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A review of the toxicity of triazole fungicides approved to be used in European Union to the soil and aqueous environment

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Abstract. This review provides the summarized current knowledge on the degradation and effects on the non-target organisms from soil and aquatic environment of the triazole fungicides approved to be used in most of the European Union also taking into account stereospecific differences. Synthetized data reveal that triazole fungicides are usually persistent in aqueous environment and soil, and manifest moderately acute and chronic toxicity against the organisms living in these environments. Furthermore, the enantiomers of triazole fungicides proved to have distinct distribution and effects on these environments. These data are important for assuring a sustainable agriculture by production and use of single-stereoisomer and/or encouraging a management of agricultural crops with minimum effects on environment.

***Keywords*:** degradation; acute and chronic toxicity; fish; crustaceans; aquatic invertebrates; algae; aquatic plants; earthworms; stereoisomers.

1. Introduction

The number of chemical products, including pesticides, is continuously growing worldwide. The global pesticide usage in 2020 has been estimated to about 3.5 million tons [1]. In the European Union (EU), the total quantity of pesticides used in the period 2011-2018 was 360 million kilograms every year [2]. Furthermore, fungicides and bactericides were sold in the highest quantities in the EU in 2019 [3].

The extensive usage of pesticides has increased the crop yield and led to significant reduction in harvest losses. On the other hand, indiscriminate usage of these chemicals has led to human and environmental adverse effects, as pesticide may pollute water, air and/ or soil ecosystems [1]. Fungicides may pose a risk both to environment and to the human health. Regarding the human health hazards, fungicides can be irritating to the skin and eyes, can be teratogenic, carcinogenic, mutagenic or reproductive toxicants [4, 5]. Due to wide use in medicine, agriculture and urban application to buildings, fungicides can easily reach soil and aquatic ecosystems, occur in surface water, can be highly toxic to a broad range of organisms from water and soil, and can affect the development of the populations of microorganisms and the activity of the enzymes found in soil [6-8].

Wrong and/ or excessive application of the fungicides can lead to hazardous influence on soil and aquatic ecosystems, the pollutants being usually the same in these ecosystems, but their fate and effects on living organisms may be distinct [9]. The hazardous effects of toxic compounds on soil is usually due to the reduced mobility and availability of the soil components (humus, minerals) as a result of their interactions with toxicants. The tests regarding the effects of various types of chemicals, including pesticides, on the soil ecosystems are usually focussed on the degradation of chemicals in soil and on their effects on the earthworms as model organisms (survival, growth, reproduction and behavioural changes) because these species are easy to handle in the laboratory conditions [9, 10]. The effects on aquatic ecosystems are due to the runoff from the agricultural field and/ or industrial wastewater. During the precipitations, the fungicides could be carried away by water, they can penetrate the soil layers, may reach surface waters and groundwater, and affect the organisms living in aqueous environment [11]. Classical tests on aquatic organisms like crustacean, algae or aquatic plants demonstrated that fungicides can be toxic to non-target aquatic organisms and can pose a risk to aquatic biota [6, 11].

Literature data reveal that triazole fungicides residues were found in soil [12]. For example, the maximum concentration of tebuconazole in agricultural soils was registered as 0.19 mg/kg [13]. Similarly, triazole fungicides were identified as contaminants of aquatic ecosystems with concentrations of 1 ng/L up to 0.92 mg/L [14].

In order to assure a sustainable agriculture, the crop management must ensure not only profitability, but also healthy ecosystems. It implies to use pesticides that have low toxicological effects on the environment. This study focusses on triazole fungicides: difenoconazole, epoxiconazole, metconazole, paclobutrazol, tebuconazole, tetraconazole, triadimenol, triticonazole. These fungicides are considered because they were

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approved to be used in most of the EU states in 2022. The physicochemical properties of these chemicals reveal their low molecular weight, moderately lipophilic and moderately flexible character underlining that they may adsorb to soil, sediments and organic surfaces in aquatic ecosystems [6, 8]. These properties also indicate that they may persist in sediments due to an increase of exposure duration locally at low concentrations and also potentially downstream due to sediment remobilization [6]. Consequently, the aim of this study is to synthetize the persistence / degradation rates and the effects of the investigated fungicides on model organisms living in soil and aquatic environment.

2. Materials and methods

The toxicological impacts of pesticides on environment are generally evaluated by determining or predicting their environmental concentrations and by assessing their potential toxicity against various organisms. The REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation (EC) No 1907/2006 of the European Parliament and the Council of 18 December 2006 is one of the guidance documents describing the information requirements with regard to chemical properties, use, exposure, risk management, and safety assessment [15]. This document establishes the required tests for assessing aquatic toxicity of chemicals and these tests include the following organisms representing different taxonomic groups: earthworms, aquatic algae and plants, crustaceans, invertebrates (usually *Daphnia* sp.) and fishes. These organisms are widely used as indicators of health in environmental monitoring.

Within this study, the investigated triazole fungicides are: difenoconazole, epoxiconazole, metconazole, paclobutrazol, tebuconazole, tetraconazole, triadimenol, triticonazole (Figure 1). All these fungicides belong to the class of 1,2,4-triazoles that are heterocyclic compounds sharing the structural element of a five-membered ring of two carbon and three nitrogen atoms.

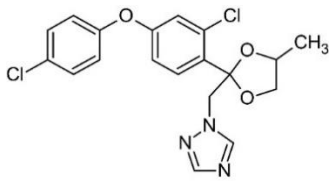
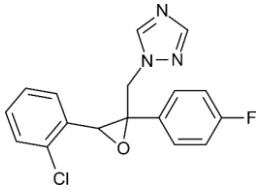
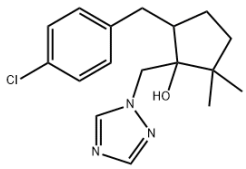
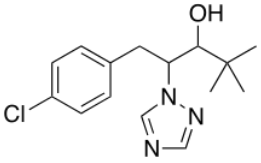
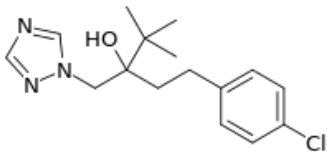
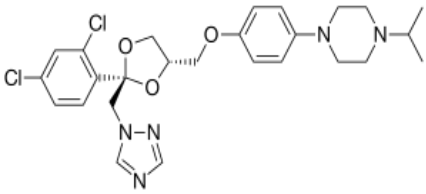
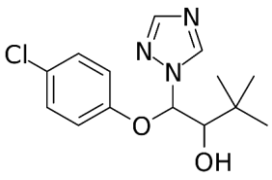
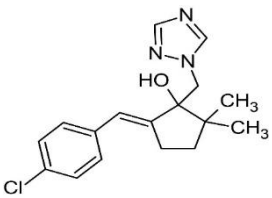
	
Difenoconazole / 1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1,2,4-triazole	Epoxiconazole / 1-[[3-(2-chlorophenyl)-2-(4-fluorophenyl)oxiran-2-yl]methyl]-1,2,4-triazole
	
Metconazole / 5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentan-1-ol	Paclobutrazol / (2R,3R)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)pentan-3-ol
	
Tebuconazole / 1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	Tetraconazole / 1-[2-(2,4-dichlorophenyl)-3-(1,1,2,2-tetrafluoroethoxy)propyl]-1,2,4-triazole
	
Triadimenol / 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)butan-2-ol	Triticonazole / (5*E*)-5-[(4-chlorophenyl)methylidene]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentan-1-ol

Figure 1. The fungicides considered in this study: common name, IUPAC name and 2D formula.

In order to obtain information regarding the persistence and the effects of investigated fungicides on the organisms living in soil and the aqueous environment, we have used the PRISMA recommendations [16, 17], *i.e.* we have used the information available in the Pesticide Properties Database [18] and in the specific literature. When searching the literature, we have taken into account only studies assessing the effects of a single fungicide, information has been extracted only from research and review articles published in English until February 2022 and contained in well-known scientific databases (Science Direct Freedom Collection, Web of Science, Springer Link Journals, SCOPUS, etc.).

The Pesticide Properties Database (http://sitem.herts.ac.uk/aeru/ppdb/) [18] and specific published literature have been used to extract, for the investigated fungicides, the eco-toxicity available data for aquatic model organisms and for soil model organisms. The following data were retrieved for fungicides in general and, when available, for their stereoisomers: (i) the rates of degradation in water, in water sediment and in soil (expressed as half-life, DT_{50}, defined as the time necessary for an amount of a chemical to be reduced by half through degradation) due to aquatic photolysis and hydrolysis, and due to degradation in soil respectively; (ii) the lethal concentration 50 (LC_{50}, the concentration of the investigated chemical causing the death of 50% of the tested population [19]) after 96 hours for fish (usually *Oncorhynchus mykiss*), crustaceans (*Americamys bahia*), sediment dwelling organisms (usually *Chironomus riparius*) and earthworms (*Eisenia foetida*) after 14 days in the case of acute exposure; (iii) the median effective concentration (EC50, the concentration of investigated chemical that reduces to 50% the grows of tested population [19]) after 48 hours for aquatic invertebrates (*Daphnia magna*), after 72 hours for algae and after 7 days for aquatic plants (*Lemna gibba*) in the case of acute exposure; (iv) the chronic 21 day NOEC (No Observed Effect Concentration, the highest tested concentration that does not conduct to statistical significant difference of effect, $p<0.05$, when compared to the control group in long-term eco-toxicity studies [19]) for fishes (usually for *Oncorhynchus mykiss*), invertebrates (*Daphnia magna*); (v) the chronic 28 day NOEC for sediment dwelling organisms (*Chironomus riparius*) for water and sediment phases; (vi) the chronic 96 hours NOEC for algae grows and 56 days chronic NOEC earthworm reproduction (mg kg^{-1}). Specific literature has been used also to extract information regarding the toxicity against aquatic organism *Tetrahymena pyriformis* and the distinct effects manifested by stereoisomers of the co investigated fungicides.

3. Results and discussion

3.1. Effects of triazole fungicides on the aqueous environment

Pesticides are known to degrade in water environment by hydrolysis, photolysis, and microbial degradation [20]. Consequently, information extracted from PPDB and specific literature for the investigated fungicides refer to their degradation rates in aqueous environment and are presented in Table 1.

Table 1. Degradation rates in aqueous environment for the investigated fungicides. In parenthesis are presented the organisms that were used for testing. NA means not available information [18, 21].

Fungicide	**Aqueous photolysis DT_{50} at pH=7 (days)**	**Aqueous hydrolysis DT_{50} (days)**	**Water sediment DT_{50} (days)**	**Water phase only DT_{50} (days)**	**Sediment dwelling organisms - Acute 96 hours LC_{50} (mg L^{-1})**
Difenoconazole	stable	stable for pH 5 to pH 9	1053	3	0.77 (*Chironomus riparius*)
Epoxiconazole	53	Stable for pH 5 to pH 9 at 25 °C, some hydrolysis at elevated temperatures	103.6	1000	0.0625 (*Chironomus riparius*)
Metconazole	83	stable pH 4 to pH 9 at 20^0C	465	8	NA
Paclobutrazol	stable	stable for pH 4 to pH 9 over 30 days at 25 °C	787	164	NA
Tebuconazole	no significant photolytic degradation	stable for pH 5 to pH 9, at 25 °C, 28 days days	365	42.6	1.899 (*Chironomus dilutes*)
Tetraconazole	217	stable for pH 4 to pH 9, 120 hours	340	2	NA
Triadimenol	9	stable for pH 4 to pH 9 at 20 and 40 °C	91	53	NA
Triticonazole	300	stable at all relevant pHs	stable	stable	NA

Data presented in Table 1 reveal that the investigated fungicides are persistent in water, especially in water sediment. They are not susceptible to hydrolysis for wide ranges of pH and temperature values and their degradation by aqueous photolysis is also low. Among the investigated fungicides, the epoxiconazole is the most persistent in water phase and the triadimenol is the least persistent in water environment.

Table 2 reveals the acute toxicity data and Table 3 the chronic toxicity data extracted from the PPDB for the investigated fungicides against fishes, crustacean, invertebrates (*Daphnia magna*), algae, sediment dwelling organisms and aquatic plants, respectively. No supplementary data have been identified in specific literature.

Table 2. Available data regarding the acute toxicity against fish, crustacean, algae, aquatic plant and sediment dwelling organisms for the investigated fungicides [18]. In parenthesis are presented the organisms that were used for testing. NA means not available data.

Fungicide	**96 hours acute toxicity against fish LC_{50} (mg L^{-1})**	**96 hours acute toxicity against crustaceans (*Americamysis bahia*) LC_{50} (mg L^{-1})**	**48 hours acute toxicity against *Daphnia magna* EC_{50} (mg L^{-1})**	**7 days acute toxicity against *Lemna gibba* grows, EC_{50} (mg L^{-1})**	**72 hours acute toxicity against algae growth EC_{50} (mg L^{-1})**	**96 hours acute toxicity against sediment dwelling organisms, LC_{50} (mg L^{-1})**
Difenoconazole	1.100 (*Oncorhynchus mykiss)*	0.150	0.770	2.500	0.032 (*Scenedemus subspicatus*)	0.770 (*Chironomus riparius*)
Epoxiconazole	>0.920 (*Oncorhynchus mykiss*)	NA	3.130	0.014	10.690 (*Pseudokirchneriella subcapitata*)	0.062 (*Chironomus riparius*)
Metconazole	2.100 (*Oncorhynchus mykiss*)	NA	4.200	0.527	1.700 (*Raphidocelis subcapitata)*	NA
Paclobutrazol	23.600 (*Lepomis macrochirus*)	NA	33.200	0.008	7.200 *(Pseudokirchneriella subcapitata)*	NA
Tebuconazole	4.400 (*Oncorhynchus mykiss*)	0.460	2.790	0.144	1.960 (*Scenedemus subspicatus)*	1.899 (*Chironomus dilutes*)
Tetraconazole	4.300 (*Lepomis macrochirus*)	0.420	3.000	0.520	2.400 (*Ankistodesmus bibaiamus)*	NA
Triadimenol	21.300 (*Oncorhynchus mykiss*)	NA	51.00	NA	9.600 (*Pseudokirchneriella subcapitata)*	NA
Triticonazole	3.600 (*Oncorhynchus mykiss)*	NA	9.00	1.100	>1.000 (*Pseudokirchneriella subcapitata)*	NA

Table 3. Available data regarding the chronic toxicity against fish, crustacean, algae, aquatic plant and sediment dwelling organisms for the investigated fungicides [18]. In parenthesis are presented the organisms that were used for testing. NA means not available data.

Fungicide	**Fish chronic 21 day NOEC (mg L^{-1})**	**Aquatic invertebrates (*Daphnia magna*) - chronic 21 day NOEC (mg L^{-1})**	**Sediment dwelling organisms (*Chironomus riparius*) - chronic 28 day NOEC, static, water (mg L^{-1})**	**Sediment dwelling organisms (*Chironomus riparius*) - chronic 28 day NOEC, sediment (mg kg^{-1})**	**Algae - chronic 96 hours NOEC, growth (mg L^{-1})**
Difenoconazole	0.023 (*Oncorhynchus mykiss*)	0.0056	0.015	10.0	0.87 (Unknown species)
Epoxiconazole	0.01 (*Oncorhynchus mykiss)*	0.63	>= 0.00625	0.03	0.0078 *(Pseudokirchneriella subcapitata)*
Metconazole	1.14 (*Oncorhynchus mykiss*)	0.16	2.12	8.23	NA
Paclobutrazol	3.3 *(Salmo gairdneri)*	NA	NA	NA	NA
Tebuconazole	0.010 *(Oncorhynchus mykiss)*	0.01	2.51	42.9	0.1 (Unknown species)
Tetraconazole	0.3 *(Pimephales promelas)*	0.19	4.45	NA	NA

Fungicide	Fish chronic 21 day NOEC (mg L^{-1})	Aquatic invertebrates (*Daphnia magna*) - chronic 21 day NOEC (mg L^{-1})	Sediment dwelling organisms (*Chironomus riparius*) - chronic 28 day NOEC, static, water (mg L^{-1})	Sediment dwelling organisms (*Chironomus riparius*) - chronic 28 day NOEC, sediment (mg kg^{-1})	Algae - chronic 96 hours NOEC, growth (mg L^{-1})
Triadimenol	3.13 *(Oncorhynchus mykiss)*	0.1	0.1	0.667	1 *(Unknown species)*
Triticonazole	0.01 *(Oncorhynchus mykiss)*	0.092	0.08	NA	NA

Information presented in Tables 2 and 3 reveal that, besides their persistence in water, the triazole fungicides usually manifest moderately acute and chronic toxicity against fish, crustaceans, invertebrates, algae, sediment dwelling organisms and aquatic plants. Epoxiconazole is nontoxic for the algae *Pseudokirchneriella subcapitata*, but is reveals high toxicity for the aquatic plants *Lemna gibba* and exposes both acute and chronic toxicity against sediment dwelling organism *Chironomus riparius*. Among the studied fungicides, the paclobutrazol reveals the highest acute toxicity against *Lemna gibba* and the difenoconazole manifest chronic toxicity against *Daphnia magna*.

There is not information available in PPDB regarding the toxicity of these fungicides on *Tetrahymena pyriformis* (TPT). When searching the scientific literature databases for the TPT caused by the investigated fungicides, only one study has been identified revealing an inhibitory effect of difenoconazole on population growth of *Tetrahymena pyriformis* ($IC50 = 6.8$ μg mL^{-1}) [22].

3.2. Effects of triazole fungicides on the soil environment

Within this study we do not consider the effects of triazole fungicides on the population of microorganisms and on the activity of enzymes found in soil, because these effects are treated elsewhere [8]. We take into consideration the degradation of fungicides in soil and the effects of these pesticides on earthworms as model organisms for soil environment. These data are illustrated in Table 4.

Table 4. Available data regarding the degradation of triazole fungicides in soil and their effects on earthworms (*Eisenia foetida*) [18]. NA means not available data.

Fungicide	Soil degradation DT_{50} in filed conditions (days)	Earthworms - Acute 14 day LC_{50} (mg kg^{-1})	Earthworms - Chronic 56 days NOEC, reproduction (mg kg^{-1})
Difenoconazole	20-265	> 610	0.2
Epoxiconazole	1-248	> 500	> 3.24
Metconazole	27-368	> 500	> 20
Paclobutrazol	27-120	> 500	0.845
Tebuconazole	26-92	1381	10
Tetraconazole	136-1688	71	8.2
Triadimenol	24-84	> 390.5	NA
Triticonazole	36-242	> 500	> 125

Data presented in Table 4 compared to with the thresholds specified in scientific literature [19] emphasize that most of the investigated triazole fungicides are persistent in soil and manifest moderately effects on the earthworms. Tetraconazole is very persistent, whereas tebuconazole and triadimenol reveal moderate persistence in soil. The highest acute toxicity against earthworms is revealed by tetraconazole and the lowest acute toxicity against earthworms is revealed by tebuconazole. Tebuconazole, tetraconazole and triticonazole are the triazole fungicides that reveal low chronic toxicity against the reproduction of earthworms.

3.3. Distinct effects of the stereoisomers of triazole fungicides on the soil and aqueous environment

It is widely recognized that stereoisomers of triazole fungicides have distinct biological effects, but evaluation of the environmental risks does not usually take into consideration this property. It is also true when evaluating the public health hazards [23]. Published data revealed that distribution characteristics of enantiomers of chiral pesticides in sediments samples collected from a river network of an agricultural area reflected enantioselectivity that was usually correlated with the microbial community [24].

Information regarding the effects of distinct stereoisomers of triazole fungicides on soil and/or water environment and extracted from specific literature, are revealed in Table 5. We were not able to identify information regarding the selectivity of the stereoisomers of paclobutrazol.

Table 5. Distinct effects of the stereoisomers of triazole fungicides on the soil and aqueous environment. NA means not available data.

Fungicide	Effects on soil environment	Effects on aqueous environment
Difenoconazole	The half-lives of degradation were considerably different between enantiomers of difenoconazole under both aerobic and anaerobic conditions. The (2R,4R)- and (2R,4S)-difenoconazole were the stereoisomers preferentially degraded in soil [25].	Significant differences were observed in the values of 96 hours EC_{50} among the stereoisomers of difenoconazole against *S. obliquus*, the order of toxicity being (2S,4S) > (2S,4R) > (2R,4R) > (2R,4S). The order of toxicity produced by the stereoisomers of difenoconazole is similar when comparing the LC_{50} values toward both *Daphnia magna* and *Danio rerio*. The (2S,4S)-difenoconazole was 2.1−6.8 times more toxic than (2R,4S)-difenoconazole to all three investigated aquatic species [25].
Epoxiconazole	There was a preferential degradation of (R)-stereoisomer under field condition [26].	The (R)-epoxiconazole had a different effect in the energy metabolism of the zebrafish compared to (+)-epoxiconazole and there were differences in the mechanism of toxic effects between the two enantiomers [27]
Metconazole	NA	Aquatic toxicity of the metconazole stereoisomers against *Daphnia magna* is (1R,5R)-metconazole > metconazole racemate > (1R,5S)-metconazole > (1S,5S)-metconazole ≈ (1S,5R)-metconazole [28].
Tebuconazole	In both aerobic and anaerobic soils, the (S)-tebuconazole degraded faster than (R)-tebuconazole, and the enantioselectivity was correlated with soil organic carbon content [29]. One study reveals that (S)-tebuconazole accumulated in higher content in *Eisenia fetida* [30] and another study emphasizes that the R-enantiomer of tebuconazole was preferentially bioaccumulated by these organisms [31].	The (R)-tebuconazole was about 1.4-5.9 times more toxic than (S)-tebuconazole against aquatic organisms (*Scenedesmus obliquus, Daphnia magna, and Danio rerio*) [29]. The (R)-tebuconazole degraded faster (DT_{50}=136 days) than (S)-tebuconazole (DT_{50}=151 days) in sediment, conducting to the accumulation of (S)-enantiomer [32]. Tebuconazole demonstrated enantioselective bioaccumulation in adult *Danio rerio*, the (R)-enantiomer being preferred [33]
Tetraconazole	The (R)-tetraconazole was preferentially degraded in wheat soil by comparison to (S)-tetraconazole [34, 35] and earthworms have been reported to preferentially bioaccumulate (S)-tetraconazole [36]	NA
Triadimenol	S-(+)-triadimefon was preferentially degraded (DT_{50}=11.27 days) in soil than R-(−)-enantiomer (DT_{50}=13.20 days) after foliar application [37].	There were registered distinct 48 hours LC_{50} values for stereoisomers and racemate of triadimenol to *Daphnia magna*: 15.924 µg/mL for racemate, 11.624 µg/mL for SR-(−)-triadimenol, 8.894 µg/mL for RS-(+)-triadimenol, 28.204 µg/mL for SS-(−)-triadimenol and 17.047 µg/mL for RR-(+)-triadimenol [37].
Triticonazole	S-triticonazole was preferentially bioaccumulated in earthworms [38].	The 96h-EC50 for triticonazole stereoisomers against the aquatic microalgae *Chlorella pyrenoidosa* values were different: of 1.939 mg/L for racemate, 0.853 mg/ (R)-enantiomer and 22.002 mg/L for (S)-enantiomer [39].

Data presented in Table 5 reveal distinct levels of degradation and effects of the stereoisomers of triazole fungicides on soil and aquatic environment underlying that chiral fungicides should be evaluated at stereoselective level when assessing the environmental risks. Sometimes, there are reported contradictory data regarding the effects of the stereoisomers of these fungicides on the organisms found in soil. It may be due to the distinct characteristics of soils used in the evaluation as the activity of soil microorganisms influence degradability and bioavailability [40].

4. Conclusions

Within this study, a synthesis of the available data regarding the toxicity of the triazole fungicides approved to be used in the most of the European Union countries on the model organisms for the aquatic and soil environments is performed. Information synthetized reveals that triazole fungicides are usually persistent in aqueous and soil environments and manifest moderately acute and chronic toxicity against the organisms living in these environments. Tradimenol is the least persistent in both soil and water environment and it also reveal a lower toxicity against the majority of the investigated model organisms. It underlines that, being a broad-spectrum systemic fungicide and when appropriate, triadimenol should be preferred for use instead of other triazole fungicides in crop management. Furthermore, the degradation rates and the effects of these fungicides on the soil and aqueous environment reveal stereoselectivity. These data underline the importance of following the recommended dose and application intervals of fungicides for each type of crop and to consider enantioselective toxicity when evaluating the influence of chiral compounds, such as to limit the hazardous effects of triazole fungicides on soil and aqueous environment. The use of one enantiomer instead of the commercial racemic mix may help to reduce the environmental risk of fungicide. An adequate management of the use of triazole fungicides allows to

mitigate their effects on the organisms living in aqueous and soil environments and contributes to development of a sustainable agriculture.

Conflict of interest

The authors have no conflict of interest, hence none declared.

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