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Plant Sciences '13

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The systemic fungicide mefenoxam is an important fungicide in the control of late blight disease caused by *Phytophthora infestans*. The susceptibility or resistance of *P. infestans* to mefenoxam is commonly assessed *in vitro* through measuring the mycelial growth of the pathogen in response to increasing concentrations of the fungicide in amended media. However, recent observations suggest that the prior exposure of an isolate in culture to mefenoxam can cause a rapid increase in the observed pathogen resistance in subsequent mefenoxam resistance assays. This change has thus far been observed in several isolates from clonal lineages US-23 and US-24, with significantly increased resistance occurring after a single transfer. This acquired resistance might pose a challenge to accurate *in vitro* mefenoxam sensitivity assays, and, more importantly, as an effective resistance mechanism for previously sensitive isolates in the field. A genetic basis for this acquired resistance seems unlikely, given the speed of the change. Thus exploration of various possible physiological or epigenetic mechanisms using a variety of molecular techniques (Southern blot, RT-PCR, RNA-Seq might prove fruitful in elucidating the underlying mechanism.