhaps a consequence of the potentially lower cost, local sourcing, and lower mammalian toxicity of many of these products relative to mainstream synthetics that have, regrettably, resulted in well-publicized human poisonings in earlier times.

Some of these plant products have inspired synthetic pesticides such as pyrethroids or could have inspired neonicotinoid and ryanodine receptor insecticides.[22−25] Although natural plant-derived triketones such as leptospermone show promise as bioherbicides, they provided the molecular scaffold for the synthetic triketone herbicides such as mesotrione.[26] Other phytochemicals are being used directly as biochemical biopesticides. These include an extract of the weed *Reynoutria* spp., which induces resistance to pathogens in crops,[27] and the compound sarmentine from *Piper longum*, which provides burndown-type weed management.[28]

Ashworth and coauthors[29] addressed MITC and other biofumigants using, for example, *Brassica* species incorporation in soil, which releases volatile isothiocyanate chemicals into the soil. They pointed out the disadvantages of the plant release scenario in soil, including relatively low release efficiency and rapid degradation and sorption within the soil, causing growers' reluctance to rely on biofumigants. On the other hand, bionematicides that do not operate by diffusion as vapors in the soil, such as ivermectins and ivermectin mixed with other chemicals, are showing promise in transitioning to a "fumigant-free" control strategy.[30]

RNAi is being rapidly developed for pest management.[31−37] RNAi may be ruled a biopesticide by the U.S. EPA because it leads to natural compounds that can be made to be highly selective with very little or no adverse environmental impact. Patents for different double-stranded RNA (dsRNA)-derived constructs to be used as insecticides, fungicides, nematicides, and herbicides have been filed by companies and public sector laboratories. Some of these products are at the trade name stage, and development is rapid.

■ HIGHLIGHTS AND CHALLENGES

At the symposium it was stated that high levels of pest management (95% or better almost all of the time) that are expected with conventional pesticides may not be realistic for some biopesticides. Also, high levels of pest control with many biopesticides are more likely in integrated pest management systems that do not rely on a single technology for the control of a pest. In the long run, such an approach, although more complicated for the farmer, may be more sustainable because of the lower probability of evolved resistance to multiple technologies.

It is abundantly clear that research on semiochemicals for control of pests is advancing rapidly, especially the use of repellents and attractants. Attractants can be deployed several ways: (1) in traps for monitoring populations of pests (numbers and timing); (2) in attract-and-kill strategies that use baits laced with toxicants; or (3) in mating-disruption approaches, whereby an attractant pheromone is released in a large area to mask the gradients of pheromone emitted by female moths (for example), which would allow males to use the plume of pheromone to locate the female for mating, termed a "confusion" strategy. In addition, attractants can be utilized as part of a "push-pull" scenario, in which a repellent can push a pest species away from a specific habitat while an attractant pulls that species toward a different location, away from the host that needs protection from the pest.

One exciting highlight in the utilization of semiochemicals was the presentation of the novel delivery technology called specialized pheromone and lure application technology (SPLAT). Because nearly all attractants and repellents utilized in pest control are highly biodegradable (as well as chemically and physically degradable), their residence time in the environment is often less than optimal for the management of a pest. Progress on development of new slow-release technology has been gathering momentum recently, and the advances presented by Mafra-Neto et al.[38] are highly encouraging. The maximum value of highly specific pheromones, kairomones, or repellents will be realized only when a broadly applicable technology is developed for uses in multiple situations and becomes a somewhat standardized technology; the SPLAT slow-release methodology shows considerable promise toward that end.

Development of new classes of insecticides has often followed from identification of a natural pesticide's mechanism of toxic action. The current search for new target sites in insects, ticks, mites, and nematodes has focused on elucidation of receptors that are sensitive to natural ligands that may be encountered in a pest's habitat. Many secondary compounds in plants and microbes apparently have defensive functions, and we may be able to exploit that chemistry if we can determine the effects of those defensive compounds, for example, at specific receptors that are functionally important in the physiology of the pest species. Several classes are notable for being under-exploited in the management of pests: octopamine receptors, tyramine receptors, neuropeptide receptors, and potassium channels are examples of target sites currently under investigation for expanded utility in pest management. Once mechanisms are understood, the natural ligands may be supplemented by the development of biorational derivatives and analogues and sometimes unrelated synthetic molecules. Among invertebrate groups of animals (insects, acarines, arachnids, nematodes, mollusks), their receptors vary in ways that can make a pesticide less broadly useful, but which may allow improved selectivity for controlling pests with minimal effects on nontarget species of many kinds. Creating selective toxicity differences for target/nontarget impacts is one of the inherent advantages to be gained from comprehension of how receptors function normally and how those processes can be disrupted biochemically or chemically. If a substantial series of closely related compounds are obtained (through bioprospecting or synthesis), quantitative structure−activity relationships can be developed, which often represent predictive information for us to find or design improved bioactive molecules.

The excitement offered in the 1970s with the publication of "third-generation pest control" by Carroll M. Williams[39] waned in the intervening years but is now on the upswing. Biopesticides are still only 3% of the global annual market for pesticides, but the market share is increasing, in part due to successful biopesticide products such as spinosad and avermectin. These products and others in the pipeline must offer efficacy against key pests, a useful spectrum of activity, robust performance, and a viable manufacturing and supply chain for continued success. The genes controlling the activity in some products, such as the Gram-positive Bt toxins, can be moved in such a way that control is delivered through the seed rather than through the air, water, or soil, an advantage for some biopesticides. However, Bt toxins are not efficacious against all pest species; for instance, hemipterans are less susceptible to Bt toxins.[40] Bonning and co-workers[41] discussed important advances in the modification of Bt toxins allowing them to be more effective pest control agents among less susceptible insects. This includes the addition of a short peptide sequence on a Bt cytolytic toxin (Cyt2A) showing efficacious effects against hemipteran pests (*Acyrthosiphon pisum* and *Myzus persicae*). This advance in biotechnology allows for a wider utilization of Bt toxins against a variety of pests.

It is evident that there is accelerated growth in biotechnology for pest control. The use of dsRNA has made rapid advances as a biotechnological tool for pest control. The RNAi pathway is a naturally evolved pathway, which creates a response against sequence-specific invading nucleic acids and is triggered by dsRNA. Successful use of RNAi machinery includes the identification of genes that have an essential physiological function, gene targets with high transcript levels and high protein turnover, and genes that have specific sequences that can be targeted. Siegfried[42] identified several areas of advancement of RNAi in pest management. Advancements include the use of baits for urban pest management,[43] nanoparticle stabilization for controlling the African malaria mosquito,[44] microbial formulation for spraying,[45] and plant expression for row crop agriculture.[46] This form of biopesticide offers new levels of target specificity for possible control of Varroa mites[47] or viruses[48] inside a bee hive without harm to the bees, a remarkable feat.

High-throughput discovery and microencapsulation (including in nanoparticle-based formulations) are technologies that can speed the development of biopesticides. Combinations of active chemicals are the rule in nature, perhaps because of synergies and/or reduced chances of evolved resistance. An organism may biosynthesize hundreds of related terpenes, for example, only some of which are active and then only in limited proportions. For example, there is good evidence of synergies in insect-active essential oil components, even involving compounds that are inactive when tested in isolation.[49] Whether mixtures will become more common in biopesticide products is an open question. Mixtures can increase the range of product properties, but they also raise regulatory questions for an approval process that values single, or just a few, active ingredients in a new pesticide product.

An example of the pitfalls to avoid with mixtures is provided by the second-generation insecticide toxaphene, for which a few of the more than 175 plus isomers and congeners of chlorinated camphene were responsible for most of the useful insecticidal activity. At least some of the compounds in this witch's brew were herbicidal, as toxaphene was also sold as a herbicide. The herbicidal components were never identified.[50] The bulk of the 175 related compounds contributed to widespread environmental contamination, and some possessed significant toxicity to nontarget organisms, including threatened or endangered wildlife.[51] It is important to understand the physical, chemical, and toxicological properties of each component of a mixture and its role in the utility of the mixture prepared for commercial use. This is often difficult for complex mixtures of naturally occurring or synthetic chemicals.

Goldblum, Warren, and Burlingame of Allylix discussed the future opportunities for novel pest control agents composed of terpenes, the most diverse class of biomolecules, or their derivatives.[52] Technology now exists for sustainable production of sesquiterpenes, a group of terpenes with many high-value applications including flavors and fragrances, cosmetic products, food ingredients, pharmaceuticals, and insecticides. Nootkatone, the flavor- and fragrance-defining chemical in grapefruit, is an effective acaricide and repellant. Terpene-based biopesticide products have the potential to compete with conventional pesticides on both efficacy and economic bases.

Because of the economic hurdles on the path from discovery to commercialization of new pesticides and new uses of existing pesticides, the IR-4 project was established in 1963 as a public sector program to facilitate registration of minor-use or specialty pesticides, including biopesticides. The biopesticide program of IR-4 was established in 1982 to assist in the registration of biochemical biopesticides such as plant extracts, pheromones, and minerals in addition to microbial and biotechnology projects.[53,54] Since its inception, IR-4 has provided over U.S, $6.7 million in grants for biopesticide R&D efforts.

Many of the symposium attendees echoed the need for additional sources of funds for research, development, education, and commercialization of biopesticides to advance this relatively new industry, much as public funds and incentives are being devoted to biofuels, bioenergy, and other aspects of the bioeconomy.

■ ASSOCIATED CONTENT

Supporting Information

Table of the structures of compounds discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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