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French registry of workers handling engineered nanomaterials as an instrument of integrated system for surveillance and research

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Abstract. Despite the lack of data on the human health potential risks related to the engineered nanomaterials (ENM) exposure, ENM handling spreads in industry. The French government officially charged the InVS to develop an epidemiological surveillance of workers occupationally exposed to ENM. An initial surveillance plan was proposed on the basis of literature review and discussions with national and international ENM and occupational safety and health (OSH) experts. In site investigations and technical visits were then carried out to build an adequate surveillance system and to assess its feasibility. The current plan consists of a multi-step methodology where exposure registry construction is paramount. Workers potentially exposed to carbon nanotubes (CNT) or nanometric titanium dioxide (TiO₂) will be identified using a 3-level approach: 1-identification and selection of companies concerned with ENM exposure (based on compulsory declaration and questionnaires), 2-in site exposure assessment and identification of the jobs/tasks with ENM exposure (based on job-exposure matrix, further supplemented with measurements), and 3-identification of workers concerned. Data of interest will be collected by questionnaire. Companies and workers inclusion questionnaires are designed and currently under validation. This registration is at the moment planned for three years but could be extended and include other ENM. A prospective cohort study will be established from this registry, to pursue surveillance objectives and serve as an infrastructure for performing epidemiological and panel studies with specific research objectives.

1. Introduction

During the last decade important body of toxicological and exposure data was generated in the framework of occupational safety and health (OSH) research focusing engineered nanomaterials (ENM) [1,2]. However the lack of epidemiological and biomedical data on the human health potential risks related to the ENM exposure is a substantial gap for validating experimental results, risk-assessment modeling and developing consistent risk management guidelines if needed [3]. Considering that despite these uncertainties, ENM handling spreads in industry, the French Ministries of Health and of Labour have given the French Institute for Public Health Surveillance (*Institut de Veille Sanitaire, InVS*) responsibility for designing the protocol of an epidemiological surveillance system of workers likely to be exposed to engineered nanomaterials (ENM).

2. Exploratory feasibility study

An initial surveillance plan was proposed within a multidisciplinary working group held by the French Institute for Public Health Research (*Institut de recherche en santé publique, IReSP*) on the basis of literature review and discussions with national and international ENM and OSH experts [4]. An exploratory study was then conducted with the aim of assessing the feasibility of an epidemiological surveillance system of workers occupationally exposed to ENM in France. Ten companies producing or incorporating carbon nanotubes (CNT), carbon black, titanium dioxide (TiO₂), or amorphous silica were contacted to be visited from 2008 to 2010. These four ENM were chosen considering available toxicological data, quantities manufactured in France and projected for production development, the

choice of France in the framework of the sponsorship program for the testing of ENM sponsored by the Organisation for Economic Co-operation and Development (OECD) and social perception factors. In site investigations and technical visits of eight companies which had agreed to participate allowed to collect critical information such as the number of workers likely to be exposed to nanomaterials, conditions of exposure, medical follow-up, and collaboration issues. The main conclusions outlined by this exploratory study were as followed: 1-relatively good acceptance of cooperation in public research laboratories and R&D facilities, but some disagreement issues on the ENM definition in some ENM producing facilities; 2-variable likelihood of exposure (low on R&D facilities but probable on facilities producing precipitated silica, carbon black, TiO_2); 3-generally small number of workers likely to be exposed on each site (from 15 to 120 on private facilities and 250 on the public R&D laboratories), 4-absence of a specific medical follow-up for nanoworkers other than annual clinical exams including in some cases lung function tests, blood analysis (blood cell counts, creatinine, transaminase, C Reactive Protein), or chest radiography [4]. According to these conclusions, an operational plan of the French integrated surveillance system should account for possible cooperation and comprehension issues by supplying all necessary tools and conditions before its actual implementation on the national level.

3. French ENM integrated surveillance system development

3.1 Definition and objectives of a surveillance system

Public health surveillance is the ongoing, systematic collection, analysis, and interpretation of health-related data with the *a priori* purpose of preventing or controlling disease or injury [5]. Four major goals are commonly assigned to epidemiological surveillance: 1-to detect timely unusual health situations, 2-to assess the magnitude of a health problem to make decisions affecting public health policy and allocation of resources, 3-to contribute to further research, and 4-to evaluate the effects of prevention and intervention efforts [6]. Occupational health surveillance is a specific field of public health surveillance related to either occupational exposure (hazard surveillance) or adverse health outcomes (injuries, disorders or diseases). Actually, it might be intended to embrace both workers' health surveillance and work environmental surveillance and thus to introduce the concept of indicators of change that are either exposure indicators or effect indicators [7]. Surveillance information may be collected by a variety of means, such as administrative registers and statistics, expert assessment systems, workers survey or questionnaires, exposure databases registers of accidents and diseases, and multi-source policy-directed systems. Depending on the source of classification and the level of analysis for classifying systems, four types of surveillance systems could be distinguished: registers, workplace observations and occupational health and safety (OHS) service data, working conditions survey, and integrated systems [8]. The integrated surveillance systems look at multi-source information focused on both exposure and health outcome information that is combined into one system. Such systems are considered to be well responsive to workplace or organizational-level needs and promising for improving workplace health and safety [8,9]. Exposure data is the focus in the integrated surveillance system and existence of an exposure registry enables the development of such systems [8].

3.2 Exposure registry

While the term register is applied to the file of data that can be related to a population base, i.e. the actual document or database, the registry is the system of ongoing registrations [10]. An exposure registry is a system for collecting and maintaining in a structured record, comparable information on persons with known or suspected occupational or environmental exposure to a hazardous substance [11]. Because exposure registries may have unintended consequences and high costs to workers, employers and society, they are not warranted in every situation. A registry would be warranted if it meets established criteria or rationale. Scientists and OHS experts recognized that in the case of nanotechnology workers with unknown exposure level and unknown health hazards there might be good reasons to consider registration of workers with ENM exposure [12,13].

3.3 French multi-company ENM exposure registry

Since carbon black and amorphous silica have been produced at nanometric size for decades in France, for starting this registry a priority was given to two more recent ENM: CNT and TiO₂. The French registry is intended as an individual registration of the ENM handling workers likely to be exposed either to CNT or TiO₂ while their employment in the nanotechnology-related industrial or R&D companies in France. The workers registration is planned to be exhaustive in terms of the exposed workforce on a company-level. The development of the ENM registry is based on a multi-level and multi-step approach, as presented in Figure 1.

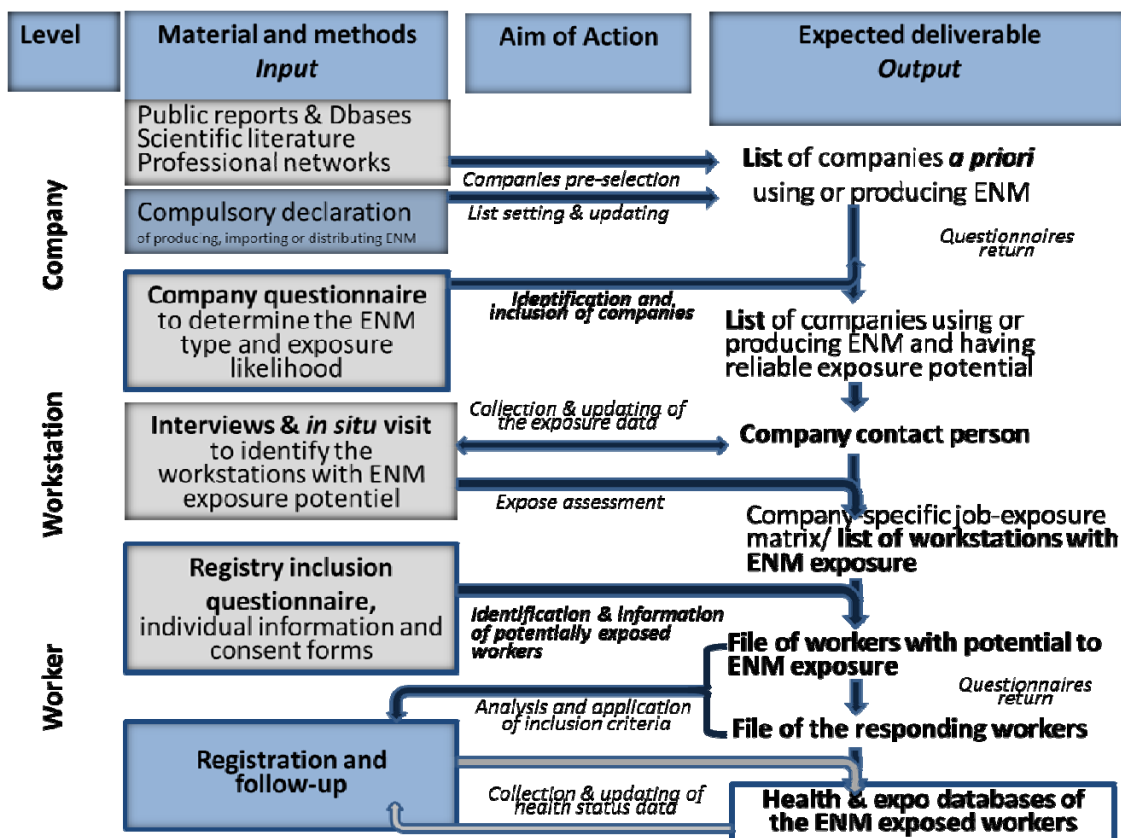


Figure 1. Multi-step development of the French ENM exposure registry.

One or more specific actions are associated to each level, resulting in a specific deliverable. At company level, the expected deliverable is a list of companies producing or using TiO₂ or CNT based on the detailed description of process/tasks and work conditions known to have a reliable potential of ENM emission and exposure. Various available sources including published data and reports as well as information exchange within the professional network might be useful for pre-selecting such companies. Furthermore, this preselected company list could be completed and systematically updated thanks to the compulsory registration of ENM. This registration is instituted by law entering in application on the first of January 2013 and requiring a compulsory declaration of types, quantities and use purposes of ENM produced, imported or distributed in France and downstream users. Founded on the European Community definition of the nanomaterials, this registration should resolve uncertainties in identification of the ENM of interest for the surveillance system and facilitate the relationship with companies. At the workstation level the expected deliverable is the list of workstation with exposure concern which will be abstracted for each company from the company-specific job-exposure matrix (JEM). Human resources department will then be asked to extract a file of workers who are affected to one or more workstations on the list. Finally, on individual level, workers likely to be exposed to ENM

will be contacted and provided with registry-related documents, namely a detailed information letter, individual participation consent form and the registry inclusion questionnaire.

3.3.1 Methods and tools for exposure assessment

Considering the difficulties to measure ENM exposure in workplace in a scientifically and methodologically relevant way along with the heterogeneity and uncertainties of available industrial hygiene measurement data, the French ENM registry is firstly designed to contain qualitative and semi-quantitative exposure data. The methods used to gather these data may include expert exposure assessment, technical observation visits and review of company data on exposure and exposure management. Additional tools specifically developed for the ENM surveillance are questionnaires and company-specific ENM JEMs:

3.3.1.1 Company enrolment questionnaire is designed with aim to address the likelihood of ENM exposure by analysis of the process used to produce or transform ENM at companies pre-selected as of first attention and to establish contacts with company OSH manager and occupational physician for further collaboration (see Fig.1). This questionnaire was reviewed by inner and outer InVS exposure experts and cross-validated with other questionnaires on ENM exposure [14,15] to harmonize it for potential international collaborative studies.

3.3.1.2 Company-specific ENM JEMs. In contrast with generalist JEMs, where exposure assessment must take into account a large number of occupational categories to link the information on exposure to specific workplace hazard for use in large population-based studies, specific JEMs designed for a company or industrial sector have a more specific field of application and may be developed using a more detailed classification of occupations and better exposure information [16]. Within the specific ENM JEMs, workstations in each company will be analysed and classified by industrial hygienists in terms of exposure likelihood and exposure frequency and intensity level, resulting in qualitative or semi-quantitative indicators of exposure. Focusing the exposure assessment on a company should allow more precision in the JEM data and reduce misclassification issues. The semi-quantitative ENM JEMs could be by further consolidated or replaced with quantitative data from available company industrial hygiene measurement data [17] and/or from supplementary studies focused on exposure biomarkers [18] or exposure measurement which may be conducted in frame of collaborative scientific projects.

3.3.1.3 Worker registry inclusion questionnaire is designed with aim to further individualize occupational exposure data assessed through the specific ENM JEMs. This should enable us to compute individual cumulative exposure scores and to model the exposure with accounting for personal protective equipment compliance and work regimen (partial time/shift work, etc.). Moreover, this questionnaire encompasses items on past occupational history and associated exposure but also items on health status and anamnesis, life-style and habits such as smoking, alcohol consumption and physical activity. By gathering this information it will be possible to address most potential confounding factors in future epidemiological studies of potential health effects of the ENM. The questionnaire is designed in accordance with questionnaires from three other national population-based health surveys for further comparisons of health statistics.

3.3.2 Connection with existing national databases and registers

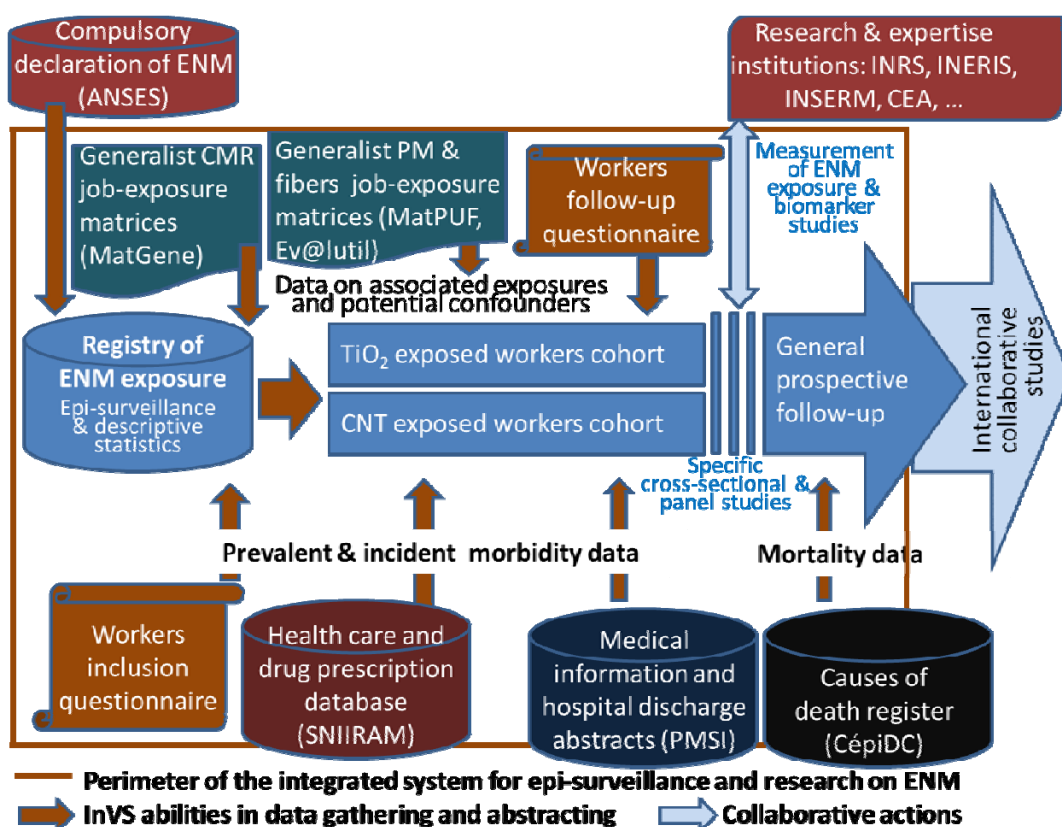
Intended as an individual registration of the ENM handling workers, the registry will enable InVS to use workers' identifying information for connecting the registry record with other public health databases and national registers. Actually, the national register of causes of death, registers of cancer, medical database of the standardized hospital discharge summaries from the national hospital information system (*Programme de médicalisation des systèmes d'information, PMSI*), medical insurance database of health care and drug consumption from the national health insurance information system (*Système national d'information inter-régimes de l'assurance maladie, SNIIRAM*) are some of relevant available sources of information on workers' health status and disease history. The abstracting of data from these sources is possible only within special inter-institutional agreements after approval of the Research ministry consultative commission on the treatment of

information in the field of health research (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, CCTIRS*) and autorisation of the French authority of privacy and individual rights protection (*Commission nationale de l'informatique et des libertés, CNIL*). The obtaining of CCTIRS and CNIL approvals is expected for early 2013.

On the other hand, workers' past and present occupational history encoded using the most recent editions of international classifications, such as the International standard industrial classification (ISIC 2008), and the international standard classification of occupations (ISCO 2008), should enable the InVS to extract relevant information on occupational exposure from other exposure databases available on national and international level. For instance, national population-based JEMs such as *MatGene* for exposure to occupational agents classified as carcinogenic, mutagenic or repro-toxic (CMR), *Ev@lutil* for asbestos and other fibers, *MatPUF* for particulate matter exposures might be useful for abstracting data on associated exposures. These databases are developed by InVS in collaboration with Universities or other research and expertise institutions. When necessary, the Eurostat correspondence tables would be used to recode occupations and activities into other ISIC or ISCO editions.

3.4 Layout of an integrated ENM surveillance system

The occupational surveillance of the ENM exposure and possible health effects may enter into operation with the ENM registry and general prospective follow-up of the ENM exposed workers



. Figure 2. Pattern of the French integrated ENM surveillance system.

The connexion with other health and exposure databases as well as workers follow-up questionnaires (intended on every two-year basis) should make it possible to gather and abstract all necessary information for meaningful statistical analyses within epidemiological cohorts and collaborative panel and cross-sectional studies on specific scientific questions (Figure 2). These collaborations are suitable and might be strengthened by specific collaboration agreements. A collaboration agreement has been signed with the French agency for food, environmental and occupational health safety (*Agence*

nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES) and two other agreements are about signature at the National Institute of Safety Research (*Institut national de recherche et de sécurité, INRS*) and the Occupational medical inspection department at the ministry of Labor.

The registration of first potentially exposed workers should start in 2013. The registration is at the moment planned for three years but can be extended and include other ENM. The ENM exposure registry should be considered as an instrument of integrated system for epidemiological surveillance and national and international OSH research in the field of ENM. This will be able to provide early data concerning human health potential risks associated with ENM in France.

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