

Fungicide and Nematicide Update

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Concepts for Developing New Plant Protection Compounds

Recently, several highly active fungicides with different spectra of activity were registered for use in the United States. These include metalaxyl (Ridomil); the sterol inhibitors triadimefon (Bayleton), propiconazol (Tilt), and imazalil (Fungaflo); the dicarboximides iprodione (Rovral) and vinclozolin (Ronilan); and fosetyl Al (Aliette). The successes in discovering these and other compounds currently in development are the result of increased research emphasis in phytopathology by industry.

Increased research emphasis has also been directed toward screening for new nematicides and bactericides. Judging from the number of developmental compounds, however, these efforts have been less successful. A serious need exists for new nematicides because of the banning of the fumigants DBCP (1,2-dibromo-3-chloropropane) and EDB (ethylene dibromide). Research emphasis needs to be directed toward discovering more novel approaches of nematode control, such as antifeeding and anti-hatching compounds and chemical confusants. New bactericides are needed because current commercial standards, such as copper and the antibiotics, often fail to provide control and because resistance has developed to many of the antibiotics. Difficulties involved in developing new bactericides include identifying compounds with activity against several pathogenic species of bacteria in the genera *Pseudomonas*, *Xanthomonas*, and *Erwinia* and obtaining accurate crop loss information necessary to ensure that the benefits of the compounds to growers justify developmental risks. Developing a viricide was considered almost impossible a few years ago, but new concepts of viral cross protection and plant immunization and rapid advances in genetic engineering are increasing the probability that such a compound may be discovered in the near future.

Criteria for the selection of compounds for screening are becoming more scientific as more information is obtained concerning structure-activity relationships. The random screening concept is still heavily relied on to identify new chemistry, however. In the random screen, compounds are screened indiscriminately for activity. Once a lead structure is discovered, chemists attempt to

improve activity by synthesizing analogs based on knowledge of structure-activity relationships. While empirical by design, this concept of screening has led to the discovery of numerous compounds. Recent examples are the predecessors of metalaxyl, which were synthesized for the herbicide screen, and the sterol-inhibiting fungicides, which were first tested as pharmaceuticals.

As more information becomes available on the biochemistry of the host and pathogen and on the chemical structure-biological activity relationships, the more feasible the concept of biorationally designed screening becomes. Biorational design draws heavily on basic research support groups in biochemistry, botany, and plant physiology to obtain information on plant/pathogen biochemistry, modes of action, and metabolism. In the future, chemists may be able to design compounds with specific modes of action, based on knowledge of the biochemical reaction they wish to alter. Although current implementation of extensive biorationally designed screens is not feasible because of lack of knowledge of several target organisms, the importance of such screens should increase in the future. Utilization of computers has tremendously increased the potential of biorational design because of the ability to retain large volumes of data on structure-activity relationships. Computers have also become very beneficial for synthesis planning and molecular modeling.

In addition to traditionally synthesized chemistry, increased screening emphasis is also being directed toward such projects as natural products, including fermentation, and biologicals. Examples of natural products in use or under development in phytopathology are the agricultural antibiotics streptomycin and oxytetracycline, the rice blast fungicide validamycin A, and the nematicide avermectin. The concept of induced resistance resulting from elicitation of the plant's immunization system has been the subject of much attention in recent years. Several researchers have shown that a plant's defensive systems can be activated by applying extracts from plant pathogens or by inoculating with certain microorganisms. Fosetyl Al has been reported to stimulate defense reactions and the synthesis of phytoalexins against oomycetes. Additional basic research is needed to identify these elicitors and determine what potential they offer as disease control agents.

The beneficial aspects of biological

control of plant diseases have been demonstrated. Examples of successful commercial introduction are *Agrobacterium radiobacter* against *Agrobacterium tumefaciens* on fruit trees and *Bacillus subtilis* as a seed dressing. Problems associated with commercialization of biologicals include maintaining viability and activity of selected strains and producing consistent results on major agronomic crops under varying environmental conditions. In the future, genetic engineering may offer the potential of increasing the competitiveness or antagonism of beneficial organisms.

Development of a compound from synthesis to registration normally takes 7-9 years. As indicated, the initial stage of development is the random screen. Pathogens included in this screen are usually from different taxonomic groups and normally of worldwide economic importance, eg, *Phytophthora infestans*, *Pyricularia oryzae*, and *Meloidogyne incognita*. A compound that shows activity in the random screen is included in subsequent laboratory trials designed to define its range of activity against a larger spectrum of organisms and its level of activity in rate range trials. The mode of action of the compound is also investigated. Studies are designed to determine the level of protective, curative, and systemic disease control.

A compound with sufficient activity in the random screen is included in subsequent field trials. These trials, which are normally conducted on small plots on research farms, are designed to define spectrum of activity and dosage rates under field environmental conditions. Compounds are screened on such diseases as apple scab (*Venturia inaequalis*), brown rot (*Monilinia* spp.) of stone fruit, late blight (*Phytophthora infestans*), and powdery mildew (*Erysiphe* spp., *Uncinula* spp.).

At the end of every testing season, a biological profile of each compound is prepared, comparing its biological efficacy to current commercial standards. Compounds with superior activity are proposed for commercial development. At this time, inputs on market potential, production costs, preliminary toxicology, and environment and metabolism concerns are brought together to determine the fate of the compound. Once a compound is promoted to commercial development, a considerable amount of research and development (R&D) time and money is invested in expanded biological testing; toxicology,