Nanoethics and Nanotoxicology

P. Houdy M. Lahmani F. Marano
(Eds.)

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With 112 Figures and 31 Tables

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Translation from the French language edition of
"Les Nanosciences – 4. Nanotoxicologie et nanoéthique"
© 2010 Editions Belin, France

ISBN 978-3-642-20176-9 e-ISBN 978-3-642-20177-6
DOI 10.1007/978-3-642-20177-6
Springer Heidelberg Dordrecht London New York

Library of Congress Control Number: 2011935632

Cover design: WMXDesign GmbH, Heidelberg

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

All is poison, nothing is poison,
only the dose matters

Paracelsus (1493–1541)
Swiss alchemist and physician

Foreword to the French Edition

Science moves forward inexorably, and the ever more powerful means of investigation at its disposal provide a continuous supply of new discoveries and novel applications. The same is also true in the nanosciences. History has shown that scientific progress can lead to worldwide benefits, but sometimes also to unprecedented human disasters. This observation is not restricted to the products of the nanotechnologies, but the development here may be taken as an opportunity for a documented raising of awareness regarding their risks, consulting the general public on broad scale, and above all, informing the whole of society as objectively as possible.

Indeed, the very real problems raised by asbestos and the questions posed by the unknown long term impacts of genetically modified organisms (GMO) – more and more common in our everyday food supply – have caused considerable discord between the scientists who develop them, the companies who wish to industrialise them, and the consumer organisations. This kind of controversy is broadly covered by the media, with a view either to warn the public on behalf of competent and responsible organisations, or to achieve more or less dubious political ends.

The real problem here is to carry out a rigorous investigation of the potential dangers and risks raised by the use, development, and commercialisation of current or new products likely to threaten people's health or the environment, with harmful consequences for future generations. There is no doubt that the specific properties of nanoscale objects can radically enhance their chemical reactivity, and transform their electronic or magnetic behaviour, sometimes increasing their capacity to enter deep into living systems.

This book is the last of four volumes providing as complete a picture as possible of the current state of our knowledge in the nanosciences. The vocation of the series is didactic, aimed at graduate students, research scientists, and engineers. From a scientific standpoint, it reviews the state of the art in nanobiotechnology and nanotoxicology. But what is novel in this fourth volume is that it emphasises the efforts made by researchers to cater for the consequences of their work, and the ways engineers set up safety systems when potentially dangerous products go into mass production.

To my knowledge, this is the first book in which scientific knowledge and ethical and social recommendations can be found side by side, along with specific policies developed by national and international authorities to handle the potential problems of nanotechnology.

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Preface to the French Edition

Nanotoxicology studies the toxicity of nanomaterials, nanoparticles, and more generally, any naturally occurring or man-made objects with dimensions in the range 1–100 nanometers. Such small dimensions induce specific properties, making these objects much more reactive, for example, than larger ones, and in particular, they allow them to pass through certain natural biological barriers. The potentially harmful effects that may result thus constitute one of the quite legitimate reasons for the concern they inspire.

A key objective of this book is to set out some up-to-date scientific studies of nanotoxicity, and exemplify the preventive measures taken during fabrication or manipulation of nano-objects. Another is to describe the way the public is informed about these new scientific discoveries, and also the legal arrangements currently under preparation for regulating their use.

Considering the controversy to which the nanosciences have given rise – as witnessed for all forms of scientific innovation – it seems important to expose the ethical considerations taken into account in the context of nanotechnology. Indeed, scientists have been questioned, sometimes forcefully, about the social consequences of their research, and it seems opportune to set up a responsible debate between the so-called hard sciences and the social sciences from the very beginning of any scientific project with wide-ranging industrial and social impacts. Such attempts to raise public awareness are of course relevant both on the national and international level.

The book is divided into five main parts. The first two concern nanotoxicology, and are purely scientific, providing specific examples of the potential or proven impacts of nanoparticles on humans and on the environment. The last three concern nanoethics. After a brief introduction to the basic ethical issues, there is a fairly exhaustive discussion of the implications for national and international authorities regarding the way the public demand for information is being treated, and also regarding the degree of transparency with which current developments in nanotechnology are being presented, as well as the need for rigour, responsibility, and caution in their use.

The reader will thus find one of the first books to combine both scientific and societal aspects of an emerging field, containing many references for each of its disciplines.

Acknowledgements

We would like to thank all members of the French nanoscience community who gave a very favourable welcome to the writing of these four pedagogical introductions to nanotechnology and nanophysics, nanomaterials and nanochemistry, nanobiotechnology and nanobiology, and nanotoxicology and nanoethics, without whom they would have been impossible. Special thanks go, of course, to all those who contributed to these books.

Given the current debate over the nanosciences, it seemed important to mention in the context of a scientific textbook that research scientists do indeed take into account the potential risks involved in their innovations, and give considerable thought to all the necessary precautions before they are industrialised.

From the ethical standpoint, it is more and more important to inform the general public, and the book discusses the various authorities concerned with the citizen's demand for information when new technologies with suggested or proven risks are launched on the market. This part of the book was put together by Françoise Roure, president of the information technology department of the French Ministry for Trade and Industry. Her contribution played a key role in harmonising with the prior scientific chapters.

The latter were coordinated by Francelyne Marano, co-editor of the book, for the first part and by Jean-Yves Bottero for the second. We would like to express our most sincere gratitude for his scientific actions and for organising the working groups at the CEREGE.

We are particularly grateful to the late Professor Hubert Curien, who supported this undertaking from the start, and to Jean-Marie Lehn, Axel Kahn, and Alain Grimfeld, who have also given it their backing.

We warmly acknowledge the material and financial support of the French Ministry of Research, the French national science research organisation (CNRS), and the French atomic energy authority (CEA), and especially Jean Therme, Director of the CEA, Grenoble, who supported this project from the beginning.

The editors of the nanobooks would like to express their gratitude to Stephen N. Lyle for his excellent translation of the four nanovolumes of this Nanoscience series: *Nanotechnolgies and Nanophysics*, *Nanomaterials and Nanochemistry*, *Nanobiotechnology and Nanobiology*, and *Nanotoxicology and Nanoethics.*

Marcel Lahmani
Francelyne Marano
Philippe Houdy

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Introduction. Nanomaterials and Nanoproducts: World Markets and Human and Environmental Impacts

Eric Gaffet

Nanotechnology and nanoscience lie at the meeting point of many disciplines, from physics to chemistry, biology, and mechanics. Today they have become established as one of the main fields of research for the coming years. The first volume of this series, entitled *Nanoscience: Nanotechnologies and Nanophysics*, shows how useful it can be to structure matter on the nanoscale, with implications in fields as disparate as magnetism, data storage, biology, and electronics, with the development of completely new components, e.g., near-field techniques, lithographic processes, fullerenes, and spin electronics.

The second volume, *Nanomaterials and Nanochemistry*, presents a complete overview of nanomaterials, their fundamental properties, and novel applications that may come from fullerenes, carbon nanotubes, and other previously unimagined materials. This book provides a broad panorama of the main methods used to synthesise nanomaterials, and the resulting production processes, not forgetting the self-assembly of complex structures, one of the most promising channels of investigation opened up by nanochemistry.

The third book in the series, *Nanoscience: Nanobiotechnology and Nanobiology* provides an exhaustive and accessible overview of biological nano-objects, building blocks for existing and future constructions. After detailing the methods used for investigation in nanobiotechnology, there is a review of the many current and potential applications here, such as the synthesis of activatable nanoparticles able to accurately target cancer cells.

Coming directly from laboratory work in a highly accelerated way compared with other fields of research, the introduction and implementation of nanomaterials in nanoproducts has already become an industrial and economic reality. As in other industrial sectors, it is important to consider the social consequences (nanoethics) and the impact of these novel products on both human health and the environment (nanotoxicity), in order to avoid possible risks in the future. This is indeed a crucial issue to guarantee a responsible development of nanomaterials and nanotechnology, and it is the subject of the present volume.

1 Nanotechnologies

This field of research and development consists in building structures, devices, and systems using processes for structuring matter on the atomic, molecular, and supramolecular level, with characteristic length scales of 1–100 nanometres (nm). These so-called building blocks form a relatively small fraction of nanomaterials in terms of the quantity produced. In the field of nanomaterials, one must also consider nanoparticles and nanostructured coatings, but also dense bulk materials and nanocomposites (with organic, inorganic, or metallic matrices).

Matter is expected to behave in new ways, owing to the relative importance of the laws of quantum physics that find their full expression on this length scale. Many industrial and medical applications are currently being developed at a tremendous rate, and some have already been fully implemented.

For these reasons, one may consider the advent of the nanosciences (nanotechnology and nanomaterials) as a turning point in the industrial development of the twenty-first century.

2 Nanomaterials

A nanomaterial can be defined as a material made up of nano-objects, for which at least one of the three physical dimensions lies in the range 1–100 nm, and displaying specific nanoscale properties. These nano-objects may be particles, fibres, or tubes (one speaks of fillers and strengtheners), or structural constituents.

These nano-objects are used either as-is, e.g., catalysts for chemical reactions, vectors for carrying medicines to target cells, substances for polishing wafers and hard disks in microelectronics, etc., or for synthesising nanomaterials. The latter fall into three categories:

1. *Nanostrengthed Materials.* The nanobjects are incorporated or produced in a matrix in order to ensure some new functionality or modify its physical properties. A good example is provided by nanocomposites, where these modifications improve resistance to wear.
2. *Surface-Nanostructured Materials.* Here the nano-objects are used to constitute a surface coating. Fabrication procedures for these coatings exploit techniques of physical deposition like physical vapour deposition (PVD), electron beams, laser ablation, and so on, or techniques of chemical deposition, like chemical vapour deposition (CVD), epitaxy, sol–gel, and so on.
3. *Bulk-Nanostructured Materials.* Nano-objects can also be constituents of bulk materials which, through features of their intrinsic nanometric structure, like porosity, microstructure, or nanocrystalline lattice, display specific physical properties.

3 Social and Economic Aspects

3.1 Nanotechnology and Nanomaterials Markets

The European Commission estimates that the world nanotechnology market was slightly above 40 billion euros in 2001. But by 2008, the global market for products resulting from nanotechnology was expected to reach more than 700 billion euros. In 2010–2015, the economic consequences of nanotechnologies should weigh in at around 1 000 billion euros per year, if all sectors are included, according to the US National Science Foundation, with some 340 billion euros of this specifically in the area of nanomaterials (Hitachi Research Institute). As a consequence, nanotechnological enterprises may directly employ 2 to 3 million people in the world.

3.2 Financing in France

The study [1] assessed public investment in the nanotechnologies. It shows that France is making a considerable effort in this direction. According to this study, taking into account the whole range of credits made available and the means allocated in this field by the French national research organisation (CNRS) and the French atomic energy authority (CEA), including staffing costs, the final figure is 551.6 million euros without including tax, or 637 million euros all included, for 2003. However, although it is sometimes possible to identify a specifically nanotechnological activity, such a distinction cannot always be made, and would generally have little meaning.

Quantitatively speaking, there is a very significant level of public funding in the field of nanotechnology and nanomaterials in France, both in absolute value and also in relation to France's main European partners, i.e., Germany and Great Britain. But this financing is well below the level in Japan and the United States.

In France, since 2005, calls for national programmes (ANR, A2I, etc.) have supported coordinated assessment of the effects nanoparticles may have on health. Eighteen months after the recommendations made by reports from the French agency for health and safety at work and in the environment (*Agence française de sécurité sanitaire de l'environnement et du travail* AFSSET) [2] and the French commission for prevention and safeguards (*Comité de la prévention et de la précaution* CPP) [3], which stress the need to coordinate ways of controlling risks on a national, if not European, level, a panel of experts was set up within the French public health authority (*Haut Conseil à la Santé Publique* HCSP), with the title *Groupe de veille sur les impacts sanitaires des nanotechnologies* (GVISN).

This interministerial watchdog is briefed to provide analyses and make recommendations with regard to relevant questions raised either within or outside the group, in order to provide the government (the Ministry of Health and other ministries that may be concerned by this subject, such as environment, agriculture, research, and industry) with the support and advice it will need to define policy and handle new issues raised by nanomaterials and nanotechnology with regard to health and safety. At the beginning of 2009, on the basis of information provided by the GVISN, the HCSP made a pronouncement regarding carbon nanotubes [4].

At the end of 2005, all governments taken together had spent some 18 billion dollars to finance the nanotechnology and nanomaterials sector. With close to 6 billion dollars more in 2006, it was estimated that this world level of funding had equalled the whole of the Apollo programme which took men to the Moon.

3.3 Production and Applications of Nanomaterials

World Market

There are many applications of nanomaterials, as can be seen from Table 1 [5]. The world nanoparticle market for energy applications was estimated as around 54.5 million euros in 2000 and was expected to reach 77 million euros in 2005, i.e., a mean annual growth rate of 7%. This market has been driven by increasing awareness of the need to protect the environment. Nanoparticles are used for catalysis applications in the car industry, ceramic membranes, fuel cells, photocatalysis, propellants and explosives, antiscratch coatings, structural ceramics, and thermal spray coatings.

The world nanoparticle market for biomedical, pharmaceutical, and cosmetic applications [6] was estimated at 85 million euros in 2000 and was expected to reach 126 million euros in 2005, i.e., a mean annual growth rate of 8.3%. This is the market represented by the inorganic particles used to produce antibacterial agents, biological tags for research and diagnostics, biomagnetic separation processes, drug carriers, contrast media for magnetic resonance imaging (MRI), orthopedic devices, and solar protection screens.

The worldwide annual production of nanocomposites currently amounts to just a few thousand tonnes, mainly in cabling and packaging. However, by 2010, this production is expected to leap to 500 000 tonnes per year. Markets have been identified in the transport, engineering, and high technology sectors, due to the potential these materials have for strengthening structures while making them lighter, together with different design possibilities, e.g., reduction of thickness.

By 1995, the production of carbon black had already reach around 6 million tonnes per year worldwide. By 2005, global production was estimated at 10 million tonnes. The production of silica is around 300 000 tonnes per year, while titanium oxide has reached some 3.5 million tonnes for particles with micrometric dimensions, and close to 3 800 tonnes of nanoparticles were produced in 2000. The volume of aluminium nanoparticules is estimated at around 100 tonnes per year worldwide.

Table 1. Applications of different types of nanomaterial

Nanomaterial	Field of application
Nanoceramics	Structural composite materials Anti-UV components Mechanochemical polishing of wafers in microelectronics Photocatalysis applications
Nanometals	Antibacterial and or catalysis sectors Conducting films for screens, sensors, or energy generating materials
Nanoporous materials	Aerogels for thermal insulation in electronics, optics, and catalysis Biomedical applications to drug carriers and implants
Nanotubes	Electrically conducting nanocomposites Structural materials Single-sheet nanotubes for electronics and screens
Bulk nanomaterials	Hard coatings Structural components for the aeronautic industry, cars, ducts in the petroleum and gas industries, the sports sector, and anticorrosion applications
Dendrimers	Medical applications, including administration of medicines, fast detection techniques Cosmetics
Quantum dots	Optoelectronics (screens) Photovoltaic cells Inks and paints for anticounterfeit tagging
Fullerenes	Sports (nanocomposites) and cosmetics sectors
Nanowires	Applications in conducting layers of screens or solar cells and in electronic devices

French Production of Nanomaterials and Their Current Uses

According to a report published in 2007 by the French *Institut national de recherche et de sécurité* (INRS) [7], a first general survey of French nanoparticle production could already be drawn up. This information was consolidated in 2008 by elements from an AFSSET report entitled *Nanomaterials and Safety at Work* [2].

The main themes of the INRS report regarding the different nanoparticles produced in France can be summarised as follows:

- *Titanium Dioxide.* The French production of TiO_2 is around 240 000 tonnes. Different sizes of particle are used, depending on the sector, in the range 150–400 nm as pigment or opacifier in the paint and plastics industries, positioning them at the upper end of the nanoparticle range. The production of nanometric titanium dioxide is all carried out by 270 workers at one site, and reaches some 10 000 tonnes per year for three applications: architectonics, cosmetics, and air purification systems.

- *Silica.* With a production of 200 000 tonnes of SiO_2, France is the second largest producer of natural silica in the world, extracting from one particular rock called diatomite. This production occurs at two extraction sites and involves about a hundred workers. As far as synthetic silica is concerned, i.e., precipitated silica, pyrogenic silica, and fumed silica, the annual production is greater than 100 000 tonnes and involves some 300 people. The main use is rubber reinforcement for tyres (where it is associated with carbon black in a 1:1 ratio), shoe soles, and rubber technical parts for wires and cables. In the food industry, these silicas are used as substrates for vitamins, acidifiers, and anticaking agents. The paint industry uses them as matting agents, while toothpaste manufacturers use them as thickeners and mild abrasives.
- *Nanoclays.* Two countries share the whole market here, Germany and the US. One site is currently under development for nanoclay production in France. A volume of around 100 tonnes is planned for 2007. About 50 people should be employed there.
- *Single-Wall Carbon Nanotubes (SWCNT).* The production capacity for this category of nanotubes is between a few grams and a few tens of kilograms per day. At the present time, the maximal capacity is produced by an American company with 40 kg/day, using chemical vapour deposition (CVD) and a gaseous mixture of $Fe(CO)_5$ and CO (the HiPCO process). French production of SWCNT is currently limited to university research laboratories. Several sites are equipped to produce quantities of around 10 g, either using a similar, low temperature process (CVD or catalytic CVD), or using a high temperature process (arc or plasma).
- *Multiwall Carbon Nanotubes (MWCNT).* These have produced by one French company since 2006. This production unit, with a capacity of 10 tonnes per year, was a pilot project, involving about 10 people. Production there will be increased to several hundred tonnes per year by the end of the decade.
- *Carbon Black.* This is essentially composed of spheres with diameters in the range 10–500 nm, in aggregations of between ten and a few hundred particles. French production was 240 000 tonnes in 2005. It is carried out at four production sites, and involves a workforce of around 350 people. Seventy percent of carbon black is used by the tyre industry. The proportion, which may reach 30% of the weight of a tyre, is tending to fall, being replaced by precipitated silica. The rubber industry also uses it to make protective sheaths for cables and in the composition of conveyor belts, drive belts, and joints.
- *Aluminas.* A single production site in France produces ultrahigh purity aluminas. These are made using an alum process, i.e., aluminium sulfate with multihydrated ammonia. Two horizontal units are being set up at the site to take production to 1 000–1 700 tonnes per year from 2008. Other

producers share the alumina market. This so-called speciality alumina is synthesised by the Bayer process which uses bauxite as raw material. French production of speciality aluminas represented 468 000 tonnes in 2004. This includes a proportion of ultrafine and nanostructured alumina on top of the traditional range.

Future Developments and Markets

According to the investigation by Rocco in 2004 [8], there are four main stages in the development of nanotechnology and nanomaterial production: passive nanostructures, active nanostructures, systems of nanosystems, and molecular nanosystems. Currently commercialised nanoproducts belong mainly to the first category of passive nanostructures.

An active nanostructure is one that can modify its own state, e.g., morphology, shape, and mechanical, electronic, magnetic, optical, or biological properties, and so on, during its use. As an illustration, a mechanical actuator might change size, while the morphology and/or chemical composition of nanoparticles used as drug carriers in medicine might evolve in order to get through biological barriers, for example. These novel states of nanostructures might in turn evolve, in particular, to make them harmless at the end of their life cycle. Such changes will be all the more complex as the structures and systems are required to become more bulky and to implement several functions.

Examples of such active nanostructures are the nanoelectromechanical systems (NEMS), biological nanodevices, transistors, amplifiers, pharmaceutical and chemical carriers, molecular machines, light-activated molecular motors, nanofluidic systems, sensors, and radiofrequency identification devices (RFID).

In the field of tagging and identification, it should be stressed that some systems are already operational. As an illustration, in 2006, Hitachi presented the smallest RFID chip ever made. With dimensions $0.05 \times 0.05\,\mathrm{mm}^2$, it has been referred to as smart dust. It contains a 128 bit read-only memory (ROM) that can stock a 38 digit identity number and it is easily integrated into a sheet of paper, for example. Recall that an RFID chip is used for automatic identification of whatever it tags. RFID chips can contain all kinds of information and are found on a great many different items, from passports to labels on products on sale at the supermarket, not to mention concert tickets. The advent of RFIDs in the form of a dust makes it easy to integrate them into ever more varied items. In parallel with these developments, a UK company has developed a device that can locate such RFID chips at up to a distance of 180 m [9] and to an accuracy of 2 cm in a 3D region. The possibility of such a high degree of miniaturisation has raised questions about tracking and checking up on individuals without them knowing.

In medicine, nanomaterials are already used in commercialised medical equipment, such as bandages, implants, prosthetics, and others. Medical biology uses nanoelements for in vitro diagnosis of infectious diseases, immunological disorders, and cancers. Some devices for day-to-day medical observation of biological parameters, e.g., glycaemia, will usefully benefit from the extreme miniaturisation made possible by nanotechnology. The medical imaging sector is also investigating the possibilities for improving the contrast and resolution of MRI images by placing nanoparticles in target organs. Pharmacological research has long been exploring the possibility of carrying therapeutic drugs as close as possible to lesions, using nanoparticles designed to target sick cells. Therapeutic trials are under way, especially in the field of cancer treatment. Nanotechnologies may one day be able to customise drugs. Some nanoparticle contrast agents and drugs have already been accepted by the relevant regulatory bodies.

One application in particular has seen rapid development and no doubt benefits significantly from progress in miniaturisation as procured by nanotechnology, and that is deep brain stimulation by microelectrodes placed in the brain [10]. Since the 1980s, a team in Grenoble (France) led by Professor A.L. Benabid has discovered that electrical stimulation of a certain part of the brain can reduce or completely remove the shaking symptoms of those suffering from Parkinson's disease. Since then, in collaboration with several international teams, applications to other medical problems have been proposed, including acute dystonia (a neurological movement disorder), epilepsy, and others. The technique was then tested – with the agreement of the French *Comité consultatif national d'éthique pour les sciences de la vie* (CCNE)[1] – in the treatment of obsessive–compulsive disorders (OCD) and depressive syndromes that could not be relieved by conventional medical treatments. At the present time, some 35 000 people are being treated by this 'brain pacemaker', including about 1 000 in France. Other research is investigating the brain–machine interface, with a view to controlling muscular movements either by acting directly on the nerve or muscle fibres, or by going through the central nervous system. These are promising applications for people suffering from paralysis or anomalous movements (tics).

However, these techniques carry the risk of side-effects, in particular when the electrode is implanted, since it may be rejected or cause brain hemorrhage. This is why the idea of using nanoscale electrodes came into being. In France, the CLINATEC project is a biomedical research center devoted to nanomedicine, focussing primarily on implanted devices and the brain–machine interface. It is important to debate the possible abuses of nanotechnology in medical applications, in particular for specific medical applications like deep brain stimulation.

It should also be stressed that there is a very clear dual development of nanotechnology and nanomaterials for specific defence applications. For example, items for personal protection such as bullet-proof vests and helmets incorporating carbon nanotubes, ultrafast and ultrasensitive detection devices,

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[1] National Consultative Committee for the Life Sciences.

chemical and bacteriological carriers, exoskeletons (powered mobile frameworks worn by the soldier and interfaced on the human brain, which should make it possible to carry 80 kg for 80 km at more than 50 km/h, developed by DARPA, USA), not to mention the development of thermobaric bombs which use pyrophoric nanoparticles and produce equivalent blast waves to a nuclear weapon [11] – the first tests were carried out by the United States and Russia in 2007. This all-pervading dual aspect of nanotechnological applications raises the question of whether we should renew international negotiations about the proliferation of weapons of mass destruction with a view to drawing up new treaties.

3.4 Nanomaterials and Safety

Our current understanding of the effects of micro- and nanoparticles in atmospheric pollution has raised fears regarding the consequences of man-made nanoparticles for human health. While very few reliable data are available in this field, studies published about the interactions of nanoparticles at the cellular level suggest that we should be cautious. Recently, work by Donaldson et al. [4] tends to show that some carbon nanotubes can induce similar effects to asbestos fibres, inducing mesothelioma.

As shown as early as 2005 in a summary note [12], the important scientific questions regarding nanoparticles and health must be concerned with the whole life cycle and must consider the following specific features:

- The physicochemical characterisation and classification of nanoparticles according to their level of surface reactivity, a good indicator of potential biological effects.
- The detection and characterisation of exposure to these particles by everyone from factory employees to users.
- Their potential biological effects on humans.

These issues concern workers in the nanotechnology and nanomaterials sectors, who may be exposed to high concentrations of nanoparticles, but also the population at large, whose exposure to these nanoparticles is less direct and related to the life cycle of the nano-object in question.

Finally, the risks associated with nanoparticle explosions must also be given due attention. At the present time, little has been done, e.g., with regard to staff involved in the production of nanomaterials from such nanoparticles.

Given the importance of these issues, some websites have been set up to monitor publications in this area:

- *The Virtual Journal of Nanotechnology Environment, Health and Safety* [13].
- *Nanotechnology: Health and Environmental Implications – An Inventory of Current Research* [14].
- *Safe Production and Use of Nanomaterials* [15].

4 The Need for Studies in Nanotoxicity and Nanoethics

As discussed by Roure [16], the highly diverse industrial economy of nanotechnology and nanomaterials is well under way. Given the speed with which laboratory research is transformed into nanoproducts, some already commercialised, and given their all-pervading tendencies [17], the time has come to assess our current understanding of nanotoxicity, and also to address the relevant ethical questions. Indeed, research in nanoscience and nanotechnology stands out by the difficulty in distinguishing the fundamental from the technological. Synergies arise through the NBIC convergence (nanotechnology, biotechnology, information technology, and cognitive science) and their effects are difficult to quantify in the mid to long term. This fourth volume of the *Nanoscience* series aims to present the state of the art, both in the field of nanotoxicity and with regard to what we shall define as nanoethics. We hope it will contribute to a responsible and safe use of nanomaterials and nanotechnology.

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