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ASSESSMENT OF GENERAL TOXICITY AND PROOXIDANT EFFECTS OF CeO_2 AND SiO_2 NANOPARTICLES ON *Danio rerio*

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Abstract

A diversified use of nanomaterials leads to their accumulation in the environment and involvement into remediation. In water biocoenosis, nanomaterials influence fishes. Lipid peroxidation (LPO) in aquatic bioindicators is considered the parameters generally used to assess an impact of man-caused water pollution. It should be taken into account that the level of LPO products can be due not only to anthropogenic pollution, but also to the presence of peroxide substrates in fish tissues. We firstly showed the effect of silica and cerium nanoparticles in water environment with direct assay of the enzyme activity of the bioindiator used. Our purpose was to evaluate the prooxidant effects of CeO_2 (15.8 nm) and SiO_2 (40.9 nm) nanoparticles (NPs) on the *Danio rerio* model, to study LPO as influenced by the NPs doses, and to find out if there are any adaptive mechanisms in *Danio rerio* to withstand the NPs in the habitat. Complete death of the test objects occurred on days 80 and 84 when CeO_2 NPs used. The first signs of the CeO_2 NPs toxic effect at a dose of 10 mg/dm^3 in the feed appeared on day 45, on day 56 the test-organism number was 33 % lower, and on day 65 a more than 54 % decline occurred. SiO_2 NPs led to 33 % reduced survival. The presence of the nanoparticles in the habitat depressed the antioxidant system of *Danio rerio* but the signs of adaptation were manifested by the end of week 2, and a significant increase in catalase (CAT) and superoxide dismutase (SOD) activity proceeded by the end of the test. At 10 and 100 mg/dm^3 of CeO_2 NPs the malonic dialdehyde (MDA) level decreased by 11.0 % and 61.0 %, respectively. For SiO_2 NPs the changes were similar with the MDA level decrease of 50.0 and 41.5 % at 10 and 100 mg/dm^3 dosage, respectively. SOD activity when influenced by CeO_2 NPs (10 mg/dm^3 and 100 mg/dm^3) decreased by 75 and 69 %, respectively, and for SiO_2 NPs the indexes were 50 and 26 % lower as compared to control. Similar changes were characteristic of CAT activity. Thus, the investigated nanoparticles possess sufficient toxic properties that necessitates their further study.

Keywords: *Danio rerio*, survival, catalase, superoxide dismutase, nanoparticles of silicone and cerium dioxide, mass spectrometry

According to some estimates, by 2020, nanotechnology advances will provide the establishment of industries, which will employ about 6 million people with a combined production of goods by $ 3 trillion [1]. Naturally this will increase the flow of ultrafine materials into the environment, where they will be involved in the biological processes. In the aqueous environment, nanomaterials may be incorporated into various processes, such as become the components of effluents or emissions; they are not biodegradable, and leave the biological cycle very slowly [2]. This necessitates the study of the bodies of terrestrial and water (natural and anthropogenic) ecosystems upon exposure of nanomaterials, primarily, of those the forms of which have significant potential applications. These include nanopreparations containing cerium and silicon and used in many biotechnological and medical productions [3]. Research has shown that the toxic effect of CeO_2

and SiO_2 is detected only when particles are up to 10 nm in size, but there is no exact evidence confirming their low toxicity to humans and animals. A limited number of landmark works on the effects of nanoparticles (NPs) of CeO_2 and SiO_2, the inconsistency of the data, as well as the expansion of the applications of materials based on the CeO_2 and SiO_2 NPs necessitate the biological assessment of these nanomaterials, including in the environmental objects [4, 5].

It should be noted that information on the effects of cerium- and silicon-containing nanoparticles is ambiguous. Using the freshwater fish *Catostomus commersonii*, it was shown that these nanoparticles were characterized by unstable manifestation of their activity [6]. The investigation on the *Danio rerio* model revealed no toxic and damaging effects [7], while demonstrated the perspectives of using cerium-containing nanoparticles for therapeutic purposes [8]. Furthermore, the data on severe toxicity of these materials have gained widespread, particularly, the ability of the CeO_2 NPs has been found to cause pulmonary inflammations when tested in rats [9], induce oxidative stress and, as a result, the breaks of single-strand DNA [10, 11].

In its assessment, the studied parameters are the products of lipid peroxidation (LPO) in the tissues of hydrobionts considered as biological indicators of anthropogenic pollution of water bodies. However, when interpreting these results, it is important to consider that revealed values can be related not only to the reaction to anthropogenic pollution, but also to endogenous substrates of peroxidation in the tissues.

We were the first to study the effect of nanoparticles of silicon and cerium dioxide in an aquatic environment with immediate assessment of enzyme system of the bioindicator organism.

Our purpose was to determine the biological effects of the CeO_2 and SiO_2 NPs in an aquatic environment depending on the preparation dose and routes of contamination.

Tecnique. The investigations were performed on a model of *Danio rerio* aged 1 month and selected by weight.

The preparations of SiO_2 (d = 40.9 nm) and CeO_2 (d = 15.8 nm) nanoparticles, used in the research, were synthesized by a vapour-phase method in the Shared Knowledge Center at The A.N. Tupolev Kazan National Research Technological University. Materials research certification of the preparations included electronic scanning and transmission microscopy using JSM 7401F and JEM-2000FX microscopes (JEOL, Japan), as well as X-ray diffraction analysis (DRON-7 X-ray diffraction meter, NPO Burevestnik, Russia). Atomic force microscopy was performed using SMM-2000 microscope (OJSC PTOTON-MIET, Russia). The scanning used MSCT-AUNM (Park Scientific Instruments, USA) cantilevers with a spring constant at k = 0.01 N/m and the needle radius of curvature of 15-20 nm. Quantitative morphometric analysis of the derived images was performed using regular software microscope.

The aquarium fish *Danio rerio* (a species of ray-finned freshwater fish in the *Cyprinidae* family) aged 1 month (n = 75) were kept in a single aquarium stand (V = 300 l) for 21 days. Next, five groups (n = 15 each) were allocated using the analogue method, placing each group in a separate fish tank (V = 10 l, stocking density of 15 individuals), in the water of which the studied nanoparticles were added: CeO_2 NPs (10 mg/dm^3) in group I; CeO_2 NPs (100 mg/dm^3) in group II; SiO_2 NPs (10 mg/dm^3) in group III, SiO_2 NPs (100 mg/dm^3) in group IV; and group V as a control (without addition of nanoparticles). After adaptation of the model object within 21 days (a preliminary experiment stage) the nanoparticles of SiO_2 (SiO_2 NPs) and CeO_2 (CeO_2 NPs) as lyosols were administered with feed (*Chironomidae* larvae) every 7 days (10 and 100 mg/dm^3

feed by groups according to the design of experimen; in control, the nanoparticles were not added). To prepare lyosols, the nanoparticles were dispersed in water and sterilized by sonication (UZDN-2T, NPP Akadempribor, Russia; f-35 kHz, 300 W, A-10 μA, 30 min). The experiment lasted for 84 days.

The toxic effect of nanopreparations was evaluated by the survival of the test object calculated as the percentage of animals alive at the end of the experiment from the baseline number. The concentrations of the nanopreparations were distributed to the following groups of toxicity: for bioindicator survival 0-39 % — Tox, 50 % — LC_{50}, 40-69 % — LOEC and 70-100% — NOEC.

To identify the products of lipid peroxidation (LPO) and the status of antioxidant protection systems, on day 7, 14 and 84, five *Danio rerio* fish were homogenized (TissueLyser LT, Qiagen N.V., Germany). To prepare an extract, nine volumes of Tris buffer (Tris-HCl 50 mmol/l, dithiothreitol DTT 1.0 mmol/l, EDTA 1.0 mmol/l, sucrose 250 mmol/l, pH 7.5) was added to one volume of the homogenate. After centrifugation (10 min at 15000 rpm), the supernatant was collected, and the content of malondialdehyde (MDA), as well as the activity of key antioxidant enzymes, such as catalase (CT, EC 1.11.1.6) and superoxide dismutase (SOD, EC 1.15.1.1), were measured in it, using a CS-T240 automatic biochemistry analyzer (Dirui Industrial Co., Ltd, China) and commercial biochemical test kits for veterinary use (Randox Laboratories, Ltd, UK).

Throughout the experiment the following conditions were maintained: average temperature 22±2 °C, pH 7.3±0.07, dissolved oxygen concentration 5±0.2 mg/l; 12/12 hours (day/night). The fish were fed every 2 days. Conditions for growth and maintenance of test objects were in compliance with the rules of OECD (Organisation for Economic Co-operation and Development) [12]. The experiments were performed in accordance with the provisions of the Geneva Convention and the principles of Good Laboratory Practice (National Standard of the Russian Federation GOST R 53434-2009), as well as recommendations set out in The Guide for the Care and Use of Laboratory Animals (National Academy Press Washington, DC 1996). Animal care was carried out according to Good Laboratory Practice as per regulations on conducting preclinical research in the Russian Federation (GOST 3 51000.4-96).

The results are provided as mean (*M*) and standard error of mean (*m*). Statistical analysis was performed using ANOVA standard methods (Statistica 10.0 software package, StatSoft Inc., USA), and subsequent safety evaluation using a Tukey's test of additivity in SPSS 17.0 (IBM Corporation, USA). The differences were statistically significant at $p < 0.05$.

Results. In our experiment, fish mortality in the presence of nanoparticles of both elements on day 1 was not observed (data not shown). A longer exposure to nanoparticles affected the number of *Danio rerio* (Fig. 1). The first signs of toxicity of CeO_2 NPs at a dose of 10 mg/dm^3 feed were observed on day 45, while on day 56 the number of fish was reduced by 33 %, on day 65 already by 54 %, and by day 84 deaths of 100 % test objects were recorded. At a CeO_2 NPs concentration of 100 mg/dm^3, the death of *Danio rerio* was noted on day 80.

On day 7 and 28, both doses of CeO_2 NPs and SiO_2 NPs (10 and 100 mg/dm^3) were classified as NOEC (survival of the test object within 70-100 %). On day 56, both doses of CeO_2 NPs moved into the LOEC group (the concentration maintaining 40-69 % survival of the test object), while those of SiO_2 NPs remained in the NOEC group.

Finally, by day 84 both doses of CeO_2 NPs were toxic (Tox means concentrations at which the survival of the subject is 0-39 %), while for SiO_2 NPs the 10 mg/dm^3 dose effect was still ranked as NOEC, and only for the 100 mg/dm^3 dose toxicity category was changed to LOEC.

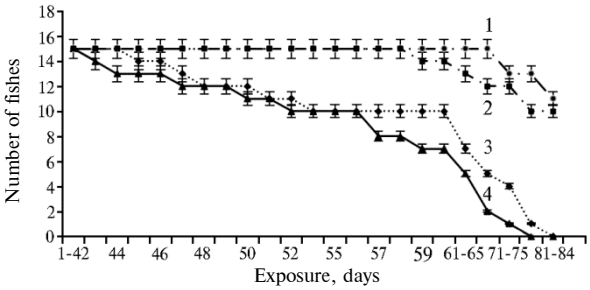

Fig. 1. Dynamics of the bioindicator *Danio rerio* population depending on the dose of SiO_2 NPs (1, 2) **and CeO_2** (3, 4) **added with feed, and time of exposure:** 1, 3 — 10 mg/dm^3, 2, 4 — 100 mg/dm^3 (n = 75).

It should be noted that the high toxicity of cerium nanoparticles which has been revealed in these experiments contradicted our working hypothesis, based on a series of papers about the ability of CeO_2 NPs to exhibit antioxidant properties, acting as an analogue of superoxide dismutases (SOD) and catalases. These reported neutralizing free radicals and protecting cells from oxidative damage [13]. On these grounds, the authors suggested the use of CeO_2 NPs in the treatment of neurological disorders and for the cell radioprotection [13, 14]. However, the ability of CeO_2 to trigger oxidative stress was shown in cell culture [15, 16] and model objects, such as rats [17, 18] and the nematode *Caenohabditis elegans* [19].

Our data also showed the invalidity of the assumptions made [20] on the biological inertness of the silicon dioxide nanoparticles. Thus, contact of the SiO_2 NPs with the test object manifested in a decreased survival of *Danio rerio* by 7 %, and by 33 % at the end of the experiment, although the total loss of the test object was not observed. Previously, against application of the SiO_2 NPs chromosomal aberrations were identified, as well as the development of the oxidative stress [21, 22]. In a model of *Carassius auratus gibelio* (crucian carp), the ability of the Si/SiO_2 nanoparticles to induce an inflammatory response was demonstrated [23]. Similar results were also obtained in other test objects [24-26].

1. The content (μmol/l) **of malondialdehyde in homogenates of *Danio rerio* depending on dose of and time of exposure to nanoparticles** (NPs) **of CeO_2 and SiO_2** ($M\pm m$, n = 75)

Nanopreparation	10 mg/dm^3	100 mg/dm^3
	Day 7	
CeO_2 NPs	0.615±0.011*	0.269±0.006*
SiO_2 NPs	0.346±0.008**	0.404±0.003**
Control	0.691±0.005	
	Day 14	
CeO_2 NPs	0.245±0.003**	0.251±0.004*
SiO_2 NPs	0.252±0.005*	0.269±0.006*
Control	0.461±0.008	
	Day 84	
SiO_2 NPs	4.100±0.105*	4.500±0.095**
Control	0.693±0.001	

*, ** Differences vs. control are statistically significant at $P < 0.05$ and $P < 0.01$, respectively.

The contact of *Danio rerio* with CeO_2 NPs and SiO_2 NPs during the first two weeks of the experiment was accompanied by a decreased content of MDA in all groups compared to the control (Table 1). For example, on day 7 the MDA content decreased by 11 and 61 % compared to control when the CeO_2 NPs were used at doses of 10 and 100 mg/dm^3. For SiO_2 NPs the dynamics was similar, i.e. a decrease in the MDA content on day 7 by 50.0 and 41.5 %, respectively, at doses of 10 and 100 mg/dm^3. On day 14 of the experiment, the same dynamics was observed. An increase in terms of exposure up to 84 days resulted in the elevated MDA production and, consequently, an increased lipid PO. Thus, in the presence of SiO_2 NPs at a dose of 10 mg/dm^3 the MDA concentration was 11-fold higher than that in the control, and at a dose of 100 mg/dm^3 — 12-fold. Similar results were obtained when assessing the effect of silicon nanoparticles in crucian carp [23].

The presence of nanoparticles in feed and water affected the activity of antioxidant enzymes (SOD and CT) in the test object. On day 7, the SOD value in *Danio rerio* in all study groups was lower than in the control. For example, in

the option with CeO_2 NPs, it decreased by 75 % at a nanopreparation dose of 10 mg/dm^3 and by 69 % at a dose of 100 mg/dm^3, and with SiO_2 NPs by 50 and 26 %, respectively, at a dose of 10 and 100 mg/dm^3. On day 14, the SOD activity in the presence of nanoparticles differed depending on their type. CeO_2 NPs induced a decrease in the SOD values, such as by 41 % for 10 mg/dm^3, and by 29 % for 100 mg/dm^3 (Table 2). When SiO_2 NPs were added to the feed, the SOD activity parameters exceeded those in the control samples only on day 20, reaching values 1.96 and 1.48 times as much as control ones at doses of 10 and 100 mg/dm^3, respectively.

2. The catalase (CT) **and superoxide dismutase** (SOD) **activity in homogenates of *Danio rerio* depending on dose of and time of exposure to nanoparticles** (NPs) **of CeO_2 and SiO_2** ($M\pm m$, $n = 75$)

Nanopreparation	CT, μmol/L		SOD, % of epinephrine inhibition	
	dose of 10 mg/dm^3	dose of 100 mg/dm^3	dose of 10 mg/dm^3	dose of 100 mg/dm^3
	Day 7			
CeO_2 NPs	93.1±0.7*	51.4±0.5**	17.6±2.8*	48.5±1.7*
SiO_2 NPs	15.9±0.4	46.9±1.0*	35.6±1.2**	52.4±2.6*
Control	16.4±0.5		70.6±0.5	
	Day 14			
CeO_2 NPs	97.4±2.1**	83.3±2.9*	28.1±1.5	33.7±1.1
SiO_2 NPs	77.1±2.8**	29.3±1.4	93.6±3.7*	70.6±2.1*
Control	16.2±0.3		47.6±0.6	
	Day 84			
SiO_2 NPs	15.9±0.9*	20.2±1.1	6.1±0.2**	10.8±1.1*
Control	23.1±0.8		59.3±1.8	

*, ** Differences vs. control are statistically significantat $P < 0.05$ and $P < 0.01$, respectively.

A significant decrease in SOD activity by the end of the experiment was quite expected, and is determined by the development of toxic reactions similar to those described previously in the presence of xenobiotics and cadmium [27]. We also observed similar dynamics for catalase (see Table 2).

Therefore, our results indicate that at the initial stages of NPs exposure to the body there is a pronounced reduction in the function of cell protection systems against oxidative stress. This is probably a consequence of the NPs ability to act as an analogue of catalase, and exert activity, to some extent similar to the effect of SOD [28]. It is also specific that the CT and SOD activity, which changes in the presence of CeO_2 NPs and SiO_2 NPs, is recovered with time [29]. Therefore, we believe it is natural that the changes in SOD and CT values in *Danio rerio* under the influence of nanoparticles are opposite to the dynamics previously described for toxic substances, such as the insecticide imidacloprid, whose action first manifested in the increased activity of CT and SOD, and then in its significant decrease [30].

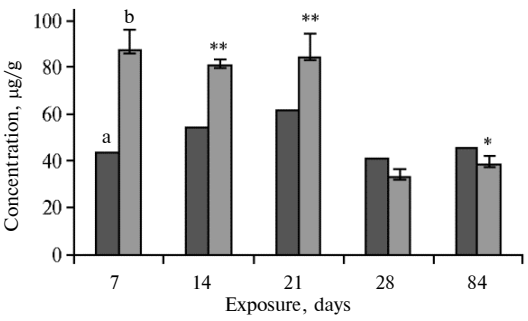

Fig. 2. The amount of silicon in tissues of *Danio rerio* depending on time of exposure to SiO_2 NPs (100 mg/dm^3 water)**:** a — control; b — experiment.
*, ** Differences vs. control are statistically significant at $P < 0.05$ and $P < 0.01$, respectively.

It is therefore difficult to explain the death of *Danio rerio* in the experiment. The reason could be that the ultradispersive nature of oxide particles may lead to their accumulation in the tissues of fish. It has previously been shown in several studies [24, 27, 30]. Such a fact was also observed in our experiments, especially in the first weeks, which is well seen on the example of silicon (Fig. 2). However, further on the silicon content in the body of *Danio rerio* decreased, probably due to homeostasis activity [25]. In

addition, SiO_2 NPs do not prevent the regeneration of tissues [23], but can cause both prothrombotic effects and increased concentrations of fibrinogen, as well as of anti-inflammatory cytokines in the blood plasma [22, 31]. Moreover, the markers of oxidative stress (SOD, CT) are not affected [22]. An interesting explanation of the death of the test organism after the contact with NPs was proposed by S.N. Petrache et al. [26], who linked it with the influence of CeO_2 on *Escherichia coli*, which is accompanied by a decrease in feed intake and subsequent changes in metabolism [32]. Similar data were reported by M.C. Arnold et al. [33].

Thus, the investigated nanoparticles (NPs) possess toxic effects, because their entry into the body of *Danio rerio* (a bioindicator) is accompanied by a total (in case of CeO2 NPs) or partial (in case of SiO2 NPs) loss of the test object at the end of the experiment. In the initial period of exposure, there is a depression of the antioxidant system, but by the end of the 2nd week the signs of adaptation develop. The content of malondialdehyde at a SiO_2 NPs dose of 10 mg/dm^3 increased by 11 times, and at a dose of 100 mg/dm^3 by 12 times; and similar changes were found for CeO_2 NPs.

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