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Authors: Guseva Canu I, Schulte PA, Riediker M, Fatkhutdinova L, Bergamaschi E

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METHODOLOGICAL, POLITICAL AND LEGAL ISSUES IN THE ASSESSMENT OF THE EFFECTS OF NANOTECHNOLOGY ON HUMAN HEALTH

Irina Guseva Canu[1]*, Paul Schulte[2], Michael Riediker[1,3,4], Liliya Fatkhutdinova[5], Enrico Bergamaschi[6]

[1] Institute for Work and Health (IST), University of Lausanne, Suisse

[2] National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio, USA

[3] IOM (Institute of Occupational Medicine) Singapore, Singapore

[4] School of Material Science & Engineering, Nanyang Technological University, Singapore, Singapore

[5] Kazan State Medical University, Kazan, Russia

[6] Department of Public Health Sciences and Pediatrics, University of Turin, Italy

* Corresponding author:

Prof. Irina Guseva Canu,

Institute universitaire romand de la Santé au Travail (IST)

Route de la Corniche, 2

CH-1066 Epalinges-Lausanne, Suisse

Tel: +41 21 314 62 27

Email: irina.guseva-canu@chuv.ch; irinacanu@hotmail.com

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ABSTRACT

Engineered nanomaterials (ENMs) raise questions among the scientific community and public health authorities about their potential risks to human health. Studying a prospective cohort of workers exposed to ENMs would be considered the gold standard for identifying potential health effects of nanotechnology and confirming the “no effect” levels derived from cellular and animal models. However, because only small, cross-sectional studies have been conducted in the past 5 years, questions remain about the health risks of ENMs. This essay addresses the scientific, methodological, political, and regulatory issues that make epidemiologic research in nanotechnology-exposed communities particularly complex. Scientific challenges include the array of physicochemical parameters and ENM production conditions, the lack of universally accepted definitions of ENMs and nanotechnology workers, and the lack of information about modes of action, target organs, and likely dose-response functions of ENMs. Standardization of data collection and harmonization of research protocols are needed to eliminate misclassification of exposures and health effects. Forming ENM worker cohorts from a combination of smaller cohorts and overcoming selection bias are also challenges. National or international registries for monitoring the exposures and health of ENM workers would be helpful for epidemiological studies, but the creation of such a registry and ENM worker cohorts will require political support and dedicated funding at the national and international levels. Public authorities and health agencies should consider carrying out an ENM awareness campaign to educate and engage all stakeholders and concerned communities to engage in discussion of such a project.

METHODOLOGICAL, POLITICAL AND LEGAL ISSUES IN THE ASSESSMENT OF THE EFFECTS OF NANOTECHNOLOGY ON HUMAN HEALTH

INTRODUCTION

Engineered nanomaterials (ENMs) raise questions among the scientific community and public health authorities about their potential risks to human health. Commercial use of ENMs began in the early 2000s, and within the subsequent decade they became a topic of concern for health researchers. By 2010, at a conference on nanomaterials and worker health,[1] participants recognized the need for epidemiological studies or, possibly, exposure registries of persons handling ENMs, to support the responsible development of nanotechnologies. Among a few dozen opportunities identified then for epidemiologic studies of potentially exposed workers,[2] only one led to published results.[3] The other studies either were never launched or were impeded by difficulties.

Studying a prospective cohort of workers exposed to ENMs would be ideal for identifying potential medium- and long-term health effects of nanotechnology[1] and confirming the "no effect" levels derived from cellular, animal, and read-across testing models. However, there are a large number of commercial ENMs and only small, cross-sectional studies of a few of them have been conducted in the past 5 years,[4 5] leaving many questions about ENM health risks. This essay discusses possible explanations for this deficiency by addressing issues that make epidemiologic research in nanotechnology-exposed communities particularly complex.

SCIENTIFIC CHALLENGES RELATED TO THE EMERGENT NATURE OF ENMs AS A POTENTIAL OCCUPATIONAL HAZARD

In principle, epidemiologic investigation of ENM health effects should not be inherently different from that of other occupational hazards, but many factors related to ENMs make such studies rather uncommon and difficult. For instance, ENMs are both chemical molecules and physical objects with a large hyper-reactive

surface. Most ENMs are relatively new. However, ultrafine particles such as carbon black and amorphous silica, which have been used for decades may also coincide with the contemporary definition of ENMs. The many physicochemical parameters and production conditions resulting in their high heterogeneity sustain the challenges and inconsistencies in identifying, characterizing, and classifying them. Additional challenges are posed by the newness of exposure scenarios; questions about biologically relevant metrics, biological endpoints, and potential health outcomes; the need for practical instrumentation for exposure assessment; and the difficulties in identifying exposed populations in workplaces.[6]

The lack of universally accepted definitions of "engineered nanomaterial" and "nanotechnology worker" is a critical challenge for collecting necessary data, especially if one wishes to include multiple countries and regions in a study.[7] The working term *Nano-Objects and their Aggregates and Agglomerates* (NOAA) (see Box 1) has only recently facilitated the recognition of different ENMs as such, whereas the nanotechnology workforce is not an explicit employment category and its parameters are difficult to ascertain. Because nanotechnology is not an industry in itself but crosses many industry and occupation sectors, the nanotechnology workforce varies across countries and regions according to ENM resources, research, and regulations.[6]

One major factor that adds to the complexity of conducting epidemiologic research is the multitude of different ENMs, with varying types of toxicity (e.g., direct and indirect genotoxicity, generation of oxidative stress, inflammation, immunotoxicity, etc.), dose-response functions, and target organs. Some ENMs have been shown to have deleterious health effects in laboratory animals but others have not[1]. Also, some of the effects have occurred only with extraordinarily large doses that are not representative of worker exposures.[8 9] There is still debate as to whether modern scientific knowledge is sufficient to conclude that the risks of nano-sized substances require separate toxicological assessment. The lack of information about modes of action, target organs, and likely dose-response functions of ENMs adds a serious challenge to epidemiologic studies involving nanomaterial workers.

Timing is another critical issue. Products containing “novel ENMs” became commercially available in the late 1990s. Accordingly, the first potentially exposed workers were and are scientists in academic and commercial laboratories, followed by those involved in pilot and start-up operations.[10] For large companies, this represents less than 5% of the workforce,[11] that is, from a dozen to a few hundred workers.[12 13] Although the general belief is that workers’ involvement in the handling, machining, and processing of ENM-containing products is rapidly expanding, there are few confirmative data. There are limited data on number of workers involved with handling ENM-containing products for disposal or recycling.

From a practical perspective, epidemiologists face both methodological and organizational challenges owing to the lack of standardization of data collection and harmonization of research protocols. These challenges hamper the registration of ENM-exposed workers and further pooling of individual company cohorts.[14 15]

METHODOLOGICAL CHALLENGES

One of the primary challenges of assessing individual ENM exposure involves registration of ENM-exposed workers on a universal or selective basis. Quantitative methods for personal ENM exposure monitoring are only starting to become commonplace, and these methods still place many constraints on conducting field research. Constraints include high costs, a lack of validated standardized protocols, and limits on detection and quantification.[16-18] Indeed, these issues lead to concerns about exposure misclassification as well as the health effects of exposure. Because medium- and long-term effects by definition occur only after a relatively long latency period following exposure to ENMs, possibly they are only now becoming clinically detectable. The effects known from epidemiological studies of ultrafine particles and short-term effects, currently evaluated by means of biomarkers of inflammation or oxidative stress, are very common and not specific to ENM.[4 19] Thus, cross-sectional studies using effect biomarkers are quite limited for drawing conclusions about the relationship between exposure to ENMs

and observed effects, especially when the biomarkers used reflect early biochemical or functional changes lacking clinical significance.[4 5 20] Furthermore, co-exposures frequent in the workplace and individual lifestyle factors require rigorous assessment to control for potential confounding biases[15]. Clearly, only a longitudinal follow-up of a large number of workers exposed to (the same) ENMs could ultimately resolve the question of health risks.[2 14] However, the formation of such cohorts from a combination of smaller cohorts raises the concern of uncontrollable heterogeneity of ENMs. The heterogeneity of ENMs and the ability to identify cohorts of adequate size with the same or similar exposures are among the greatest methodological and practical challenges. It is likely that this issue could be addressed only by assembling cohorts from many companies. Alternatively, instead of assembling cohorts on the basis of similar exposures, it might be useful to base the exposure criteria on the similarity of mechanisms of biologic effects (such as oxidative damage and genotoxicity) of different ENMs.[4] However, assembling a large enough group of subjects similarly exposed over time still remains a challenge, even though more is known about mechanisms of the different ENMs.

The creation of ENM worker cohorts also raises the concern of serious selection bias. Selection can take place in several ways. For instance, companies with exemplary safety and prevention programs may readily agree to participate in epidemiological studies. These companies most likely would be large, economically strong, and have resources to dedicate to occupational health surveillance.[6 11] Participation in a health surveillance program might, in turn, encourage the company's commitment to protecting the health of its workers. Nevertheless, most large national and international companies declined to participate in such surveillance offered by the French EpiNano program.[21] Some of these are complex organizations with a regulatory affairs department that scrutinizes every study proposal and thus are not inclined to participate in studies. Such companies can also consult at the level of their activity sector and refuse participation through their professional or trade associations.[11 22] In contrast, small-scale ENM-production companies and start-ups were willing to participate in the EpiNano program, despite limited resources and personnel.[21 23 24] It was observed that participation of small companies strongly depends on certain

factors related to the employer: its sensitivity toward potential, still unknown risks of ENM; its degree of responsibility for its employees; its concern about losing proprietary information; its availability to participate; and the social climate in the company.[21]

Selection could manifest differently in private and public research and development laboratories; public research laboratories participated more readily in the EpiNano program.[21] At the individual worker level, selection operates very differently and may either reinforce or offset the selection effect observed at the company level. For example, because of a perception that the work environment is safe and free of risk, nanotechnology workers who have available engineering controls and personal protective equipment will likely have little interest in participating in medical or epidemiological surveillance programs.[25] In contrast, in companies with insufficient risk management and communication, such studies might be supported by worker representatives resulting in relatively high individual participation. According to the EpiNano program experience, selection operates much stronger at the company level (only 16% participation rate) than at the individual level (99% acceptance of passive follow-up and 42% participation in both passive and active follow-up).[21]

Finally, the healthy worker survivor effect could be an additional methodological issue. In epidemiological studies of ENM-exposed communities, the dose–response estimates could be biased if past exposure predicts future values of a time-dependent variable, which is a risk factor for survival and also predicts subsequent exposure.[26] Although there is a relatively simple solution for controlling the last type of bias (for example, by using causal models such as G-estimation[27]), the treatment of selection and heterogeneous, small cohorts requires a more complex effort at the political and regulatory level.

POLITICAL AND REGULATORY CHALLENGES

All major projects leading to the creation of a national exposure registry and national or international cohorts will require political support to mobilize laws and create dedicated funding.[28 29] Exposure registries of ENM workers would help in the planning and development of epidemiological studies.

However, similar to cohorts, such registries would involve the need to recruit numerous companies, since the ENM workforce appears to be widely distributed and of low concentration in any one facility. Because such registries are costly, are difficult to maintain, and involve numerous ethical, legal, and social issues, it is not clear whether a public health or occupational health case could be made for universal or selective registries. This uncertainty is due to the lack of a coherent message on the toxicity of ENMs (partly because of the highly diverse universe of potential ENMs). In addition, companies' concern for not disclosing proprietary information is a major hurdle. Several regulatory attempts to create an ENM exposure registry have failed at the European level, and access to workplaces is an important barrier in launching human studies of the risks of ENMs.[6]

To counter companies' possible resistance to participating in epidemiological programs and to sharing the information necessary for characterizing exposure to ENMs and identifying exposed workers, public authorities and health agencies need to engage companies in active discussions as well as carry out an ENM awareness campaign. This would communicate state-of-the-art information on ENMs in order to engage stakeholders and concerned communities in the project.[30] Because of the diverse factors involved (environment, economy, health, industry), which are not necessarily compatible, it is difficult to build effective, coherent communication among all stakeholders. Conflicting interests in the ENM field reflect the many expectations and fears about the emerging nature of ENMs.[11] On the one hand there is concern that even discussion of potential health effects of ENMs will hinder development of the technology. On the other hand economic forecasts for development of ENM-related industries enhance the general and scientific mistrust of ENMs because their growth appears to be a forgone conclusion. In addition, given the many data gaps regarding workplace exposures and likely health effects, one concern is that the expanding development, production, and use of ENM could be "a large and largely uncontrolled asbestos-experiment with very long term consequences engaging increasing numbers of workers across the globe."[25] Conflict of interests are both the cause and the consequence of the debate surrounding the precautionary principle application with regard to ENMs. The non-uniformity of precautionary principle definition, particularly

when it applies to ENM production, use and release[31], nourishes the division between “those who want to innovate quickly at all costs and those who want to think about the consequences first”[32]. The decision making on this subject is politically and ideologically influenced and remains challenging[31]. Although the precautionary principle is a general principle of the European Commission (EC) law, relied on the provision for the protection of both consumers (Art 153 EC Treaty) and the environment (Art. 174 EC Treaty), applying that, in balancing the conflicting interests, consumer interests should overweigh economic interests when negative effects on human health are at stake [33], the requirement of the appropriate labeling, informing the consumer about the use of ENMs in certain products (e.g., food and cosmetic products) is very challenging to enforce [33 34]. Putting aside the most severe option of precautionary principle, requiring bans on ENMs until they are shown to be safe (“No data, no market”), even its softer options including: 1-demanding labeling, 2-insisting the government agencies be notified when products contain particular ENM, and 3-taking steps to minimize human or environmental exposure until they have received further testing are challenging to achieve[34 35].

For many companies, the information required for registration of ENMs and follow-up of ENM-exposed workers is considered confidential technical or commercial information, and sharing it would be detrimental to competition.[6] Companies’ reluctance about epidemiology and health surveillance could also be explained by the desire to avoid unsuitable responses and expenses that might be triggered by false alarms from inconsistent or clinically doubtful results.[36] ENM exposure registration and health monitoring within a company may lead to unfounded employee expectations and to misuse of collected data if it were diverted for ethically unacceptable purposes (such as giving up a job or leaving employment for perceived health reasons).[25 36] Therefore, current epidemiological studies are for exploratory research rather than occupational health monitoring and should be carried out as such, despite the additional logistical efforts and communication necessary for their acceptance by participants.

Although voluntary participation raises a selection bias concern, mandatory participation may also prove ineffective. For example, the EpiNano program, based on a vigorous, mandatory obligation to declare ENMs in France since 2013 (R-nano), classified 64 of 127 companies that declared TiO_2-nanoparticles or carbon nanotubes in 2015 as ineligible, and the data declared by the eligible companies did not make it possible to identify exposed workers or to estimate their exposure even qualitatively.[21 24] Corporate engagement will require discussions with companies represented in the program consortium, as well as labor, governmental public health, and research organizations.[30] Multisource project funding is also, at least for large companies, an element to consider.[2] However, the cooperation of research bodies, public authorities, and companies is not easy to achieve logistically, and sometimes it is deemed unacceptable with respect to the Charter of Independence. In the case of ENMs, it would be essential to create a climate of trust and mutual commitment, backed up by a steering committee and rigorous collaborative research protocol, allowing access to company data. Moreover, because of the small number of ENM-exposed workers in individual companies, scientific and political coordination at the national or even international level, as well as at the professional field level, is necessary in order to harmonize the research and collection protocols upstream of data collection.[14 16] To this end, the creation of a specific resource fund seems fundamental.[2 37] Yet, of the funds dedicated to research on ENM at the European level, so far none has been designated to finance this effort. Compared with research and technological development funding, environmental, health and safety research funding for nanotechnology was only 2.3%[38]. No epidemiological project has benefited from European or international funding, which clearly explains why only small, cross-sectional studies have been carried out so far. National governmental funding, although essential, is insufficient for raising awareness, and recruiting companies for a sufficiently long period to allow the forming of a large cohort of ENM-exposed workers. In France, an allocation from the Ministry of Health for the EpiNano program was limited to a 3-year recruitment of companies. This funded effort enabled the registration of 150 workers potentially exposed to carbon nanotubes and TiO_2 nanoparticles,[21] instead of the 1,500 workers initially expected.[12 39] In the United States, where more

than 100 workers exposed to carbon nanotubes have been identified in 14 companies and provided clinical examinations, currently available national funding is sufficient for only a cross-sectional study.[40]

Many scientists internationally are ready for collaborations to enable searching for methodological and technical solutions for evaluating exposures and identifying workers potentially exposed in certain professional sectors.[14 16 22 39] Among other efforts, a roadmap toward a globally harmonized approach for occupational health surveillance and epidemiological study of nanomaterial workers, established in 2012,[14] has enabled researchers to achieve some progress in the last 5 years (Table 1). Moving forward requires strong political and corporate support and dedicated funding to establish collaborative research projects at national and international levels.

CONCLUSION

Nanotechnology and resulting ENMs represent an emerging and therefore unclear potential risk to human health. Studies of ENM effects on human health face many issues: practical issues such as the temporality of nanotechnology development and penetration into everyday life and consumer products; scientific issues requiring fundamental and applied research to characterize and classify the different ENMs according to their toxicity; methodological issues in measuring individual exposure to ENMs and investigating their specific medium- and long-term health effects through prospective follow-up; and political and regulatory issues. At present, the last seem to be the most challenging. Their resolution through concerted action, supported by scientific input from public health agencies capacities, and specific funding at the national and international levels should certainly facilitate the establishment of a multidisciplinary consortium promoting epidemiological research in a coordinated way.

DISCLAIMER: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Box 1. Some definitions of nanomaterials and related terms legally accepted

International Organization for Standardization (ISO):

"Nano-objects, and their aggregates and agglomerates greater than 100 nm (NOAA) can exhibit properties, including toxicological properties, which are different from those of non-nanoscale (bulk) material" (ISO/TS 80004-2:2015);

"Nanoscale is the size range from approximately 1-100 nm" (ISO/TS 27687:2008);

"Nanomaterial is a material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale" (ISO/TS 80004-1: 2010);

"Aggregate is a particle comprised of strongly bonded or fused particles where the resulting external surface area may be significantly smaller than the sum of calculated surface areas of the individual components" (ISO, 2008);

"Agglomerate is a collection of weakly bound particles, or aggregates or mixtures of the two, and for which the resulting external surface area is similar to the sum of the surface areas of the individual components (ISO, 2008);

European Commission, Recommendation on the Definition of Nanomaterials:

"Nanomaterial means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm -100 nm." "In specific cases and where warranted by concern for environment, health, safety or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%."(Recommendation n. 696/2011)

[In 2014, Norwegian Environment Agency and Danish Ministry of the Environment adopted this definition as regulatory definition]

European Parliament and the Council of the European Union on the provision of food information to consumers:

"Engineered nanomaterial means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale;

"Properties that are characteristic of the nanoscale include: (i) those related to the large specific surface area of the materials considered; and/or (ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material." (EC, 2011)

European Commission. Cosmetics Directive:

"Nanomaterial means an insoluble or biopersistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm." (EC, 2009)

European Commission, Biocides Directive:

"Nanomaterial means a natural or manufactured active substance or non-active substance containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1-100 nm. Fullerenes, graphene flakes, and single wall carbon nanotubes with one or more external dimension below 1 nm shall be considered as nanomaterials." (EC, 2012)

French Ministry of Ecology, Sustainable Development and Energy:

"Substance at nanoscale is intentionally produced at nanometric scale, containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for a minimum of 50% of particles in the number size distribution, one or more external dimensions is in the size range 1 nme100 nm. By derogation from this definition, fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm are considered as substances at nanoscale." (ANSES, 2012)

Table 1. Progress achieved following the establishment of a roadmap toward a globally harmonized approach for occupational health surveillance and epidemiological study of nanomaterial workers in 2012. [14]

Roadmap element	Progress achieved	Comments
Exposure assessment		
Qualitative description of exposure and context	Yes	Many reports (EU, USA, ISO*) NECID** Ontology
Identify emission sources and exposure types	Yes	Various papers but patchwork
Measure exposure parameters	Yes	Slow but steady flow of research articles
Identify descriptors for modelling	Yes	Models exist but are not ready for everyday use
Strategy to feed an exposure registry	Some	Strategy is established (NECID), but actual data are not yet gathered
Hazard assessment		
Identify potential pathophysiological mechanisms	Some	Many toxicity tests done Novel nano-bio-interactions not fully established, especially in relation to human pathophysiology
Find markers for short-term health effects	Yes	Many useful markers, but they are not specific to nanomaterials or to nano-specific pathways or diseases
Find markers for long-term health effects	Yes	Many useful markers, but they are not specific to nanomaterials or to nano-specific pathways or diseases
Strategy to feed occupational health databases	No	Researchers and countries work in isolation
Epidemiology and Risk Assessment & Management		
Propose adequate epidemiological designs	Limited	Traditional approaches only partially fit for purpose
Set up exposure and health effect registries	Limited	Some national efforts in USA and France
Identify different risk assessment and management cultures	No	

Identify different data collection and protection philosophies	No

*International Organization for Standardization. **Nano Exposure & Contextual Information Database (http://www.perosh.eu/development-of-a-nano-exposure-and-contextual-information-database-necid)