Plant Pathology Seminar Series

Triazole Fungicides: The Implications of Fungal Resistance in Agriculture and Human Medicine

Ryan K. Solemslie

Triazoles are a group of fungicides that inhibit ergosterol synthesis in fungi by affecting lanosterol 14 alpha-demethylase encoded by the *cyp51A* gene (Bowyer and Denning 2014). These fungicides, also known as demethylation inhibitors (DMIs), inhibit cell wall formation and are classified in Fungicide Resistance Action Committee (FRAC) Group 3 (FRAC 2018) based on the mode of action. Since triazole fungicides have activity against a diversity of fungi, including many plant pathogens such as mildews, rusts, and soilborne pathogens of cereals, fruits, vegetables, and ornamentals (Hof 2001; Paul et al. 2008), these chemicals have been used widely in agriculture (Parker et al. 2014). In human medicine, many antifungal drugs are triazoles. Medical triazoles are particularly useful against the ubiquitous saprophyte *Aspergillus fumigatus*, an opportunistic human pathogen (Snelders et al. 2012). However, resistance to triazole fungicides has been detected in many fungi, including cross resistance among triazole fungicides (Snelders et al. 2012). Since the late 1990s, resistance to triazoles has been detected with increasing frequency in isolates of *A. fumigatus* recovered from aspergillosis patients (Howard et al. 2009). Studies in the Netherlands found a common resistance mechanism in the *cyp51A* gene in the resistant isolates, i.e., a 34 bp tandem repeat in the gene promoter and a leucine/histidine substitution in the coding region (TR_{34}/L98H) (Snelders et al. 2008). Investigations demonstrated that the three-primary medical triazoles (itraconazole, posaconazole, and voriconazole) exhibit a similar binding mechanism to five triazole fungicides used widely in agriculture, i.e., they bind to lanosterol 14 alpha-demethylase, with a high level of cross resistance to agricultural and medical triazoles (Snelders et al. 2012). Resistant isolates of *A. fumigatus* have also been found on agricultural products such as ornamental bulbs harvested from crops treated routinely with triazole fungicides (Dunne et al. 2017). This has been hypothesized as a link between the development of triazole resistance in agricultural isolates of plant pathogenic fungi and non-target fungi in surrounding environments, as well as a mode of dissemination of resistant isolates on infected bulbs (Dunne et al. 2017). Evidence indicates that resistant isolates of *A. fumigatus* (TR_{34}/L98H) have emerged as a result of widespread exposure to triazole fungicides in agriculture, forestry (to preserve wood products), and veterinary medicine (Ford 2004; Woo et al. 2010). It is important that plant pathologists contribute to developing guidelines for triazole fungicide use in agriculture (FRAC guidelines) and other applications order to avoid misuse of these fungicides and, thereby, reduce selection pressure for resistance in target and non-target fungi. This will extend the utility of triazoles for disease control while also minimizing threats to human and animal health.

4:10 pm | Monday, March 25 | Johnson Hall 343

Plant Pathology 515, Spring 2019

College of
Agricultural, Human, & Natural Resource Sciences
Washington State University

References:

Bowyer, P., and Denning, D. 2014. Environmental fungicides and triazole resistance in *Aspergillus*. Pest Management Science 70:173-178.

Dunne, K., Hagen, F., Pomeroy, N., Meis, J.F., and Rogers, T.R. 2017. Intercountry transfer of triazole-resistant *Aspergillus fumigatus* on plant bulbs. Clinical Infectious Diseases 65(1):147-149.

Ford, M.M. 2004. Antifungals and their use in veterinary ophthalmology. Veterinary Clinics of North America: Small Animal Practice 34(3):669-691.

Fungicide Resistance Action Committee. 2018. FRAC code list 2018: fungicides sorted by mode of action (including FRAC code numbering). Fungicide Resistance Action Committee:1-14 Accessed: March 1. http://www.frac.info/docs/default-source/publications/frac-code-list/frac_code_list_2018-final.pdf?sfvrsn=6144b9a_2

Hof, H. 2001. Critical annotations to the use of azole antifungals for plant protection. Antimicrobial Agents and Chemotherapy 45(11):2987-2990.

Howard, S.J., Cerar, D., Anderson, M.J., Albarrag, A., Fisher, M.C., Pasqualotto, A.C., Laverdiere, M., Arendrup, M.C., Perlin, D.S., and Denning, D.W. 2009. Frequency and evolution of azole resistance in *Aspergillus fumigatus* associated with treatment failure. Emerging Infectious Diseases 15(7):1068-1076.

Paul, P.A., Lipps, P.E., Hershman, D.E., McMullen, M.P., Draper, M.A., and Madden, L.V. 2008. Efficacy of triazole-based fungicides for Fusarium head blight and deoxynivalenol control in wheat: a multivariate meta-analysis. Phytopathology 98:999-1011.

Parker, J.E., Warrilow, A.G.S., Price, C.L., Mullins, J.G.L., Kelly, D.E., and Kelly, S.L. 2014. Resistance to antifungals that target CYP51. Journal of Chemical Biology 7:143-161.

Snelders, E., van der Lee, H.A.L., Kuijpers, J., Rijs, A.J.M.M., Varga, J., Samson, R.A., Mellado, E., Donders, A.R.T., Melchers, W.J.G., and Verweij, P.E. 2008. Emergence of azole resistance in *Aspergillus fumigatus* and spread of a single resistance mechanism. PLoS Med 5(11):1629-1637.

Snelders, E., Camps, S.M.T., Karawajczyk, A., Schaftenaar, G., Kema, G.H.J., van der Lee, H.A., Klassen, C.H., Melchers, W.J., and Verweij, P.E. 2012. Triazole fungicides can induce cross-resistance to medical triazoles in *Aspergillus fumigatus*. PLoS ONE 7(3):e31801. doi:10.1371/journalpone.0031801.

Woo, C., Daniels, B., Stirling, R., and Morris, P. 2010. Tebuconazole and propiconazole tolerance and possible degradation by Basidiomycetes: A wood-based bioassay. International Biodeterioration and Biodegradation 64:403-408.