**Kotvitska A. A., Tsubanova N. A., Kononenko N. M., Ostapets M. O. Formation and development perspectives of eco-pharmacy. Journal of Education, Health and Sport. 2019;9(2):521-531. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2613883**
**http://ojs.ukw.edu.pl/index.php/johs/article/view/6757**

**The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).**
**1223 Journal of Education, Health and Sport eISSN 2391-8306 7**

**The authors declare that there is no conflict of interests regarding the publication of this paper.**
**Received: 05.02.2019. Revised: 11.01.2019. Accepted: 28.02.2019.**

# FORMATION AND DEVELOPMENT PERSPECTIVES OF ECO-PHARMACY

**A. A. Kotvitska[1], N. A. Tsubanova[2], N. M. Kononenko[3], M. O. Ostapets[3]**

**[1]Rector of the National University of Pharmacy, Kharkiv, Ukraine**
**[2]Department of General Pharmacy and Safety of Drugs, Institute of Qualification Improvement for Pharmacists of the National University of Pharmacy, Kharkiv, Ukraine**
**[3]Department of Pathological Physiology, National University of Pharmacy, Kharkiv, Ukraine**

## Abstract

The aim of our research is to analyze the impact of pharmacy on human ecology and environment, to generalize and structure the identified interactions and interrelations. We are using methods of scientific analysis such as generalization, comparison, content analysis.

The main components and development perspectives of a new interdisciplinary direction, namely eco-pharmacy, are presented in this article. The classification of drugs according to their eco-pharmacological profile have been presented for the first time. The criteria by which drugs can be considered as eco-pharmacological or eco-pharmacologically hazardous have been defined. The reference points, according to which the patient's treatment can be characterized as eco-pharmacotherapy, are identified. The issue of safe disposal of unsuitable drugs has been updated.

A new interdisciplinary direction that combines pharmacy, ecology and chemistry, namely eco-pharmacy, has been suggested. Optimization and personification of therapy with the prescription of primarily eco-pharmacological drugs will allow to evolve into the level of eco-pharmacotherapy and to reduce the amounts of prescriptions for eco-pharmacologically

hazardous drugs. One of the most important issues of eco-pharmacy at the present stage is the improvement of disposal of unsuitable drugs.

**Key words: pharmacy, ecology, environment.**

**Introduction.** The rapid development of scientific research, the introduction of innovative technologies, the improvement of production processes, the interconnectivity and the scale of world economic processes condition objective prerequisites of problems appearing in the modern world, which have a global nature, relate to the vital interests of all humanity and need pressing solutions. Such problems are characterized by the following features: large-scale manifestations extending beyond one country or groups of states; the acuity of manifestation; the complex character; the possibility of being solved only by the general efforts of all mankind [9].

One of such global problems is the effect of all the components of pharmacy on the human ecosystems, country, planet. According to the definition, pharmacy is a scientific and practical economic activity aimed at search and synthesis of active and auxiliary substances, creation and study of pharmacological effects, production of drugs in industrial and pharmacy conditions; ensuring control over their quality, planning, organization and economy, management and marketing, information and education, as well as ensuring the rational and safe use of drugs and healthcare products [3].

*Highlighting of previously unsettled parts of the general problem*

Based on the definition, the effect of pharmacy on ecology can be large-scale and multi-directional. Constantly growing medicine production causes the significant damage to the environment, increasing the number of pathogens, epidemics and serious diseases. Pollution of air, water, soil and food leads to the emergence of cardiovascular and oncological diseases, dystrophic changes, allergy, hormonal dysfunction, changes in the immune and endocrine systems, decrease in lifespan and birth of a child with different congenital defects.

According to the United National Organization, from 25 to 33 % of the world's registered diseases are directly related with the low quality of the human environment, in 18 % of the cases the reasons of the untimely death are unfavorable environmental conditions, 1 % is due to the negative effect of industrial and domestic waste, which is connected with a significant survival time of microorganisms in pharmaceutical and medical waste. Thus, 1 gram of domestic waste contains 0.1-1 billion of microorganisms, while in medical waste their number increases to 200-300 billion [8].

According to current knowledge, more than 1.8 billion tons of pharmaceutical and medical waste have been accumulated in the world, which is approximately 300 kg per inhabitant of the planet [8]. Therefore, a special attention should be paid to the process of handling of the pharmaceutical waste generated at the enterprise, as well as to the careful regulation and control of technological processes in pharmaceutical enterprises that can have a negative effect on the environment.

**The aim** of the article is to analyze the effect of pharmacy on human ecology and the environment, to generalize and structure the identified interactions and interconnections.

**Results and their discussion**. Pharmacy has a significant effect on human life and the environment. The main factors and their impact on humans and the environment are presented on Figure 1.

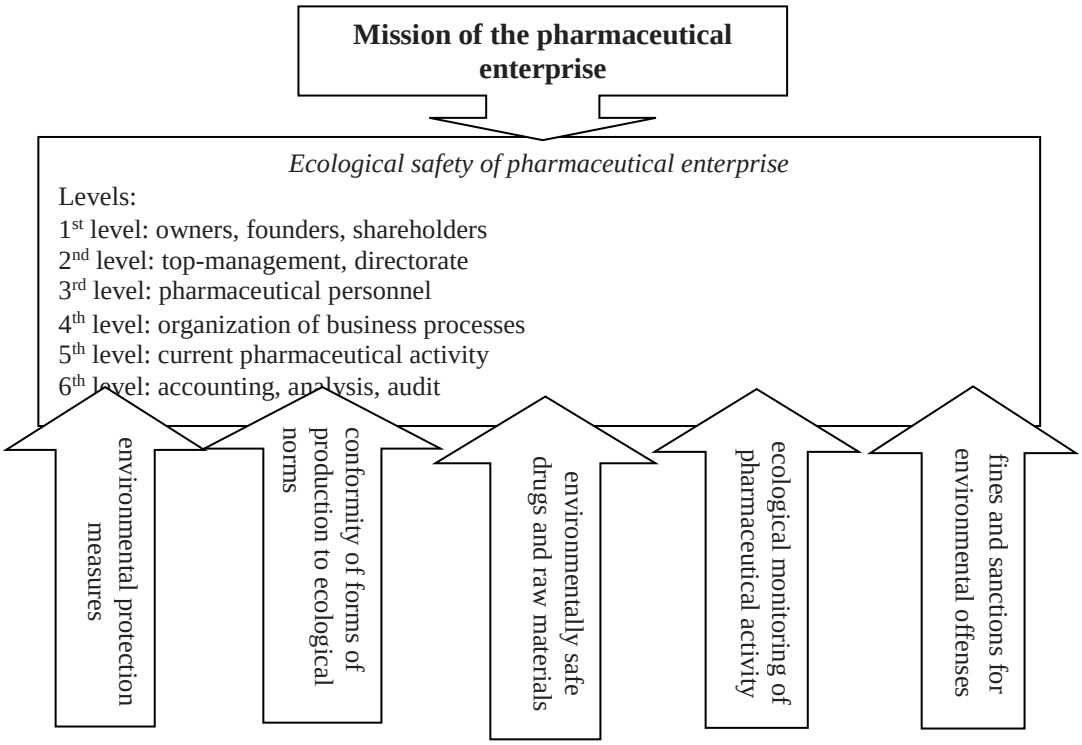


Figure 1. Methodology of environmental management at a pharmaceutical enterprise

Nowadays, in the context of view of environmental control the biggest attention is paid just to the medicine production. Monitoring of the impact of pharmaceutical enterprises on the ecology is conducted by methods of ecological management of a pharmaceutical enterprise. This very direction of activity of pharmaceutical enterprises in the focus of ecological impact has a clear organizational structure and aims to achieve the provisions specified in the environmental policy of pharmaceutical enterprises through the implementation of programs on environmental protection and management of the

environmental aspects of the enterprise. Application of the methodology of environmental management at a pharmaceutical enterprise allows to guarantee the full compliance of the enterprise with environmental standards and ensures the maximum impact reduction of economic activity of the pharmaceutical enterprise on the environment (Fig. 1).

At the stage of supply, storage and use of medicinal substances, drugs and medical products carried out by health care institutions (HCI) such as medical and preventive, sanitary-preventive, pharmaceutical, medical and social protection institutions etc., the environmental control is regulated by the Good Pharmaceutical Practice (GPP). The GPP Guideline is based on the provision of quality of pharmaceutical services and includes recommendations for the development of national standards for promoting healthy lifestyle, supplying and optimizing the use of drugs.

At the stage of administration of drugs, the patient is directly exposed to the active pharmaceutical ingredient (API), which influences the ecosystem of the human body.

In the human body, API is usually subjected to metabolic processes, which are aimed at the increasing of the molecule hydrophilicity, increasing its polarity, reducing its activity and toxicity. The first phase of API metabolism consists in the structural modification, which creates or releases functional groups. The second phase of metabolism is characterized by conjugation reactions with other groups or molecules. The third phase is binding and removal of API and their metabolites from the cell and organism. Hydrophilic compounds are excreted with urine. More hydrophobic molecules or substances, which have a high molecular weight (>300 kDa) enter the intestine, get eliminated from bile and removed with feces.

By origin, all API can be divided into two groups – those of natural origin and those of artificial origin (xenobiotics).

For the metabolism of API of natural origin, only one biotransformation phase may be enough, whereas in the metabolic processes of artificially synthesized API all phases of biotransformation are involved. For example, the first phase of metabolism of the known xenobiotic, namely acetylsalicylic acid, is the hydrolysis reaction that occurs in the gastrointestinal tract and the liver, after that the API in the form of salicylic acid enters into the general circulation. The second phase of biotransformation of salicylates occurs in many tissues, in particular in endoplasmic reticulum and mitochondria of hepatocytes (enzymes of the cytochrome system 450 CYP2C19, CYP3A are involved). There are the following metabolic products: salicylic acid (glycine conjugate), ether, or phenolglucuronide, and ester, or acylglyukuronides; also there are other metabolites in some small quantities. Metabolites of acetylsalicylic acid remain as xenobiotics for the human body and are able to perform a lot of

side effects (of the cardiovascular system and blood (hematopoiesis, hemostasis) such as thrombocytopenia, anemia, leukopenia; of the gastrointestinal tract such as NSAIDs-gastropathy (dyspepsia, pain in the epigastric region, nausea and vomiting, severe bleeding in the gastrointestinal tract), reduced appetite; allergic reactions such as hypersensitivity reactions (bronchospasm, edema of the larynx and urticaria), formation of the «aspirin» bronchial asthma and the «aspirin» triads on the basis of the hapten mechanism (eosinophilic rhinitis, recurrent polyposis of the nose, hyperplastic sinusitis), etc.).

The consequences of biomodification of the xenobiotic molecule can be as follows: the reduction of toxicity; the increase of toxicity; the change of character of the toxic action; the initiation of the toxic process.

In most cases, the metabolism of API leads to the formation of low-level and low-toxic metabolites, which is an evolutionarily produced way of protection of the body from toxic actions of xenobiotics. For example, rhodanides formed during the metabolism of cyanides, are several hundred times less toxic than the starting substances. The situation has radically changed over the past 100 years, when against the backdrop of global ultra-fast development of the pharmaceutical industry, and the synthesis of thousands of new pharmacologically active molecules, the human body turned out to be unable to effectively metabolize new chemicals (to non-toxic and pharmacologically inactive metabolites), which biotransformation nowadays leads to the emergence of reactive and highly toxic metabolites.

Thus, it can be argued that presently there is a tendency of overloading of the human body with new pharmacologically active compounds.

The problematic issue of modern pharmacotherapy is the initiation of the toxification process (metabolic processes accompanied by the increased toxicity) in some patients during the use of several API. One of the examples is the development of the toxification process under the use of opioid analgesics (morphine, methylphenamine, heroin, methadone, codeine). When being administrated, narcotic analgesics are metabolized by N-dealkylation with the formation of appropriate derivatives. A comparative analysis of toxicity of narcotic analgesics and their metabolites allowed to define that the toxicity of norcodeine is 6 times more than those of codeine and 2 times more than those of morphine, which indicates that biotransformation does not always lead to detoxification of API.

Unfortunately, nowadays there is a significant increase in amounts of negative reactions and changes in the ecosystem of the organism caused by excessive, and in some cases, inadequate use of drugs (polypragmasy, overdoses of API, ungrounded prescription etc.).

In our view, it is advisable to introduce a new gradation of drugs in accordance with their eco-pharmacological profile.

It is known that API of natural origin, which are fully metabolized to pharmacologically inactive and, accordingly, non-toxic metabolites, do not induce an imbalance of ecosystems of the organism (in the first place, they do not influence the microbiota) and can be attributed to eco-pharmacological drugs such as probiotics, amino acids, essential phospholipids, and others.

Drugs that are not subject to complete detoxification under conditions of biotransformation, and their metabolites remain pharmacologically active and toxic, have a negative effect on the ecosystem of the organism (including the induction of development of dysbiosis of different localization). Therefore, eco-pharmacologically hazardous drugs are as follows: non-steroidal anti-inflammatory drugs, antibacterial drugs etc.

Taking into account all of the above, in our opinion, one of the effective means of optimizing of the therapy may be the introduction of eco-pharmacotherapy, which is primarily based on the principles of the personalized therapy.

In our view, the reference points of eco-pharmacotherapy are as follows:

- an individual calculation of doses of API for each patient with considering gender, age, comorbid diseases, nutritional habits, chronopharmacological profile of medicines, pharmacogenetic peculiarities;
- mandatory prediction of possible medical interactions and their elimination;
- prevention and treatment of dysbiosis under the use of eco-pharmacologically hazardous drugs (especially in the treatment by antibiotics);
- giving preference to eco-pharmacological drugs.

It should be noted that the concern of ecologists consists in the scale of the problem of environmental pollution by the metabolites of the drugs after their elimination. It is known that the total consumption of API in the world is more than 3 million tons per year. Due to the elimination, several hundred thousand tons of various immutable drugs and their metabolites are annually released into the environment [4].

Analytical studies of the identification of content of different drugs and their metabolites in soil, water, sewage systems, surface water supplies, groundwater and drinking water carried out in most developed and economically stable countries, indicate their significant concentrations (μg/l) in samples of the purified sewage water and the water of surface reservoirs [1]. First of all, this condition may be due to the fact that modern

technologies for water treatment in treatment facilities are not suitable for the removal of drugs and their metabolites. According to Pal et al. (2013), drugs and their metabolites present the new groups of pollutants. Determination of their concentration in the environment (such as water bodies, soil, air) is an indirect assessment tool of potential factors of ecological imbalance of the environment [7]. Published information on medications, which are environmental pollutants, is extremely limited and available mainly in the EU, UK, USA and Canada; there is virtually no data from the rest of the world. Although the concentration of drugs and their metabolites in the environment is not very high, they can potentially affect human health and functioning of natural ecosystems.

Focusing on the same issue, as noted in the review by C.G. Daughton [4], there is a problem of environmental pollution with illicit drug ingredients (IDIs), primarily narcotic substances. Cocaine, morphine, amphetamine, etc. have a strong pharmacological activity, and their presence in the form of complex mixtures in water has a significant negative impact on aquatic organisms and human health. It is proposed to implement the program FEUDS (Forensic Epidemiology Using Drugs in Sewage), which is essentially a forensic epidemiology with continuous monitoring of the content of narcotic drugs in sewage [4].

By means of the indirect method, the FEUDS indicators allow to analyze the level of the use of narcotic drugs for every region. Such an application of pollution parameters of the water ecosystem connected with the quantitative parameters of the use of narcotic drugs can potentially lead to the paradigm of association of human and environmental communities as a single patient and an interconnected whole.

It should be noted that with each passing year the concentration of API in the surface and underground water supplies is increasing. There is an especially dangerous situation with antibiotics, which concentration here and there in the sewage and water reservoirs of some countries is 30 times higher than concentrations, which are normally found in the body of patients treated with these antibiotics. It also means that bacteria near the sewage disposal site have a strong selection pressure that contributes to the development of resistance. It is getting particularly problematic in terms of the recent research, which has proven that the process of disinfection and chlorination of sewage transforms some antibacterial drugs, such as doxycycline, into the new components, which have a much more powerful antibacterial effect [5, 11].

In contrast to other chemical pollutants (organochlorine pesticides, polychlorinated biphenylamines, etc.), API are usually intended for individual use, and therefore their inputs to the environment have neither geographical, nor climatic constraints [1]. Drugs and their

metabolites are constantly entering the environment as modern humankind cannot exist without the permanent use of drugs, while other pollutants are used sporadically and have greater spatial heterogeneity. Unlike persistent organic pollutants (POP), virtually all API are not bioaccumulative and volatile substances. The main ways of AFI transformation are as follows: aerobic biodegradation (surface reservoirs, soil, mud at treatment facilities), hydrolysis and photodegradation (surface reservoirs). Hydrolysis and photolysis in the moist surface soils, hydrolysis and anaerobic biodegradation in the deeper layers of soil represent the less significant ways of degradation. Provided the long and constant input into the environment, even drugs and their metabolites with low persistence can cause the effects of genuine stable pollutants [1]. It is positively correlated with the rate, amount and constant flow of API to the environment, and unfortunately, these indicators cannot be offset by the rate of transformation of drugs into the natural ecosystem.

The eco-pharmacy issue of no less importance is the safe disposal of drugs. Drugs with expired shelf life; drugs which have undergone mechanical, chemical, physical, biological or other impact that prevents their further use; unregistered drugs, except for cases stipulated by the current legislation of Ukraine; drugs for which previously unknown hazardous properties have been detected, a serious adverse reaction or a serious adverse event has been recorded; falsified drugs etc. are subject to the disposal. According to the Order of the Ministry of Health of Ukraine No. 349 of 08.07.2004 “On Approval of the Rules for Recycling and Destruction of Substandard Medical Products”, the procedure for conducting and selecting a method of destruction of medical waste is determined after establishing their hazard class.

Thus, drugs belonging to toxic substances, including biotechnology products and biological agents (vaccines, serums), antibiotics, should be disposed on specially designated objects. Wastes belonging to the 3$^{rd}$ hazard class can be disposed at the landfill of solid household waste, and wastes of the 2nd hazard class must be disposed by special methods. Nowadays it is common that pharmacies and hospitals are still practicing multiple breeding and discharging poor quality injectable medicines of 2$^{nd}$ and 3$^{rd}$ hazard class into the urban sewage. Their decomposition at the treatment facilities is about 68 %.

The problem of environmental pollution by unsuitable drugs is becoming global for economically developed countries of the world as well. Nowadays the pharmaceutical contamination has been found in the water bodies of the USA, Europe, Asia, Australia and many other countries. It has been established that in the water environment of developed countries, the level of pharmaceutical contamination is in the range of 1-100 ng/l or higher.

According to the experts from the WHO (Pharmaceuticals in drinking-water report, World Health Organization 2012), API are found even in drinking water, which undergoes a sufficiently powerful cleaning system [4]. In the ground and underground waters of some regions of the USA and Germany, there have been detected more than thirty API in concentrations, which are hazardous for human under conditions of consumption of this water; primarily these were antibiotics, non-steroidal anti-inflammatory drugs, narcotic and non-narcotic analgesics, hypolipidemic agents etc. [2].

It should also be noted that drugs that have expired, represent a combination of biological active substances, which action on the human body is usually unpredictable. Such preparations are extremely dangerous for use and for the usual ways of disposal. Unnecessary drugs that are stored at home can be a source of poisoning of residents.

In developed countries, sales and recycling companies have begun to receive unsuitable drugs with the help of pharmacies. For example, since 2008 in Australia, there has been launched the public program RUM (Retuniso Unwanted Medicine), aimed at collection of unnecessary or unsuitable medicines from the population. The Medications Return Program (MRP) has been implemented in Canada since 1999. This program was launched in one state, and further supported in other provinces and states. Since 2010, there has been an initiative partner program in the USA, called Dispose My Meds. The program helps the population to dispose unnecessary drugs. In Kazakhstan (the city of Astana), collection of drugs with expired shelf life from the population is realized through the special containers in pharmacies of Astana [7, 10].

In Ukraine, there is currently no system of collecting unsuitable medicines from the population. There is also no information about the risks associated with the entry of hazardous wastes (drugs) into household waste, sewage and further into the environment.

Thus, the new interdisciplinary direction of eco-pharmacy to some extent combines pharmacy, ecology and chemistry, covers all the links of «life» of a medical product, from production to disposal, and also allows to assess the impact of the drug on the human ecosystem and the environment.

Eco-pharmacy with its meta-knowledge status has been initially intended to play the role of communicator, which allows to assess the degree of commonality of results, models and methods of individual sciences, primarily pharmacy, ecology, chemistry, and to translate the language of a particular science into a high level of interdisciplinary communication. The status of the interdisciplinary direction has led to another important feature of eco-pharmacy: its openness, readiness for dialogue as a direct participant or unpretentious mediator, who sees

his mission in the worldwide provision of mutual understanding between the participants of the dialogue.

Perspectives of the development of eco-pharmacy are first of all its development as science and applied direction. It is advisable to introduce eco-pharmacy as a course in the training process for pharmaceutical workers. At the postgraduate stage of the education of specialists in pharmacy and medicine, the main aspects of eco-pharmacy, namely eco-pharmacology and eco-pharmacotherapy, should be introduced into the program of thematic improvement cycles.

With regard to the applied aspect of the implementation of eco-pharmacy, the Vinnytsia Regional Pharmacy Association "CUM DEO" with the participation of scientists from the National University of Pharmacy, have worked out the possibility of developing and implementing a pilot project named "Return unnecessary drugs to pharmacies for further safe disposal", which will reduce the risks for consumers and society of inappropriate use of drugs, accidental poisoning and toxic effects on the environment.

**Conclusion.** Eco-pharmacy is a new interdisciplinary direction that combines pharmacology, industrial pharmacy, ecology and chemistry. Optimization and personification of therapy with the prescription of eco-pharmaceutical drugs in the first place will allow to upgrade to the level of eco-pharmacotherapy and to reduce the number of prescriptions of eco-pharmacologically hazardous drugs. One of the most important issues of eco-pharmacy at the present stage is to improve the disposal of unsuitable drugs. The introduction and dissemination of the principles of eco-pharmacy will significantly reduce tensions on the human ecosystem and minimize the impact of drugs on the environment.

**References**

1. Bardik Yu.V., Bobilyova O.O. & Povyakel L.I., 2005, Ekologo-gigienichni ta toksikologichni problem zhittediyalnosti lyudini. Liki yak polyutanti dovkillya [Ecological-hygienic and toxicological problems of human life. Medications as environmental pollutants]. Suchasni problem toksikologiyi [Modern Problems of Toxicology] 4: 12-18.

2. Boyd G.R., Reemtsma H., Grimm D.A. & Mitsa S., 2013, Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. Science of the Total Environment 311 (1-3): 135-149.

3. Chernykh V.P. & Percev I.M., 2016, Farmatsiya [Pharmacy], [in:] V.P. Chernykh (ed.), Farmatsevticheskaya entsiklopediya [Pharmaceutical Encyclopedia]. Morion, Kyiv: 1762-1764.

4. Daughton C.G., 2011, Illicit drugs: contaminants in the environment and utility in forensic epidemiology. Reviews of Environmental Contamination and Toxicology 210: 59-110.

5. Gruchlik Y., Linge K. & Joll C., 2018, Removal of organic micropollutants in waste stabilisation ponds: a review. Journal of Environmental Management 206: 202-214.

6. Li Y., Huang C., Yang J., Peng J., Jin J., Ma H. & Chen J., 2017, Multifunctionalized mesoporous silica as an efficient reversed-phase/anion exchange mixed-mode sorbent for solid-phase extraction of four acidic nonsteroidal anti-inflammatory drugs in environmental water samples. Journal of Chromatography A, 1527: 10-17.

7. Pal R., Megharaj M., Kirkbride K.P. & Naidu R., 2013, Illicit drugs and the environment--a review. Science of the Total Environment 463: 1079-1092.

8. Sagaydak-Nikituyk R.V. & Golubtsova K.K., 2016, Teoretichni zasadi upravlinnya ekologichnimi rizikami farmatsevtichnih pidpriemstv [Theoretical principles of management of ecological risks of pharmaceutical enterprises]. Scientific Journal “ScienceRise” 18 (1): 42-47.

9. Vdovenko I.A., Setko N.P. & Konstantinova O.D., 2013, Ekologicheskie problemyi reproduktivnogo zdorovya [Ecological problems of reproductive health]. Higiena i sanitariia 4: 24-28.

10. Yadav M.K., Short M.D., Aryal R., Gerber C., Van den Akker & Saint C.P., 2017, Occurrence of illicit drugs in water and wastewater and their removal during wastewater treatment. Water Research 124: 713-727.

11. Zhang M., Chen L., Ye C. & Yu X., 2017, Co-selection of antibiotic resistance via copper shock loading on bacteria from a drinking water bio-filter. Environmental Pollution 233: 132-141.