PRESIDENZA DEL CONSIGLIO DEI MINISTRI
National Bioethics Committee

NANOSCIENCES AND NANOTECHNOLOGIES

Approved in the plenary meeting of the 9th of June 2006

Summary: Presentation – 1. Introduction – 2. Nanotechnologies and health: the "nanobiotechnologies" – 3. Nanobiotechnologies' critical profiles – 4. Adequacy of existing methodologies in assessing the risks associated with the products of nanotechnologies – 5. Normative policy trends – 6. Bioethical synthesis and recommendations – Essential bibliography.

PRESENTATION BY THE NBC'S PRESIDENT

On Prof. Luca Martini's suggestion, in the plenary meeting of the 23rd of April 2004, the *National Bioethics Committee* has decided to create a working group dedicated to the bioethical problems arising from the spread of the *nanosciences* and by the consequent establishment of new, and often hard to imagine by the general public, *nanotechnologies*. Prof. Salvatore Amato, Prof. Demetrio Neri, Prof. Adriano Bompiani, Prof. Paola Binetti, Prof. Isabella Coghi and Prof. Renata Gaddini immediately decided to join the group and afterwards Prof. Silvio Ferrari and Doctor Laura Guidoni also joined. From the 27th of May 2004 to the 16th of March 2006, the group met fourteen times and also invited precious contributions from external experts. In fact, Doctor Renzo Tomellini, chemist, head of the nanosciences and nanotechnologies unit for the European commission; Prof. Paolo Milani (Physics Department at the Universita' degli Studi di Milano – Centre of excellence in Nanotechnologies); Prof. Enzo di Fabrizio (Univarsita' Magna Gracia in Catanzaro, member of the Area Science Park in Trieste); Doctor Guido Rasi (CNR); Prof. Mauro Ferrari (Ohio State University – Institute of nanotechnologies and microtechnologies for biomedical application – and Universita' di Pisa) collaborated with the Committee, and therefore are dutifully thanked for their great generosity and the sincere friendship they showed us.

The document's draft, drawn up by Prof. Marini (warmly thanked by all the Committee for his efforts in drawing up a considerably complex text), was brought to the NBC's attention during the plenary meetings of April and May 2006. With some variations, born through intense group discussions during the plenary meetings, the text was finally unanimously agreed upon on the 9th of June 2006.

Those who will read this document, will immediately perceive its most apparent characteristic, which is its in depth and full introduction to a long and subtle series of cutting-edge bioethical issues that are mostly not yet known by the wider public. From this point of view, it is fair to believe that, with this document, the NBC has been truly pioneering in this field. However, behind this informative role, which the NBC has always felt necessary to undertake, the document precisely highlights numerous and thorny bioethical issues, the solution of which (if not final, at least possible) will be made possible only by further experiences and by even richer scientific reflections. We must in fact assess data that many bioethicists' impatience disregards: that is, that not all bioethical issues (and in particular the most recent ones) are such that they can have, in a short space of time, solutions so convincing that they can be considered consolidated. The bioethicists' task, in many cutting-edge cases, like the ones discussed in this document, is not to offer ethical certainties to the general public, but to exactly and precisely describe the problematic importance of issues that are destined to stay unresolved maybe for a very long time. It is for this reason, maybe, that more than naïve leaps forward, what suits bioethicists is careful and cautious evaluation.

Prof. Francesco D'Agostino
President of the *National Bioethics Committee*

1. INTRODUCTION

Having been introduced a few decades ago[1], "nanosciences" and "nanotechnologies" apply to particles whose size is measured in nanometres, equivalent to a billionth of a metre (or, if preferred, a millionth of a millimetre), a dimension that is tenth of thousand of times smaller that the width of a human hair[2].

The term nanosciences is used to indicate the numerous and varied scientific fields (physics, chemistry, biology) that have an interest in nanotechnologies. These should allow original industrial and commercial applications in a variety of sectors, from medicine to information technology and communication, from energy production to the production of new materials. A branch of nanotechnologies, the one most known in the biomedical field, is dedicated to the construction of devices on a molecular scale, through the transferral of the laboratory of synthesis on the nanometric scale (molecular nanotechnologies). Then there are the nanostructures, which today constitute the cutting-edge of miniaturisation and have applications especially in the field of electronics. Finally, nanostructured materials are being developed, which involve the introduction of materials whose size is only a few tenths of a nanometre, in products such as ceramic or steel, with the purpose of improving their characteristics.

As nanotechnologies have as their object the manipulation of materials at the atomic and molecular level, the nanometric dimension of the manipulated material opens applicative horizons that were unthinkable in the past, because the properties observable at this level can be used, even on a different level, to develop procedures and products characterised by new functions and performances, in a possibly unlimited number of sectors[3].

We must consider, as examples, the diagnostic and therapeutic possibilities (in particular the miniaturised devices to be implanted in the human body for diagnostic purposes or a material capable of improving the biocompatibility of transplanted organs), the applications in the information technology and communications fields (as in the case of the support in storing data with a very high density of registration), the electromagnetic molecular devices and, more in general, the new "nanomaterials", characterised by extremely original and diverse properties, like being anti-scratch and self-cleaning or extra-resistant to a variety of situations. Some of the aforementioned products, in addition, have already been introduced into the market: bandaging and cardiac valves, electronic components, anti-crease and anti-stain fabrics, anti-scratch paint, sun creams and cosmetics are becoming part of the European citizens' consumption habits and have reached a market value estimated at around 2.5 billions of euros[4]. Less known are, instead, some applicative possibilities of the

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[1] Cf. R.FEYNMAN's predictions at the end of the 1950s: *There's Plenty of Room at the Bottom,* in *Eng. And Sci.*, 1960, number 23, p.22. Possibilities of development in the application of such technology have been presented a few years later, by K.E. DREXLER, *Engines of Creation. The Coming Era of Nanotechnology*, anchor, New York, 1986 and ID., *Nanosystems: Molecular Machinery, Manufacturing and Computation,* 1992.

[2] In the international measurement system, the prefix "nano" indicates $10^{-9,}$ that is, a billionth of a unit (0,000000001).

[3] We must clarify that what has been said also applies to nanosciences and to the scientific principles that can be inferred on the basis of the study of phenomena that can be observed at the nanometric level.

[4] Reliable estimates predict, by 2015, the development of a volume of business in the hundreds of billions of euros each year: cf. the document of the DEPARTMENT OF TRADE AND INDUSTRY,

nanotechnologies in the food sector (with particular reference to the tracing of food through the use of miniaturised labelling systems), in energy production and conservation (the new fuel cells or the new light nanostructured solids, able to guarantee efficient systems of hydrogen accumulation), in environmental protection (photocatalytic techniques based on nanotechnologies) and in security (selective surveys systems of chemical or bacteriological agents and techniques, like the marking of banknotes, able to increase the protection of goods)[5].

From a conceptual point of view, the interdisciplinary (or "convergent") approach to nanotechnologies focuses around two alternative methodologies: the first, based essentially on assembly procedures, consists of the miniaturisation of materials or devices (the so-called *top-down* approach), whilst the second, based on synthesis procedures, tries to create new structures starting at the atomic and molecular level (the so-called *bottom-up* approach or "atomic technology"). It is especially the second methodology, although still at the embryonic state, that seems destined to "revolutionise" current production processes, significantly contributing to the saving in raw materials and to the reduction of the emission of polluting substances during the entire life cycle of the new products.

The variety and multiplicity of the aforementioned applications make nanotechnologies into true "horizontal technologies" or "enabling", because they can, as it has been mentioned, permeate all technological sectors. This requires and includes an interdisciplinary approach, necessary to combine a variety of knowledge and competences to aid scientific research and the development of the relative technological applications: from chemistry to physics, from engineering to biology, from computing to genetics. It is therefore easy to understand why the entire scientific community (and also especially industry and, more in general, the wider public) looks at nanotechnologies as the "technologies of the future" and asks for the highest economic, financial and, not least, political/institutional support for them.

Next to the enthusiasm of many, and although agreeing with the idea that the ability to work at "nanoscale" level constitutes a triumph of human ingenuity, we also point out the caution of those who believe that they can identify some criticisms for nanotechnologies. For these technologies, as for many others, we feel the need to assess not only the advantages that they will be able to bring to the improvement of the quality of life, but also the risks (especially for the environment and human health) connected and consequent to the development of nanotechnological applications. On the other hand, the public perception of the nanotechnologies' real or perceived risks seems widespread, also because it has been recently fuelled by some newspapers and by literature, which have represented with success, apparently without distorting available scientific data, narrative situations in which issuing invisible nanoparticles in the environment turns into existential threats for mankind's survival[6]. It therefore appears evident that there's a need to promote, with regards to

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New Dimensions for Manufacturing: a UK strategy for nanotechnology, London, 2002, p24. Currently, the global expense for research in this sector is 7 billion euros per year (source: La Repubblica, 27th of March 2006, p. 14). Only in the European Union, the financial support offered by the European Community's Frame Programs of scientific research and technological development, will go from 1300 million euros for the period 2002-2006 (VI Frame Program) to about 4800 million euros for the period 2007-2011 (VII Frame Program).

[5] For an outline of the variety of applications of the nanosciences and nanotechnologies, we firstly refer you to the European Commission's documents *Verso una strategia Europea in favore delle nanotechnologie* e *Nanoscienze e nanotechnologie: Un piano d'azione per l'Europa 2005-2009*, on which we'll return later.

[6] For all, look at M. CRICHTON's *best-seller*, *Prey*, Milan, 2002.

nanosciences and nanotechnologies, an open and constructive debate between science and society, in order to distinguish between scientific data and sensationalism or unfounded fears about the effects of these new technologies on health, safety, environment and society. As well as providing a first organic and systematic study on the bioethical implications of nanotechnologies and "nanobiotechnologies", with this *Opinion* the NBC intends to promote a wider circulation and an easier understanding of these issues even by a non-specialist public, in accordance with its institutional aims. For this purpose, the *Opinion* first of all describes the nanotechnologies' most important applications (immediate and hypothetical) in biomedicine (paragraph 2), and then evaluates some critical profiles of the nanobiotechnologies (paragraph 3) and the adequacy of the existing methodologies to assess the risks – in particular those of a toxicological and ecotoxicological nature – associated with nanotechnological products (paragraph 4). In addition, both international and European normative policy trends will be examined (paragraph 5), whilst the concluding paragraph (paragraph 6) will summarise the document and its bioethical recommendations.

2. NANOTECHNOLOGIES AND HEALTH

Potentially "positive" aspects of the applications of nanobiotechnologies

The application of nanotechnologies in biomedicine has the objective of achieving a complete and constant monitoring of the human organism and of contributing to healthcare, working at the molecular level to achieve medical and clinical benefits through the use of nanodevices and nanostructures. In particular, the February 2005[7] report on nanomedicine by the *European Science Foundation*, identifies three main areas in the development of the research on the production of nanomaterials and nanodevices: the optimisation of already existing devices for a wider application in the medical sector; the development of new multifunctional systems for the diagnosis of illnesses and the focused administration of drugs; an increase in the competences and knowledge which would allow the production of increasingly more reliable, specialised, renewable materials, increasing their efficiency and lowering costs.

According to statements we have found in the literature on this topic, statements that are often still completely futuristic and at the level of conjecture, the development of the ability to use nanoparticles in medicine opens new horizons. An important example, from the ones cited, regards the gold nanoparticles, as it has been proven that they can act as heat "concentrators", causing the selected area to overheat, which is lethal for the surrounding cells[8].

Through the use of biolinkers, the nanoparticles can be designed to act on precise targets. The idea of using, as transporters of anti-tumour drugs, vesicles or viral particles coated with molecules able to direct the vector towards the cells that need to be selectively eliminated is not new. The biolinker molecules are absorbed or incorporated in the nanoparticles and are able to bind themselves to specific cells or tissues, directing in such a way the nanoparticles and their contents to the target

[7] Cf. European Science Foundation Policy Briefing, number 23, February 2005.

[8] In recent literature refer to Zharov, V.P., M. Everts, D.T. Curiel, J.W. Kim. Integrated Photothermal Nanodiagnostics and Therapy with Gold Nanoclusters. Nanomedicine, 2005, Enhancement of tumor thermal therapy using gold nanoparticle–assisted tumor necrosis factor- delivery Rachana K. Visaria, Robert J. Griffin, Brent W. Williams, Emad S. Ebbini, Giulio F. Paciotti, Chang W. Song, and John C. Bischof Mol Cancer Ther 2006 5: 1014-1020.

organs. Up until now few clinical studies exist on this topic, however they are destined to a rapid increase.

Besides strengthening, as in this case, already existing techniques, nanobiotechnologies should allow the construction of multiple sensitive devices of *in vitro* analysis and measuring, the production of new tissues and artificial organs, the training of biological systems to repair other biological systems in support of regenerative medicine[9], the conception of "3-D displays" for biomolecular signals emission, sensors and mechanisms for the mobile and *in vivo* telemetric control, the elaboration of multifunctional diagnostic systems in connection with the intelligent administration of drugs, the refining of bioanalytic methods in order to understand the functioning mechanisms of cellular and molecular systems.

We presume that, in a short time, we could be able, through instruments of analysis that use nanoimages, to know the beginning and the progression of an illness, monitoring in real terms and *in vivo* the cellular and molecular processes. A biotechnological marker to identify the stress of the neurons is in phase of elaboration by an international net of researchers, according to a study recently published on *The Journal of Experimental Medicine.* According to this study, the mutation of a gene that regulates the protein Eaat2 indicates the reduced presence of the neurotransmitter that, if in low concentration, is often a sign of the possibility of nervous cells becoming ill. If applied on a large scale, the *marker* could support the prevention of illnesses of the central nervous system, often followed by just as serious cardiovascular syndromes, which reduce the amount of nutrients and oxygen reaching the tissues.

In addition it will be possible to identify new biological objectives for analysis and therapies, a more rapid passage from experimentation on animals to clinical application for human beings, the closing of the *gap* between molecular and cellular technologies and clinical diagnosis. In the long term, we should be able to design nanoinstruments of analysis *in vivo* and non-invasive, with a high level of sensitivity, reproducibility and reliability, in order to use them to identify the symptoms of illnesses, in the design and synthesis of new molecules, in the analysis of all sub-cellular components at the molecular level, and in the development of cellular functions in support of the immune system. Particularly precious seem to be the indications we could obtain to identify the profiles of genic expression responsible for specific differentiating trends in multipotent stem cells.

These new therapeutic and pharmacological perspectives will be possible through the setting up of nanocapsules with a particular composition that, overcoming the biological barriers, will be able to transport the drug and to release it in a focused manner. In the long term, we can hypothesize the conception of bioreactive synthetic systems able not only of intercellular transport of macromolecules for a therapeutic purpose, but also able to self-regulate, creating nanostructures made by biosensors

[9] A nanotechnological "bridge" that would allow torn nervous tissues to reconstitute and start carrying out their original physiological functions again is the basic idea of the project, by a team of MIT researchers, whose positive results have recently been published in Proceedings of the National Academy of Sciences of the United States of America (Dynamic reassembly of peptide RADA16 nanofiber scaffold. H. Yokoi, T. Kinoshita, and S. Zhang (2005). PNAS 102: 8414-841). The group identified a peptide that reorganises itself, assuming its original form of nanofibers "bridge", in length and width, even after having been fractured by ultrasounds. The procedure has been successfully repeated four times. This work allows us to hypothesize important developments, for example in the creation of new structures for 3-D cellular cultures, for the repairing of tissues in regenerative medicine, for the therapy in serious plegic and neurodegenerative pathologies.

joined with transport mechanisms[10]. The design of nanostructured sensitive supports (for example, artificial biological tissues) could, in addition, allow the immediate identification and the control in time of the manifestation of degenerative phenomena, preventing the spreading of cancer, of neurovegetative, cardiovascular, pulmonary, ocular diseases, and others.

What do we know about the health risks associated with nanotechnological products?

Despite such inviting possibilities, there's no lack, in literature, of more cautious reflections. The high surface/mass relationship, the "atomic" dimensions and the ease with which nanoparticles can absorb and carry other substances: the same characteristics that make nanomaterials attractive, also suggest a certain caution in their use in biomedicine. In fact, if the extreme penetrability of nanoparticles is the secret of their potential, we must not underestimate the risks connected with their nano-dimensions, seen as a variety of sources highlight how the possible interactions between nanoparticles and the human body are still unclear. Little known, until today, is the effect that materials of atomic dimensions can have on the human organism: the little we know, although extremely promising with regards to the possible applications, seems not completely reassuring with regards to the possibility of even serious undesired collateral effects[11].

We must stress that the use of substances of submicronic dimensions in the pharmaceutical industry has long shown a level of interaction with biological systems and has allowed us to establish the first safety rules in the field. However, especially most recent studies on ultrafine powders (those of dimensions smaller than a tenth of a micron), and in particular those relative to the smallest fractions of these classes of *aerosol*, arouse the greatest worry and direct the course of the first specific investigations. Ultrafine powders derived from carbon combustion, carbon black, diesel engine particles and soldering fumes: these are the materials containing significant fractions of nanometric dimensions which, as we already know, have adverse effects on health (even if some of these materials, mostly considered undesirable pollutants, are often not subjected to specific tests). To the listed substances, considered dangerous, we must then add materials specifically produced and already on the market: sun protective creams with titanium dioxide, self-cleaning and insulating glass (also with TiO2), materials supporting and prolonging catalytic processes, semiconductive metal nanotubes, pigments and carbon black *toner*, *fillers* containing amorphous silicones, organic nanoparticles used in the pharmaceutical industry and others. There's no evidence that these materials are considered dangerous.

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[10] On this point, it is possible to imagine situations like the ones described by A. DIASPRO, Nanobiorobot. Oltre la fantascienza, in Darwin, 2005, p. 54 e ss. In scientific literature, see Role of nanotechnology in targeted drug delivery and imaging: a concise review. Otilia M. Koo, Israel Rubinstein, Hayat Onyuksel, Nanomedicine: Nanotechnology, Biology, and Medicine 1 (2005) 193–212; Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer Ernest S. Kawasaki, Audrey Player, Nanomedicine: Nanotechnology, Biology, and Medicine 1 (2005) 101–109; Donaldson K, Tran CL., An introduction to the short-term toxicology of respirable industrial fibres. Mutat Res. 2004 Sep 3;553(1-2):5-9.

[11] We report the results that have emerged from the first international Symposium on the implications of nanomaterials on the workers' health, organised by the British Health and Safety Executive and by the National Institute for Occupational Safety and Health, which took place the 12th, 13th and 14th of October 2004 in Buxton, in the United Kingdom.

We must also however report other statements. The nanomaterials already in mass production (or "bulk NP, where NP stands for Nano Particles), are already known and tried (also with regards to the potential adverse effects) in comparison to the "engineered NP". However, the knowledge regarding nanotubes, originally considered as a variety of fullerene, but also revealed as morphological curiosities in the area of natural carbon particles, is very advanced[12]. It's especially the nanotubes, and their potential applications (even as equipment to operate in the ultrafine), to generate less known and potentially dangerous risks. The main preoccupation is that, as has already been demonstrated in other fields, materials that are not toxic when in sufficiently big particles can be harmful when in nanometric dimensions. That the dimension of the inhaled particles is to be taken into account is by now a known fact. From the notorious fine powders, deriving from the combustion of petrol and diesel oil, which are one of the main elements of urban pollution, we already know that the smallest they are, the more dangerous they are. The PM 2.5 (where PM stands for "Particulate Matter"), with a diameter smaller than 2.5 micron, produce worse effects than the PM 10: in fact they reach the lungs' deepest parts and seem able to cause tumours. If, as it appears, the biological effect depends on the exposed surface, in equal doses the more the particles are small, the more they are dangerous. A NASA toxicologist, Chiu-Wing Lam, studied the effect of carbon nanotubes, molecules discovered at the beginning of the 1890s, which are predicted to give us materials a hundred times more resistant and six times lighter than steel, and are today produced only in small quantities. Instilling in mice's lungs a suspension of aggregated nanotubes, an operation which is not exactly considered equivalent to inhalation, the animals had the same reaction of irritation caused by the powder. Instead, when the nanotubes were administered as separate particles, lesions appeared in the lungs. Nanotubes are long and thin particles. In the case of asbestos, one of the most critical factors is its fibrous form. Could it be the same for nanomaterials? Some investigations conducted in past years – and, according to Green Peace, ignored by the media – give us worrying results: inhaling a 5 milligrams dose of nanotubes per kg of body weight, 15% of animals died, but not because of the substance's toxicity. Nanotubes aggregated to the point of obstructing the rats' bronchial tubes: the rats were suffocated[13]. The biological damage therefore can depend, with different effects, both on the nanoparticles' dimensions, and on the nanoparticles' state of aggregation.

Other studies look at the molecular systems used to take drugs over the hematoencephalic barrier or inside cells. Up until now no harmful effects have been observed, but there's very little research in this field. The Center for biological and environmental nanotechnology at Rice University (USA) is one of the main laboratories with regards to the study of environmental impact. There, it was observed how the *buckyball*, molecules made up of 60 carbon atoms[14], "travel" on the ground: it appears that, if they can aggregate, they are absorbed like any other organic

[12] Unlike diamonds and graphite, solids at infinite lattice, fullerenes are the only finite form of carbon. In October 1996 the Nobel Prize for Chemistry was given to researchers Harold Kroto, Robert F. Curl e Richard E. Smalley for discovering fullerene (also called by some "*buckyball*"), which takes its name from the American architect Buckminster Fuller, known for his projects of habitation modules in geodetic dome shape based on pentagons and hexagons.

[13] See what is reported by C. PALMERINI, *Nanoinquinamento*, in *Panorama*, 26th September 2003.

[14] The *buckyball*, the basic component of the fullerene, is made up of 60 carbon atoms arranged in 20 hexagons and 12 pentagons, like a football. When this structure is forced to stretch, through a variety of chemical-optical-electrical procedures, a nanotube is formed.

compound, but that, left free to disperse, they penetrate the ground without being absorbed. One of the fears is that such molecules could join in this way to other contaminants, like pesticides, and maybe penetrate in the organism of worms or other animals, entering the food chain.

Prevention in working places and for the environment: current state of knowledge

For now, the only subjects at risk of inhaling nanotubes are those who produce them: researchers in 16 companies around the world. Some Japanese companies have already announced that they want to start producing them in large quantities and experts think that there's a potentially large relevant market. The objections to the criticisms regarding their safety is that laboratories take the necessary precautions and that, in any case, nanotubes are not made to be breathed in.

In work hygiene is by now consolidated the distinction of powders according to their granulometry (or, more precisely, according to their "equivalent diameter") on the basis of their ability to reach various parts of the respiratory tract and to get stuck there. Particles whose dimensions are between 5 micron and 0.5 micron are part of the so-called "breathable fraction". Particles with a smaller diameter and especially extremely fine ones, until about a decade ago were considered inert substances: it was believed, that is, that they were inhaled and exhaled without interfering with the structure of the pulmonary epithelia. In particular, the reduced interaction of these particles with the typical mechanisms for the removal of the respiratory tree (mucociliary, macrophage and lymphatic) led us to think that their participation to the pathogenesis of pulmonary damage was insignificant.

Physics has long since shown that ultrafine powders are kept in suspension by the Brownian motion: therefore, they are not subject to inertial fall or to sedimentation and they tend to stay suspended in the air indefinitely, from which they are removed only by currents or by rain. In addition, because of the Brownian motion, the distribution of these powders in space depends only from the way in which they are diffused. From this derives that the environmental hygiene and the technical normative that regulates the sampling of confined air and defines its classes (UNI-EN 481) has in effect neglected (and, indirectly but substantially, underestimated) ultrafine fractions. The European Normative Committee, aware of all this, has long since warned analysts, highlighting the particular difficulty of applying the regulations of the "sampling convention" when sampling and characterising soldering fumes. We refer to the points following in this document for the evaluation of the adequacy of existing methodologies in assessing the risks associated with nanotechnology products. We must stress that particles smaller than 0.5 micron, whose absorption is regulated almost exclusively by their diffusion, should be evaluated using, instead of the "equivalent diameter" criteria, the so-called "diffusive diameter".

Only in more recent years, and especially in the field of the studies on atmospheric pollution of urban areas, epidemiological and experimental data have called the attention back on fine powders: the by now known PM 10 and in particular the smaller fractions (the PM 2.5 – which represent about 60% of the PM 10 – and the PM 1)[15].

[15] Oberdorster G, Oberdorster E, Oberdorster J. *Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles*. Environ Health Perspect. 2005 Jul;113(7):823-39. Review.

There are two critical points of the respiratory apparatus through which, essentially by diffusion, nanoparticles penetrate in the organism: during turbulent air movements at the nasal coana level and at the alveolar level, where instead air is in "flat calm". Easily going through the alveolar epithelium and the endothelium, ultrafine powders go into the blood where, probably due to a mechanism of oxidation, they actively participate to ateromasic processes: from this derives an increase of cardiovascular pathologies (heart attack, thrombosis, etc.), which has been observed in epidemiology and experimentation. In addition, because of the emetic distribution, it can potentially affect all organs: in fact, the organs that appear particularly affected are those that have a tight vascular net, like liver and spleen, as it has been shown with regards to the workers in the carbon industry, especially if already affected by pulmonary pathologies. However, the accumulation of particles in the liver and spleen does not seem to lead to particular pathologies, with the exception of a possible procoagulatory action at the epathic level.

Instead, the nasal absorption seems to be associated with a peculiar tropism (maybe through the cranial nerves) with the encephalic tissue: in particular, the powders' small dimensions would allow them to overcome the so-called hematoencephalic barrier, with the consequent increase in toxic neuropathies. The passage of radioactive nanoparticles, administered to rats by inhalation, to the olfactory lobo has been experimentally demonstrated. However, the differences between the various types of powders are not negligible: essential is the particles' chemical composition, because of the relative toxicological properties linked not only to their structural components (essentially carbon), but also to the presence of pollutants (dangerous are the metals) even in traces. Rats exposed to soldering fumes show clear evidence of neurological illnesses caused by manganese.

The skin penetration of NP has been experimentally studied, but with controversial results. Only the smallest particles – but a very small percentage of them – seem able to go through the corneal stratum, and this happens especially when the skin is subjected to a trauma. The nanoparticles' coalescence through the forces of Van der Waals tends to generate particles of a diameter of tenths of millimicrons. In the case of nanotubes, particles of dishomogeneous dimensions can be generated. Such particles tend to be stringy (with a diameter of around 20 nanometres and a length up to one mm) or flat in shape. The same can be said of semiconductive metal nanotubes.

Some experimental data (intratracheal administration of *multi-wall nanotubes* to rats) highlight inflammatory responses and fibrotic pulmonary reactions similar to the ones due to the inhalation of asbestos. Other experimental studies have demonstrated the possibility of the passage of nanoparticles into the pulmonary interstice. The inflammatory response of the pulmonary parenchyma, measured in quantity of neutrothreads present in the liquid of the bronchoalveolar wash, seems to be linked to the superficial area of the inhaled particles and, if the surface is equal, it is emphasised in the case of ultrafine particles. Titanium dioxide and *carbon black* particles are known causes of fibrosis and tumours in rats. Moreover, all chronic inflammatory pathologies of the lung seem to be linked with a higher occurrence of neoplasis and maybe the only licit conclusion is to admit that there's still not enough knowledge of the chronic effects and/or pulmonary neoplasia of nanoparticles.

Finally, we must mention two other difficult aspects of the risks involved in the production processes. The quantity of energy used to bring the reagents (generally graphite) to a plasma state and the need to use metal catalysts (especially aluminium), as well as the dimensions of the nanomaterials so obtained, make the electric risk and

the risk of explosions particularly critical and difficult to manage. Because the powders' capability to explode is linked to their mass-surface relationship and to their concentration, it is clear that the risk of explosion (especially high for metal powders) is always present. The use of technologies in inert atmosphere have so far prevented big accidents, but it is the little knowledge of these particles' explosive behaviour in their ultrafine state, which makes this a problem deserving of attention and deeper study. Similar considerations can be made with regards to the validity of protective equipment and devices in the industrial manipulation of nanomaterials. For the protection of the respiratory system it seems that class 3 (FFP3) anti-dust facial masks can offer sufficient protection, at least for powders with a diameter bigger than 2 nanometres.

3. ADDITIONAL CRITICAL PROFILES OF NANOTECHNOLOGIES

General aspects

It must be taken into account that the problems we will discuss in this paragraph, should we go beyond the phase of research and strictly controlled experimentation, are mere hypothesis (or "*Apocalyptic Nightmare*")[16], which at the moment appear difficult to verify because of the lack of specific studies and official information. Many of these critical profiles are typical or common to any technological innovation, but, in this case, we are faced with a sector with extensive scientific and social potential, which could redefine the traditional barriers between biology, physics and chemistry, so that according to some[17] it is indispensable to elaborate a new ethics in support to the science of the future, anticipating and preventing the consequences of certain choices. The USA Senate, in approving, on the 18th of November 2003, the *21st Century Nanotechnology Research and Development Act*, has highlighted the risks of "self-replicating nanoscale machines or devices; the release of such machines in natural environments; encryption; the development of defensive technologies; the use of nanotechnology in the enhancement of human intelligence; and the use of nanotechnology in developing A.I. (Artificial Intelligence)". Similar doubts on the possible negative outcomes have been put forward, more cautiously, and then immediately put aside in the document titled *Social and Economic Challenges of Nanotechnology*, published in July 2003 by the *UK Economic and Social Research Council.* For these reasons, the NBC believes that it is appropriate to examine some of the most uncertain aspects of nanotechnologies, making no claim to having exhausted the issue and wanting to avoid alarmism, with the only aim to accept the invitation made in the document of the *Economic and Social Research*, point 27: "We need to have rational and mature public dialogue informed by good science. This will explore the acceptable uses of new technologies, and processes whereby the outcomes of dialogue help to shape the policies introduced by the Government"[18]. In particular we will examine the

[16] As in BERT GORDIJN, From utopian dreams and apocalyptic nightmares towards a more balanced view, in Proceedings of the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST) Third Session (held in Rio de Janeiro from the 1st to the 4th of December 2003), p. 115 and following.

[17] Ibidem

[18] "Engagement of the scientific community in regular dialogue with the general public in order to discover likely public concerns early, and continuation of dialogue to address and alleviate public concerns by the presentation of clear facts" is also the anxiety expressed by the *ESF Scientific Forward Look on Nanomedicine* in "European Science Foundation Policy Briefing", February, 2005, n. 23, p. 5.

following profiles: the combination between inorganic and organic molecules (the problem of self-replication); the social and economic fallouts (nanopoverty); the control of the individual and the protection of privacy; the military or terrorist uses; the repercussions on human identity.

A singular aspect: the combination between organic and inorganic molecules

It seems appropriate to dwell on the problems that nanotechnologies could give in the form that is called "advanced"[19]. In this case, nanotechnologies do not only give us new technological opportunities for the production of materials or plastic and chemical substances (fullerene, nanotubes, nanoparticles, nanocapsules, nanopores, *nano dots*, *nano wires*), but combine inorganic nanomaterials and organic molecules, intervening in the cellular metabolism to affect molecule production or the transmission of information, or to create new cellular structures or supports for the construction of new complex molecules or atom assemblers to create new molecular orders. Therefore we have the intentional alteration of living organisms through DNA manipulation to create *moleculesize machines*, devices that synthesize a variety of macromolecules piece by piece, penetrating and integrating into the cells of living organisms. The already mentioned work by Drexler calls these biological devices "assemblers" and describes them as "living machines" capable of self-reproducing, hypothesizing that "with assemblers, we will be able to remake our world or destroy it"[20]. These are mere suppositions, capable of suggesting the scientifically questionable adventures of the novel *Prey* by Crichton, but absolutely futuristic in relation to the current development of this technology. Futuristic, but not unfounded, because research is studying in more depth the idea of creating nanomaterials, applying the "bottom up" model of construction of cellular structures. There's a very subtle (although not only semantic) difference between "construction bottom up", for "self-assembly of DNA to sort carbon nanotubes", and self-replication.

"Nanopoverty"

If in reality nanotechnologies should keep their promises to increase the length and quality of life, to improve physical conditions, to reduce pollution and the cost of energy and raw materials, the differences between rich and developing countries could become even more apparent. Even now, many of these countries have an extremely limited access to electricity, information, education, drugs; the introduction of even more sophisticated technologies which are even more connected to one another, presents the risk of turning the current differences in development into discrimination, an intolerable form of "poverty of poverty": the "nanopoverty". On this subject, as on the economic effects of biotechnologies, there's a profound divergence of opinions and some even think that only nanotechnologies could help developing countries to overcome some of their pressing needs, as the investments of India Thailand, Chile, Argentina, Mexico in this sector, seem to show[21].

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[19] J. P. DUPUY, *Complexity and Uncertainty. A Prudential Approach To Nanotechnology* prepared for the March 1-2, 2004 meeting of the Directorate-General for Health and Consumer Protection of the European Commission, "Mapping Out Nano Risks".

[20] Cf. K. E. DREXLER, *Engines of Creation. The Coming Era of Nanotechnology*, cit., p. 174.

[21] For the opposite point of view: F. SALAMANCA-BUENTELLO, D.L. PERSAD, E. B. COURT, D.K. MARTIN, A.S. DAAR et Al. *Nanotechnology and the developing world*, in PloS Medicine, April 2005, 2, p. 4 .

Biosurveillance and privacy

We have already mentioned that one of the most promising uses of nanobiotechnologies in medicine regards the possibility of preventing the arising of illnesses through miniaturised cybernetic laboratories (*lab on a-chip technology*). Diagnostic nanospheres are already being trialled on humans. It is also believed that these chips would make genetic tests simpler and more immediate. Everyone could keep him/herself under constant medical observation. Nanoparticles could be used also as support for the release of drugs aimed at annihilating or repairing individual cells. Materials of nanometric dimensions can constitute the substrata in which viruses or DNA molecules can be encapsulated or ordered. The interaction between biomolecules and nanoparticles, nanotubes or nanometric surfaces can be used to identify specific proteins or viruses, as well as to carry the molecules to the target. The extraordinary advantages of these techniques in prevention and aimed care, let us hypothesize the possibility to eliminate, essentially through prevention, the incidence of deadly diseases, like cancer, during the current generation. However, we must take into account the complex problem of the enormous psychological pressure that this potential self-monitoring could create. Is the idea of being constantly under observation tolerable? How would it impact on the relationship between health and illness? How would it be possible to continue to guarantee the privacy of sensitive data? The same technology that allows the introduction of "DNA chips" in the organism to carry out medical screenings or to release drugs, also allows the building of nanosensors, nanocameras and nanomicrophones. A functional and mobile telemetric control with sensors and devices *in vivo*, could be used both for diagnostic purposes as well as political purposes, in order to achieve an integral control of the whole population without it realising it (not even partially)[22]. We stress that all this is already possible without the use of nanotechnologies. The so-called *smart tags*, based on *RFID (Radio Frequency Identification)* technology, are currently used to control access to ticket offices or in transport. These are objects that are much smaller than a tenth of a millimetre and therefore completely invisible. There is no technological difficulty in further reducing their dimensions and in widening their functions to control, integrally and inadvertently, every aspect of private life. Nanotechnologies could increase this risk, because it would be extremely difficult to prevent the same nanochip that releases a drug to also be programmed to carry out other functions. These are futuristic possibilities, but technologically possible.

Some go even further and hypothesize the creation of a nanochip able to condition the nervous system from a distance. The same mechanism that allows us to overcome the cerebral barriers to interact with specific molecules or to release a drug could be used, maybe with a judge's authorisation, to repress certain violent impulses or to control certain forms of sexual perversions. Crichton also wrote about this problem, a long time ago and without yet thinking of nanotechnologies, in another novel, *The Terminal Man*, in which he hypothesized the use of a system of electrodes to control from a distance crisis of homicidal violence caused by a strange form of epilepsy. In the *Introduction* Crichton reported statements by James V. McConnell of Michigan University: "Listen, we can do these things. We can control behaviour. Now, who's going to decide what's to be done? If you don't get busy and tell me how

[22] A. GRUNWALD, *Nanotechnology* - A New Field of Ethical Inquiry? in Science and Engineering Ethics, 2005, 11, pp. 187-201.

I'm supposed to do it, I'll make up my own mind for you. And then it's too late"[23]. We must not transform novelistic hypothesis in bioethical problems, however we also cannot ignore that the problem of control and eventual conditioning from a distance becomes extremely current as an effect of the biometric measures of identification and examination, which are increasingly more invasive and sophisticated, and also as an effect of the extreme miniaturisation of the possible monitoring instruments. If the electronic tag is considered a licit way to control subjects on probation, what would stop us from using the much more refined and safe nanotechnologies? If chemical castration is invoked to prevent certain sexual crimes, why not ask, if the technology is available, the inhibition of any violent behaviour through a nanochip? Even if these are mere hypothesis, or even novelistic suggestions, a reflection on the ethical limits of biosurveillance, on the relationship between freedom and safety, does not seem to be deferrable: when does control become conditioning and when does conditioning become a violation of personal integrity?

Terrorist and military uses

We point out that a nanochip capable of operating in the human body can be more easily programmed to destroy than to cure. The ability to interfere with the cellular metabolism would open, to those interested in bacteriological war or terrorism, enormous destructive capabilities. If then these nanomachines could self-replicate, the instrument would be even more dangerous than the atomic bomb, but more precise, less costly, simpler to build and to use but harder to identify. The very small size would make their transportation and release in the environment extremely simple. In this case the risks would be worsened by the fact that nanoparticles can reproduce and can easily penetrate both the skin and the hemato-cerebral barrier. The nanoparticles' ability to interact with sub-cellular structures is not very known and the scientific community is far from being unanimous in excluding its potential dangers[24]. On the other hand, if it's possible to hypothesize the strengthening of immunity barriers (*mosquito nets*) to reduce the incidence of infectious diseases, it is just as possible to hypothesize the elaboration of opposite systems that would inhibit the immunity defences. The biotechnological mechanisms of the two operations are the same. In abstract, terrorists could easily get relatively innocuous forms of toxins or chemical substances and with a small manipulation make them into instruments of death, through the possibility of making them interact with the organism, altering the metabolic processes. This is a simple technology, much simpler than the one needed to create traditional chemical or bacteriological weapons. For example, it is theoretically possible, through a nano-machine, to build in great quantity, molecule by molecule, the anthrax toxin without having access to the *Bacillus anthracis*[25]. The same technology could be used to attack mechanical or electronic systems, blocking nuclear plants, power plants, airports, information systems. The self-replicating nanoparticles could act in the same way as computer viruses: automatically activating themselves and spreading until the destruction of the basic functioning elements. What measures can we adopt against these dangers? Clearly the issue is not stopping research, but causing an awareness of the profound ambivalence of certain

[23] New York, Harper Collins Publishers, 1972, p. XV.

[24] C. ZANDONELLA, *The Tiny Toolkit*, in *Nature*, 423, 1st of May 2003, p. 11.

[25] J. ROTHSTEIN WOLFSON, Social and Ethical Issues in Nanotechnology: Lessons from Biotechnology and Other High Technologies, in Biotechnology Law Report, 376- 22, Number 4 (August 2003), p. 381.

developments[26], supplying information and feeding public debate. To minimise the risks and highlight the advantages could, in the short term, have a reassuring effect, but would end up, in the long term, creating a void of conscience and therefore of democracy. In ethical choices it is not always possible to guarantee everybody's good, but it is certainly important for everybody to participate in the decisional process.

Human identity

We state that nanotechnologies, in conjunction with biotechnology, electronic and medicine, will allow us to radically intervene on the human body to repair it or to develop its abilities. It is possible to think about the construction of organs or tissues for transplants but also to repairing or widening compromised sensorial functions, for example widening the electromagnetic spectrum of visual perception. The connections between electronic and the nervous system are already being studied, through *nanoelectronic neuro-implants (neurobionics),* which would allow us to correct sight or hearing defects. If it was possible to connect cerebral activity to systems of data elaboration, what would open up, which is suggestive as well as futuristic, is the possibility of *uploading*: extracting the information contained in a human brain and replicating it in a calculator. Specialised nanomachines should pass cerebral tissue through the scanner, atom by atom. Then the information should be digitalised and implemented through appropriate software that would allow for it to be preserved and transferred. Looking at this same issue from the point of view of the machine rather than the man, attempts at building "organic computers" that use "flash memory chips", integrated with cellular structures or transistors assembled with carbon nanotubes and DNA fragments, have already been made. The construction of these biological hybrids, from nanomachines to *labs on a chip* and up to organic based computer, profoundly alters the distinction between biology, chemistry and physics, but also the distinction between material and immaterial, material and device. As well as nano-ethics, nano-philosophy has also been mentioned, to highlight the need to rethink all the conceptual categories of human identity "bottom up", starting with the idea that what exists is not man but the nano-particle, with all of the possible ways to assemble it. Even without going that far, facing the purely hypothetical problem of how to qualify, ethically and legally, the content of the brain once it has been scanned and preserved in a nano-chip, it is easy to guess the profound changes that the notion of human identity and personal integrity could undergo[27]. For example, could the development of neurological, mnemonic or visual capabilities be indiscriminately allowed? Who will decide the limits and the possibilities of use? Will the technological domain allow the "production" of biologically superior beings, feeding new forms of racism?

4. ADEQUACY OF EXISTING METHODOLOGIES IN ASSESSING THE RISKS ASSOCIATED WITH THE PRODUCTS OF NANOTECHNOLOGIES

Numerous documents, in recent years, have tried to identify and describe the potential risks linked to or due to the development of nanotechnological

[26] K. GEISER, *Nanotechnology and Environmental and Public Health Considerations*, in "New Solutions", Vol 14(1), 2004, p. 8-18.
[27] R. W. BERNE, *Towards the Conscientious Development of Ethical Nanotechnology*, in *Science and Engineering Ethics*, 2004, 10, pp. 627-638.

applications[28]. In 2005 the European Commission set up the basis for further studies on this issue, asking the independent experts of the Scientific Committee on Emerging and newly Identified Health Risks (SCENIHR) to elaborate a scientific opinion on the adequacy of existing methodologies in assessing the potential risks associated with engineered products or products incidentally derived from nanotechnologies[29]. This opinion, which at the moment is the most exhaustive study on this issue and which we take into account in this paragraph, was elaborated on the basis of acts adopted by the European Commission because of the increasing importance of nanotechnologies in the context of European industrial research and economy, like the conclusions of the European Union Council on the European strategy on nanotechnologies[30], which highlights the importance of the "analysis of the potential risks during the vital cycle of all products that are created starting with nanotechnologies", and the European Union's Plan of Action on nanotechnologies[31]. These documents will be examined in the following paragraph.

The SCENIHR's opinion first of all describes the properties of nanomaterials, then identifies the sources of nanoparticles and examines the suitability of existing procedures in collecting and measuring such structures. In addition, the opinion deals with the toxicological and ecotoxicological profiles of nanoparticles and the potential effects due to an eventual exposition to them, with the purpose of defining, on one hand, the most efficient methods of measuring such exposition, to identify and characterise the risk linked to it and to integrally assess the mentioned elements; and, on the other hand, to fully appreciate the possible interactions between nanoparticles and living systems. The opinion, finally, identifies the most significant gaps in the scientific knowledge necessary to correctly evaluate the risks associated with nanotechnologies and defines the relevant normative profiles on this issue.

To fully appreciate the potential negative effects of nanotechnologies on human health and the environment, the SCENIHR first of all suggests a distinction between two typologies of nanostructure: those in which the structure itself is a free

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[28] Cf. on this topic, as well as the report *The Social and Economic Challenges of Nanotechnology* approved in July 2203 by the British Economic and Social Research Council, which started the public debate on the argument, also the results of the workshop organised in Brussels by the European Commission in March 2004 (cf. *Nanotechnologies: A Preliminary Risk Analysis*); the document N*anosciences and Nanotechnologies: Opportunities and Uncertainties*, adopted on the 29th of July 2004 by The British Royal Society and by The British Royal Academy of Engineering, in http://www.nanotec.org.uk/finalReport.htm (which, although it excludes the existence of valid reasons to worry about the potential risks of nanotechnology applications, highlighted the need to study the issue in more depth and recommended to apply the same caution to nanostructured materials imposed by law on new chemical products); the document elaborated in October 2004 by the Health and Safety Executive of the British Government (in http://www.hse.gov.uk/research/rrhtm/rr274/htm); the report *Down on the Farm* drawn up by the Action Group on Erosion, Technology and Concentration (ETC Group) in November 2004; and the report titled *Characterising the Potential Risks Posed by Engineered Nanoparticles*, adopted in December 2005 by the British Department for Environment, Food and Rural Affairs. This last document identifies three main areas that need to be studied more in depth to create an effective management system for the potential risks linked to or due to the spreading of nanoparticles: a) nanoparticles characterisation, definition and measurement; b) assessment of the nanoparticles' impact on human beings and the environment; and c) understanding of the nanoparticles' origins and of how they move in the environment, also through the human body.

[29] In http://europa.eu.int/comm/health/ph_risk/committees/04_scenihr/04_scenihr_en.htm

[30] Cf. the Commission's communication towards the European strategy in favour of nanotechnologies [document COM92004) 338 def. of the 12th of May 2004], approved by the European Union Council on the 24th of September 2005.

[31] Cf. the document *Nanosciences and Nanotechnologies: A Plan of action for Europe* 2005-2009 [document COM92005) 243 def. of the 7th of June 2005].

particle and those in which the nanostructure is an integral part of a bigger object. Nanoparticles can be naturally generated, or they can be the accidental product of an industrial process, or they can be specifically created to develop applications based on their particular properties[32].

The first problem we encounter in assessing the risks of the spreading of nanoparticles for human beings and for the environment comes from the difficulty of collecting and measuring structures and materials that are below the threshold of being "visible to the naked eye". In fact, referring to the sector under consideration, the SCENIHR believes that using the criteria of the mass concentration is insufficient, and suggests integrating this criteria with other, more suitable criteria (like the concentration number and the surface area), which currently are not taken into account by the applicable laws. In addition, according to the opinion under examination, existing methods for the analysis of the environmental impact of nanoparticles are inadequate in determining the nanoparticles' distribution and persistence in a variety of environmental systems. According to the group of experts from the Commission, from this derives the need to opportunely change the current exposition assessment methods and, in particular, to develop methodologies and instruments that would allow us to *routinely* measure the representative exposition to nanoparticles.

Examining nanoparticles' toxicological and ecotoxicological profiles, the SCENIHR first of all highlights that only some conventional toxicology and ecotoxicology tests have been proven useful in assessing the risks associated with nanoparticles, whilst taking into account the fact that, at the moment, scientific data capable of identifying systematic rules about the toxicological and toxicological properties of nanotechnology products, are not available. From this, according to the SCENIHR, derives that the assessment of the toxicological and ecotoxicological risk should be made case by case, with specific reference to the nanoparticles' ability to affect pre-existent clinical conditions or to increase the predisposition to certain illnesses. A corollary of what has been stated is the need to base the assessment criteria of the toxicological and ecotoxicological risks associated with the spreading and distribution of nanoparticles, on profiles different from the "equivalent material: the correct assessment of the potential risks deriving from nanotechnologies, therefore requires the development of new investigative techniques that will take into account, also *in itinere*, the possible uses of the products under consideration and the potential exposition, both for man and for the environment.

With regards to the possible interactions between nanoparticles and living organisms, the SCENIHR's opinion first of all highlights that, if the nanoparticles interact with living organisms because of their size and properties, we cannot however exclude that bigger structures (e.g. the nanotopographic characters of medical devices) could also present specific risks for human and environmental health. Therefore, in considering the specific risks deriving from nanoparticles, what seems important is not only their size, but also their shape and composition, as well as the amount of absorbed surface; equally important are the modification, aggregation, dissolution or degradation phenomena of the nanoparticles' surface, from which the release of nanoparticles can occur. Given that the immediately soluble nanoparticles lose their specific properties in the physiological environment, it is important to verify

[32] These properties will be influenced primarily by the nanoparticles' surface (in relation to the volume) and by the quantic effects that occur at nanometric level. A careful identification of their physicochemical properties is essential for the purpose of making *routinely* available adequate risk assessment methods.

if they dissolve into harmful molecules or not. With regards to essentially insoluble nanoparticles, there's a chance of biopersistence, arising from the long term exposition and from specific effects associated to nanoparticles. In addition, the nanoparticles' movement can happen at a more extensive level and in different places in comparison to what happens with bigger particles: therefore a systemic distribution and accumulation of such particles could happen. It has been proven that nanoparticles are able to move from their entry point in the human body and reach other areas, including the blood and the brain, although the amount and the importance of this movement is not clear and few studies have been carried out on this issue. In particular, it is uncertain whether nanoparticles can reach the foetus, even though the systemic distribution seems probable in medical applications requiring the parenteral administration of nanoparticles.

In current research, the proof of the toxicity for man of the systemic exposition to nanoparticles intentionally produced is minimal: however, states the SCENIHR, the current guidelines on experiments identifying and characterising the risk of chemical substances and products, do not yet require the identification of the nanoparticles' systemic distribution, despite the existence of some potentially suitable methods[33]. It is different for nanoparticles of natural origin and those generated unintentionally by human activity: they have an exposition risk which potentially extends to an individual's entire life. Their main form of contact with man is inhalation, but the increasing use of nanoparticles in high consumption products (like cosmetics, pharmaceutical preparations and food) means that the exposition surface of the skin, the gastro-intestine and the parenteral surfaces, are acquiring an increasing importance. With regards to the environment, nanoparticles' release and propagation can instead happen through air, water, soil, with the consequence that a variety of species can be affected by the exposition: therefore, the need to obtain data on human exposition (with specific reference to workers and consumers) and on other species', including micro-organisms, is even more urgent.

In conclusion, the SCENIHR's opinion highlights that, in current research, there's no sufficient data able to identify systematic rules to assess the toxicological and ecotoxicological risks of nanotechnology products. In fact, if the existing toxicological and ecotoxicological methods allow us to assess the majority of the risks in theory, it is also true that the scientific uncertainty about the seriousness and the amount of possible negative effects deriving from the spreading of nanoparticles, should lead to elaborating of new methods or to changing those available today. In any case, whether existing assessment methods need adapting, or whether new methods of analysis, where available, have not reached a normative consent, the SCVENIHR points out the need to: assess the risks case by case; set up adequate methods to define the physicochemical properties of nanoparticles; develop methods and instruments that will allow us to carry out the *routine* measurements of the representative exposition to nanoparticles; modify toxicity and ecotoxicity tests and introduce new tests aimed at optimising the risk assessment process; put in place suitable methodologies to assess the nanoparticles' systemic distribution. In particular, the hoped-for new assessment methods should give us information regarding how nanoparticles spread in human tissue and in environmental areas.

For the aforementioned purposes, the SCENIHR states the need to fill the gaps in the scientific knowledge regarding the nanoparticles' characteristics and the

[33] According to the SCENIHR, a toxicity mechanism for some particles consists of the emission of a type of reactive oxygen and of the consequent oxidation process of the cells under consideration.

understanding of the impact and persistence of these structures on man and on the environment, with specific reference to the risks of a toxicological nature. In fact, despite the growing number of scientific publications about nanosciences and nanotechnologies, there's still a significant *gap* in the knowledge of relative data, in particular with regards to the characterisation of the mechanisms and the kinetic of the release of nanoparticles, starting with a wide *range* of nanoparticles' processes and products; with regards to the current levels of exposition to nanoparticles both for humans and for the environment; to the possibility of extrapolating toxicological data relative to nanoparticles of different sizes and shapes; to the study of the levels of exposition to nanoparticles through the analysis of the response of "*target* organs"; to the exposition levels and to the effects on the health of the workers employed in the making and the treatment of nanoparticles[34]. In this perspective, the issues regarding the movement of nanoparticles within the human body and the interaction mechanisms at the sub-cellular and molecular level have particular importance. Therefore, the monitoring of occupational exposition and the epidemiological data relative to the potential impact of nanoparticles on human health are a priority of future research and will lead to normative and risk management implications, for example in the elaboration of suitable guidelines for toxicological tests, in the definition of *standard* of occupational and environmental qualities and in the revision of the legal classification and labelling of industrial products.

5. NORMATIVE POLICY TRENDS

First of all we must highlight, from a general and introductive point of view, the lack of International and European legal regulations to expressly control nanotechnologies applications, even though there are general principles that can find useful application with regards to the issues under discussion, like, for example, the prevention principle, of early assessment of the impact on the environment, and the precaution principle. In addition, in International law, there is a pactional source, the Cartagena Protocol on biosecurity (signed in Montreal on the 29th of January 2000), in addition to the Convention on biological diversity (Rio de Janeiro, 5th of June 1992), which has a certain importance for the purposes of this investigation.

The precaution principle, in the formulation accepted by multilateral treaties on the protection of the environment, takes for granted, as it's known, a sort of inversion of the probationary responsibilities, giving those who want to carry out a dangerous activity (and not the potential victims) the responsibility to show that the activity does not threaten a "serious and irreversible" damage for the environment and the human *habitat*, as well as the responsibility to adopt suitable measures to dispel the potential risks linked to or consequent to the activity under consideration. Intended in this way, the precaution principle could be cited (also in national regulations) if the spreading in the environment of nanoparticles and other nanostructured materials, which tend to bioaccumulate in organisms and in the food chain, was expected. It is true, however, that any discussion regarding this, is still at the embryonic state: in the document *Nanosciences and Nanotechnologies: Opportunities and Uncertainties*, adopted by The Royal Society of Engineering on the 29th of July 2004, scientific data that would justify requesting a moratorium in the release of particles in the environment, formulated by some environmental

[34] The cognitive gaps include the characterisation, the collection and the measurement of nanoparticles; the response dose, the impact and persistence of nanoparticles in the human body and in the environment; and all the aspects relative to nanoparticles' toxicology and ecotoxicology.

associations (ETC Group and Greenpeace)[35], are refuted, but at the same time governments are invited, in line with the precaution principle, to adopt normative measures adequate to the risk that nanoparticles could present from a toxicological and ecotoxicological point of view.[36]

The Cartagena Protocol, "in conformity with the precaution approach ratified by Principle 15 of the Rio Declaration", aims at "contributing and ensuring an adequate level of protection for the safe transferral, manipulation and use of living modified organisms resulting from modern technology, which could have negative effects on the sustainable preservation and use of biological diversity, also in consideration of the risks to human health, with particular attention to transfrontal movements" (cf. art. 1). To this end, the Protocol regulates the transfrontal movements of living modified organisms, foreseeing the recourse to risk assessment procedures in order to ensure, on one hand, the sustainable preservation and use of biological diversity and, on the other hand, the protection of human health. It is clear that, to understand the level of useful application to nanotechnologies of the regulation introduced by the Protocol, we need to correctly appreciate the significance of the definitions used by the pactional instrument, and in particular those of "living modified organism"[37] and "modern biotechnology"[38]: in any case, beyond an assessment of merit, it is clear that the Cartagena Protocol only incidentally touches the issues posed by nanobiotechnologies and does not give them any specific consideration[39].

The policy and normative trends taken up by the European Union are instead more focused, as they can help in identifying the main legal problems caused by nanotechnologies, not just from the point of view of the protection of health and the environment: in fact, next to the mentioned profiles, the European Union's documents

[35] The request of a moratorium was formulated during the Johannesburg summit on sustainable development, held from the 26th of August to the 4th of September 2002. In paragraph 6, we will discuss the reactions about this proposition, which in the ETC Group intentions should have been about nanotechnological research as well as nanotechnological applications.

[36] Cf., p.77.

[37] That is, the "living organisms characterised by a new combination of genetic material obtained through modern biotechnology", where for "living organisms" we must intend every "biological entity able to transmit or replicate genetic material, including sterile organisms, viruses and viroids" (cf. art. 3, letters g and h).

[38] That is, that the "application of *in vitro* techniques of nucleic acid, including the re-combination of the deoxyribonucleic acid (DNA) and the direct inoculation of the nucleic acid in cells and organelles"; or "the fusion of cells outside of the taxonomic family, which would overcome the physiological barriers of reproduction or re-combination and which are different from the traditional techniques used in breeding and selection" (cf. art. 3, letter i).

[39] It is important to highlight that the notion of LMO accepted by the Cartagena Protocol, coincides only partially with the one elaborated in the European community. Art. 2, number 2, of directive number 2001/18, in fact, it defines the OGM as "an organism, different from a human being, whose genetic material has been modified in a different way from what happens in nature" (intending as "organism" any biological entity able to reproduce or to transfer genetic material: cf. art.2, number 1, in the directive). It therefore seems clear, on one hand, the explicit exclusion of the human being from the field of application of the European community, and on the other hand, the clear reference to the use of modern biotechnology in the Protocol. The genetic modification techniques relevant for the Protocol purposes, do not find exact correspondence in those relevant for the purposes of the number 2001/18 directive, which excludes from its field of application the "conventional" genetic modification techniques listed in the attachments IA, part 2, and IB. The Protocol, finally, includes in the notion "living organisms" every "biological entity able to transmit or replicate genetic material, including sterile organisms, viruses and viroids", which therefore is able to regulate the emission on the market also of those LMO containing the sterility gene (for, example, the so-called *terminator* seeds), which instead are excluded from the application field of the European Community.

raise peculiar aspects, regarding the protection of privacy and of the right of intellectual property or, more in general, the international cooperation in this sector[40].

A certain *favour* of the European Union towards nanotechnologies is stated by the title of the first document dedicated to them, the communication *Towards a European Strategy in Favour of Nanotechnologies*, adopted by the Commission on the 12th of May 2004. This communication, in short, identifies as the main objective of the European Union policy in the sector under examination, the strengthening of the competitive "supremacy" achieved in this sector by Europe and suggests, to this end, an integrated and responsible strategy, capable of joining the aspects connected to industrial development to the aspects more directly linked to the aforementioned needs of environmental and health safety[41]. After expressing the hope that the knowledge acquired by the European Union in the field of nanosciences will be fully used through the realisation of adequate research infrastructures and the allocation of adequate levels of investment (public and private), essentially for the purpose of allowing the development of commercially sustainable products and processes, the Commission's communication highlights how, facing by now a rapid evolution of nanotechnologies, it is indispensable to identify and resolve the security problems, real or perceived, from the beginning, at the same time promoting a dialogue based on trust with the public. From this point of view, the Commission also deems necessary to elaborate a new approach to assess and manage the risks, one that would allow the adaptation of consolidated and traditional procedures used for this purpose[42].

The basic content of the Commission's communication, which was the object of a wide public consultation[43], has been favourably received by the European Union Council, gathered on the 24th of September 2004, and has also received the approval of the Economic and Social Committee, which gave its opinion about it on the 10th of November 2004. In the light of such confirmations, the Commission adopted, in June 2005, a specific Action Plan on the issue of nanotechnologies, titled *Nanosciences and Nanotechnologies: a Plan for Europe 2005-2009*, which defines a series of articulated and interconnected interventions aiming at carrying out the main objectives identified by the communication[44]. In fact, the Action Plan, after stressing

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[40] Also, take into account the problems, mentioned in paragraph 3, regarding the fair access, at a reasonable cost, to nanotechnologies and to the imbalance between regions and individuals in the preparation and in the ability to use the technological innovations brought by nanotechnologies, which could cause, in the medium term, a "nano divide".

[41] Cf. the document COM(2004) 338 def. of the 12th of May 2004, also in *Guce* number C222 of the 4th of September 2004, p.7.

[42] For the initiatives proposed on this issue, see further on, the 2005 European Union Action Plan. Instead, for the lines of action (or "dynamics") aimed at promoting the progress of nanotechnologies, the 2004 communication stresses the strengthening of investments, the coordination of research and technological development activities, in order to raise scientific excellence, interdisciplinary and competition in this sector, as well as industrial valorisation; the development of a high quality and competitive research infrastructure; the promotion of interdisciplinary education and training for research personnel, as well as a stronger entrepreneurial spirit; the creation of favourable conditions for industrial innovation in order to guarantee a translation of research in products and processes that bring wealth, are safe and have acceptable costs; the respect of ethical principles, the integration of social consideration in the initial phases of the research process and on the promotion of the dialogue with the public; the early consideration of the risks to public health, safety and health at work, environment and consumers, caused by products derived by nanotechnologies; the integration of the aforementioned actions through cooperation and other adequate initiatives at the international level.

[43] For the outcome of such consultation, ended on the 15th of October 2004, cf. the report *Nanoforum*, on http://www.nanoforum.org.

[44] Cf. the document COM(2005) 243 def. of the 7th of June 2005, also in *Guce* number C172 of the 12th of July 2005, p. 22. It is important to stress that the new document by the Commission finally puts on

the progress in nanosciences in a wide range of sectors and highlighting the need for dealing directly and early with the health, safety and environmental risks connected to the development of nanotechnologies, analyses the priorities of the proposed strategy, pointing out the desirable actions[45].

In particular, the Action Plan expresses the Commission's will to increase the allocation of funds in favour of nanotechnologies in the future VII Program, research, technological development and demonstration, relative to the period 2007-2013[46], reinforcing interdisciplinary research during the whole cycle of creation, transferral and use of knowledge, and suggesting specific support for the nanoelectronic sector. In addition, the Commission intends to reinforce the support given to research concerning the potential impact of nanotechnologies on human health and the environment (with specific reference to nanoparticles and to the so-called nanotubes), through the carrying out of toxicological and ecotoxicological studies, as well as the development of methodologies and instruments adequate in monitoring and reducing the exposition to potentially harmful agents, in particular in the place of work (like research laboratories). To these priorities, finally, is added the promotion of the support to nanotechnologies in those sectors considered fundamental for European Union's competitiveness, like medicine, chemistry and space. For these reasons, and taking into account that the infrastructure for scientific research and innovation in the nanotechnology sector presumes a critical mass of resources that at times can be beyond the possibilities of single governments, the Action Plan hopes for the promotion and development of excellence through the institution of appropriate university networks, the integration of transnational resources, as well as the cooperation of small and medium businesses.

Because the Action Plan's underlying strategy mainly aims at boosting industrial and commercial development, in accordance with the European Union's mercantilist objectives, the Commission's document also discusses profiles relative to the promotion and support of businesses' technological innovation and the protection of intellectual property rights, also through the institution of a monitoring system for patents in this sector, the harmonisation of the practices overseeing patents' requests at an international level and the reaching of an agreement on the adoption of a European Community patent[47]. With regards to international cooperation, finally, the Commission proposes the adoption of a binding act, like a declaration or a "code of

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the same level of interest, starting with the title, nanosciences and nanotechnology, thus satisfying not only elementary methodological and conceptual needs, but also the observations of those who highlighted, in the May 2004 communication, a focus centred more on the technological-industrial and commercial applications, than on scientific research: suffice to think that in the communication's text the term "nanosciences" appears only once.

[45] With regards to the nanobiotechnology sector, the Commission clarifies that the Action Plan is a complement of the European strategy on the sciences of life and biotechnology, adopted by the Commission in 2002 [cf. the document COM(2002)27 def. of the 23rd of January 2002, also in *Guce* number C%% of March 2002, p.3]. Some uncertainly is caused by the opinion expressed on this issue by the European Commission, which simply vaguely refers to the precaution principle, limiting its application to "realistic risks of a certain severity". This field of application differs form the one recognised by the communication on the precaution principle adopted by the Commission in 2000 [cf. the document COM(2000)1 of the 2nd of February 2000], according to which the precaution principle "is applicable in all cases where a preliminary scientific assessment indicates that there are reasonable reasons to fear that the *potential risks* could have negative effects on the environment or on human, animal and plant health, but the scientific data do not allow a detailed risk assessment" (italic added).

[46] Cf. COM(2005)119 of the 6th of April 2005, in *Guce* number C125 of the 24th of May 2005, p. 12.

[47] Another priority indicated in the Action Plan is the development of education, training and interdisciplinary learning, which would involve exact, human and social sciences.

good conduct", for the responsible use and development of nanotechnologies, which would be the basis for an open and shared system of nomenclature, metrology and risk assessment, that will allow the creation of a toxicological, ecotoxicological and epidemiological databases, as well as a European electronic archive of scientific publications on nanotechnologies. In addition, the Commission invites the member States to reinforce the support given to scientific research and to promote cooperation from less developed countries in this sector, highlighting, at the same time, the contribution of nanotechnological applications in achieving the objective of sustainable development[48].

Finally, assessing the activity of the so-called normative bodies on this issue, we can refer to the fact that, at the beginning of 2005, promoted by the British Standard Institution (the United Kingdom's national normative body), the International Organisation for Standardisation (ISO) asked its members to assess the opportunity of discussing a new set of regulations relative to nanotechnologies (ISO/TS/P199). This initiative, basically, aims at instituting a technical committee (ISO/TC229) to look into regulations in the field of nanotechnology, with specific reference to classification (including calibration and certification), to environmental aspects and to risk management. From this point of view, the relative trial methods should include procedures to determine the physical, chemical, structural and biological characteristics of those materials and devices whose performance, in their expected use, depend on one or more parts being smaller than 100 nanometres.

It is easy to observe that the ISO's proposition takes into account the predictable growth of the industrial applications of nanotechnologies and of their probable spreading also in the domestic environment. The consequent impact of these applications, in sectors that vary from communications to health and from the manufacturing and materials industry to information technology, persuaded the ISO to gain the necessary instruments, on one hand, to give researchers, the industry and politicians, regulations able to sustain the technological and commercial development of products using nanotechnologies; and, on the other hand, to offer to civil society the appropriate instruments to assess the risks and protect health and the environment. Also moving in the same direction is the European Committee for Standardisation (CEN), which, at the beginning of 2004, instituted a working group on nanotechnologies within its *Bureau Technique* (CEN/BT/WG166). This working group has the task of consulting the interested parties and putting in place a strategy able to identify the possible responses to market expectations; in addition, it intends to be the coordinating and connecting point for other initiatives on nanotechnologies by other individual European countries (like in the case of the National Body of Unification in Italy).

6. SYNTHESIS AND BIOETHICAL RECOMMENDATIONS

From nanotechnologies we expect interdisciplinary and very different applications: extra-resistant and light materials, drugs capable of hitting only the right "target", efficient and extremely fast computers. The production of nanomaterials (the leading sectors are electronics, pharmaceuticals, energy production and "intelligent" materials) is beginning to have an important place in industry and the production costs are constantly being reduced: it is therefore certain that the application of

[48] The Commission clarifies that this is with regards to water purification, healthy and safe diet, more effective administration of vaccines, cost reduction of health checks, preservation and more efficient energy use.

nanotechnologies will increase, starting with electronic devices in cars. Scientists, industry and the Government anticipate that the manipulation of matter at the nanometric level will produce enormous benefits and will open possibilities of applications unimaginable until recently, but even the strongest supporters of these new technologies agree that such small structures could hide considerable dangers. In fact, what we still don't know about atomic or molecular technology, could generate potentially serious risks, that could have negative effects on the health of living creatures, the environment, the protection of privacy and even the construction of new weapons of mass destruction.

This is, in synthesis, what has been analytically discussed in previous pages. This document does not mean in any way to question the benefits that can derive (and have in part already been derived) by the progress of nanotechnologies. But, facing developments that are necessarily open to ambivalent outcomes, it seems appropriate to stress the issues we need more information and more public debate about, in order to clarify all their bioethical implications.

We therefore suggest the following reflections:

1) To avoid the shallows that have characterised the debate on biotechnologies or on GMOs, mostly dominated by the sterile confrontation between scientists and technophobes, it seems urgent not only to promote the coordination of disciplines (from material engineering, to biology, to social sciences etc.) that contribute to form this sector of scientific knowledge, and of the subjects (universities, research centres, businesses, government agencies) at the centre of the nanotechnological revolution, but also to facilitate the understanding of the relevant problems by the civil society, to stimulate society's participation in crucial decisions, to accompany the apparently unavoidable emission of nanotechnological products on the market through democratic and transparent instruments of information, revision and control[49].

In this perspective, it has been stressed in particular that the specificity of the applications based on nanotechnologies could require the adaptation of the traditional and consolidated risk assessment methods, especially with regards to biomedical technologies and nanobiotechnologies. The European Commission's documents examined earlier state how the study of the potential risks for public and environmental health, linked to nanotechnologies, as well as presenting peculiar profiles because of the nanoparticles' extremely reduced dimensions, could become a challenge for classic physics and chemistry. In fact, some nanotechnological applications generate new toxicological and ecotoxicological data and require particular adaptations in the processes of product production, manipulation, preservation, transport and disposal, ending up extending the *risk assessment* procedures to the entire life cycle of these products.

If, in the current state of scientific research, it seems difficult to predict which properties and characteristics of nanotechnologies' derived products will have favourable market conditions (and therefore the potential risks linked to them), it is however necessary that the application of these technologies respect the *standard* of protection of public health, consumers, workers and the environment, established by the Treaty of Rome and by the Nice Charter on the fundamental rights of the European Union, as well as the fundamental ethical principles recognised by

[49] On this topic, see the conclusions reached in the document titled *Mind the Gap*, published in February 2003 in the journal *Nanotechnology* by a group of researchers of the Joint Centre for Bioethics at Toronto University.

numerous legal instruments both European and International, like the Oviedo Convention on biomedicine.

The regulatory dimension of nanotechnologies, in particular, should ensure the most suitable preventive measures to neutralise the possible risks, as well as resorting to measures of a different nature if there are still relevant margins of scientific uncertainty regarding their existence or the assessed risks and the damage that could derive from them, especially in the long term[50].

As well as through an adequate change to the existing regulations and the introduction of *ad hoc* codes of conduct, the new challenges imposed by this technological revolution could be faced at the institutional level too, for example through the creation of ad hoc ONU offices and bodies, able to pick up the inheritance of organisations dissolved at the beginning of the 1990s (*UN Centre on Transnational Corporations e UN Centre on Science and Technology for Development*).[51]

In conducting this first reflection, we can state that the bioethical considerations regarding this wide sector, which goes under the name of "nanotechnologies", are still limited, and they seem mostly directed to (overly) "exalt" their positive potential; or to warn against the fearfully negative potential that this economic-industrial field of development presents. These reflections appear to many people to be "reductive", preconceived and far from factual reality. In addition, there are also those who request a more "balanced" discussion (e.g. BERT GORDIN, 2003) and a stronger adherence of the judgement on nanotechnologies to the reality of current developments, with regards to a variety of initiatives that are part of this industrial sector (DETERSON, 2003).

2) Therefore, the NBC deems useful to formulate wider considerations, as follows.

a) In consulted literature, the question of whether it is legitimate to intervene on atoms and molecules to build functional structures of nanometric dimensions is not asked; for the purpose to both replicate those already existing in nature, or to design and create new ones in order to give them (or recognise in them) particular properties, not found in the natural order of things.

The basis of the ethical justification is the fact that chemistry – in itself - already operates at the atomic and molecular levels to recognise and manipulate matter; so that – consequently – to use scientific knowledge deriving from more in depth studies on organic or inorganic matter, in order to produce nanostructures, would not be – in itself – an ethically relevant fact. It is thought that nature's changing action is an innate tendency in man, and we must simply accept that we are able, at this moment in time, to dominate also this sector for different purposes, although with evident

[50] In this conditions, the application of the precaution principle seems therefore unavoidable, taking into account the uncertain character of the scientific data relative to the potential risks of the nanotechnological applications, the European Commission's trend could provoke some perplexity, which, in the 2005 Action Plan examined earlier, simply vaguely refers to this principle, confining its application to the "realistic risks of a certain gravity". This field of application is different from the one recognised by the communication on the precaution principle adopted by the Commission in 2000 [cf. the document COM(2000)1 of the 2nd of February 2000], according to which the precaution principle "is applicable in all cases where a preliminary scientific assessment indicates that there are reasonable reasons to fear that the *potential dangers* could have negative effects on the environment or on human, animal and plant health, but the scientific data do not allow a detailed risk assessment" (italics added).

[51] In this way, also see the ETC Group document mentioned in note 26.

industrial and commercial pitfalls, exploring new combinations of atoms and molecules.

But - as it is known – not everyone acritically accepts this reductive interpretation of human development, which has other dimensions – including those of a spiritual nature – that are not exhausted in the manipulation of matter.

Linked to this problem is the notorious ethical discussion on the danger of "autonomous", autopoietic development of technology, which increasingly tends to be detached from humanity's reality. We could therefore ask ourselves if nanotechnologies correspond to this model of exaggerated industrial development.

From a bioethical point of view – the answer can only be the traditional one: technological development must be directed towards very clear objectives of personal and social value, compatible with the individual and collective safety and good, promoting in the democratic context a social participation in defining the objectives and in controlling the results. The nanotechnological industry should also abide by these requirements.

b) However, a strange aspect of this sector – which concerns more closely the bioethical questions we are discussing – is connected to the possibility of creating structures composed of organic matter (for example proteins) and inorganic matter (for example metals) in manufactured goods of nano dimensions, proposed as nanomotors, or nanoconductors or nanosensors etc., to obtain a wider range of possibilities of use for this technology in the field of communications as well as healthcare (diagnosis and therapy).

It seems apparent that – in some cases – organic matter that joins in new combinations with inorganic matter represents a bio-chemical component that has particular capabilities, because of its intrinsic structure, with regards to fulfilling the possible properties of the manufactured good, and would not in itself represent an ethical problem, if it was non-living matter. The bioethical problem however is at the start, and can at times involve the "living status" of the organic matter used, but always – in any case – has something to do with the origin and the methods of acquisition of the organic component. Whilst there would be no problem, for example, about a so-called cellular reactor in a culture of living *Saccharomyces cerevisiae*, genetically modified to create drugs, encapsulated in a polymer with molecular permeability, ethical problems would instead occur, for some, about the hypothetical derivation from human embryo cells for the cellular reactor; or – at a different level of legitimacy and problematic – about the production of reactors with human living cells, carried out without the informed consent of the tissue donor. Obviously, these are only examples indicative of the ethical-legal problems.

Should these situations occur, there would be, for similar applications of nanotechnologies, bioethical questions to carefully consider, but not dissimilar (in their intrinsic nature) from ethical reflections already discussed about these problems in applications at the microscale or at the larger level.

Particular bioethical "sensibility" should be applied with regards to the possible production – for example – of nanotechnological manufactured goods that include human genes (for example artificial chromosomes; nanocapsules of polymers enclosing and supplying genetic human products) with regards to the "instructions" for their use, and not only about their adherence to the international patenting rules in their production.

In the same way, there would be ethical questions regarding the presentation to the consumer of such manufactured goods in advertising and placing on the market,

because there would be a duty to inform the consumer of the origin of the biological material in the manufactured good, and to allow him/her to exercise his/her freedom of choice in accordance with his/her personal ethical sensibility.

In conclusion, under these profiles, it seems possible to refer to – also for nanomanufactured goods – well known "principles" protecting human rights, already experimented in bioethics and codified by private, public, commercial, penal etc. law, national or international, when using devices and inventions in response to various human needs, and operating at the normal current scale dimensions.

3) These general bioethical considerations on the social "acceptance" of techniques included in that very wide and varied sector, known under the name nanotechnologies, after all, are very similar to those already discussed about the extraordinary development of "biotechnologies and genetic engineering" (for example genetically modified organisms), a development that strongly posed the question of the moral "legitimacy" of the modification of the genome of living beings (vegetable, animal, human), but also of the "justice" in the enjoyment and in the wider access to the (eventual) benefits. These questions gave rise to a variety of responses, which were influenced by the positive or negative contributions offered by these technologies to the solution of problems, especially economic and social, emerged in the different environmental and social contexts in which the human population lives.

In our ethical judgement, matured within western society, the answers given do not cover every need; but even in sectors where "positive" judgement on nanotechnologies is more uniform (e.g. the case of biotechnological production of drugs) the benefit offered by such technologies is still completely unbalanced.

Some authoritative voices who participated – during international encounters – to this initial bioethical reflection on the social "falls" of nanotechnologies, have already expressed the opinion that few individuals and industrialised countries will be the ones to mostly benefit from them, whilst the distance between rich and developing countries will increase (see for example J.C. TEALDI, 2003); others have stated that this is an opportunity to start a new chapter of particularly profitable industrialisation, especially for developing countries (SALVATERRA, 2003). This opinion does not appear – at the moment – to go beyond the petition of principle.

In any case, the ethical profile of the "justice principle" in the potential benefits is certainly strongly felt in the international discussion on the issue of "nanotechnologies", as it is with regards to genetic "biotechnology".

4) In the sector that particularly interests the NBC, we must list the bioethical considerations on the issue of using nanotechnologies in medicine, which demand particularly careful consideration.

The possibility to define a competitive and "winning" "nanomedicine" in contrast with currently practiced medicine, which is also technologically advanced (obviously this is only a prospect, at least in many cases) is supported by two trends:

- the first, considered as a development coherent with medical tradition, for the improvement of diagnosis and treatment in some morbid forms (ALIVISATOS, 2001; BACHMANN, 1998; CHEMLA et al, 2000; JORDAN et al., 2000; RANDAL, 2001; REICHERT et al., 2000; WEST e HALAS, 2000; WOLFE, 2002; DIASPRO, 2005);
- the second, innovative but susceptible to many ethical reservations – aimed at increasing some intellectual human "capabilities", already existing and considered to be within the range of normality, through the boosting action of microchips

compatible with the organic matter in the nervous and sensorial systems (DREXLER, 1986; FREITAS, 1988 b; KAKU, 1997; KURZWEIL, 1999).

What is put forwards again is a "scheme", already discussed, for a genetic intervention of "enhancement" (the realisation of which, probably, should be more easily allowed by the nanotechnological "vector").

The desirability of this second line of development for future medicine must be ethically contested, and rightly GOTJN (2004) states that – if this was the predominant thought in society – the continuation of research in this direction should appear as devoid of meaning from an ethical point of view.

Instead, any reasonable effort in the first direction is not contested, provided that research and expected outcomes are motivated by substantial benefits for the patient, and are also in proportion to the investment of resources that – necessarily – are taken away from other sectors of health care.

Without a doubt, in the literature produced so far, it is stated that considerable results can be expected – with the use of the nanotechnologies' criteria – with regards to a better identification of the drug's target (ALIVISATOS, 2001; BOGUNIA-KUBIK and SUBISAKA, 2002; DAVIS, 1997;MEHNER and MADER, 2001; MOGHIARI et. al, 2001; RANDAL, 2001; TATON, 2001; WEST and HALAS, 2000; WOOLIEY, 2001; WUSTHOFF, 2002); in diagnostics (ALIVISATOS, 2001; CHEMLA et. al., 2000; RANDAL, 2001; RELCHERT et. al., 2000; WEST and HALAS, 2000; WOLFE, 2002); in prosthesis and implants (ALIVISATOS, 2001; BACHMANN, 1998; MURPHY and others 2001; TATON, 2001); in cancer therapy (ALIVISATOS, 2001; JORDAN et. al., 2000; RANDAL, 2001; SCHATTENFROM, 2000; DIASPRO, 2005).

It seems justified, at the moment, to give credit to these statements as they come from serious researchers, although we are still waiting for proven documentation of practicability and efficacy in the use of nanovectors, or nanosensors, etc., as it is hypothesised in literature.

5) Finally, we must discuss the bioethical problem that today appears fundamental and on which there is not enough information: the risk linked to experimenting with and using nanotechnologies, in particular in medicine.

Given that it is not justified to "globally" examine the "risk of nanotechnologies" as if they were a homogeneous category – it seems clear that we still badly lack information about the effects of each type of nanotechnological device on living matter, cells, tissues, organs and organisms.

In current society prevails the idea (highlighted also in the recent NBC's Opinion on the precaution principle; 2004) of "risk acceptance"; but such risk should be strictly checked not just by traditional criteria and methods of experimentation and before its biological and clinical applications, but also by training, monitoring of sensible parameters, awarding of responsibility to individuals, preventive and not merely repressive control by the Control Authority, etc.

There is no doubt – in any case – that still too little is known about the biological dynamics between organism and "guest" to allow reliable predictions about the organic reaction to the use of artificial micro-nanostructures proposed in medicine. Currently, we are reasoning by analogy; but our notions on the action – at the molecular level – of microparticles already produced by the industrial society and dispersed in the biosphere, are just as episodic and fragmented.

A very serious program has been put into place by the British government, which promotes a series of investigations on the biological effects of nanoparticles, with

research conducted on animals too; in addition, research funds have opportunely been allocated by the European Community and by a variety of OCDE countries.

As long as we don't know the reactions at the cellular and tissue level - acute and chronic – of the "grafting" of foreign or genetically modified material (although protected by capsules of permeable polymers), or of the effects of miniaturised "analytical robots" inserted in the digestive tract or of other devices (for example implants of miniaturised cerebral stimulators) in animals, it will not be possible to move on to the trial phase on humans.

This pre-clinical process seems necessary, and it involves protracted observation (long term effects).

6) Still with regards to the ethical and legal profile, we cannot forget the possible interferences with private life (see the case of microscopies and what has already been described on information nanotechnologies) but we also cannot underestimate the positive aspects offered by the storing and transmission of data, hypothesised by nanotechnologies (F. GALEMBECK, 2003) in less dangerous sectors and maybe their easier social control, in comparison with the biomedical sector, with regards to the safety of use.

It must be remembered that, in relation to the environmental risks and the "trespassing" of them during the production of nanodevices, "guidelines" have been issued (FORSESIGHT, 2000), which require limiting production to not self-replicating devices with a controlled duration of action and in any case adding – in every program of production and use – an assessment of the effect on the environment.

It can seem pleonastic to state that these "guidelines" – although minimal – should be imposed by the Supervising Authority.

Rationality and moral sense of responsibility must also guide development in this sector, as it is expected in every human activity.

Inalienable premise to the ethical evaluation is also the need for the expected benefits to be accessible by the needy, independently from social factors of discrimination or economic obstacles, which the community will have to avoid with appropriate forms of solidarity.