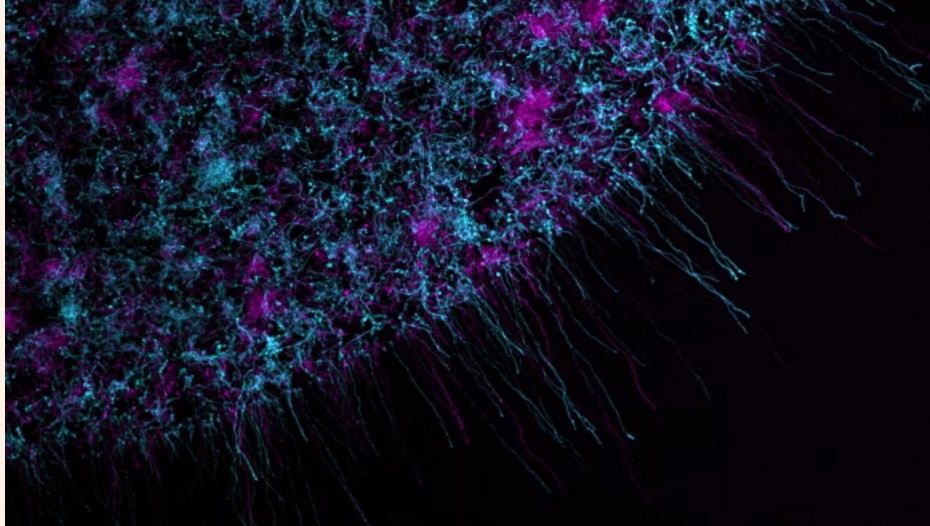
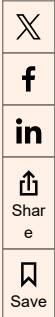


# Crop chemicals boost drug resistance of killer fungi, scientists warn

Medical experts call for curbs on agricultural fungicides



Two strains of the deadly fungus *Aspergillus fumigatus* stained different colours, under the microscope © Manchester Fungal Infection Group, University of Manchester

Clive Cookson in London 4 HOURS AGO

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Fungicides applied to agricultural crops are contributing to a rising death toll from fungal infections by driving the evolution of drug-resistant strains, scientists warn.

As they work to develop compounds that target fungal infections in humans, scientists are urging the agrochemical industry and its regulators to pay more attention to the health implications of cross-resistance, which enables fungi to defeat the drugs designed to kill them.

*The Last of Us*, a post-apocalyptic TV series in which a brain-destroying fungus wipes out most of humanity, increased public interest in the field, but with real fungal infections already contributing to millions of deaths a year experts are urging health officials to pay more attention to the growing threat from anti-fungal resistance.

AFR is an “under-recognised component of the [antimicrobial resistance](#) crisis, which has focused largely on bacterial infections”, said Paul Verweij, professor of clinical mycology at the Netherlands’ Radboud university. “We have strong evidence that selection for resistant strains that infect people takes place in the environment through the use of agricultural fungicides,” he added.

The fungal death toll is often estimated at about 2mn a year but fungal diseases are frequently misdiagnosed, said David Denning, professor of infectious diseases at Manchester university. His revised estimates suggest that nearly double that number — 3.75mn people worldwide — die annually as a result of fungal infections.

Aspergillus species cause the most deaths. Disease begins when someone breathes in fungal spores — usually outdoors but sometimes in homes where mould has spread. The fungus then grows in the lungs, normally in people with depressed immunity or existing pulmonary problems.



'The Last of Us' TV series alerted the public to the threat of fungal disease © Liane Hentscher/HBO

When a farmer applies a fungicide, it protects the crop but also affects trillions of other fungi living in the soil and surrounding environment, which evolve resistance through a “bystander effect”.

This has important implications for human health because people are almost always infected with Aspergillus from fungus in the environment rather than from another person with aspergillosis, Denning said.

The same chemicals, azoles, are the basis of both agricultural fungicides and the antifungal drugs used to treat aspergillosis. Azole resistance levels vary around the world but are typically 10-20 per cent in environmental samples of Aspergillus from northern Europe. However, resistance can reach 50-60 per cent, according to one [study](#) in Vietnam’s Mekong Delta region.

“There is so little surveillance for fungal infections and resistance around the world that we don’t really know what’s out there,” said Tom Chiller, head of fungal diseases at the US [Centers for Disease Control](#) and Prevention.

## The most lethal fungal killers

**Fungal infection**

**Estimated annual deaths worldwide**

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Source: Professor David Denning, University of Manchester

Invasive Aspergillus	1.8mn
Invasive Candida	1mn

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It is harder to develop medicines to kill fungal pathogens than bacterial ones without harming patients because fungi are multicellular organisms more closely related to humans, Chiller said. “So it is particularly important to protect our limited [stock] of effective anti-fungal drugs.”

Protection would involve imposing some restrictions on the agricultural use of chemicals that kill fungi in the same way as human treatments.

An antifungal treatment called olorofim developed by the Manchester-based biotech company F2G is the first of a new drug class designed to treat azole-resistant Aspergillus. Olorofim is in clinical trials that will take at least two more years to complete, said Mike Birch, the company’s chief operating officer. Denning is a founder of F2G.

But Nippon Soda, a chemical company based in Tokyo, launched an agricultural fungicide called ipflufenquin in Japan in 2021, which has a mechanism of action very similar to F2G’s olorofim — leading to [concerns among medical mycologists](#) that cross-resistance will evolve.

“The issue affects anyone developing antifungal drugs because regulatory requirements make the development time for human medicines much longer than for agricultural chemicals,” said Birch. “Regulators need to put in place mechanisms to balance the needs of agriculture and medicine.”

Chinami Yokota, who leads pesticide development for Nippon Soda, said: “Both medicines and agrochemicals are necessary in modern society and both must be fully effective in their respective fields. We will continue to co-operate with the reviews by national authorities and related organisations, as we make an effort to provide the information required to support the registration of our products including ipflufenquin.”

CropLife International, an industry organisation promoting sustainable use of agricultural products, has set up an expert group that aims to limit the occurrence and spread of resistant strains of human fungal pathogens in agricultural settings, through appropriate mitigation measures.

One focus of attention is the management of accumulated waste from plants protected with azole fungicides, which CropLife said may become [hotspots](#) for resistant Aspergillus strains.

Regulators of agrochemical products, such as the US Environmental Protection Agency, have traditionally looked just at direct toxicity when assessing the effects of pesticides on people, wildlife and the environment.

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But the CDC's Chiller was encouraged that his EPA counterparts were now consulting widely about a new framework that would assess the wider risk of antifungal resistance arising from new products.

“We have to recognise the growing public health threat from resistant fungi while ensuring that farmers have effective chemicals to prevent and treat fungal diseases in crops,” Chiller said.