Nanoparticles as Potential Agents of Chemical and Biological Weapons

УДК 606; 601.4; 608.3
https://doi.org/10.35825/2587-5728-2022-6-4-304-319
https://elibrary.ru/cgefod

Ján Lakota

Centre of Experimental Medicine, SAS, Dúbravská cesta 9, 841 04 Bratislava, Slovakia Faculty of Management Comenius University, Odbojárov 10, 820 05 Bratislava, Slovakia

Received 25 October 2022. Accepted 23 December 2022

The wide distribution in industry, medicine, agriculture, and other areas of human activity of nanoscale objects raise the question of the possibility of their dual use, which in this work means the use for deliberate mass destruction of people. The *aim of the work* is to consider nanoparticles as potential agents of chemical and biological weapons. Nanoparticles of any type have been shown to have biological activity. This is due to an increase in the surface activity of particles during the transition from microscale to nanoscale and their ability to penetrate the cell, especially cell nucleus. Being non-biological objects, interacting with cell receptors, distorting intracellular signaling pathways and affecting the genetic regulation of the cell, they can cause a variety of pathological effects (oxidative stress, neuroinflammation, neurodegeneration, etc.). Therefore, with the transition from microscales to nanoscales, essentially remaining chemical compounds, particles of non-toxic materials can transform into potential biological and chemical damaging agents. The existing possibilities of their mass use through the respiratory system, skin, gastrointestinal tract and through the introduction of injectable forms of drugs suggest that based on damaging agents of this type, weapons of mass destruction of a new type that are not subject to the Conventions on the Prohibition of Chemical and Biological Weapons can be developed. It is necessary to start developing methods for detecting nanoparticles and other nanoobjects in various environments surrounding a person, food and dosage forms

Keywords: *genotoxic effects; intracellular signaling pathways; nanomaterials; nanoparticles; nanotechnology; NP toxicity; oxidative stress; weapon of mass destruction.*

For citation: *Lakota Ján. Nanoparticles as Potential Agents of Chemical and Biological Weapons // Journal of NBC Protection Corps. 2022. V. 6. № 4. P. 304–319. EDN: CGEFOD. https://doi.org/10.35825/2587-5728-2022-6-4-304-319*

Introduction

On December 26th, 1959, Richard Feynman gave a classic talk at the annual meeting of the American Physical society at California Institute of Technology entitled «There's Plenty of Room at the Bottom». This is generally considered to be a seminal event in the history of nanotechnology. In particular, he said: «…When we get to the very, very small world - say circuits of seven atoms - we have a lot of new things that would happen that represent completely new opportunities for design. Atoms on a small scale behave like nothing on a large scale, for they satisfy the laws of quantum mechanics. So, as we go down and fiddle around with the atoms down there, *we are working with different laws, and we can expect to do different things*.»[1]

The *aim of the work* is to consider nanoparticles as potential agents of chemical and biological weapons.

Main

For an introduction to the problematic, we will use the information which is freely available on internet[2]. According to IUPAC proposed terminology for biologically related polymers, the IUPAC defined a nanoparticle as «a particle of any shape with dimensions in the 1×10^{-9} and 1×10^{-7} m range» [1]. In general, the unique properties of nanomaterials are attributed to quantum effects,

[1] https://calteches.library.caltech.edu/1976/ (date: 31.12.2021).

[2] https://en.wikipedia.org/wiki/Nanoparticle (date: 25.18.2022).

larger surface area, and self-assembly. Quantum effects can begin to dominate the behavior of matter at the nanoscale – particularly at the lower end – affecting the optical, electrical, and magnetic behavior of materials. This is attributed to the fact that matter at nanoscale no longer follows laws of classical physics. It rather follows the laws of quantum mechanics, which can be explained by size effect, quantum confinement and density of states (DOS). Secondly, nanomaterials have a larger surface area when compared to the same mass of material produced in bulk form. The smaller the particle size, the more the proportion of surface atoms, leading to an increased reactivity due to rise in number of the active sites. In some cases, inert materials in their bulk form turn out to be reactive when produced in their nanoscale form. Effect of larger surface area applies to all nanomaterials in different shapes, whether nanocoatings, nanowires, nanotubes, or nanoparticles. Thirdly, self-assembly is a process that rests on the organization of components producing an ordered pattern or structure. At nanoscale it reflects the information encoded in individual molecules such as shape, charge, polarizability, and so on that determine their attractive or repulsive interactions. Molecular self-assembly usually takes advantage of supramolecular interactions (ionic, hydrophobic, van der Waals, hydrogen, and coordination bonds), but can also make use of kinetically labile covalent bonds. This intrinsic mobility leads to ordered nanostructures upon equilibration between aggregated and nonaggregated states, thus providing several interesting properties such as error correction, self-healing, and high sensitivity to external stimuli [2]. By Gleiter's definition the size effects in microstructures arise when its size d is reduced up to a critical value when scale length of physical phenomenon (free path length of electrons, phonons, etc.; coherent length, screening length, etc.) becomes to be equal to or compatible with characteristic size (length, thickness, diameter) of building blocks of microstructures. Basically, the properties of a material are characterized by a specific «length scale», usually on the nanometer dimension. If the physical size of the material is reduced below this length scale, its properties change and become sensitive to size and shape. Size effects constitute a peculiar and fascinating aspect of nanomaterials. The effects determined by size pertain to the evolution of structural, thermodynamic, electronic, spectroscopic, electromagnetic, and chemical features of these finite systems with changing size, which are different from the bulk and their isolated atoms/molecules. Classical laws of physics fail to explain the origin of the novel properties of materials in this size regime. Moreover, nanocrystals possess a high surface area and a large fraction of the atoms in a nanocrystal are on its surface, which in turn depends on the size of the particle (30% for a 1-nm crystal, 15% for a 10-nm crystal) [3]. Size effects constitute a peculiar and fascinating aspect of nanomaterials. Nanomaterials are closer in size to single atoms and molecules than to bulk materials, and to explain their behavior it is necessary to use quantum mechanics. Basically, quantum mechanics is a scientific model that was developed for describing the motion and energy of atoms and electrons. The most salient quantum effects together with other physical properties arising at nanoscale are as follows:

Due to the smallness of nanomaterials, their mass is extremely small and gravitational forces become negligible. Instead, electromagnetic forces are dominant in determining the behavior of atoms and molecules.

Wave-corpuscle duality of matter: For objects of very small mass, such as the electrons and nucleons, wave-like nature has a more pronounced effect. Thus, electrons and nucleons exhibit wave behavior, and their position is represented by a wave (probability) function.

One of the consequences is a phenomenon called «tunneling». Classical physics states that a body can pass a barrier (potential barrier) only if it has enough energy to «jump» over it. Therefore, if the object has lower energy than that needed to jump over the energy barrier (the «obstacle»), in classical physics, the probability of finding the object on other side of the barrier is zero. On the other hand, in quantum physics a particle with energy less than that required to jump the barrier has a finite probability of being found on the other side of the barrier mainly due to the tunneling effect (Figure 1). It should be noted that tunneling is the penetration of an electron (or a nucleon) into an energy region that is classically forbidden i.e., «it does not work». To have tunnel effect, the thickness of the barrier (i.e., energy potential) must be comparable to the wavelength of the particle; in other words, electron (or quantum) tunneling is attained when a particle (an electron) with lower kinetic energy is able to exist on the other side of an energy barrier with higher potential energy, thus defying a fundamental law of classical physics [4]. Therefore, this effect can be observed only at a nanometer level.

An interesting feature of quantum mechanics laws which «govern» in the nanoworld is the observation of magnetism in non-magnetic nanoparticles Enhanced magnetism in clusters of elements that are ferromagnetic as bulk solids such as iron, cobalt, or nickel is well known and has been demonstrated in Stern–Gerlach deflection experiments. Theoretical studies predicted high spin ground states for clusters of up to 13 atoms even in nonmagnetic elements such as Pd and Pt.

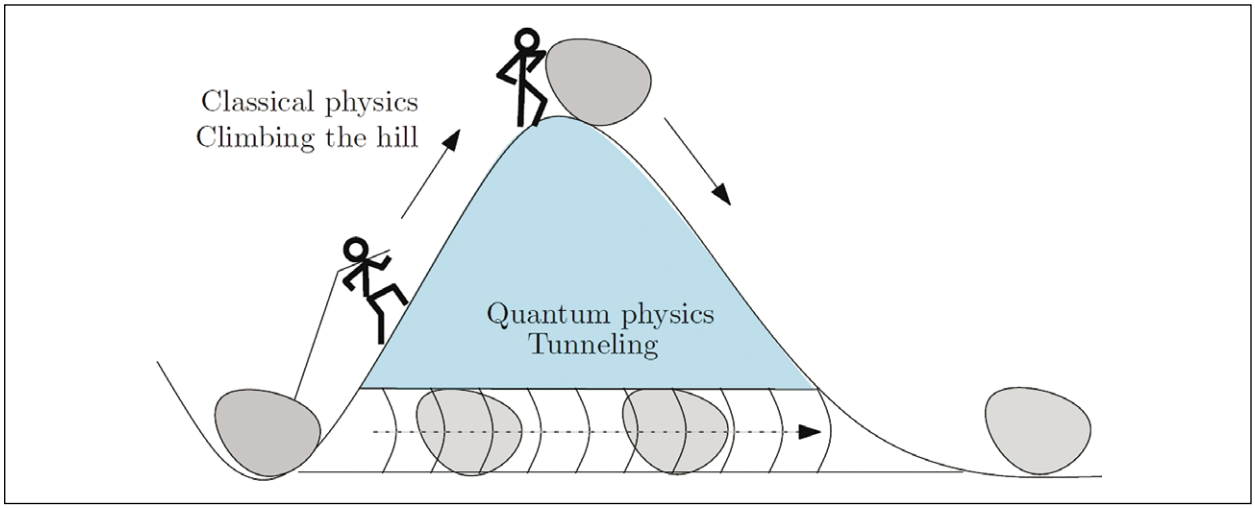

Figure 1 – *Quantum tunneling. Quantum tunneling is the effect when a quantum mechanical particle faces an energy barrier but after the energy barrier there is an energy downhill, and it has a probability of «passing through» the energy hill. (https://i.stack.imgur.com/VuqhM.png; date: 11.09.2022)*

Nanoparticles comprising several hundred atoms of Au, Pd, and Pt embedded in a polymer reveals magnetic moments corresponding to several unpaired electron spins per entire particle [5].

Chemical properties of nanomaterials also change at nanoscale. As the percentage of surface atoms in nanoparticles is large compared with bulk objects, the reactivities of nanomaterials are more than bulk materials [6]. The following are some of the reasons responsible for the change in chemical properties at nanoscale:

The preponderance of surface is a major reason for the change in behavior of materials at the nanoscale. As up to half of all the atoms in nanoparticles are surface atoms, properties such as electrical transport are no longer determined by solid-state bulk phenomenon.

The atoms in nanomaterials have a higher average energy than atoms in their bulk counterparts because of the larger proportion of surface atoms. For example, catalytic materials have a greater chemical activity per atom of exposed surface as the catalyst is reduced in size at the nanoscale.

Defects and impurities may be attracted to surfaces and interfaces, and interactions between particles at those small dimensions can depend on the structure and nature of chemical bonding at the surface.

Molecular monolayer may be used to change or control surface properties and to mediate the interaction between nanoparticles.

For an illustration we show change in surface area on the reduction of size (Table 1).

Types of nano materials: Nanoparticles (NPs) are broadly divided into various categories depending on their morphology, size, and chemical properties[3].

Classification based on dimension:

Zero Dimensional Nanomaterials. Zero-dimensional (0-D) structures include materials with all dimensions at nanoscales of 1 to 100 nm. Most of these materials are spherical in shape; however, cubes and polygonal shapes with nano-dimensions are also found under this class.

One Dimensional Nanomaterials. One-dimensional (1-D) structures are materials with two dimensions at the nanoscale and the other

Table 1 – *Change in Surface Area on Size Reduction**

Size of the cube side	Number of cubes	Collective surface area
1 m	1	6 m^2
0.1 m	10^3	60 m^2
0.01 m	10^6	600 m^2
0,001 m (1 mm)	10^9	6000 m^2
10^{-9} m (1 nm)	10^{27}	6×10^9 m^2 (6000 km^2)

**https://en.wikipedia.org/wiki/Quantum_nanoscience (date: 11.09.2022)*

[3] Nanomaterials: Types & Examples. https://studiousguy.com/nanomaterials-types-examples/ (date: 11.09.2022).

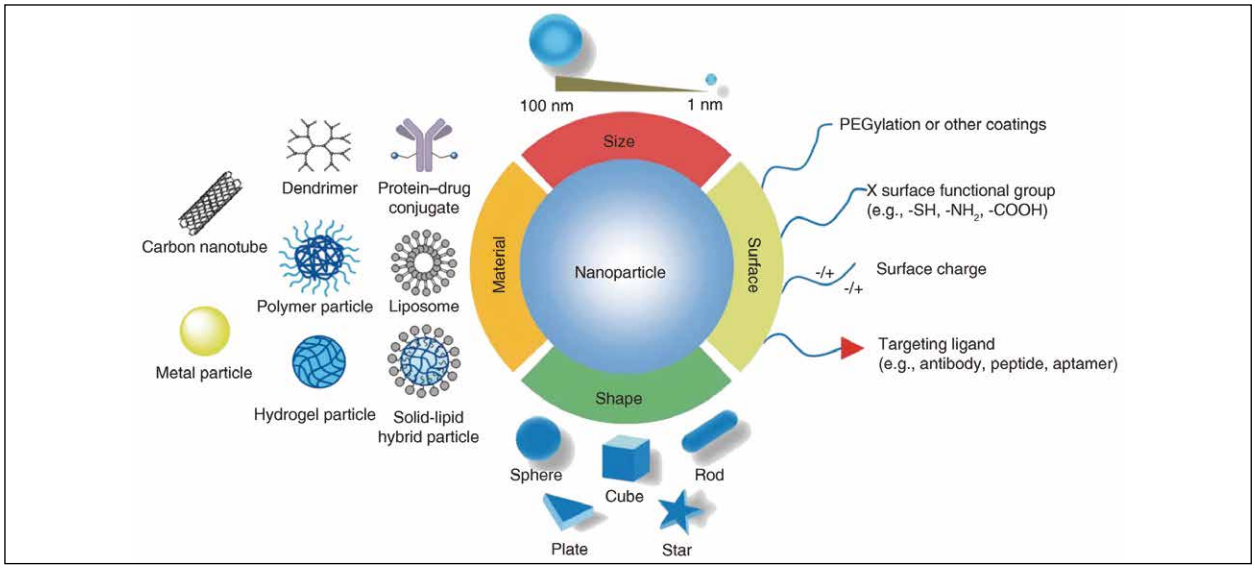

Figure 2 – *Examples of some nanoparticles with different chemical composition. (https://www.futuremedicine.com/cms/10.2217/nnm-2020-0132/asset/images/large/figure2.jpeg; date: 11.09.2022)*

dimension is beyond the nanoscale (>100 nm), meaning that one dimension is outside the nanoscale.

Two Dimensional Nanomaterials. Two-dimensional (2-D) structures are materials with one dimension at the nanoscale, and two of the dimensions are not confined to the nanoscale. 2-D nanomaterials exhibit platelike shapes.

Three Dimensional Nanomaterials. Three-dimensional (3-D) structures are materials having three arbitrary dimensions beyond the nanoscale (>100 nm). However, these materials possess a nanocrystalline structure or involve the presence of peculiarities at the nanoscale. They can be composed of multiple arrangements of nanosize crystals, most typically in different orientations.

Classification based on Chemical Composition (Figure 2):

Organic Nanomaterials. As the name suggests, organic nanomaterials are the class of carbon-based nanomaterials whose covalent interactions make them compatible for biomedical purposes. In recent years, a significant increase in the studies focused on the uses of nanomaterials with the organic structure for regeneration of bone, cartilage, skin, or dental tissues. There is numerous evidence for several advantages of using natural or synthetic organic nanostructures in a wide variety of dental fields, from implantology, endodontics, and periodontics, to regenerative dentistry and wound healing. Biomedicine stands to profit from the use of organic nanocarriers. Some of the advantages of the nanostructures include higher colloidal stability, improved dispersibility, and improved surface reactivity. The most prominent characteristic of organic nanomaterials continues to be their ability to control the delivery of drugs such as small molecule drugs, proteins, and DNA; however, there are several other potential applications of organic nanomaterials, such as polymers for coatings, nanoscale optoelectronics, and other technical applications.

Inorganic Nanomaterials. Inorganic nanomaterials are the class of nanomaterials primarily composed of metal-based nanomaterials, metal-oxide-based nanomaterials, ceramics, a few non-metals-based nanomaterials, and other nanostructured materials whose central core is composed of inorganic materials that define their fluorescent, magnetic, electrical, and optical properties. Numerous studies have shown that inorganic nanomaterials including gold nanoparticles, nonporous and mesoporous silica nanoparticles, magnetic nanoparticles, and quantum dots have shown great potential in bioimaging, targeted drug delivery, cancer therapies, and other technological sectors, such as biosensing, chemical sensing, electronics, and optical applications.

Hybrid Nanomaterials. Hybrid nanomaterials are defined as unique chemical conjugates of organic and/or inorganic materials, i.e., these are mixtures of two or more inorganic components, two or more organic components, or at least one of both types of components. The resulting material is not a simple mixture of its components but a synergistic material with properties and performance to develop applications with unique properties determined by the interface of the components at the molecular or supramolecular level. Its functionality is associated with the improvement of physicochemical properties. For the electrochemical or biochemical properties through the optimization mainly of magnetic,

electronic, optical, and thermal properties or a combination of them (see Figure 2).

We present some examples of nanoparticles in more detail [7].

Carbon-based NPs. Fullerenes and carbon nanotubes (CNTs) represent two major classes of carbon-based NPs. Fullerenes contain nanomaterial that are made of globular hollow cage such as allotropic forms of carbon. They have created noteworthy commercial interest also in nanocomposites for many commercial applications such as fillers, efficient gas adsorbents for environmental remediation, and as support medium for different inorganic and organic catalysts. CNTs serve as target-specific delivery of drugs and therapeutic agents to the site of action - delivery of vaccines, genetic material, proteins. It should be noted that at least two types of aqueous dispersible graphene, corresponding to single-layer (SLG) and few-layer graphene (FLG), are biodegraded by human myeloperoxidase (hMPO) mediated catalysis. Graphene can be degraded either by recombinant hMPO or by hMPO secreted by activated neutrophils [8].

Metal NPs. Metal NPs are purely made of the metal's precursors. Due to well-known localized surface plasmon resonance (LSPR) characteristics, these NPs possess unique optoelectrical properties. NPs of the alkali and noble metals i.e., Cu, Ag and Au have a broad absorption band in the visible zone of the electromagnetic solar spectrum. The facet, size and shape-controlled synthesis of metal NPs is important in present day cutting-edge materials. Due to their advanced optical properties, metal NPs find applications in many research areas. Gold NPs coating is widely used for the sampling of SEM, to enhance the electronic stream, which helps in obtaining high quality SEM images. There are many other applications, which are deeply discussed in applications section of this review [8].

Ceramics NPs. Ceramics NPs are inorganic nonmetallic solids, synthesized via heat and successive cooling. They can be found in amorphous, polycrystalline, dense, porous, or hollow forms. These NPs are getting great attention of researchers due to their use in applications such as catalysis, photocatalysis, photodegradation of dyes, and imaging applications.

Semiconductor NPs. Semiconductor materials possess properties between metals and nonmetals. Semiconductor NPs possess wide bandgaps and therefore showed significant alteration in their properties with bandgap tuning[4]. Therefore, they are very important materials in photocatalysis, photo optics and electronic devices. As an example, variety of semiconductor NPs are found exceptionally efficient in water splitting applications, due to their suitable bandgap and band edge positions.

Polymeric NPs. These are normally organic based NPs, and, in the literature, a special term «polymer nanoparticle (PNP)» is used. They are mostly nanospheres or nano capsular shaped. The former are matrix particles whose overall mass is generally solid, and the other molecules are adsorbed at the outer boundary of the spherical surface. In the latter case the solid mass is encapsulated within the particle completely. The PNPs are readily functionalize and thus find bundles of applications.

Lipid-based NPs. These NPs contain lipid moieties and effectively using in many biomedical applications. Generally, a lipid NP is characteristically spherical with diameter ranging from 10 to 1000 nm. Like polymeric NPs, lipid NPs possess a solid core made of lipid and a matrix contains soluble lipophilic molecules. Surfactants

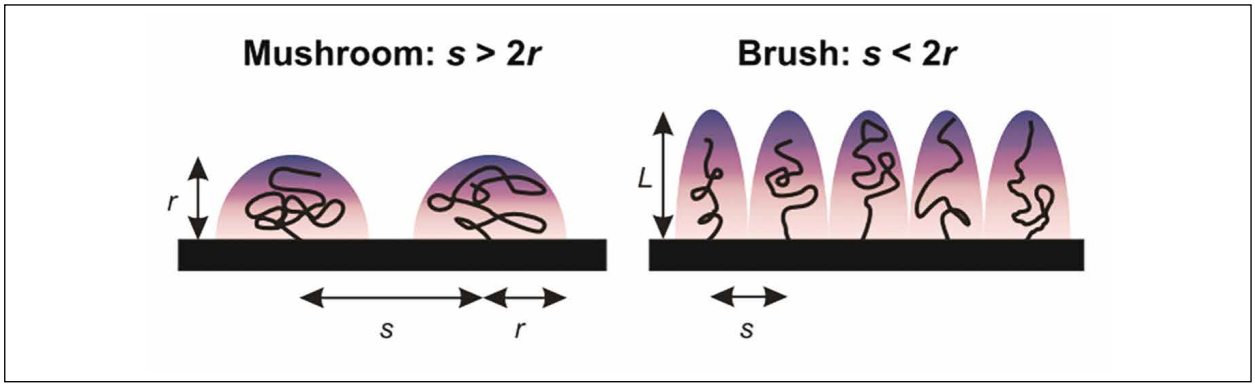

Figure 3 – *Mushrooms versus Polymer Brushes: a sketch illustrating how surface-tethered polymer chains can take on either «mushroom» - like or «brush» - like molecular conformations, depending on how closely packed the polymer chains are. The mushroom regime occurs when the distance between neighboring chains s, is greater than twice the radius of the polymer. The brush regime is encountered when s < 2r and the polymer chains are extended away from the surface at a height of L [9]*

[4] Band gap. https://en.wikipedia.org/wiki/Band_gap (date: 10.07.2022).

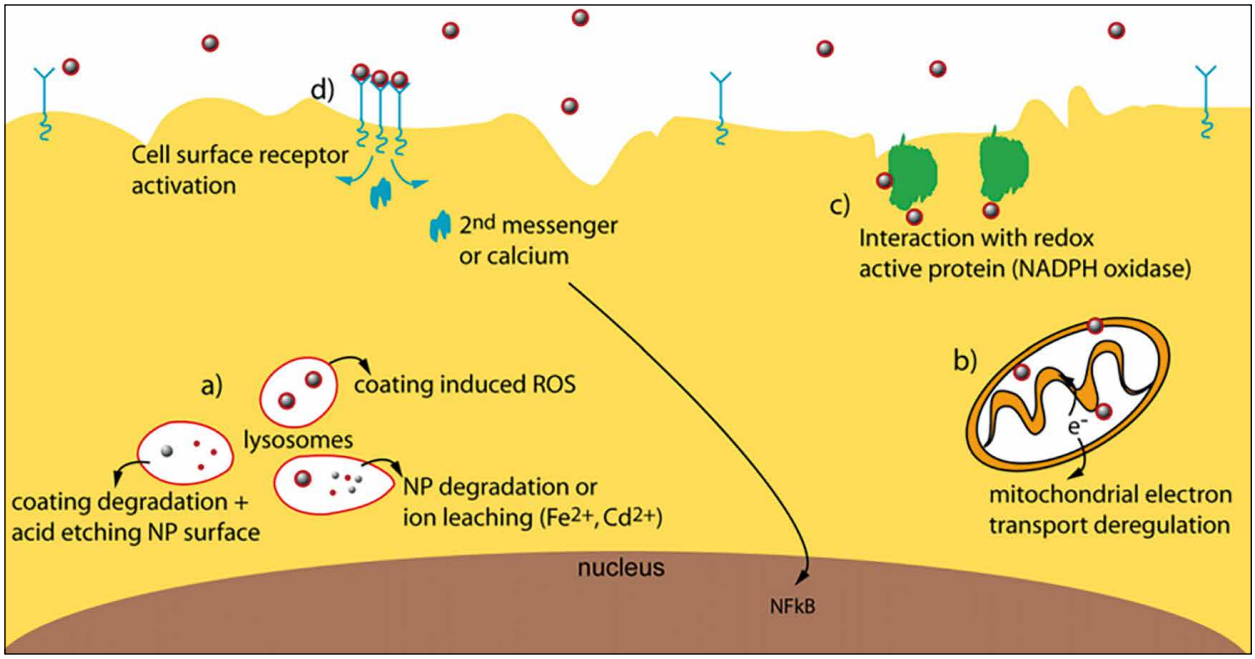

Figure 4 – *Schematic overview of the different pathways by which NPs can induce oxidative stress. (a) NPs l present in the acidic environment of lysosomes can induce ROS by direct reactivity of their surface coating, degradation of the coating and direct interaction of the acidic media on the metal surface or degradation of the whole nanoparticle and production of ions (Fe^{2+}, Cd^{2+}) which can induce ROS species by various chemical reactions. (b) Nanomaterial can also directly interact with oxidative organelles such as the mitochondria by destabilizing the outer membrane, deregulating the mitochondrial membrane potential and hereby disrupting the electron transport chain of the oxidative phosphorylation. (c) Nanoparticles can directly interact with redox active proteins such as NADPH oxidase and hereby stimulate large ROS production in cells of the immune system. (d) Interaction of nanoparticles with surface located receptors can lead to receptor activation and triggering of intracellular signaling cascades (activation of second messenger or calcium waves), finally resulting in expression of stress response genes which can upregulate ROS [11]*

or emulsifiers stabilized the external core of these NPs. Lipid nanotechnology is a special field, which focus the designing and synthesis of lipid NPs for various applications such as drug carriers and delivery and RNA release in cancer therapy.

The molecular chain between the surface binding and functional group not only determines the thickness of the surface layer, but also contributes to its stability. One of the most common spacers, widely used in the design of biologically compatible and stable NPs and nanomaterials is polyethylene glycol (PEG) and the process of PEG addition to nanomaterial is known as PEGylation. PEG has proven to be exceptionally good for stabilization of nanomaterials in biological fluids, preventing their agglomeration and increasing hydrophilicity of the whole system. PEGylation is used to increase the circulation time and the probability of reaching the biological target and to reduce the uptake by the reticuloendothelial system. PEG increases the «stealth» of the nanomaterials by preventing the binding of the opsonin proteins (opsonization), If the binding of opsonins to NPs is prevented, macrophages do not perceive them as biological garbage or dangerous species and they are able to circulate in the blood until they reach the target. The behavior of the surface (PEG) layer strongly depends on the density of the individual PEG linkers (Figure 3).

NPs with brush conformation generally have longer circulation time in human blood, since dense packing prevents the protein adsorption. PEG is not biodegradable, thereby it can accumulate in the cells. Furthermore, it can be degraded into smaller fragments under the influence of light, heat or shear stress. The resulting degradation products might affect the properties of nanomaterials and cause tissue damage.

It is increasingly recognized that treating patients with PEGylated drugs can lead to the formation of antibodies that specifically recognize and bind to PEG (i.e., anti-PEG antibodies). Anti-PEG antibodies are also found in patients who have never been treated with PEGylated drugs but have consumed products containing PEG. Consequently, treating patients who have acquired anti-PEG antibodies with PEGylated drugs results in accelerated blood clearance, low drug efficacy, hypersensitivity, and, in some cases, life-threatening side effects [10].

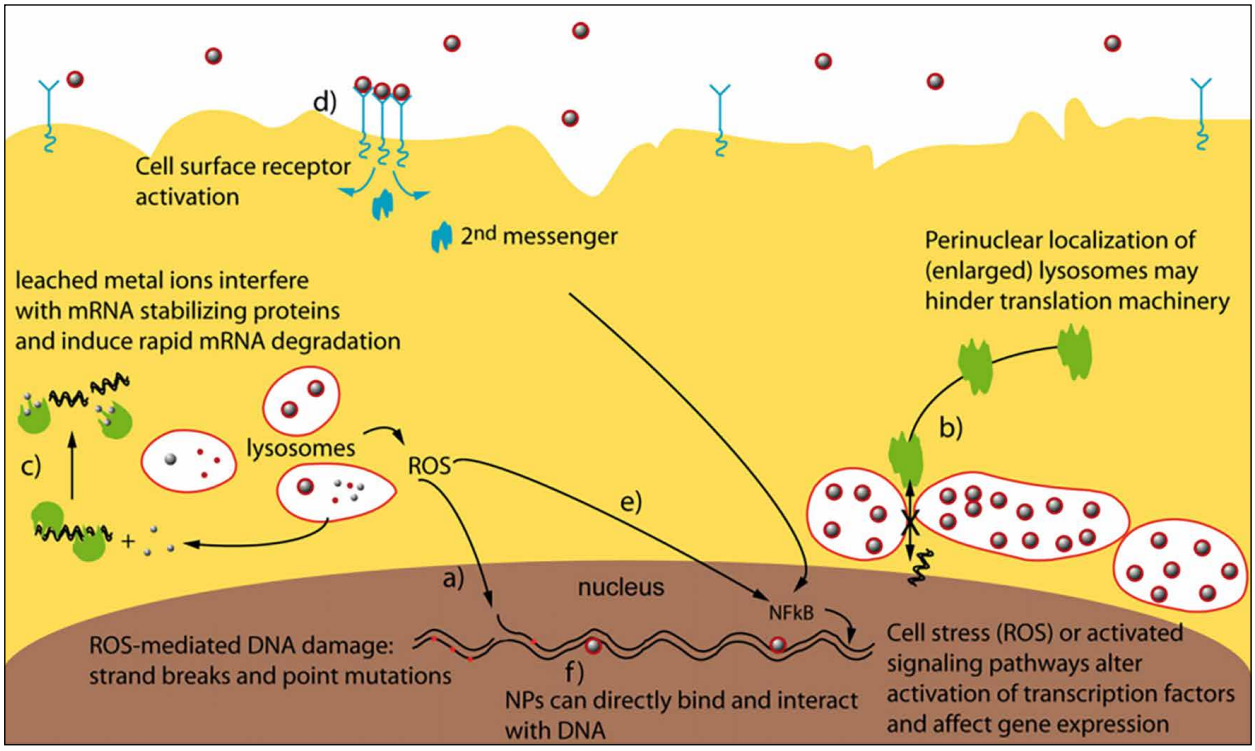

Figure 5 – *Schematic overview of the different mechanisms by which NPs can induce genotoxic effects or affect intracellular signaling pathways. (a) High levels of induced ROS by NPs localized in lysosomes can directly induce DNA point mutations or lead to single or double strand breaks. (b) The proximal perinuclear localization of large numbers of NP-loaded lysosomes can hinder the cellular transcription and translation machinery and hereby affect global protein synthesis. (c) Leached metal ions from lysosomal located NPs can transfer to the cell cytoplasm via specialized complexes (e.g. divalent metal transporter) where it can then interact with mRNA stabilizing proteins which contain metal responsive domains; resulting in the release and degradation of the mRNA (e.g. mRNA of transferrin receptor in response to ferric ions). (d) Interaction of nanoparticles with surface located receptors can lead to receptor activation and triggering of intracellular signaling cascades (activation of second messenger or calcium waves). (e) NP-mediated ROS induction and associated protein and lipid peroxidation can also indirectly affect gene expression patterns by activation of stress response or repair genes. (f) Nanosized particles (such as Au NPs) can penetrate the nucleus and bond to and interact with DNA directly [11]*

Tests. The increasing frequency of resulting cell—NP interactions necessitates a more profound knowledge of nanoparticle effects on cells. To date, this question is far from answered, as many ambiguous findings have been reported in the literature, mostly based on experiments with cultured cells [11]. The assessment of NP toxicity has been complicated due to a great variety in:

(1) types of used NPs,

(2) stabilizing NPs coating agents,

(3) physicochemical parameters of the NPs (diameter, surface charge, surface topography, surface area),

(4) incubation conditions (time and concentration),

(5) type of cells used,

(6) type of assay used,

(7) possible interference of the NPs with the assay readout.

As one can see, a direct comparison of results between different studies is practically impossible. As such, the safety of NPs for biomedical applications and their exposure to (cultured!) cells remains unclear.

Common mechanisms of cytotoxicity NPs are shown in Figure 4 and 5. They include oxidative stress (Figure 4) or genotoxic effects and effects on intracellular signaling pathways (Figure 5).

When evaluating the NP toxicity, one needs to take so called «key parameters» which are necessary to receive comprehensive results (Figure 6).

A schematic overview of a possible workflow in the design of cellular NP toxicity studies is shown in Figure 7.

Toxicity of NPs. By reducing a particle size below about 100 nm, the physicochemical characteristics of the particle will change so that their application will improve in many aspects, such as: electromagnetic, catalytic, thermal stability, flexibility, conductivity, and pharmacokinetic and targeting properties. Biological effects related to nanoparticles exposure also differ from that of

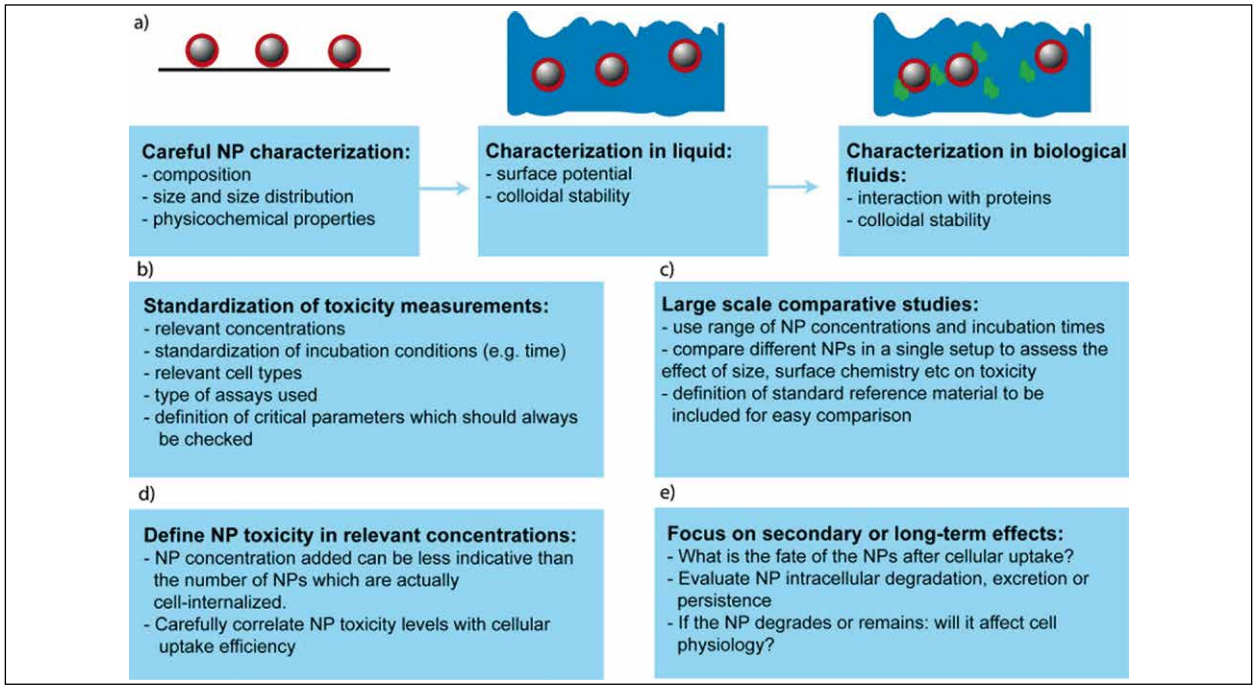

Figure 6 – *Schematic overview of the key parameters involved in evaluating NP toxicity: (a) NP characterization in dry state (left), in liquid (middle) and in biological fluids (right). (b) standardization of toxicity measurements, (c) use of large-scale comparative studies, (d) defining NP toxicity in function of relevant concentration and e) focus on secondary and long-term effects [11]*

larger particles. When bulk materials degrade to smaller pieces, their surface chemistry changes, and consequently, their chemical reactivity increases. That is why some nanomaterials are very reactive or catalytically active. Additionally, nanomaterials can pass easily into cells and affect cellular function. Basically, there are two factors which show the potential effects of harmful particles: their large surface area and the reactivity or intrinsic toxicity of the surface. Due to the larger surface area of the small particles per unit mass, the intrinsic toxicity of the particle surface increase. Intriguingly, the complexity of nanomaterial interaction mechanisms with living organisms might come from their different behaviors in contact with biological systems. Therefore, unlike toxicology, nanomaterial properties such as morphology, size, surface charge, coating, agglomeration state, and so on are crucial in nanotoxicology. It should be noted that knowledge is still scant about the human health effects of these materials.

Immune System. In implementing the nanosafety regulations, immuno-nanosafety is crucial. Different physicochemical properties of nanomaterials beside the surface absorption of biomolecules affect their interaction with this system [12–15]. Nanoparticles might be covered by environmental molecules such as allergens or bacterial lipopolysaccharide (LPS), thus triggering the immune responses [16–18]. Severe activation of the complement system by bloodstream nanoparticles might result in hypersensitivity and anaphylaxis [19]. The nanoparticle-induced inflammation might disappear after their degradation by polymorphonuclear leukocytes (PMNs) of the immune system while LPS contamination of nanomaterials can fall into an inflammatory response [17, 20]. Regardless of the detrimental effects of nanoparticle-induced inflammation, activation of «cytoplasmic multiprotein complex» (NLRP3), considering the accessibility of the cytoplasm by nanomaterials, is a key to triumphant immunization by nanoparticle vaccine adjuvants [21]. However, this «triumphant immunization» can have disastrous consequences for humans. In a recent paper «SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein» the infection with COVID-19 and nanoparticle mRNA vaccination against the virus triggers the microglial innate immune activation with profound neurological consequences for the patient [22]. Contradictory results of nanomaterial impacts on the acquired immunity usually come from differences in the sizes of studied nanoparticles along with different specificities of animal models [23–25]. Finally, due to the susceptibility of high-risk groups, exploiting the deleterious effects of nanoparticles on the immune systems of immunocompromised, pregnant women, elderly, and the very young populations is mandatory.

Respiratory System. The respiratory system is one of the main entry routes of NPs [26]. The

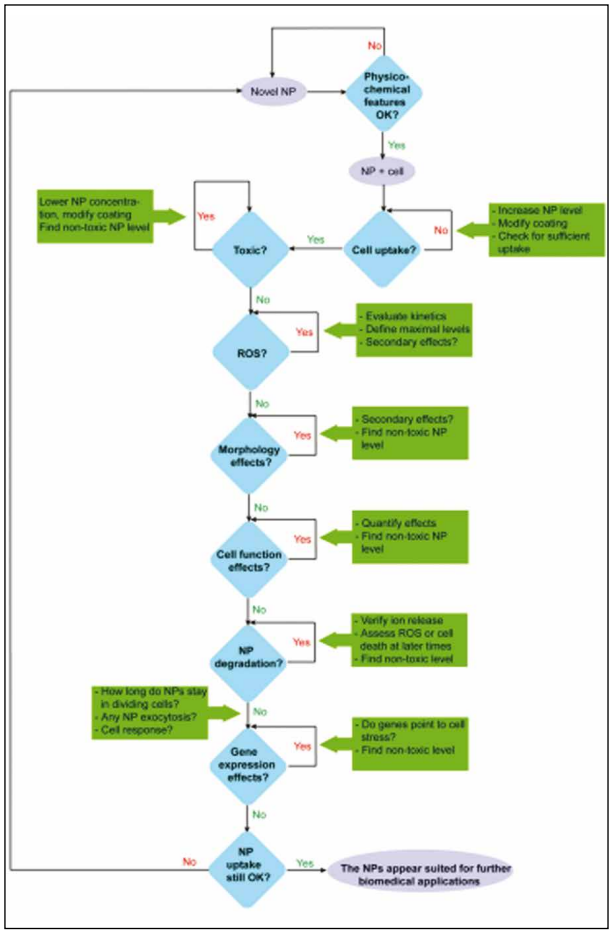

Figure 7 – *Schematic overview of a possible workflow in the design of optimized cellular NP toxicity studies. Please see the main text for more details [11]*

possibility of inhalation of NPs can occur during their production or consumption or they even may be present as soot particles or air pollutants. Deposition of NPs in the airways and alveoli is largely based on the size of nanoparticles and is predictable according to a mathematical model [27]. Once deposited in the lungs, the nanoparticles have different destinations; they may encounter cellular uptake or clearance, or they may even persist there and form granulomas. In the respiratory tree, cellular uptake of nanomaterials from the epithelial surface occurs through endocytosis, providing nanoparticles a direct entry into the blood and lymph and thereby allowing them to translocate to other parts of the body. In addition, olfactory epithelium can translocate some metal nanomaterials such as manganese, cadmium, nickel, and cobalt to the brain via olfactory nerves [28].

The mucociliary escalator and phagocytosis by macrophages are the two main clearance pathways of NPs. Different physicochemical properties of NPs such as size, agglomeration state, surface charge, and coating can affect their clearance, distribution in the respiratory system, and translocation to other systems [29]. For example, administration of large multiple walled carbon nanotubes (CNT) to rats by transtracheal intrapulmonary spraying can result in their translocation into the pleural cavity, thus inducing pleural lesions, whereas small multiple walled CNT just cause harm to the lung tissue itself [30, 31]. Most of our knowledge of the pulmonary effects of NPs on human health comes from the workers of nanomaterial factories as well as human cell in vitro studies. In these studies, depending on type and exposure of NPs, the following effects were seen reduced lung function, pro-inflammatory cytokines secretion, elevated oxidative stress markers, small airway injury, deposition of extracellular matrix proteins, and reduced antioxidant enzymes, for example,

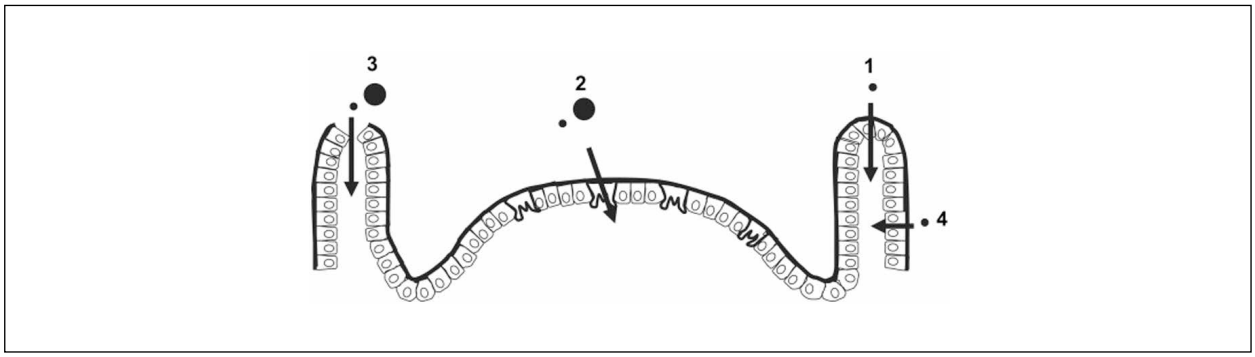

Figure 8 – *Summary of particles translocation across the gastrointestinal tract 1. Endocytosis through 'regular' epithelial cells. Very small particles tentatively generally <50–100 nm in diameter. 2. M-cell-uptake (transcytosis) at the surface of intestinal lymphoid aggregates. This is the quintessential pathway for gut particle uptake and is very well described, especially for small nanoparticles (20–100 nm) and large microparticles (100–500 nm). 3. Persorption. Volkheimer's concept of passage through «gaps» at the villous tip following loss of enterocyte(s) to the gut lumen. Small and large nanoparticles potentially access this route, but, quantitatively, it is unlikely to be efficient. 4. Putative paracellular uptake. Generally junctional complexes are unlikely to allow even the smallest of nanoparticles to permeate but certain drugs and/or dietary situations, and especially diseases, may alter this situation allowing influx of]very small nanoparticles. (Taken and corrected from [35])*

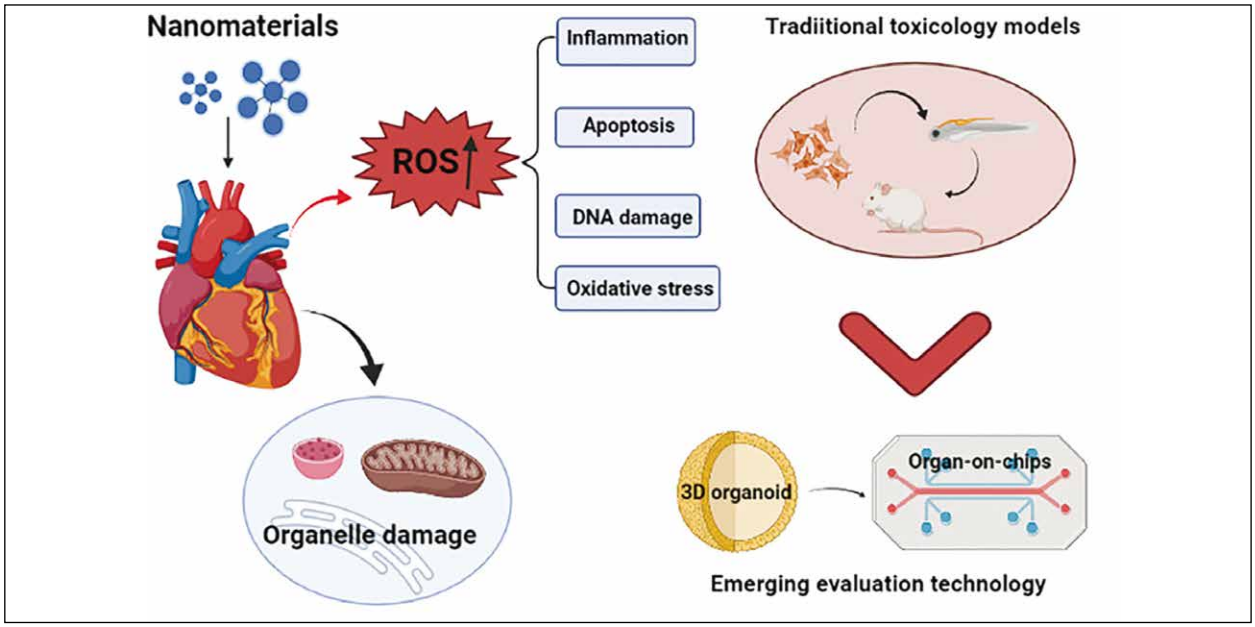

Figure 9 – *Schematic representation of cardiac toxicity and the principles of the toxicity assays. The figure is taken from [53]*

superoxide dismutase and glutathione peroxidase. Other potential toxic effects of NPs include activation of the immune system and induction of asthma, granuloma formation, fibrosis, genotoxicity, and carcinogenic effects obtained from animal models studies [32–34].

Gastrointestinal Tract. The gastrointestinal tract is one of the routes of NPs entry either by direct consumption of food and water or through swallowing of drugs, cosmetics, inhaled NPs, or dissolution from food packaging. Presently, among those, metal or metal oxide nanoparticles are most likely to be ingested due to their applications as dietary nano-supplements and nano-additives. Figure 8 illustrates the probable pathways of particles translocation in the gastrointestinal tract, which occur via endocytosis, M cells transcytosis, persorption, and paracellular uptake into and across the mucosa [35].

The information on the NPs influence on the gastrointestinal tract is small, and some of that is contradictory [35]. Most likely, through a so-called «Trojan horse effect», intracellular dissolution of metal NPs results in the releasing of ions which are responsible for the cytotoxic effects. In contrast, several studies manifest neither cytotoxic nor ROS generation effects of these nanomaterials on the intestinal cell cultures [36–38]. The adverse effects of NPs also might occur due to the altered membrane permeability and compromised integrity of the epithelial barrier. This disruption of the gut barrier could have some consequences such as absorption of pathogenic microorganisms or destructive toxins from the gut lumen). Notably, NPs affect the gut microbiota as well. The shapes and dimensions of the NPs are some of the important factors affecting their antimicrobial activity [39]. The interference of NPs with the intestinal microbiota might be another mechanism for nanoparticle-induced gut inflammation [40, 41]. Possibly, one of the microbiota-mediated toxic effects of the NPs is colitis [42].

Cardiovascular System. The heart is a specialized target organ where nanoparticles accumulate, causing damage to the heart [43–45]. At present, most researchers have agreed that the primary toxicity effects and mechanisms are membrane damage, metal-toxicity, mechanical disturbance, oxidative stress, inflammation, mitochondrial damage, and DNA damage [46–50] (Figure 9).

With the deepening of research, the traditional toxicology model has many drawbacks, and it is bound to be gradually replaced by newer and more efficient technologies [51]. Nowadays, 3D cell culture and organ-on-a-chip technology have a microenvironment that is more similar to the human body, and there are no species differences and ethical issues; thus, they will become new models for environmental toxicology evaluation with great potential [52].

In general, the accumulation of nanoparticles into the heart can cause damage to myocardial cells and finally to cardiac function. A large amount of ROS induces severe oxidative stress damage and inflammation, and further causes abnormal elevation of myocardial enzymes, lipid peroxidation damage, mitochondrial dysfunction, and genetic toxicity [53] (Figure 10).

Nervous System. The brain has some characteristics which make it vulnerable to NPs

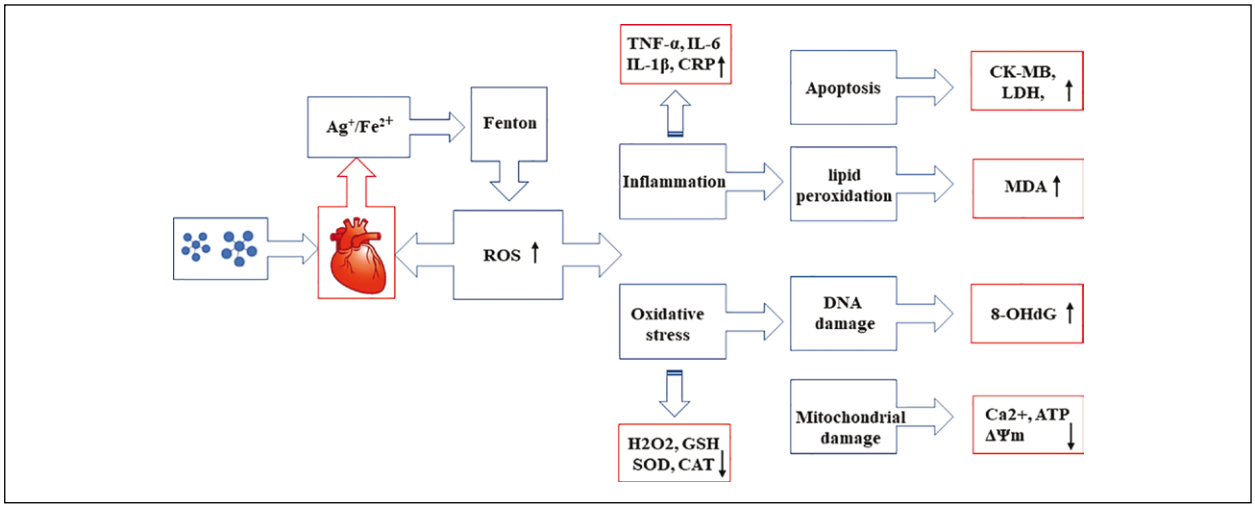

Figure 10 – *A more detailed explanation of the possible cardiac damage caused by NPs. The figure is taken from [53]*

harmful effects; it has a high content of easily peroxidizable unsaturated fatty acids, high oxygen consumption rate, and a relative paucity of antioxidant enzymes compared with other organs [54]. The biokinetics of inhaled nanoparticles to the brain are as follows: (a) deposited NPs on the nasal mucosa of the upper respiratory tract translocate to the olfactory bulb or the trigeminus; and (b) NPs deposited in the lower respiratory tract will cross the air-blood barrier into blood and enter the brain across the BBB or they may translocate from the enervated tracheobronchial epithelia via the vagus nerve to the brain [55].

Different physicochemical properties of NPs such as size, shape, oxidation state, agglomeration, surface charge, and coating can affect their neurotoxicity [56]. Our knowledge about the adverse effects of NPs on the human CNS is scarce and comes from an occupational disease associated with manganese that resembles Parkinson's disease and is called Manganism [57]. Due to the different types of NPs, there are diverse mechanisms of neuron injury. However, neurotoxicity of organic and metallic NPs comes from oxidative stress, apoptosis, and the inflammatory response [58]. There are other mechanisms for a neuronal injury such as the effect on pumps and voltage-gated channels which can lead to neuron excitability or apoptosis, and an increase or decrease of some neurotransmitters like glutamate, norepinephrine, serotonin, and dopamine. Disturbed homeostasis of neurotransmitters causes impaired spatial recognition memory. NPs can also alter the electrophysiological properties of neurons like synaptic plasticity, which affects spatial learning and memory ability [59].

Reproductive System. The toxicity of NPs on female reproductive and developmental health has been studied in various models. Because of genomic similarities to humans and short generation time, the mouse is a commonly used animal model [60]. The other animal model is the zebrafish, which is the choice model for some developmental molecular mechanism studies [61]. It has been shown that TiO_2 can cause ovarian dysfunction and up-regulation of the gene related to biosynthesis of estradiol. In addition, ovarian cell damage led to hormonal imbalance and decreased fertility [62]. Decreased implantation, reduction of uterine weight, and increase of fetal resorption rate have also been reported. Many NPs including quantum dots, TiO_2, SiO_2, and carbon nanomaterials can penetrate the placental barrier. Placental damage caused by NPs may potentially lead to deformity or developmental retardation of the fetus. Surface modifications of NPs can reduce the transplacental ability [60]. Overall, NPs may cause altered organogenesis and morphology as well as defects in the reproductive and nervous systems of the offspring [60]. Some of the fetal toxicity of NPs in murine models are revealed as: skeletal abnormalities, decreased testosterone, sperm production, and motility, reduction of progesterone, FSH level, and corticosterone, altered gene expression associated with apoptosis, oxidative stress, and neurotransmitters in the brain [63].

Skin. Human skin, in contrast with other internal exposure routes, directly touches the NPs deposition [64]. Skin and NPs properties and ambient conditions (i.e., temperature, UV irradiation, humidity, and clothing) affect particle-skin interactions. For instance, adsorption of dermis proteins to the surface of positively charged gold nanorods results in an extensive aggregation of these particles [64, 65]. Primarily, nano-enabled products which make contact with the skin face an acellular and impermeable layer, the stratum corneum. NPs can reach viable skin cells either through the stratum corneum or the lining of hair follicles [64]. A healthy skin permits the penetration of NPs smaller than 4 nm. The penetration of

particles of 4–20 nm is also possible via hair follicles. Remarkably, particles greater than 21 nm cannot permeate through a healthy and functional skin, but they might pass through a damaged one [66]. Nevertheless, certain ingredients (e.g., urea, glycerol, and alpha hydroxyl acids) are found to enhance the percutaneous absorption of desirable NPs [64]. Numerous elicited adverse effects of NPs on human epidermal keratinocytes (HaCaT) such as ROS production, antioxidant depletion, oxidative stress, pro-inflammatory responses, cell toxicity, and apoptosis prove the possible risks of these particles [67, 68]. Other effects of NPs such as sensitivity or allergic contact dermatitis may develop due to the released metal ions which act as a sensitizer. Moreover, combined exposure of a NPs with allergens or fragrances might provoke an allergic contact dermatitis [69, 70].

***

Nanoparticles of any type have biological activity. This is due to an enormous increase in the surface activity of the particles during the transition from micron size to nanoscale. At this size they are ruled by the laws of quantum mechanics. They can penetrate the cell nucleus. Being non-biological objects, interacting with cellular receptors, distorting intracellular signaling pathways and affecting the genetic regulation of the cell, they can cause a variety of pathological effects (oxidative stress, DNA damage, neuroinflammation, neurodegeneration, etc.). Therefore, with the transition from micro sizes to nanoscales, essentially remaining chemical compounds, particles of non-toxic materials can transform into extremely potent biological and chemical damaging agents. The existing possibilities of their mass use and their entry through the respiratory system, skin, gastrointestinal tract and through the introduction of injectable forms of drugs suggest that based on damaging agents of this type, weapons of mass destruction of a new type that are not subject to the Conventions on the Prohibition of Chemical and Biological Weapons can be developed. It is necessary to start developing methods for detecting nanoparticles and other nanoobjects (including their effects on biological objects) in various environments surrounding a person (organism), food, and application forms using newer approaches such as 3D tissue cultures and organs on the chips.

Authors Contribution/Вклад авторов

Elaboration of the concept of the paper; collection, analysis, and systematization of scientific literature; writing and edition of paper / Разработка концепции статьи; сбор, анализ и систематизация научной литературы; написание статьи.

Conflict of interest statement

I am declaring that I prepared the article from sources freely available on the Internet and free available publications, figures, and other possible legal sources. I, as a sole author declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Peer review information

The article has been peer reviewed by two experts in the respective field. Peer reviews are available from the Editorial Board and from Russian Science Citation Index database.

Funding. There are no funding sources to declare.

References

1. Vert M., Doi Y., Hellwich K.H. et al. Terminology for biorelated polymers and applications (IUPAC Recommendations 2012) // Pure Appl. Chemistry. 2012. V. 84. № 2. P. 377–410. https://doi.org/10.1351/PAC-REC-10-12-04

2. Kumar N., Kumbhat S. Chapter 8. UNIQUE PROPERTIES // In: Essentials in Nanoscience and Nanotechnology. First Ed. John Wiley & Sons, 2016. ISBN 9781119096115.

3. Gleiter H. Nanostructured Materials: Basic Concepts and Microstructure // Acta Mater. 2000. V. 48. P. 1–29.

4. Scholl J.A., García-Etxarri A., Koh A.L. et al. Observation of quantum tunneling between two plasmonic nanoparticles // Nano Lett. 2013. V. 13. P. 564–569.

5. Issa B., Obaidat I.M., Albiss B.A., Haik Y. Magnetic nanoparticles: surface effects and properties related to biomedicine applications // Int. J. Mol. Sci. 2013. V. 14. № 11. P. 21266–21305. https://doi.org/10.3390/ijms141121266

6. Bastús N.G., Casals E., Ojea I. et al. The reactivity of colloidal inorganic nanoparticles // In: The Delivery of Nanoparticles [Internet] / Ed. Hashim A.A. London: IntechOpen; 2012. www.intechopen.com/books/2259. https://doi.org/10.5772/2647

7. Khan I., Saeed K., Khan I. Nanoparticles: properties, applications and toxicities // Arabian J.

Chem. 2019. V. 12. P. 908–931. https://doi.org/10.1016/j.arabjc.2017.05.011

8. Kurapati R., Mukherjee S.P., Martin C. et al. Angew. Chem. Int. Ed. 2018. V. 57. P. 11722 –11727. https://doi.org/10.1002/anie.201806906

9. Backmann N., Kappeler N., Braun T., et al. Sensing surface PEGylation with microcantilevers // Beilstein J. Nanotechnol. 2010. V. 1. P. 3–13. https://doi.org/10.3762/bjnano.1.2

10. Thi T.T.H., Pilkington E.H., Nguyen D.H. et al. Truong. The importance of poly(ethylene glycol) alternatives for overcoming PEG immunogenicity in drug delivery and bioconjugation // Polymers. 2020. V. 12. P. 298. https://doi.org/10.3390/polym12020298

11. Soenen S., Rivera-Gil P., Montenegro J.-M. et al. Cellular toxicity of inorganic nanoparticles: Common aspects and guidelines for improved nanotoxicity evaluation // NANO TODAY. 2011. V. 6. № 5. P. 446-465. https://doi.org/10.1016/j.nantod.2011.08.001

12. Zolnik B.S., González-Fernández A., Sadrieh N., Dobrovolskaia M.A. Nanoparticles and the immune system // Endocrinology. 2010. V. 151. № 2. P. 458–465. https://doi.org/10.1210/en.2009-1082

13. Esmaeili F., Ghahremani M.H., Esmaeili B. et al. PLGA nanoparticles of different surface properties: preparation and evaluation of their body distribution // Int. J. Pharm. 2008. V. 349. № 1-2. P. 249-255. https://doi.org/10.1016/j.ijpharm.2007.07.038

14. Mahon E., Salvati A., Bombelli F.B. et al. Designing the nanoparticle–biomolecule interface for "targeting and therapeutic delivery" // J. Contro.l Release. 2012. V. 161. № 2. P. 164–174.

15. Binnemars-Postma K.A., Ten Hoopen H.W, Storm G., Prakash J. Differential uptake of nanoparticles by human M1 and M2 polarized. Macrophages: protein corona as a critical determinant // Nanomedicine (Lond). 2016. V. 11. № 22. P. 2889–2902. https://doi.org/10.2217/nnm-2016-0233

16. Smulders S., Kaiser J.P., Zuin S. et al. Contamination of nanoparticles by endotoxin: evaluation of different test methods // Part Fibre Toxicol. 2012. V. 9. P. 41. https://doi.org/10.1186/1743-8977-9-41

17. Lieder R., Petersen P.H., Sigurjónsson Ó.E. Endotoxins-the invisible companion in biomaterials research // Tissue Eng. Part B Rev. 2013. V. 19. № 5. P. 391–402. https://doi.org/10.1089/ten.TEB.2012.0636

18. Vetten M.A., Yah C.S., Singh T., Gulumian M. Challenges facing sterilization and depyrogenation of nanoparticles: effects on structural stability and biomedical applications // Nanomedicine. 2014. V. 10. № 7. P. 1391–1399. https://doi.org/10.1016/j.nano.2014.03.017

19. Sharma L.R., Subedi A., Shah B.K. Anaphylaxis to pegylated liposomal Doxorubicin: a case report // West Indian Med. J. 2014. V. 63. № 4. P. 376–377. https://doi.org/10.7727/wimj.2013.270

20. Kotchey G.P., Hasan S.A., Kapralov A.A. et al. A natural vanishing act: the enzyme-catalyzed degradation of carbon nanomaterials // Acc. Chem. Res. 2012. V. 45. № 10. P. 1770–1781. https://doi.org/10.1021/ar300106h

21. Eisenbarth S.C., Colegio O.R., O'Connor W. et al. Crucial role for the Nalp3 inflammasome in the immunostimulatory properties of aluminium adjuvants // Nature. 2008. V. 453. № 7198. P. 1122–1126. https://doi.org/10.1038/nature06939

22. Albornoz E.A., Amarilla A.A., Modhiran N. et al. SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein // Mol. Psychiatry. 2022. https://doi.org/10.1038/s41380-022-01831-0

23. van Zijverden M., Granum B. Adjuvant activity of particulate pollutants in different mouse models // Toxicology. 2000. V. 152. № 1-3. P. 69–77. https://doi.org/10.1016/s0300-483x(00)00293-6

24. Lutsiak M.E., Kwon G.S., Samuel J. Biodegradable nanoparticle delivery of a Th2-biased peptide for induction of Th1 immune responses // J. Pharm. Pharmacol. 2006. V. 58. № 6. P. 739–747. https://doi.org/10.1211/jpp.58.6.0004

25. Xiang S.D., Scholzen A., Minigo G. et al. Pathogen recognition and development of particulate vaccines: does size matter? // Methods. 2006. V. 40. № 1. P. 1–9. https://doi.org/10.1016/j.ymeth.2006.05.016

26. Omlor A.J., Nguyen J., Bals R., Dinh Q.T. Nanotechnology in respiratory medicine // Respir. Res. 2015. V. 16(1). P. 64. https://doi.org/10.1186/s12931-015-0223-5

27. Andujar P., Lanone S., Brochard P., Boczkowski J. Respiratory effects of manufactured nanoparticles // Rev. Ma.l Respir. 2011. V. 28. № 8. P. e66-75. https://doi.org/10.1016/j.rmr.2011.09.008

28. Karmakar A., Zhang Q., Zhang Y. Neurotoxicity of nanoscale materials // J. Food Drug Anal // 2014. V. 22. № 1. P. 147–160. https://doi.org/10.1016/j.jfda.2014.01.012

29. Wang, L., Davidson D.C., Castranova V., Rojanasakul Y. Pulmonary effects of carbon nanomaterials // In: Biomedical Applications and Toxicology of Carbon Nanomaterials / Eds. Chen C., Wang H. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA, 2016. P. 163–193. https://doi.org/10.1002/9783527692866.ch6

30. Xu J., Alexander D.B., Futakuchi M. et al. Size- and shape-dependent pleural translocation, deposition, fibrogenesis, and mesothelial proliferation by multiwalled carbon nanotubes // Cancer Sci. 2014. V. 105. № 7. P. 763–769. https://doi.org/10.1111/cas.12437

31. Wang Q., Wang Q., Zhao Z., et al. Pleural translocation and lesions by pulmonary exposed multi-walled carbon nanotubes // J. Toxicol. Pathol. 2020. V. 33. № 3. P. 145–151. https://doi.org/10.1293/tox.2019-0075

32. Brouwer D., Kuijpers E., Bekker C. et al. Field and laboratory measurements related to occupational and consumer exposures // In: Safety of Nanomaterials along Their Lifecycle: Release, Exposure, and Human Hazards / Eds. Wohlleben W., Kuhlbusch T.A.J., Schnekenburger J., Lehr C.-M. CRC Press, 2014. P. 277–314.

33. Working, IARC Monograph. Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers,

and carbon nanotubes // Ann. Ist. Super Sanita. 2014. V. 50. P. 111–118.

34. Shvedova A.A., Kisin E.R., Yanamala N. et al. MDSC and TGFβ are required for facilitation of tumor growth in the lungs of mice exposed to carbon nanotubes // Cancer. Res. 2015. V. 75. № 8. P. 1615–1623. https://doi.org/10.1158/0008-5472.CAN-14-2376

35. Powell J.J., Faria N., Thomas-McKay E., Pele L.C. Origin and fate of dietary nanoparticles and microparticles in the gastrointestinal tract // J. Autoimmun. 2010. V. 34. № 3. P. J226–J233. https://doi.org/10.1016/j.jaut.2009.11.006

36. Zhang T., Xu M., He L. et al. Synthesis, characterization and cytotoxicity of phosphoryl choline-grafted water-soluble carbon nanotubes // Carbon. 2008. V. 46. № 13. P. 1782–1791. https://doi.org/10.1016/j.carbon.2008.07.033

37. Bouwmeester H., Poortman J., Peters R.J. et al. Characterization of translocation of silver nanoparticles and effects on whole-genome gene expression using an in vitro intestinal epithelium coculture model // ACS Nano. 2011. V. 5. № 5. P. 4091–4103. https://doi.org/10.1021/nn2007145

38. Lai X., Blazer-Yost B.L., Clack J.W. et al. Protein expression profiles of intestinal epithelial co-cultures: effect of functionalised carbon nanotube exposure // Int. J. Biomed. Nanosci. Nanotechnol. 2013. V. 3. № 1–2. P. 127–162. https://doi.org/10.1504/IJBNN.2013.054508

39. Chen H., Wang B., Gao D. et al. Broad-spectrum antibacterial activity of carbon nanotubes to human gut bacteria // Small. 2013. V. 9. № 16. P. 2735–2746. https://doi.org/10.1002/smll.201202792

40. Chen H., Wang B., Zhao Y., Feng W. Nanoparticle effects on gastrointestinal microbiome // Nanomed. Nanotechnol. Biol. Med. 2016. V. 12. № 2. P. 457.

41. Bouwmeester H., van der Zande M., Jepson M.A. Effects of food-borne nanomaterials on gastrointestinal tissues and microbiota // Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 2018. V. 10. № 1. P. e1481. https://doi.org/10.1002/wnan.1481

42. Pietroiusti A., Magrini A., Campagnolo L. New frontiers in nanotoxicology: gut microbiota/microbiome-mediated effects of engineered nanomaterials // Toxicol. Appl. Pharmacol. 2016. V. 299. P. 90–95. https://doi.org/10.1016/j.taap.2015.12.017

43. Huerta-García E., Zepeda-Quiroz I., Sánchez-Barrera H., et al. Internalization of titanium dioxide nanoparticles is cytotoxic for H9c2 rat cardiomyoblasts // Molecules. 2018. V. 23. № 8. P. 1955. https://doi.org/10.3390/molecules23081955

44. Panov V., Minigalieva I., Bushueva T. et al. Some peculiarities in the dose dependence of separate and combined in vitro cardiotoxicity effects induced by CdS and PbS nanoparticles with special attention to hormesis manifestations // Dose Response. 2020. V. 18. № 1. https://doi.org/10.1177/1559325820914180

45. Savi M., Rossi S., Bocchi L. et al. Titanium dioxide nanoparticles promote arrhythmias via a direct interaction with rat cardiac tissue // Part Fibre Toxicol. 2014. V. 11. P. 63. https://doi.org/10.1186/s12989-014-0063-3

46. Akhtar M.J., Ahamed M., Alhadlaq H. Gadolinium oxide nanoparticles induce toxicity in human endothelial HUVECs via lipid peroxidation, mitochondrial dysfunction and autophagy modulation // Nanomaterials (Basel). 2020. V. 10. № 9. P. 1675. https://doi.org/10.3390/nano10091675

47. Li Y., Li F., Zhang L., et al. Zinc oxide nanoparticles induce mitochondrial biogenesis impairment and cardiac dysfunction in human iPSC-derived cardiomyocytes // Int. J. Nanomedicine. 2020. V. 15. P. 2669–2683. https://doi.org/10.2147/IJN.S249912

48. Salehcheh M., Alboghobeish S., Dehghani M.A., Zeidooni L. Multi-walled carbon nanotubes induce oxidative stress, apoptosis, and dysfunction in isolated rat heart mitochondria: protective effect of naringin // Environ. Sci. Pollut. Res. Int. 2020. V. 27. № 12. P. 13447–13456. https://doi.org/10.1007/s11356-020-07943-w

49. Song Y., Wu L., Cao J., Song B. Preparation of nano zinc particles and evaluation of its application in mouse myocardial infarction model // J. Nanosci. Nanotechnol. 2021. V. 21. № 2. P. 1196–1201. https://doi.org/10.1166/jnn.2021.18662

50. Trigueiro N.S.S., Gonçalves B.B., Dias F.C. et al. Co-exposure of iron oxide nanoparticles and glyphosate-based herbicide induces DNA damage and mutagenic effects in the guppy (Poecilia reticulata) // Environ. Toxicol. Pharmacol. 2021. V. 81. P. 103521. https://doi.org/10.1016/j.etap.2020.103521

51. Pennarossa G., Arcuri S., De Iorio T. et al. Current advances in 3D tissue and organ reconstruction // Int. J. Mol. Sci. 2021. V. 22. № 2. P. 830. https://doi.org/10.3390/ijms22020830

52. Chen X., Zhang Y.S., Zhang X., Liu C. Organ-on-a-chip platforms for accelerating the evaluation of nanomedicine // Bioact. Mater. 2020. V. 6. № 4. P. 1012–1027. https://doi.org/10.1016/j.bioactmat.2020.09.022

53. Cheng Y., Chen Z., Yang S. et al. Nanomaterials-induced toxicity on cardiac myocytes and tissues, and emerging toxicity assessment techniques // Sci. Total Environ. 2021. V. 800. P. 149584. https://doi.org/10.1016/j.scitotenv.2021.149584

54. Hu Y.L., Gao J.Q. Potential neurotoxicity of nanoparticles // Int. J. Pharm. 2010. V. 394. № 1-2. P. 115–121. https://doi.org/10.1016/j.ijpharm.2010.04.026

55. Kreyling W.G. Discovery of unique and ENM-specific pathophysiologic pathways: Comparison of the translocation of inhaled iridium nanoparticles from nasal epithelium versus alveolar epithelium towards the brain of rats // Toxicol. Appl. Pharmacol. 2016. V. 299. P. 41–46. https://doi.org/10.1016/j.taap.2016.02.004

56. Fu P.P., Xia Q., Hwang H.M. et al. Mechanisms of nanotoxicity: generation of reactive oxygen species // J. Food Drug Anal. 2014. V. 22. № 1. P. 64–75. https://doi.org/10.1016/j.jfda.2014.01.005

57. Dobson A.W., Erikson K.M., Aschner M. Manganese neurotoxicity // Ann. N. Y. Acad. Sci. 2004. V.

1012. P. 115–128. https://doi.org/10.1196/annals.1306.009

58. Song B., Zhang Y., Liu J. et al. Is Neurotoxicity of Metallic Nanoparticles the Cascades of Oxidative Stress? // Nanoscale Res. Lett. 2016. V. 11. № 1. P. 291. https://doi.org/10.1186/s11671-016-1508-4

59. Han D., Tian Y., Zhang T. et al. Nano-zinc oxide damages spatial cognition capability via over-enhanced long-term potentiation in hippocampus of Wistar rats // Int. J. Nanomedicine. 2011. V. 6. P. 1453–1461. https://doi.org/10.2147/IJN.S18507

60. Sun J., Zhang Q., Wang Z., Yan B. Effects of nanotoxicity on female reproductivity and fetal development in animal models // Int. J. Mol. Sci. 2013. V. 14. № 5. P. 9319–9337. https://doi.org/10.3390/ijms14059319

61. Dooley K., Zon L.I. Zebrafish: a model system for the study of human disease // Curr. Opin. Genet. Dev. 2000. V. 10. № 3. P. 252–256. https://doi.org/10.1016/s0959-437x(00)00074-5

62. Gao G., Ze Y., Li B. et al. Ovarian dysfunction and gene-expressed characteristics of female mice caused by long-term exposure to titanium dioxide nanoparticles // J. Hazard Mater. 2012. V. 243. P. 19–27. https://doi.org/10.1016/j.jhazmat.2012.08.049

63. Shimizu M., Tainaka H., Oba T., Mizuo K. et al. Maternal exposure to nanoparticulate titanium dioxide during the prenatal period alters gene expression related to brain development in the mouse // Part Fibre Toxicol. 2009. V. 6. P. 20. https://doi.org/10.1186/1743-8977-6-20

64. Monteiro-Riviere, N.A. Safety of nanoparticle skin penetration / In: Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Nanocarriers / Eds. Dragicevic N., Maibach I.H. Berlin, Heidelberg: Springer Berlin Heidelberg, 2016. P. 363–376. ISBN 9783662478622.

65. Mahmoud N.N., Al-Qaoud K.M., Al-Bakri A.G. et al. Colloidal stability of gold nanorod solution upon exposure to excised human skin: Effect of surface chemistry and protein adsorption // Int. J. Biochem. Cell Biol. 2016. V. 75. P. 223–231. https://doi.org/10.1016/j.biocel.2016.02.020

66. Larese Filon F., Bello D., Cherrie J.W., et al. Occupational dermal exposure to nanoparticles and nano-enabled products: Part I-Factors affecting skin absorption // Int. J. Hyg. Environ. Health. 2016. V. 219. № 6. P. 536–544. https://doi.org/10.1016/j.ijheh.2016.05.009

67. Shvedova A.A., Castranova V., Kisin E.R. et al. Exposure to carbon nanotube material: assessment of nanotube cytotoxicity using human keratinocyte cells // J. Toxicol. Environ. Health A. 2003. V. 66. № 20. P. 1909–1926. https://doi.org/10.1080/713853956

68. Wright C., Iyer A.K., Wang L. et al. Effects of titanium dioxide nanoparticles on human keratinocytes // Drug Chem Toxicol. 2017. V. 40. № 1. P. 90–100. https://doi.org/10.1080/01480545.2016.1185111

69. Hirai T., Yoshioka Y., Higashisaka K., Tsutsumi Y. Potential hazards of skin exposure to nanoparticles // In: Biological Effects of Fibrous and Particulate Substances / Eds. Otsuki T., Yoshioka Y., Holian A. Japan: Springer, 2016. P. 123–135. ISBN 9784431557319

70. Roach K.A., Stefaniak A.B., Roberts J.R. Metal nanomaterials: immune effects and implications of physicochemical properties on sensitization, elicitation, and exacerbation of allergic disease // J. Immunotoxicol. 2019. V. 16. № 1. P. 87–124. https://doi.org/10.1080/1547691X.2019.1605553

Author

Centre of Experimental Medicine, SAS, Dubravska cesta 9, 841 04 Bratislava, Slovakia Faculty of Management Comenius University, Odbojárov 10, 820 05 Bratislava, Slovakia.

Ján Lakota, MD, PhD.

Contact person: Ján Lakota; jan.lakota@savba.sk

Наночастицы как потенциальные агенты химического и биологического оружия

Ян Лакота

Центр экспериментальной медицины, SAS, Dubravská cesta 9, 841 04 Братислава, Словакия Факультет менеджмента Коменский университет, Odbojárov 10, 820 05 Братислава, Словакия

Получено 25 октября 2022. Принято к публикации 23 декабря 2022 г.

Широкое распространение в промышленности, медицине, сельском хозяйстве и других областях деятельности человека объектов наноразмеров ставит вопрос о возможности их двойно-

го использования, под которой в данной работе подразумевается использование для преднамеренного массового поражения людей. *Цель работы* – рассмотреть наночастицы в качестве потенциальных агентов химико-биологического оружия. Показано, что наночастицы любого типа обладают биологической активностью. Это связано с увеличением поверхностной активности частиц при переходе с микронного размера к наноразмерам и их способности проникать в ядро клетки. Будучи не биологическими объектами, взаимодействуя с клеточными рецепторами, искажая внутриклеточные сигнальные пути и влияя на генетическую регуляцию клетки, они способны вызвать разнообразные патологические эффекты (окислительный стресс, нейровоспаление, нейродегенерация и др.). Поэтому с переходом от микроразмеров к наноразмерам, по своей сути оставаясь химическими соединениями, частицы нетоксичных материалов могут трансформироваться в потенциальные биолого-химические поражающие агенты. Существующие возможности их массового применения через органы дыхания, кожу, желудочно-кишечный тракт и путем введения инъекционных форм лекарственных средств позволяют утверждать, что на основе поражающих агентов данного типа может быть разработано оружие массового поражения нового типа, не подпадающее под действие Конвенций по запрещению химического и биологического оружия. Необходимо уже сейчас приступить к разработке методов обнаружения наночастиц и других нанообъектов в различных средах, окружающих человека, продуктах питания и лекарственных формах.

Ключевые слова: *внутриклеточные сигнальные пути; генотоксические эффекты; наноматериалы; нанотехнологии; наночастицы; окислительный стресс; оружие массового поражения; токсичность наночастиц.*

Библиографическое описание: *Лакота Ян. Наночастицы как потенциальные агенты химического и биологического оружия // Вестник войск РХБ защиты. 2022. V. 6. № 1. P. 304–319. EDN: CGEFOD. https://doi.org/10.35825/2587-5728-2022-6-4-304-319*

Информация о конфликте интересов

Я заявляю, что подготовил статью из источников, находящихся в свободном доступе в Интернете, а также свободно доступных публикаций, рисунков и других возможных легальных источников. Я, как единственный автор, заявляю, что исследование проводилось при отсутствии каких-либо коммерческих или финансовых отношений, которые могли бы быть истолкованы как потенциальный конфликт интересов.

Сведения о рецензировании

Статья была рецензирована двумя экспертами в соответствующей области. Рецензии доступны в редакции и в базе данных Российского индекса научного цитирования.

Финансирование. Источников финансирования для декларирования нет.

Список источников / References

Стр. 315–318.

Об авторе

Центр экспериментальной медицины, SAS, Dubravská cesta 9, 841 04 Братислава, Словакия Факультет менеджмента Коменский университет, Odbojárov 10, 820 05 Братислава, Словакия.

Ян Лакота. MD, PhD

Контактное лицо: Ян Лакота; jan.lakota@savba.sk