Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 100 (2018) 86-98 EISSN 2392-2192

Nanotoxicology and Human Health

Paolo Di Sia

University of Padova, School of Engineering & Department of Neuroscience,
Stradella S. Nicola 3, I-36100 Vicenza, Italy

E-mail address: paolo.disia@gmail.com

ABSTRACT

The particular chemical-physical properties of nanomaterials make them exploitable in different fields of application. Nanoparticles represent fundamental instruments for medicine and biology, because they can be used for biomedical applications (diagnosis, therapy, theranostics, etc.). However, their development with therapeutic efficacy requires in-depth knowledge of the interactions with cells, for both improving their efficiency use and to reduce its toxic effect. Physics and mathematical modelling help in understanding the diffusion mechanisms of charges inside a nanostructure and therefore in the comprehension of carrier dynamics at that scale.

***Keywords*:** Biological systems, Nanotoxicology, Nanobiotechnology, Nanobiomaterials, Health, Nanophysics, Mathematical Modelling

1. INTRODUCTION

Nanosciences are the meeting point of different disciplines ranging from physics and mathematics to supramolecular chemistry, from material science to molecular biology, and represent an established reality in the world of research. Nanotechnologies aim to exploit and apply methods and knowledge deriving from nanosciences. Metallic and non-metallic nanoparticles, potentially usable in anitumoural therapy, are characterized by spectroscopy and electron microscopy, and their effects (in terms of biodistribution and toxicity) are

(Received 08 May 2018; Accepted 22 May 2018; Date of Publication 23 May 2018)

evaluated using *in vitro* models (normal and transformed cell lines) and *in vivo* (mammals and non-mammals). Since the conventional parameters of traditional toxicology are no applicable to nanostructures, a new discipline, nanotoxicology, studies the safety of nanotechnologies and aims to evaluate the risks associated with exposure to nanomaterials, considering the entry ways of nanostructures in the human organism and investigating the molecular mechanisms related to toxicity [1].

Human body can come into contact with nanomaterials of synthetic origin through three main ways:

a) inhalation through the respiratory tract;
b) ingestion through the gastro-intestinal tract;
c) absorption through the cutaneous way [2].

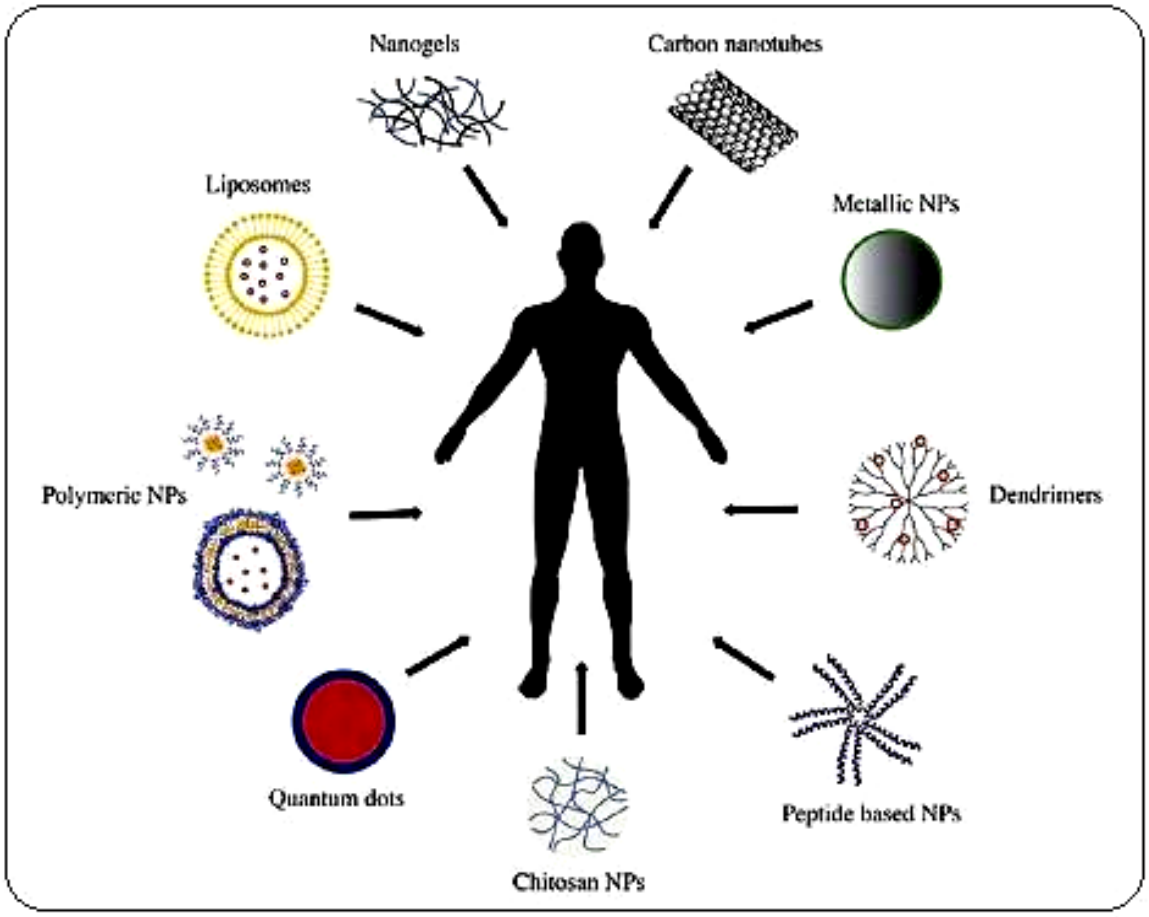

Figure 1. Example of nanostructures used for the production of new drug delivery systems.

Once inhaled, ingested or absorbed, nanostructures can reach the bloodstream, transported and accumulated at the level of various organs. Studies conducted *in vivo* on animals have shown that nanoparticles can induce inflammatory reactions at pulmonary and cardiovascular levels, and to be accumulated in many organs such as liver, spleen, lymph nodes and bone marrow [3,4].

Nano- and microparticles are daily ingested; mainly they are expelled from the respiratory tract by mucociliary clearance or directly ingested in the gastro-intestinal tract (such as silicates and nanoparticles of TiO_2), because present in food products, water, toothpastes, drugs, etc. [5].

The main used nanostructures have a well-defined size, biocompatibility, are inert towards the immune system and have good selectivity (Figure 1) [6,7].

The human exposure to nanostructured particulate is subject of increasing attention in response to the widespread release of nanoparticles from anthropogenic sources and to the rapid development of nanotechnologies. The innovative properties of nanostructures, such as their small size, the extensive surface area, the chemical composition, the solubility and geometry, can contribute to their potential toxicological profile towards biological systems, the human organism (consumers, patients and workers) and the environment.

Therefore, while on one side nanotechnologies are extraordinarily developing in the perspective of expected benefits, on the other the problem of their safety is more insistently placed.

2. INTERACTION OF NANOMATERIALS WITH BIOLOGICAL BARRIERS

In the event that nanoparticles overcome the previously indicated barriers, further ones protect the internal organs:

a) the “blood-brain barrier”, that protects the brain;
b) the “blood-testicular barrier”, that protects the male reproductive system;
c) the “placenta”, that protects the developing embryo.

Parameters such as size, form, chemical composition, solubility, surface structure, state of aggregation can modify the absorption and translocation of nanoparticles from the entry point to the final destination within the human body.

3. THE RESPIRATORY PATH

One of the main ways through which we voluntarily or accidentally enter in contact with nanostructures is represented by the lungs. The deposition efficiency of inhaled nanoparticles depends mainly on their diameter and aerodynamic characteristics; in fact, size and shape are important for determining which compartment of the respiratory system will result predominantly exposed among upper air ways, lower air ways and alveoli.

Particles are efficiently deposited in the entire respiratory tract, from the nasal cavity to alveoli, through diffusion mechanisms [8-10]. Small nanoparticles have the possibility to travel more deeply into the respiratory tree, to settle and be absorbed by the pulmonary epithelium entering therefore in circulation, while those with a larger diameter are more easily stopped at the level of upper respiratory cavity and expelled through mechanisms of mucociliary clearance (Figure 2).

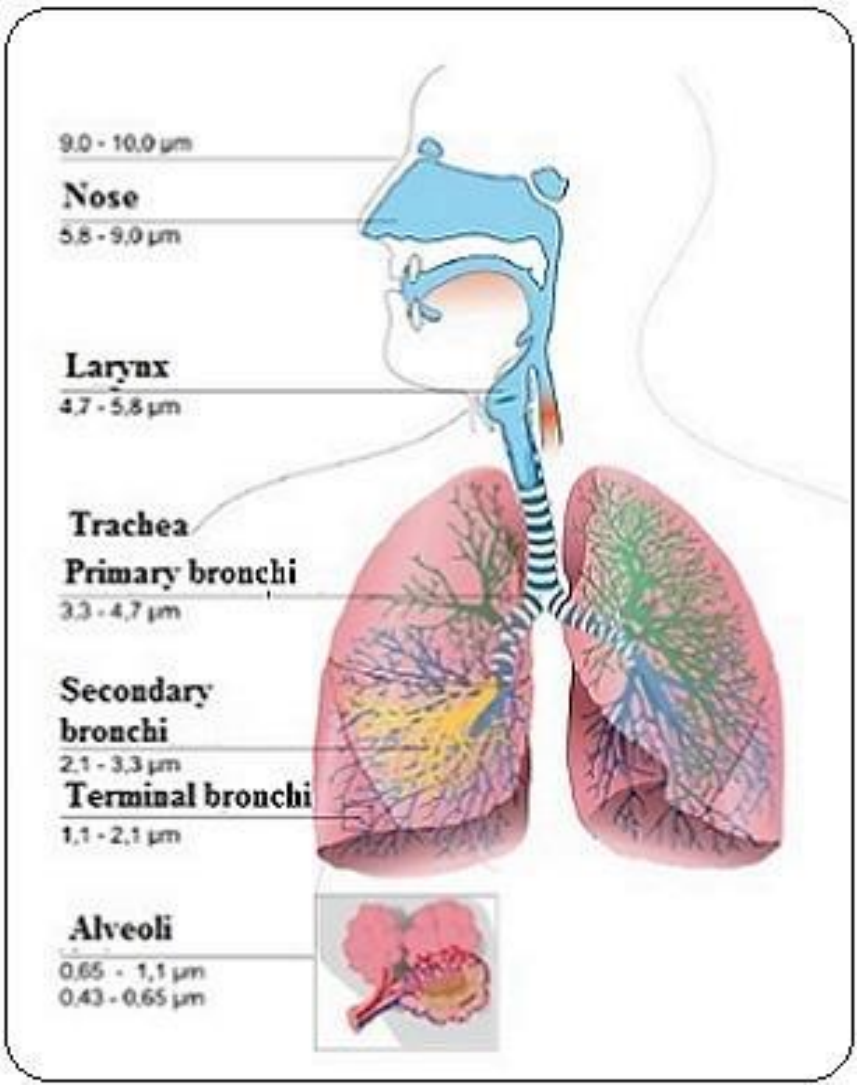

Figure 2. Penetration of dust into the respiratory system.

Pulmonary clearance depends not only by the total mass of inhaled nanoparticles, but also by their size and surface area. The muco-ciliary transport is essential for clearance of the upper respiratory tract, while at the alveolar level nanoparticles translocate via trans-cytosis through the epithelium of the respiratory tract reaching the pulmonary interstice, where later they can be phagocytosed by alveolar macrophages or directly enter the circle blood or via lymphatic way.

Recent studies have shown that it is possible a translocation of inhaled nanoparticles to extrapulmonary sites, such as circulatory system, heart, liver and brain [11-13]. Factors that most influence the pulmonary toxicity of nanomaterials concern the number and size of nanoparticles, the surface coating, the degree of aggregation/agglomeration, the surface charges, the synthesis method. The aggregated nanoparticles can also disaggregate, in contact with particular liquids, and can behave like single nanoparticles, moving to internal organs.

4. GASTRO-INTESTINAL ABSORPTION

As previously introduced, ingested nano- and microparticles (from 100 to 3000 nm) are expelled by the respiratory tract or directly ingested in the gastro-intestinal tract with food products, water, drugs, etc. [14]. Once ingested, they are conveyed to the stomach and subjected to normal digestive processes.

In the enteric tract, the absorption kinetics is complex and can occur by diffusion through the mucus layer, by contact with enterocytes, by translocation; the smaller is the nanoparticles diameter, the faster will be the total absorption process. If nanomaterials resist to gastric digestion, they can move from the lumen of intestinal tract through M-cells of Peyer's plates and, once reached the sub-mucosal tissue, can reach both the lymphatic follicles (inducing an immune response) and the capillaries, reaching therefore different peripheral organs [15].

The translocation of the ingested particles by the intestinal lumen to blood and the systemic circulation may be influenced by chemical-physical properties of nanoparticles such as dimension, form, composition and charge; studies both on rats and on humans have demonstrated that TiO_2 particles of size 150-500 nm, once ingested, can move to the systemic circulation and accumulate in liver and spleen.

Experimental evidence allows to state that even larger particles can be absorbed with persorption mechanisms inside vacuoles and thus cross the intestinal epithelium for localizing at the level of liver and other organs [16]. Other studies show however that ultrafine metal nanoparticles, once ingested, are not significantly translocated to the systemic circulation and hence to other organs [17].

5. SKIN ABSORPTION

The possibility of nanomaterials transport through healthy skin is still controversial, especially for particles larger than 1 μm, while there are numerous experimental evidences on the possibility of trans-dermal transport in case of damaged skin, depending by physical variables as form, size and surface charge of nanoparticles. Once the dermis is reached, nanoparticles can reach the lymphatic vessels, transported by macrophages and dendritic cells; from the lymphatic circle it is supposed that these nanostructures can access the bloodstream and be distributed to the whole body.

6. CROSSING OF BLOOD-BRAIN AND PLACENTAL BARRIERS

Nanomaterials that circulate in the blood can enter the central nervous system through the overcoming of the blood-brain barrier. Despite this is a highly selective barrier and allows the passage only by trans-cellular way, in many pathologies, such as hypertension and allergic encephalomyelitis, the permeability of the hemato-encephalic barrier decreases and allows the passage of nanoparticles. The surface charge of nanoparticles can alter the integrity of the blood-brain barrier, with possible consequences on the use nanomaterials for drug delivery in the central nervous system, but also on toxicity in the brain. It has been shown that nanoparticles induce oxidative stress; this last is one of the factors involved in

neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (Figure 3) [18].

The placenta is a particular secondary biological barrier, because it performs its function only for a limited period, the nine months of pregnancy of woman. During this period, the human placenta presents variable thickness and permeability, resulting thicker and less permeable during the first quarter, thinner and more permeable in the last three months. In the latter time, therefore, there is a possibility that external substances (including external nanoparticles) can cross it.

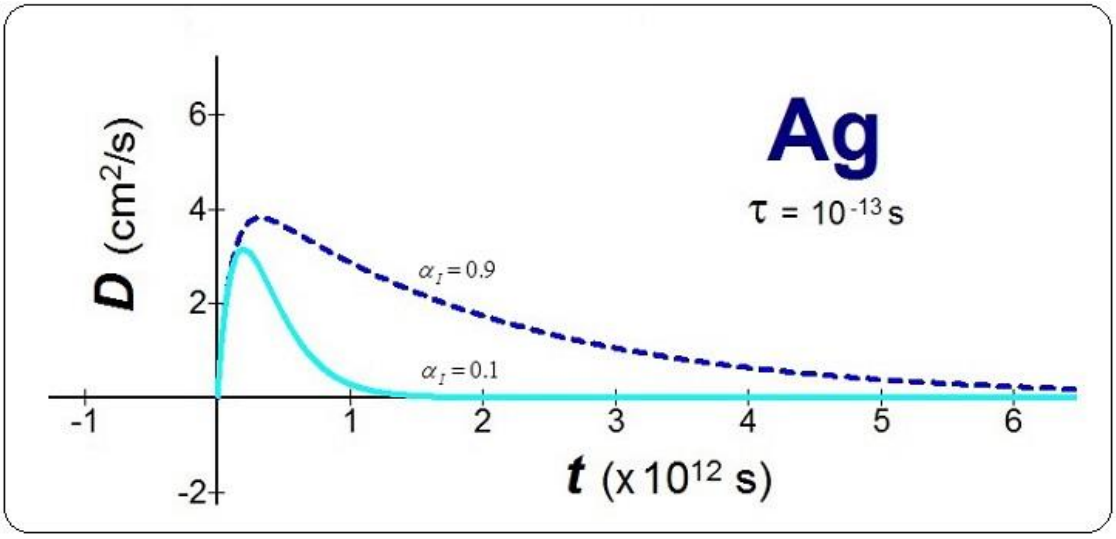

Figure 3. Diffusion vs time for nanosilver [8,10,13].

The assumption of potentially harmful agents in the very early stage of pregnancy can cause structural and functional alterations of the organ. There is indirect evidence that the assumption of some nanoparticles at this time can cause serious damage to placenta, associated with a high rate of spontaneous abortions and embryo malformations [19].

7. UPTAKE AND INTRACELLULAR FATE OF NANOMATERIALS

Still work must be done to get adequate information on the mechanisms involved in cell uptake of nanoparticles; however, it seems that the mechanism of internalization and the intracellular fate of a nanosystem are influenced by particular factors, such as:

a) chemical-physical properties of the material with which the nanosystem is composed (chemical composition, dimensions, shape and geometry, surface charge, state of aggregation, surface coating) [20];
b) the experimental conditions adopted by *in vitro* experiments;
c) the characteristics of used cells and therefore the cell line and the state of differentiation.

In particular, the surface characteristics of nanoparticles are a crucial factor, since, in addition to determine the biocompatibility, they play a fundamental role in cell adhesion [21]. It has been shown that the adhesion between cells, extracellular matrix and particles is regulated mainly by integrins, a protein family of receptors involved in superficial adhesion. The cytoskeletal matrix interacts not only with integrins but also with proteins responsible for cellular internalization processes, including especially endocytosis, which is the main mechanism of entry of nanoparticles.

In general, a substance can enter the cell through simple diffusion or through endocytic processes such as phagocytosis, macropinocytosis, clathrin-mediated endocytosis and caveolae-like mediated endocytosis. Simple diffusion is the only one of the listed processes that does not require energy, but simply exploits the presence of a concentration gradient; usually only small and apolar molecules, which diffuse through the double phospholipidic layer, exploit this process.

The term endocytosis indicates instead the internalization by a cell of macromolecules and solutes within membranous vesicles originating from plasmatic membrane invagination (Figure 4).

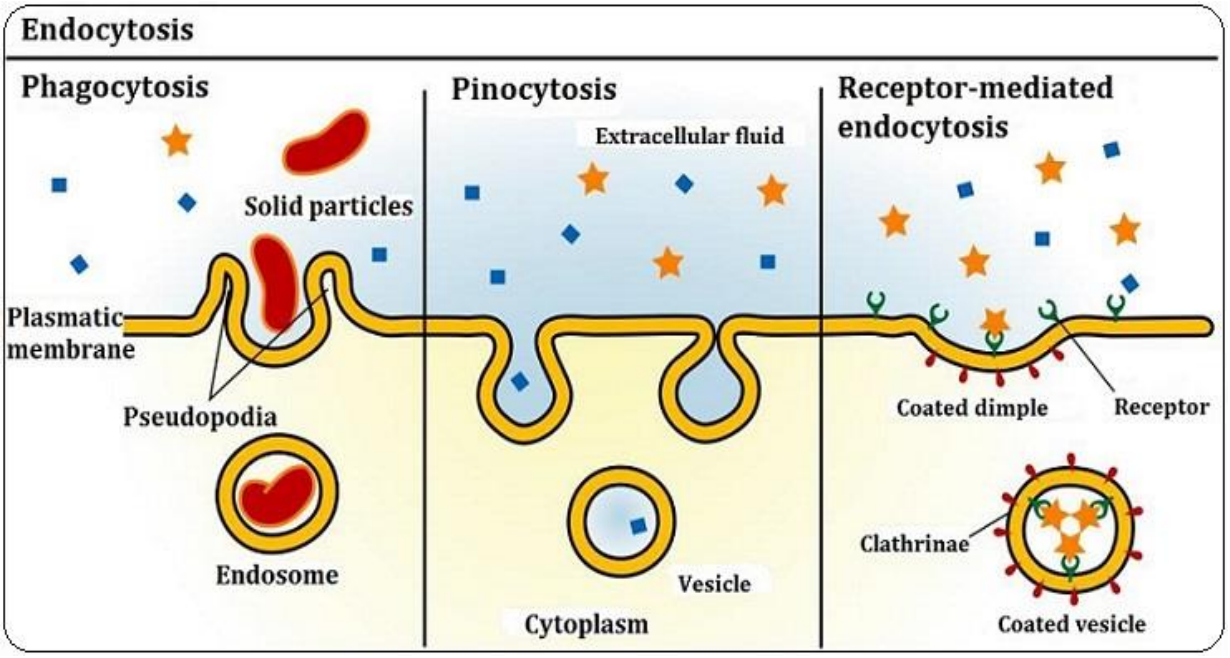

Figure 4. The different types of endocytosis.

Phagocytosis is possible only for some specialized cell types called phagocytes, such as macrophages, monocytes and neutrophils, which are able to remove material even larger than 0.5 μm (bacteria, yeasts, debris), through a specific interaction between receptors of the phagocytic cell and ligands on the surface of particle. This leads to a consequent invagination of the membrane, favored by the actin protein, and to the formation of vesicles (the phagosomes) containing the material to be eliminated.

Macropinocytosis consists in the formation of large and irregularly shaped vesicles (macropinosomes), generated by actin-dependent plasma membrane invagination too [22]. The intracellular fate of macropinosomes is strongly dependent by the degree of specialization of the cell; in macrophages, for example, they blend with lysosomes, while in other cell types they constitute a distinct vesicle population that does not interact with endocytic compartments, but promote the recycling of the content towards the plasmatic membrane.

Clathrin-mediated endocytosis (CME) is the most frequent endocytic pathway and is normally used by the cell for the continuous supply of nutrients, antigens and growth factors [23]. CME is a type of receptor-mediated endocytosis; the initial phase consists in the recognition, by the cell, of the substance to be internalized through the interaction with specific membrane receptors.

The cytoplasmatic portion of the receptor bound to its ligand has a high affinity for clathrin. When a sufficient number of receptors linked to the specific ligand and to clathrin are found on the plasmatic membrane, they tend to merge into a single region by lateral diffusion; the clathrin molecules thus form, binding to each other, a kind of net that induces a localized flexion of the membrane, forming the so-called “coated dimple”.

This deepens further to close in itself, separating from the cell membrane and forming a real coated vesicle. These vesicles move to the inner regions of cytoplasm and at some point in their progression they lose the clathrinic coating; the disassembled clathrin is recycled, the naked vesicles merge together giving rise to the endosomes, within which the low pH value promotes the dissociation between ligands and receptors. Finally the endocytated material can be accumulated inside the cell, or undergo to lysosomal degradation or transcytosis.

The endocytosis mediated by caveolae is active only in some types of cells, especially endothelial, muscular and adipose cells. Caveolae take their name by the protein that originates them, the caveolin, and consist of small invaginations of the plasmatic membrane rich in glycosphingolipids and cholesterol, and associated with particular types of molecules [24]. The endocytosis mediated by caveolae is a defined non-acid and non-digestive internalization pathway, because in the caveole no acidification of the content is going on and because there is no fusion of vesicles with lysosomes; the endocytated material can be transferred directly into the Golgi apparatus or into the endoplasmatic reticulum.

Examples in literature regarding the uptake of nanostructures show how the cell is able to simultaneously use several different mechanisms and how the characteristics of nanostructures significantly influence their intracellular fate. In addition to surface characteristics, that play a fundamental role in cell adhesion, the surface charge is another fundamental property in determining cellular uptake of nanoparticles. The plasmatic membrane has in fact a net negative charge due to the presence of the phosphatidylserine in the inner sheet and furthermore the distribution of ions on the same cell membrane causes a positive polarization towards the external environment. The anionic nanoparticls are then endocitated in smaller amount than the cationic ones.

The influence of the presence of charges on the surface of nanoparticles has been proven [25], experimentally verifying how the internalization of nanoparticles, coated with albumin and positively charged, by monocytes and macrophages, is greater than that of the same type of particles without charge. However, it has also been shown that there is no increase in the internalization efficiency from dendritic cells of nanopaticles in positively charged polystyrene [26].

The antithetical conclusion supports the thesis that there are no fixed rules for the mechanisms used in the uptake of nanoparticles, but there is simply a strong dependence by the chemical-physical characteristics of materials and by the type of cellular system used for *in vitro* experiments. For example, it has been observed how, depending on the cell type with which nanoparticles come into contact, their ability to penetrate inside cells varies. Studies performed on alveolar macrophages isolated by mice demonstrated how silica nanoparticles are rapidly internalized due to the exceptional ability of such cells to phagocytize external particles. On the contrary, for human lung carcinoma cells (A549) the speed of uptake is considerably lower [27].

Moreover, these cells of pulmonary origin can be involved in different internalization mechanisms; by simple diffusion in the case of fluorescent microspheres of polystyrene [28], or by clathrin-mediated endocytosis, for example for silica-coated magnetic nanoparticles [29,30].

8. ONGOING STUDIES ON THE TOXICITY OF NANOPARTICLES

Nanoparticles toxicity studies available in the literature are generally of two types:

a) "epidemiological studies" of human effects;
b) *in vivo* "experimental studies" in animals and *in vitro* on cell cultures conducted with artificial nanoparticles.

Different nanoparticles in terms of shape, size and composition have different toxicological characteristics. According to the emerging risks of the European Commission (SCENIRH), nanoparticles have different toxicological properties by original substances and therefore there is the need to assess the risks "on a case by case basis".

Artificial nanoparticles produced with nanotechnologies presumably will represent an important source of exposure for humans; agencies involved in risk assessment are promoting the development of strategies for the definition of risk related to the industrial use of nanomaterials both in food and in other industrial areas that can cause environmental contamination.

Most of studies have identified the missing information for the definition of the risk and indicated a series of goals that must be achieved in the coming years, as to evaluate the exposure to artificial nanomaterials in air and water, methods to study their toxicity and to predict the impact on environment and human health.

9. CONCLUSIONS

People are exposed to natural and anthropogenic nanomaterials for a long time, while artificial nanoparticles are new agents, to which we begun in recent years to be exposed.

Nanoparticles are commonly found in food, either endogenous (proteins, such as ferritin) or exogenous ones, voluntary (artificial, such as TiO_2) or accidental (primary or secondary contaminants). In the gastro-intestinal lumen, in addition to the ingested ones, endogenous nanoparticles can be found, in the form of nano-crystals originating by the intra-

luminal precipitation of partially soluble salts. The human gastro-intestinal system is therefore continuously exposed to nanomaterials of various origin, shape, size and composition.

A correct assessment of the associated risk for human health requires a complete and robust set of qualitative and quantitative data on exposure, absorption, distribution, metabolism, excretion and toxic effects, to be linked with modelling about nanotransport. Studies must also clarify the relative importance of different ways of exposure, the mechanisms of possible toxic effects, the relation between substance toxicity in bulk and in nanoform [31-39].

Biography

Paolo Di Sia is currently adjunct professor by the University of Padova (Italy). He obtained a bachelor in metaphysics, a master in theoretical physics and a PhD in theoretical physics applied to nanobiotechnology. He interested in classical-quantum-relativistic nanophysics, theoretical physics, Planck scale physics, metaphysics, mind-brain science, history and philosophy of science, science education. He is author of 250 works to date (papers on national and international journals, international book chapters, books, internal academic notes, works on scientific web-pages, popular works, in press), is reviewer of two mathematics academic books, reviewer of 12 international journals. He obtained 9 international awards, has been included in Who's Who in the World every year since 2015, selected for 2017 and 2018 "Albert Nelson Marquis Lifetime Achievement Award", is member of 7 scientific societies and of 30 International Advisory/Editorial Boards.
https://www.paolodisia.com

References

[1] Gatti, A. M., Montanari, S. 2015. *Case Studies in Nanotoxicology and Particle Toxicology.* Cambridge: Academic Press.

[2] Oberdorster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Kreyling, W., and Cox, C. 2004. Translocation of inhaled ultrafine particles to the brain. *Inhalation Toxicology* 16(6-7): 437-445. doi: 10.1080/08958370490439597.

[3] Singh, S., Nalwa, H. S. 2007. Nanotechnology and health safety: toxicity and risk assessments of nanostructured materials on human health. *Journal of Nanoscience and Nanotechnology* 7: 3048-70.

[4] Di Sia, P. 2016. Advances in Analytical Modelling for (Nano)medicine. *International Journal of Innovative Science, Engineering and Technology* 3(5): 511-515.

[5] Lomer, M. C., Thompson, R. P., Powell, J. J. 2002. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. *The Proceedings of the Nutrition Society* 61(1): 123-30.

[6] Etheridge, M. L., Campbell, S. A., Erdman, A. G., Haynes, C. L., Wolf, S. M., and McCullough, J. 2013. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. *Nanomedicine* 9(1): 1-14. doi: 10.1016/j.nano.2012.05.013.

[7] Di Sia, P. 2014. Interesting Details about Diffusion of Nanoparticles for Diagnosis and Treatment in Medicine by a new analytical theoretical Model. *Journal of Nanotechnology in Diagnosis and Treatment* 2(1): 6-10.

[8] Di Sia, P. 2011. An Analytical Transport Model for Nanomaterials. *Journal of Computational and Theoretical Nanoscience* 8: 84-89.

[9] Di Sia, P. 2012. An Analytical Transport Model for Nanomaterials: The Quantum Version. *Journal of Computational and Theoretical Nanoscience* 9(1): 31-34.

[10] Di Sia, P. 2012. Modelling at Nanoscale. In: *Plasmonics - Principles and Applications*. Rijeka: InTech. doi: 10.5772/50755.

[11] Gwinn, M. R., Vallyathan, V. 2006. Nanoparticles: Health Effects-Pros and Cons. *Environmental Health Perspectives* 114(12): 1818-25. doi: 10.1289/ehp.8871.

[12] Di Sia, P. 2014. Relativistic nano-transport and artificial neural networks: details by a new analytical model. *International Journal of Artificial Intelligence and Mechatronics* 3(3): 96-100.

[13] Di Sia, P. 2015. A new analytical transport model for (nano)physics. *International Research Journal of Engineering and Technology* 2(7): 1-4.

[14] Butler, M., Boyle, J. J., Powell, J. J., Playford, R. J., Ghosh, S. 2007. Dietary microparticles implicated in Crohn's disease can impair macrophage phagocytic activity and act as adjuvants in the presence of bacterial stimuli. *Inflammation Research* 56(9): 353-61. doi: 10.1007/s00011-007-7068-4.

[15] Hoet, P. H., Brüske-Hohlfeld, I., Salata, O. V. 2004. Nanoparticles - known and unknown health risks. *Journal of Nanobiotechnology* 2(1): 12. doi: 10.1186/1477-3155-2-12.

[16] Hagens, W. I., Oomen, A. G., de Jong, W. H., Cassee, F. R., Sips, A. J. 2007. What do we (need to) know about the kinetic properties of nanoparticles in the body?. *Regulatory Toxicology and Pharmacology* 49(3): 217-29. doi: 10.1016/j.yrtph.2007.07.006.

[17] Wachsmann, P., Lamprecht, A. 2012. Polymeric nanoparticles for the selective therapy of inflammatory bowel disease. *Methods in Enzymology* 508: 377-97. doi: 10.1016/B978-0-12-391860-4.00019-7.

[18] Saraiva, C., Praça, C., Ferreira, R., Santos, T., Ferreira, L., Bernardino, L. 2016. Nanoparticle-mediated brain drug delivery: Overcoming blood–brain barrier to treat neurodegenerative diseases. *Journal of Controlled Release* 235(10): 34-47. https://doi.org/10.1016/j.jconrel.2016.05.044.

[19] Muoth, C., Aengenheister, L., Kucki, M., Wick, P., Buerki-Thurnherr, T. 2016. Nanoparticle transport across the placental barrier: pushing the field forward!. *Nanomedicine* 11(8): 941-57. doi: 10.2217/nnm-2015-0012.

[20] Chithrani, B. D., Chan, W. C. 2007. Elucidating the mechanism of cellular uptake and removal of protein-coated gold nanoparticles of different sizes and shapes. *Nano Letters* 7: 1542-1550.

[21] Gupta, A. K., Gupta M. 2005. Cytotoxicity suppression and cellular uptake enhancement of surface modified magnetic nanoparticles. *Biomaterials* 26: 1565-1573.

[22] Swanson, J. A., Watts, C. 1995. Macropinocytosis. *Trends in Cell Biology* 5: 424-8.

[23] Takei, K., Haucke, V. 2001. Clathrin-mediated endocytosis: membrane factors pull the trigger. *Trends in Cell Biology* 11: 385-91.

[24] Shin, J. S., Abraham, S. N. 2007. Caveolae-not just craters in the cellular landscape. *Science* 293: 1447-8.

[25] Roser, M., Fischer, D., Kissel, T. 1998. Surface-modified-biodegradable albumin nano- and microspheres II: effects of surface charges on in vitro phagocytosis and biodistribution in rats. *European Journal of Pharmaceutics and Biopharmaceutics* 46: 255-63.

[26] Foged, C., Brodin, B., Frokjaer, S., Sundblad, A. 2005. Particle size and surface charge affect particle uptake by human dendritic cells in a vitro model. *International Journal of Pharmaceutics* 298: 315-22.

[27] Jin, Y., Kannan, S., Wu, M., Zhao, J. X. 2007. Toxicity of luminescent silica nanoparticles to living cells. *Chemical Research in Toxicology* 20: 1126-1133.

[28] Geiser, M., Rothen-Rutishauser, B., Kapp, N., Schürch, S., Kreyling, W., Schulz, H., Semmler, M., Im Hof, V., Heyder, J., Gehr, P. 2005. Ultrafine Particles Cross Cellular Membranes by Nonphagocytic Mechanisms in Lungs and in Cultured Cells. *Environmental Health Perspectives* 113: 1555-60.

[29] Kim, J. S., Yoon, T. J., Yu, K. N., Noh, M. S., Woo, M., Kim, B. G., Lee, K. H., Sohn, B. H., Park, S. B., Lee, J. K. 2006. Cellular uptake of magnetic nanoparticles is mediated through energydependent endocytosis in A549 cells. *Journal of Veterinary Science* 7: 321-326.

[30] Choi, H. S., Liu, W., Misra, P., Tanaka, E., Zimmer, J. P., Ipe, B. I., Bawendi, M. G., and Frangioni, J. V. 2007. Renal Clearance of Nanoparticles. *Nature Biotechnology* 25(10): 1165-1170. doi: 10.1038/nbt1340.

[31] Di Sia, P. 2013. The Nanotechnologies World: Introduction, Applications and Modeling. In: *Fundamentals and Applications*. Houston: Studium Press LLC.

[32] Di Sia, P. 2014. Present and Future of Nanotechnologies: Peculiarities, Phenomenology, Theoretical Modelling, Perspectives. *Reviews in Theoretical Science* 2(2): 146-180.

[33] Di Sia, P. 2017. Nanotechnologies among Innovation, Health and Risks. *Procedia - Social and Behavioral Sciences Journal* 237: 1076-1080. http://dx.doi.org/10.1016/j.sbspro.2017.02.158.

[34] Di Sia, P. 2015. Present and Future of Nano-Bio-Technology: Innovation, Evolution of Science, Social Impact. *The Online Journal of Educational Technology* (TOJET). Special Issue 2 for INTE 2015: 442-449.

[35] Som, C., Berges, M., Chaudhry, Q., Dusinska, M., Fernandes, T. F., Olsen, S. I., Nowack, B. 2010. The importance of life cycle concepts for the development of safe nanoproducts. *Toxicology* 269: 160-169.

[36] Scown, T. M., Van Aerle, R., Tyler, C. R. 2010. Review: do engineered nanoparticles pose a significant threat to the aquatic environment? *Critical Reviews in Toxicology* 40: 653-670.

[37] Theng, B. K. G., Yuan, G. 2008. Nanoparticles in the Soil Environment. *Elements* 4(6): 395–399. doi: https://doi.org/10.2113/gselements.4.6.395.

[38] Fröhlich, E., Roblegg, E. 2012. Models for oral uptake of nanoparticles in consumer products. *Toxicology* 291(1-3): 10-17. doi: 10.1016/j.tox.2011.11.004.

[39] Di Sia, P. 2019. Agri-food sector, biological systems and nanomaterials. In: *Food Applications of Nanotechnology*. Boca Raton: CRC Press (Taylor & Francis Group).