European Commission

Science for Environment Policy

Anti-fungal compounds: emerging environmental contaminants

Azole fungicides are active ingredients in a range of pharmaceutical and personal care products, and are also used in agriculture. This study reviewed the sources, presence and risks of these compounds in the environment, finding evidence of toxic effects on aquatic organisms. The researchers provide directions for future research and warn caution should be exercised until more toxicity data becomes available.

23 September 2016
Issue 471

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Source: Chen, Z. & Ying, G. (2015). Occurrence, fate and ecological risk of five typical azole fungicides as therapeutic and personal care products in the environment: A review. *Environment International*, 84: 142–153. DOI: 10.1016/j.envint.2015.07.022.

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Azole fungicides are used to treat fungal infections in agriculture and human medicine. Usually administered in the form of tablets and ointments, azole fungicides can also be found in common household products, from shampoo and soap to toothpaste and shower gel. Climbazole, which is used in anti-dandruff shampoos and anti-ageing creams, is reportedly used in Europe at a rate of 100–1 000 tonnes per year[1].

Over the past 10 years, these compounds have emerged as a new class of environmental pollutants. After use, they are flushed into wastewater treatment plants (WWTPs) and released into rivers where they may have adverse effects on non-target organisms. They are mainly emitted via hospital and municipal wastewater treatment plants.

This study investigated the occurrence, life cycle in the environment and toxic effects of the five most commonly used azole fungicides: climbazole, clotrimazole, ketoconazole, miconazole and fluconazole (most of which are authorised in the EU for use in either human or veterinary medicines and none of which is approved as an active substance to be used in plant-protection products). The researchers performed a review of the literature on these compounds, using studies conducted in various EU countries including Belgium, Germany, Poland, Spain, Sweden and the UK.

The authors found that azole fungicides are not entirely removed by traditional wastewater treatment (specifically, activated sludge and anaerobic-anoxic-oxic technologies)[2]. They are also resistant to degradation by microbes and are therefore frequently detected in surface water and sediment.

They report high levels in dewatered sludge (a product of WWTPs) up to several micrograms per gram (except for fluconazole) and suggest that soil may be contaminated when this sludge is applied during farming. Overall, environmental levels were similar between countries and usually lower in surface water than WWTP effluents. This could be due to dilution, adhering to sediment or bioaccumulation in aquatic organisms.

The toxicological effects of azole fungicides depend on their physicochemical properties. They can include changes to the expression of genes involved in breaking down toxic compounds and the production of hormones (steroidogenesis), potentially leading to endocrine disruption in fish.

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1. The EU's Scientific Committee on Consumer Safety (SCCS) is in the process of carrying out a risk assessment as to the safety of climbazole.

2. Removal of these substances is not regulated by the Urban Waste Water Treatment Directive (91/271/EEC). Only in the areas where treatment beyond secondary or biological is necessary to fulfil other Council Directives, and if under these Directives it is considered that the removal of these substances is necessary, an adequate treatment, regulated by the aforementioned Council Directives, will be applied.

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To better understand the environmental risk, the researchers applied a risk quotient (RQ) approach, using the ratio between measured environmental concentration (MEC) and predicted no-effect concentration (PNEC)[3] to determine if there was a low, medium or high risk to organisms[4].

Three compounds — ketoconazole, miconazole and fluconazole — posed low risk at all sites assessed in the study. Clotrimazole showed low risk at 97.2% of sites and high risk at 1.9%. However, the final fungicide, climbazole, showed medium risk at over half (59.1%) of sites.

According to their risk evaluation, the authors say certain azole fungicides such as climbazole and clotrimazole pose medium to high risk to aquatic organisms, with algae particularly likely to be affected.

They also say the effects may be more severe than the evaluation suggests, due to the chemical mixture effect. Because azole fungicides interfere with drug metabolism, they may increase the bioaccumulation or toxic effects of other chemicals.

Overall, this review shows that azole fungicides are common in domestic wastewater and sludge, and therefore in the surface water and sediment of rivers and in sludge-treated soil. The residues can have adverse effects on aquatic organisms, including toxic effects in algae and endocrine disruption in fish.

The authors say action is needed to reduce the discharge of these emerging contaminants and to further evaluate the risks to the environment. Specifically, they say more research is needed into advanced treatment technologies such as UV disinfection and chlorination to remove the compounds, the factors influencing their dissipation in the environment, and their toxic pathways. They also say that risks to humans demand further study, as previous studies have shown that some azoles can bioaccumulate in wild fish, which may then be consumed by humans. Furthermore, such research may raise questions about the concentrations of antifungal substances in personal care products.

To cite this article/service: "Science for Environment Policy": European Commission DG Environment News Alert Service, edited by SCU, The University of the West of England, Bristol.

3. Method as outlined by the European Commission Technical Guidance Document on Biocides (Section 5.5): https://echa.europa.eu/documents/10162/16960216/tgdpart2_2ed_en.pdf

4. Low risk: RQ < 0.1, Medium risk: 0.1 ≤ RQ < 1, High risk: RQ ≥ 1.