Nanomaterials (NMs) are applied in many spheres related to food products manufacturing including nanodispersed forms of food substances, nano-encapsulates, and nano-micelles, food additives with improved functional characteristics, new packaging materials with enhanced gas-, photo-barrier, and antimicrobial properties. High chemical and catalytic activity of nanoparticles (NPs) and their ability to penetrate through biological barriers and accumulate in a body makes a lot of NMs toxic, and their toxic properties are to be taken into account when assessing safety of the abovementioned products. There are some priority NMs from the point of view of risk assessment and prospective hygienic standardization; they are silver NPs, NPs of amorphous silicon dioxide (aerosil), titanium dioxide NPs, and carbon nanotubes. Results of toxicological-hygienic research performed on laboratory animals revealed that a probable allowable daily dose of silicon dioxide (SiO2) NPs consumed with food should not exceed 1 mg/kg of body weight. And as nanosized SiO2 is used as a food additive, an issue of its hygienic standardization and regulation is truly vital. Silver NPs exert various toxic effects that have been examined in vivo; these effects are based on their ability to promote a dozed release of cytotoxic ions of silver (Ag+) in target organs (first of all, in the liver) under exposure to endogenous oxidants. Signs of silver NPs toxicity become obvious starting from a dose equal to 1 mg/kg of body weight and a maximum no-observed-adverse-effect-level (NOAEL) can be estimated as 0.1 mg/kg. If values are recalculated for a human body taking into account adjusting coefficients, a non-hazardous dose of silver NPs under oral exposure amounts to 70 µg a day. This estimation coincides with the upper permissible level that is fixed in Russia for consumption of silver as a chemical element. Titanium dioxide NPs and carbon nanotubes considered as possible food contaminants in the long term cause population health risks that require profound toxicological-hygienic assessment.

Key words: nanoparticles, silicon dioxide, titanium dioxide, carbon nanotubes, food additives, package, risk assessment.

Introduction

Artificial nanomaterials (NM) are applied in food products manufacturing in several spheres; they are nanodisperse forms of food substances with higher biological availability, digestibility, and compatibility with other components of food products; nano-encapsulates and nano-micelles that allow to obtain water-soluble form of lipophilic nutrients; food additives including those with improved functional properties; new packaging materials with better gas-, photo-barrier, and antimicrobial features. As per forecasts made in the beginning of the 21st century, experts expected hundreds of food products, food additives and ingredients, and packaging materials manufactured with application of nanoparticles (NPs) and NM to appear on the market. However, there are certain problems related to practical implementation of innova-
tive technologies, such as nanotechnological products being more expensive than conventional ones, absence of sufficient regulatory base, and public concern with possible risks associated with effects produced by NP and nano-objects on people and the environment. All the above mentioned resulted in nanotechnologies being applied in food manufacturing in much smaller volumes than it was expected [1, 2]. Our short review focuses on basic risks related to application of nanomaterials in food products.

**Regulatory base for nano-safety**

NMs possess high chemical and catalytic activity and they are able to penetrate through biological barriers and accumulate in a body; these properties make many NMs toxic, and it should be taken into account when assessing possible risks associated with their effects on a body. Volumes of NMs production and their insolubility in water and biological media are considered to be their basic risks criteria in the EU countries, the USA, etc. In Russia a system of control over NMs safety was created; the system includes about 50 various regulatory and methodological documents approved by Rospotrebnadzor. Apart from the above-mentioned factors, it considers and takes into account such NM-related risk factors as their well-proven biological activity and toxicity, ability to penetrate a body and accumulate in organs and systems, migrate together with environmental objects, and exert certain influence on ecological systems [1, 3].

According to the CU TR 021/2011\(^1\) NM-containing food products or products manufactured with nanotechnologies and therefore having certain properties that make them principally different from products manufactured with "conventional" technologies are to be considered "innovative products" (new type products), and it is obligatory to assess their conformity through state certification. At present, there are about 60 nanoindustry products that have been certified in the RF and the Customs Union countries as innovative food products. Basically, they are biologically active additives (BAA) that contain nano-sized food substances; complex food additives such as emulsifiers, and certain technological aids and composite packaging materials that contain nano-clays. Besides, elements of nanotechnologies are widely used in membrane processing (nano- and ultra-filtration) of milk, lactoserum, juices, drinking water, etc. However, food products obtained with such technologies are conventional as per their structure and properties.

We analyzed a range of food products distributed on the market together with regulatory documents that fix requirements to their structure and safety; our analysis revealed that volumes of NPs and NMs application in food manufacturing were probably underestimated. Here we primarily mean that there are certain food additives that can contain nano-substances but sizes of their particles are not controlled or regulated by either Russian or foreign regulatory documents. Among them, there are such most interesting permissible food additives as amorphous silicon dioxide and titanium dioxide. Application of colloid metallic silver with particles smaller than 100 nm and multi-wall carbon nanotubes (MW CNTs) in food products is also of great interest if it comes to probable health risks.

**Amorphous silicon dioxide**

Amorphous silicon dioxide (SiO\(_2\)), or E551, is applied as a substance that prevents food products from caking and as a carrier. CU TR 029/2012\(^2\) fixes its permissible concentrations in spices (not more than 30 g/kg), food

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\(^1\) CU TR 021/2011. On food products safety: The Customs Union Technical Regulations [web-source] // KODEKS: an electronic fund of legal and reference documentation. – URL: http://docs.cntd.ru/document/902320560 (date of visit January 16, 2017).

\(^2\) CU TR 029/2012. Requirements to safety of food additives, flavoring agents, and technological aids (last supplemented on September 18, 2014) [web-source] // KODEKS: an electronic fund of legal and reference documentation. – URL: http://docs.cntd.ru/document/902359401 (date of visit January 16, 2017).
products that are tightly wrapped in foil (30 g/kg), icing sugar (10 g/kg), salt and its substitutes (10 g/kg), cheese and cheese products (10 g/kg), flavoring agents (50 g/kg). Food raw materials that contain E551 are allowed for use in manufacturing children's nutrition. E551 content is not regulated in pelleted food products, biologically active additives (BAA), and sugary confectionary (except chocolate). Apart from above mentioned food products, amorphous SiO2 can possibly enter a body with medications and cosmetics (toothpastes etc.).

Fine-dispersed pyrogenic E551 (aerosil) accounts for a considerable part of the overall volumes of applied E551; specific surface area of aerosil is equal to 300–380 m²/g, that is, according to a simplest geometric calculation, it consists of nanoparticles (NPs). Experts analyzed the structure of this E551 form with transmission electron microscopy (TEM) and atomic force microscopy, dynamic light scattering and spectrum acoustics; the analysis revealed that this material on its ultrastructural level was made of weakly bound (agglomerated) spherical NPs sized 20–60 nm [4]. At the same time, JECFA specification for this food additive [5] doesn't contain any information on a size of its particles, and this size, as a rule, is not controlled and declared by food products manufactures; consequently, a considerable part of food products distributed on the market can contain this substance in its nano-form. As per data given in [6], at present food exposure of a man to SiO2 NPs can exceed 1.8 mg/kg of body weight per day.

Experimental research performed on laboratory animals revealed that SiO2 NPs were biologically accessible under introduction into the gastrointestinal tract [6]. A sub-acute 92-day experiment performed on rats showed that when nano-sized SiO2 of "Aerosil" type was introduced in a dose equal to 100 mg/kg of body weight, animals had leucopenia, a share of T-helpers decreased, and a share of cytotoxic lymphocytes grew up, immune-regulatory index (CD4/CD8) also went down, and an imbalance occurred between pro- and anti-inflammatory cytokines, such as TNF-α and IL-10; all the above mentioned changes indicated there was an adverse effect on the immune system [7]. Morphologic examination revealed that the mucous tunic of the small intestine was the primary target organ for SiO2 NPs introduced with food; experts observed there a massive lymph-macrophage and eosinophilic infiltration of villi that was a sign of a stronger local immune reaction [8]. Taking into account 2 tenfold assurance factors when transferring data obtained in vivo model onto a human body, we still understand that the possible allowable daily dose of SiO2 NPs introduced with food shouldn't exceed 1 mg/kg of body weight, and it calls for obligatory hygienic standardization and regulation of nano-sized SiO2, used as a food additive.

**Nano-sized titanium dioxide**

Titanium dioxide TiO2 is applied in food industry as a white dye E171 in fish, dairy, and confectionary products as well as in BAA shells and capsules. This substance can also be found in cosmetics sunscreens, varnish-and-paint products, pharmaceuticals, and photocatalytic neutralizers — air purifiers. JECFA specification for this food additive [9] doesn't contain any information on sizes of its particles. Commercial TiO2 products that are distributed on the market are two crystalloid modifications, rutile and anatase [10]. The latter is highly likely to contain NPs. Given all that, we can state that TiO2 NPs can most probably be introduced into a body, notably with food or BAA [11].

Experts performed an experiment on animals that involved inhalation exposure to TiO2 NPs and this exposure led to emphysema-like damage to the lung tissues [12]. When TiO2 NPs in a dose equal to 1 mg/kg of body weight or more were introduced into laboratory animals orally during a sub-acute experiment, experts revealed disorders in functioning of energy and amino-acid metabolism enzymes [13], P 450 cytochrome system [14], immune system [15, 16], and
liver proteome [17]. When these NPs enter the intestines, they can damage enterocytes and become biologically accessible to a certain extent [18, 19]. Maximum NOAEL (no-observed-adverse-effect level) of TiO₂ NPs for rats in anatase and rutile forms amounts to less than 1 mg/kg of body weight during a 30-day experiment. And here it is impossible to precisely assess exposure of a man to these NPs, as we don't have any idea on what part of E171 food additive is a nano-material. Available data on oral toxicity of nano-sized TiO₂, as opposed to its traditional form ("titanium white" with micron-sized particles [10]), allowed French Agency for Food, Environmental and Occupational Health & Safety (ANSES) to make a proposal in 2017 to reconsider nano-sized E171 safety for people [20].

**Nano-sized colloid silver**

By 2016, 20 various biologically active additives that contain metallic silver NPs have been registered in the RF; this active component in BAA is a source of silver micromolecule. Besides, silver NPs can migrate into food products from packaging materials with anti-microbe properties. Valid legislation forbids to apply silver NPs in food manufacturing as disinfectants (preservatives or technological aids). However, as there are a lot of developments in the sphere, we can assume that such products can be registered and occur on the market some time in future. Silver NPs are the most widely used NM in production of perfume and cosmetics, varnish-and-paint, and disinfectants (by 2016 more than 130 products of the kind have been registered in the RF), and it makes involuntary contamination of food products with these NPs quite possible. As per data taken from literature, in 2011 the overall silver NPs production in the world amounted to more than 500 tons in terms of Ag, but in 2015 it could well exceed 1,000 tons and it corresponds to about 140 mg/kg per each person in the world.

As per data obtained via TEM, sizes of silver NPs are, as a rule, from 8–10 to 60–80 nm; these particles are round-shaped, sometimes they can have triangle or polyhedral shape, their contours are sharp, and their electron density is high. Industries produce several types of silver NPs. First of all, there is so called "ions-free silver" obtained via laser ablation or via electric explosion of a metal target. Secondly, they produce "cluster" silver that is synthesized through a photocatalytic procedure with polyvinylpyrrolidone (food additive E1201); and finally, there is colloid silver obtained via chemical reduction (under exposure to aldehydes) and stabilized with citric acid anion (E330) and colloid silver obtained via so called "biochemical synthesis" when silver salt is reduced with quercetin and sodium dioctyl sulfosuccinate (E480).

Silver NPs that are introduced into the gastrointestinal tract with food and water can be absorbed in it (biological accessibility amounts to about 1–3% as per data of radioisotopic research) [21, 22]. Absorbed NPs are distributed in organs and systems and their maximum quantity is accumulated in the liver and spleen; small quantities of NPs can penetrate through the blood-brain barrier in the brain and persist there for a long time [23]. Research performed with radioisotope markers revealed that small quantities of silver NPs (less than 1% of a consumed dose) can penetrate through the fetoplacental barrier of pregnant rats and accumulate in fetuses as well as be excreted with breast milk [24].

As per data obtained in multiple experiments that are described in literature, silver NPs produce toxic effects on eukaryote cells in a culture, water and soil organisms, and laboratory animals under inhalation, epicutaneous, and oral exposure.

Experts give rather controversial data on toxic impacts exerted by silver NPs under multiple oral introduction into laboratory animals. Thus, the following research [23] didn't reveal any signs of silver NPs toxicity for rats in a dose equal to 90 mg/kg of body weight. On the other hand, when silver NPs were introduced in a dose that exceeded 125 mg/kg of body weight, they produced toxic effects on rats' liver [25]. When mice were exposed to silver NPs in doses higher...
than 1 mg/kg of body weight, histopathologic changes occurred in their liver and kidneys [26]. Some adverse shifts in integral and biochemical parameters were detected in rats that were exposed to silver NPs in doses equal to 1 mg/kg of body weight and doses were introduced daily during a month [27]. As per data taken from [28], a threshold dose of silver NPs that produced adverse effects on mice amounted to less than 0.01 mg/kg.

Scientific Research Institute of Nutrition and Rospotrebnadzor's Federal Scientific Center for Medical and Preventive Health Risk Management Technologies performed joint research to examine silver NPs that were the most widely spread in Russia and had the greatest practical significance, namely silver stabilized with polyvinylpyrrolidone. The substance was examined via modeling its intragastric introduction into the gastrointestinal tract of rats and mice in doses ranging from 0.1 to 10 mg/kg of body weight recalculated per silver; the experiments were subacute and lasted for 90–92 days. Various dose-dependent effects on behavioral reactions were revealed in male BALB/c mice with Open field Animal test; these effects included a decrease in frequency of actions that required physical efforts and shorter periods of time spent on such actions; greater anxiety as per parameters of frequency and duration of orientation and exploration activities and grooming. Morphological research revealed changes in liver and spleen tissues, and, to a smaller extent, heart and kidneys tissues; a range of these changes and their intensity grew together with an increase in NMs doses [29]. A similar experiment performed on male Wistar rats allowed to reveal adverse shifts under exposure to a NM dose equal to 10 mg/kg of body weight recalculated per Ag as per parameters of body weight growth, relative lungs weight, average volume of an erythrocyte, hemoglobin concentration in erythrocytes, and relative fraction of neutrophils and lymphocytes. When NM doses were within 1–10 mg/kg of body weight, the following effects were detected in rats' liver: there was an increase in activity of key enzymes of the 1st and 2nd stages in xenobiotics detoxification system, a decrease in activity of common arylsulphatase A and B, and β-galactosidase (but there were no changes in their non-sedimentary activity). Lower uric acid concentration and more active alkaline phosphatase were detected in blood plasma. Sub-acute introduction of silver NPs didn't lead to any significant changes in normal microbiota structure, but still it inhibited growth of certain transitory components, including opportunistic microorganisms [30]. Experts analyzed microelement status of rats that were exposed to silver NPs and revealed dose-dependent accumulation of Ag in the liver, kidneys, and spleen and it was accompanied with an authentic decrease in Cu concentration in the liver, a decrease in Zn and Co concentration and an increase in Mn concentration in the liver, an increase in Cd, Cr and Ni concentration in the spleen. Parameters showing proper provision with Se (excretion with urine, concentration in blood plasma, and activity of glutathione peroxidase erythrocytes) were authentically lower in rats that received silver NPs in doses equal to 1–10 mg/kg of body weight and it proves there is antagonism between Ag (contained in NPs) and Se [31]. Morphological changes in rats' liver, spleen and kidneys became more apparent as NM doses grew. And also there was an edema in the liver, eosinophilic and lymph-macrophage infiltration in the hepatoporal tracts, middle-sized and large fatty vacuoles in hepatocytes cytoplasm. A threshold NM dose that induced such changes amounted to not more than 1.0 mg/kg of body weight [32].

Obtained experimental data are well in line with a hypothesis about a basic mechanism of toxic effects produced by silver NPs in vivo: these particles are assumed to induce a dose-release of cytotoxic silver ions (Ag⁺) under exposure to endogenous oxidizers (superoxide-anion, peroxides, peroxynitrite, hypochlorite-ion and others) produced by
mononuclear cells in relevant target organs (first of all, the liver). And here an asserted effect produced by silver NPs on microbiota components in the recovery medium of the large intestine contents turns out to be rather insignificant.

Obtained data allowed to come to a conclusion that significant signs of silver NPs toxicity become obvious starting from a dose equal to 1 mg/kg of body weight introduced orally, and a maximum no-observed-adverse-effect level (NOAEL) can be estimated as being equal to 0.1 mg/kg of body weight. When we recalculate this dose for a human body and take into account two tenfold assurance factors, we realize that a safe NPs dose recalculated per silver should amount to 0.001 mg/kg that corresponds to 70 µg of silver per day for a man with body weight equal to 70 kg. We should note that this estimation coincides with the upper permissible level of consumption for silver as a chemical element that is now accepted in the RF.

**Carbone nanotubes**

Carbone nanotubes (CNTs) have some unique physical and chemical properties and are now being widely used in composite construction materials, ion current sources, microelectronics, and other products. There are proposals on CNTs application as plant growth stimulators [33], agrochemicals carriers [34], agents for controlling rodents-depredators [35], and components of packaging for food products [36]. Data on oral toxicity of both one-wall CNTs and multi-wall ones are fragmentary. There is some evidence that they exert adverse influence on male reproductive sphere [35], and induce an increase in hepatic enzymes levels, antioxidant stress, and unfavorable changes in lipoproteins levels [37]. A lot of effects produced by CNTs in subacute experiments are more obvious under exposure to extremely low doses (less than 0.1 mg/kg of body weight) than high ones (50 mg/kg of body weight and higher). Obtained data indicate that food contamination with CNTs is a probable health risk factor that requires more profound toxicological and hygienic assessment.

**Conclusion**

All the reviewed data on probable health risks caused by NPs and NMs occurrence in food products allow us to formulate the following recommendations: 1) it is advisable to include statements on obligatory declaring of particles size for food additives into valid regulatory documents that allow application of nano-substances; it is also advisable to make specific marking on food products that contain artificial NPs and NMs; it is necessary to work out hygienic standards for concentrations of priority NMs (silicon and titanium dioxide, CNTs, and colloid silver) in consumer products as well as interstate standards on procedures for controlling contents of artificial nanocomponents in food products.

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