

Conceivable interactions of biopersistent nanoparticles with food matrix and living systems following from their physicochemical properties

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Summary

In this paper, we made an attempt to assess the conceivable interactions of insoluble biopersistent nanoparticles with food matrix and living systems following from their physicochemical properties and to outline the analytical methods for the nanoparticles determination in food matrix. It is reasoned that adsorption of species and agglomeration and ageing of nanoparticles are phenomena originating in the relaxation of surface free energy. Further it has been deduced that nanoscale materials have a unique ability to interact with proteins and other biopolymers. The deductions also underline the catalytic activity of nanoparticles, primarily in oxidative reactions which may lead to the formation of reactive oxygen species and to the oxidation stress. The ability of nanoparticles to act as nuclei or germs in the induced heterogeneous crystallization is also considered.

Keywords

nanotechnology; nanomaterial; physicochemical properties; food; agglomeration; catalysis; nucleation

Nanostructure science and technology (nanoscience and nanotechnology) is a broad and interdisciplinary area of research and with development growing explosively worldwide in the past few years. Without doubts, nanotechnology belongs to the most promising technologies of this century. Nanomaterials (NM) are utilized for a number of application areas, such as electronic components, clothes, paints, house-cleaning products, varnishes, environmental remediation technology, energy capture and storage technology, military technology etc. They are applied also in medical and cosmetic products as well as for agriculture and food [1].

Since NMs are applied worldwide, their safety, implications on human and environmental health and potential risks are under discussion where current opinions range from “completely harmless and safe” to “extremely hazardous”. The conflicting results in the literature about the nanotoxicity are due to the lack of standardized physicochemical characterization of the different types of nanoparticles and even different manufactures or batches of the same engineered nanoparticle.

Numerous reports written by national and international expert groups have been published on the risks connected with NMs and most of them are available on Internet; just several of them are quoted here [1–8].

The three principal organs exposed to nanoparticles (NPs) are the lungs, the skin and the digestive system. Considering the latter case, NPs enter the digestive system contained mainly in food. A striking observation is that nanotechnologies are being used throughout all phases of food production [6]. Roughly two classes of application can be distinguished based on the likelihood of consumer exposure to nanoparticles or residues of the nanotechnologies applications. In the first class, nanotechnology is applied as a production tool, implying that no addition of NPs to the food will take place. Examples are the use of nanosieves (e.g. to filter out bacteria) or addition of nanofillers into food packaging materials. In the second class, NPs are purposely introduced into the food. A diversity of NP types is currently applied in the food production chain, which can be divided to inert particles and nanodelivery systems. Inert particles are used

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for a variety of purposes. Examples are aluminium oxide, lanthanum particles and nanoscale iron powder in the process of water purification and/or soil cleaning. In food storage, silver and, in rarer cases, zinc oxide NPs are applied. Silicate NPs, nanocomposite and silver, magnesium and zinc oxide are used in food packaging materials. Inert NPs are also processed in food commodities, examples are calcium oxide, magnesium oxide, silver, silicate, silicon oxide and white gold NPs [6].

It is generally recognized that a knowledge gap exists in the physicochemical properties of nanoparticles [1–10]. Complete information on relevant physicochemical properties of engineered NPs is essential for proper risk assessment [6]. Detailed knowledge of physicochemical properties is necessary also for the dose assessment and for the predictability of the interaction of NPs with food and biological matrices. Hence, aim of this paper is to summarize the known physicochemical properties of NPs, to assess the interaction with food matrix and living systems based on the structure and chemical composition of NP surface and to outline the analytical methods for the NPs determination in food matrix. The toxicity of soluble or biodegradable nanomaterials will be close to the bulk chemical agents [1] so that the nanosize may not be an issue; accordingly, attention will be paid here to the properties of insoluble biopersistent NPs that might accumulate in the body. Not only the currently used NPs will be considered, but also those that can be expected to be applied in the food chain in future, such as fullerenes and carbon nanotubes.

TERMINOLOGY

The basic terminology necessary for understanding this paper is taken over from the SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks) report [1]. A more detailed terminology can be found in [1–9].

Nanoscale – having one or more dimensions of the order of 100 nm or less.

Nanoscience – the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale.

Nanotechnology – the design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanoscale.

Nanomaterial – material with one or more external dimensions, or an internal structure, which

could exhibit novel characteristics compared to the same material without nanoscale features.

Nanoparticle – particle with one or more dimensions at the nanoscale.

Nanocomposite – composite in which at least one of the phases has at least one dimension on the nanoscale.

Nanostructured – having a structure at the nanoscale.

It should be noted that the upper limit for nanoparticle dimensions is not exactly 100 nm. The limit is arbitrary due to lack of knowledge on the relationship between particle size, its kinetic behaviour and effects on the surrounding matrix. It is thus not known whether the size range of interest is exactly at 100 nm or below or above [6].

GENERAL PROPERTIES OF NANOPARTICLES

Comparing with the bulk material, atoms or molecules on a solid surface miss nearest neighbours above the surface, and thus have unsatisfied bonds exposed to the surface. Surface atoms or molecules are thus under an inwardly directed force conveying an extra potential energy. As a consequence, the bond distance between the surface atoms or molecules and the sub-surface atoms or molecules, is smaller than that between interior atoms or molecules. The extra energy possessed by the surface atoms is called the surface free energy [11]. Due to the vast specific surface area, all nanostructured materials possess a huge surface energy and, thus, are thermodynamically unstable or metastable [11] and their properties may differ from those of the bulk material. Hence, nanostructures are often inherently unstable owing to their small constituent sizes and high chemical activity. Two principal factors cause nanomaterials to differ significantly from bulk materials, namely, the great relative surface area and quantum effects.

The principal parameters of nanoparticles are their size, shape (including aspect ratios where appropriate) and the morphological sub-structure of the substance. Further characteristics that need to be determined for each type of nanomaterial include: composition, solubility, surface area per mass, surface layer composition (in particular important if this differs from the composition of the bulk material) and surface charge [1–8, 11]. The particle morphology is an extremely important factor. For example, not only rutile and anatase nanoparticles of TiO₂ are known, but also nanorods, nanotubes, nanowires and other nanoparti-

cle forms are reported to occur [7]. It is a matter of course that each nanoform will interact with the surrounding matrix in a different way.

Agglomeration, adsorption and ageing of nanoparticles

As written above, nanomaterials possess huge surface free energy which makes them inherently unstable and highly reactive. It is a basic thermodynamic rule that close systems tend to reach the minimum of the free energy [12]. There are several ways of reducing the surface energy, among them the agglomeration of nanoparticles, the surface adsorption and ageing of nanoparticles are the most important [11].

The high surface energy and unbalanced surface forces may bring about the interparticle interaction. At the nanoscale, particle-particle interactions are either governed by weak van der Waals forces, stronger polar and electrostatic interactions or covalent interactions. Hence, free nanoparticles quickly tend to agglomerate or aggregate giving bigger particles. In the agglomerates, the NPs are bound only loosely and they can be released into the surrounding matrix. From the thermodynamical point of view, the release takes place if the energy of interaction between the NP and the matrix is greater than the energy of the interparticle interaction. The agglomerates retain the high surface area per mass so that they may retain the properties connected with the high specific surface.

The tendency of NPs to agglomerate can be enhanced or hindered by the modification of the surface layer. For example, in the presence of chemical agents (surfactants), the surface and interfacial properties may be modified. The agglomerates may break down and individual nanoparticles will be free to interact with the surrounding matrix. How tightly the nanoparticles are stuck together in the agglomerates is thus a key factor. Nanoparticles suspended in gas tend to stick to each other more readily than in liquids [11, 13].

A sole naked NP could exist only in vacuum. The unbalanced surface forces attract molecules from the surrounding matrix. When NP is placed in gas or in a liquid, the adsorption of molecules from surroundings will occur. The adsorption can be described by the adsorption equilibrium and can be either mono- or multilayer [12]. Regarding porous NPs, the gas or liquid may enter also the pores. The deposition of an adsorbate can modify the surface properties of NPs so that the agglomerates may break down and individual nanoparticles will be released.

Due to the crucial role of the surface interac-

tions, the term free NP can be easily misunderstood. It should be kept in mind that the surface of NPs undergoes modification due to adsorption of molecules from surroundings and that the composition of NP surface may be substantially different from the composition of the bulk material. The interaction forces, either attractive or repulsive, essentially determine the fate of NPs.

The surface energy can be relaxed also through the surface restructuring by combining surface unbalanced bonds into strained new chemical bonds and through the composition segregation or impurity enrichment on the surface by solid-state diffusion. Both these processes may take some time. Thus, the properties of nanoparticles may change during ageing due to the changes in surface structure and composition.

Agglomeration, adsorption and ageing of nanoparticles represent ways of relaxation of the surface free energy.

Behaviour in solutions of ions

In a solution of ions, the adsorption of ions may occur. The adsorption of ions can be expected in case of inorganic NPs, but also in case of polymeric NPs when the polymers contain polar groups in their structure.

During the polar adsorption, those ions are preferentially adsorbed which match better the crystalline structure of the NP, or those ions forming an insoluble compound on the NP surface [14]. The adsorbed ions determine the charge of NPs. The surface charge stabilizes NPs against agglomeration. The NPs in ionic solution thus will be probably charged and will be surrounded by an atmosphere of oppositely charged ions. When NPs move, they leave behind their ionic atmosphere which leads to the appearance of the zeta potential [12]. Under the influence of potential differences arisen in the solution, electrokinetic phenomena can take place, such as the stream potential. The charge of NPs strongly depends on pH [9, 11, 13].

Nanoparticles and crystallization

If NP is slightly soluble, according to the Kelvin equation the saturation solubility is a function of the particle size and increases with a decreasing diameter of the particle [12, 14]. In this case, the small NPs will dissolve and recrystallize giving bigger particles.

Nanoparticles can act as nuclei for the heterogeneous crystallization [15]. The nucleation is the first stage of crystallization process. Homogeneous nucleation occurs in the bulk of a homogeneous solution and resides in the formation of a cluster nucleus with a critical diameter. If the cluster

diameter is lower than the critical one, it is thermodynamically unstable and disintegrates back into the primary atoms or molecules. The critical diameter is a threshold beyond which the nuclei are ready to step into a spontaneous growth. The crystallization can be induced and facilitated by impurities, i.e. nanoparticles acting as foreign surfaces.

Catalysis

Due to small dimensions, the crystalline NPs have a great number of structural defects. Owing to high surface energy and abundance of structural defects, catalytic effects of NPs can always be expected, mainly in the case of inorganic NPs. Nano-scale catalyst particles are expected to have a great future impact in novel chemical catalysis [5].

Many transition metal oxides are selective oxidation catalysts, and some of them, in particular mixtures of them, are renowned for catalysing the selective oxidation of alkenes, alkanes and aromatic substances [16]. Iron oxide, manganese oxide and iron sulfide NPs have band gaps that could enhance the photocatalytic adsorption of solar radiation. In addition, these materials are acidic and may be coated with water, which would enhance their catalytic ability to crack hydrocarbons, so producing free radicals [17, 18]. Acidic solids such as silica-aluminas, in particular zeolites, are excellent for catalysing reactions of the carbocation type which are initiated by protons [16].

Considering metals, gold has traditionally been regarded inactive as a catalytic metal. However, the advent of nanoparticulate gold on high surface area oxide supports has demonstrated its high catalytic activity as a heterogeneous catalyst in both gas and liquid phases. Bimetallic catalysts containing gold show activity that is superior to that of either component separately in the synthesis of hydrogen peroxide and in a number of selective oxidations. Noble metals of groups 8–11 (Ru, Os, Rh, Ir, Pd, Pt, Ag, Au) are oxidation catalysts in non-selective or deep oxidation. Very much use has been made of catalysts containing two or more metals. Combinations Pt-Ir and Pt-Rh achieved industrial prominence in petroleum reforming and ammonia oxidation, combination Pt-Sn in alkane dehydrogenation. Much work has been focused on catalysts containing an element of groups 8–10 (Fe, Ru, Os, Co, Rh, Ir, Ni, Pd, Pt) plus one of group 11 (Cu, Ag, Au) [16].

The possible catalytic influence of NPs, mainly for the oxidation reactions, should always be taken into account. The catalysis of processes by solid surfaces starts with the chemisorption of the substrate. The catalytic effects thus will depend on the

modification or functionalization of the surface of NPs. Impurities occurring at the NP surface may even increase the catalytic activity since they may act as promoters [17, 18].

Regarding fullerenes, it has been found that they form 6 oxidation states in the reduction range [19]. These oxidation states can participate in many redox reactions. For example, it has been proven by a spectroelectrochemical study (simultaneous EPR, visible/near IR and electrochemical) that re-oxidation of fullerene monoanion in the presence of oxygen is coupled with the formation of superoxide anion [20] which is a strong oxidizing agent. In situ spectroelectrochemical study of a dry and oxygen-free solution proved that the electrochemistry of single-wall carbon nanotubes is controlled by capacitive charging [21]. A very complex redox behaviour of carbon nanotubes leading to the formation of highly reactive oxygen species can be expected in the presence of water and oxygen.

INTERACTION OF NANOPARTICLES WITH FUNCTIONAL GROUPS OF BIOMOLECULES

Besides water and minerals, biomolecules represent one of the major food components. Nanoparticles can have the same dimensions as some biomolecules and can interact with these [22]. The four major classes of biomolecules are carbohydrates, proteins, lipids and nucleic acids. Along with those, in less amounts, in food occur pigments, flavours, vitamins and preservatives.

Main structural units occurring in biopolymers

Carbohydrates are the most abundant biopolymer component of food. They are aldehydes or ketones with many hydroxyl groups, usually one on each carbon atom that is not part of the aldehyde or ketone functional group.

Proteins are polymers of amino acids. For chains under 40 residues the term peptide is frequently used instead of protein. To be able to perform their biological function, proteins fold into one, or more, specific spatial conformations, driven by a number of non-covalent interactions such as hydrogen bonding, ionic interactions, Van der Waals forces and hydrophobic packing.

Lipids are broadly defined as any fat-soluble (lipophilic), naturally-occurring molecules, such as fats, oils, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E and K), monoglycerides, diglycerides, phospholipids and others.

Nucleic acids are macromolecules composed of chains of monomeric nucleotides. Each nucleotide consists of three components: a nitrogenous

heterocyclic base, which is either a purine or a pyrimidine; a pentose saccharide; and a phosphate group. The saccharides and phosphates in nucleic acids are connected to each other in an alternating chain, linked by shared oxygens, forming a phosphodiester bond. This gives nucleic acids polarity. The most common nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

Interaction of nanoparticles with hydroxyl groups

The hydroxyl groups can be found mainly in the structure of saccharides and polysaccharides, alcohols and some minor food components. The nanoparticles with electron acceptors on their surface and with the ability of forming the hydrogen bonds could react with hydroxyl groups.

Interaction of nanoparticles with aromatic rings

The cation/ π -electron interaction is recognized as an important non-covalent bonding force in a wide range of molecular systems [23]. The gas-phase studies of ion-molecule complexes established that cations bind strongly to simple aromatic systems. It has been documented that cation/ π -electron are important for molecular recognition in many biological systems. These interactions also can play an important role in protein-ligand interactions.

From this it follows that the inorganic nanoparticles, and mainly the particles with adsorbed cations, may interact with benzene and heterocyclic aromatic rings. The aromatic rings can be encountered in the structure of proteins (histidine, phenylalanine, tryptophan, tyrosine) and nucleic acids (all nucleobases), but also in minor food components such as antioxidants, pigments, flavours, etc.

Enzymes catalyse and control the rates of chemical reactions; almost all of them are proteins. If the enzyme is adsorbed on a nanoparticle (or vice-versa, a nanoparticle is stuck to the enzyme molecule), the enzyme mobility will decrease. Thus, it can be expected that also the enzyme activity will decrease upon interaction with a NP.

Interaction of nanoparticles with amino groups

Side amino groups occur mainly in proteins (arginine, lysine) and nucleic acids; amino groups occur also in some minor food components. Since these groups are donors of an electron pair, they behave as bases and will interact with electron acceptors. Thus, polar interaction with transition metal oxides and positively charged particles can be expected.

NH groups occur also in peptide bonds. However, these groups will obviously be sterically inac-

cessible for NPs since they are situated in the main framework of the polypeptide molecule. Also, these groups are weaker donors of electrons due to the conjugation of the lone electron pair with the adjacent C=O bond.

Interaction of nanoparticles with sulphur-containing groups

These groups occur mainly in proteins (cysteine, methionine) but also in some minor food components, such as flavours. Sulphur-containing groups, mainly the thiol groups, are known to interact strongly with gold [24] and silver [25].

INTERACTION OF NANOPARTICLES WITH FOOD MATRIX

As said in the previous section, the components present in large amounts in food are biomolecules, minerals and water. Due to a high surface area, the nanoparticles can interact strongly with all the components of the food matrix.

Interaction of nanoparticles with biopolymers

From the above facts it follows that nanomaterials have a unique ability to interact with functional groups of biopolymers. Adsorption of NPs to enzymes may change their activity so changing the shelf-life of food. The shelf-life can be also affected by the interaction of NPs with preservatives. It is necessary to keep in mind that the substances adsorbed will have different properties from those which are free. For example, thiols form self-assembled monolayers on gold particles. The melting temperature of adsorbed thiols is increased by about 30 °C in comparison with free thiols [24].

It is known that fats form polymorphs [26]. Since nanoparticles can act as nuclei for the heterogeneous crystallization, they may bring about formation of different polymorphs from those occurring normally, or may bring about fat recrystallization. Both the formation of different polymorphs and recrystallization may lead to changes in food consistency and sensory properties.

The sensory properties can be also greatly affected by the interaction with pigments and flavours. The interaction with vitamins may modify their bioavailability.

Interaction with water and minerals

Table salt and other minerals are present in almost all kinds of food. Adsorption of both, the ions and water, can be expected. The water adsorption capacity of some nanoparticles is very high, a typical example is SiO₂. The interaction of NPs

with water may bring about considerable changes in food consistency. The nanoparticles with a high water adsorption capacity can be used as thickeners in food.

INTERACTIONS OF NANOPARTICLES WITH A LIVING SYSTEM

In order to understand and categorize the mechanisms for nanoparticle toxicity, information is needed on the response of living systems to the presence of nanoparticles of varying size, shape, surface and bulk chemical composition, as well as the temporal fate of the nanoparticles. The biopersistent micro- and nanoparticles commonly found in food are typically oxides of silicon, aluminium and titanium, such as aluminosilicates or the permitted food additives silicon dioxide (SiO₂, E551), magnesium oxide (MgO, E530) and titanium dioxide anatase (TiO₂, E171). The antimicrobial properties of nanosilver are known for ages and such properties have recently been discovered for nano-zinc oxide and magnesium oxide [10]. Here the consequences following from general properties of NPs and their interaction with biopolymers are outlined.

On the molecular level, the interaction of NPs with biopolymers, water and ions can be expected. As shown above, NPs can interact with all functional groups in biopolymers via physical, polar or chemical adsorption. Ionic crystal nanoparticles have been observed to accumulate protein layers [1]. Many biomolecules consist of long folded macromolecular chains. Here, nanoparticles, of a few nm in size, may intrude into the complex folded structures and can bring about, for example, DNA damage [1, 9]. This situation is not possible for larger particles, which indicates that the interaction of nanoparticles with living systems is also affected by the NP dimensions.

Durable, biopersistent NPs may accumulate in the body. The target organs of accumulation can be assessed from the nature of NPs, i.e. their hydrophobicity or hydrophilicity, and the nature of matrix where the accumulation takes place. For example, brain is a hydrophobic matrix with a high content of cholesterol. A strong interaction with, and thus the deposition of fullerenes, carbon nanotubes and carbon NPs in brain might be expected. Oxyradical-induced lipid and protein damage was investigated in fish exposed to nC₆₀. Fullerenes are lipophilic and localize into lipid-rich regions such as cell membranes *in vitro*, and they are redox active. Lipid peroxidation was significantly elevated in the brain of exposed fish. This is in agreement

with the partitioning of nC₆₀ into lipid-rich environments [27]. Surface modification or functionalization of NPs may alter the path of nanoparticles [1].

Charged NPs in ionic solutions are surrounded by an atmosphere of oppositely charged ions. When NPs move, electrokinetic phenomena can take place, such as the stream potential. The electrokinetic phenomena can give rise to potential differences in the body. Charge of NPs may play an important role in penetrating through pores, canals, etc. The fundamental membrane processes of living cells, for example, generation of ion gradients, sensory transductance, conduction of impulses and energy transduction, are electrical in nature [28]. All these processes may be affected by the presence of charged NPs.

NPs are oxidation catalysts or can induce transfer of electrons. In this way, reactive oxygen species are formed, which may induce oxidative stress and inflammation [9]. Increased oxidative stress generally describes a state in which cellular antioxidant defense mechanisms are inadequate to completely inactivate the reactive oxygen species because of their excessive production, loss of antioxidant defenses, or both. A major consequence of oxidative stress is damage to nucleic acid bases, membrane lipids and proteins, which in turn may contribute to the development of various diseases [29, 30].

A physico-chemical property omitted up to now in the prediction of adverse health effects is that NPs can act as nuclei for the induced crystallization. This could be important for enhanced deposition of uric acid, cholesterol or for blood clotting. Nanoparticle-induced platelet aggregation and vascular thrombosis has been reported recently [31]. Nanoparticles are found to enhance the rate of protein fibrillation by decreasing the lag time for nucleation. Protein fibrillation is involved in many human diseases, including the Alzheimer and Creutzfeld-Jacob disease [32].

A comprehensive review of NPs sources, properties and toxicity was published recently [9].

ANALYTICAL TOOLS FOR THE DETECTION OF NANOPARTICLES IN FOOD AND FEED MATRIX

A number of analytical tools exists for the characterization of pristine nanomaterials, both the single-particle techniques and the techniques characterizing the ensemble of nanoparticles. The methods are reviewed, for example, in [1, 6, 9]. The technology is still in rapid development.

Due to the variety of applications of nanoparticles, there are many different ways to analyse particles. There is no 'best' technique for 'all' situations and combination of techniques is usually necessary. Properties of NPs may depend on the surrounding matrix. Harmonization and standardization of the methods is needed.

Some of the analytical methods can be used to trace and detect NPs in more or less complex matrices, like water/electrolytes and organisms/tissues. But the detection and quantification of NPs in complex matrices like food and feed is only possible in very special cases. This is both because of the size of NPs that makes single particles constitute infinitely small amounts of chemicals that require extremely low detection limits, but also due to interactions with solutes or cell constituents that obscure clear analytical signals. The lack of tools to detect and quantify NPs in food and feed is a major constraint to describe mobility, exposure, uptake, metabolism and risks associated with the use of NPs in food or feed.

Thus, no individual technique can satisfy a meaningful characterization of NPs. The optimum set of techniques should be selected on the basis of the investigated NP type and its surrounding matrix. Since the characteristics of the NPs (e.g. particle size, size distribution, potential agglomeration and surface charge), can change in different matrices, or as a result of dilution, it is crucial for toxicity studies and consumer exposure assessment that the physico-chemical characterization is performed in the matrix containing the NPs as administered to consumers [6]. Consequently, development of analytical devices for determination of NPs in food matrix is urgently needed.

CONCLUSIONS

Very little information is available on the oral toxicity of nanomaterials and the information on physico-chemical properties of NPs is also limited. These pieces of information are essential for proper risk assessment and for understanding the mechanisms of nanoparticle toxicity [6]. In this paper we made an attempt to assess conceivable interactions of insoluble biopersistent nanoparticles with food matrix and living systems following from their physico-chemical properties and to outline the analytical methods for the NPs determination in food matrix.

Our deductions indicate that nanoscale materials have a unique ability to interact with all biopolymers, particularly with proteins. The deductions underline the catalytic activity of the NPs

primarily in oxidation reactions. These reactions may lead to the formation of reactive oxygen species and to the oxidation stress. However, other catalysed reaction paths should also be considered. The ability of NPs to act as nuclei or germs in the induced heterogeneous crystallization is also indicated. This item was not considered up to now. However, indications exist that the heterogeneous crystallization could take place in living systems [31, 32]. Our deductions represent an assessment of the most probable behaviour of NPs and their interaction with food matrices and living systems. In order to support the conclusions, quantum-chemical calculations would be desirable to predict the dependence of physico-chemical properties on particle size.

There remain many unknown details about the interaction of nanoparticles with biological systems. Our conclusions on the interaction of NPs with living systems can be arbitrarily used also for other ways of exposition and they support the conclusion that nanoparticles, on exposure to tissues and fluids of the body, will immediately adsorb onto their surface some of the macromolecules that they encounter at their portal of entry [1].

The available experimental data do not unambiguously suggest that all materials with nanoscale dimensions are inherently hazardous. However, consideration of the basic science of how materials interact with biological systems does indicate that material's properties can change when size is decreased into the nanoscale range [3] and that nanomaterials may be more biologically active than bulk materials. It is obvious that the effects of NPs will depend on the number and size of NPs present in the matrix. Many questions remain still unanswered and further basic research is needed on such issues as dose descriptors or interactions with subcellular structures. Such research should take an interdisciplinary approach, involving experts in physics, physical chemistry, chemistry, material science, toxicology, molecular biology, medicine and bioinformatics. We believe that our deductions could be conducive to find the directions in further research.

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