

Feasibility of an epidemiological surveillance system for workers occupationally exposed to engineered nanomaterials

Summary report

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Nanomaterials are experiencing a worldwide rapid and major industrial development. Divided on the nanometric scale, matter acquires new physical or chemical properties due to the increase in specific surface area and the presence of quantum effects. This industrial development is accompanied by questions about the potential risks to human health. With this in mind, the Ministry of Health (Direction générale de la santé, DGS) has demanded that the Institute for Public Health Research (Institut de recherche en santé publique, Iresp) studies the feasibility of a surveillance system for health effects of occupational exposure to engineered nanomaterials. In response to this request, the IReSP has set up a multidisciplinary working group made up of researchers and professionals from universities, research organisations and various health safety agencies. The group has put the French Institute for Public Health Surveillance (Institut de veille sanitaire, InVS) in charge of developing a surveillance protocol for workers with occupational exposure to engineered nanomaterials. The InVS's assignment has been confirmed by both the DGS and the Ministry of Labour (Direction générale du travail, DGT).

DEFINITIONS EMPLOYED

The InVS has used the following definitions for the purpose of its study. The nanometric scale is defined as lying between approximately 0 and 100 nm. 'Nano-objects' have one, two or three external dimensions on the nanometric scale and designate nanoparticles as well as nanofibres or nanofilms. Nanomaterials are entirely or partially composed of nano-objects, giving them the improved or special nanometric-scale properties. Nanomaterials are called engineered or manufactured if the purpose of the industrial process is the production of nanomaterials. The aggregation of primary nanometre particles involves strong bonds, while agglomeration is based on weaker links.

DIVERSITY OF NANOMATERIALS

The term nanomaterials covers a very wide variety of materials, as it includes the nano-objects themselves (in the form of powder, aerosol, suspensions or films) as well as bulk nanocharged materials (including nano-objects) or even surface or volume nanostructured materials. The great variability of nano-objects in terms of chemical composition, shape, size, level of aggregation or agglomeration, crystalline state, electrical charge, porosity or surface treatment adds even more to the diversity of the materials. According to whether nanomaterials are present in the form of bulk materials, liquid suspension or powder, the circumstances of exposure of workers vary. The best-documented situation of occupational exposure to date involves handling nano-object powder.

SUSPECTED HEALTH EFFECTS

To construct an epidemiological surveillance system, it is essential to identify the health events that should be considered. While there are epidemiological studies investigating the health effects related to exposure to materials such as carbon black, amorphous silicas or titanium dioxide, none has clearly set out to study the effect of their nanometric form. With regard to emerging nanomaterials such as carbon nanotubes or fullerenes, no epidemiological study has been conducted to date. The results of toxicological studies (toxicokinetics of particles in the body, study of the short- and long-term effects) and human experimental studies (study of the short-term effects) have therefore been used to target the health events of interest. Epidemiological studies on the effects of particulate air pollution have also been used, as analysis of the scientific literature indicates a convergence between the issue of the health effects of particulate air pollution and that of nanomaterials. Some arguments resulting from toxicological studies are likely to indicate that a large part of the health effects related to particulate air pollution are in fact due to the finest particles, of diameter less than 100 nm.

Inhalation is the principal way of penetration of nano-object aerosols into the body. At the respiratory tract level, nano-objects could be involved in the occurrence of pulmonary and systemic inflammation, the induction or aggravation of chronic respiratory pathologies such as asthma or chronic obstructive pulmonary disease and exacerbation of the associated respiratory symptoms, increased frequency of pulmonary infections, or the occurrence of fibrosis or even a pulmonary cancer. More specifically, carbon nanotubes, due to their similarity in shape to asbestos fibres, could cause development of pleural plaques and pleural mesothelioma.

The toxicology literature describes the possibility of translocation of nanoparticles across the alveolo-capillary barrier into the blood circulation, thus opening access to most of the body's organs and systems. While this phenomenon appears to be of little importance quantitatively and variable according to the chemical and physical characteristics of the materials under consideration, a direct effect of nano-objects on organs located at a distance from the lungs can be considered in theory. Moreover, the toxicological studies describe a possibility of some nanoparticles gaining access directly to the cerebral structures by migration along the axons of the olfactory nerves, from the nasal mucosa to the olfactory bulb.

At the same time, epidemiological studies have shown an effect of particulate air pollution on cardiovascular morbidity and mortality. The impairment of the cardiovascular system may include a change in cardiac rhythm, dysfunction of the autonomic nervous system, change in blood pressure and vascular tone, alteration in coagulation, endothelial dysfunction and progression of atherosclerosis. In terms of pathologies, exposure to particulate air pollution is associated with an increased risk of myocardial infarction, ischemic cerebrovascular accidents, thromboses, cardiac arrhythmias, heart failure or even cardiac arrest. In summary, while it seems very important to orient the surveillance system toward pulmonary and cardiovascular pathologies, it is essential that it maintains an unspecific feature to allow study of health events affecting other organs or systems, such as the liver, kidneys, central nervous system, reproductive system, etc.

CHARACTERISATION OF EXPOSURE TO NANOMATERIALS

While qualitative or semi-quantitative exposure assessment can be considered in the context of establishing a surveillance system, quantitative assessment is more difficult due to the current uncertainties in measuring aerosols of nano-objects. The mass concentration usually used to assess exposure to dust in an occupational environment does not allow to describe precisely exposure to objects of nanometre size. Toxicological studies suggest that metrics such as the number concentration or surface concentration are more appropriate. But these new metrics are not specific, as they measure the nano-object of interest as well as the ultrafine particles in the ambient background. While methods and equipment now allow the number concentration and surface concentration to be measured, only some research laboratories are capable of implementing and interpreting them. In addition, the natural tendency of nano-objects to aggregate or agglomerate makes it necessary to define the particle size fraction on which measurements should be performed.

IDENTIFICATION OF COMPANIES HANDLING NANOMATERIALS IN FRANCE

The identification of workers likely to be exposed to aerosols of nano-objects necessarily involves locating the enterprises involved in the manufacture, formulation or use of nanomaterials. A field industrial study undertaken by the Institut national de recherche et de sécurité (INRS) has allowed the enterprises producing nano-objects and the principal sectors of activity using them to be precisely identified. However, there is no exhaustive inventory of the user companies. In the future, the French law no. 2010-788 of 12 July 2010 on national commitment to the environment provides that companies manufacturing, importing or distributing substances in the nanoparticle state declare to administrative authorities the identity, quantities and uses of these substances, as well as their client companies. This provision will facilitate establishment of a registry of workers with the aim of epidemiological surveillance.

EXPLORATORY STUDY WITH ENTERPRISES

In order to set up an epidemiological surveillance system for workers likely to be exposed to nanomaterials and to assess its feasibility, it was helpful to interact with companies, research organisations and laboratories producing or handling nanomaterials and to visit the sites concerned. With this aim, a selection of nano-objects was made based on the available information: quantities manufactured in France and projections for development of production, available toxicological data, the choice of France in the framework of the sponsorship programme for the testing of manufactured nanomaterials supported by the Organisation for Economic Cooperation and Development (OECD), and social perception factors. Four nano-objects were finally chosen: carbon nanotubes, nanometric titanium dioxide, carbon black and amorphous silicas.

For each of the four nano-objects selected, a production company was contacted, and all *a priori* accepted an exchange with the InVS and a site visit. A public sector research and development site and a research laboratory were also visited. With regard to users, out of three companies contacted in the cosmetic and tyre sectors, only one agreed to host the InVS.

At the end of the exchanges and visits carried out, it was possible to classify the enterprises in three categories:

- public or private sector enterprises active in research and development working on emerging nanomaterials, notably carbon nanotubes. Exposure seems unlikely (industrial process fully enclosed, suitable personal protective equipment worn, etc.) and collaboration on an epidemiological surveillance system seems to be easily build;
- private sector companies producing carbon black, amorphous silicas, or nanometric titanium dioxide. Manufacture is long-standing (fifty years for carbon black and precipitated silica, twenty years for nanometric titanium dioxide). Exposure to aggregates and agglomerated forms of nano-objects is probable and collaboration on a monitoring system can be envisaged;
- private sector companies using nano-objects. In exchanges with these companies, the definition of nanomaterials is at the core of the discussions. It is difficult to form an opinion in terms of probability of exposure as only one industrial site could be visited. Collaboration on a monitoring system appears to be complicated.

Regardless of the type of company considered, the industrialists report generally a low number of workers likely to be exposed to nanomaterials. The workers are most often subject to annual medical monitoring that is however not specific to their possible exposure to nano-objects.

SURVEILLANCE SYSTEM PROPOSED BY THE INVS

After studying the various possible epidemiological protocols and the existing data, the InVS proposes establishing a two-part epidemiological surveillance system, with on the one hand a prospective cohort study and on the other hand repeated cross-sectional studies. The prospective cohort study will pursue surveillance objectives and can serve secondarily as a basis for performing studies with specific research objectives. It will be limited to few high-priority nanomaterials and will necessitate

collaboration with the enterprises. In the long term, use of quantitative exposure assessment thanks to close collaboration between the INRS and the InVS is planned in the cohort study. Wholly complementary to the cohort study, the repeated cross-sectional studies would only fulfil a surveillance objective and would involve all nanomaterials. They would rely on the occupational health services belonging to the Federation of occupational health services in small and medium companies (Centre interservices de santé et de médecine du travail en entreprise, CISME) which is currently conducting an initiative to aid occupational physicians in identifying workers likely to be exposed to nanomaterials. They should allow workers rarely involved in epidemiological studies, subcontractors and employees of small and medium enterprises, to be included. The protocol for the repeated cross-sectional studies depends heavily on the adherence of occupational physicians to this initiative, the data they will collect and their standardisation; it is not developed in this report.

Establishment of a cohort of exposed workers should allow non specific follow-up of possible medium- and long-term health effects of occupational exposure to nanomaterials. It will also serve as a source to facilitate the establishment of *ad hoc* studies exploring specific research hypotheses. The absence of a substantial hypothesis on the potential risks to human health of exposure to nanomaterials and the numerous uncertainties inherent in the project suggest adoption of a pragmatic approach and initial proposal of a surveillance system that is simple but capable of modification. Health follow-up will be oriented toward monitoring the respiratory and cardiovascular effects but will maintain an unspecific feature.

At first, and in terms of feasibility, the field of investigation will be restricted only to workers exposed to powders of nano-objects (including those incorporating aggregate and agglomerated forms). The cohort will involve workers potentially exposed to the four nano-objects specified as high-priority in the framework of the exploratory study: carbon nanotubes, carbon black, amorphous silicas and nanometric titanium dioxide. The field of study can subsequently be extended to other circumstances of exposure and other types of materials.

A step-by-step protocol can be proposed. The first step will consist of creating an exposure registry of workers potentially exposed to nanomaterials. The enrolment of the subjects in this exposure registry is considered to be the inclusion phase in the cohort. This step will have to be individualised in the protocol insofar as it will involve the collaboration of numerous enterprises and will provide the information necessary for finalising the subsequent steps of the protocol. Registration of workers should be open and supplemented over time by new workers. It will be accompanied by collection of information allowing exposure to be assessed qualitatively and semi-quantitatively (activity sector, profession, description of the tasks performed, frequency, duration, etc.). The information will be updated at regular intervals. Causes of death will be followed up, constituting a minimal surveillance system as of the first step. The exposure registry system will be started up over an initial period of three years. In the USA, the National Institute for Occupational Safety and Health (NIOSH) has recommended setting up registration for exposed workers.

The second step will include various aspects, with the establishment of passive health follow-up based on medical records collected for administrative purposes by health insurance systems and hospitals, use of the medical data originating from occupational health services, development of active health follow-up by individual questionnaire and quantitative evaluation of exposures based on measurement campaigns in the enterprises. The protocol for this second step will be finalised during the next three years, both because it necessitates further developments (passive follow-up and active follow-up by questionnaire) and because it relies on information resulting from the exposure registry (use of medical data from the occupational health services, choice of the sampling strategy for quantitative evaluation of exposures).

With the aim of facilitating the establishment of *ad hoc* studies exploring specific research hypotheses, the researchers of the IReSP group have underlined the interest of establishing a biobank and implementing standardised clinical examinations. This follow-up, which can turn out to be very onerous, raises numerous ethical, economic and operational questions, however, and it is premature to take a definitive position on this subject. The necessity of establishing this type of monitoring and research tool will be reconsidered later in the light of the information resulting from the exposure registry and the development of epidemiological and toxicological knowledge.

CONCLUSION AND RECOMMENDATIONS

In conclusion, it is expedient to equip France as soon as possible with a system establishing an epidemiological surveillance system in relation to nanomaterial exposure, although no specific hypothesis allows surveillance to be targeted precisely at present. This tool should be designed first with a view to allowing epidemiological monitoring and facilitating epidemiological research in the field.

Although motivated by a concern for practical feasibility, this is an ambitious project as it necessitates bringing together and collaborating with a large number of enterprises.

The proposal to establish a monitoring system for workers potentially exposed to intentionally produced nanomaterials calls for specification of the respective roles of the InVS and the research organisations. Insofar as there are no epidemiological studies documenting the human health risks associated with the nanometric form of a material, the surveillance system proposed by the InVS has the task of eliciting hypotheses and precedes epidemiological research. It involves a new approach in the field of monitoring occupational risks, consisting of monitoring any non-specific abnormal events in a population of exposed workers.

The review carried out in the context of this report has revealed a certain number of research topics in epidemiology which specialised teams could undertake. Epidemiological studies dealing with the short-term effects of occupational exposure to nanomaterials, making use of early biomarkers of health effects, and exposure could be proposed as of now. In the same way, retrospective cohort studies studying the causes of death of workers who have been exposed to titanium dioxide or carbon black and amorphous silicas would allow the issue to be better documented. Calls for research proposals could be oriented in this direction.

Special thanks to the working-group chaired by Alfred Spira from the French Institute for Public Health Research (Iresp) and composed of: Jean-Claude André, Centre national de la recherche scientifique ; Daniel Bloch, Commissariat à l'énergie atomique ; Jorge Boczkowski, Institut national de la santé et de la recherche médicale (Inserm), Patrick Brochard, Institut de santé publique, d'épidémiologie et de développement – Université Bordeaux 2 ; Raphaël Chevallier, Direction générale du travail (DGT) ; William Dab, Conservatoire national des arts et métiers ; Mireille Fontaine, Direction générale de la santé ; Marcel Goldberg, Inserm ; Bertrand Honnert, Institut national de recherche et de sécurité (INRS) ; Hélène Lacroix, Iresp ; Danièle Luce, Inserm ; Pascale Maisonneuve, Agence française de sécurité sanitaire des produits de santé ; Patricia Maladry, DGT ; Francelyne Marano, Université Paris 7 ; Rachel Nadif, Inserm ; Jean-Claude Pairon, Centre hospitalier intercommunal de Créteil ; Anca Radauceanu, INRS ; Nathalie Thieriet, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail ; Olivier Witschger, INRS.

For further information:

Full report: Boutou-Kempf O. Éléments de faisabilité pour un dispositif de surveillance épidémiologique des travailleurs exposés aux nanomatériaux intentionnellement produits. Saint-Maurice: Institut de veille sanitaire; 2011. 69 p. Available from the URL: <http://www.invs.sante.fr>

This summary was translated in English with the help of the Editorial Support unit (CeVE), Scientific direction, InVS.

Key words: nanomaterial, nano-object, epidemiological surveillance, prospective cohort, exposure registry

Suggested citation:

Boutou-Kempf O, Marchand JL, Imbernon E. Feasibility of an epidemiological surveillance system for workers occupationally exposed to engineered nanomaterials. Summary report. Saint-Maurice: French Institute for Public Health Surveillance; 2012. 4 p. Available from the URL: <http://www.invs.sante.fr>