Chitin Synthesis Inhibitors: New Class of Insecticides

Lack of specificity is one reason why the broad spectrum insecticides developed during the past three decades have often been associated with environmental damage. Not only do these chemicals kill beneficial insects as well as harmful ones, but they also have toxic effects on other kinds of animals, including fish, birds, and mammals. But despite a growing emphasis on biological methods for controlling pests, few entomologists think that the use of chemicals can be totally eliminated. Attempts are therefore being made to develop more specific agents that will do the job without leading to further environmental degradation.

The recent discovery of a new class of chemicals, the chitin synthesis inhibitors, may be a step toward achieving this goal. Chitin, a polysaccharide, is a major component of the tough outer coverings (cuticles) of insects. As insects develop from immature larvae to adults, they undergo several molts during which they form new cuticles and shed their old ones. A chemical that interferes with chitin synthesis and kills insects before they mature will prevent them from reproducing. Such a compound may thus be used to keep in check the populations of insect pests that might otherwise be economic threats to farm or forest. Higher animals that do not produce chitin should not be affected by the inhibitors provided the agents do not have additional untoward effects at the doses used.

However, inhibitors of chitin synthesis might not be totally specific for insect pests. Beneficial insects make the polysaccharide as do all the other members of the arthropod phylum. This phylum includes spiders, and such economically important crustaceans as crabs, crayfish, lobsters, and shrimp, in addition to the insects. Theoretically, the inhibitors could also cause declines in the populations of these species, but this might not necessarily occur in practice. Experience with diflubenzuron, at present the best studied inhibitor, indicates that this compound has relatively few adverse effects on nontarget species with the possible exception of some aquatic insects and small crustaceans.

Diflubenzuron was discovered by scientists at Philips-Duphar, B.V., in the Netherlands and is being developed by the Thompson-Hayward Chemical Company for market in the United States under the trade name Dimilin. Many investigators are enthusiastic about the potential use of this compound for controlling a wide variety of insect pests. It is relatively specific, having only a low, short-term toxicity for fish, birds, and mammals. For example, the LD_{50} (the dose that kills 50 percent of the exposed population) of this agent for birds and mammals is in the range of 4.5 to 10 grams per kilogram of body weight. By contrast, the LD_{50} for Parathion, an insecticide that acts as a nerve poison, is 5 milligrams per kilogram of body weight when administered orally to rats.

However, assessing the environmental impact of an insecticide is a complicated matter. Short-term toxicity for higher animals is only one problem that must be resolved before the Environmental Protection Agency (EPA) will register an agent for use. Also important are questions regarding the length of time that a chemical persists in the environment, whether it accumulates in the tissues of plants and animals, and whether it or any of its breakdown products have long-term harmful effects, such as carcinogenicity, that might not become apparent until it has been used for many years. Most investigators think that the evidence thus far supports the conclusion that diflubenzuron is safer in these respects than many agents used in the past, but some questions have been raised about the length of time that the compound persists in the environment.

Diflubenzuron (Fig. 1) is a benzoylphenyl urea; a number of these compounds are now being explored for their insecticidal activity. Although other mechanisms of action had been suggested in the past, the current consensus is that diflubenzuron acts by inhibiting chitin synthetase, the final enzyme in the pathway by which chitin is synthesized from glucose. However, this hypothesis has not yet been tested directly because technical difficulties prevent the isolation of the pure enzyme for study.

Indirect evidence supporting the hypothesis comes from the work of the Philips-Duphar group, which is under the direction of Arie Verloop, and of Edwin Marks of the Metabolism and Radiation Laboratory of the Agricultural Research Service (ARS) of the U.S. Department of Agriculture (USDA) in Fargo, North Dakota. They compared the action of diflubenzuron with that of Polyoxin-D, a known inhibitor of chitin synthetase, and found that the two agents produce identical effects on insect cuticles.

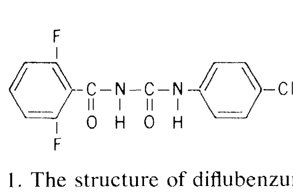

Fig. 1. The structure of diflubenzuron.

Because all insects need to synthesize chitin during development, diflubenzuron can control a wide variety of insect pests, according to C. Duane Ferrell of Thompson-Hayward. He says that it is especially effective against most "worms"—that is, the caterpillars of moths and butterflies—that feed on foilage. The EPA has already registered the agent for use against the gypsy moth, a serious defoliator of forests. In addition, diflubenzuron can control certain beetles, flies, mosquitoes, gnats, rust mites, and weevils, including the boll weevil.

But Ferrell points out that the compound is not effective against all species of insect pests. It does not control cockroaches or ants, for example. Similarly, in field trials, many species of beneficial insects were not affected by the agent.

The reason for the differing susceptibilities is unclear, although several explanations are possible. The less susceptible insects may feed in such a way that they ingest little of the compound; or they may not absorb it efficiently either from the digestive tract or through the cuticle; or they may have ways of detoxifying the agent. A major problem with most chemical insecticides is that insect pests evolve detoxification methods and become resistant to them. It remains to be seen whether the same problem will develop with chitin synthesis inhibitors.

However, insects that are susceptible to diflubenzuron can be controlled by low doses of the agent. In most cases, application of 0.5 to 2 ounces per acre will do the job. At these concentrations there appears to be relatively little effect on species other than the targets. For example, Richard Ridgway of the ARS says that field experiments on cotton that were performed in North Carolina under ARS auspices showed that the agent reduced boll weevil populations up to 99.9 percent without adversely affecting beneficial insects that help to control the cotton budworm and certain other pests.

The budworm and its relatives have become economically important only because heavy insecticide applications directed against the boll weevil also decimated the insects that prey on these insects. Ridgway says that this is the first time in his experience that the boll weevil has proved to be more susceptible to an insecticide than the beneficial insects. Thompson-Hayward now has an application pending with EPA for permanent registration of diflubenzuron for use against the boll weevil. Also pending are applications to register the agent for use against the mosquito and some soybean pests.

The most extensive studies of the action of diflubenzuron in the field have been made in conjunction with the Expanded Gypsy Moth Research and Applications Program of the Forest Service. Gypsy moth larvae are voracious eaters of forest foliage, and the pest is spreading southward and westward across the United States.

Field trials with diflubenzuron conducted in Pennsylvania during the past 3 years showed that the agent reduced the population of gypsy moth larvae by 95 percent and protected against defoliation. Its effects on a wide variety of nontarget species—everything from soil and water microorganisms to birds and small mammals—were minimal.

One aspect of diflubenzuron action that can be a handicap under some circumstances is that it does not act immediately. Affected larvae do not die until they molt. While they live, which may be as long as a week, gypsy moth caterpillars and other foliage eaters will continue to feed, and a heavy infestation can do considerable damage even though the days of the insects are numbered. The insecticide must therefore be applied early in the life cycles of these insects in order to minimize foliar damage.

Most studies aimed at determining whether diflubenzuron has adverse environmental effects have indicated that the compound is benign, at least compared with some agents used in the past. Gary Booth of Brigham Young University, who has conducted many laboratory and field studies on the environmental effects of diflubenzuron, says that it is the safest insecticide that he has ever seen. Nevertheless, some questions about the safety of the compound have been raised. Most of the concerns proved unfounded on further experimentation, but at least one—the issue of environmental persistence—still bothers a few investigators. Not surprisingly, Thompson-Hayward officials say that they think this issue has been satisfactorily resolved.

When the Philips-Duphar group first determined the half-life of diflubenzuron in the soil, the value they found was quite high—up to 16 weeks. However, the investigators subsequently found that the particle size of the suspended material (it is not very soluble in water) greatly influences the rate at which it breaks down after application to soil. When the agent was applied as a suspension of particles much smaller than the ones used in the earlier investigations, the half-life was a week or less.

Not everyone agrees that diflubenzuron breaks down that rapidly, however. According to Robert Metcalf of the University of Illinois, studies performed in his laboratory showed no significant degradation after 4 weeks in soil; he also says that the compound is very stable in water. Meanwhile, Booth determined a half-life in soil of about 1 month; but he maintains that diflubenzuron breaks down in water in less than a week.

According to C. A. Shadbolt of Thompson-Hayward, Metcalf may have seen little breakdown of diflubenzuron in soil because he applied it in such a way that large particles—the kind that are not readily degraded—were deposited. Other possible explanations for the discrepancies are that the investigators used different conditions for their studies. Some were done in the laboratory and others in the field, for example. In any event, the situation points out the difficulty of determining how a material is going to behave when it is sprayed outdoors and subjected to a variety of different environmental conditions.

Stability on Foliage

Investigators generally agree, however, that diflubenzuron is very stable on foliage. This could be considered a mixed blessing. On one hand, it may mean that fewer applications will be needed for insect control than if it were rapidly degraded. On the other hand, residues could remain on food crops at the end of the growing season. This might be undesirable even though the agent does not appear toxic to mammals.

Obviously, the longer a compound persists in the environment the greater the likelihood that it will accumulate in living organisms and possibly cause damage. This was a major problem with DDT, which is very stable. Plants contained only low concentrations of DDT, but the compound became progressively more concentrated as it passed up the food chain to the herbivorous animals that ate the plants and then to the animals that ate the herbivores, and so on. This does not seem to be a problem with diflubenzuron, however. Even Metcalf, who is concerned about the stability question, agrees that the agent shows much less tendency to build up in tissues of animals high in the food chain—fish, for example—than in those of insects.

Another concern that was raised about diflubenzuron but now appears to be laid to rest is that it might inhibit the synthesis of the complex polysaccharides found in connective tissue, bone, and cartilage. Because these polysaccharides are structurally similar to chitin and are synthesized from the same kind of precursor, some investigators feared that diflubenzuron might inhibit the formation of these materials just as they inhibit that of chitin. However, studies in several laboratories have failed to detect any such effect of the compound in either experimental animals or in cultured tissues. Nor have investigators turned up any indications that diflubenzuron has harmful effects on reproduction in birds or mammals or on the progeny of females treated with the agent during pregnancy. Several studies, however, have shown that some species of aquatic insects and small crustaceans are quite sensitive to the agent, which causes at least transitory declines in their populations.

Probably the last question that remains to be answered concerns the carcinogenic potential of diflubenzuron and its breakdown products. Thompson-Hayward officials say that thus far the compound has passed the tests that aim to detect carcinogenicity. Nonetheless, an EPA official has questioned whether *p*-chloroaniline, one of the breakdown products of diflubenzuron, is carcinogenic, and this issue has not yet been resolved to the EPA's satisfaction.

To date, the USDA and Thompson-Hayward have spent several million dollars to assess the effectiveness of diflubenzuron and its environmental impact. Trying to predict exactly what will happen when a new compound is released into the intricate web of life covering the surface of the earth is extremely difficult and some unforeseen problem may yet arise. Nevertheless, most investigators agree that the diflubenzuron is, on balance, one of the least hazardous insecticides yet developed. Even the researchers who expressed strong reservations about this compound itself are enthusiastic about the possibility of developing other, even safer, chitin synthesis inhibitors. Efforts to do this, most of them carried out at chemical companies and therefore proprietary in nature, are under way. Thus, diflubenzuron may be just the first of a new series of insecticides that are less detrimental to the environment than those of the past.—JEAN L. MARX