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TEST-MODEL AND QUANTITATIVE R_{DDS} CRITERION INDEX WHICH ARE APPLIED TO ESTIMATE ANTIMICROBIC POTENTIAL OF NANOMATERIALS USED FOR WATER PURIFICATION AND TREATMENT: SUBSTANTIATION AND METROLOGIC ASSESSMENT

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To reduce population health risks which occur when people consume drinking water from centralized water supply systems is a vital medical-biologic and technical problem. It can be sold, among other things, via development and application of new materials for water purification and treatment. Some natural and artificial nanomaterials have antimicrobic properties as they can eliminate microorganisms of various taxonomy (bacteria, yeast-like and mold fungi) and bacterial biofilms. However, certain results which were obtained when antimicrobic potential of nanomaterials was estimated are controversial; they are frequently only qualitative or semi-quantitative due to absence of a standard test protocol and well-grounded criterial assessment apparatus. So, the goal of this paper was to give methodological grounds and to create a unified and standardized test-model; to optimize parameters of a procedure and to substantiate a system of criteria applied for quantitative assessment of antimicrobic activity which is characteristic for nanomaterials applied for water purification and treatment.

The research was performed on the following objects: samples of nanomaterials based on titanium dioxide which were applied for water purification and treatment. The authors have substantiated a test-model, suggested a criterion index R_{DDS}, made up a standard test protocol for quantitative assessment of antimicrobic potential possessed by nanomaterials.

The developed technology has been tested on samples of nanomaterials based on titanium dioxide. We have calculated and assessed metrological parameters of the procedure (repeatability standard deviation and repeatability limit) which conform to the requirements existing for similar procedures when confidence probability is assumed to be equal to 95 %; such requirements are fixed by the ISO (International Standardization Organization) and correspond to the GLP (Good Laboratory Practice) principles. The relevance of the test-model was validated; this relevance provides an objective quantitative assessment of antimicrobic potential which is possessed by materials applied for disinfection of water objects contaminated with microbiota of various taxonomy, as well as for control and prevention of bacterial infections which can be communicated with water.

Key words: *nanomaterials, test-model, antimicrobic potential, quantitative criterion index R_{DDS}, metrological assessment.*

Reduction of population health risks related to drinking water consumption from centralized water supply systems is a vital medical, biological, and technical tasks. It can be solved, among other things, by developing and implementing new materials for water treatment and purification [1–5]. Some natural and artificial nano-materials based on TiO_2 [6–8], ZnO [9], silver [10–13] and more complicated compounds [7,14–18], have antimicrobic properties and can eliminate microorganisms of various taxonomy (bacteria, yeast-like and mold fungi) as well as bacterial biofilms [19–22].

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Therefore, application of nanomaterials is of great interest for those who deal with disinfection of drinking water from centralized water supply systems [23–28].

However, experimental data on antimicrobic properties of nanomaterials are controversial and they are frequently only qualitative or semi-quantitative. Methodical procedures applied for modeling in the sphere are diverse, there are no standard test reports which could be implemented into routine practices at certified laboratories. But above all, there is no substantiated criterial apparatus for quantitative assessment of antimicrobic effects produced by nanomaterials and it prevents experts from analyzing experimental data arrays in conformity with the requirements set forth by the GLP (Good Laboratory Practice) as its standards call for strict observation of a test procedure with optimized conditions and parameters that help to obtain comparable and authentic data [19, 29–32].

Our research goal was to give procedural substantiation and to develop a unified and standardized test-model; to optimize parameters of the developed procedure and to substantiate a criterial apparatus for quantitative assessment of antimicrobic effects produced by nanomaterials applied for water treatment and purification; to test all the development on innovative nanomaterials.

Data, materials and methods. We took *Escherichia coli* ATCC 8739 and *Staphylococcus aureus* ATCC 25923 strains provided by the Russian collection of industrial microorganisms. Museum microorganisms strains had typical morphological, cultural, and physiological-biochemical features that were characteristic for corresponding taxonomic bacterial groups; they also possessed good growth properties.

To obtain standardized test-models, we cultivated them in 50-ml vials containing 10 ml of a medium at 35–37°C for 18–24 hours until a stationary growth phase was reached for an optimized medium with the following structure: 500 ml of beef-extract broth; 10.0 grams of dextrose; 1.0 gram of $CaCO_3$; 0.2 grams of $MgSO_4$; 0.02 grams of $CaCl_2$; 0.02 grams of $FeCl_3$; 0.01 ml of a 10% solution of microelements per 1,000.0 ml, pH being 7.2–7.4. Suspension of a test-culture was diluted as per McFarland standard test until we obtained operating concentration of cells Log 2 CFU/ml in saline.

To test the developed procedure, we applied samples based on nano-structured titanium dioxide TiO_2 that was deposited on various substrates via different techniques. The samples were kindly given to us by Professor V.E. Borisenko, the scientific supervisor of the Center for Nanoelectronics and Innovative Materials at the Belarus State University for Informatics and Electronics, Minsk.

Description of a modeling experiment procedure. We examined antimicrobic potential of nanomaterials based on TiO_2 making their samples enter a direct contact with a standardized suspension of test-cultures. Samples of nanomaterials sized 3.5×3.5 cm^2 were put into a sterile glass cup that contained 50 ml of a standardized test-culture. The samples were exposed to it for 30 minutes with simultaneous activation that was stimulated with a visual light lamp, its model being 01200100011(EL-PL10PW, 50 Hz, 10 wt, G23D type, pure white color. Microorganisms population after the exposure was assessed via inoculation of 0.1-1 ml of suspension on surfaces of differential-diagnostic nutrient media, Endo for ***E. coli*** and yolk-salt agar for ***S. aureus***. Inoculations were cultivated at optimal temperature equal to 35–37°C for 18–36 hours.

Measurement results processing. To perform quantitative assessment after incubation, we calculated typical formed colonies on three parallel Petri dishes that contained not less than 250 colonies. The quantity of microorganisms, CFU/ml, was calculated as per the following formula (1):

$$X = \frac{\bar{N}}{V_1}, \qquad (1)$$

where

$\bar{N}$– is the quantity of typical colonies on a dish; V_1 – is the volume of an inoculated sample (0,1–1,0 ml).

An arithmetic mean of the results obtained in 5 parallel measurements was assumed to be the final measuring result.

We checked eligibility of two single measuring results obtained under repeatability conditions via calculating an absolute discrepancy between common logarithms of single measuring results; the value of this discrepancy was than compared with the value of repeatability limit ***r***.

If the condition (2) was true for the value of the absolute discrepancy between common logarithms of two single measuring results

$$\left| \lg X_1 - \lg X_2 \right| < r, \qquad (2)$$

than both single measuring results were considered to be eligible.

We checked homogeneity of dispersions, statistical struggling and overshoots as per Cochran's Q test.

We calculated a standards deviation in repeatability as per the following formula (3):

$$Sr = \sqrt{\sum_{i=1}^{g} \frac{(y_{i1} - y_{i2})^2}{2p}}. \quad (3)$$

The value of repeatability limit *r* was calculated as per the following formula (4)

$$r = 2{,}8Sr. \quad (4)$$

To quantitatively assess antimicrobic effects, we introduced a term "antimicrobic potential" and substantiated index R_{DDS} calculated as per the following formula (5):

$$R_{DDS} = \frac{Lg_0 - Lg_{30}}{Lg_0}, \quad (5)$$

where Lg_0 is a common logarithm of population level before exposure;

Lg_{30} is a common logarithm of population level after 30-minute exposure.

To perform metrological assessment of the procedure, we calculated a standard deviation in repeatability and repeatability limit according to the requirements set forth by legal metrology[1]. We excluded results with a number of colonies being greater than 250 CFU/dish from our calculations.

Results and discussion. Statistical data for assessing metrological characteristics of the procedure were obtained as per results of analysis performed on 5 measuring series that were accomplished at various time moments but under repeatability conditions (Table). Antimicrobic potential that innovative nanomaterial had was calculated as per the developed standard procedure and on the basis of RDDS criterion (Table). We developed and applied the following criterial scale for assessing antimicrobic potential of a material:

$1{,}0 \geq$ RDDS $> 0{,}7$ means antimicrobic potential is apparent;

$0{,}7 \geq$ RDDS $> 0{,}5$ means antimicrobic potential is average;

$0{,}5 \geq$ RDDS $> 0{,}1$ means antimicrobic potential is insignificant;

RDDS $\leq 0{,}1$ means a material doesn't have any antimicrobic potential.

Thus, although various specimen of water microbiota have different resistance to influence exerted by nano-structured materials as it has been mentioned in works by some authors [8, 18, 32–35], we were the first to quantitatively assess antimicrobic potential as per *RDDS* criterion [36–38].

We detected that, according to a criterial scale suggested by us, antimicrobic effects were more apparent in relation to gram-negative microflora, than in relation to gram-positive one. We also revealed that exposure to nanomaterials led to changes in phenotypic properties that were characteristic for test-cultures. There were changes in tinctorial properties of *Escherichia coli* ATCC 8739 test culture and it led to Gram staining variability, typical shapes of vegetative cells also changed and they became smaller in size.

The developed procedure for quantitative assessment of antimicrobic potential possessed by nanomaterials has its operating characteristics, and we accomplished the first metrological assessment of them. We calculated a standard deviation in repeatability *Sr* and repeatability limit *r* taking into account eligibility of single measuring results which were obtained under repeatability conditions; we also checked dispersions in terms of their homogeneity, statistical struggling and overshoots as per Cochran's Q test.

Conclusion. As we developed the procedure how to quantitatively assess antimicrobic potential of nanomaterials, we managed to substantiate the following standard conditions that are necessary to perform any research and to develop a standard test report:

1. To model real-life parameters of water treatment, testing should be made only with nanomaterials entering a direct contact with a suspension of microorganisms in saline. As opposed to application of agar-based plates, such a technique allows to provide homogenous distribution of active components in water masses and to avoid distortion of test results via eliminating effects of test-cultures shielding with organic components of nutrient media and ability of nanomaterials to diffuse into dense media.

2. An important stage in the assessment is exposure of a test-culture and a nanomaterial sample to visible light for 30 minutes under photoactivation. The suggested conditions are quite sufficient for antimicrobic properties of nanomaterials to reveal themselves even in such cases when antimicrobic potential of a nanomaterial is average or weak (insignificant). In order to assess dynamics in

[1]State Standard ISO 5725-6-2002. Accuracy (validity and precision) of measuring techniques and results. Part 6. How to apply precision values in practice: The RF State Standard. Available at: http://docs.cntd.ru/document/1200029980 (date of visit June 16, 2018).

Table

Antimicrobic potential RDDS of nanomaterials samples: test results *

Sample	*Escherichia coli* ATCC 8739					*Staphylococcus aureus* ATCC 25923				
	Lg_0	$X_{cp} \pm Sr$ r	Lg_{30}	$X_{cp} \pm Sr$ r	R_{DDS}	Lg0	$X_{cp} \pm Sr$ r	Lg_{30}	$X_{cp} \pm Sr$ r	R_{DDS}
1	2,39	2,35 ± 0,058 0,162	0	0 ± 0,00 0,00	1,00 – apparent	2,32	2,32 ± 0,029	0,30	0,18 ± 0,16 0,448	0,92 – apparent
	2,34		0			2,36		0,30		
	2,44		0			2,29		0,30		
	2,31		0			2,33		0,00		
	2,30		0			2,30		0,00		
2	2,39	2,37 ± 0,033 0,092	2,08	2,09 ± 0,067 0,188	0,12 – insignificant	2,32	2,30 ± 0,024 0,067	2,04	2,15 ± 0,098 0,274	0,07 – insignificant
	2,35		2,10			2,29		2,05		
	2,41		2,00			2,27		2,25		
	2,32		2,18			2,30		2,23		
	2,36		2,12			2,33		2,18		
3	2,38	2,36 ± 0,06 0,168	1,70	1,65 ± 0,134 0,375	0,30 – insignificant	2,35	2,35 ± 0,02 0,056	1,79	1,75 ± 0,05 0,018	0,25 – незначительный
	2,40		1,83			2,36		1,81		
	2,34		1,53			2,33		1,73		
	2,28		1,68			2,38		1,74		
	2,36		1,51			2,33		1,68		
4	2,34	2,34 ± 0,061 0,171	1	0,82 ± 0,117 0,328	0,65 – average	2,29	2,26 ± 0,049 0,138	1,18	1,01 ± 0,11 0,308	0,55 – average
	2,34		0,70			2,27		1,08		
	2,44		0,85			2,30		0,95		
	2,27		0,48			2,26		0,95		
	2,32		0,90			2,18		0,90		
5	2,38	2,38 ± 0,01 0,028	2,39	2,37 ± 0,05 0,14	0,003 – none	2,21	2,26 ± 0,11 0,308	2,22	2,27 ± 0,12 0,336	–0,002 – none
	2,38		2,34			2,23		2,24		
	2,38		2,44			2,12		2,11		
	2,37		2,31			2,37		2,37		
	2,36		2,36			2,38		2,39		

Note: the data are given as an arithmetic mean of 5 measurements; *Sr* is a standard deviation in repeatability; *r* is repeatability limit.

antimicrobic effects, other exposure schemes can be chosen.

3. Epidemically significant museum strains *Escherichia coli* ATCC 8739 and *Staphylococcus aureus* ATCC 25923 are biologic test models; *Escherichia coli* is a rod-shaped gram-negative bacteria, and *Staphylococcus aureus* is a coccal gram-positive microflora specimen. The suggested strains are widely applied in routine practices of certified microbiologic laboratories as they are standard ones used in assessing efficiency of disinfectants and antiseptics, in determining growth properties of nutrient media, including test performed in conformity with international standards.

4. It is necessary to ensure that museum test-cultures are prepared for any experiment in full conformity with standardized procedures as only such preparation can provide representative and reproducible results; it is a non-standardized test-culture that usually makes the greatest contribution into uncertainties detected in the process of testing.

5. Target concentration of test-cultures should be chosen in such a way that allows to model an actual microbe load in drinking water that is equal to 2 lg CFU/ml.

6. Working surface of samples should amount to 3.5×3.5 cm^2 that is an optimal value for revealing antimicrobic potential.

7. To quantitatively assess antimicrobic effects, we introduced a term "antimicrobic potential" and substantiated R_{DDS} index calculated as per the formula (6):

$$R_{DDS} = \frac{Lg_0 - Lg_{30}}{Lg_0},$$

where Lg_0 is a common logarithm of population level before exposure;

Lg_{30} is a common logarithm of population level after 30-minute exposure.

8. We suggested a criterial assessment scale that can be applied in every day practices:

$1 \geq R_{DDS} > 0.7$ means antimicrobic potential is apparent;

$0.7 \geq R_{DDS} > 0.5$ means antimicrobic potential is average;

$0.5 \geq R_{DDS} > 0.1$ means antimicrobic potential is insignificant;

$R_{DDS} \leq 0.1$ means a material doesn't have any antimicrobic potential.

When $R_{DDS}=1$, tested nanomaterials obviously have the maximum possible antimicrobic potential; when $R_{DDS}=0$, it means a material doesn't have any antimicrobic potential; when $R_{DDS} < -0.3$, it means that influence exerted by a nanomaterials stimulates activity of microorganisms.

The suggested approaches and criterial scale can be widely implemented into practice when it is necessary to assess antimicrobic properties of new materials applied for water purification and treatment.

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