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# Trends in Agricultural Triazole Fungicide Use in the United States, 1992–2016 and Possible Implications for Antifungal-Resistant Fungi in Human Disease

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**BACKGROUND:** The fungus *Aspergillus fumigatus* (*A. fumigatus*) is the leading cause of invasive mold infections, which cause severe disease and death in immunocompromised people. Use of triazole antifungal medications in recent decades has improved patient survival; however, triazole-resistant infections have become common in parts of Europe and are emerging in the United States. Triazoles are also a class of fungicides used in plant agriculture, and certain triazole-resistant *A. fumigatus* strains found causing disease in humans have been linked to environmental fungicide use.

**OBJECTIVES:** We examined U.S. temporal and geographic trends in the use of triazole fungicides using U.S. Geological Survey agricultural pesticide use estimates.

**DISCUSSION:** Based on our analysis, overall tonnage of triazole fungicide use nationwide was relatively constant during 1992–2005 but increased >4-fold during 2006–2016 to 2.9 million kg in 2016. During 1992–2005, triazole fungicide use occurred mostly in orchards and grapes, wheat, and other crops, but recent increases in use have occurred primarily in wheat, corn, soybeans, and other crops, particularly in Midwest and Southeast states. We conclude that, given the chemical similarities between triazole fungicides and triazole antifungal drugs used in human medicine, increased monitoring for environmental and clinical triazole resistance in *A. fumigatus* would improve overall understanding of these interactions, as well as help identify strategies to mitigate development and spread of resistance. https://doi.org/10.1289/EHP7484

## Background

Invasive aspergillosis is a severe and frequently fatal fungal disease (mortality rate 25–59%) that most commonly affects people who are immunocompromised (e.g., because of transplantation or malignancy) or have structural lung disease (e.g., chronic obstructive pulmonary disease) (Kontoyiannis et al. 2010; Pappas et al. 2010; Steinbach et al. 2012). Approximately 15,000 U.S. hospitalizations with invasive aspergillosis are estimated to occur annually based on medical coding data, with incidence increasing over the past decade in part because of the growing numbers of patients at risk (Benedict et al. 2019; Vallabhaneni et al. 2017). In high-risk groups, such as solid organ transplantation recipients, the incidence can approach 1% (Pappas et al. 2010). However, medical coding likely does not encompass all diagnosed cases, and the lack of national public health surveillance limits understanding of the true burden. Furthermore, many more undiagnosed cases likely exist. A systematic review of 31 studies of autopsy-confirmed misdiagnosis among intensive care unit patients during 1966–2011 (5,863 examinations, 14 countries represented) indicated that aspergillosis was one of the most commonly missed diagnoses (Winters et al. 2012).

*Aspergillus fumigatus* (*A. fumigatus*), the species of pathogenic fungi that causes most invasive aspergillosis (Patterson et al. 2000), is common in the environment, particularly in decaying plant material but also at low levels in ambient air (Tekaia and Latgé 2005). Unlike many other fungi, it is thermotolerant up to 65°C and grows optimally at normal and febrile human body temperatures (~37–40°C), including during fever response, a key factor in its human pathogenicity, as well as at the elevated temperatures found in composting organic matter (Kwon-Chung and Sugui 2013). Although it is widely present in agricultural areas, it is not known to cause disease in plants. Mold-active triazole antifungal medications (e.g., voriconazole) are the mainstay of treatment for invasive aspergillosis, having substantially improved patient survival following their introduction in the 1990s (Herbrecht et al. 2002; Verweij et al. 2016a). Only three main classes of antifungal medications (triazoles, echinocandins, and polyenes) are available to treat systemic fungal infections like aspergillosis.

Whereas relatively few fungi cause invasive disease in humans, fungi are the most common cause of plant infections. Fungicides have been widely used for centuries to treat plant infections, prevent crop loss, and increase agricultural yield; fungicides are also used to preserve wood and other materials (Morton and Staub 2008; Russell 2005; ECDC 2013; U.S. EPA 2015; Wise et al. 2019; Wise and Mueller 2011). Data on global triazole usage are limited, and the United Nations' Food and Agriculture Organization provides data on combined triazole and diazole use, making it difficult to determine the amount of triazole use alone (FAOSTAT 2019). Sales data suggest that triazoles are widely used agricultural fungicide classes, comprising over a quarter of estimated global fungicide sales (ECDC 2013). Fungal pathogens of agricultural crops have developed resistance to many classes of fungicides, including triazoles (Cools and Fraaije 2008; Hu et al. 2016; Price et al. 2015), prompting the Fungicide Resistance Action Committee (https://www.frac.info/home) and other organizations to devote substantial resources to preventing and managing resistance. Notably, certain agricultural triazole fungicides, including bromuconazole, difenoconazole, epoxiconazole, propiconazole, and tebuconazole are structurally highly similar to medical triazoles used to treat aspergillosis (e.g., voriconazole, itraconazole, and posaconazole) (Snelders et al. 2012).

Like plant pathogens that have developed resistance to triazole fungicides, *A. fumigatus* strains resistant to medical triazoles have emerged globally, prompting public health concerns. Resistant aspergillosis is associated with treatment failure and high mortality, ranging from 42% to 88% (Lestrade et al. 2019; Resendiz-Sharpe et al. 2019; van der Linden et al. 2011). Death occurs more commonly in resistant infections, with 90-d mortality being 25% higher in patients with resistant vs. susceptible aspergillosis in a European study (Lestrade et al. 2019). Resistance in *A. fumigatus*

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can develop in two ways. First, it can develop inside the body under selection pressure from long-term use of triazole medications. During the 1990s, small numbers of triazole-resistant infections were identified in patients receiving long-term triazole prophylaxis or therapy (e.g., for aspergilloma, cavitary lung disease, or other noninvasive aspergillosis), with resistance mechanisms involving point mutations in the triazole target and ergosterol synthesis gene, *CYP51A* (Camps et al. 2012; Heo et al. 2017; Howard et al. 2013, 2009). Resistance occurs less frequently in invasive aspergillosis, presumably because the fungus has less time to grow in the body. Given the contribution of antifungal use to triazole resistance in *A. fumigatus*, it is notable that triazole use in U.S. hospitals declined by 21% during 2006–2012, the most recent years with available data (Vallabhaneni et al. 2018).

In the late 1990s, a new resistance mechanism was identified in patients who had *A. fumigatus* infections, and the same mechanism was identified in *A. fumigatus* exposed to triazole fungicides in the environment. This mechanism, $TR_{34}$ /L98H (which we will refer to as $TR_{34}$), includes a 34-base pair tandem repeat (TR) in the *cyp51A* promoter coupled with a specific point mutation in the coding region and can confer resistance to all triazole medications, known as pan-resistance (Abdolrasouli et al. 2018). In contrast to the resistance mechanism that can develop inside the human body, this environmental resistance was observed in isolates primarily from patients who had never taken triazole medicines (Snelders et al. 2008; Verweij et al. 2007), with subsequent studies finding that 53–64% of patients with resistant infection lacked exposure to medical triazoles (van der Linden et al. 2011, 2013).

Because triazoles are widely used in agriculture as fungicides, researchers suspected that the $TR_{34}$-based resistance developed in the environment under fungicide-induced selection pressure (Bromley et al. 2014; Snelders et al. 2009) and that infections resulted from exposure to already-resistant *A. fumigatus* rather than resistance developing in the patient (Berger et al. 2017). Subsequent research provided additional evidence for this hypothesis and identified a second genotype, $TR_{46}$/Y121F/T289A ($TR_{46}$), thought to be linked to fungicide use (Astvad et al. 2014; Chowdhary et al. 2014b, 2015; Lavergne et al. 2015; Le Pape et al. 2016; Montesinos et al. 2014; Steinmann et al. 2015; van der Linden et al. 2013, 2015; Vermeulen et al. 2012). Although the TR-based mechanisms may not be definitive markers of environmental resistance, one report described a resistant isolate with a $TR_{120}$ mechanism in a patient on long-term triazole therapy for chronic aspergillosis (Hare et al. 2019). Overall, evidence suggests that isolates with $TR_{34}$ and $TR_{46}$ mutations result from environmental triazole exposure (Buil et al. 2019).

$TR_{34}$- and $TR_{46}$-mediated resistance has become common in patients with aspergillosis in parts of Europe, where up to 20% of infections are now resistant to medical triazoles (Bueid et al. 2010; Lelièvre et al. 2013; Resendiz-Sharpe et al. 2019; van der Linden et al. 2015; Vermeulen et al. 2013). Resistant *A. fumigatus* strains with $TR_{34}$ and $TR_{46}$ mutations have also been reported among azole-naïve patients in the Middle East, Asia, Africa, Australia, and South America (Chowdhary et al. 2014a, 2017; Meis et al. 2016; Vermeulen et al. 2013; Verweij et al. 2016a). In addition, environmental isolates with $TR_{34}$ and $TR_{46}$ mutations have been detected in Europe, Asia, South America, and East Africa (Alvarez-Moreno et al. 2019; Badali et al. 2013; Chowdhary et al. 2012, 2014b; Dunne et al. 2017; Le Pape et al. 2016; Mortensen et al. 2010; Schoustra et al. 2019; Vermeulen et al. 2012). Further supporting a link between fungicide use and clinical resistance, triazole fungicides similar to medical antifungals were introduced for agricultural use in the Netherlands just before the first $TR_{34}$ strain was found in human clinical settings in the late 1990s (Meis et al. 2016).

In the United States, associations between agricultural triazole fungicide use and human infections have not been investigated, but a small number of infections caused by resistant *A. fumigatus* strains have been identified (CDC 2019). The first TR-based resistance in patients was reported in 2016, including retrospectively identified isolates (2 $TR_{34}$ and 2 $TR_{46}$) collected as early as 2008 (Vazquez and Manavathu 2016; Wiederhold et al. 2016). An additional 6 isolates were detected through 2018 (Beer et al. 2018). Together, these 10 isolates likely reflect only a small proportion of the true number of resistant infections given the lack of standardized surveillance and limited clinical testing. Resistant *A. fumigatus* strains with the $TR_{34}$ mutation have also been found in peanut crop debris in the U.S. state of Georgia that had been treated with propiconazole and tebuconazole, triazoles that are structurally similar to medical triazoles (Hurst et al. 2017), demonstrating the presence of this resistance in the U.S. agricultural environment. Because of this emergence in the United States, the CDC has placed triazole-resistant *A. fumigatus* on its Watch List for antimicrobial resistance threats (CDC 2019).

Given the increased global incidence of triazole-resistant *Aspergillus* infections, recent identification of triazole resistance mechanisms linked to environmental agricultural fungicide use in the United States, and triazole agricultural fungicides with the same mechanism of action as triazole antifungal medications, we characterized trends in U.S. agricultural triazole use to explore possible implications for antifungal-resistant human infections. We also examined available data regarding the use of triazole fungicides for purposes other than food production, including turf and other landscape maintenance and flower production.

## Methods

We analyzed publicly available state-level estimates of annual agricultural pesticide use from the U.S. Geological Survey (USGS) (Baker and Stone 2015; Stone 2013; Thelin and Stone 2013) for 15 triazole fungicides used in the United States during 1992–2016 (USGS 2017). Data for the District of Columbia, Hawaii, Alaska, and territories were not included in the estimates. Methods for these estimates are described in detail elsewhere (Baker and Stone 2015; Stone 2013; Thelin and Stone 2013). Briefly, for states other than California, proprietary farm survey data collected by Gfk Kynetec, Inc., on the amounts of pesticide used on specific crops are aggregated by the U.S. Department of Agriculture (USDA) to estimate pesticide-by-crop use rates within crop reporting districts (CRDs). Each CRD covers multiple counties and each county is assigned to a single CRD. County-level pesticide use estimates are then derived by applying CRD-level pesticide-by-crop use rates to county-level estimates of the harvested acreage of each relevant crop (based on USDA Census of Agriculture data) and state-level use estimates are derived by summing the county-level estimates. When survey-based pesticide-by-crop use rates are missing for a CRD in a given year, two different approaches are used to account for the missing data (Thelin and Stone, 2013). Estimates based on the first approach assume zero use for counties with missing data and are referred to as low-use estimates. Estimates based on the second approach extrapolate rates based on data for nearby CRDs and are referred to as high-use estimates. Specifically, pesticide-by-crop use rates are estimated using the median rate for all contiguous CRDs; or, if data are missing for all contiguous CRDs, the median rate for all CRDs adjacent to contiguous CRDs; or, if data are missing for all of these CRDs, the median of all nonzero rates for all CRDs within the same USDA Farm Resource Region. To simplify interpretation, we used the mean of the low and high annual agricultural pesticide use estimates in this report, rather than presenting each separately. For California, the USGS inputs data on county-level pesticide use from the state's pesticide use reports (PURs), collected by the California Department of Pesticide Regulation.

Fifteen triazoles in the USGS data set are used primarily as fungicides. Because 7 of these triazoles (difenoconazole, metconazole, myclobutanil, propiconazole, prothiconazole, tebuconazole, and triadimefon) accounted for 93% of triazole use, we grouped the remaining 8 fungicides (cyproconazole, fenbuconazole, flusilazole, flutriafol, ipconazole, tetraconazole, triadimenol, and triticonazole) into a single category. Three of the 5 agricultural triazoles documented to be structurally similar to medical triazoles (Snelders et al. 2012) are registered for use in the United States (difenoconazole, propiconazole, and tebuconazole).

Based on USGS classifications, we grouped crops into eight categories: corn, cotton, orchards and grapes (stone fruit trees, citrus, nut trees, apples, pears, and grapevines), rice, soybeans, vegetables and fruit (vegetables and non-orchard fruit, including beans, peas, greens, berries, and melons), wheat, and other crops. The other crop category includes pasture and hay (cropland for pasture, fallow and idle cropland, pastureland, and other hay), alfalfa, sorghum, non-wheat grains, tobacco, peanuts, sugarcane, sugar beets, and other miscellaneous crops (Baker and Stone 2015; Stone 2013; Thelin and Stone 2013).

We characterized estimated U.S. triazole fungicide usage stratified by year, specific compounds, crop type, and geographical location. To aid in interpretation, we used the mean of the low and high annual agricultural pesticide estimates rather than presenting each separately. We also examined state-specific use of triazoles, including by crop type, over five time periods (1992–1996, 1997–2001, 2002–2006, 2007–2011, and 2012–2016) and compared use during the periods 2012–2016 vs. 1992–1996. To calculate differences over time, we summed the mean metric tons of fungicide use for years 2012–2016 and subtracted that value with mean metric tons for years 1992–1996. All analyses were completed in R (Version 3.6.3; R Development Core Team) and maps were created in ArcGIS (ArcGIS Desktop version 10.5.1; Esri Inc.).

Given that triazole fungicides are used in the environment for purposes other than food production, we separately examined California's PUR data for 2017, the most recent year with available data, because the system includes data on a wider range of uses than the USGS data set (California Department of Pesticide Regulation 2017). We examined triazole use in turf (golf course turf, landscape maintenance, bermudagrass, rights of way, and turf/sod), ornamental (garland chrysanthemum, greenhouse flower, greenhouse plants in containers, greenhouse transplants, outdoor flower, outdoor plants in containers, and outdoor transplants), treated lumber, and other (airport, animal burrows, animal premise, beehive, Christmas tree, nonagricultural outdoor buildings, commercial storages or warehouses, commodity fumigation, dairy equipment, ditch bank, farm building, agricultural building, food processing plant, timberland forest, other fumigation, seed grass, greenhouse fumigation, household, industrial processing water, industrial site, industrial disposable water waste disposal systems, public health, regulatory pest control, research commodity, and structural pest control).

## Results

Estimated triazole fungicide use was relatively constant between 1992 (428 metric tons) and 2006 (539 metric tons) but increased 434% from 2006 to 2016, to 2,880 metric tons (Figure 1, Table S1). Triazole use by compound differed over time (Figure 2A, Table S2). The estimated use of propiconazole and tebuconazole, the most widely used fungicides in 2016, increased little from 1992 to 2006, whereas use increased by 366% for propiconazole and 229% for tebuconazole during 2006–2016. First use of three newer triazoles—difenoconazole, metconazole, and prothiconazole—was reported after 2006, and usage increased to a total of 732 metric tons in 2016. In contrast, the estimated use of myclobutanil and triadimefon decreased during 1992–2016 (Figure 2A, Table S2).

The estimated triazole fungicide use by crop type also changed substantially over time (Figure 2B, Table S3). During 1992–2005, the primary use was on wheat, orchards and grapes, and other crops. Use on wheat began to increase markedly in 2007, with use increasing 683% during 2006–2016, resulting in the highest use among all crops in 2016 (1,253 metric tons). Use on corn and soybeans also increased dramatically, with use on corn growing from 0 to 437 metric tons during 2006–2016, while use on soybeans increased from 61 to 361 metric tons. Use on other crops, rice, vegetables, and cotton increased steadily over time but at a slower rate. Use on orchards and grapes remained relatively constant (Figure 2B, Table S3).

The estimated geographical distribution of triazole fungicide use shifted as use by crop type changed over time (Figure 3, Tables S4 and S5). The two states with the highest use during the 2012–2016 period, North Dakota (1,800 metric tons) and Georgia (1,008 metric tons), also had the largest increase since 1992–1996. This was primarily due to application on wheat in North Dakota and other crops, such as peanuts, in Georgia (Figure S1). Although California had the third highest usage during 2012–2016 (711 metric tons), application increased <50% since 1992–1996; triazoles were used primarily on orchards and grapes. The geographic shift is apparent as triazole use increased in the Midwest with wheat, corn, and soybeans (Figure S1, Tables S4 and S5).

The estimated triazole fungicide use for nonfood settings (e.g., turf, flowers, landscape maintenance) are unknown. However, in California, based on estimated PUR data in a single year, 5% of reported triazole fungicide use occured in nonfood production settings (Table S6).

## Discussion

Based on our analysis of USGS estimates, overall U.S. triazole fungicide use in agriculture was relatively constant during 1992–2005 and increased >4-fold during 2006–2016 based on USGS estimates. Although estimated triazole usage increased in nearly every crop type and state over the period, the increase occurred primarily in wheat, corn, soybeans, and other crops in the Midwest and Southeast. These increases may have implications for triazole resistance in pathogenic fungi for humans, particularly in *A. fumigatus*, based on evidence from Europe and elsewhere (Bueid et al. 2010; Lelièvre et al. 2013; Resendiz-Sharpe et al. 2019). Given that resistance mutations previously associated with environmental triazole use have recently been detected in U.S. patient and environmental *A. fumigatus* isolates (Beer et al. 2018; Hurst et al. 2017), additional study of the role of agricultural fungicides is warranted.

Several factors may explain the dramatic increase in U.S. triazole fungicide use after 2006, including increased corn production in response to higher prices, plant diseases in certain regions, ability to use new fungicides on field crops, and marketing of fungicides for use on field crops (Mueller et al. 2017; Wise and Mueller 2011). For example, when soybean rust caused by the fungus *Phakopsora pachyrhizi* was first identified in the United States in 2004, several fungicides were registered or granted emergency exemptions for treatment of soybeans, including myclobutanil, propiconazole, tebuconazole, and tetraconazole (Battaglin et al. 2011; Sconyers et al. 2006; Wise and Mueller 2011). Another class of fungicides called strobilurins have been marketed to increase soybean and corn yield, frequently in combination with triazoles (Swoboda and Pedersen 2009; Wise and Mueller 2011). Fungicides are also used preemptively and in targeted ways in what are called insurance

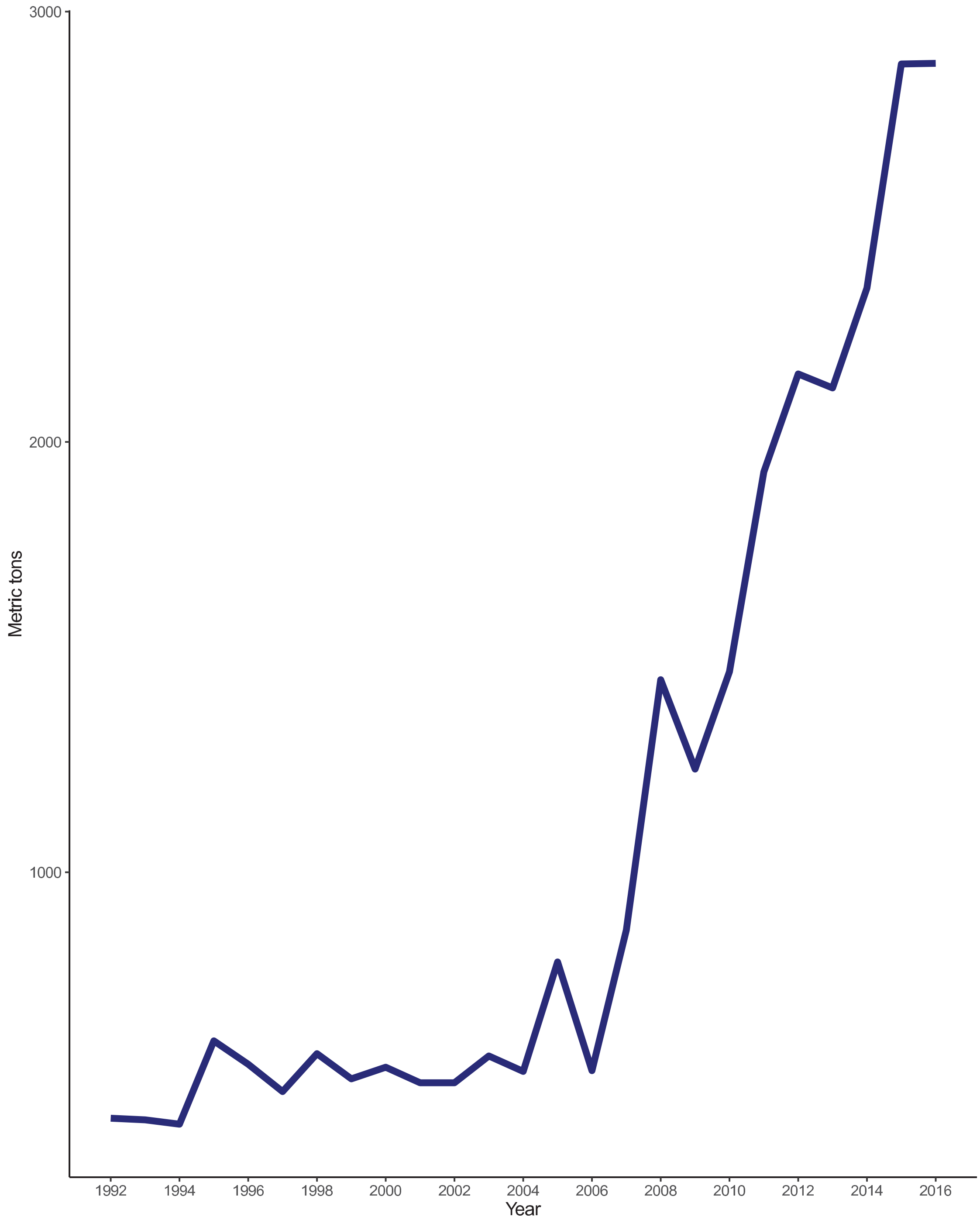

**Figure 1.** Average agricultural triazole fungicide use by year in metric tons, United States, 1992–2016. Estimates were derived by averaging low and high U.S. Geological Survey (USGS) agricultural pesticide estimates for each year. For corresponding numeric data, see Table S1. Data from the USGS National Water-Quality Assessment: The Pesticide National Synthesis Project (USGS 2017).

applications, cover sprays, or prophylactic treatments when they are added to spray tanks being used to apply other pesticides like herbicides or insecticides (DiFonzo 2012). More research may be helpful to understand the reasons behind the large increases in triazole fungicides.

Because both triazoles and *A. fumigatus* can travel in the environment, exposure and resistance selection should be considered beyond the sites of application at agricultural fields. For example, triazoles have been detected in surface waters across the United States (Battaglin et al. 2011; Nowell et al. 2018; Sanders et al. 2018; Smalling and Orlando 2011). Further, triazoles can be transported long distances in the atmosphere (Désert et al. 2018; Schummer et al. 2010), and residues have been detected in amphibians living in remote locations in the Sierra Nevada, dozens of miles downwind from where they were applied (Smalling et al. 2013). This mobility means that *A. fumigatus* in areas outside agricultural land may be exposed to triazoles, providing opportunity for resistance to develop. *A. fumigatus* spores, like spores of fungal plant pathogens, can travel long distances in the air (Brown and Hovmøller 2002). Triazole-resistant *A. fumigatus* isolates with fungicide-associated TR mutations have been found inside the homes and in the yards of aspergillosis patients, in hospital

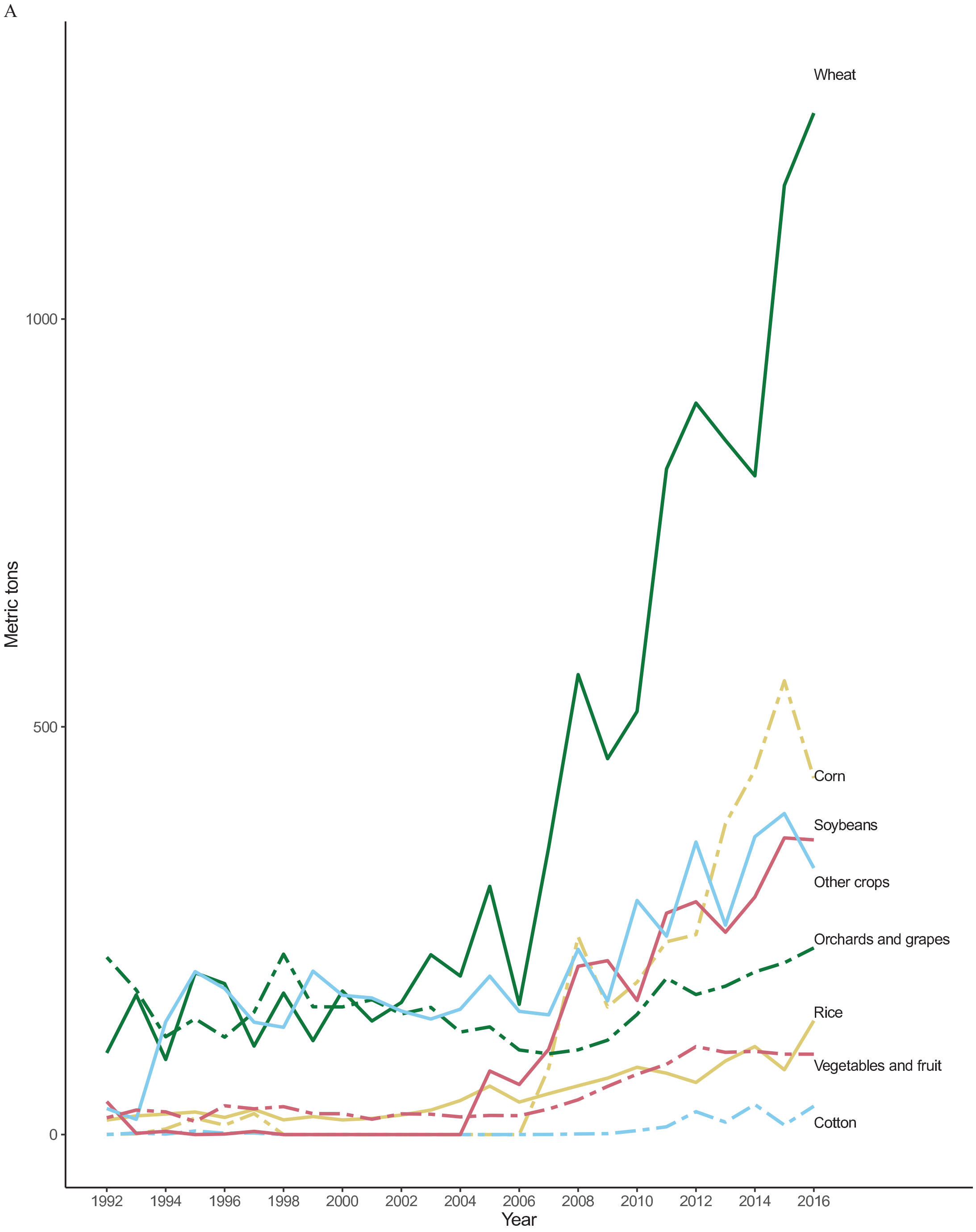

**Figure 2.** Average agricultural triazole fungicide use by crop and compound type in metric tons, United States, 1992–2016. (A) Triazole use by compound type in metric tons, 1992–2016. Fifteen triazoles included in the U.S. Geological Survey (USGS) data set were grouped into eight triazole categories: *a*) difenoconazole, *b*) metconazole, *c*) myclobutanil, *d*) other, *e*) propiconazole, *f*) prothiconazole, *g*) tebuconazole, and *h*) triadimefon. The following triazoles were grouped into the "other" triazole compound type category: cyproconazole, fenbuconazole, flusilazole, flutriafol, ipconazole, tetraconazole, triadimenol, and triticonazole. For corresponding numeric data, see Table S2. (B) Triazole use by crop type in metric tons, 1992–2016. Crops were grouped into eight categories: *a*) corn, *b*) cotton, *c*) orchards and grapes (stone fruit trees, citrus, nut trees, apples, pears, and grapevines), *d*) other crops, *e*) rice, *f*) soybeans, *g*) vegetables and fruit (all vegetables and non-orchard fruit, including beans, peas, greens, berries, and melons), and *h*) wheat. The following crop combinations were grouped into the "other" crop type category: pasture and hay (cropland for pasture, fallow and idle cropland, pastureland, and other hay); alfalfa; and other (sorghum, non-wheat grains, tobacco, peanuts, sugarcane, sugar beets, and other miscellaneous crops). For corresponding numeric data, see Table S3. Data from the USGS National Water-Quality Assessment: The Pesticide National Synthesis Project (USGS 2017). Estimates were derived by averaging low and high USGS agricultural pesticide estimates for each year.

gardens, and in air samples taken from inside hospitals (Chowdhary et al. 2014b; Lavergne et al. 2017; van der Linden et al. 2013).

Data on nonfood production uses of triazole fungicides in the United States were limited to a single state, California, where 5% of triazole fungicides in 2017 were used for turf, landscape, flowers, lumber, and other. This proportion is likely to be different in other states and nationally and is an important topic of further study, particularly because some of these uses may be closer to population centers. Residential use of triazole

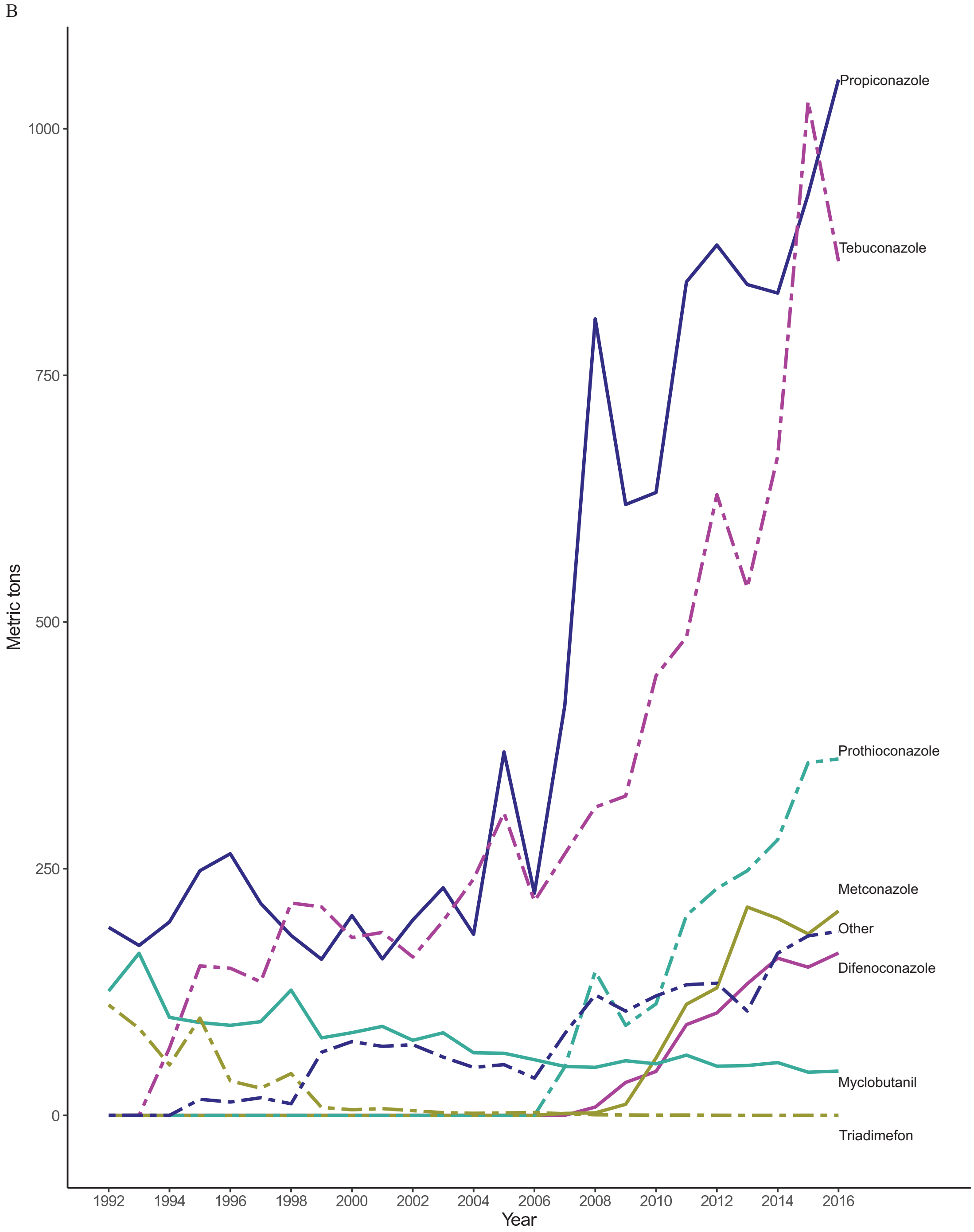

**Figure 2.** (*Continued.*)

fungicides could also be examined because consumers can purchase some of these fungicides (e.g., propiconazole) in stores and online.

Important parallels can be drawn between the challenges with agricultural use of medically important triazoles and agricultural use of medically important antibacterial drugs. In recent years, the U.S. Food and Drug Administration has required that new antimicrobial drugs used in food-producing animals undergo a risk assessment to determine potential impacts on bacteria of human health concern (Center for Veterinary Medicine 2019a, 2019b). The evaluation of potential human health impacts of agricultural triazole fungicide should be considered in more depth. Given that greater use of an antimicrobial is known to select for increased antimicrobial resistance, and that triazole-resistant infections are emerging in plants, greater triazole resistance in human pathogens may emerge as well (Chowdhary et al. 2013). Although detection of $TR_{34}$ and $TR_{46}$ has been limited in the United States to date (Beer et al. 2018), surveillance, reporting, and susceptibility testing for *A. fumigatus* infections are not routinely conducted, suggesting that such infections are likely more widespread than what is reported. For example, only 62% of the infectious disease doctors surveyed through the Emerging Infections Network in the United States reported having access to susceptibility testing for *A. fumigatus*, and such tests were not routinely ordered. Nevertheless, physicians reported seeing resistance in the United States, with 19% observing any triazole

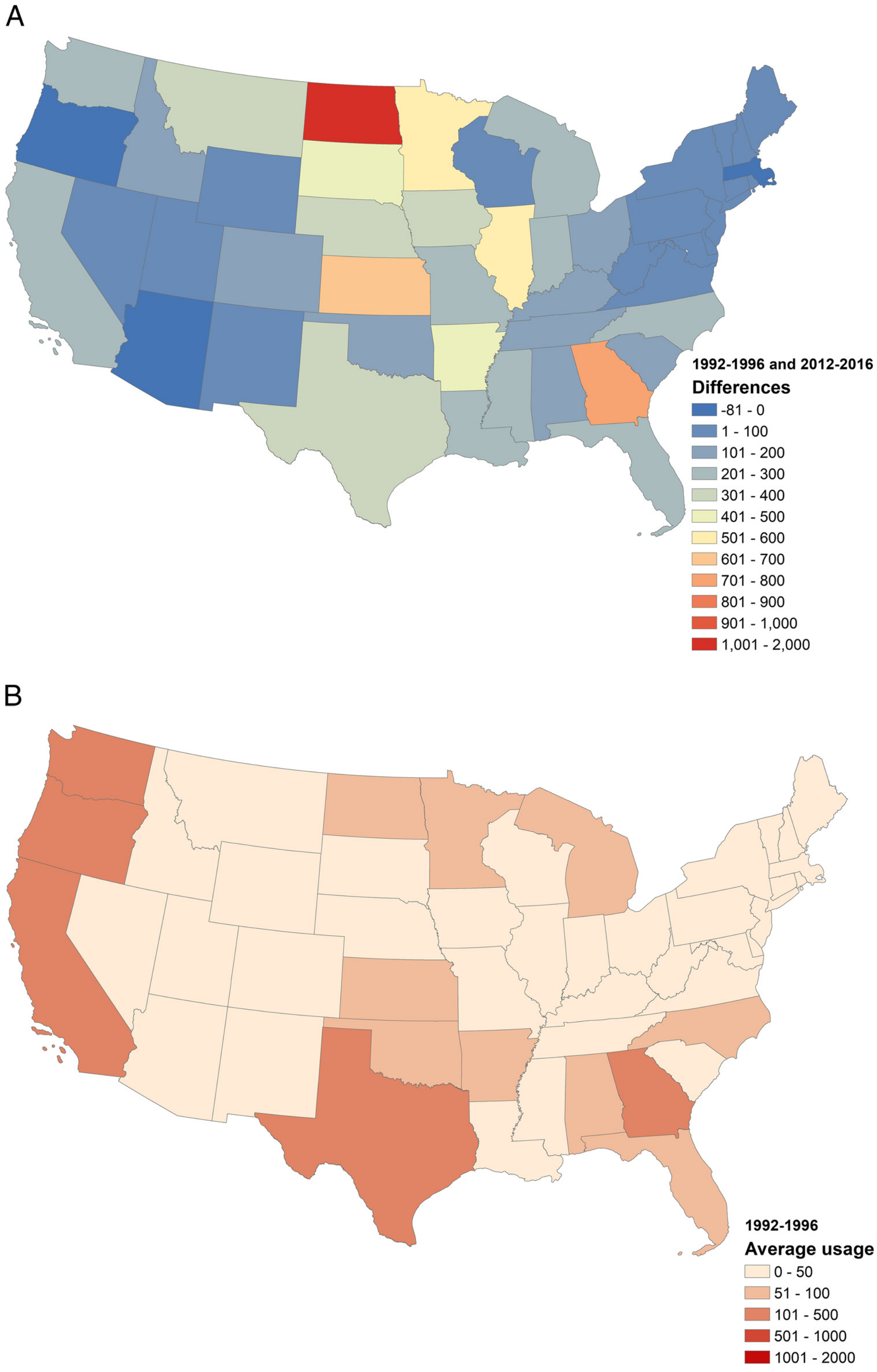

**Figure 3.** Agricultural triazole fungicide usage map by state in metric tons, United States, 1992–2016. (A) Differences in triazole fungicide usage 1992–1996 and 2012–2016 (in metric tons), (B) triazole fungicide usage 1992–1996 (in metric tons), (C) triazole fungicide usage 1997–2001 (in metric tons), (D) triazole fungicide usage 2002–2006 (in metric tons), (E) triazole fungicide usage 2007–2011 (in metric tons), and (F) triazole fungicide usage 2012–2016 (in metric tons). Estimates from the District of Columbia, Hawaii, Alaska, and the territories were not included in the maps. For corresponding numeric data, see Tables S4, S5, and S6. Data from the U.S. Geological Survey (USGS) National Water-Quality Assessment: The Pesticide National Synthesis Project (USGS 2017). Estimates were derived by averaging low and high USGS agricultural pesticide estimates for each year.

resistance and 7% pan-resistance. Fourteen percent were aware of a possible link to environmental fungicide use (Walker et al. 2018). In contrast, testing for resistance in *A. fumigatus* in Europe is more widespread. The European Centre for Disease Prevention and Control recommends triazole antifungal susceptibility testing on all clinical *A. fumigatus* isolates when starting antifungal therapy (ECDC 2013).

Several limitations are inherent in this descriptive analysis of U.S. fungicide use. First, the USGS data are estimates based on a proprietary farm survey (except for California, which has a state

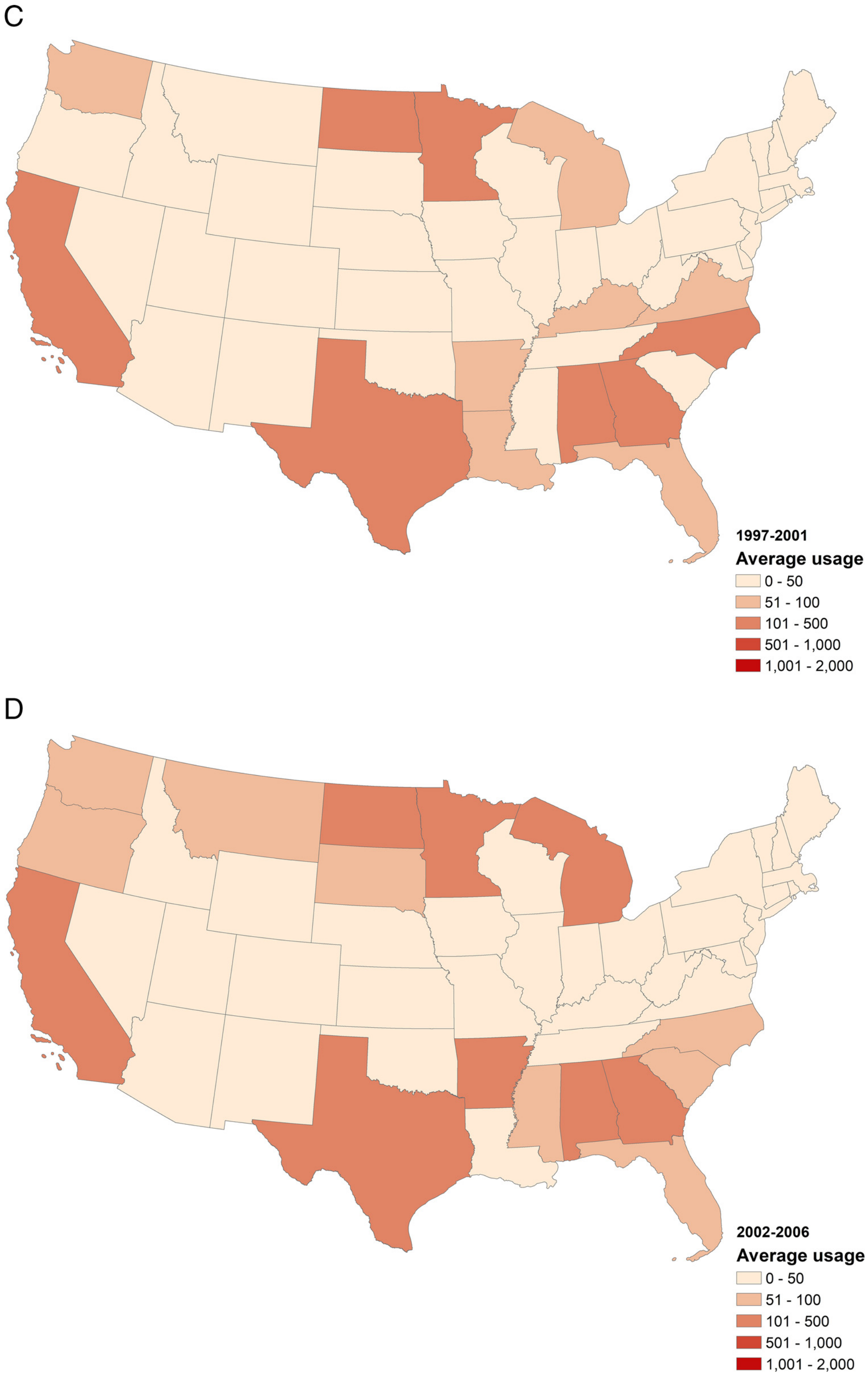

**Figure 3.** (*Continued.*)

reporting system), and some degree of error is expected. In this descriptive analysis, we took the mean of the USGS low and high triazole estimates, which is a simplification involving differing estimates. Second, we did not adjust triazole usage by units of acreage treated, arable land by state or crop, restriction of certain crops in a state, and availability of seed treatment data, although these may be areas of further study. Finally, although available evidence points to environmental fungicide use as a driver of TR-based triazole resistance in *A. fumigatus* globally, direct associations between quantity, use pattern, and timing of agricultural fungicide use and resistant human infections in the United States have not yet been established.

Research and partnerships may allow for opportunities to intervene early before *A. fumigatus* resistance becomes a larger clinical problem in the United States. First, more robust laboratory-based

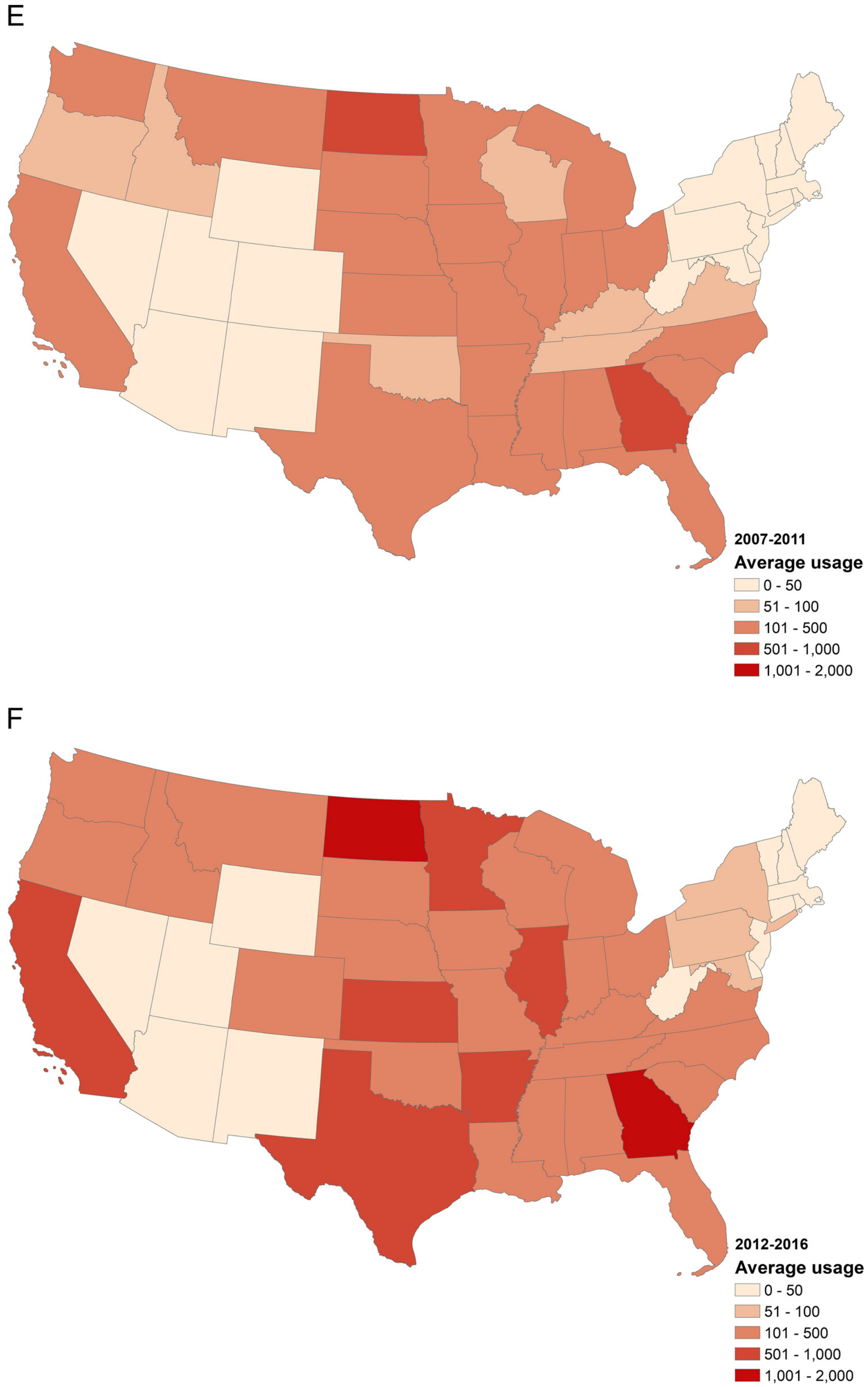

**Figure 3.** (*Continued.*)

surveillance for *A. fumigatus* infections (Verweij et al. 2016b), including systematic antifungal susceptibility testing and microbiome studies, could better determine the burden of resistant infections, as well as geographic and temporal trends. Second, wider-scale environmental testing could assess the distribution of resistance in the environment and agricultural sector. Third, interdisciplinary One Health partnerships could identify ways to mitigate resistance, including exploring alternative fungicides and integrated pest management (Chowdhary et al. 2013; Fisher et al. 2018). Finally, antifungal stewardship in human medicine plays an important role in the judicious use of these limited and important medications (Fitzpatrick et al. 2020), and hospital stewardship programs have been shown to reduce the burden of antimicrobial-resistant human infections (Ananda-Rajah et al. 2012; Baur et al. 2017).

These analyses demonstrate that triazole fungicide use in agriculture has increased >4-fold during 2006–2016 in the United States, driven primarily by increases in propiconazole and tebuconazole, with the largest increases in central parts of the United States. Exposure of *A. fumigatus* to fungicides can select for mutations that cause resistance to the primary antifungals used to treat human aspergillosis. Data on agricultural triazole use can inform further research, risk assessments, and policy decisions related to resistant fungal infections associated with patient illness and death.

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