Loss of the EBDC Fungicides: Impact on Control of Downy Mildew of Lettuce

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Ethylene bisdithiocarbamate fungicides (EBDCs) were first introduced during the 1940s and are used on a wide variety of fruit, vegetable, ornamental, and field crops (29). The EBDC group includes mancozeb, maneb, metiram, nabam, and zineb. Their multisite mode of action enables these fungicides to control a wide range of fungal pathogens on over 70 crops worldwide. Because of their broad spectrum of activity, efficacy, low phytotoxicity, and cost-effectiveness, EBDCs were the fungicides of choice on many vegetable crops until the development of highly effective specific-site fungicides, such as the benzimidazoles, phenylamines, and demethylation inhibitors. The systemic activity of many of the specific-site fungicides gave them a decided advantage over protectants such as the EBDCs. After numerous fungal pathogens developed resistance to specific-site fungicides, the EBDCs were an obvious choice for mixing or alternating with many specific-site fungicides for management of resistance (6,27).

During the past several years, the legal status of many crop registrations of EBDCs in the United States has changed dramatically. In July 1987, the U.S. Environmental Protection Agency initiated a Special Review of all EBDC fungicides (29). A Special Review is a process by which the agency explores and clarifies the risks and benefits associated with the use of a pesticide. Prior to official regulatory action by the agency (6 September 1989), manufacturers of EBDC fungicides voluntarily removed 42 crops from the list of those for which uses of EBDCs were registered in the United States (22). This action was in response to rising public concern about ethylene thiourea (ETU) residues on produce. In laboratory tests, certain levels of ETU, a metabolite and degradation product of EBDC fungicides (25,28), may cause tumors in mice and rats (26). Actual exposures of humans to ETU, and risks posed by such exposures, are still being studied by the Environmental Protection Agency (28).

The expense to chemical manufacturers for successfully developing and registering new pesticides has risen substantially since registration of the EBDC fungicides several decades ago. These costs have limited many new pesticide registrations to crops on which expenses may be easily recouped, usually those grown on large areas or requiring large amounts of pesticides; these include corn, wheat, potatoes, apples, soybeans, cotton, and peanuts. Many vegetable crops are grown on relatively small areas and have low sales potential for chemical manufacturers, and growers of these crops have been left with few or, in some instances, no fungicidal alternatives to the EBDCs. Lettuce (*Lactuca sativa* L.) is such a crop. Downy mildew (*Bremia lactucae* Regel) of lettuce in Florida provides a case study for examining the complexities of disease control and the impact of the loss of EBDC fungicides.

Downy mildew and lettuce production in Florida

Lettuce production in Florida is concentrated on the Histosols of the Everglades Agricultural Area near the southeast corner of Lake Okeechobee. During the 1987–1988 growing season, approximately 87% of the state's $60 million lettuce crop was harvested on 4,735 ha in this area (9); the remainder was produced in central Florida near Zellwood.

Downy mildew is a serious problem in many lettuce-producing areas of the world (21). This disease reduces marketable yield and promotes deterioration of harvested lettuce during transit and storage (20). The disease is favored by moist, cool conditions and in Florida is most prevalent during the winter and early spring. Control tactics include the use of resistant cultivars, fungicide sprays, crop rotations, and cultural practices that do not favor propagation of the pathogen (21). The interaction of *B. lactucae* with lettuce involves a classical gene-for-gene relationship (8,13). Evidence for a minimum of 13 dominant resistance genes and matching complementary pathogen genes for avirulence has been presented (20).

Although lettuce has been grown commercially in Florida since the 1950s (2), large-scale production of crisphead lettuce on organic soils there did not begin until 1968 (18). During the early years, growers relied heavily on cultivars adapted to the environmental conditions of Wisconsin (cv. Montello) and New York (cv. Ithaca). Therefore, early breeding efforts in Florida focused on developing cultivars specifically adapted to local conditions. The release of cv. Shawnee during the late 1970s was considered a major breakthrough for lettuce production in Florida (18).

Outbreaks of downy mildew of lettuce have been sporadic in Florida, but several epidemics during the 1980s had a major impact on the lettuce industry there. Information about races of *B. lactucae* in Florida is scant. In 1983, however, the presence of a new race was indicated by susceptibility of the romaine cultivars Valmaine and Floricos 83, which had shown resistance in 1981 (11). Similarly, Florabibb, a butterhead-type lettuce, also was resistant and later proved susceptible (12). Breeding for downy mildew resistance was not a major priority for Florida lettuce breeders because the disease occurred only sporadically and new races of the pathogen were likely to appear and circumvent host resistance. Incorporating resistance to lettuce mosaic virus remained an important emphasis until a successful seed-indexing program (7) brought it under control. Furthermore, another disease, referred to as corky root and now reported to be caused by the bacterium *Rhizomonas suberifaciens* (30), was endemic to the Histosols of the Everglades Agricultural Area and required attention. Two cultivars, South Bay and Raleigh, resistant to corky root and adapted to conditions in Florida were released in 1984 (10). These cultivars currently account for 99% of Florida's crisphead production. Their susceptibility to *B. lactucae* (10) mandated that downy mildew be held in check by integrating cultural and fungicidal controls.

Prior to 1980, EBDC fungicides, particularly maneb and zineb, were reported as being superior to all other fungicides then registered for control of downy mildew (2,3,15). Relatively low cost and compatibility with other pesticides made maneb useful in disease-prevention programs. However, reports of epidemics during 1982–1983 and again in 1986 indicated that under conditions favorable for disease, maneb alone was insufficient. Reports from other areas substantiated this observation (21).

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The role of EBDC fungicides in control of the epidemics of 1986 and spring of 1989

Maneb and zineb remained the fungicides of choice for control of lettuce downy mildew during the 1970s and early 1980s (16). The introduction of metalaxyl for control of this disease in the United Kingdom in 1978 (4) inspired U.S. growers' optimism for its future registration in the United States. By all accounts, metalaxyl was superior to maneb for control of downy mildew (3,31). Because of the compound's systemic activity, only one or two applications were required for excellent control. During the 1982–1983 growing season, the Florida Department of Agriculture and Consumer Services requested and received a crisis exemption for use of metalaxyl to quell a late-season outbreak of downy mildew in the Everglades Agricultural Area. Downy mildew, either because of lack of favorable environmental conditions or because of control by growers, was not reported as a major problem again until February 1986. A second crisis exemption for use of metalaxyl was then approved, and a Special Local Needs registration under Section 24(c) of the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) was approved on 6 March 1986. Because insensitivity of *B. lactucae* to metalaxyl in the United Kingdom and on other crops had been reported (4), the special registration specifically stated that metalaxyl was to be applied only in conjunction with a preventive disease management program involving full-season use of protectant fungicides. Tank mixes of metalaxyl with the maximum rate of maneb permitted under its registration were specified. This strategy had been suggested and implemented for suppressing the potential development of fungicide-resistant pathotypes on other crops (5). The use of metalaxyl + maneb quickly brought the epidemic under control. Because of abnormally high temperatures during the growing season of autumn 1986 to spring 1987, downy mildew was restricted to a minor outbreak at a single location.

B. lactucae was not reported again in the Everglades Agricultural Area until January 1989, when it was observed at a single location. Lettuce-producing farms in that area are separated from one another by several kilometers of intervening sugarcane. Despite this, downy mildew spread to all other farms within weeks. Recommended tank mixes of metalaxyl + maneb failed to control the epidemic. Fungicide trials then under way in commercial fields indicated the possible presence of a metalaxyl-insensitive pathotype, and this possibility was later confirmed (17). Less favorable environmental conditions and repeated applications of maneb and copper fungicide finally brought the epidemic under control, but not before substantial economic losses occurred.

The origin of the metalaxyl-insensitive strain has been a source of conjecture. Insensitivity to metalaxyl (as Ridomil 2E) was first reported in California during 1987 (20). Examinations of metalaxyl-insensitive isolates in California, using techniques developed by Michelmore and Crute (14), revealed that these isolates were of pathotype IV, mating type B2 (20). Several metalaxyl-insensitive isolates from Florida have been examined, and these resemble California pathotype IV, mating type B2 (T. Schettini, *personal communication*).

Much of the lettuce sold in Florida during the summer and early autumn is shipped from the Santa Maria area of California, the area that experienced severe epidemics of downy mildew incited by metalaxyl-insensitive strains during 1987. These facts led to a hypothesis that the metalaxyl-insensitive strain causing epidemics in Florida originated in California.

Downy mildew in the absence of EBDC fungicides: The 1989–1990 epidemic

In September 1989, manufacturers withdrew the registrations of EBDC fungicides for use on lettuce, but maneb with the old label could be legally used until supplies were exhausted. Florida lettuce growers, however, feared public rejection of maneb-treated lettuce, as had occurred with apples from trees treated with Alar (23), and they decided not to spray with maneb. The loss of maneb, the heavy losses incurred during the spring 1989 epidemic, and the possibility of continued resistance of *B. lactucae* to metalaxyl encouraged the Florida Department of Agriculture and Consumer Services to seek a registration for fosetyl-Al under provisions of Section 18 of FIFRA. This compound had been efficacious in previous tests and was being utilized with some success in California, where it had already been registered under the provisions of Section 18.

The autumn of 1989 was cooler than normal, and *B. lactucae* was initially observed on 21 November, far earlier than any other documented outbreak. Because of the relatively high water table, the high water-retention quality of the organic soil, and the prevailing high humidity of the Everglades Agricultural Area, leaf wetness conditions were favorable for downy mildew infection almost daily. By early January, the disease had spread throughout the entire area. As soon as the outbreak began, isolates of *B. lactucae* were collected to test for sensitivity to metalaxyl. Both laboratory tests and field trials confirmed the presence of a metalaxyl-insensitive strain.

Researchers in California demonstrated that *B. lactucae* in their problem areas is heterogeneous with respect to metalaxyl sensitivity (20). Furthermore, some of the commercially available lettuce lines in California are resistant to the metalaxyl-insensitive pathotype (20). This situation has allowed California growers to achieve a measure of control utilizing metalaxyl and tank mixtures of metalaxyl and fosetyl-Al. The tank mixtures are often more efficacious than either compound alone (M. J. Snyder, *personal communication*). Such is not the case in Florida. Thus far, there is no apparent advantage of mixtures of metalaxyl and fosetyl-Al over fosetyl-Al alone, and alternation of metalaxyl with fosetyl-Al has not given adequate control (R. N. Raid, *unpublished*). The epidemic of 1989–1990 was apparently caused by a nearly homogeneous metalaxyl-insensitive population of *B. lactucae*.

Although small-plot experiments demonstrated the efficacy of fosetyl-Al in control of downy mildew in Florida, commercial control using this compound alone during the 1989–1990 epidemic was incomplete. Growers are currently restricted by provisions of the product registration to six applications and a total of 14.3 kg a.i./ha. With conditions favorable for epidemic development during the entire term of the crop, these restrictions do not allow for adequate disease control.

Combinations of fosetyl-Al with broad-spectrum protectants such as the EBDC fungicides have been more effective than fosetyl-Al alone. At present, copper fungicides and captan are the only broad-spectrum fungicides that may legally be applied to lettuce in the United States. The acidity of fosetyl-Al in solution makes unbuffered concentrated solutions containing copper fungicides and fosetyl-Al phytotoxic to lettuce (24). California growers, who apply fungicides primarily with tractor-drawn sprayers in volumes of 375–560 L/ha, have demonstrated that dilute sprays of copper and fosetyl-Al may be safely applied. On the organic soils of the Everglades Agricultural Area, however, ground applications of pesticides throughout the entire cropping season are impractical because of dust raised by tractor wheels. This dust, which cannot be economically removed from mature lettuce, renders heads totally unmarketable. Therefore, fungicides have traditionally been applied aerially. Even with the relatively high spray volumes required by the present fosetyl-Al registration (93 L/ha compared with standard aerial spray volumes of 28–47 L/ha), application of fosetyl-Al with copper-based fungicides may result in phytotoxicity (24). Captan, alone or in combination with fosetyl-Al, has not been nearly as effective as maneb for control of downy mildew (R. N. Raid, *unpublished*), and its future registration for use on lettuce is also uncertain.

Despite initial efforts to grow lettuce without EBDC fungicides, the threat of total crop failure caused by the 1989–1990 epidemic of downy mildew ultimately forced most growers to use old-label maneb supplies in tank mixtures with fosetyl-

Al for disease control. This program is effective when begun before the onset of downy mildew. However, the cost of controlling downy mildew throughout the entire term of the crop has risen dramatically, from approximately $50/ha in 1980 to nearly $450/ha in 1990.

The loss of maneb for further use in control of downy mildew has dealt a severe blow to the Florida lettuce industry. Experience with the downy mildews has shown that broad-spectrum fungicides, such as the EBDCs and chlorothalonil, are necessary components in disease-control programs designed to minimize development of fungicide resistance (1,27). Without an effective substitute for maneb, development of an isolate of *B. lactucae* that is insensitive to fosetyl-Al remains a definite possibility. In fact, laboratory results show that resistance to both fosetyl-Al and metalaxyl may be induced in certain *Pythium* species (19). Therefore, the emergence of a strain of *B. lactucae* resistant to both of these fungicides is also possible (19). A program monitoring sensitivity of field isolates of *B. lactucae* to metalaxyl is currently in place, and a similar program for fosetyl-Al is being planned. Breeders are currently attempting to incorporate resistance to at least pathotype IV of *B. lactucae* into lettuce types adapted to conditions in Florida. In addition, management of downy mildew by combining EBDC fungicides with fosetyl-Al or metalaxyl, with emphasis on minimizing ETU crop residues, is being investigated. Research examining alternatives to EBDC fungicides is also in progress.

The multitude of factors that must be considered in controlling downy mildew of lettuce makes this problem extremely complex, not only in Florida but also in other lettuce-producing areas. The loss of the EBDC fungicides further complicates this situation. This article is intended to serve as a case study to inform the scientific community and regulatory agencies of various factors involved in disease management. We hope these factors will be taken into account as decisions are made concerning the future of the EBDCs and other fungicides.

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