anses
French agency for food, environmental and occupational health & safety

Press Kit

Assessment of the risks associated with nanomaterials, issues and update of current knowledge

15 May 2014

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The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) issued an internal request in order to update current knowledge and review the issues relating to the assessment of risks associated with nanomaterials to human health and the environment.

Maisons-Alfort, 15 May 2014

Press Release

Highlighting the toxicity of certain nanomaterials, ANSES is calling for a stronger regulatory framework

Confronted with the wide range of nanomaterials in everyday life and the many questions surrounding them, ANSES today published a review of the available literature on health and environmental issues relating to manufactured nanomaterials. This spells out what scientists currently know about the toxic effects of some nanomaterials on living organisms and the environment. It also emphasises the complexity of understanding the various situations to which humans and the environment are exposed, and the limitations of existing risk assessment methodologies. Due to this complexity, it is difficult to assess the specific risks associated with nanomaterials. Given the time it would require, the Agency recommends the immediate implementation of tools to improve risk management through a stronger regulatory framework at European level.

Some "older" nanomaterials have been around for almost a century and certain nanoparticles can also be produced naturally. It was not however until the late 1990s that technological developments emerged that led to a wide diversification of industrial applications. Nanomaterials are now found in many everyday products: cosmetics, textiles, food, paints, medical applications, etc. This technological deployment has been accompanied by studies on their potential health impact, yet many doubts remain as to their effects on health and the environment. This uncertainty has led to questions about the degree to which these risks are controlled, and the appropriate regulatory framework.

Issues and update of current knowledge

ANSES has consequently set a high priority on the investigation of nanomaterials and has initiated a great deal of expert appraisal work on this subject. At the same time, the Agency has also been coordinating the Nanogenotox joint action, whose scientific objective was to provide the European Commission and Member States with a rigorous and reliable method for detecting the genotoxic potential of manufactured nanomaterials.

In 2012, ANSES set up a permanent group of experts whose mission is to continuously update knowledge of the health and environmental issues related to exposure to nanomaterials, and also a dialogue committee on "Nanomaterials and health" whose members include interested stakeholders.

Finally, the Agency issued an internal request in order to update current knowledge of the effects of nanomaterials on health, and of the corresponding regulatory and societal context at both the national and international levels. The results of this work were published today.

This summary of knowledge shows that despite the advances in scientific knowledge, major uncertainties remain about the effects of nanomaterials on health and the environment. It identifies a wide variety of hazard characteristics and notes the great complexity involved in understanding exposure situations for humans and the environment, thus making it difficult to conduct specific risk assessments. Given the time it would require, the Agency recommends implementing without delay tools to improve risk management through a stronger regulatory framework at European level.

Effects of certain nanomaterials on living organisms

Drawing on a review of all available data and scientific publications around the world, the report documents the effects identified on living organisms. Based on *in vitro* and *in vivo* animal tests, it first demonstrates the ability of nanomaterials to cross physiological barriers, and then highlights the toxicity of certain nanomaterials, noting that there are currently no data directly concerning humans, due to the lack of epidemiological studies.

Given these factors and faced with the complexity of the subject, the Agency has made several recommendations with a view to stimulating research to fill the numerous scientific gaps in our knowledge, and to developing regulations and standards that provide better protection for humans and the environment.

ANSES's recommendations

Regarding research, the Agency recommends implementing multidisciplinary projects to develop knowledge of the characteristics and hazards of nanomaterials, throughout the product life cycle. This mainly involves promoting the development of appropriate safety tests for assessing the health risks of products containing nanomaterials intended to be placed on the market.

In addition, ANSES is calling immediately for a strengthened regulatory framework for manufactured nanomaterials at the European level, in order to better characterise each substance and its uses, taking into account the entire product life cycle.
ANSES believes that the array of available scientific data on the toxicity of certain nanomaterials is sufficient to consider regulating them according to the European CLP (classification, labelling and packaging of substances and mixtures) and REACh (chemicals) Regulations. In this context, ANSES recently published recommendations on adapting the REACh Regulation to take into account the specific characteristics of nanomaterials[1].
This regulatory framework would enhance the traceability of nanomaterials intended to be used in consumer products, from production through to distribution, mainly with a view to improving characterisation of population exposure, and better targeting the risk assessments to be conducted. These risk assessments could lead to restrictions on their use or to their prohibition, in the framework of the REACh Regulation.

[1] ANSES Opinion on the modification of the REACh annexes with a view to taking nanomaterials into consideration

1. What are manufactured nanomaterials?

There are several different definitions of nanomaterials[2], although they all concur that they are materials whose size or structure has at least one dimension measuring between 1 and 100 nanometres approximately. This nanoscale, falling between the scale of atoms and that of solid materials, gives them specific physical, chemical or biological properties that do not exist at a larger scale.

Because of the many innovative applications which might be possible due to these physical, chemical or biological properties, scientific and technical research on nanomaterials is a rapidly developing field. .

Their use is booming and they are now found in many everyday products available on the market: cosmetics, textiles, food, paints, etc.

Nevertheless, the physico-chemical properties that appear at the nanoparticle state have led to questions about potential physical (fire, explosion), health (large surface area, strong ability to cross physiological barriers, possible interactions with biomolecules, etc.) and environmental risks (persistence in the environment).

For this reason, the presence of nanomaterials in everyday products raises questions, that are sometimes controversial, mainly concerning the state of available knowledge, and, ultimately, the risks associated with these substances.

The various examples of current applications or claimed uses include:

- in computing and electronics: nanosilver as an antibacterial agent for computer keyboards and mice;
- in medicine: targeted transport of active substances (vectorisation), contrast agents in medical imaging, antibacterial operating tables;
- in cosmetics and hygiene products: sunblock lotions with UV filters, toothpaste containing abrasive silicon dioxide nanoparticles, hairdryers or adhesive plasters containing nanosilver as an antibacterial agent;
- in food: silicon dioxide nanoparticles used as an anti-caking agent in table salt, for example;
- in construction: paints and varnishes, self-cleaning windows;
- in sport and leisure: tennis rackets containing carbon nanotubes for strength, soft toys containing nanosilver as an antibacterial agent;
- in the area of security and defence (Ministry of Sustainable Development 2013): explosives, special coatings for objects, etc.

[2] The Report entitled “Assessment of the risks associated with nanomaterials: Issues and update of current knowledge” lists the definitions of nanomaterials used to date in its Annex 2.

Areas of application by type of nanomaterials

Nanomaterials	Areas of application	Examples of finished products
Nano-oxides	Structural composites – Anti-UV components – Mechanical-chemical polishing of substrates for microelectronics – Photocatalytic applications – Construction	Food additives, paints, cosmetics, inks, tyres
Nanometallic materials	Antimicrobial and/or catalysis sectors – Conductive layers in screens, sensors or energetic materials	Medical dressings, food wrap films, coatings (refrigerator), work surfaces, self-cleaning windows or walls, clothing, food contact materials, ingestible food packaging
Carbon blacks	Transport, Construction, Printing	Tyres, inks, paints
Nanoporous materials	Aerogels for thermal insulation in the fields of electronics, optics and catalysis – Biomedical field for applications such as vectorisation or implants	Water filtration membranes, paints, adhesives, fertilisers
Carbon nanotubes	Electrically-conducting nanocomposites – Structural materials – Nanoelectronics, biomedical	Tennis rackets, flexible screens, vehicle bumpers, headlamps, batteries, tyres
Bulk nanomaterials	Transport, construction, sports equipment	Hard coatings – Structural components for the aerospace and automotive industries, pipes for the oil and gas industries, the sports sector or the anti-corrosion sector
Dendrimers	Medical field – Cosmetics field	Administration of drugs, rapid detection
Quantum dots	Optoelectronic applications (screens)	Photovoltaic cells, inks and paints for applications such as anti-counterfeiting marking
Fullerenes	Sport (nanocomposites) and cosmetics sectors	Mascaras, beauty creams, golf balls
Nanowires	Electronics, optoelectronics, photovoltaic	Applications in the conductive layers of screens or solar cells and electronic devices

2. Assessment of the risks associated with nanomaterials - an international issue

Issues in terms of risk assessment

Compared to chemicals, when assessing nanomaterials, several additional complicating factors must be addressed. For instance, there is no current consensus at the European or international levels on a common definition and terminology for nanomaterials. There are also no standard protocols for toxicology and ecotoxicology tests, although some progress has been made in this direction, and the existing methods and tests for "conventional" chemicals must on the whole be adapted to take into account the specific characteristics of nanomaterials. Measuring techniques and instruments need to be developed and/or standardised, particularly for measuring exposure.

A single chemical name of a substance (for example titanium dioxide) may encompass **different nanometric forms, and therefore different toxicities,** meaning that it may not be possible to extrapolate the assessment of one given type of nanomaterial to another, despite it apparently being made of the same substance. Finally, unlike a molecule of a "conventional" chemical, the physico-chemical parameters of a nanomaterial, and its potential toxicity, may change between its production and its fate after disposal or recycling. It is therefore difficult to characterise a nanomaterial at each stage of its life cycle and to produce relevant and comprehensive exposure scenarios.

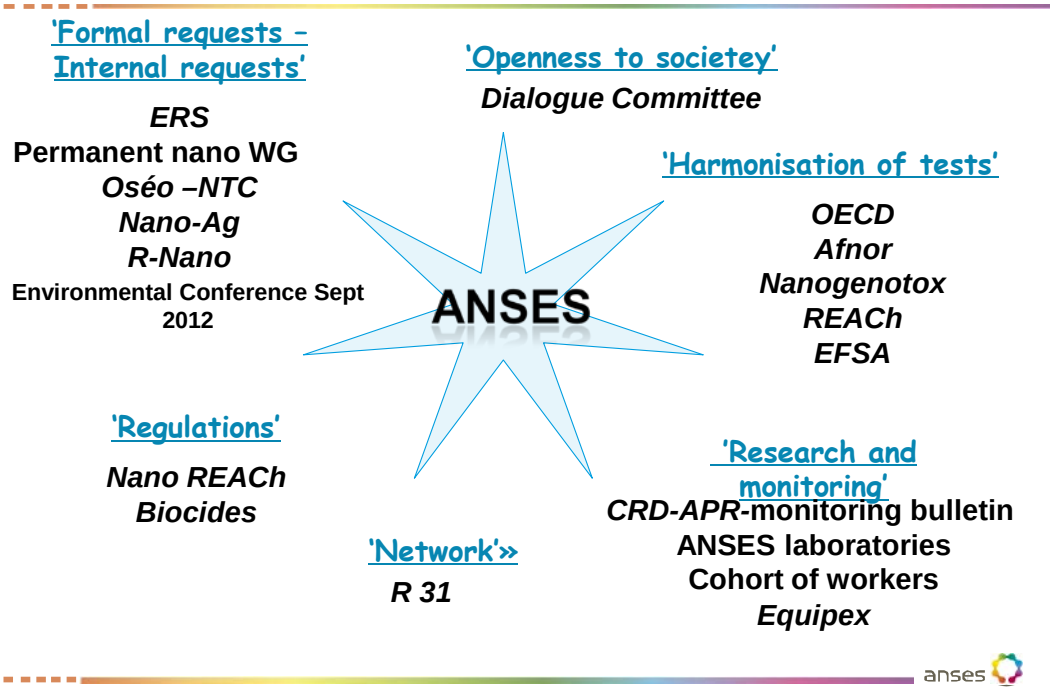
In this context of uncertainty relating to the risks of manufactured nanomaterials, on the occasion of the Fifth Ministerial Conference on Environment and Health organised by the World Health Organization's Regional Office for Europe, 53 health ministers from the member countries asked for the health and environmental issues related to nanomaterials and nanotechnologies to be listed as one of the key challenges in the 2010 Parma Declaration on Environment and Health.

Therefore, work on the development of new risk assessment methodologies, especially for people in the workplace, or on defining health and environmental safety tests, was undertaken by various institutions including the ISO[3], OECD[4] and the European Commission.

Responding to these issues

[3] International Organization for Standardization

[4] Organisation for Economic Cooperation and Development



In France, this concern is mainly expressed by:

- the national "environmental health" and "occupational health" plans that have emphasised the need to conduct research and expert appraisal work to characterise the hazards, exposures and risks to human health and the environment,

- the entry into force of the mandatory reporting of uses of substances with nanoparticle status as well as annual amounts produced, imported and distributed in France, in accordance with Articles L. 523-1 to L. 523-8 of the French Environmental Code (*Grenelle* II Act of 12 July 2010).

ANSES's risk assessment work

ANSES has published several expert reports on the health issues associated with exposure to nanomaterials, for the general and working populations (in 2006, 2008 and 2010). These reports in particular highlighted the difficulties of assessing the risks associated with such exposure, and described the need for more knowledge and new tools in order to characterise the hazards and exposures to nanomaterials.

In 2010, the Agency published a report on a tool for assessing and managing the risks associated with occupational exposure to nanomaterials, as well as a 'state of the art' review of knowledge of the toxicity and ecotoxicity of carbon nanotubes (2012), and an assessment of the risks associated with an industrial development programme for carbon nanotubes (2013).

Furthermore, since 2013, the Agency has been managing the scheme for mandatory reporting of nanoparticle substances for the Ministry of Ecology.

ANSES also contributes to various national, European and international studies that are investigating the toxicity and ecotoxicity of nanomaterials. In particular, it is involved in the international work of the OECD and EFSA[5], and in studies seeking to increase our understanding of the exposure of specific populations to nanomaterials, for example in the workplace. This includes the European joint action, Nanogenotox, coordinated by the Agency and co-funded by the European Commission. Its results, published in 2013, highlighted the need to adapt OECD guidelines on genotoxicity testing of chemicals to the specific characteristics of nanomaterials.
The assessment of silicon dioxide as an active insecticidal substance was completed by ANSES in 2013, leading to its approval in early 2014 at the European level under the Biocides Regulation (EU) No. 528/2012.

Finally, ANSES received a formal request relating to the modification of the annexes of the European REACh Regulation, with a view to taking nanomaterials into consideration. In its Opinion, the Agency proposes some amendments to the annexes that would provide better information on the forms and quantities of nanomaterials used. In 2015, ANSES will finalize assessing titanium dioxide (TiO_2) in the context of REACh. This work was initiated in 2014, in close collaboration with ECHA[6], to establish an optimal definition of the forms of nanomaterials covered by registration. This step is vital to ensuring consistent and effective assessment of TiO_2.

- **Monitoring scientific developments in real time**

A science and technology watch on manufactured nanomaterials and their potential risks to human health and the environment is essential to ensure that knowledge in this rapidly growing field is regularly kept up to date. To meet this need and ensure consistency between the different expertise activities coordinated by ANSES, the Agency inaugurated a **permanent working group of experts on "Nanomaterials and health - food, environment, work",** under the auspices of the **Expert Committee on "Assessment of the risks related to physical agents, new technologies and development areas",** whose primary objective is to produce a regular review of the state of knowledge on the hazards, exposures and health and environmental risks associated with manufactured nanomaterials, for all their uses.

All the work conducted and systems that have been set up facilitate the acquisition of new knowledge on nanomaterials and their potential risks. In this context, the Agency issued an internal request in January 2012 with the aim of producing an updated summary of knowledge of the health and environmental issues associated with exposure to manufactured nanomaterials. The report and opinion relating to this request were published today.

[5] European Food Safety Authority
[6] European Chemicals Agency

The main expert work conducted by the Agency

2006: “The effects of nanomaterials on human health and the environment”

2008: “Nanomaterials and occupational safety”

2009: “Nanoparticles in food and feed”

2010: “Assessment of the risks associated with nanomaterials in consumer products”

2010 - 2013: Coordination of the European joint action, Nanogenotox

2011: “Development of a tool for managing risks specifically related to nanomaterials”

2012: “Toxicity and ecotoxicity of carbon nanotubes: ‘review of current knowledge”

2014: “Modification of the REACh annexes with a view to taking nanoparticles into consideration”

2014: “Assessment of the risks associated with nanomaterials: issues and update of current knowledge”

- **A dedicated dialogue committee**

Alongside the permanent working group, a dialogue committee on "Nanomaterials and Health" was set up in 2012. Bringing together the main interested stakeholders - associations, trade unions, companies and industrial federations - the committee's mission is to advise the Agency on society's expectations in terms of expertise and research. It has some twenty members who are selected following a public call for expressions of interest, and it meets between two and four times a year.

This body is a forum for debate, reflection and information on the scientific issues related to the potential effects of nanomaterials on health, their assessment and the activities of ANSES (expert appraisal, PNR-EST, R31, etc.).

3. National Research Programme for Environmental and Occupational Health

One of ANSES's missions is to organise and support research. This is expressed in its work in conducting the National Research Programme on Environmental and Occupational Health (PNR-EST), a vital tool for acquiring the knowledge with which to support public policy-making and health risk assessment work.

The Agency thus organises a call for research projects (APR) every year, that in particular concerns the risks associated with nanoparticles. In 2013, research projects were expected for the following "nano" topics:

- Detection, identification and characterisation of nanoparticles, especially of manufactured nanoparticles (in biological fluids, tissues, environmental compartments),
- Fate and behaviour of manufactured nanoparticles released into the environment,
- Emissivity of products containing nanoparticles under normal or foreseeable conditions of use,
- Assessment of the exposure of workers and the general population to manufactured nanoparticles,
- Toxicology of nanoparticles and nanomaterials. Methodological research, reference methods.

Since 2011, projects on nanoparticles have on average accounted for 11% of proposals from researchers in response to PNR-EST calls for projects (between 2011 and 2013, 694 projects were proposed in response to four calls for projects, 79 of which were on "nano" topics). In this same period, 98 were funded, including 11 related to nanoparticles.
These projects examine different aspects and involve research teams from very different backgrounds. Three overall themes are covered by the work:

- Exposure to nanoparticles, particularly of workers, for instance during welding (via welding fumes) or operations causing abrasion of nanomaterials, as well as work on protection. A 2011 project led by two teams from Inserm and the Créteil Intermunicipal Hospital is entitled "*Cancer broncho-pulmonaire et exposition professionnelle aux fumées de soudage*" [*"Bronchopulmonary cancer and occupational exposure to welding fumes"*].

- Understanding the fate of nanoparticles in the environment (transfer via the food chain, transformations). The project entitled "*Etude des processus de transformation en milieux naturels complexes des nanoparticules minérales manufacturées par l'utilisation des isotopes stables métalliques" ["Study of transformation processes of manufactured mineral nanoparticles in complex natural environments using stable metal isotopes"]*, is being led by three laboratories associated with the University of Paris 7, Pierre and Marie Curie University, the Paris Institute of Earth Physics, CNRS and the French Institute of Research for Development (IRD).

- The movement of these particles in the body, especially from the lung or intestine, and their toxic effects. In 2013, the project entitled "*Devenir et toxicité de nanoparticules de dioxyde de titane après exposition orale chez le rat: impact de la taille des particules sur le franchissement de la barrière digestive et le risque de cancérogenèse colorectale*" [*"Fate and toxicity of titanium dioxide nanoparticles following oral exposure in rats: impact of particle size on the crossing of the intestinal barrier and the risk of colorectal*

carcinogenesis"] was selected. This project is being conducted by five teams belonging to three organisations: INRA, CEA and the French National Synchrotron Facility.

R31 and nanos

The R31 network, laid down by Article R1313-1 of the French Public Health Code, is a group of establishments coordinated by ANSES for its missions on environmental and occupational health, food, animal welfare and plant health. Representing a wide range of institutions (research organisations, risk assessment agencies and players in the healthcare system), the R31 network aims to strengthen cooperation between them.

Nanotechnology is a favourite theme for the R31 insofar as most of its members are concerned in one way or another (with health effects, consumer exposure, worker exposure, pollution of the natural environment, development of safer processes, etc.). The R31 seeks to capitalise on the variety of its members, which cover a range of activities from knowledge creation to the implementation of regulations, a particular advantage in this transition period, which began with an awareness of the "nano" risk in the early 2000s and has progressed to a desire for specific regulation. The initiatives taken in 2013 included the organisation of two seminars for discussions.

- The first, on the metrology of nanoparticles in complex media, was organised jointly with the National Laboratory of Metrology and Testing (LNE). It brought together around twenty people and addressed three issues: specific aspects of metrology at the "nanoscale", taking complex matrices (soil, biological fluids) into account, and the interface between metrology and regulations (for instance with regard to the "nano database").

- The second, on toxicology and ecotoxicology, was co-organised with INRA and attracted around fifty participants. The themes were: *in vivo* and *in vitro* studies, reproducibility of toxicity tests, practical examples of applications to the study of the environment, indoor air, medicinal products and food.

4. Toxicity and ecotoxicity of carbon nanotubes: review of the state of knowledge

Among the many nanomaterials available, carbon nanotubes have special properties that make them particularly attractive as additives for materials (electrostatic dissipation and mechanical reinforcement properties), coatings (giving adhesives and inks electrical conductivity, for example), energy (extending the lifetime of energy storage systems) and catalysis. They are also of interest to the medical field (drugs, imaging).

A wide range of carbon nanotubes are available and their physico-chemical characteristics (agglomeration and/or aggregation state, chemical composition, particle size and distribution, shape, solubility/dispersibility, etc.) vary depending on the way they are manufactured (catalysts and post-processing in particular) and implemented.

In late 2012, the Agency published a review of current knowledge of the toxicity and ecotoxicity of carbon nanotubes, for humans and the environment.

Some carbon nanotubes are toxic to humans…

The toxicity of carbon nanotubes has been studied for around a decade, and includes work on cellular responses *in vitro* and short-term studies in rodents.

The 2011-2012 literature review identified a convergence in work on some effects of multi-wall carbon nanotubes: these can cause genotoxic effects *in vitro* (DNA and chromosome breaks), chromosomal aberrations (sister chromatid exchanges, abnormal number of chromosomes), cell damage such as deleterious effects on cell proliferation, apoptosis (cell death) and inflammatory processes.

Although it has not been established that all the routes of exposure and carbon nanotubes studied present a hazard, the fact remains that teratogenic effects (that can cause abnormal development of the embryo, even in the absence of maternal toxicity), respiratory health effects (such as granuloma formation, fibrosis) and carcinogenic effects (mesothelioma) have been demonstrated. These effects depend on the route of exposure, dose and period after exposure. Their detection, and/or persistence after the end of the exposure period was highlighted.

…and further research is needed

However, although we are beginning to better understand the hazards associated with certain carbon nanotubes, we still do not know all the mechanisms involved. New fundamental research is needed (for example, to better understand the production mechanisms of reactive oxygen-derived species or the genotoxicity of carbon nanotubes). Similarly, it is essential to improve the physico-chemical characterisation of carbon nanotubes, before exposure as well as in the exposure environment.

The long-term effects of carbon nanotubes should also be studied. Cell culture models could be developed for this in large-scale toxicological studies so as to determine the changes in regulatory pathways controlling cellular homeostasis.

Lastly, knowledge is required of the bioavailability of carbon nanotubes after pulmonary administration, with systemic absorption being suggested as a possible route of exposure. The biopersistence of carbon nanotubes in the body (mainly in the lungs and liver) is an additional

source of concern, given the long-term hazard of these materials, and should also be studied in depth.

Environmental toxicity of carbon nanotubes: effects observed on plants and small organisms…

Regarding the ecotoxicity of carbon nanotubes, the review of current knowledge published by the Agency in 2012 helped to demonstrate that multi-wall carbon nanotubes in soil could exhibit antimicrobial activity and affect the nutrient cycles in which microorganisms are involved.

This review also confirmed that the carbon nanotubes had:

- contradictory effects on plants. For example, in various species of plants (radish, rapeseed, ryegrass, lettuce, maize and cucumber), no effect on germination was reported, while in others, there was an observed reduction (tomato) or increase (onion, cucumber) in root elongation.

- negative effects on growth, reproduction, viability and elimination in *Daphnia*.

In addition, ecotoxicity studies generally show that carbon nanotubes can be ingested by organisms; consequently, assessment of the environmental risk associated with their release and transport in the environment needs to be improved.

… which means more in-depth research is needed

However, in most of the studies described, the ecotoxicological effects were observed at high concentrations that probably do not reflect environmental conditions. Nevertheless, an impact of carbon nanotubes on ecosystems at lower concentrations cannot be ruled out. Broader and more detailed knowledge is needed in this area, in order to better predict the potential consequences of carbon nanotubes on the environment in the short and long terms.

Finally, exposure to carbon nanotubes can occur at any time in the life cycle of products containing them (during their manufacture, transport, use or disposal). In most cases, the carbon nanotubes in consumer products are incorporated into matrices and are not in free form. The possibility that they may be released as the products wear out, or when they are disposed of, must be taken into account.

Since products containing carbon nanotubes are already being produced and provided to a wide group of consumers, studies on the exposure of workers and the public to carbon nanotubes are essential. Before continuing to develop the production of carbon nanotubes and multiply their uses and availability on the market, it seems important to assess the potential exposure of the population under actual conditions and gain a better understanding of the life cycle of these materials. This is a prerequisite for assessing occupational and environmental risks.

5. Development of a tool for the graduated management of risks specifically related to nanomaterials

In 2005, discussions began within the working groups of national and international standards organisations (ISO and AFNOR) on nanotechnologies, and specifically their safety. In 2008, France in particular stated its desire to propose a draft standard at the international level with the intention of developing a risk control method based on the specific physico-chemical and toxicological properties of nanomaterials. France was then given three years to complete this project.

The Ministry of Health, in consultation with the Ministries of the Environment and Labour, asked the Agency to prepare a collective expert appraisal report for forwarding to AFNOR, as input for the document it was submitting to the ISO with a view to developing common standards at the international level. The method proposed by the Agency's experts is **a graduated risk management approach known as "control banding".**

Graduated management of risks is an instrument combining risk assessment and management. It is specifically intended to guide risk management in a context of uncertainty relating to the input data needed for risk assessment (uncertainty about the hazards of nanomaterials and the exposure levels). It takes into account existing information and available technical and scientific data, and relies on a number of assumptions.

The method proposed by ANSES is a tool that is regularly upgraded according to available knowledge. Products containing nanomaterials or the nanomaterials themselves are classified into risk control bands, defined from the hazard level of known and/or similar products and taking into account the assessment of exposure at the work station. In this process, a qualitative risk assessment is combined with a proposed means of individual or collective prevention that should be implemented, based on the estimated level of risk. This tool therefore allows the risk to be managed in a graduated way (risk control bands), taking into account both the potential hazards of the studied nanomaterials and the estimated exposure levels.

"Control banding" can potentially be used in any work environment in which nanomaterials are manufactured or used (industrial workshops, research laboratories, pilot plants, etc.). This approach is especially suitable for SMEs and SMIs that do not necessarily have at their disposal the metrological characterisation devices or in-depth toxicological studies needed for an actual risk assessment process.

6. NANOGENOTOX

Launched in March 2010 and coordinated by ANSES, the European Joint Action, Nanogenotox, brought together 30 partners (scientific organisations and ministries) from 13 EU Member States. Several French organisations took part. The project had a total budget of €6.2M: 45% from the European Commission (Second programme of Community action in the field of health) and the remaining 55% from partner organisations and ministries in the participating Member States. For France, funding was primarily provided by the Directorate General for Health. Its objective was to provide the European Commission and Member States with a rigorous and reliable method of detecting the genotoxic potential of manufactured nanomaterials likely to cause cancer or reproductive toxicity in humans. In this framework, 14 manufactured nanomaterials, selected according to their possible uses in different types of products (cosmetics, food, consumer products) and their potential routes of exposure (oral, dermal, inhalation), were studied.

The final conference for Nanogenotox was held in Paris on 22 February 2013 and was attended by about 200 participants from around the world: scientists, national policymakers from the Member States and the European Union, and representatives of the various stakeholders. This event was an opportunity to take stock of the knowledge generated during the project and to discuss the implications of its results.

Work from the Nanogenotox project has reaffirmed the need for a comprehensive and reliable physico-chemical characterisation of raw and dispersed materials. Nanogenotox proposed standard procedures for this characterisation and a common dispersion protocol. From its results, adaptations to existing OECD guidelines for *in vitro* and *in vivo* testing were proposed.

Studies to be pursued

The Nanogenotox joint action generated a wealth of scientific output in terms of scientific data and lessons learned on the use of test protocols.
Nanogenotox provided new data that will be vital to scientists, assessors and decision-makers:

- Each nanomaterial is unique, therefore assessment test results cannot be extrapolated to all nanomaterials with the same chemical name, for example. However it is possible to use identical test methods and dispersion protocols for a group of nanomaterials that may have different chemical names.
- The guidelines on the regulatory genotoxicity tests for nanomaterials must be adapted, as they do not take into account the specific characteristics of nanomaterials.
- A physico-chemical parameter can be measured by various methods and achieve good correlation between results. A single measuring device can be used for several physico-chemical parameters.

- Many methods for characterising physico-chemical parameters have been used to ensure that the characterisation of nanomaterials is as comprehensive as possible.
- Genotoxic effects have been observed in tests at low doses whereas at higher doses, the effects no longer occur. This "low-dose" effect warrants further study.

The results from Nanogenotox have now led to extensive work being carried out by members of the OECD Working Party on Manufactured Nanomaterials, which will be continued in the coming years, especially through the Sponsorship Programme for the Testing of Manufactured Nanomaterials.

7. Reporting of substances with nanoparticle status: “R-Nano”

It became clear that gaining a better understanding of the spread of nanomaterials would require improved knowledge of the market, whether in terms of substances marketed in France, uses, sectors concerned, quantities, etc.
With this in mind, France decided to introduce the mandatory reporting of substances with nanoparticle status, in a pure state or contained in mixtures or certain materials (*Grenelle* II Act of 12 July 2010).

On 11 August 2011, ANSES therefore received a formal request from the Ministries of Health, Ecology and Labour, to:

- determine the physico-chemical parameters needed to characterise the identity of a nanomaterial;
- identify the requirements with a view to developing a tool for collecting reports;
- develop the dedicated database and website for the reporting scheme.

The scheme came into force on 1 January 2013: the first reports, made in 2013, concerned nanoparticle substances manufactured, imported and/or distributed during 2012.

Objectives of the reporting scheme

The national reporting scheme provides:

- a better understanding of the substances placed on the national market, their volumes and their uses,
- traceability in the sectors in which they are used,
- information for the public and workers,
- the available information from respondents on the toxicological and ecotoxicological properties of these substances,
- and ultimately enables the adapted management measures to be assessed, especially with respect to the most vulnerable populations.

Main principles of the reporting scheme

Manufacturers, importers and distributors in France must submit an annual report to the Ministry of the Environment, via the dedicated website www.r-nano.fr, on the identity, quantities and uses of these substances, as well as the identity of the business users to whom they were sold.

The report must be made for all amounts above 100 grams of nanoparticle substance produced, imported or distributed per year.

The products covered by the mandatory reporting scheme are:

- nanoparticle substances in a pure state,
- nanoparticle substances contained in mixture without being bound,
- articles intended to release such substances in normal or reasonably foreseeable conditions of use.

This scheme therefore covers all forms likely to lead to extraction or release of the substance under normal or reasonably foreseeable conditions of use, and therefore to human or environmental exposure.

Review of the first six months of the scheme

As administrator of the www.r-nano.fr website and the reporting database, ANSES provided the Ministry of the Environment with an analysis of these data, which the Ministry used to publish, in November 2013, a review of all the reports submitted by 30 June 2013.

The main results from the 2013 annual scheme, concerning nanoparticle substances produced, imported and distributed in 2012, are as follows:

3409 reports were submitted

670 French entities submitted at least one report

Of the French players submitting a declaration: 22% were importers, 6% were producers, 68% were distributors, and 4% were classified as "other",

280,000 tonnes of nanoparticle substances were produced in France in 2012

220,000 tonnes of nanoparticle substances were imported into France in 2012

making a total of 500,000 tonnes of substances with nanoparticle status placed on the French market in 2012

Most French players in the field of nanoparticle substances are therefore distributors or users of substances. Production concerns only a small number of respondents, while imports account for a significant share.

However, the data from this first year of the reporting scheme should be treated with caution. They probably still only provide a partial picture of the market for nanoparticle substances, because of the novelty of this requirement and the many different stakeholders involved.

Outlook

The detailed information contained in the reports is now made available to the scientific organisations appointed by decree (Decree No. 2012-233) for the purposes of risk assessment, for example in epidemiological studies monitoring cohorts of workers exposed to nanomaterials or in environmental monitoring studies.
All of this information should facilitate the risk prevention work of companies and competent organisations, mainly aimed at protecting workers.

Moreover, as well as the substance assessments already begun, this inventory should help the public authorities to target other substances requiring risk assessment, by focusing on the exposure situations of greatest concern (large and/or vulnerable populations).

Categories of substances produced and/or imported in larger quantities (above 100 tonnes)

Mass produced and/or imported (in kg)	Chemical name
274,837,135	carbon black
155,071,912	silicon dioxide/amorphous silicon
34,501,525	calcium carbonate
14,321,436	titanium dioxide
2,193,565	aluminium oxide
1,568,000	copolymer of vinylidene chloride
538,473	Magnetic iron oxide, yellow
492,000	silicic acid, aluminium salt and sodium
287,695	zinc oxide
242,188	Magnetic iron oxide, yellow
208,979	2,2'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[n-(2,4-dimethylphenyl)-3-oxobutyramide]
173,641	di-iron trioxide
150,975	silicic acid, aluminium salt, magnesium salt and sodium salt
150,584	pyrrolo(3,4-c)pyrrole-1,4-dione, 2,5-dihydro-3,6-diphenyl
141,232	2-[(2-methoxy-4-nitrophenyl)azo]-n-(2-methoxyphenyl)-3-oxobutyramide
138,100	2-propenoic acid, 2-methyl-methyl ester, polymer with 1,3-butadiene, butyl 2-propenoate and ethenylbenzene)
138,000	pyrrolo[3,4-c]pyrrol-1,4-dione, 3,6-bis([1,1'-biphenyl]-4-yl)-2,5-dihydro-[a])
136,500	aluminium hydroxide
134,740	4,4'-diamino[1,1'-bianthracene]-9,9',10,10'-tetraone
107,796	cerium dioxide