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PHARMACEUTICAL FUNGICIDE IN THE AQUATIC ENVIRONMENT: DEVELOPMENT OF PREDICTED ENVIRONMENTAL CONCENTRATION OF TERBINAFINE IN RIVERS

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Abstract: This article reviews important aspects of environmental pollution by terbinafine and its different contamination sources as housing sector, hospitals, pharmaceutical companies, veterinary clinics and livestock complexes. The study is focused on terbinafine which represent the greatest threat. PECs were developed by using available information from datasets and statistical data from bulletins about consumption of pharmaceuticals in Kazakhstan in the period of 2013-2019 for a fungicide terbinafine. Furthermore, along with acute and chronic toxicological data, projected environmental rates allowed estimating the risks of anti-fungal medication.

Keywords: terbinafine, fungicide, predicted environmental concentrations, environmental risk, acute and chronic toxicity, consumption of pharmaceuticals, pharmaceuticals in aquatic environment.

Introduction and background: The production and widespread use of pharmaceutical products and personal care products has led to the emergence of new environmental pollutants [1]. Over the past decade, drugs and their conversion products (metabolites of drug compounds) are detected in environmental objects in many countries of the world [2]. The first reports of pharmaceuticals in the aquatic environment were published in the 1970s, when the presence of drugs and drug metabolites in wastewater effluent was detected. Since then, Work on the determination of pharmaceutical substances in the environment and the development of highly sensitive analytical methods for their determination are being carried out at an increasing pace in the USA, Canada, Brazil, Israel and in many European countries [3]. The main pollution factors are unused medicines falling into the sewage system, drains or vapors of landfills containing unused medicines that are not claimed by private individuals and organizations. As well as, household drains of settlements and clinics containing medicinal substances used by the population and patients, contaminated waters and irrigation of farms can be considered using veterinary drugs[2,3]. In 2008, worldwide pharmaceutical sales totalled US$ 602 billion, an increase of around 5–7 per cent per year (IMS Health 2009), parallel with the major advances in medical technology and increased health care expenditure [4].

At the beginning of the 21st century, the European Environment Agency (EEA) identified the effects of active pharmaceutical substances to the environment as a new problem requiring a mandatory response[5]. The latest global report provides information on the results of testing 713 drugs for their environmental impact. It was revealed that the concentration of 631 medicinal substances was higher than the maximum permissible norms. In the course of in Germany, research revealed that every year from health care providers about 16,000 tons of drugs are disposed of to the population, of which 60–80% are usually go down the toilet or throw out together with ordinary household waste[6]. In addition to damage for the environment these actions also have extremely negative economic consequences. For example, in the United Kingdom, measures to eliminate medical damage waste, according to some estimates, can cost for the National Health Service in the amount of 100 million to 300 million pounds annually [3,4].

Recent evidence indicates that the use and consumption of pharmaceuticals per capita in the European Union has doubled or nearly tripled on a time span of only 14 years (2000- 2014) and suggests an inference of an even bigger absolute consumption amount due to continuous global population increase [7]. This critical piece of information highlights the demand of further investigation of these substances and their possible effects on the environment. The numerous potential effects of pharmaceutical substances along with their sources in the environment have been widely studied during the past years. After administration, some drugs are metabolized, while others remain intact until they are excreted. Pharmaceuticals and their metabolites can either enter the aquatic systems via excretion or disposal wastewater. Due to their high polarity and low volatility, most pharmaceuticals are most likely to be transported to the water column [8].

Recently some pharmaceuticals are associated with adverse effects of growth in marine ecosystems and with harmful impacts on human health. Furthermore, pharmaceutical compounds were detected in groundwater, mostly clarified because of the direct or indirect effect of wastewater. Pharmaceuticals from algae to fish in different quantities and around the world have also been found in biota [9].

There is also widespread concern regarding possible bioaccumulation and persistence of released pharmaceuticals. In addition, pharmaceuticals released as mixtures also pose concerns, because the cumulative environmental effects of pharmaceuticals have long been unknown [6,7].

Considering the large quantity and variety of pharmaceuticals ingested and discharged into the environment, the aim of this analysis was to prioritize and determine their environmental risk by measuring PEC of terbinafine based on consumption in hospitals and pharmacies from 2013 to 2019.

Additionally, given the acute and chronic toxicity of various aquatic taxa for selected pharmaceuticals with the highest PECriver, the possible danger to the aquatic environment was examined.

Materials and methods. Consumption data, being the term "consumption" the dispensation or sales of pharmaceuticals, were obtained from Ministry of Health of Republic of Kazakhstan over the period 2013–2019 in pharmacies and hospitals. Compound selection was based on medical prescriptions for the elderly in Kazakhstan in the last years. This information does not include consumption through mutual insurance companies, as this data was not available for the public health system. Hospital data was given as the number of pills, capsules or any formulation of each active pharmaceutical ingredient dispensed (called activities). From the composition and the number of activities of each pharmaceutical, the total consumption (in kg year−1) was calculated. The consumptions of the antifungal drug in pharmacies were directly provided in mg year−1 by the "Pharmaceutical and Medication Management" of KazStat.

To calculate the predicted environmental concentrations the following equations adapted from Besse et al. (2008) were used (1):

$$\mathrm{PEC_f}\left(\frac{\mu g}{L}\right) = \frac{\mathrm{consumption}\times 10^9\times(100-\mathrm{R})}{365\times \mathrm{inhab}\times \mathrm{V}\times \mathrm{D}} \times 10^6 \quad (1)$$

Consumption is the quantity of terbinafine in free base and hydrochloride form consumed in Kazakhstan; R is 0% removal rate (conservatively, it has been assumed there is no loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation); Inhab is the number of inhabitants in a defined zone (in Kazakhstan, a mean value of 17,446,487 during the period of 2013–2019); V (L/day) volume of wastewater per capita and day = 200 (ECHA default).

In the calculation of PECs, there are several uncertainties which are related to the input parameters of the PEC formula. These uncertainties can produce a bias in the PEC calculation and can alter the results obtained, and thus, their applicability. Persistent hydrophilic substances will be present to a greater extent in the treated liquid effluent, hydrophobic ones in the sludge. Expectable removals in WWTPs can thus be inferred to some extent from the substances degradation rates and Kow or Koc values [11].

The values can be different in WWTP locations according to the served population, capacity, the configuration and type of treatment, in operating parameters and in hydraulic and solid retention times. Other factors such as meteorological conditions, sampling procedure (grab, composite or flow-proportional and sampling period (seasonality) can also affect the empirical PEC [12].

The PNEC is based on the following data (2):

$$PNEC(\frac{\mu g}{L}) = \frac{\text{lowest chronic NOEC}}{10} \quad (2)$$

where 10 is the assessment factor used.

Environmental risk classification (3):

$$\frac{PEC}{PNEC} \quad (3)$$

For data interpretation, the maximum probable risk for ecological effects from contaminated water was followed as recommended by Wentsel et al. (1996):

RQ b 1.0 indicates no significant risk;

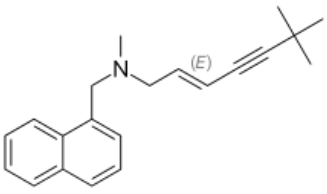
1.0≤ RQ b 10 indicates a small potential for adverse effects;

10 ≤ RQ b 100 indicates significant potential for adverse effects;

RQ ≥ 100 indicates that potential adverse effects should be expected.

Results and discussion. The mean total consumption of antifungal terbinafine in the six years studied (2013–2019) was 573.23 kg per year[10]. Total sold amount API in Kazakhstan in 2013-2019, derived from free base and hydrochloride salt forms (data from KazStat). Reduction of A may be justified based on metabolism data.

Table 1 – Physical and chemical structure of terbinafine [13]

Terbinafine	
Common name	Lamisil
Chemical name (IUPAC)	[(2E)-6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalen-1-ylmethyl)amine
Synonym(s)	terbinafin
Chemical class (when available/relevant)	antifungal
CAS number	78628-80-5
Molecular formula	$C_{21}H_{25}N$
Molecular structure	
Molecular weight (g.mol^{-1})	291.43 g/mol

Fungicidal pharmaceutical terbinafine was studied and identified its physical and chemical structure, as well as its estimated environmental emissions.

Terbinafine is an antifungal medication that fights infections caused by fungus. Terbinafine tablets are used to treat infections caused by fungus that affect the fingernails or toenails. Terbinafine oral granules are used to treat a fungal infection of scalp hair follicles in children who are at least 4 years old[13].

The most frequently used macrolides in human medicine by Vyshkovskii index Lamisil(0,5101), Exifin(0,4263), Fungoterbin(0,315),Terbinafine(0,2598),Terbizil (0,175),

Termycon (0,1676), Atifin (0,1442), Binafin (0,0732), Lamycan (0,07), Terbinafine hydrochloride (0,0583).

Environmental Risk Classification has been identified by PEC formula:

PEC = 0.086 μg/L

Estimated environmental emissions. Terbinafine was detected below the limit of quantification (LOQ) in both the raw sewage water and the final effluent at all five WWTPs. In the digested, dewatered sludge, terbinafine was detected at concentrations ranging between 4 and 30 μg/kg at three of the WWTPs. At the other two WWTPs, terbinafine was detected below the LOQ.

In addition, raw sewage water, raw sewage water particles, raw sludge, and digested dewatered sludge was collected from the Umeå WWTP in April 2008 to assess the fate of the chemicals during the treatment process. Terbinafine was not detected in the raw sewage water or the final effluent; however, it was detected in the raw sludge, at a concentration of 40 μg/kg. Terbinafine appears to be effectively removed from the water during treatment. However, if the sewage sludge is land applied, terbinafine may still enter the environment. In Sweden, approximately 43 kg of terbinafine, is used per year[14].

Environmental behavior. Terbinafine has high potential to bioaccumulate, thus Octanol-water partition coefficient (log Kow) is 5,81,and Sediment – water partition coefficient (Log Pow) is 8,94, while Biococentratoin factor is equal to 5248.

Degradation: 4% (aerobic, 28d, 20-24°C, OECD 301B) not readily biodegradable. Transformation of test item in aerobic/water/sediment systems (OECD308, 101 days). Degradation - DT50 (freshwater phase) = 3-8 days DT50 (total system) = 16-31 days (Reference 8).Ultimate Biodegradation = 19.5% - 27.30%. Average of parent in % (total system) at day 101 = 5.2-7.1%. Extraction was done up to four times with ethanol. Method is acceptable as during work-up of day 0 sample. The DT50 32 days therefore the phrase 'The substance is degraded in the environment' is chosen.

Terbinafine is not readily biodegradable. In water sediment systems the DT50 for the total system is ≤ 32 days. Therefore the phrase 'The substance is degraded in the environment' is thus chosen.

A NOEC of 0.53 μg/l for green algae has been used for this calculation. PNEC = 0.53 μg/L /10 = 53 ng/l

PNEC (μg/L) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for green algae (= 0.53 μg/L) has been used for this calculation since it is the most sensitive of the three-tested species.

PEC/PNEC = 0.086/0.053 = 1.62, i.e. PEC/PNEC ≤ 1 which justifies the phrase "Use of terbinafine has been considered to result in moderate environmental risk."

Conclusion. This research shows the significance of data on use and time trends for estimating the frequency and risk of pharmaceuticals consumed in surface waters by elderly people. The mean total consumption of these pharmaceuticals in the period studied (2013–2016) was 573.23 kg per year. According to Vyshkovskii index the most common name is Lamisil(0,5101). The terbinafine hydrochloride has high potential for bioaccumulation. Since Octanol-water partition coefficient is more than four (log Kow > 4). PEC/PNEC = 0.086/0.053 = 1.62.Through this analysis it is clear that PEC estimation allows for better prioritization of compounds, which are highly likely to be found in the environment. Lastly, projected environmental rates along with acute and chronic toxicological data permitted the risk estimation of these compounds.

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BIRD LITTER AS AN ORGANIC FERTILIZER

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Nowadays modern environmental problems in the Turkestan region are associated with local accumulation of livestock waste (bird droppings, cattle manure). If untreated litter and other livestock wastes are used, enterprises pollute the soil with helminths, pathogens, toxic chemical compounds. In recent years, the region continues to experience a steady decrease in the amount of humus in the soil, and this leads to a decrease in fertility, and soil properties such as physical, chemical, and water-physical are also deteriorating.

If we make conditions for an accelerated process of biofermentation of organic waste by composting, then all these problems can be solved. The composting process, on the one hand, makes it possible to obtain valuable organic fertilizer, on the other hand, it is a cleaning process,