Does Fungicide Use In Plants Promote Resistance To Antifungal Drugs In Human Pathogens?

DR. PAUL VINCELLI

LEXINGTON, KY.

Fungicides are a critical component of modern agriculture, serving as important tools to help control destructive plant diseases. Of course, all valuable technologies carry risks as well as benefits, and those of us who value the appropriate use of fungicides also have an obligation to understand the risks as well as the benefits.

There is an emerging body of research suggesting a risk that plant pathologists and agriculturalists may have not fully appreciated: that the use of fungicides for plant disease control may increase the risk of drug resistance in fungi that attack humans. **Let me say up front that this issue has not surfaced in the USA or anywhere else in the Americas.** However, I know of no reason it couldn't, and it is important to be aware of the potential.

EXAMPLE: Aspergillosis

The fungus *Aspergillus fumigatus* occurs widely, including in the USA. It is common saprophyte on decaying vegetation. *A. fumigatus* does not cause plant disease, but it can cause a very serious human disease called *aspergillosis*. Aspergillosis is an infection of the lungs that is often fatal if not successfully treated. It is rare in people with healthy immune systems, but those with compromised immune systems are vulnerable.

Triazole fungicides (which are members of the DMI group of fungicides) are commonly used for treatment of aspergillosis. These drugs are very closely related, chemically, to important fungicides used for plant disease control, including propiconazole and tebuconazole. Certain triazole fungicides are used for materials preservation, as well.

Resistance to clinical triazole drugs in *A. fumigatus* is increasing problem in some countries in Europe and Asia, resulting in failure of treatment. Thus, resistance to triazole fungicides in this human pathogen puts patient at grave risk, because drug therapy must rapidly bring the disease under control or the patient can suffer serious health impairment or death.

Triazole Resistance in A. *fumigatus*

In recent years, resistance to triazole fungicides in *A. fumigatus* has been reported in numerous countries in Western Europe. It is interesting that, globally, agricultural use of triazole fungicides is reported to be highest in Western Europe. Triazole-resistant *A. fumigatus* has been reported in China and India. Triazole resistance in *A. fumigatus* has not been reported in the Americas.

It is well-known that resistance to triazole drugs in *A. fumigatus* may occur by spontaneous mutation of the fungus within the lungs of patients treated with a clinical triazole. Scientists don't dispute that this happens. However, hypothetically, spontaneous mutation to resistance could also occur in *A. fumigatus* growing saprophytically in some microsite in an agroecosystem site that was treated with triazole fungicide for plant disease control. There is a growing body of evidence that this has occurred in Europe.

An Environmental Origin?

Here are some of the lines of evidence suggesting an environmental origin to many cases of triazole resistance in *A. fumigatus* collected from diseased patients.

• Biochemical studies show that certain plant-applied triazoles poison fungi in precisely the same way as do clinical triazole drugs for aspergillosis. Also, triazole-resistant strains of *A. fumigatus* are cross-resistant to both the plant-applied triazoles and the triazole drugs. This means that, as far as the fungus is concerned, all triazoles are identical, whether they were applied to plants or administered to humans.

• Triazole-resistant isolates of *A. fumigatus* have been detected in flower beds, from a commercial plant nursery, and from compost samples from a garden center.

• The fungicide-resistance mutation in *A. fumigatus* of greatest concern is called TR_{34}/L98H. This mutation now accounts for the majority of triazole-resistant cases of aspergillosis in the Netherlands, where much of this research has been conducted. Several studies show that isolates of TR34/L98H found in the environment are genetically closely related to TR_{34}/L98H isolates cultured from patients. This suggests a common origin for isolates with the TR_{34}/L98H mutation.

• The evolution of the TR_{34}/L98H mutant somewhere in the environment is estimated to have happened in 1997. Triazole fungicides were used in Europe for plant disease control for several before this. Several years of use for plant disease control would have provided an opportunity for triazole-resistant *A. fumigatus* to evolve in the agroecosystem. The first clinical case of the TR_{34}/L98H mutant was in 1998, consistent with the postulated initial emergence of the TR34/L98H mutant in the environment in 1997.

Conclusion

The hypothesis that using fungicides to control plant diseases may accelerate resistance development in a human pathogen, is controversial and not yet fully accepted by the scientific community. However, there is a growing body of scientific research in support of this hypothesis, and it makes sense biologically.

This is not an apparent present threat to human health in the USA. However, the principles illustrated by these cases from other continents are of interest.

It is important to note that certain triazoles are used for preservation of materials (paints, plastics, etc.), not just for plant disease control. Thus, we don't know for sure whether the use of triazoles for plant disease control is the reason for the increasing number of cases of triazole-resistant aspergillosis in some countries. However, treatment for plant disease control certainly provides an excellent opportunity for selection of resistant strains of non-target fungi in a fungicide-treated environment.

So the bottom line is that commercial fungicides provide great benefits, but that they also carry risks, as we all know. One potential risk is that resistance to clinically important drugs may develop, if a human pathogen is exposed to crop-protection fungicides that have a mode of action identical to the drugs used to treat the human illness. So findings like these remind me of the value of using fungicides judiciously and only as directed by product labels.

References

• Simone et al, 2012. Molecular epidemiology of Aspergillus fumigatus isolates harboring the TR34/L98H azole resistance mechanism. J. Clin. Microbiol. 50(8):2674. DOI:10.1128/JCM.00335-12.

• Snelders et al, 2012. Triazole fungicides can induce cross-resistance to medical triazoles in Aspergillus fumigatus. PLoS One 7(3), e31801.

• Stensvold et al, 2012. Azole-resistant invasive aspergillosis: Relationship to agriculture. Curr Fungal Infect Rep 6:178–191

• Van der Linden et al, 2011. Clinical implications of azole resistance in Aspergillus fumigatus, the Netherlands, 2007–2009. Emerging Infectious Diseases 10(11):1846 DOI: http://dx.doi.org/10.3201/eid1710.110226.

• Verweij et al, 2009. Possible environmental origin of resistance of Aspergillus fumigatus

• to medical triazoles. Appl. Environ. Microbiol. 75(12):4053. DOI:10.1128/AEM.00231-09. Δ

DR. PAUL VINCELLI: Extension Professor and Provost's Distinguished Service Professor, University of Kentucky