Development of an Integrative Program of Nanosafety: Promote the Coordination Between Industries and Risk Assessor

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Abstract. Nanomaterials are widely present in many industrial sectors (e.g., chemical, biomedical, environment), and their application is expected to significantly expand in the coming years. However, nanomaterial use raises many questions about the potential risks to human health and the environment and, more specifically, to occupational health. The available literature supports the ability of the lung, gastrointestinal tract, and skin to act as significant barriers against systemic exposure to many nanomaterials. However, because a potential risk issue exists about the toxicity of nanomaterials to the biological material, tools need to be developed for improving the risk management of the regulators. The goal is to develop a tool that examines the current knowledge base regarding the health risks posed by engineered nanoparticles to improve nanotechnology safety prior to the marketing phase. The approach proposed during this work was to establish a safety assessment constructed on a decision-control pathway regarding nanomaterial production and consumer’s product to integrate different aspects. These aspects include: (1) primarily research and identification of the nanomaterial base of physicochemical properties, toxicity, and application; (2) the occupational exposure risk during the manufacturing process; (3) and the engineered nanomaterial upon the consumer product. This approach provides important parameters to reduce the uncertainty related to the production of nanomaterials prior their commercialization, reduce the reluctance from the industry, and provide a certification tool of sanitary control for the regulators. This work provides a better understanding of a critical issue of nanomaterials and consumer safety.

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1. Introduction

Nanotechnology is growing in an exponential cadence around the world [1], and there is much anticipation in industrial and economical fields of using this technology. Today, the use of nanotechnology in aerospace, construction, chemistry, foods, cosmetics, and textiles and by vehicle manufacturers is undeniable. Based on the data acquired from Woodrow Wilson Center since 2005, we estimate that 1,750 products were commercially available in January 2013, representing an annual revenue of $750 billion US dollars, which is three times more than the $224 billion in revenue from the same source in 2009 [2]. This increase is expected to reach $1 trillion in 2015, representing 2 million jobs [3].

Although nanotechnology has generated a lot of revenue, several hundreds of workers are potentially exposed during the development of nanoparticles in the laboratory and during production. Unfortunately, research from the health and safety organization (HSO) working to improve the evaluation of risks to workers is lagging far behind. Multiple in vivo studies in animal and syntheses of the literature helped to highlight that manipulation or production of nanoparticles in both research and development. Several studies demonstrated that nanoparticles can affect different organs (i.e., the heart, lungs, kidneys, and the reproductive system) [4; 5], and nanoparticles can cause toxic effects, which have been addressed as granulomas, fibroses, and tumor responses in the lungs, and genotoxic and cytotoxic effects [6]. These issues are a major concern in the international scientific community, especially in terms of Nanosafety. Moreover, it appears that, in general, the “nano” size of a substance is oftentimes more toxic than the larger size of the same substance.

Despite all of these preliminary efforts to understand the toxicity of nanoparticles and the concerns raised by the HSO about these issues, there is not enough information available in literature to determine specific exposure limits. There is also not enough information to establish a unique methodology for evaluating occupational exposures to nanomaterials; therefore, a precautionary approach is suggested by the experts.

For this work, we developed a methodology to anticipate the potential risk of nanomaterials, and then used this information to develop a better safety assessment. The objective of this study was to develop an assessment table matrix to allow safe handling of nanomaterials prior to commercialisation. More specifically, the study aims included: (1) conducting a literature review of the health issues related to nanotechnology, (2) developing a health assessment table matrix to identify the determinants of occupational exposure to nanomaterials, and (3) validating the assessment table matrix by experts in safety assessment, in collaboration with companies using nanotechnology.

2. Methodology

The first step in our approach was to conduct an analysis of the scientific literature by using different databases such as PubMed, MEDLINE, ScienceDirect, and TOXNET, while taking into account the importance of the physicochemical and toxicity identifications of nanomaterials.

In addition, we reviewed reports and reference documents from recognized organizations (e.g., Institut de recherche Robert-Sauvé en santé et en sécurité du travail [IR SST, The Research Institute Robert-Sauvé Occupational Health and Safety]; Agence nationale de sécurité sanitaire de l’alimentation, de l’environnement et du travail [Anses, the French Agency for Food, Environmental, and Occupational Health Safety]; Institut National de la Recherche et de la Sécurité [INRS, the French National Research and Safety Institute] Institut national de l’environnement industriel et des risques [INERIS, the French National Institute for Industrial Environment and Risks]). We also reviewed information from the search engine, Google, and from SAFENANO’s Web site (safenano.org), the Organisation for Economic Co-operation and Development’s site (www.oecd.org), The Project on Emerging Nanotechnologies’ site (www.nanotechproject.org), and NanoImpactNet’s site (www.nanoImpactnet.eu).
2.1. Data Synthesis

Nanoparticles have specific properties that make it difficult to characterize their physicochemical properties. However, the literature suggests that many parameters (i.e., size, chemical composition, surface reactivity, solubility, and the formation of aggregates/agglomerates) influence exposures, which are essential for better characterizations of the nanomaterials [7-10]. These parameters, which do not comprise the final list of factors, influence the risk of exposure and the potential health effects on exposure.

Exposure pathways are the concerns that profoundly influence the exposure assessment of nanomaterials. Because of their “nano” size, the main pathway for nanoparticles is via the airway route. So far, the available data show that nanoparticles can be distributed to different regions of the respiratory tree according to their size [4]. After inhalation, nanomaterials can also be found in the gastrointestinal tract via swallowing. The absorption of nanomaterials through the skin is still under investigation; however, it has been shown that professional tasks such as handling and maintenance of nanomaterials can result in dermal exposure to workers [11]. At the same time, the real nature of nanomaterials (i.e., powder and liquid suspension), the synthesis methods used, the degree of confinement, the quantity, the protection in the workplace, and the ability of the products to reach the air or the work surface are all factors that influence the exposure assessment [12; 13].

Appropriate toxicological tests to determine the effects of nanomaterials on health require specific tools that are yet to be harmonized and developed. This data collection will depend heavily upon the cooperation of industry and research [11; 14; 15].

2.2. Methodologies for assessment of nanomaterials

Several methods on the exposure assessment of nanomaterials are proposed in the literature (e.g., Lux Research Inc., DuPont and Environment Defense; Federal Office of Public Health Switzerland). These methods are mostly based on the standard model of risk assessment of chemicals using a strategy of quantitative or qualitative treatment of the data. An approach that is more qualitative and corresponds to the Control Banding model is very popular for this assessment [16]. The major methods used for assessment are discussed in the following paragraphs:

The Lux Research method is a quick and easy tool for qualitatively assessing the risk of specific nano-finished products to humans and the environment throughout a life-cycle approach. However, several important criteria are not used in the assessment criteria for this tool (e.g., criteria quotations for risk assessment of toxicity, non-differentiation between risks to human and environmental risks, how to handle products containing several types of nanomaterials) [17].

The DuPont and Environment Defense method is used to assess the nano-specific risks to humans and the environment from products containing manufactured nanomaterials. These risks are evaluated over the nanomaterials’ entire life cycle. This method contains elements to aid management so they can base their decisions on the risk assessment (e.g., evaluate the effectiveness of risk management, methodological framework of actions to be taken based on an analysis of the situation). In comparison to the Lux Research method, the number of criteria is insufficient in DuPont and Environment Defense method, and the quotes tool does not take into account the toxicity and ecotoxicity at each stage of the life cycle [17].

The Federal Office of Public Health Switzerland has proposed a method of a precautionary matrix for synthetic nanomaterials to estimate and distinguish nano-specific risks of a product containing nanomaterials for workers, consumers, and the environment [14]. The method is to combine the scores associated with each of the criteria considered with a formula to derive a risk score. Different risks (i.e., employee, worker, and environment) are then characterized in terms of scores. However, this method is limited because it estimates the potential effects of nanomaterials. The score, given the level of these potential effects, is based only on two criteria for the entire life cycle: redox activity level and/or catalytic nanomaterial and stability in the relevant media (physiological and environmental conditions). This method considers that the toxicity remains constant during entire life
cycle of the product and that the mechanism of toxicity is restricted only based on the formation of reactive species of oxygen.

The Control Banding model proposed by Paik et al. (2008) is an approach based on using a limited number of factors to assess the level of risk to reduce the complexity and increase the applicability [18]. This model uses three levels, or bands, of engineering controls based on the fundamentals of hygiene, plus a fourth level of control for most at-risk situations. In this approach, regular updating of new information is needed to ensure continuous and effective control of exposure [13].

2.3. Development of the assessment table matrix

As previously stated, the current data on the toxicity of nanomaterials remain fragmented and do not provide quantitative risk assessment of exposures. Therefore, using a methodology for determining safety assessment (qualitative) exposures to nanomaterials is an alternative to help reduce the risk of exposure to nanomaterials. Among the recent methods of qualitative assessment proposed in the literature, two have captured our attention: the model control banding specific case of nanomaterials proposed by the National Agency Food, Environment and Occupational Health Safety [19] and the methodological guide for characterizing emissions and occupational exposures to nanomaterials developed jointly by the Commissariat à l’Energie atomique et aux énergies alternatives (CEA, Atomic Energy and Alternative Energies Commission), INERIS and INRS [19; 20]. We designed our evaluation matrix based on these two methods.

The motivation of this new approach is based on the literature, which report the existence of a particular biological reactivity of nanoparticles in relation to their sizes, compared to the observed particles of the same composition, but in larger sizes. This reactivity of nanoparticles on cell and tissue biomaterials can represent a hazard to humans if they are exposed. However, continued development of this new technology is sufficiently important to our economy, but with respect to biological integrity.

From this complete review, we are proposing a new table matrix based on the published approaches, as well as the risk assessment methods used in toxicology since they were developed by the National Research Council in 1983 and used a default approach in environmental risk assessment [16]. This new approach contains the different phases such preliminary assessment of exposure, exposure dose/response characterization, and risk characterization (See Tables 1A and 1B in the appendix at the end of this paper). Each of these phases is associated with techniques and methodologies proposed to characterize the nanomaterial. Each phase drives the assessors to different plateau; thus, each plateau of the assessment can be stopped during the evaluation if the risk is considered to be negligible.

3. Results

The strategy of this table matrix is based on recommendations concerning the characterization of potential exposure to nanomaterials that are currently documented in the literature. This strategy relies on a step-by-step approach and takes into account proposals for the techniques and methods used to better characterize nanomaterials.

The Table Matrix developed in this works can be used by all employees responsible for health workers and consumer safety, stakeholders, and users of nanotechnology. The purposed of this table matrix is to contribute to a better understanding of nanomaterials to anticipate their potential effects. The analytical framework of this table matrix consists of the following four main steps [21]:

1. Primary evaluation of the exposure
2. Characterization of exposure and dose/ response
3. Risk Characterization
4. Restitution of the results.
This table matrix operates on a decision tree that describes each step for evaluation (Figure 1).

Figure 1. The decision tree for a safety assessment of nanomaterials.

4. Preliminary Assessment of Exposure

The preliminary assessment is one of the predominant steps in the evaluation of nanomaterials. In this step, technical equipment are used to identify nanomaterials (e.g. Condensation particles counter, Optical particles counter, SMPS, ELPI…).

4.1. Characteristics of nanomaterials

This step is based on the criteria used to identify nanomaterials. Materials that do not meet the definition of nanomaterial will not be considered in the evaluation table matrix.

4.2. Scientific and technical information

These data refer to all available technical and scientific documentation about the nanomaterials, such as the following:

- Name of the material or nanomaterials, the unique registration number [9], and the main commercial uses
- Structural formula and the molecular and basic morphology of the chemical
- Composition of the nanomaterials used, including the degrees of purity and impurities and additives, and descriptions of surface chemistry (i.e., coating or modification)
- Catalytic activity.

4.3. Characteristics of nanomaterials

In this step, we document public or confidential information available about the potential nanomaterial study. This part includes a list of what we know about the nanoparticles, including the following:

- Raw materials, intermediate products, and final products
- Characteristics of the materials (e.g., fine powders, granular, colloids)
- Chemical composition of metals, oxides, or polymers
- Shape (e.g., spherical, cuboidal, aggregates/agglomerates)
• Size (e.g., number)
• Physicochemical properties (e.g., specific air, surface reactivity, solubility)
• Type of nanomaterials (e.g., carbon nanotubes, quantum dot, dendrimers)
• Dispersion medium (e.g., aerosols, gels, colloids).

At this step, the facts available should give us enough information to decide whether the particle is nanomaterial. If we have determined that it is not a nanomaterial, then we stop the process here.

4.4. Potential exposure to nanomaterials

During this step, we will investigate the potential exposure to nanomaterials to precisely target our analysis of the various manufacturing processes and working conditions. This step include three options that complement one another: the site visit, an analysis of the manufacturing processes, and an analysis of the finish product. For the last option, there is no question of analyzing each finished product; instead, there is a question about whether there is instability in nano-finished products that can induce toxicity.

4.4.1. Site visit

A visit to the production site allows investigators to take note of all working processes, including the delivery of raw materials, packaging and storage of final products, and waste disposal. The analysis must also take into account the following:

• Potential emission sources
• Routes of exposure (e.g., inhalation, dermal, ingestion)
• Magnitude and duration of exposure
• Ability of atmospheric contamination
• Configuration of the workplace
• General and local ventilation (system efficiency)
• Personal protective equipment (individual or collective)
• Preventive and safety measures.

During nanomaterials manufacturing, many techniques are designed to control the characteristic parameters such as size, shape, composition, and the degree of agglomeration of the nanoparticles to disperse systems and grains for bulk materials. These processes can affect the potential risk of exposure and the exposure routes. Therefore, an analysis of the manufacturing processes is necessary for the preliminary assessment. The instability of nanomaterials in the finished product is possible, and can subsequently cause a health risk to the consumer, especially to children. A thorough evaluation of the product before it is placed on the market would reduce this risk.

4.5. Characteristics of nanomaterials

At this step, we know that nanomaterials are present in the workplace and that there is a potential source of exposure. This next step of the process will provide information about quantitative exposure and the dose/response relevant interaction. The quantitative exposure is subdivided to contain the measurement and the physicochemical tests steps.

4.5.1. Characterization of exposure

The measurement of the sample uses different techniques, which will allow us to identify and characterize the target nano-aerosol at potential emission sources. Nano-aerosol can be measured at the source, in the breathing zone, in an area near or far from a work station. After identifying the likely nanoparticles at different emission sources, many types of additional measures may be considered to determine the number concentration (x/cm^3) or surface (μm^2/m^3), particle size distribution, chemical composition, specific surface area and surface reactivity, the shape of these particles, their crystalline
structure, and solubility and their ability to form aggregates or agglomerates. The choice of instrument will be based on the type of study to be performed.

The physicochemical analysis is one of the critical steps in the risk assessment of aerosol (or nano-aerosol) because it is used to identify different chemical components such as ions, metals, and organic compounds. This analysis also provides information on the shape and size, chemical nature, the aggregates or agglomerates, and the type of aerosol. Moreover, the capacity of transition metals, such as copper, chromium, and vanadium, to catalyze the production of reactive species should not be underestimated [22]. All of these features can better assess the risk of potential exposure.

The exposure quantification provides no information about the toxicity of nanoparticles. This is essential to mention that toxicity of nanoparticles is not yet proven before this step. Thus, care must be taken to protect the health and safety of workers and consumers. In this regard, a better understanding of the physicochemical characteristics of nanomaterials and the biomonitoring or biological indicators of the exposure will increase the safety of workers. The next step will provide information about and quantification of the toxicity resulting from the exposure. Specifically, this step will help address the question: is there a reason to be aware of this exposure or not?

4.5.2. Toxicology assessment (dose/response quantification)

As with any chemical, the potential toxicity associated with the nanoparticles depends, in particular, on their physicochemical properties (i.e., size, surface reactivity, solubility in biological fluids). At this step, we need a test that provides rapid and low-cost information about the toxicity. So the in vitro tests represent a priori the better approaches. Tests to determine viability or proliferation, membrane integrity, oxidative stress and inflammation, or metabolic activities need to be prioritized as a first step to characterize toxicity.

However, knowledge of different exposure routes appears to be an essential prerequisite to the toxicological evaluation. Plus, nanoparticles are capable of producing reactive oxygen species [15], resulting in phenomena of oxidative stress and inflammatory responses, which can potentially induce DNA damage and lead to genotoxicity [23]. During the toxicological assessment of nanoparticles, one should pay particular attention to the target organs (i.e., liver, kidneys, lungs, Central Nervous System, and spleen). Toxicological tests may also be referred to the potential immunologic and reproductive toxicant nanoparticles.

4.6. Characterization of the risk of exposure

An analysis of the results allows for data to be produced on the basis of the previous tests. An analysis will provide the relevant information based on the samples collected, the techniques used to make the samples, the instruments and analytical methods employed, and the comparison of the results with the bibliographic data.

5. Discussion

This new approach presented in this paper represents the first intention to develop an integrated strategy to assess nanomaterials during the synthesis, far before the commercial integration in the finished nano-products. This approach is based on the default environmental risk assessment approach developed and published in the red book in 1983[16], but adapted for the nanotechnology reality and limitation. Nevertheless, it is more than that reason why our group wanted to make a significant effort in finding a balance between protection of biological integrity and economic capacity for manufacturers to incorporate these analyses into the Risk Assessment for Health. The objective of this work was to identify and maximize the analysis with the concept of integrity of a Risk Assessment for Health expert, but also based on an economic realistic perspective. This approach should allow manufacturers to identify the limitation of utilization with regard to their nano-products.
6. Conclusion

This work combines different and complementary steps, including, but not limited to, considering the method and preparing for analysis, noting the observations, conducting the analyses, quantifying the exposure and dose response, following a general process for evaluation, and comparing the observation and measurements to scientific literature. This new table matrix was also validated with European and Canadian company generated nanomaterial. The Table matrix we develop here provides a better understanding about the critical issue of nanomaterials with regard to worker and consumer safety.

7. Reference List

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8. Appendix

Table 1a. The table matrix for the preliminary assessment

| Steps                        | Objectives                                                                 | Methodology                                                                                     | Techniques and Materials                  |
|------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------|
| Preliminary assessment of nanomaterials | Identification of nanomaterials | General Technique and Scientific Information  
(Material Safety Data Sheets and technical information fact sheets provided by the producer, articles or summary documents from the scientific literature)  
- Characteristics of nanomaterials (e.g., powders, fiber or colloid, shape, and length; aggregates or agglomerates)  
- Mass volume, specific area; specific surface volume  
- Applications of nanomaterials (foods, medical biology, environment)  
- Toxicological properties (e.g., toxicity data sheet)  
Analysis of the Manufacturing Process  
- Synthesis process, confinement degree in every step of the synthesis  
- Raw materials used, intermediate products and final products  
- Quantities of nanomaterials handled; application of the nanomaterials  
- Ability of the nanomaterials to be suspended in the air  
Site visit:  
- Potential emission sources of aerosol and dust levels; background, number, and importance  
- Ability of nanomaterials to contaminate working atmospheres  
- Information about any exposure or co-exposure likely increasing the risk  
- Technical activities at work (close to the target source; time, habit)  
- Routes of exposure (e.g., inhalation, dermal, ingestion)  
- Importance and duration of the exposure  
- Configuring the workplace  
- General ventilation and local (system efficiency)  
- Actual performance of prevention measures (e.g., ventilation, filtration, personal protective equipment) for the products handled  
- Fire and explosion risks  
- Measurement, prevention, and safety procedures | Scientific literature |
Table 1b. The table matrix for the exposure, dose response assessment and for the risk characterization risk.

| Steps                        | Objectives                                                                 | Methodology                                                                 | Techniques and Materials                                                                 |
|------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| **Exposure and dose/response characterization** | Characterization of Materials | • Measurement of target aerosol and the background aerosol | Condensation particle counter (CPC) | Optical particle counter (OPC) | Scanning mobility particle sizer (SMPS) and fast mobility particle sizer (FMPS) | Electrical low-pressure impactor (ELPI) | Electronic microscopy (EM) | Cascade impactor (Siotas, micro-orifice uniform deposit impactor [MOUDI]) | Chromatography analysis (inductively coupled plasma-mass spectrometry [ICP-MS] or gas chromatography-mass spectrometry [GC-MS]) |
|                              |                              | • Physical and chemical properties of nanomaterials (e.g., size, morphology, surface area, surface reactivity) |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Particle number concentration (particles/cm³), surface geometry (µg/m³), particle mass concentration (µg/cm³) |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Morphological properties (e.g., size distribution, shape) |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Particle size distribution (e.g., number, mass) |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Chemical composition (e.g., inorganic, ionic, organic compounds) |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Solubility of liquid materials |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              | Quantification of the exposure | **Toxicological tests (In vitro or in vivo)** |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Acute toxicity, cytotoxicity |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Altered membrane |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Blood parameters |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Oxidative stress |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Inflammatory response |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Genetic modification |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
| **Risk characterization** | **Analysis and interpretation of the results** | **Method and preparation of analysis** |                                                                           |                                                                             | Technical and scientific expertise, scientific literature                                                                                   |
|                              |                              | • Terms of observations and analyses |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Exposure response |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • General process of evaluation (e.g., exposure, aerosol) |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              |                              | • Comparison of the results with scientific literature |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |
|                              | Retrieval of results         |                                                                           |                                                                           |                                                                             |                                                                                     |                                                                             |                                                                              |                                                                                             |