Title: 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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Abstract

Background

The fungus *Aspergillus 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

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25 improved patient survival; however, triazole-resistant infections have become common in parts of Europe and
26 are emerging in the United States. Triazoles are also a class of fungicides used in plant agriculture, and certain
27 triazole-resistant *A. fumigatus* strains found causing disease in humans have been linked to environmental
28 fungicide use.
29
30 **Objectives**
31 We examined U.S. temporal and geographic trends in use of triazole fungicides using U.S. Geological Survey
32 agricultural pesticide use estimates.
33
34 **Discussion**
35 Based on our analysis, overall tonnage of triazole fungicide use nationwide was relatively constant during 1992–
36 2005 but increased >4-fold during 2006–2016 to 2.9 million kg in 2016. During 1992–2005, triazole fungicide use
37 occurred mostly in orchards and grapes, wheat, and other crops, but recent increases in use have occurred
38 primarily in wheat, corn, soybeans, and other crops, particularly in Midwest and Southeast states. We conclude
39 that given chemical similarities between triazole fungicides and triazole antifungal drugs used in human
40 medicine, increased monitoring for environmental and clinical triazole resistance in *A. fumigatus* would improve
41 overall understanding of these interactions, as well as help identify strategies to mitigate development and
42 spread of resistance.
43
44 **Background**
45
46 Invasive aspergillosis is a severe and frequently fatal fungal disease (mortality rate 25%–59%) that most
47 commonly affects people who are immunocompromised (e.g., because of transplantation or malignancy) or
48 have structural lung disease (e.g., chronic obstructive pulmonary disease (COPD)) (Kontoyiannis et al. 2010;

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49 Pappas et al. 2010; Steinbach et al. 2012). Approximately 15,000 U.S. hospitalizations with invasive aspergillosis
50 are estimated to occur annually based on medical coding data, with incidence increasing over the past decade,
51 in part because of growing numbers of patients at risk (Benedict et al. 2019; Vallabhaneni et al. 2017). In high
52 risk groups, such as solid organ transplantation recipients, incidence can approach 1% (Pappas et al. 2010).
53 However, medical coding likely does not encompass all diagnosed cases, and the lack of national public health
54 surveillance limits understanding of the true burden. Furthermore, many more undiagnosed cases likely exist. A
55 systematic review of 31 studies of autopsy-confirmed misdiagnosis among intensive care unit patients during
56 1966–2011 (5,863 examinations, 14 countries represented) indicated that aspergillosis was one of the most
57 commonly missed diagnoses (Winters et al. 2012).
58
59 *Aspergillus fumigatus*, the species of pathogenic fungi that causes most invasive aspergillosis (Patterson et al.
60 2000), is common in the environment, particularly in decaying plant material but also at low levels in ambient air
61 (Tekaia and Latgé 2005). Unlike many other fungi, it is thermotolerant up to 65 degrees Celsius and grows
62 optimally at normal and febrile human body temperatures (roughly 37–40 degree Celsius), including during
63 fever response, a key factor in its human pathogenicity, as well as at elevated temperatures found in composting
64 organic matter (Kwon-Chung and Sugui 2013). Although it is widely present in agricultural areas, it is not known
65 to cause disease in plants. Mold-active triazole antifungal medications (e.g., voriconazole) are the mainstay of
66 treatment for invasive aspergillosis, having substantially improved patient survival following their introduction in
67 the 1990s (Herbrecht et al. 2002; Verweij et al. 2016a). Only three main classes of antifungal medications
68 (triazoles, echinocandins, and polyenes) are available to treat systemic fungal infections like aspergillosis.
69
70 Whereas relatively few fungi cause invasive disease in humans, fungi are the most common cause of plant
71 infections. Fungicides have been widely used for centuries to treat plant infections, prevent crop loss, and
72 increase agricultural yield; fungicides are also used to preserve wood and other materials. (Morton and Staub

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73 2008; Russell 2005; Kleinkauf and European Centre for Disease Prevention and Control 2013; US EPA 2015; Wise
74 et al. 2019; Wise and Mueller 2011). Data on global triazole usage are limited, and the Food and Agriculture
75 Organization provides data on combined triazole and diazole use, making it difficult to determine the amount of
76 triazole use alone (FAOSTAT). Sales data suggest that triazoles are widely used agricultural fungicide classes,
77 comprising over a quarter of estimated global fungicide sales (Kleinkauf and European Centre for Disease
78 Prevention and Control 2013). Fungal pathogens of agricultural crops have developed resistance to many classes
79 of fungicides, including triazoles (Cools and Fraaije 2008; Hu et al. 2016; Price et al. 2015), prompting the
80 Fungicide Resistance Action Committee (FRAC) and other organizations to devote substantial resources to
81 preventing and managing resistance (FRAC | Home). Notably, certain agricultural triazole fungicides, including
82 bromuconazole, difenoconazole, epoxiconazole, propiconazole, and tebuconazole are structurally highly similar
83 to medical triazoles used to treat aspergillosis (e.g., voriconazole, itraconazole, and posaconazole) (Snelders et
84 al. 2012).
85
86 Like plant pathogens that have developed resistance to triazole fungicides, *A. fumigatus* strains resistant to
87 medical triazoles have emerged globally, prompting public health concerns. Resistant aspergillosis is associated
88 with treatment failure and high mortality, ranging from 42% to 88% (Lestrade et al. 2019; Resendiz-Sharpe et al.
89 2019; van der Linden et al. 2011). Death occurs more commonly in resistant infections, with 90-day mortality
90 being 25% higher in patients with resistant versus susceptible aspergillosis in a European study (Lestrade et al.
91 2019). Resistance in *A. fumigatus* can develop in two ways. First, it can develop inside the body under selection
92 pressure from long-term use of triazole medications. During the 1990s, small numbers of triazole-resistant
93 infections were identified in patients receiving long-term triazole prophylaxis or therapy (e.g., for aspergilloma,
94 cavitary lung disease, or other non-invasive aspergillosis), with resistance mechanisms involving point mutations
95 in the triazole target and ergosterol synthesis gene, *CYP51A* (Camps et al. 2012; Heo et al. 2017; Howard et al.
96 2013, 2009). Resistance occurs less frequently in invasive aspergillosis, presumably because the fungus has less

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97 time to grow in the body. Given the contribution of antifungal use to triazole resistance in *A. fumigatus*, it is
98 notable that triazole use in U.S. hospitals declined by 21% during 2006–2012, the most recent years with
99 available data (Vallabhaneni et al. 2018).
100
101 In the late 1990s, a new resistance mechanism was identified in patients who had *A. fumigatus* infections, and
102 the same mechanism was identified in *A. fumigatus* exposed to triazole fungicides in the environment. This
103 mechanism, TR34/L98H (which we will refer to as TR34), includes a 34-base pair tandem repeat (TR) in the
104 *cyp51A* promoter coupled with a specific point mutation in the coding region and can confer resistance to all
105 triazole medications, known as pan-resistance (Abdolrasouli et al. 2018). In contrast to the resistance
106 mechanism that can develop inside the human body, this environmental resistance was observed in isolates
107 primarily from patients who had never taken triazole medicines (Snelders et al. 2008; Verweij et al. 2007), with
108 subsequent studies finding that 53%–64% of patients with resistant infection lacked exposure to medical
109 triazoles (van der Linden et al. 2011, 2013).
110
111 Because triazoles are widely used in agriculture as fungicides, researchers suspected that the TR34-based
112 resistance developed in the environment under fungicide-induced selection pressure (Bromley et al. 2014;
113 Snelders et al. 2009) and that infections resulted from exposure to already-resistant *A. fumigatus* rather than
114 resistance developing in the patient (Berger et al. 2017). Subsequent research provided additional evidence for
115 this hypothesis and identified a second genotype, TR46/Y121F/T289A (TR46), thought to be linked to fungicide
116 use (Astvad et al. 2014; Chowdhary et al. 2014b, 2015; Lavergne et al. 2015; Le Pape et al. 2016; Montesinos et
117 al. 2014; Steinmann et al. 2015; van der Linden et al. 2013, 2015; Vermeulen et al. 2012). Although the TR-based
118 mechanisms may not be definitive markers of environmental resistance, one report described a resistant isolate
119 with a TR120 mechanism in a patient on long-term triazole therapy for chronic aspergillosis (Hare et al. 2019).
120 Overall, evidence suggests that isolates with TR34 and TR46 mutations result from environmental triazole

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121 exposure (Buil et al. 2019).

122

123 TR34 and TR46-mediated resistance has become common in patients with aspergillosis in parts of Europe, where
124 up to 20% of infections are now resistant to medical triazoles (Bueid et al. 2010; Lelièvre et al. 2013; Resendiz-
125 Sharpe et al. 2019; van der Linden et al. 2015; Vermeulen et al. 2013). Resistant *A. fumigatus* strains with TR34
126 and TR46 mutations have also been reported among azole-naïve patients in the Middle East, Asia, Africa,
127 Australia, and South America (Chowdhary et al. 2014a, 2017; Meis et al. 2016; Vermeulen et al. 2013; Verweij et
128 al. 2016a). In addition, environmental isolates with TR34 and TR46 mutations have been detected in Europe,
129 Asia, South America, and East Africa (Alvarez-Moreno et al. 2019; Badali et al. 2013; Chowdhary et al. 2012,
130 2014b; Dunne et al. 2017; Le Pape et al. 2016; Mortensen et al. 2010; Schoustra et al. 2019; Vermeulen et al.
131 2012). Further supporting a link between fungicide use and clinical resistance, triazole fungicides similar to
132 medical antifungals were introduced for agricultural use in the Netherlands just before the first TR34 strain was
133 found in human clinical settings in the late-1990s (Meis et al. 2016).

134

135 In the United States, associations between agricultural triazole fungicide use and human infections have not
136 been investigated, but a small number of infections caused by resistant *A.fumigatus* strains have been identified
137 (CDC 2019). The first TR-based resistance in patients was reported in 2016, including retrospectively identified
138 isolates (two TR_{34} and two TR_{46}) collected as early as 2008 (Vazquez and Manavathu 2016; Wiederhold et al.
139 2016). An additional 6 isolates were detected through 2018 (Beer 2018). Together, these 10 isolates likely reflect
140 only a small proportion of the true number of resistant infections given lack of standardized surveillance and
141 limited clinical testing. Resistant *A. fumigatus* strains with the TR_{34} mutation have also been found in peanut crop
142 debris in the U.S. state of Georgia that had been treated with propiconazole and tebuconazole, triazoles that are
143 structurally similar to medical triazoles (Hurst et al. 2017), demonstrating this resistance was also present in the
144 U.S. agricultural environment. Because of this emergence in the United States, CDC has placed triazole-resistant

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145 *A. fumigatus* on its "Watch List" for antimicrobial resistance threats (CDC 2019).

146

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

153

154 **Methods**

155

156 We analyzed publicly available state-level estimates of annual agricultural pesticide use from the U.S. Geological
157 Survey (USGS) (Baker and Stone 2015; Stone 2013; Thelin and Stone 2013) for 15 triazole fungicides used in the
158 United States during 1992–2016 (USGS 2017). Data for District of Columbia, Hawaii, Alaska, and territories were
159 not included in the estimates. Methods for these estimates are described in detail elsewhere (Baker and Stone
160 2015; Stone 2013; Thelin and Stone 2013). Briefly, for states other than California, proprietary farm survey data
161 collected by Gfk Kynetec, Inc. on amounts of pesticide use on specific crops are aggregated by the U.S.
162 Department of Agriculture to estimate pesticide-by-crop use rates within Crop Reporting Districts (CRDs). Each
163 CRD covers multiple counties and each county is assigned to a single CRD. County-level pesticide use estimates
164 are then derived by applying CRD-level pesticide-by-crop use rates to county-level estimates of the harvested
165 acreage of each relevant crop (based on U.S. Department of Agriculture's Census of Agriculture data) and state-
166 level use estimates are derived by summing the county-level estimates. When survey-based pesticide-by-crop
167 use rates are missing for a CRD in a given year, two different approaches are used to account for the missing
168 data (Thelin and Stone, 2013). Estimates based on the first approach assumes zero use for counties with missing

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169 data and are referred to as "low" use estimates. Estimates based on the second approach extrapolates rates
170 based on data for nearby CRDs and are referred to as "high" use estimates. Specifically, pesticide-by-crop use
171 rates are estimated using the median rate for all contiguous CRDs; or, if data are missing for all contiguous CRDs,
172 the median rate for all CRDs adjacent to contiguous CRDs; or, if data are missing for all of these CRDs, the
173 median of all non-zero rates for all CRDs within the same USDA Farm Resource Region. To simplify
174 interpretation, we used mean of the low and high annual agricultural pesticide use estimates in this report,
175 rather than presenting each separately. For California, USGS inputs data on county-level pesticide use from the
176 state's Pesticide Use Reports (PUR), collected by the Department of Pesticide Regulation (California Department
177 of Pesticide Regulation).
178
179 Fifteen triazoles in the USGS dataset are used primarily as fungicides. Because seven of these triazoles
180 (difenoconazole, metconazole, myclobutanil, propiconazole, prothiconazole, tebuconazole, and triadimefon)
181 accounted for 93% of triazole use, we grouped the remaining eight fungicides (cyproconazole, fenbuconazole,
182 flusilazole, flutriafol, ipconazole, tetraconazole, triadimenol, and triticonazole) into a single category. Three of
183 the five agricultural triazoles documented to be structurally similar to medical triazoles (Snelders et al. 2012) are
184 registered for use in the United States (difenoconazole, propiconazole, and tebuconazole).
185
186 Based on USGS classifications, we grouped crops into eight categories: corn, cotton, orchards and grapes (stone
187 fruit trees, citrus, nut trees, apples, pears, and grapevines), rice, soybeans, vegetables and fruit (vegetables and
188 non-orchard fruit, including beans, peas, greens, berries, and melons), wheat, and other crops. The other crop
189 category includes pasture and hay (cropland for pasture, fallow and idle cropland, pastureland, and other hay),
190 alfalfa, sorghum, non-wheat grains, tobacco, peanuts, sugarcane, sugar beets, and other miscellaneous crops
191 (Baker and Stone 2015; Stone 2013; Thelin and Stone 2013).
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193 We characterized estimated U.S. triazole fungicide usage stratified by year, specific compounds, crop type, and
194 geographical location. To aid in interpretation, we used mean of the low and high annual agricultural pesticide
195 estimates rather than presenting each separately. We also examined state-specific use of triazoles, including by
196 crop type, over 5 time periods (1992–1996, 1997–2001, 2002–2006, 2007–2011, and 2012–2016) and compared
197 use during the periods 2012–2016 versus 1992–1996. To calculate differences over time, we summed the mean
198 metric tons of fungicide use for years 2012–2016 and subtracted that value with mean metric tons for years
199 1992–1996. All analysis was completed in R (Version 3.6.3, RStudio) and maps were created in ArcGIS (ArcGIS
200 Desktop 10.5.1, Esri Inc.).
201
202 Because triazole fungicides are used in the environment for purposes other than food production, we separately
203 examined California's PUR data for 2017, the most recent year with available data, because the system includes
204 data on wider range of uses than the USGS dataset (California Department of Pesticide Regulation 2017). We
205 examined triazole use in turf (golf course turf, landscape maintenance, bermudagrass, rights of way, and
206 turf/sod), ornamental (garland chrysanthemum, greenhouse flower, greenhouse plants in containers,
207 greenhouse transplants, outdoor flower, outdoor plants in containers, and outdoor transplants), treated lumber,
208 and other (airport, animal burrows, animal premise, beehive, Christmas tree, non-agricultural outdoor buildings,
209 commercial storages or warehouses, commodity fumigation, dairy equipment, ditch bank, farm building,
210 agricultural building, food processing plant, timberland forest, other fumigation, seed grass, greenhouse
211 fumigation, household, industrial processing water, industrial site, industrial disposable water waste disposal
212 systems, public health, regulatory pest control, research commodity, structural pest control.
213
214 **Results**
215
216 Estimated triazole fungicide use was relatively constant between 1992 (428 metric tons) and 2006 (539 metric

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217 tons), but increased 434% from 2006 to 2016, to 2,880 metric tons (Figure 1, Table S1). Triazole use by
218 compound differed over time (Figure 2A, Table S2). Estimated use of propiconazole and tebuconazole, the most
219 widely used fungicides in 2016, increased little from 1992 to 2006, whereas use increased by 366% for
220 propiconazole and 229% for tebuconazole during 2006–2016. First use of three newer triazoles difenoconazole,
221 metconazole, and prothiconazole was reported after 2006, and usage increased to a total of 732 metric tons in
222 2016. In contrast, estimated use of myclobutanil and triadimefon decreased during 1992–2016 (Figure 2A, Table
223 S2).
224
225 Estimated triazole fungicide use by crop type also changed substantially over time (Figure 2B, Table S3). During
226 1992–2005, the primary use was on wheat, orchards and grapes, and other crops. Use on wheat began to
227 increase markedly in 2007, with use increasing 683% during 2006–2016, resulting in the highest use amongst all
228 crops in 2016 (1253 metric tons). Use on corn and soybeans also increased dramatically, with use on corn
229 growing from 0 to 437 metric tons during 2006–2016, while use on soybeans increased from 61 to 361 metric
230 tons. Use on other crops, rice, vegetables, and cotton increased steadily over time but at a slower rate. Use on
231 orchards and grapes remained relatively constant (Figure 2B, Table S3).
232
233 The estimated geographical distribution of triazole fungicide use shifted as use by crop type changed over time
234 (Figure 3, Table S4, Table S5). The two states with the highest use during the 2012–2016 period, North Dakota
235 (1,800 metric tons) and Georgia (1,008 metric tons), also had the largest increase since 1992–1996. This was
236 primarily due to application on wheat in North Dakota and other crops, such as peanuts, in Georgia (Figure S1).
237 Although California had the third highest usage during 2012–2016 (711 metric tons), application increased <50%
238 since 1992–1996; triazoles were used primarily on orchards and grapes. The geographic shift is apparent as
239 triazole use increased in the Midwest with wheat, corn, and soybeans (Figure S1, Table S4, Table S5).
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241 In California, based on estimated PUR data in a single year, 5% of reported triazole fungicide use occurred in
242 non-food production settings (e.g., turf, flowers, landscape maintenance) (Table S6).
243
244 **Discussion**
245
246 Based on our analysis of USGS estimates, overall U.S. triazole fungicide use in agriculture was relatively constant
247 during 1992–2005 and increased >4-fold during 2006–2016 based on USGS estimates. Although estimated
248 triazole usage increased in nearly every crop type and state over the period, the increase occurred primarily in
249 wheat, corn, soybeans, and other crops in the Midwest and Southeast. These increases may have implications
250 for triazole resistance in pathogenic fungi for humans, particularly in *A. fumigatus*, based on evidence from
251 Europe and elsewhere (Bueid et al. 2010; Lelièvre et al. 2013; Resendiz-Sharpe et al. 2019). Given that resistance
252 mutations previously associated with environmental triazole use have recently been detected in U.S. patient and
253 environmental *A. fumigatus* isolates (Beer 2018; Hurst et al. 2017), additional study of the role of agricultural
254 fungicides is warranted.
255
256 Several factors may explain the dramatic increase in U.S. triazole fungicide use after 2006, including increased
257 corn production in response to higher prices, plant diseases in certain regions, ability to use new fungicides on
258 field crops, and marketing of fungicides for use on field crops (Mueller et al. 2017; Wise and Mueller 2011). For
259 example, when soybean rust caused by the fungus *Phakopsora pachyrhizi* was first identified in the United States
260 in 2004, several fungicides were registered or granted emergency exemptions for treatment of soybeans,
261 including myclobutanil, propiconazole, tebuconazole, and tetraconazole (Battaglin et al. 2011; Sconyers et al.
262 2006; Wise and Mueller 2011). Another class of fungicides called strobilurins have been marketed to increase
263 soybean and corn yield, frequently in combination with triazoles (Swoboda and Pedersen 2009; Wise and
264 Mueller 2011). Fungicides are also used preemptively and in targeted ways in what are called insurance

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265 applications, cover sprays, or prophylactic treatments when they are added to spray tanks being used to apply
266 other pesticides like herbicides or insecticides (DiFonzo 2012). More research may be helpful to understand the
267 reasons behind the large increases in triazole fungicides.
268
269 Because both triazoles and *A. fumigatus* can travel in the environment, exposure and resistance selection should
270 be considered beyond the sites of application at agricultural fields. For example, triazoles have been detected in
271 surface waters across the country (Battaglin et al. 2011; Nowell et al. 2018; Sanders et al. 2018; Smalling and
272 Orlando 2011). Further, triazoles can be transported long distances in the atmosphere (Désert et al. 2018;
273 Schummer et al. 2010), and residues have been detected in amphibians living in remote locations in the Sierra
274 Nevada, dozens of miles downwind from where they were applied (Smalling et al. 2013). This mobility means
275 that *A. fumigatus* in areas outside agricultural land may be exposed to triazoles, providing opportunity for
276 resistance to develop. *A. fumigatus* spores, like spores of fungal plant pathogens, can travel long distances in the
277 air (Brown and Hovmøller 2002). Triazole-resistant *A. fumigatus* isolates with fungicide-associated TR mutations
278 have been found inside the homes and in the yards of aspergillosis patients, in hospital gardens, and in air
279 samples taken from inside hospitals (Chowdhary et al. 2014b; Lavergne et al. 2017; van der Linden et al. 2013).
280
281 Data on non-food production uses of triazole fungicides in the United States were limited to a single state,
282 California, where 5% of triazole fungicides in 2017 were used for turf, landscape, flowers lumber, and other. This
283 proportion is likely to be different in other states and nationally, and is an important topic of further study,
284 particularly because some of these uses may be closer to population centers. Residential use of triazole
285 fungicides could also be examined, since consumers can purchase some of these fungicides (e.g., propiconazole)
286 in stores and online.
287
288 Important parallels can be drawn between challenges with agricultural use of medically important triazoles and

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289 agricultural use of medically important antibacterial drugs. In recent years, the Food and Drug Administration
290 has required that new antimicrobial drugs used in food-producing animals undergo a risk assessment to
291 determine potential impacts on bacteria of human health concern (Center for Veterinary Medicine 2019a,
292 2019b). Evaluation of potential human health impacts of agricultural triazole fungicide should be considered in
293 more depth. Given that greater use of an antimicrobial is known to select for increased antimicrobial resistance,
294 and that triazole-resistant infections are emerging in plants, greater triazole resistance in human pathogens may
295 emerge as well (Chowdhary et al. 2013). Although detection of TR34 and TR46 has been limited in the United
296 States to date (Beer 2018), surveillance, reporting, and susceptibility testing for *A. fumigatus* infections are not
297 routinely conducted, suggesting that such infections are likely more widespread. For example, only 62% of the
298 infectious disease doctors surveyed through the Emerging Infections Network in the United States reported
299 having access to susceptibility testing for *A. fumigatus*, and such tests were not routinely ordered. Nevertheless,
300 physicians reported seeing resistance in the United States, with 19% observing any triazole resistance and 7%
301 pan-resistance. Fourteen percent were aware of a possible link to environmental fungicide use (Walker et al.
302 2018). In contrast, testing for resistance in *A. fumigatus* in Europe is more widespread. The European Centre for
303 Disease Prevention and Control recommends triazole antifungal susceptibility testing on all clinical *A. fumigatus*
304 isolates when starting antifungal therapy (Kleinkauf and European Centre for Disease Prevention and Control
305 2013).
306
307 Several limitations are inherent in this descriptive analysis of US fungicide use. First, the USGS data are estimates
308 based on a proprietary farm survey (except for California, which has a state reporting system), and some degree
309 of error is expected. In this descriptive analysis, we took the mean of the USGS low and high triazole estimates,
310 which is a simplification involving differing estimates. Second, we did not adjust triazole usage by units of
311 acreage treated, arable land by state or crop, restriction of certain crops in a state, and availability of seed
312 treatment data, although these may be areas of further study. Finally, although available evidence points to

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313 environmental fungicide use as a driver of TR-based triazole resistance in *A. fumigatus* globally, direct
314 associations between quantity, use pattern, and timing of agricultural fungicide use and resistant human
315 infections in the United States have not yet been established.
316
317 In the United States, research and partnerships may allow for opportunities to intervene early before *A.*
318 *fumigatus* resistance becomes a larger clinical problem. First, more robust laboratory-based surveillance for *A.*
319 *fumigatus* infections (Verweij et al. 2016b), including systematic antifungal susceptibility testing and microbiome
320 studies, could better determine the burden of resistant infections, as well as geographic and temporal trends.
321 Second, wider-scale environmental testing could assess the distribution of resistance in the environment and
322 agricultural sector. Third, interdisciplinary One Health partnerships could identify ways to mitigate resistance,
323 including exploring alternative fungicides and integrated pest management (Chowdhary et al. 2013; Fisher et al.
324 2018). Finally, antifungal stewardship in human medicine plays an important role in judicious use of these
325 limited and important medications (Fitzpatrick et al. 2020), and hospital stewardship programs have been shown
326 to reduce the burden of antimicrobial-resistant human infections (Ananda-Rajah et al. 2012; Baur et al. 2017).
327 These analyses demonstrate that triazole fungicide use in agriculture has increased >4-fold during 2006–2016 in
328 the United States, driven primarily by increases in propiconazole and tebuconazole, with the largest increases in
329 central parts of the United States. Exposure of *A. fumigatus* to fungicides can select for mutations that cause
330 resistance to the primary antifungals used to treat human aspergillosis. Data on agricultural triazole use can
331 inform further research, risk assessments, and policy decisions related to resistant fungal infections associated
332 with patient illness and death.
333
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335
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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government.

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Figure 1: Average agricultural triazole fungicide use by year in metric tons, United States, 1992–2016

Estimates were derived by averaging “low” and “high” USGS agricultural pesticide estimates for each year.

For corresponding numeric data, see Table S1.

Data from USGS. 2017. USGS NAWQA: The Pesticide National Synthesis Project.

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704 Figure 2: Average agricultural triazole fungicide use by crop and compound type in

705 metric tons, United States, 1992–2016

706

707 A. Triazole use by compound type in metric tons, 1992–

708 2016

709

710 Fifteen triazoles included in the USGS dataset were grouped into 8 triazole categories:

711 1. Difenoconazole

712 2. Metconazole

713 3. Myclobutanil

714 4. Other

715 5. Propiconazole

716 6. Prothiconazole

717 7. Tebuconazole

718 8. Triadimefon

719

720 The following triazoles were grouped into other triazole compound type category: cyproconazole,

721 fenbuconazole, flusilazole, flutriafol, ipconazole, tetraconazole, triadimenol, and triticonazole.

722

723 For corresponding numeric data, see Table S2.

724

725 B. Triazole use by crop type in metric tons, 1992–2016

726

727 Crops were grouped into 8 categories:

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1. Corn
2. Cotton
3. Orchards and grapes (stone fruit trees, citrus, nut trees, apples, pears, and grapevines)
4. Other crops
5. Rice
6. Soybeans
7. Vegetables and fruit (all vegetables and non-orchard fruit, including beans, peas, greens, berries, and melons)
8. Wheat

The following crop combinations were grouped into 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 USGS. 2017. USGS NAWQA: The Pesticide National Synthesis Project.

Estimates were derived by averaging "low" and "high" USGS agricultural pesticide estimates for each year.

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749 Figure 3: Agricultural triazole fungicide usage map by state in metric tons, United States, 1992–2016

750

751 A: Differences in triazole fungicide usage 2012– 16 and 1992–96 (in metric tons)

752

753 B: Triazole fungicide usage 1992–1996 (in metric tons)

754

755 C: Triazole fungicide usage 1997–2001 (in metric tons)

756

757 D: Triazole fungicide usage 2002–2006 (in metric tons)

758

759 E: Triazole fungicide usage 2007–2011 (in metric tons)

760

761 F: Triazole fungicide usage 2012–2016 (in metric tons)

762

763 Estimates from District of Columbia, Hawaii, Alaska, and the territories were not included in the maps.

764

765 For corresponding numeric data, see Table S4, S5, and S6.

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767 Data from USGS. 2017. USGS NAWQA: The Pesticide National Synthesis Project.

768

769 Estimates were derived by averaging "low" and "high" USGS agricultural pesticide estimates for each

770 year.

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