REVIEW ARTICLE

Environmental contamination by pharmaceuticals and its impact on human health

Contaminación ambiental por productos farmacéuticos y su impacto en la salud humana

Andrés Sebastián Moreno-Barragán[1]✉ iD , Carlos Andrés Benalcázar-Pozo[1] iD , Abdel Bermúdez-del Sol[1] iD

[1]Universidad Regional Autónoma de Los Andes, Ambato. Ecuador.

ABSTRACT

Introduction: pharmacological contaminants are described as widely used compounds not regulated by environmental legislation.
Objective: to characterize environmental contamination by drugs and their negative impact on human health.
Methods: a narrative review of the available literature was carried out using synthetic and historical-logical analytical methods by means of articles retrieved from databases such as PubMed, Scopus, Cinhal, SciELO. A total of 600 articles were found, of which 26 were included.
Results: at present, several problems have been identified regarding the environmental impact caused by contamination by excessive waste of pharmacological products in the environment, such as toxic affections in animals that have caused structural, morphological and reproductive damage in many of them, as well as the direct or indirect impact that human beings may receive.
Conclusions: Environmental contamination by drugs affects both directly and indirectly human beings; this depends on complex interactions between drugs, compounds present in wastewater and ecosystem dynamics. Environmental contamination by drugs affects the behavior of animals, which influences the decrease in fish populations and the poisoning of others used in livestock farming. This phenomenon affects the agricultural and livestock sectors, which has an indirect impact on food and human health.

Keywords: Pharmaceutical Preparations; Environmental Contamination; Waste; Ecosystem; Environmental Legislation.

RESUMEN

Introducción: los contaminantes farmacológicos se describen como compuestos ampliamente utilizados no regulados por la legislación ambiental.
Objetivo: caracterizar la contaminación ambiental por medicamentos y su impacto negativo en la salud humana.
Métodos: se realizó una revisión narrativa de la bibliografía disponible utilizando los métodos analíticos sintético e histórico lógico mediante los artículos recuperados desde las bases de datos como PubMed, Scopus, Cinhal, SciELO. Se encontraron 600 artículos, de los cuales se incluyeron 26.
Resultados: en la actualidad, se han identificado diversas problemáticas sobre el impacto ambiental que ha provocado la contaminación por desechos desmedidos de productos farmacológicos al medio ambiente, tales como afecciones tóxicas en animales que ha causado un daño estructural, morfológico y reproductivo de mucho de ellos, así como también el impacto directo o indirecto que pueden recibir los seres humanos.
Conclusiones: la contaminación ambiental por fármacos afecta tanto de forma directa indirecta al ser humano; esto depende de complejas interacciones entre fármacos, compuestos presentes en las aguas residuales y la dinámica del ecosistema. La contaminación ambiental por fármacos afecta el comportamiento de los animales, lo cual influye en la disminución de las poblaciones de peces y el envenenamiento de otros con uso en la ganadería. Este fenómeno afecta los sectores agrícola y ganadero, que repercute de manera indirecta en alimentación y la salud humana.

Palabras clave: Preparaciones Farmacéuticas; Contaminación Ambiental; Residuos; Ecosistema; Legislación Ambiental.

REVIEW ARTICLE

INTRODUCTION

Nowadays, the acquisition and access of the population to medicines is wide, which causes accumulation of these in the home.[1] It is common to find in homes anti-epithelitic drugs, analgesics, anti-allergic drugs, dietary supplements, as well as specific drugs for different types of diseases either acute or chronic. As life expectancy increases and the population in general ages, the consumption of different types of medicines grows, improving the quality of life and health of users.[2]

In Ecuador, a study conducted during 2017 by Ortiz Simbaña,[3] surveyed 330 medical students and 110 engineering students, showing as a result that 50 % of them recognized having a family medicine cabinet at home. On the other hand, 59 % of the respondents used the medicines sporadically, while 13 % used it at least twice a month.

In many cases, leftover medicines are kept out of their packaging, making it difficult to identify the expiration date; it is also common for medicines to be stored without their package inserts. Medications that are out of their primary packaging (blister packs) or when their packaging is cut and the expiration date information is not available, become unfit for consumption.[4]

Página 2

Until a few decades ago, pharmaceutical products were not considered environmental pollutants, since their accumulation or that of their transformation products in soils, water, air, plant tissues and animal tissues was unknown. However, in some countries these products have begun to be quantified to determine their ecotoxicity.[5]

Improper disposal of expired, damaged or unused drugs can contaminate the environment due to the chemical composition of the soil and its components, as well as in aquatic systems.[6] Improper disposal results in drugs becoming incorporated into the ecosystem and circulating in it, either through water or other agents.

Although there is a culture of discarding expired drugs, once identified, this is done to avoid harmful reactions to the wrong medication. However, it is the responsibility of individuals to properly dispose of expired, unused or unwanted medications from their homes in order to reduce the amount of medication entering the environment.[2,7]

Although drug recycling is of great importance, the appropriate routes to inform and educate the population have not been properly exploited, resulting in significant levels of misinformation, and therefore bad practices.[6,8] In this sense, health personnel, as well as administrative and biotechnology industry personnel, play a very important role.

Activities aimed at monitoring and controlling the waste of products with bioactive and/or pharmacological effects are supervised by health agencies. However, there is little data available on regulations; and even more scarce is the dissemination of information on the results caused by industrial waste and pharmaceutical products improperly excreted into the environment.[9,10]

In Ecuador there are not enough studies carried out and published on the subject, so it was decided to carry out the present article, with the objective of describing environmental contamination by drugs and their negative impact on human health.

METHODS

A descriptive bibliographic review of the literature on environmental contamination by drugs and its effect on human health was carried out. For this purpose, a search for information was carried out in the databases PubMed, Scopus, Cinhal, SciELO.

Various combinations of terms were used for the search: environmental contamination, expired drugs, ecotoxicology, emerging pollutants, waste management, wastewater, human health. We included studies that responded to the subject matter, published in Spanish and English.

After obtaining the records, the selection process of the documents was carried out in three phases: a first phase in which the titles and abstracts were reviewed, discarding those that did not respond to the objective of the study. In the second phase, duplicates were eliminated using Mendeley software. The third phase consisted of reading the texts in extenso to eliminate those that were not of interest.

The articles were chosen for their relevance to the purpose of the review based on the clinical and research experience of the authors.

REVIEW ARTICLE

DEVELOPMENT

Currently, among the main wastes generated in daily activities are those derived from the cleaning of equipment. Before being dumped into nature, these residues go through cleaning and inactivation processes, where different chemicals are added in order to minimize the environmental impact. However, although these have a minimal impact, in the long term the sum of these impacts becomes representative.[11,12]

The advance of the biotechnology industry has led to an increase in the number of plants manufacturing different products, such as pharmaceuticals and medical equipment. Many of these production processes result in waste substances or drugs with biological effects, which are discharged into nature. Due to the varied nature of these wastes, they may contain radioactive, biological, acidic and pure chemical wastes, among others.[12,13]

Hospitals have also become a major source of emerging pollutants, due to the various activities carried out. Among these wastes are leftover medicines, surgical material, patient excreta, laboratory wastes and products from research activities, among others.[14]

Identification of drug contamination

In 1977, salicylic acid and chlorophenoxyisobutyrate were discovered in the Missouri River in the United States, confirming that drug pollution can be caused by waste disposed of in pharmaceutical plants as unaltered drugs.[15] Their results were ignored for several years, due to the erroneous belief that dilution was the solution to pollution.[16] This led to a lack of interest in the subject, and thus a lack of knowledge about the harmful effects on ecological and human health due to pharmaceuticals in rivers.

An international study published during the year 2021 by Proceedings of the National Academy of Sciences (PNAS), indicates the finding of significant amounts of active pharmaceutical ingredients around several rivers of the planet. The study reports that the greatest accumulation was found in the low- and middle-income zone; the most identified compounds were carbamazepine, metformin and caffeine.[17]

A study conducted by the IMDEA Water Institute studied 258 rivers around the world, including the Amazon in Brazil and the Thames in London, measuring the presence of 61 pharmaceuticals, such as caffeine, metformin and carbamazepine. The studies were conducted in more than half of the world's countries, monitoring the presence of pharmaceuticals in 36 countries that had not been investigated.[14]

An investigation in Australia found 69 different drugs in more than 190 invertebrates in streams near Melbourne. The researchers calculated that a platypus feeding on these animals received half the daily dose of antidepressants prescribed for humans. This research is part of the Global Monitoring of Pharmaceuticals Project led by the University of York, which is currently the first global investigation of drug contamination in the environment.[5]

Several studies have concluded that:[14,18,19]
- Water contamination by pharmaceuticals is present in all continents of the world.
- Strong correlations are considered in the socioeconomic status of a country, as well as a higher amount of pharmaceutical pollution in its rivers (with lower-middle-income countries being the most polluted).
- High levels of pharmaceutical environmental pollution are associated with countries whose median age is high and with high local rates of poverty and unemployment.

REVIEW ARTICLE

Página 4

- Countries and regions such as sub-Saharan Africa, South America and parts of South Asia are the most polluted in the world due to their poor research.
- Activities associated with higher levels of pharmaceutical pollution were inadequate wastewater treatment and pharmaceutical manufacturing infrastructures, discharge of waste septic tank contents into rivers, and dumping of garbage along riverbanks.

Drugs as emerging contaminants

The most damaged environmental area resulting from contamination by pharmaceuticals has been fauna, as they have been affected by various diseases that have limited their development and mating.[11]

As mentioned above, pharmaceuticals have a variety of physicochemical compositions, which determine their metabolism by the human organism. This same variability of properties determines that, when they are disposed of in the environment, they can circulate through the ecosystem, either through water or consumed by flora and fauna.

Antibiotics, after being consumed by humans, are only partially metabolized in the organism, but most of them are excreted and discharged into the environment through urine or feces; therefore, in most cases, part of the antibiotics consumed by humans end up in wastewater. Such waters are usually treated in wastewater treatment plants, however, these were not designed to remove antibiotics, so in some cases these compounds are not completely removed and continue to be present in their effluents.[16,20]

According to a preliminary study on the presence of antibiotics in wastewater treatment plants (WWTP) in southeastern Spain, it has been observed that, of all the antibiotics analyzed, only some of them were present in both influent and effluent. Clarithromycin, azithromycin and ofloxacin were those found in the highest concentrations in the influents analyzed, whereas, in the effluents, those found in the highest concentrations were azithromycin, clarithromycin and ciprofloxacin.[21]

Some drugs have endocrine functions causing various effects on wildlife. Even at very low levels, some can feminize male fish and prevent the reproduction of some species.[22] An example of this is metformin and estrogens, which cause a feminization of male fish; this causes a reduction in specimens suitable for reproduction, which leads to a decrease in the fish population.

Diclofenac has a toxic effect on trout in rivers and livestock, causing intoxication and poisoning. When the carcasses are consumed by scavengers such as vultures, they suffer a similar situation, impacting the balance of the ecosystem.[23]

Psychotropic drugs are drugs of interest due to their effect on behavior. Martinez F et al.[24] point out the effect of fluoxetine (Prozac), which causes behavioral changes in fish, mollusks and crustaceans, including the adoption of risky behavior towards predators, less aggressive territorial responses or an anomalous attraction to light. Likewise, amphetamine use causes addiction in fish and modifies habitat preferences with unexpected adverse consequences of individual and population relevance.[25]

REVIEW ARTICLE

Página 5

Consequences of environmental contamination by pharmaceuticals on human health

The potential impact on human health of drug residues in the environment is poorly studied. Exposure can occur mainly through the consumption of drinking water, vegetables and tubers, meat, fish and dairy products.[26] Due to the low concentrations that contaminants are usually found, this may appear to be a negligible risk if analyzed product by product.[18] Of concern is the risk of long-term exposure (at low doses, but to a mixture of active contaminants).

The pharmacological groups whose residues cause the greatest concern are those that kill their target organisms or cells, such as antibiotics, antiparasitics and antifungals. Likewise, the exposure of different microorganisms to these can have effects on the microbial maps of the community, and in the long term, cause resistance to antibiotics.[20,27,28]

Radiological contrast media and antineoplastics are of interest because of their high persistence and because of their carcinogenic, mutagenic and teratogenic properties.[20,27]

The consequences of drug pollution that indirectly affect human health depend on complex interactions between drugs and other toxic compounds present in waters. It should be emphasized that in some places or vulnerable sectors, water is rarely treated or processed for human consumption and therefore can lead to several complications.[19]

The poisoning of livestock animals after the consumption of water with traces of drugs causes a decrease in the population of the same. Likewise, livestock will face drug-resistant infections that will cause a reduction in populations.[29] This has an effect on several areas, such as the dairy industry, by a decrease in the supply of milks. Similarly, the loss of these animals causes a decrease in the production of meat and processed foods, which are necessary for human consumption.

One of the negative effects of drug contamination is the feminization of male fish of some species, which causes a reduction in their population due to their inability to reproduce. The decrease in fish populations causes less fishing activity, affecting the economy of the populations dedicated to this activity, as well as one of their main sources of food.

Environmental policies and pharmacological waste

Emerging contaminants are characterized by their high bioconcentration, persistence, bioaccumulation and environmental mobility. Wilkinson et al.[27] seek to call the attention of the whole community to the contamination caused by discarded drugs in the environment and the damage to human health. In addition, they point out the need for legal regulations to help regulate this issue.

Niemuth et al.[30] point out a growing concern about the so-called emerging pollutants, compounds of different nature and origin, which are found in water at different concentrations and which, for the most part, are not regulated.

Rodríguez-Borlado Díaz et al.[1] identified that the population is not very familiar with emerging contaminants, including drugs. Thus, there is a need to disseminate the dimensions of the problem and to educate the population on this issue.

REVIEW ARTICLE

Environmental education as an integral knowledge management tool is a necessary strategy for a correct education on the harmful disposal of medicines and their effect on the environment. It works to raise the awareness of individuals from the individual level to the group or collective commitment.[31]

Among the public policies to be promoted is the creation of collection centers for medicines that have expired or are in poor condition. Laws should be promoted to create protocols and systems for the proper disposal of substances such as pharmaceuticals. Innovation in the field of purification and processing machines is a necessity, preparing them to eliminate this type of compounds.

CONCLUSIONS

Environmental contamination by drugs affects both directly and indirectly the human being; this depends on complex interactions between drugs, compounds present in wastewater and the dynamics of the ecosystem. Environmental contamination by drugs affects the behavior of animals, which influences the decline of fish populations and the poisoning of others used in animal husbandry. This phenomenon affects the agricultural and livestock sectors, which has an indirect impact on food and human health.

Conflict of interest
The authors declare that there is no conflict of interest.

Authors' contribution
All authors participated in the conceptualization, formal analysis, project management, writing - original draft, writing - revision, editing and approval of the final manuscript.

BIBLIOGRAPHIC REFERENCES

1. Rodríguez-Borlado Díaz B, Sanz-Rosa D, Sanz Pozo B, Llisterri Caro JL, Herrero Barbero M. Dolor, calidad de vida y salud mental en pacientes con gonalgia por gonartrosis: estudio de casos y controles. Med Fam Semer [Internet]. 2022 [citado 12/12/2022]; 48(1):45-53. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S1138359321002197

2. Burke JP. Infection control - a problem for patient safety. N Engl J Med [Internet]. 2003 [citado 12/12/2022]; 348(7):651-6. Disponible en: https://pubmed.ncbi.nlm.nih.gov/12584377/

3. Ortiz Simbaña JA. Análisis de las características del botiquín familiar de estudiantes del área de la salud en la ESPOCH, como aporte al control de la automedicación y la educación sanitaria [Internet]. Riobamba, Ecuador: Escuela Superior Politécnica de Chimborazo; 2017 [citado 12/12/2022]. Disponible en: http://dspace.espoch.edu.ec/handle/123456789/6830

4. Calderón JM, M T. Medicamentos sobrantes y caducados en el hogar ¿su almacenaje y desecho representan un problema de salud pública? Salud Colect [Internet]. 2021 [citado 12/12/2022]; 17:e3599. Disponible en: https://www.scielosp.org/article/scol/2021.v17/e3599/

REVIEW ARTICLE

5. aus der Beek T, Weber F-A, Bergmann A, Hickmann S, Ebert I, Hein A, et al. Pharmaceuticals in the environment-Global occurrences and perspectives. Environ Toxicol Chem [Internet]. 2016 [citado 12/12/2022]; 35(4):823-35. Disponible en: https://onlinelibrary.wiley.com/doi/10.1002/etc.3339

6. de Simón Gutiérrez R, Ginel Mendoza L, Hidalgo Requena A, Rico Munilla D, Cantalapiedra Fernández F. ¿Desechan correctamente los pacientes sus dispositivos de inhalación? Proyecto AIRE. Semergen [Internet]. 2022 [citado 12/12/2022]; 48(1):14-22. Disponible en: https://www.sciencedirect.com/science/article/pii/S1138359321002276

7. Randle J, Clarke M. Infection control nurses' perceptions of the Code of Hygiene: Infection control nurses' perceptions of the code of hygiene. J Nurs Manag [Internet]. 2011 [citado 12/12/2022]; 19(2):218–25. Disponible en: http://dx.doi.org/10.1111/j.1365-2834.2010.01147.x

8. Saint S, Kowalski C, Forman J, Damschroder L, Hofer T, Kaufman S. A multicenter qualitative study on preventing hospital-acquired urinary tract infection in US hospitals. Infect Control Hosp Epidemiol [Internet]. 2008 [citado 12/12/2022];29(4):333-41. Disponible en: https://europepmc.org/article/med/18462146

9. Aguilar-Shea AL, Gallardo-Mayo C. Revisión narrativa de la terapia inhalatoria en la EPOC. Med Fam Semer [Internet]. 2022 [citado 12/12/2022]; 48(3):214-8. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S1138359321002318

10. López-Simarro F, Cols-Sagarra C, Mediavilla Bravo JJ, Cañís-Olivé J, Hernández-Teixidó C, González Mohíno Loro MB. Actualización en el uso de insulinas para el médico de familia. Med Fam Semer [Internet]. 2022 [citado 12/12/2022]; 48(1):54-62. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S1138359321001398

11. Wellington EM, Boxall AB, Cross P, Feil EJ, Gaze WH, Hawkey PM, et al. The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. Lancet Infect Dis [Internet]. 2013 [citado 12/12/2022]; 13(2):155-65. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S1473309912703171

12. Brodin T, Fick J, Jonsson M, Klaminder J. Dilute Concentrations of a Psychiatric Drug Alter Behavior of Fish from Natural Populations. Science [Internet]. 2013 [citado 12/12/2022]; 339(6121):814-5. Disponible en: https://www.sciencemag.org/lookup/doi/10.1126/science.1226850

13. Kookana RS, Williams M, Boxall ABA, Larsson DGJ, Gaw S, Choi K, et al. Potential ecological footprints of active pharmaceutical ingredients: an examination of risk factors in low-, middle- and high-income countries. Philos Trans R Soc B Biol Sci [Internet]. 2014 [citado 12/12/2022]; 369(1656):20130586. Disponible en: https://royalsocietypublishing.org/doi/10.1098/rstb.2013.0586

14. Hughes SR, Kay P, Brown LE. Global Synthesis and Critical Evaluation of Pharmaceutical Data Sets Collected from River Systems. Environ Sci Technol [Internet]. 2013 [citado 12/12/2022]; 47(2):661-77. Disponible en: https://pubs.acs.org/doi/10.1021/es3030148

REVIEW ARTICLE

15. Hignite C, Azarnoff DL. Drugs and drug metabolites as environmental contaminants: chlorophenoxyisobutyrate and salicyclic acid in sewage water effluent. Life Sci [Internet]. 1977 [citado 12/12/2022]; 20(2):337-41. Disponible en: http://www.ncbi.nlm.nih.gov/pubmed/839964

16. Obaya Rebollar JC, Miravet Jiménez S, Aranbarri Osoro I, Carramiñana Barrera FC, García Soidán FJ, Cebrián Cuenca AM. Manejo de perfiles de pacientes con diabetes mellitus tipo 2 en la práctica clínica de la atención primaria en España: Programa CONTROVERTI2. Med Fam Semer [Internet]. 2022 [citado 12/12/2022]; 48(1):23-37. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S1138359321002252

17. Wilkinson JL, Boxall ABA, Kolpin DW, Leung KMY, Lai RWS, Galban-Malag C, et al. Pharmaceutical pollution of the world's rivers. Proc Natl Acad Sci USA [Internet]. 2022 [citado 12/12/2022]; 119(8). Disponible en: https://www.pnas.org/doi/abs/10.1073/pnas.2113947119

18. Huang Q, Yu Y, Tang C, Peng X. Determination of commonly used azole antifungals in various waters and sewage sludge using ultra-high performance liquid chromatography–tandem mass spectrometry. J Chromatogr A [Internet]. 2010 [citado 12/12/2022]; 1217(21):3481-8. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S0021967310003869

19. Gornik T, Kovacic A, Heath E, Hollender J, Kosjek T. Biotransformation study of antidepressant sertraline and its removal during biological wastewater treatment. Water Res [Internet]. 2020 [citado 12/12/2022]; 181:115864. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S0043135420304012

20. Muñoz-Pindado C, Muñoz-Herrera E, Arribas-Peña V, Roura-Poch P, Ruiz-Mori F, Sánchez-Belmonte S, et al. Implementación del método simplificado ApnealinkTMAir® por médicos de atención primaria para el diagnóstico del síndrome de apnea-hipopnea durante el sueño. Med Fam Semer [Internet]. 2022 [citado 12/12/2022]; 48(1):3-13. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S1138359321002185

21. Bartolomé Antonio MM. Educación ambiental para la sostenibilidad: Una alternativa para una disposición adecuada de medicamentos en el hogar. AVFT – Arch Venez Farmacol y Ter [Internet]. 2023 [citado 12/05/2023]; 40(9). Disponible en: http://saber.ucv.ve/ojs/index.php/rev_aavft/article/view/26189

22. Kidd KA, Blanchfield PJ, Mills KH, Palace VP, Evans RE, Lazorchak JM, et al. Collapse of a fish population after exposure to a synthetic estrogen. Proc Natl Acad Sci [Internet]. 2007 [citado 12/12/2022]; 104(21):8897-901. Disponible en: https://pnas.org/doi/full/10.1073/pnas.0609568104

23. Shultz S, Baral HS, Charman S, Cunningham AA, Das D, Ghalsasi GR, et al. Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. Proc R Soc London Ser B Biol Sci [Internet]. 2004 [citado 12/12/2022]; 271(suppl_6). Disponible en: https://royalsocietypublishing.org/doi/10.1098/rsbl.2004.0223

24. Martínez F, Molina R, Rodríguez I, Pariente MI, Segura Y, Melero JA. Techno-economical assessment of coupling Fenton/biological processes for the treatment of a pharmaceutical wastewater. J Environ Chem Eng [Internet]. 2018 [citado 12/12/2022]; 6(1):485-94. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S2213343717306474

REVIEW ARTICLE

25. Horký P, Grabic R, Grabicová K, Brooks BW, Douda K, Slavík O, et al. Methamphetamine pollution elicits addiction in wild fish. J Exp Biol [Internet]. 2021 [citado 12/12/2022]; 224(13):[aprox. 10 pp]. Disponible en: https://journals.biologists.com/jeb/article/224/13/jeb242145/270755/Methamphetamine-pollution-elicits-addiction-in

26. Burns EE, Thomas-Oates J, Kolpin DW, Furlong ET, Boxall AB. Are exposure predictions, used for the prioritization of pharmaceuticals in the environment, fit for purpose? Environ Toxicol Chem [Internet]. 2017 [citado 12/12/2022]; 36(10):2823-32. Disponible en: https://onlinelibrary.wiley.com/doi/10.1002/etc.3842

27. Wilkinson J, Boxall A, Kolpin D. A Novel Method to Characterise Levels of Pharmaceutical Pollution in Large-Scale Aquatic Monitoring Campaigns. Appl Sci [Internet]. 2019 [citado 12/12/2022]; 9(7):1368. Disponible en: https://www.mdpi.com/2076-3417/9/7/1368

28. Hendriksen RS, Munk P, Njage P, van Bunnik B, McNally L, Lukjancenko O, et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nat Commun [Internet]. 2019 [citado 12/12/2022]; 10(1):1124. Disponible en: https://www.nature.com/articles/s41467-019-08853-3

29. Villalobos Araya A, Estrada-König S, Chaves Ramírez S, Rivera-Castillo J, Chaverri-Fonseca F, Gutiérrez-Espeleta G, et al. Medidas para la reducción del riesgo de contaminación ambiental con residuos de antibióticos y propagación de bacterias resistentes. Biocenosis [Internet]. 2023 [citado 08/07/2023]; 34(1):31-40. Disponible en: https://revistas.uned.ac.cr/index.php/biocenosis/article/view/4823

30. Niemuth NJ, Klaper RD. Low-dose metformin exposure causes changes in expression of endocrine disruption-associated genes. Aquat Toxicol [Internet]. 2018 [citado 12/12/2022]; 195:33-40. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/S0166445X17303545

31. Reyes-Diaz MG, Tovar-Torres JV, Trillo-Cardenas AD, Peña-Donayre CJ, Orellana-Torres G del P, Hernandez-Baldeon MA, et al. Uso y desecho de medicamentos del botiquín familiar desde la educación ambiental. Biotempo [Internet]. 2023 [citado 04/04/2023]; 20(1):91-6. Disponible en: https://revistas.urp.edu.pe/index.php/Biotempo/article/view/5717