

ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ
Өсімдіктердің биологиясы және биотехнологиясы институтының

Х А Б А Р Л А Р Ы

ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН
Института биологии и биотехнологии растений

NEWS

OF THE NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN
of the Institute of Plant Biology and Biotechnology

**БИОЛОГИЯ ЖӘНЕ МЕДИЦИНА
СЕРИЯСЫ**



СЕРИЯ

БИОЛОГИЧЕСКАЯ И МЕДИЦИНСКАЯ



SERIES

OF BIOLOGICAL AND MEDICAL

4 (322)

ШІЛДЕ – ТАМЫЗ 2017 ж.

ИЮЛЬ – АВГУСТ 2017 г.

JULY – AUGUST 2017

1963 ЖЫЛДЫҢ ҚАҢТАР АЙЫНАН ШЫҒА БАСТАҒАН
ИЗДАЕТСЯ С ЯНВАРЯ 1963 ГОДА
PUBLISHED SINCE JANUARY 1963

ЖЫЛЫНА 6 РЕТ ШЫҒАДЫ
ВЫХОДИТ 6 РАЗ В ГОД
PUBLISHED 6 TIMES A YEAR

АЛМАТЫ, ҚР ҰҒА
АЛМАТЫ, НАН РК
ALMATY, NAS RK

Б а с р е д а к т о р

ҚР ҰҒА академигі, м. ғ. д., проф. **Ж. А. Арзықұлов**

Абжанов Архат проф. (Бостон, АҚШ),
Абелев С.К., проф. (Мәскеу, Ресей),
Айтқожина Н.А., проф., академик (Қазақстан)
Ақшулақов С.К., проф., академик (Қазақстан)
Алшынбаев М.К., проф., академик (Қазақстан)
Бәтпенев Н.Д., проф., корр.-мүшесі (Қазақстан)
Березин В.Э., проф., корр.-мүшесі (Қазақстан)
Берсімбаев Р.И., проф., академик (Қазақстан)
Беркінбаев С.Ф., проф., (Қазақстан)
Бисенбаев А.К., проф., академик (Қазақстан)
Бишимбаева Н.К., проф., академик (Қазақстан)
Ботабекова Т.К., проф., корр.-мүшесі (Қазақстан)
Bosch Ernesto prof. (Spain)
Жансүгірова Л.Б., б.ғ.к., проф. (Қазақстан)
Ellenbogen Adrian prof. (Tel-Aviv, Israel),
Жамбакин Қ.Ж., проф., академик (Қазақстан), бас ред. орынбасары
Заядан Б.К., проф., корр.-мүшесі (Қазақстан)
Ishchenko Alexander prof. (Villejuif, France)
Исаева Р.Б., проф., (Қазақстан)
Қайдарова Д.Р., проф., академик (Қазақстан)
Кохметова А.М., проф., корр.-мүшесі (Қазақстан)
Күзденбаева Р.С., проф., академик (Қазақстан)
Лось Д.А., prof. (Мәскеу, Ресей)
Lunenfeld Bruno prof. (Израиль)
Макашев Е.К., проф., корр.-мүшесі (Қазақстан)
Муминов Т.А., проф., академик (Қазақстан)
Огарь Н.П., проф., корр.-мүшесі (Қазақстан)
Омаров Р.Т., б.ғ.к., проф., (Қазақстан)
Продеус А.П. проф. (Ресей)
Purton Saul prof. (London, UK)
Рахыпбеков Т.К., проф., корр.-мүшесі (Қазақстан)
Сапарбаев Мұрат проф. (Париж, Франция)
Сарбасов Дос проф. (Хьюстон, АҚШ)
Тұрысбеков Е.К., б.ғ.к., асс.проф. (Қазақстан)
Шарманов А.Т., проф. (АҚШ)

«ҚР ҰҒА Хабарлары. Биология және медициналық сериясы».

ISSN 2518-1629 (Online),

ISSN 2224-5308 (Print)

Меншіктенуші: «Қазақстан Республикасының Ұлттық ғылым академиясы» РҚБ (Алматы қ.)

Қазақстан республикасының Мәдениет пен ақпарат министрлігінің Ақпарат және мұрағат комитетінде
01.06.2006 ж. берілген №5546-Ж мерзімдік басылым тіркеуіне қойылу туралы куәлік

Мерзімділігі: жылына 6 рет.

Тиражы: 300 дана.

Редакцияның мекенжайы: 050010, Алматы қ., Шевченко көш., 28, 219 бөл., 220, тел.: 272-13-19, 272-13-18,
www.nauka-nanrk.kz/biological-medical.kz

© Қазақстан Республикасының Ұлттық ғылым академиясы, 2017

Типографияның мекенжайы: «Аруна» ЖК, Алматы қ., Муратбаева көш., 75.

Г л а в н ы й р е д а к т о р

академик НАН РК, д.м.н., проф. **Ж. А. Арзыкулов**

Абжанов Архат проф. (Бостон, США),
Абелев С.К. проф. (Москва, Россия),
Айтхожина Н.А. проф., академик (Казахстан)
Акшулаков С.К. проф., академик (Казахстан)
Алчинбаев М.К. проф., академик (Казахстан)
Батпенов Н.Д. проф. член-корр.НАН РК (Казахстан)
Березин В.Э., проф., чл.-корр. (Казахстан)
Берсимбаев Р.И., проф., академик (Казахстан)
Беркинбаев С.Ф. проф. (Казахстан)
Бисенбаев А.К. проф., академик (Казахстан)
Бишимбаева Н.К. проф., академик (Казахстан)
Ботабекова Т.К. проф., чл.-корр. (Казахстан)
Bosch Ernesto prof. (Spain)
Джансугурова Л. Б. к.б.н., проф. (Казахстан)
Ellenbogen Adrian prof. (Tel-Aviv, Israel),
Жамбакин К.Ж. проф., академик (Казахстан), зам. гл. ред.
Заядан Б.К. проф., чл.-корр. (Казахстан)
Ishchenko Alexander, prof. (Villejuif, France)
Исаева Р.Б. проф. (Казахстан)
Кайдарова Д.Р. проф., академик (Казахстан)
Кохметова А.М. проф., чл.-корр. (Казахстан)
Кузденбаева Р.С. проф., академик (Казахстан)
Лось Д.А. prof. (Москва, Россия)
Lunenfeld Bruno prof. (Израиль)
Макашев Е.К. проф., чл.-корр. (Казахстан)
Муминов Т.А. проф., академик (Казахстан)
Огарь Н.П. проф., чл.-корр. (Казахстан)
Омаров Р.Т. к.б.н., проф. (Казахстан)
Продеус А.П. проф. (Россия)
Purton Saul prof. (London, UK)
Рахыпбеков Т.К. проф., чл.-корр. (Казахстан)
Сапарбаев Мурат проф. (Париж, Франция)
Сарбасов Дос проф. (Хьюстон, США)
Турсыбеков Е. К., к.б.н., асс.проф. (Казахстан)
Шарманов А.Т. проф. (США)

«Известия НАН РК. Серия биологическая и медицинская».

ISSN 2518-1629 (Online),

ISSN 2224-5308 (Print)

Собственник: РОО «Национальная академия наук Республики Казахстан» (г. Алматы)

Свидетельство о постановке на учет периодического печатного издания в Комитете информации и архивов
Министерства культуры и информации Республики Казахстан №5546-Ж, выданное 01.06.2006 г.

Периодичность: 6 раз в год

Тираж: 300 экземпляров

Адрес редакции: 050010, г. Алматы, ул. Шевченко, 28, ком. 219, 220, тел. 272-13-19, 272-13-18,
www.nauka-nanrk.kz/biological-medical.kz

© Национальная академия наук Республики Казахстан, 2017

Адрес типографии: ИП «Аруна», г. Алматы, ул. Муратбаева, 75

Editor in chief

Zh.A. Arzykulov, academician of NAS RK, Dr. med., prof.

Abzhanov Arkhat, prof. (Boston, USA),
Abelev S.K., prof. (Moscow, Russia),
Aitkhozhina N.A., prof., academician (Kazakhstan)
Akshulakov S.K., prof., academician (Kazakhstan)
Alchinbayev M.K., prof., academician (Kazakhstan)
Batpenov N.D., prof., corr. member (Kazakhstan)
Berezin V.Ye., prof., corr. member. (Kazakhstan)
Bersimbayev R.I., prof., academician (Kazakhstan)
Berkinbaev S.F., prof. (Kazakhstan)
Bisenbayev A.K., prof., academician (Kazakhstan)
Bishimbayeva N.K., prof., academician (Kazakhstan)
Botabekova T.K., prof., corr. member. (Kazakhstan)
Bosch Ernesto, prof. (Spain)
Dzhansugurova L.B., Cand. biol., prof. (Kazakhstan)
Ellenbogen Adrian, prof. (Tel-Aviv, Israel),
Zhambakin K.Zh., prof., academician (Kazakhstan), deputy editor-in-chief
Ishchenko Alexander, prof. (Villejuif, France)
Isayeva R.B., prof. (Kazakhstan)
Kaydarova D.R., prof., academician (Kazakhstan)
Kokhmetova A., prof., corr. member (Kazakhstan)
Kuzdenbayeva R.S., prof., academician (Kazakhstan)
Los D.A., prof. (Moscow, Russia)
Lunenfeld Bruno, prof. (Israel)
Makashev E.K., prof., corr. member (Kazakhstan)
Muminov T.A., prof., academician (Kazakhstan)
Ogar N.P., prof., corr. member (Kazakhstan)
Omarov R.T., Cand. biol., prof. (Kazakhstan)
Prodeus A.P., prof. (Russia)
Purton Saul, prof. (London, UK)
Rakhypbekov T.K., prof., corr. member. (Kazakhstan)
Saparbayev Murat, prof. (Paris, France)
Sarbassov Dos, prof. (Houston, USA)
Turysbekov E.K., cand. biol., assoc. prof. (Kazakhstan)
Sharmanov A.T., prof. (USA)

News of the National Academy of Sciences of the Republic of Kazakhstan. Series of biology and medicine.

ISSN 2518-1629 (Online),

ISSN 2224-5308 (Print)

Owner: RPA "National Academy of Sciences of the Republic of Kazakhstan" (Almaty)

The certificate of registration of a periodic printed publication in the Committee of information and archives of the Ministry of culture and information of the Republic of Kazakhstan N 5546-Ж, issued 01.06.2006

Periodicity: 6 times a year

Circulation: 300 copies

Editorial address: 28, Shevchenko str., of. 219, 220, Almaty, 050010, tel. 272-13-19, 272-13-18,
<http://nauka-nanrk.kz> / biological-medical.kz

© National Academy of Sciences of the Republic of Kazakhstan, 2017

Address of printing house: ST "Aruna", 75, Muratbayev str, Almaty

NEWS

OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN

SERIES OF BIOLOGICAL AND MEDICAL

ISSN 2224-5308

Volume 4, Number 322 (2017), 5 – 11

UDC57.044

B. N. Aubakirova, R. R. Beisenova, A. K. Zhamangara

L. N. Gumilyov Eurasian national university, Astana, Kazakhstan.

E-mail: itsbakhyt@gmail.com, raihan_b_r@mail.ru, kashagankizi@mail.ru

**THE EFFECT OF PHARMACEUTICAL INGREDIENTS
TO THE GROWTH OF ALGAE**

Abstract. The consumption of pharmaceuticals has been increasing every year. Drugs have started to cause concern due to their occurrence in surface water around the world. It was found that pharmaceuticals have an adverse effect to the aquatic organisms. The aim of the following study was to assess the effect of three priority pharmaceutical ingredients in Kazakhstan as amoxicillin, clarithromycin and azithromycin to the growth of aquatic species. *Chlorella sp.* was selected as object of the study. The toxicity study was conducted according to OECD Guideline for the testing of chemicals 201. According to results, the half maximal effective concentrations (EC₅₀) of amoxicillin, clarithromycin and azithromycin to *Chlorella sp.* were 853.54±0.27, 0.59±0.004 and 0.33±0.05 mg/L respectively. Overall, the results of the study showed high toxicity of macrolides to algae, while amoxicillin was considered as non-toxic substance to *Chlorella sp.*

Key words: amoxicillin, clarithromycin, azithromycin, algae, pharmaceutical ingredients, antibiotics, ecotoxicity, environment.

Introduction. Currently, pharmaceutical products are consumed everyday worldwide. In the last three decades of the studies, pharmaceuticals were classified as environmental pollutants and it was concluded that they can lead to environmental contamination and even cause risk to human health [1].

There are various ways of release of pharmaceuticals to aquatic environment. They excrete after consumption in parent form or as metabolites. Then, primarily drugs dispose via wastewater. Also, one of the major sources of release human medicines after their excretion or disposal of unused drugs is municipal wastewater [2, 3].

The environmental effect of pharmaceuticals has been considered in many reports. According to the US Geological Survey, 80% of surface water and about 25% of groundwater in the United States are contaminated with drugs [4]. These pharmaceutical substances are representative of different therapeutic classes as analgesics, beta-blockers, fibrates, antiepileptic drugs and steroids. From the ecological and hygienic point of view, antibiotics, drugs with cytotoxic action are the most unfavorable for the ecosystem [5, 6].

The study of the effect of synthetic steroids 17 α -ethinyl estradiol (EE2) and 17 α -methyltestosterone (MT) to the snails *Marisa cornuarietis* was carried out by Schulte-Oehlmann in 2004. It was found that even in concentration 0.25 μ g/L MT induced the imposex in snails in 4 weeks. EE2 led to the development of imposex in snails in concentration 0.25-1 μ g/L. Furthermore, these steroids formed germ cells in the male and female gonads [7].

Pharmaceuticals have effect on terrestrial organisms as earthworms. There was conducted the study on toxicity of three pharmaceutical compounds as acetaminophen, naproxen and ibuprofen to *Eisenia fetida* in concentration from 0.1 mg/L to 100 mg/L. The test lasted 21 days. The highest concentration of acetaminophen was toxic to the earthworms. There was above 70% of growth inhibition in concentration of acetaminophen. Moreover, the growth rate decreased in 4 times in comparison with controls [8].

In a study which set out to determine the toxicity effect of antibiotics *Lemna minor*, Aubakirova et al. pointed that sulfamethoxazole had toxic effect to macrophytes. The half maximal effect concentration

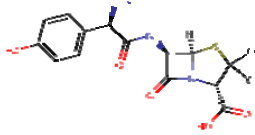
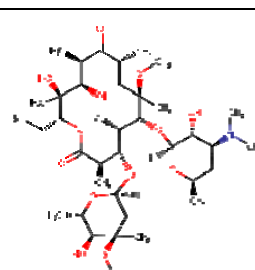
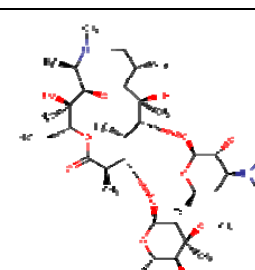
(EC₅₀) of this antibiotic was 3.67 mg/L. The concentration 100 mg/L of sulfamethoxazole led to mortality of duckweeds [9].

The present paper is focused on toxicity effect of three major used antibiotics as amoxicillin, clarithromycin, and azithromycin to *Chlorella sp.* The antibiotics were chosen using a prioritization study based on the risk of pharmaceuticals to aquatic environments in Kazakhstan. In Aubakirova et al. study it was found that these compounds are likely to occur in surface water of waters and could have an adverse effect to environmental species [10].

Chlorella sp. were selected for use in the present ecotoxicity study. Overall, algae play an important role in total biomass in the aquatic system. Moreover, algae are a major carbon sources for the aquatic environment. However, there have not been performed many toxicity test of antibiotics on algae. It can be noted, that risk assessment results pay a big attention representatives of aquatic organisms [11].

Materials and methods. Pharmaceutical ingredients were supplied from Sigma Aldrich UK and the purity of substances were >95%. Table 1 provides information about the present compounds used for the toxicity test.

Table 1 – Physico-chemical properties of study antibiotics

	Amoxicillin	Clarithromycin	Azithromycin
Chemical structure	 [12]	 [12]	 [12]
CAS-no	26787-78-0 [12]	81103-11-9 [12]	83905-01-5 [12]
Molecular formula	C ₁₆ H ₁₉ N ₃ O ₅ S [12]	C ₃₈ H ₆₉ NO ₁₃ [12]	C ₃₈ H ₇₂ N ₂ O ₁₂ [12]
Molecular weight, g/mol	365.40416[13]	747.953 [13]	748.98448[13]
pKa	3.23 [12]	8.99 [12]	8.74 [12]
Solubility in water, mg/L	3430 [12]	1.693 [13]	2.37 [13]
LogKow	0.87 [12]	3.16 [12]	4.02 [13]

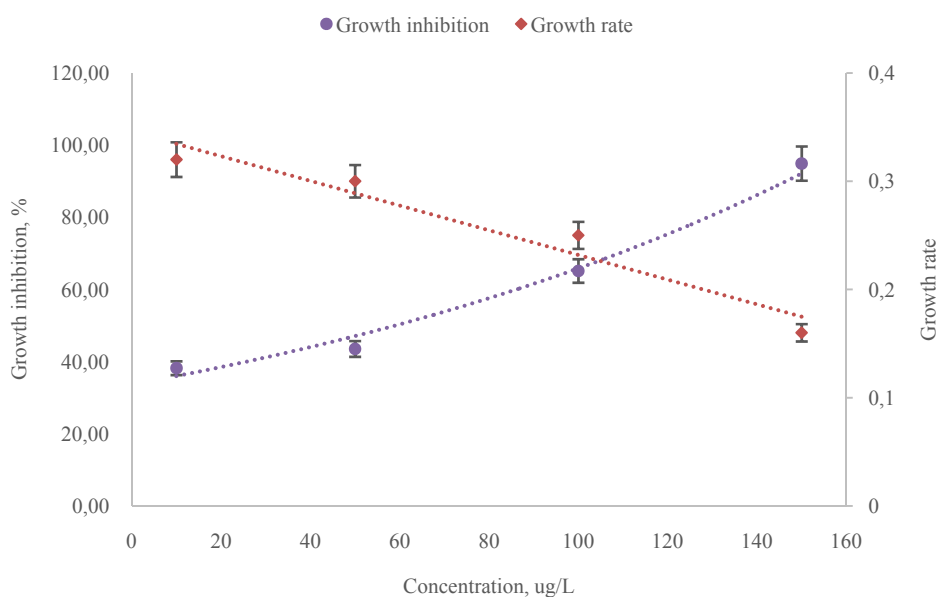
Chlorella sp. growth inhibition test was performed according to The Organization for Economic Co-operation and Development Guideline for the testing of chemicals 201 [14]. *Chlorella sp.* were presented from the “Applied Ecology” Laboratory of L.N.Gumilyov Eurasian National University. The test lasted 96 h. The *Chlorella sp.* was cultured in 100 mL of Tamiya medium in 250 ml Erlenmeyer flasks. Test samples were grown on 50 mL of this media at 29±0.5°C under constant shaking (100 cycles per minute) in culture chamber. The tested concentrations ranged 0.01-0.15 mg/L for macrolides and 1-1000 mg/L for amoxicillin. Algae numbers and biomass in each flask was assessed at the beginning and end of the test. The calculation of the algae cell was done in Goryav chamber under microscope. The measurement of biomass was conducted by photometer according to Mayer et al. method with slight modification [15]. Basically, 20 % of test sample was spiked to 1:1 mixture of DMSO and acetone and left in the dark place in room temperature for at least 3 h. In order to assess the sensitivity of *Chlorella sp.* to the test compounds, we measured optical density at 720 nm in 5 mm rectangular quartz cuvette with photometer at the beginning and end of the test.

Results and discussion. The aim of the following assessment was to evaluate the toxicity of antibiotics to *Chlorella sp.* The summary result of half maximal effect concentrations (EC₅₀) calculated of each active pharmaceutical ingredient to representatives of aquatic biota is demonstrated in Table 2. It can be noted that algae showed high sensitivity to macrolides in comparison with amoxicillin.

Table 2 – The comparison of EC₅₀ parameters of tested pharmaceuticals to *Chlorella sp.* EC₅₀ – half maximal effective concentration

Antibiotics	EC ₅₀ of <i>Chlorella sp.</i> , mg/L
Azithromycin	0.33±0.05
Clarithromycin	0.59±0.004
Amoxicillin	853.54±0.27

Clarithromycin is a macrolide antibacterial and its structure is common to erythromycin [16]. People get used to consume this drug to treat respiratory infections, skin infections, ear infections, and sexually transmitted diseases [17]. The growth inhibition and growth rate of macrolide clarithromycin is illustrated in Figure 1. The following substance demonstrated above 94% of inhibition of algae biomass in concentration 0.15 mg/L after 96 h of exposure. The growth rate decreased in 3 times ($0.16 \pm 0.08 \text{ d}^{-1}$) in comparison with controls ($0.37 \pm 0.04 \text{ d}^{-1}$). These results are in agreement with Baumann et al. results where 10% of effect concentration (EC₁₀) values ranged of 23-28 $\mu\text{g/L}$ for clarithromycin and its metabolite for *Desmodesmus subspicatus*, while this value for *Anabaena flos-aquae* was 1.1 $\mu\text{g/L}$ [18]. In 2015 Marx et al. paper has stated that clarithromycin cannot be eliminated from wastewater treatment at all and its excretion rate is 60% [19]. Baumann et al. paper highlights that the concentration of our test macrolide in STP effluents varied 30-600 ng/L. This drug was detected in surface waters in concentration 140 ng/L annually, in 2008 it reached 330 ng/L. There were found the concentration around 5-70 ng/L of this compound in main Bavarian rivers. The concentration in small rivers was up to 360 ng/L in 2004-2008 [18].

Figure 1 – The growth inhibition and growth rate of clarithromycin to *Chlorella sp.* ($p < 0,05$)

Azithromycin is a macrolide antibiotic and it has a wide spectrum. It is consumed to treat and prevent diseases as toxoplasmosis, pediatric infections and respiratory tract infections [20]. The present antibiotic can widely spread to the tissue. Azithromycin accumulate in intracellular cells as fibroblasts, phagocytic cells, and other white blood cells [21].

The high sensitivity of *Chlorella sp.* to azithromycin was seen in low concentration during the test (Figure 2). In concentration 0.2 mg/L the growth pace decreased in almost 4 times in comparison with controls. The growth inhibition reached more than 87 % even in concentration 0.15 mg/L. These results are consistent with those of other studies and suggest that macrolides are very toxic to cyanobacteria and algae, as it has impacts on the growth of Gram-positive bacteria by hindering with the protein synthesis

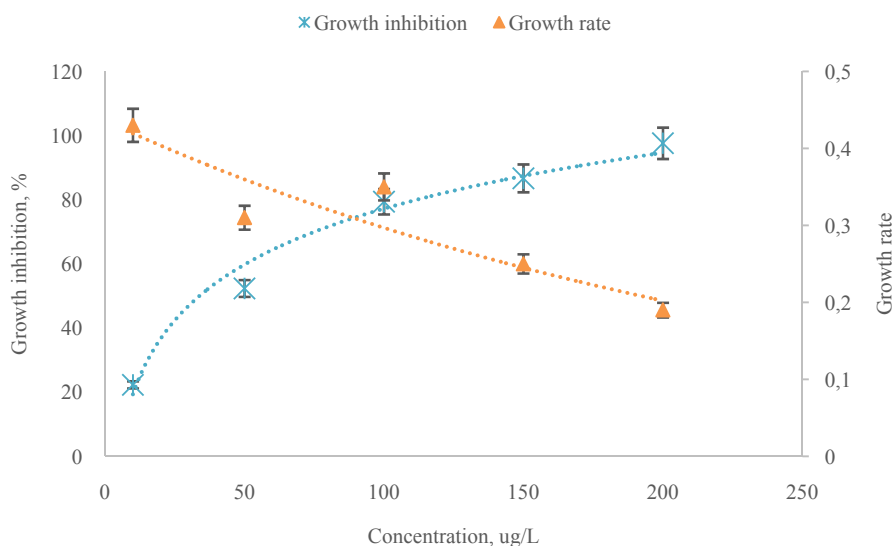


Figure 2 – The growth inhibition and growth rate of azithromycin to *Chlorella sp.* ($p < 0,05$)

[2]. There insufficient studies were conducted on toxicity of azithromycin to algae. Nevertheless, in 2016 Zhou et al argued that our tested macrolide can lead to the risk in urban rivers. According to his finding, EC_{50} value in algae test was 0.026 mg/L for azithromycin. This value is lower than 1 mg/L as in our case ($EC_{50}=0.33\text{mg/L}$), it can be concluded as very toxic to aquatic environment. Moreover, as previous our tested macrolide (clarithromycin), there is 0% of elimination in wastewater treatment of azithromycin. The concentration of following macrolide antibiotic in Yangpu District of Shanghai in China was 17 ng/L [22]. As noted by Osorio et al. (2016) azithromycin was widely spread and concentrated antibiotic in Iberian River basins in Spain [23].

Amoxicillin is a widely spread β -lactam penicillin antibiotic, that used in human and veterinary medicine and included to the significant drug on the World Health Organization [24, 25]. People consume amoxicillin to heal various infections induced by bacteria, such as bronchitis, pneumonia, tonsillitis, gonorrhoea, and infections of the nose, throat, ear, skin, or urinary tract [17]. *Chlorella sp.* did not show sensitivity to amoxicillin in high concentrations. There was a slight growth inhibition (2%) of *Chlorella sp.* to this antibiotic in concentration 1 mg/L, while in 1000 mg/L was reached only 57% (Figure 3).

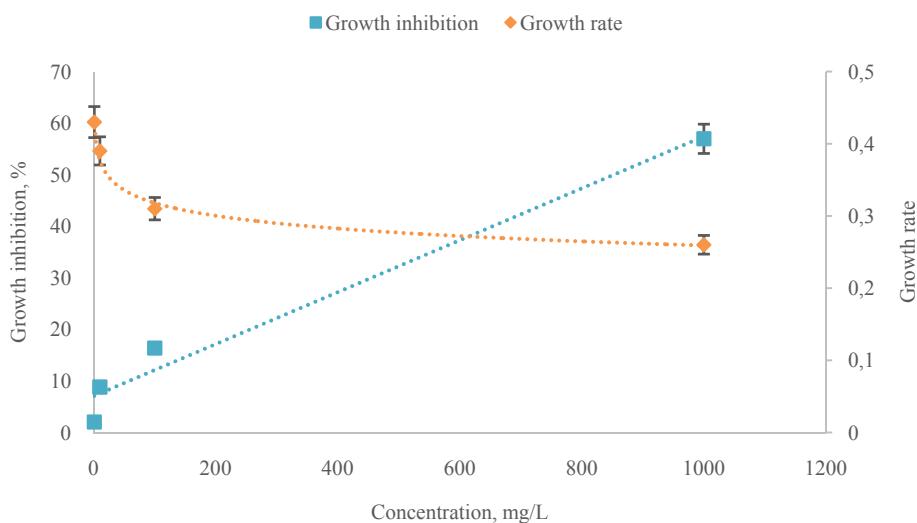


Figure 3 – The growth inhibition and growth rate of *Chlorella sp.* to amoxicillin ($p < 0,05$)

Amoxicillin showed fully logarithmic ($r^2=0.98$) decline in growth rate. In comparison with controls ($0.45\pm 0.006\text{ d}^{-1}$) the growth rate decreased twice in concentration 1000 mg/L ($0.26\pm 0.02\text{ d}^{-1}$). Although, these results hardly differ from previous study, where 72 h of exposure with amoxicillin to green algae *Pseudokirchneriella subcapitata* showed less 10% of inhibition in concentration 1500 mg/L and was considered as not toxic to algae. This inconsistency may be due to comparable different standardized approaches and species for the assessment of the antibiotic to algae. Nevertheless, our and Gonzalez-Pleiter et al. results classified amoxicillin as non-harmful to algae species [26].

In comparison with other tested substances, EC_{50} value is significantly higher and it shows that amoxicillin less toxic. A possible explanation for these results may be attributed to its quick degradation and low bioavailability [27].

To sum up, it was found that aquatic species is sensitive to macrolides. Azithromycin and clarithromycin have a higher toxicity on *Chlorella sp.* in comparison with *Lemna minor*. The EC_{50} value of them was lower than 1 mg/L and can be considered as very toxic to algae. The EC_{50} value of azithromycin to *Lemna minor* lower than 10 mg/L and therefore it is related to toxic classes of substances.

There is no doubt that pharmaceuticals play a significant role in order to treat and mitigate human and animals from diseases. However, they can influence to the environment unintendedly [28]. In the last 30 years, the occurrence, fate and risk of pharmaceuticals to the environmental species have been investigated by many researchers. However, we still have a limited data on ecotoxicological data of drugs. Therefore, it is significant to conduct toxicity studies on pharmaceuticals to establish monitoring system and prevent pharmaceutical contamination.

REFERENCES

- [1] Kummerer K. (2010) Pharmaceuticals in the Environment, Annu Rev Environ Resour, 35(1):57-75. DOI:10.1146/annurev-environ-052809-161223
- [2] Fent K, Weston A, Caminada D. (2006) Ecotoxicology of human pharmaceuticals, AquatToxicol, 76(2): 122-159. DOI: 10.1016/j.aquatox.2005.09.009
- [3] Boxall A, Rudd M, Brooks B, Caldwell D, Choi K, Hickmann S, Innes E, Ostapyk K, Staveley JP, Verslycke T, Ankley GT, Beazley KF, Belanger SE, Berninger JP, Carriquiriborde P, Coors A, Deleo PC, Dyer SD, Ericson JF, Gagné F, Giesy JP, Guoin T, Hallstrom L, Karlsson MV, Larsson DG, Lazorchak JM, Mastrocco F, McLaughlin A, McMaster ME, Meyerhoff RD, Moore R, Parrott JL, Snape JR, Murray-Smith R, Servos MR, Sibley PK, Straub JO, Szabo ND, Topp E, Tetreault GR, Trudeau VL, Van Der Kraak G. Pharmaceuticals and personal care products in the environment: what are the big questions? (2012) Environ Health Perspect, 120(9):1221-1229. DOI:10.1289/ehp.1104477
- [4] Shah S. As Pharmaceutical Use Soars, Drugs Taint Water and Wildlife. Environment 360. Accessed 22.03.2015. Available from http://e360.yale.edu/feature/as_pharmaceutical_use_soars_drugs_taint_water_and_wildlife/2263/
- [5] Sumpter J (2010) Pharmaceuticals in the Environment: Moving from a Problem to a Solution: in Green and Sustainable Pharmacy. Ed. Kummerer K., Hempel M. Springer-Verlag Heidelberg, Berlin. ISBN: 978-3-642-05198-2
- [6] Litvinova N (2009) Ecological potential of innovative production of herbal remedies [Jekologicheskij potencia linnovacionnogo proizvodstva fitopreparatov] 7(63):28-30. (In Russian)
- [7] Schulte-Oehlmann U, Oetken M, Bachmann J, Oehlmann J (2004) Effects of Ethinyloestradiol and Methyltestosterone in Prosobranch Snails: in Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks. Ed. Kummerer K. Springer-Verlag Heidelberg, Berlin. ISBN:978-3-662-09259-0.
- [8] Boxall ABA, Aubakirova BN, Khanturin MR, Beisenova RR. (2014) Toxicity of pharmaceuticals to earthworms, Bulletin of the Karaganda University, 3(75):4-10.
- [9] Aubakirova BN, Boxall ABA, Beisenova RR. (2017) Toxicity study of antibiotics to the common duckweed (*Lemna minor*), Bulletin of the Karaganda University, 1(85): 15-20.
- [10] Aubakirova BN, Beisenova RR, Boxall ABA. (2017) Prioritization of Pharmaceuticals Based on Risks to Aquatic Environments in Kazakhstan, Integr Environ Assess Manag. DOI:10.1002/ieam.1895
- [11] Ebert I, Bachmann J, Kuhnen U, Kuster A, Kussatz C, Maletzki D, Schlüter C. (2011) Toxicity of the fluoroquinolone antibiotics enrofloxacin and ciprofloxacin to photoautotrophic aquatic organisms, Environ Toxicol Chem, 30(12):2786-2792. DOI: 10.1002/etc.678
- [12] Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. (2006) DrugBank: a comprehensive resource for in silico drug discovery and exploration, Nucleic Acids Res. 34:668-672. DOI: 10.1093/nar/gkj067
- [13] Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, Han L, He J, He S, Shoemaker BA, Wang J, Yu B, Zhang J, Bryant SH. (2016) PubChem Substance and Compound databases, Nucleic Acids Res, 44(1):1202-1213. DOI: 10.1093/nar/gkv951

- [14] OECD. The Organisation for Economic Co-operation and Development. OECD guidelines for the testing of chemicals Freshwater Alga and Cyanobacteria, Growth Inhibition Test No 201. Accessed on 01.11.2016. Available from <http://www.oecd.org/chemicalsafety/testing/1946914.pdf>
- [15] Mayer P, Cuhel R, Nyholm N. (1997) A simple in vitro fluorescence method for biomass measurements in algal growth inhibition tests, *Water Research*. 31(10):2525-2531. DOI:10.1016/S0043-1354(97)00084-5
- [16] Fraschini F, Scaglione F, Demartini G. (1993) Clarithromycin clinical pharmacokinetics, *ClinPharmacokinet*, 25(3):189-204.
- [17] Drugs.com. Database for Drugs, 2016. Accessed 01.11.2015. Available from <https://www.drugs.com/>
- [18] Baumann M, Weiss K, Maletzki D, Schussler W, Schudoma D, Kopf W, Kuhnen U. (2015) Aquatic toxicity of the macrolide antibiotic clarithromycin and its metabolites, *Chemospher*, 120:192-198. DOI: 10.1016/j.chemosphere.2014.05.089
- [19] Marx C, Muhlbauer V, Krebs P, Kuehn V. (2015) Species-related risk assessment of antibiotics using the probability distribution of long-term toxicity data as weighting function: a case study, *Stoch Environ Res Risk Assess*, 29(8):2073–2085. DOI:10.1007/s00477-015-1026-4
- [20] Zubata P, Ceresole R, Rosasco M, Pizzorna M. (2002) A new HPLC method for azithromycin quantitation, *J Pharm Biomed Anal*, 27:833-836. DOI: 10.1016/S0731-7085(01)00554-4
- [21] Matzneller P, Krasniqi S, Kinzig M, Sorgel F, Huttner S, Lackner E, Muller M, Zeitlinger M. (2013) Blood, Tissue, and Intracellular Concentrations of Azithromycin during and after End of Therapy, *Antimicrob Agents Chemother*, 57(4): 1736-1742. DOI: 10.1128/aac.02011-12
- [22] Zhou H, Ying T, Wang X, Liu J. (2016) Occurrence and preliminary environmental risk assessment of selected pharmaceuticals in the urban rivers, China, *Sci Rep*, 6(1):1-10. DOI: 10.1038/srep34928
- [23] Osorio V, Larranaga A, Acena J, Perez S, Barcelo D. (2016) Concentration and risk of pharmaceuticals in freshwater systems are related to the population density and the livestock units in Iberian Rivers, *Sci Total Environ*, 540:267–277. DOI:10.1016/j.scitotenv.2015.06.143
- [24] Pan X, Deng C, Zhang D, Wang J, Mu G, Chen Y. (2008) Toxic effects of amoxicillin on the photosystem II of *Synechocystis* sp. characterized by a variety of in vivo chlorophyll fluorescence tests, *AquatToxicol*, 89(4):207-213. DOI:10.1016/j.aquatox.2008.06.018
- [25] Brittain HG, Florey K. (1994), *Analytical profiles of drug substances and excipients*. Academic Press Limited, London. ISBN: 978-0-12-260829-2
- [26] Gonzalez-Pleiter M, Gonzalo S, Rodea-Palomares I, Leganes F, Rosal R, Boltes, K, Marco E, Fernandez-Pinas F. (2013) Toxicity of five antibiotics and their mixtures towards photosynthetic aquatic organisms: Implications for environmental risk assessment, *Water Res*, 47(6):2050–2064. DOI:10.1016/j.watres.2013.01.020
- [27] Fu L, Huang T, Wang S, Wang X, Su L, Li C, Zhao Y. (2017) Toxicity of 13 different antibiotics towards freshwater green algae *Pseudokirchneriella subcapitata* and their modes of action, *Chemosphere*, 168:217–222. DOI:10.1016/j.chemosphere.2016.10.043
- [28] Daughton C, Ruhoy I. (2009) *Pharmaceuticals and Sustainability: Concerns and Opportunities Regarding Human Health and the Environment*, In: *A Healthy Future: Pharmaceuticals in a Sustainable Society*, ed. Sverige A.B. Elanders, Stockholm:15-39. ISBN:2184-01.

Б. Н. Аубакирова, Р. Р. Бейсенова, А. Қ. Жаманғара

Л. Н. Гумилев атындағы Еуразия ұлттық университеті, Астана, Қазақстан

БАЛДЫРЛАР ӨСУІНЕ ФАРМАЦЕВТИКАЛЫҚ ИНГРЕДИЕНТТЕРДІҢ ӘСЕРІ

Аннотация. Әр жыл сайын дәрілік препараттарды тұтыну көлемі ұлғаюуда. Фармацевтикалық препараттар дүниежүзінде беткей суларда анықталуы ғылымда алаңдаушылық туғыза бастады. Дәрілік заттар су ағзаларына жағымсыз әсер тигізеді. Берілген мақаланың мақсаты Қазақстандағы үш приоритетті амоксициллин, кларитромицин және азитромицин сияқты фармацевтикалық ингредиенттерінің су ағзалар түрлерінің өсуіне әсерін бағалау. Зерттеу нысанасы ретінде *Chlorella sp.* алынды. Нәтижелерге сәйкес, амоксициллин, кларитромицин және азитромицин балдырларға жартылай максималды әсер ету концентрациялары сәйкесінше 853.54 ± 0.27 , 0.59 ± 0.004 және 0.33 ± 0.05 мг/л болды. Тұтас алғанда, зерттеу нәтижелері макролидтердің балдырларға жоғары улылығын көрсетті. Алайда амоксициллин *Chlorella sp.* түріне улы емес болып танылды.

Түйін сөздер: амоксициллин, кларитромицин, азитромицин, балдырлар, фармацевтикалық ингредиенттер, экотоксикология, қоршаған орта.

Б. Н. Аубакирова, Р. Р. Бейсенова, А. Қ. Жаманғара

Евразийский национальный университет им. Л. Н. Гумилева

ВЛИЯНИЕ ФАРМАЦЕВТИЧЕСКИХ ИНГРЕДИЕНТОВ НА РОСТ ВОДОРΟΣЛЕЙ

Аннотация. Потребление лекарственных препаратов растет каждый год. Фармацевтические препараты начали вызывать беспокойство в связи их обнаружением в поверхностных водах во всем мире. Выявлено, что лекарственные субстанции оказывают негативное влияние водным организмам. Цель статьи – дать оценку таким приоритетным фармацевтическим ингредиентам, как амоксициллин, кларитромицин и азитромицин к росту водных организмов. *Chlorellasp.* был выбран как объект исследования. Согласно результатам, полумаксимальная эффективная концентрация (EC_{50}) к малой ряске амоксициллина, кларитромицина и азитромицина были 853.54 ± 0.27 , 0.59 ± 0.004 и 0.33 ± 0.05 мг/л соответственно. В целом результаты исследования показали высокую токсичность макролидов к водорослям. Тем не менее, амоксициллин оказался нетоксичным к *Chlorellasp.*

Ключевые слова: амоксициллин, кларитромицин, азитромицин, водоросли, фармацевтические ингредиенты, экотоксикология, окружающая среда.

Publication Ethics and Publication Malpractice in the journals of the National Academy of Sciences of the Republic of Kazakhstan

For information on Ethics in publishing and Ethical guidelines for journal publication see <http://www.elsevier.com/publishingethics> and <http://www.elsevier.com/journal-authors/ethics>.

Submission of an article to the National Academy of Sciences of the Republic of Kazakhstan implies that the described work has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see <http://www.elsevier.com/postingpolicy>), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. In particular, translations into English of papers already published in another language are not accepted.

No other forms of scientific misconduct are allowed, such as plagiarism, falsification, fraudulent data, incorrect interpretation of other works, incorrect citations, etc. The National Academy of Sciences of the Republic of Kazakhstan follows the Code of Conduct of the Committee on Publication Ethics (COPE), and follows the COPE Flowcharts for Resolving Cases of Suspected Misconduct (http://publicationethics.org/files/u2/New_Code.pdf). To verify originality, your article may be checked by the Cross Check originality detection service <http://www.elsevier.com/editors/plagdetect>.

The authors are obliged to participate in peer review process and be ready to provide corrections, clarifications, retractions and apologies when needed. All authors of a paper should have significantly contributed to the research.

The reviewers should provide objective judgments and should point out relevant published works which are not yet cited. Reviewed articles should be treated confidentially. The reviewers will be chosen in such a way that there is no conflict of interests with respect to the research, the authors and/or the research funders.

The editors have complete responsibility and authority to reject or accept a paper, and they will only accept a paper when reasonably certain. They will preserve anonymity of reviewers and promote publication of corrections, clarifications, retractions and apologies when needed. The acceptance of a paper automatically implies the copyright transfer to the National Academy of Sciences of the Republic of Kazakhstan.

The Editorial Board of the National Academy of Sciences of the Republic of Kazakhstan will monitor and safeguard publishing ethics.

Правила оформления статьи для публикации в журнале смотреть на сайте:

www.nauka-nanrk.kz

ISSN 2518-1629 (Online), ISSN 2224-5308 (Print)

<http://www.biological-medical.kz/index.php/ru/>

Редактор *М. С. Ахметова, Д. С. Аленов, Т. М. Апендиев*
Верстка на компьютере *Д. Н. Калкабековой*

Подписано в печать 27.07.2017.

Формат 60x881/8. Бумага офсетная. Печать – ризограф.
10,7 п.л. Тираж 300. Заказ 4.