Background paper for WHO Guidelines on Protecting Workers from Potential Risks of Manufactured Nanomaterials.

1. Introduction

Workers worldwide face new risks from manufacturing and applications of rapidly advancing new technologies based on nanometer-scale atomic structures known as nanomaterials [24].

Non-governmental organizations (NGOs) have been active in calling for increased attention to worker protection in emerging nanotechnology industries. In 2007, a broad coalition of non-governmental consumer, public health, environmental, labor, and civil society organizations spanning six continents called for strong, comprehensive oversight of nanotechnology [35]. “The people that research, develop, manufacture, package, handle, transport, use and dispose of nanomaterials will be those most exposed and therefore most likely to suffer any potential human health harms. As such, worker protection should be paramount within any nanomaterial oversight regime.” The coalition further identified lack of occupational safety and health standards specific to nanotechnologies and nanomaterials, and standard methods for measuring human exposure to nanomaterials in the workplace and called to develop written comprehensive safety and health programs addressing workplace nanotechnology issues and utilizing the precautionary principle as the basis for implementing protective measures for assuring the health and safety of workers. Similarly, in 2010 European Trade Union Confederation (ETUC) recommended “application of the precautionary principle which can take the form of a number of proactive initiatives including risk reduction measures, early warning actions with specific attention to health monitoring, and the registration of workers exposed” [33]. ETUC further called for “application of the ‘no data, no exposure’ principle, meaning that where no data on risks are available, workers must not be exposed and processes have to be performed in closed systems.”

To address potential risks of nanomaterials to workers in parallel with technology maturation, proactive approaches to occupational risk management based on qualitative risk assessment, the ability to adapt strategies and refine requirements, an appropriate level of precaution, global applicability, the ability to elicit voluntary cooperation by companies, and stakeholder involvement have been suggested [16]. Critical knowledge gaps needed to move forward our understanding of occupational risks of engineered nanomaterials and to enable science-based guidance and risk management have been discussed in a number of publications. For example, Schulte et al [15] posed the following seven questions in 2008:

1. Can an algorithm be developed to classify engineered nanoparticles by degree of potential hazards?
2. Which characteristics of particles and which measurement techniques should be used for the assessment of exposure to engineered nanoparticles?
3. What is the exposure to engineered nanoparticles in the workplace?
4. What are the limits of engineering controls and PPE with regard to engineered nanoparticles?

5. What occupational health surveillance should be recommended for workers potentially exposed to engineered nanoparticles?
6. Should exposure registries be established for various groups of workers potentially exposed to engineered nanoparticles?
7. Should engineered nanoparticles be treated as “new” substances and evaluated for safety and hazards?

Some of these remain critical today, while for others some data have been collected.

This background paper proposes draft critical questions which should be answered in the process of developing guidelines for nanotechnology worker safety and health in low and medium income countries. This background document will be used by a WHO guideline development group to identify key questions to be addressed by such guidelines.

2. Common manufactured nanomaterials

There are a number of estimates for the amount of nano-enabled products in the commerce. In 2008 US EPA analyzed submissions it received through a voluntary data reporting program (Nanoscale Material Stewardship Program, NMSP) for nanomaterials and compared them with Consumer Product Inventory maintained by The Project on Emerging Nanotechnologies and the Nanowerk database [17]. US EPA found a total of 234 unique nanoscale materials that have a molecular identity corresponding to an existing chemical on the TSCA Inventory with Nanowerk having 199, The Project on Emerging Nanotechnologies with 48, and the NMSP with 34.

However, no government maintained and publically available registry of nano-enabled product currently exists. Due to unresolved definition issues as well as bias of self-reporting, none of them are completely accurate. For example, a recent report concluded that “the CPI [Consumer Product Inventory maintained by The Project on Emerging Nanotechnologies] has substantive deficiencies that call the validity of claims associated with the CPI into question” [14]. Therefore, it is challenging to identify most widely used nanomaterials.

A possible indication of the most manufactured nanomaterials for non-pharmaceutical and non-food applications is the OECD list of manufactured nanomaterials undergoing testing through an OECD sponsorship program. US EPA analysis of the voluntary reporting program [17] concluded that “while each dataset has a significant proportion of chemicals unique to that dataset, the overlap of the datasets is remarkably consistent with the OECD testing efforts … on a representative group of 14 commercial nanoscale materials. Seven of the twelve substances common to all three datasets of existing chemicals … are targeted for testing. Only four substances are missing from all three datasets: nanoclays, dendrimers, polystyrene, and iron.” Since then, the OECD list of manufactured nanomaterials has been updated and now includes the following 13 nanomaterials: fullerenes, single-wall carbon nanotubes, multi-wall carbon nanotubes, silver, iron, titanium dioxide, aluminum oxide, cerium dioxide, zinc oxide, silicon dioxide, dendrimers, nanoclays, gold.

"When constructing this list OECD took into account those materials which are in, or close to, commercial use, as well as other criteria including, production volume, the likely availability of such materials for testing and the existing information that is likely to be available in dossiers on such materials. Thus the OECD list could be perceived as a list driven by industry needs" [6]. A recent report attempted to estimate U.S. production quantities of five nanomaterials in the OECD list: silver, carbon nanotubes, cerium dioxide, fullerenes and titanium dioxide [34]. Key findings were a "dearth of production volume information" and "the inconsistency in viable data sources across various nanomaterials." The relative order of nanomaterial production according to the upper bounds for annual U.S. production is TiO_2 > CNT > CeO_2 > fullerenes > Ag, ranging from 38 000 tons to 20 tons.

The OECD list of manufactured nanomaterials could be used as a starting point in answering the first question of the guidelines:

I. Which specific nanomaterials are most relevant with respect to reducing risks to workers in low and medium-income countries and on which these guidelines should now focus?

Manufactured nanomaterials can be produced and processed with a variety of industrial processes. A number of reviews exist for the methods of production of manufactured nanomaterials [1]. However, less has been summarized for the methods used in processing and end-use of nanomaterials.

II. What are the common industrial processes used to produce and process these specific nanomaterials in low and medium-income countries and on which these guidelines should focus?

3. Hazard assessment

A large body of research linking exposure to incidental nanoparticles which are often called "ultrafine particles" can be used in the hazard assessment of manufactured nanomaterials. For example, a recent review of scientific literature on correlation between exposure to air pollution and cardiovascular diseases [5] concluded that "although there is only limited epidemiological evidence directly linking UFPs [ultrafine particles] with cardiovascular health problems the toxicological and experimental exposure evidence is suggestive that this size fraction may pose a particularly high risk to the cardiovascular system." Experimental studies in rats have shown that at equivalent mass doses, insoluble ultrafine particles are more potent than larger particles of similar composition in causing pulmonary inflammation, tissue damage, and lung tumors [1, 20].

Carbon nanotubes (CNT) are specialized forms or structures of manufactured nanomaterials that have had increasing production and use. Consequently, a number of toxicologic studies of CNT have been performed in recent years. These studies have shown that the toxicity of CNT may differ from that of other nanomaterials of similar chemical composition [38]. The current understanding of the mechanism of biological activity of

CNTs suggests that the most appropriate health end-points for risk assessment of CNTs currently in commerce are inflammation and fibrosis [18, 19]. As a result, most operating occupational exposure limits for CNT are based on mass metrics rather than on fiber number concentration [2] as would be appropriate for the "long-fiber" paradigm of toxicity.

Material characterization for hazard assessment includes a set of physical-chemical endpoints in addition to health and fate/transport endpoints. A critical review and assessment of available characterization approaches for hazard assessment is provided in Ref. [6]. Ultimately correlations between these physical-chemical end-points and hazard properties will be used to establish predictive models. One of the recent attempts to predict toxicity of nanomaterials in a Quantitative-Structure-Activity-Relationship (QSAR) like model relates electronic energy levels in the nanoparticle structure with the oxidation potentials of reactions that would either remove antioxidants from cells or generate reactive oxygen species like hydrogen peroxide or superoxide ions [7]. Another model attempts to predict adsorption of plasma proteins and amino acids, thus providing indication of how specific nanomaterials would interact with cells *in vivo* [32]. However, both models have limitations: the former describes only one possible mechanism of toxicity and only for certain types of nanoparticles and the latter describes only the formation of "protein corona" as nanomaterials enter biological systems. Therefore, a validated comprehensive QSAR-like model for nanomaterials has of yet to be developed.

Given the paucity of validated dose-response data for nanomaterials, presently there are practically no Occupational Exposure Limits (OELs) specific to nanomaterials that have been adopted or promulgated by authoritative standards and guidance organizations [2, 22]. The vast heterogeneity of nanomaterials limits the number of specific OELs that are likely to be developed in the near future, but OELs could be developed more expeditiously for nanomaterials by applying dose-response data generated from animal studies for specific nanoparticles across categories of nanomaterials with similar properties and modes of action. Examples of approaches for developing OELs for titanium dioxide and carbon nanotubes and interim OELs from various organizations for some nanomaterials can be found in Ref [2].

III. Which hazard category or which OEL should specific nanomaterials be assigned to and how?

4. Exposure assessment

Engineered nanomaterials can have varying chemical and physical characteristics and may be structurally and compositionally homogeneous or heterogeneous or even be multi-functional. All these can affect release, transport and deposition of nanomaterials in the environment and, therefore, their exposure potential. As the size of the particle is made smaller, a greater fraction of the atoms are at the surface, which can affect the surface reactivity and toxicological properties of the particle. At the same time, nanoscale particles have a tendency to agglomerate and form larger structures, which influences the amount of time they remain airborne and their inhalability [1, 37, 39].

While it seems likely that particle size and shape will affect the deposition and fate of particles in the human body, few data about what effects these physical characteristics have on causing an adverse effect are available for engineered nanoscale particles [2]. However, information is available from the scientific literature on the role of particle size and shape on aerosol behavior including the deposition of particles and fibers in the human respiratory tract, including what effect their physical and chemical properties have on toxicity [3, 4, 40]. Less is known about dynamics of nanoscale particles in media other than air.

Currently, there are very few workplace measurements of engineered nanoparticle exposures. Exposure assessment studies that have been conducted are frequently constrained by the absence of having a defined exposure metric (e.g., mass, particle number concentration, surface area) to measure exposures that correlates with evidence of a toxic effect. Interpretation of workplace exposure measurements are further compounded by the presence of incidental nanoparticles from sources within the workplace (e.g., diesel exhaust, combustion products, electrical motors, photocopiers) and from the outdoor environment. Since incidental nanoparticles can exist in a variety of shapes, sizes, and compositions, their airborne presence often interferes with the quantitative assessment of workers' exposures to engineered nanoparticles. The limited understanding of the toxicity mechanisms associated with many engineered nanoparticles confounds the ability to identify a specific exposure metric (particle dimension, size, and surface area) that can be used to assess the potential hazard to workers [2].

There are few national and international guidance on assessing emissions of nanomaterials in the workplace. Similarly, the NIOSH nanoparticle emission assessment technique (NEAT) uses a combination of standard measurement techniques and instruments to assess potential inhalation exposures in facilities that handle or produce engineered nanomaterials [10]. The NEAT utilizes portable direct-reading instrumentation supplemented by a pair of filter-based air samples (source-specific and personal breathing zone). The use of the filter-based samples are crucial for identification purposes because particle counters are generally insensitive to particle source or composition and make it difficult to differentiate between incidental and process related nanomaterials using number concentration alone. This technique was used in 12 field studies, which demonstrated that nanomaterial emissions do occur to varying degrees and can be detected and quantified with the NEAT [11]. Factors such as work practices and the presence/absence/effectiveness of engineering controls can profoundly affect the magnitude of nanomaterial emissions.

The OECD Working Party for Manufactured Nanomaterials (WPMN) developed a similar protocol presented in a document on *Emission Assessment for Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance* [21]. This describes a procedure for the initial assessment to identify sources of emissions, and includes information on identifying potential sources of emissions, conducting particle number concentration sampling, and conducting filter-based area and personal air sampling. This protocol is presently being updated by OECD WPMN.

Some lower-cost real time measurement techniques specific to certain nanomaterials have started to appear as well. For carbon nanofibers (CNF) it was shown that "the photometer, with default factory calibration, provided a reasonable estimate of respirable CNF concentrations and will likely be the instrument of choice for direct-reading monitoring of CNFs in future studies of this type" [8].

Exposure to multi-walled carbon nanotubes was assessed in several manufacturing facilities ranging in size from laboratory to large scale production [9]. Breathing-zone and area filter samples were collected to obtain mass concentration and to conduct electron microscopy for counting fibers and energy dispersive X-ray analyzer for chemical analysis. Real-time aerosol characterization was done with a scanning mobility particle sizer, condensation particle counter, dust monitor, ultrafine condensation particle counter, and portable aethalometer. The study supports the notion that conventional exposure monitoring methods, such as personal and area sampling, combined with newly emerging nanoparticle measurement techniques can be very effective in measuring MWCNT exposure concentrations. Nanoparticles and fine particles were most frequently released after opening the chemical vapor deposition cover, followed by catalyst preparation. Other work processes that prompted nanoparticle release into air included spraying, CNT preparation, ultrasonic dispersion, wafer heating, and opening the water bath cover. All these operation processes could be effectively controlled with the implementation of exposure mitigation, such as engineering control.

Dispersing nanomaterials in liquids does not necessarily reduce potential for exposure to zero. It was shown that engineered nanomaterials can become airborne when mixed in solution by sonication, especially when nanomaterials are functionalized or in water containing natural organic matter [13]. This finding indicates that laboratory workers may be at increased risk of exposure to engineered nanomaterials.

A number of documents list exposure situations with highest potential for exposure [22, 23]. To increase effectiveness, these Guidelines would need to identify most relevant exposure situations.

IV. What are the highest exposure situations for each specific nanomaterial and each industrial process?

Presently comprehensive exposure assessment requires expensive and often research grade equipment and expertise. This can be prohibitive for small and medium size enterprises as well as for companies operating in low and medium-income countries. Therefore, a tiered approach going from more qualitative and less expensive to more quantitative and more expensive is needed to provide options and reduce costs of exposure assessment as much as possible.

V. How can exposures in these specific exposure situations best be assessed in a tiered approach?

5. Risk mitigation

Surveys of work practices based on voluntary participation reveal a broad range of risk mitigation measures implemented in nanotechnology workplaces, with potentially varying effectiveness, and the need for authoritative safety and health guidelines. A 2006 survey of private enterprises including companies and research laboratories sponsored by the International Council on Nanotechnology [25] reported that in general environmental safety and health practices including selection of engineering controls, personal protective equipment, cleanup methods, and waste management, do not significantly depart from conventional safety practices for handling chemicals and were occasionally described as based upon the properties of the bulk form or the solvent carrier and not specifically on the properties of the nanomaterial. For laboratory settings, a 2010 online survey showed that most researchers do not use suitable personal and laboratory protection equipment when handling nanomaterials that could become airborne [12].

A summary of available general national and international guidelines can be found in [26]. It shows that under the conditions of the paucity of hazard and exposure data most guidelines adopt precautionary measures aimed at minimizing exposures to the extent technologically and economically feasible. More specific guidelines focusing on specific business types and specific nanomaterial application categories have started to emerge recently as well. For example, OECD recently declassified a compilation of guidance for nanomaterial handling in the laboratories [36]. The German Chemical Industry and Paint Industry recently published its guidance for safe handling of nanomaterials used in paints and printing inks [27]. The UK Health and Safety Executive [28] and US NIOSH [38] have published guidelines for occupational risk management of carbon nanotubes.

Effectiveness of substitution, engineering controls and personal protective equipment to reduce exposures in the workplace have been reviewed [31, 29, 30]. Specifically it has been reported that there are known methods to decrease toxicity, which can be used to substitute/modify manufactured nanomaterials and which could lead to reduced risk in the workplace and to the down stream users [31]. It has been shown that exposure mitigation techniques developed to reduce exposures to incidental nanomaterials such as those found in welding fumes and diesel exhaust can be effective for manufactured nanomaterials [29, 30]. For example, the particle number concentration reduction due to the use of LEV, in combination with a downdraft welding table, was found to be 97–98% in particle number concentration and 88% in mass concentration [11]. However, questions remain regarding effectiveness of specific techniques for specific nanomaterials and processes.

VI. How effective are specific risk mitigation techniques for specific nanomaterials and specific exposure situations?

Once, the determination is made in regards to the effectiveness of risk mitigation techniques, a tiered approach for risk mitigation to desired levels can be recommended.

VII. What risk mitigation techniques should be used for specific nanomaterials and specific exposure situations?

6. Conclusions

The WHO guidelines for protecting workers health from potential risks of nanomaterials can provide a range of options for occupational risk management of nanomaterials starting from semi-qualitative (such as Control Banding) and finishing with traditional quantitative (such as those built around Occupational Exposure Limits) approaches. Such tiers would allow for a choice of measures applicable to a wide range of operating and social constraints. For each tier the following draft critical questions would have to be answered in the course of developing guidelines:

I. Which specific nanomaterials are most relevant with respect to reducing risks to workers in low and medium-income countries and on which these guidelines should now focus?

II. What are the common industrial processes used to produce and process these specific nanomaterials in low and medium-income countries and on which these guidelines should focus?

III. Which hazard category or which OEL should specific nanomaterials be assigned to and how?

IV. What are the highest exposure situations for each specific nanomaterial and each industrial process?

V. How can exposures in varying scales of industrial operation be assessed in a tiered approach?

VI. How effective are specific risk mitigation techniques for specific nanomaterials and specific exposure situations?

VII. What risk mitigation techniques should be used for specific nanomaterials and specific exposure situations?

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General comments:

1. "Nanomaterials are in essence, chemical substances that are composed from chemical building blocks (e.g., elements, molecules), those precautionary principals and regulations that protect from hazard materials (e.g., transition metals, organic solvents, radical complexes) should be applied to any manufacturing process of nanomaterials.
2. Accidental exposure to a human body either via respiratory, oral, or direct skin contact, should be avoided, using on-line manufacturing feedback controls (e.g., vacuum lines, shutters, scavenger agents)
3. National agencies should be stimulated to support research that develops standard methods for measuring potential hazards and level of exposure to various nanomaterials (e.g., carbon nanotubes, semiconductor quantum dots, dentrimers, graphene). The research should occurrence of damage on prototype biological tissues, using spectroscopy and microscopy.
4. Once methodologies are developed, and a wide collection of data is present, regulations can be worked out. Then, manufactures should be required to examine their new products before shipment to consumers."

"I appreciate the opportunity to provide some comments on the background document that identifies a number of key questions that are to be addressed in the WHO Guidelines. Developing this guideline is an important and timely undertaking that will advance the safety and health protection of workers who work with and are exposed to specific nanomaterials.

The seven questions in the background paper are essential questions to ask within the framework of developing any guideline whose goal is to protect workers from potential health risks associated with exposure to nanomaterials. Determining the most relevant nanomaterials and work processes to focus upon, identifying the hazards posed by the specific nanomaterials of concern, determining the workplace processes that are likely to result in potentially high exposures, and identifying and recommending risk mitigation methods are critical elements to address.

The seven questions are sufficiently broad and cover many important issues that a guideline must address. Within those broadly phrased questions however, a number of key issues will need to be examined, including, for example:

- At what point(s) in the life cycle of a specific nanomaterial are worker exposures of concern likely to occur?
- In the absence of OEL's for many nanomaterials, how will control banding be used to determine hazards/risks?

- How will exposures be assessed and are there alternatives to traditional exposure assessment techniques for nanomaterials that should be recommended as alternatives for low and medium-income countries?
- What role will the precautionary principle/approach play in this guideline for controlling exposures to specific nanomaterials?
- How will risk mitigation measures be evaluated?
- In recommending risk mitigation techniques, what role will substitution play in this guideline?
- What is the form of the specific nanomaterial that workers are exposed to (free material, matrix-bound, solution-bound, etc.) and what are the routes of exposure that are of concern?
- Will the traditional hierarchy of controls be recommended for all exposure scenarios of concern?
- What role will respiratory protection and other forms of personal protective equipment (PPE) play in risk mitigation efforts and will there any distinction on the use of respirators and PPE in low and medium-income countries?
- Will the guideline address worker protection issues that may arise from nanomaterial exposures resulting from accidents/process upsets and other emergencies?
- Will the guidelines recommend documentation for following any of the elements of the guideline and, if so, which elements?
- How will workers and their representatives participate in the development, implementation, and evaluation of the guideline?

In addition to the key questions included in the current background document, I think several additional broad issues need to be considered if this guideline is to adequately fulfill the goal of protecting workers from the risks of nanomaterials. Answers to these other broad questions can, I believe, enhance the usefulness and comprehensiveness of the resulting guideline. Additional key questions that ought to be considered in the process of developing this guideline include:

- *What training should be provided to workers who are at risk from exposure to the specific nanomaterials?*

  Adequate and effective training is a key component of an overall comprehensive strategy to protect workers and manage risk. Issues to address in training include the topics or elements of training (e.g., hazards of the nanomaterials, routes of exposure, methods used for controlling exposures, using respiratory protection, work practices, etc.), when training is to be provided (e.g., initial, periodic, changes in workplace circumstances, etc.) and the means/methods by which training is given. Because this is such an important element in protecting workers, this issue should be considered to be added as a key question in the development of the guideline.

- *What worker health surveillance approaches, if any, should be implemented for workers at risk from exposure to specific nanomaterials?*

  Health surveillance and medical screening are important elements in assessing the health of exposed workers and can serve to identify adverse health outcomes resulting from exposure. Typically, medical screening and health surveillance are used in circumstances where the health effects of the substances in question are reasonably well known. For many manufactured nanomaterials, our knowledge about the health effects is limited. However, we appear to have sufficient information on health effects for some nanomaterials (e.g., carbon nanotubes) to warrant some guidance on this issue. Indeed, the NIOSH draft Current Intelligence Bulletin, *Occupational Exposure to Carbon Nanotubes and Nanofibers* includes recommendations for medical surveillance and screening for workers who have occupational exposure to these substances. I think it makes sense to consider this issue regarding specific nanomaterials where it seems appropriate to do so.

- *What methods should be used to periodically evaluate the implementation effectiveness of the guideline?*

  Evaluating the effectiveness of any safety and health guideline is essential to determine if workers are receiving adequate protection that the guideline has been designed to deliver. The nanomaterials guideline should consider including some discussion about what such a review would consist of (e.g. guideline elements to examine, periodicity of conducting a review, who participates in conducting the review, implementing revisions that address deficiencies, etc.). By including this question, users of the guideline will understand the value of evaluating their implementation efforts and can revise their program as their review may warrant so that workers can be protected."

"I missed the introduction of reference to international initiatives regarding the care that must be taken in relation to the risks of nanotechnologies as those within the scope of SAICM, the ILO, the European Agency for Safety and Health at Work. I also suggest the need to include training of workers so they may be prepared to face new risks that may arise with nanotechnologies.
There is also need to refer to the need for regulation and that information on the risks accompanying the whole lifecycle of products, especially those that are exported to developing countries."

"It is a great start to the WHO publication and the set of questions asked are appropriate.

I am not sure what, if anything, the state of Nanotechnology here in Canada should be included into your document, however some reflections about the current situation here in Canada may be similar in other countries and may give the committee developing this publication some thoughts.

1. In the development of a Canadian Standards Association (CSA) "Technical Standard" for the safe handling of nanomaterials in the workplace, the issue of the "precautionary principle" came up. It appears that not everyone on the committee agreed on one specific definition. Therefore, perhaps a clear definition should be spelled out in the WHO Guideline. Just to let you know, we decided to go with the wording that appears in out Federal Environmental Protection Act.
2. Canada, as a country, has not officially articulated a Nanotechnology Strategy and many of the provinces have not. The two most active provinces, in this area, are Quebec and Alberta, however in all cases the Health, Safety, and Environmental (HSE) plans are still weak.
3. Health Canada is active in Nanotechnology and is hoping to develop a better set of directions as it relates to (HSE), however, given the very complex nature of the science, they have not published any specific regulations. They have just currently defined Nanotechnologies, so it is a start.
4. The Provinces, who have the responsibility of setting Occupational Exposure Levels (OELs) have not done so for any nanomaterials. Both the Federal Government and some of the provinces are active on CSA, ISO, and OECD nano committees. They participate on these committees with the hope to better understand the very complicated subject, and when able, implement regulations to control the exposure to nanomaterials to the public and workers.
5. I assume given the rapid rate of development in this field, any new process for nanomaterials development could be used in any low and medium income countries. It would just be a matter of industry setting up shop in these nations, so I assume the guideline not limit the discussion on any process.
6. Here in Canada, there is a lot of work in the field of Nanocrystalline Cellulose, so in essence, I am sure other new nanomaterials will be added to the list of materials in production."

"At first, I would like to congratulate for the synthesis performed.
I did some brief comments, shown below.

Low and median-income countries have restricted capabilities to typify the characteristics deemed to be relevant for analysis of nanomaterials health effects. But even if such capabilities exist, they are not widespread, restricting the ability of analysis, both in quantitative terms and in relation to different areas of a country.
In addition to these restrictions, urban and rural environments may have high background of nanoparticles. Burning of virgin forests and sugar cane, as well as diesel combustion can extend in long, these quantitative. Beside this, some nanoparticles can determine similar health effects of engineered nanomaterials as oxidative stress and thrombogenic potential.

This may require that attempts to differentiate background nanoparticles and engineered nanomaterials / or industrial processes resulting nanoparticles has to be done.
In addition and to reinforce NEAT proposal, it could be crucial to measured occupational environment of nanomaterial/particle in three stages, for mass, number and surface area bands (to be done in general facilities areas and near engines and at personal breathing zones, with portable direct-reading instrumentation supplemented with source-specific and personal breathing zone filter-based air samples): background nanoparticles with engines stopped), nanoparticles with machines running (without substrate), nanoparticles

and engineered nanomaterials (machines running with substrates). Although lack of full precision, such measurements may approach measures with previous theoretical knowledge. If nanomaterial included or produced in a specific process is known, as its potential for aggregation, it’s possible an initial approximation of its amount. Such knowledge could determine relevant individual and collective protection measures.

The second step may be stimulating the production of nanomaterials potentially biodegradable. In addition to the classic organic materials, can be of great interest to stimulate the production of engineered nanomaterials that can be destroyed in the body, as described for functionalized carbon nanotubes that can suffer the action of myeloperoxidase. In other words, to incorporate into the production process the limits of the life materials, trying to avoid their accumulation in biota.

However, as described, the inventory of products that use nanotechnology is not known in full. This situation is certainly worse in low and median-income countries. Brazil, for example, while placing among the top fifteen countries in scientific production in the area of nanomaterials and nanotechnologies, has no proper record of industries that use such products, do not know which nanomaterials and nanoproducts every industry uses and produces and is not a search option in Woodrow Wilson Inventory.

Thus, an important step towards the true knowledge of what should be evaluated in terms of public policy would require better knowledge of what is produced and used. On the other hand, time is short and not sufficient to wait until such knowledge exists. There is no need to know the whole lion to worry about it. The roar can be a good prognostic sign.

In this case, the roar has to be understood as the priority industries of each country. I return to Brazil. The main industries are primary goods, especially minerals, petroleum, agribusiness, and even construction. There are also significant imports of materials for healthcare.

The search for nanomaterials and nanoproduts used by such segments should be prioritized. Right away, though, there are groups of materials of greater use: liposomes and nanocapsules in cosmetics and medicines, carbon nanotubes, nanoclays, and metal oxides. It is of utmost importance to evaluate the use of silver nanomaterials in extensive use in Brazil and many other countries.”

- “The draft background document is considered as an appropriate starting point for developing the planned WHO guideline
- The key questions are to be supported as summarized in chapter 6.
  Furthermore, it is proposed to also address the information/training/instruction of the workforce in low and medium-income countries.
- The references are to be supported as cited. However, further relevant references could be added, if required, e.g. in chapter 5 Susan Woskie, Workplace Practices for Engineered Nanomaterial Manufacturers, Nanomed Nanobiotechnolgy 2010 2 685-692
- Tiered exposure measurement/assessment strategies are to be supported as outlined in chapter 4.
- I disagree that laboratory workers may be at increased risk of exposure to engineered nanomaterials as stated in chapter 4. The opposite has to be expected, as long as appropriate/efficient fume hoods or glove boxes are used and successful occupational safety practices (hierarchy of control, industrial hygiene practices,

adequate PPE) as they are applied also for handling of R&D substances are complied with.
- The claim that existing risk management concepts/measures are also effective for producing/processing nanomaterials is to be supported as stated in chapter 5.

CNTs are often used as an example. This may over-emphasize their industrial relevance."

"*I. Which specific nanomaterials are most relevant in reducing risks to workers in low and medium-income countries and on which these guidelines should focus on?*
The OECD list only focuses on the most common nanomaterials, which are already industrially produced in medium and large scales. The WHO guideline should also focus on new and advanced nano-materials in an early state of industrial production, for which toxicological data aren't available yet. For purposes of risk management it's essential for nanomaterials to focus on the chemical composition as well as on morphological properties.

II. What are the common industrial processes used to produce and process these specific nanomaterials in low and medium-income countries and on which these guidelines should focus on?
With regard to OSH there are no significant differences in production, handling and use of nanomaterials compared to other chemicals. For this, the WHO guideline should make use of the task-categories from the International Chemical Toolkit (ICCT) of ILO/WHO.

III. Which hazard category or which OEL should specific nanomaterials be assigned and how?
Due to limited technical and financial resources in SME a control banding approach should be preferred, that is based on the ICCT. It's to discuss, how to allocate a given nanomaterial to a hazard group of the ICCT. This is usually based on R- or H-phrases from classification and labelling schemes and is also possible with help of OELs (German EMKG). But how to deal with data gaps? In Germany hazard group C has to be used as a default for new materials with unknown toxicological properties. Beyond this, it will be very useful to categorize the nanomaterials with regard to possible risk for workers. At current state-of the art four categories have to be taken into account: biopersistent fibres, biopersistent granular dusts, particles with a specific toxicity and soluble particles.

IV. What are the highest exposure situations for each specific nanomaterial and each industrial process?
The control banding approach of the ICCT should be used for estimation of exposure. This scheme, based on three categories for quantities used and dustiness lead to an estimated exposure band. This procedure is well established, and part of several regional control banding tools, e.g. EMKG and COSHH Essentials. It´s difficult and needless for an adequate risk management in SME to have exact exposure values.

V. How exposures in these specific exposure situations can be assessed in a tiered approach?

The ICCT approach should be used on a tier1 level. For refinement several control banding tools exist, which are specially designed for nanomaterials (Dave Zalk´s and Paul Swuste´s nano tool, stoffenmanager nano), which make use of more parameters for hazard and exposure estimation.

VI. How effective specific risk mitigation techniques for specific nanomaterials and specific exposure situations are?

Please note, that the OECD compilation of guidance for nanomaterials handling in the laboratories is already published on the OECD homepage: http://www.oecd.org/officialdocuments/displaydocument/?cote=env/jm/mono(2010)47&doclanguage=en It´s my overall conclusion that risk mitigation techniques for fine and ultrafine dusts work well with nanomaterials, too. The main reason for this may be, that most of the dusts generated from nanomaterials are fine and ultrafine dusts of aggregates und agglomerates.

VII. What risk mitigation techniques should be used for specific nanomaterials and specific exposure situations?

We don't have to think about specific risk management measures for nanomaterials. The control guidance sheets of ICCT offer a good basis to describe and to communicate effective control strategies for the most common tasks with nanomaterials (e.g. transfer, weighing, mixing , ...). OSH problems from dusts generated from processing nanomaterials-containing articles can be addressed with established standardized working practices for workers protection from welding fumes and other ultrafine particles."

"The presented background document with key questions provides a clear and comprehensive overview of the issues that we meet at the workplace where nanomaterials are processed. Many of the key issues are identified. It reflects on positions of different CSO stakeholders and does endorse a precautionary approach, the *no data, no exposure* principle seems to be one of key issues here. To adopt this principle is a great challenge for industry and does not seem to meet much opposition in fundamental discussions with industrial stakeholders. This is different with the hurdles identified in the document to enhance the transparency and the traceability of nanomaterials in products that are brought on the market. Definition questions and product (and production) confidentiality seems to be the crucial issues here.

The document discusses the complexity of standard setting for nanomaterials shortly, the same problems as for conventional substances concerning the slow pace of introduction of new OELs are appearing, but also issues as metrics used for the hazard research are evolving here.

An interesting item that is discussed as well is the exposure assessment of engineered nanoparticles (ENP). The limited information that is available about the actual composition of the airborne particulate fraction at workplaces is the key here. For this item a more clear focus on the position of the concerning company in the nanomaterials production chain is indicated: raw material producer – product manufacturer – end user – waste management – cleaning and maintenance. The composition of the airborne particulates in the manufacturing industry might be quite clear, but the larger "the distance" from the manufacturing of the raw materials, the more complex the composition of the generated particles becomes. Agglomeration, aggregation, but as well

formation of process-generated nanoparticles are common processes. As a consequence, exposure to pure engineered nanoparticles in the workplace of the downstream user seems to be rare, which makes risk assessment at these workplaces even more complex. Mitigating measures as for example changing the physical/chemical properties of the particles may influence the dispersive behavior and may affect the emission of nanoparticles to the workplace air, but these as well do influence the toxicological properties of the particles.
This all leads back to questions as what are we talking about at the nano workplace? Do we really support the downstream user by providing him with a well-established OEL for the ENP that is processed in the products he is using? Do we expect the downstream user to be able to go for extensive chemical analysis, financially, but does it make sense if the complex toxicological interpretation cannot give unambiguous answers? Is he able to refine his risk management measures up to a detailed level that legitimizes his financial effort? Or should for the nanoparticles risk assessment paradigm be chosen for a more generic approach? In this respect one may think about the development of generic OELs for different groups of nanomaterials. The commonly used mass metrics approach for OELs may need to be seriously scrutinized and considered to be replaced by a particles approach. Nano Reference Values may be considered as a provisional precautionary tool. Another advantageous risk management tool for the downstream user industry, as well as for low and medium-income countries might be to formulate *good practices for workplaces using nanomaterials*. Good practices that are well-studied and well-defined and that guarantee that under these conditions the exposure to hazardous nanomaterials may be acceptable.
As a summary, the formulated critical questions in the document are highly relevant, but we might consider to broaden the scope somewhat from a narrow focus on ENP to NP that we meet at the workplace (which, as a consequence may even lead back to the use of conventional products at the workplace). This holds for the risk assessment activities as well as for the related standard setting."

"1) While I completely agree that the OECD list of MN is a good starting point, we should keep an open mind that the list could be lengthened as well as shortened. What I mean is, in addition to narrowing down the list, we should also investigate whether there are other "more traditional" MN that the industries in OECD (i.e. more advanced) countries may not be interested in sponsoring (thus preventing these MNs from inclusion in the "OECD list") but are perhaps in use in low and medium-income countries. I'm thinking about something like carbon black but I don't have any utilization figures handy at the moment.

2) I'm in the middle of reviewing research papers related to the hazard of silver nanoparticles. Many of the 300+ articles I'm reading were published quite recently (i.e. this year), which may reflect the recent boom in nanosafety research. Within the next couple of years, many more nanosafety research papers will undoubtedly be published. We may need to keep reviewing and perhaps updating the OEL / hazard categories a few times, in light of verified relevant research findings, before they are stable.

3) I agree with the tiered approach. This is what we are formulating (more like

experimenting) in Thailand right now, starting from a very qualitative approach. Aside from the overall approach, it is an interesting exercise to categorize relevant industrial processes into a dozen of major groups and then going deeper into subgroups. We also construct maps to relate each of the Thai nano industries to these groups (and subgroups) of industrial processes.

4) I wonder if compliance (or at least enthusiasm?) of local officials, factory owners, administrators and workers are going to be addressed or should we assume that whatever guideline we propose (under the name of WHO) would be respected and implemented. Do we have experts in attitude/behavior modification in our group? From interviewing a few factories in Thailand I found that compliance to chemical safety protocols would increase significantly if these protocols were implemented along with education, or at least there must be explanation to go along with whatever action to be taken. Should we build some education into the Guideline or should we leave that to the local implementor?”

“1. From the standpoint of document structure and readability, in many places the basis for positioning the italicized questions (identified by Roman numerals) in specific numbered subsections is unclear. For example, on page 4, it is not clear why the question “*III. Which hazard category or which OEL should specific nanomaterials be assigned and how?”* was inserted at the very end of section 3 entitled “Hazard Assessment” and before section 4 entitled “Exposure Assessment.” The italicized questions are repeated on page 8. Limiting their appearance to page 8 only would increase clarity.

2. With respect to the section entitled “Common manufactured nanomaterials”, the document might reference and describe information obtained by the State of California (USA) in response to its mandatory request (“chemical call-in”) that all commercial and research entities in located in the state provide information on nanomaterials they manufacture, develop or distribute. For further information, see: http://www.dtsc.ca.gov/PollutionPrevention/Chemical_Call_In.cfm

As of the present, specific information is available on carbon nanotube production in California. Information on nano silver, nano zero valent iron, nano titanium dioxide, nano zinc oxide; nano cerium oxide, and quantum dots is also being gathered and may be available for review by WHO (see http://www.dtsc.ca.gov/TechnologyDevelopment/Nanotechnology/nanometalcallin.cfm). It is surprising that “quantum dots” were not cited in section 2 of the background document as a major type of nanomaterial under development.

3. The section “Hazard Assessment” could be expanded to describe recent NIOSH recommended exposure limits (RELs) for carbon nanotubes released in draft form in November, 2010, and for titanium dioxide released in final form in 2011. The findings and recommendations of these documents merits discussion:

NIOSH 2010. Occupational exposure to carbon nanotubes and nanofibers. Draft for public comment. Current Intelligence Bulletin November, 2010.

NIOSH 2011. Current Intelligence Bulletin 63. Occupational Exposure To Titanium Dioxide. Department Of Health And Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2011–160

Mention should also be made of the guidance issued by the Institute for Occupational Safety and Health of the German Social Accident Insurance that recently recommended benchmark limits for workplace exposure to nanoparticulate (1 to 100 nm) expressed in terms of particle number concentration.

Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) Criteria for assessment of the effectiveness of protective measures. (2009). Available at: http://www.dguv.de/ifa/en/fac/nanopartikel/beurteilungsmassstaebe/index.jsp

4. The section "Exposure Assessment" would benefit from an expanded discussion of the multi-tiered factors (macro, mid-level, and task specific) that influence workplace exposure to nanomaterials described by Woskie et al in their recent publication. (Woskie, S.R., et al., Understanding workplace processes and factors that influence exposures to engineered nanomaterials. Int J Occup Environ Health, 2010. 16(4): p. 365-77). This section might also comment on studies demonstrating the potential for nanomaterial exposure during physical disruption (e.g. drilling, cutting, or sanding) of solid matrices fabricated with nanomaterials (e.g. Bello D et al. Characterization of exposures to nanoscale particles and fibers during solid core drilling of hybrid carbon nanotube advanced composites. Int J Occup Environ Health 2010; 16:434-450).

5. Finally, the background document would be greatly improved by inclusion of a section discussing the potential role of medical surveillance and exposure registries in risk management of occupational exposure to nanomaterials. Although not discussed at all in the background document, this topic has been the subject of extensive discussion in the peer-reviewed literature. While there is no consensus on the value of specific medical surveillance regimens, there is growing agreement regarding the utility of instituting worker exposure registries to facilitate epidemiological research and risk communication. For example, see:

Trout DB, Schulte P. Medical surveillance, exposure registries, and epidemiologic research for workers exposed to nanomaterials. Toxicology 269, 128-35; 2010

ACOEM. American College of Occupational and Environmental Medicine. Nanotechnology and Health. October 28, 2010. http://www.acoem.org/Nanotechnology.aspx

Fischman M et al. National Institute for Occupational Safety and Health nanomaterials and worker health conference--medical surveillance session summary report. J Occup Environ Med 2011; 53(6 Suppl): S35-37."

“Preparation of Safety guidelines and occupational risk management for any material is possible only when we have

- Systemic studies with reference to the acute and chronic toxicity ;
- Occupational exposure limits;
- Early toxicity bio-markers
- Detection techniques in various matrices

For most of the nanomaterials that are currently in use in various industrial processes, there is noticeable gap in the long term toxicity studies. It is obvious as certain CNTs in animal models are behaving as asbestos fibers and also causing mesothelioma due to similarity in long, thin and bio-persistent fiber like structure. However the cases of mesothelioma might appear only after a long period of exposure to these CNTs as in case of asbestos. Thus long term, systemic, dose dependent toxicity studies are highly desirable for different size and shape of nanomaterials currently in use.

A reference repository for nanomaterials is urgently needed. This repository can provide the reference materials to the research laboratories worldwide engaged in the toxicity assessment of nanomaterials to speed up the availability of base line information on which safety guidelines and occupational risk management procedures can be developed.

All the questions mentioned in the document are critical for developing guidelines not only for nanomaterials but for any chemicals/ materials. However due to unavailability of base line toxicity information, most of them will remains to be unanswered.

In most of the unorganized industrial setups in developing countries, the use of nanomaterials should be strictly prohibited and discouraged until the base line toxicity data and safety guidelines become available, supporting the ‘no data no exposure’ principle of ETUC. However, in organized sectors, the highest possible work safety guidelines should be practiced.

Quantitative Structure Activity Relationship (QSAR) models and other virtual target screening techniques along with system biology models can help in extrapolating toxicity data currently available for nanomaterials and thus help in categorizing the nanomaterials in various hazards categories. It is thus suggested that a classification system for nanomaterials should be developed based on various computational and knowledge based modeling techniques. Nanomaterials identified as potential toxic compounds using these techniques should be immediately discouraged for their use in various industrial setting till the further long term toxicity information generated.

In order to predict the toxicity due to exposure of nanomaterials in various industrial settings, it is important to identify the potential biological targets. *In silico* approaches might help to quickly screen out these biological targets using reverse docking approach. Identification of interacting protein partners can provide a complete picture of various biological processes that might get affected because of nanomaterial exposure. Thus these *in silico* processes can help to identify the hazard category of nanomaterials based on interacting biological partners and affected biological processes.

It has been proposed that nanomaterials have the tendency to adsorb species like organic or heavy metals in various configurations of different geometries. ENPs have been demonstrated to be a very effective adsorbent for many organic compounds because of the large surface area and the capability of π-π electron coupling with the targeted compounds.

The nanomaterial itself may not be toxic to the human but other toxic compounds used during industrial processes can easily adsorbed on the nanomaterial surface. These nanomaterials and organic pollutants conjugates may have high retention time in different biological matrices responsible for various target organ toxicity. Thus it is very important to identify the toxicity profile of chemical compounds and other materials used in the industrial processing along with the nanomaterials. Computational adsorption studies might help to understand the adsorption affinity of various organic moieties on nanomaterial surface and thus can predict the adverse effect on human. In the guidelines questioners the toxicity profile of other compounds and materials in use along with the nanomaterials in a particular industrial process is also important. Further the adsorption affinity of various toxic compounds on nanomaterial surfaces used in a particular industrial process should also be considered.
The following parameters must be applied before developing guidelines for occupational risk management of the commercial use of the nanomaterials:

- Standard Regulatory Toxicological Tests.
- Quantitative structure – activity relationship (QSAR).
- Physiologically based pharmacokinetics models
- International Reference Samples

The above parameters will be the key points in the risk assessment, depend on hazard identification, dose response and exposure assessment. This Risk Assessment will lead into Risk Management."

"1. At second paragraph of the first part of text, ETUC is recommended that in the lack of enough data about dangers and risks of exposure to nanomaterials " No Data, No exposure" approach to be used. It seems that is more practical to use the following term"as low as reasonably practicable".
2. It seems that most of this text is focused on the process and stages of the preparation of the safety and healthy guidelines for staff in environments of work place. So I suggest changing the title as followed "The Process of Protecting Workers from Potential Risks of Manufactured Nanomaterials"."

"I agree with what another contributor wrote: "It's difficult and needless for an adequate risk management in SME to have exact exposure values".
If you wait until we know the exact toxicity of nanomaterials or recommended exposure values to start making risk assessment and install protective measures, the workers there may already be sick."

Specific comments:

1. Line 10, "Non-governmental organizations (NGOs)": We definitely need to include also the other important players that early up made public statements. Notably: Policy Makers with Action Plans (e.g. EU and Switzerland) The International Risk Governance Council Insurance companies, namely SwissRe Industry associations etc. (e.g. Dupont efforts). This will show that it is widely accepted, that there is a need for these elements.

2. Line 38, “Schulte et al [15]”: This was indeed a nice summary of what had been communicated before by many people (I had been talking about this in almost every conference since 2005)… I suggest to quote at least also a few other references from other continents to show that this is a global need. Notably a few docs in Europe…
3. Line 30: Insert a new paragraph “Among the earliest occupational and public health guidance issued on manufactured nanomaterials, The Royal Society and The Royal Academy of Engineering [2004] recommended “…until there is evidence to the contrary, factories and research laboratories should treat manufactured nanoparticles and nanotubes as if they were hazardous and seek to reduce them as far as possible from waste streams.” To a large extent, this guidance still holds. In the absence of specific hazard information or exposure limits for most nanomaterials, reference or benchmark exposure limits have been proposed [BSI 2007; IFA 2009]. Although these provisional exposure limits are precautionary based on analogy with existing substances, they are not based on specific health effects data, and thus may not be sufficiently protective for workers. Progress has been made on understanding the hazards of certain nanomaterials through experimental animal studies, which has enabled standard risk assessment methods using toxicology data and development of recommended exposure limits for some nanomaterials including titanium dioxide and carbon nanotubes [NIOSH 2010; NIOSH 2011; Pauluhn 2010]. Developing global partnerships for research and risk assessment of nanomaterials has been a recognized theme early-on, including at the First International Symposium on Occupational Health Implications of Nanomaterials in 2004 [Mark 2005] and the first NATO international workshop on the toxicological issues and environmental safety of the manufacture and use of nanomaterial [Simeonova et al. 2007].”
4. Lines 45-46: Is efficacy meant here? Limits is too vague and confusing. Points at TLVs and that is not the case here.
5. Line 58: add a new sentence “These questions are organized within essential steps for risk assessment process of nanomaterials, including physical-chemical characterization, hazard assessment, exposure assessment, and risk mitigation. [Note: dose-response and risk characterization sections might be added later].”
6. Line 61: insert “There is so far very limited information about the occurrence of nanomaterials in products and industry. So far there was only one representative survey in an industrialized country – Switzerland. This study (conducted in 2007) estimated that nanoparticles are already in use by to 0.6% (Confidence Interval: 0.2% to 1.1%) of all companies in the producing industry and that 0.08% (CI: 0.06% to 0.90%) of all producing sectors' workers were potentially exposed or in proximity of nanoparticles. The highest number of applications were found in the chemical industry (21.2% of the companies having nanoparticles). This study also investigated the protection strategies and personal protection equipments were predominant. Reference for this: Schmid K, Danuser B, Riediker M. Nanoparticle usage and protection measures in the manufacturing industry - a representative survey. J Occup Environ Hyg 2010, 7: 224–232. In an accompanying targeted telephone survey, the same authors found that the people in charge for safety and health rarely based the definition of protective measure on real measurements.

Instead, they defined protective measures in analogy to known risks. In consequence, they assumed that nanoparticles would not become airborne if dispersed in a liquid and in consequence few liquid or solid applications were accompanied by measures to protect against exposure via the airways. Reference for this: Schmid K, Riediker M. Use of Nanoparticles in Swiss Industry: A Targeted Survey. Environ Sci Technol, 2008; 42(7):2253-2260. e-published ahead of print February 26. doi: 10.1021/es071818o."

7. Line 67: VCI conducted a survey among its members on potential ENMs based on the current, different definition proposals recently.
8. Line 97: replace sentence as follows "Thus the OECD list could be perceived as a list driven by industry needs" [6], although this emphasis also helps to focus priority on those nanomaterials to which workers may have the greatest potential for exposure through production and use."
9. Lines 108-110: Why a focus on low and medium income countries? At this stage also in developed countries guidelines are valuable? Remove "in low and medium income countries".
10. Lines 108-110: There is no explanation in the document as to why low and medium-income countries should be excluded while high income countries should not. Do we have a clear agreed definition for each type of country? Do we have data on which NM are produced in such countries?
11. Lines 114-115: change sentence to "However, less has been summarized for the methods used in processing and end-use of nanomaterials, but recently in a conceptual nano exposure model the whole supply chain was covered (Schneider T et al., 2011)."
12. Line 115: add a new sentence "This means there is a paucity of information on the potential fo rnanomaterials exposure in workers using nanomaterials in various applications."
13. Lines 117-119: Should we try to link to this to what implications the different production processes might have on occupational exposure?
14. Line 120: insert "We showed in the NanEX-study (http://www.nanex-project.eu and direct link to report http://www.nanex-project.eu/index.php/public-documents/doc_download/91-nanexwp7final) that most publicly available data is about production of nanomaterials, even though most companies are downstream users (they buy and further process nanomaterials and materials and products containing them – see also the above mentioned Schmid et al. reference in JOEH 2010)"
15. Line 122: insert "Useful discussion from a workshop on minimal analytical characterisation of engineered nanomaterials need for hazard assessment in biological matrices: http://www.nanoimpactnet.eu/uploads/file/Reports_Publications/D1.2%20Report%20-%20characterisation%20of%20nanomaterials%20for%20hazard%20assessment.pdf This was also recently published in the form of a peer-review article: Bouwmeester H, Lynch I, Marvin HJP, Dawson KA, Berges M, Braguer D, Byrne HJ, Casey A, Chambers G, Clift MJD, Elia G, Fernandes TF, Fjellsbo LB, Hatto P, Juillerat L, Klein C, Kreyling WG, Nickel C, Riediker M, Stone V. 2010.

Minimal analytical characterization of engineered nanomaterials needed for hazard assessment in biological matrices. Nanotoxicology [EPub ahead of print in 2010 doi: 10.3109/17435391003775266)"

16. Lines 130-132: There is also human data from Diesel and concentrated air pollution particulate studies by Nick Mills and Ken Donaldsons group that supports this further.
17. Lines 138-143: replace with "No epidemiology studies have been published to date, but the current understanding of the mechanism of biological activity of CNTs based on the experimental animal studies suggests that the most appropriate health end-points for risk assessment of CNTs currently in commerce are pulmonary inflammation and fibrosis [18, 19]. As a result, most operating occupational exposure limits for CNT are based on mass metrics, which were shown in the animal studies to be associated with these lung responses. In addition, studies in animals [Poland et al. 2008; Murphy et al. 2011] and cell systems [Sargent et al. 2009] have suggested the potential for CNTs to be carcionogenic, which suggests that fiber number concentration [2] may be a more appropriate exposure metric based on the "long-fiber" paradigm of toxicity [Donaldson et al. 2010]." Refs: Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A [2008]. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathology in a pilot study. Nat Nanotechnol *3*:423-428; Murphy FA, Poland CA, Duffin R, Al-Jamal KT, Ali-Boucetta H, Nunes A, Byrne F, Prina-Mello A, Volkov Y, Li S, Mather SJ, Bianco A, Prato M, MacNee W, Wallace WA, Kostarelos K, Donaldson K [2011]. Length-Dependent Retention of Carbon Nanotubes in the Pleural Space of Mice Initiates Sustained Inflammation and Progressive Fibrosis on the Parietal Pleura. Cardiovascular, Pulmonary, and Renal Pathology 178(6):2587-2600; Sargent LM, Shvedova AA, Hubbs AF, Salisbury JL, Benkovic SA, Kashon ML, Lowry DT, Murray AR, Kisin ER, Friend S, McKinstry KT, Battelli L, Reynolds SH [2009]. Induction of aneuploidy by single-walled carbon nanotubes. Environ Mol Mutagen 50 (8):708-717; Donaldson K, Murphy FA, Duffin R, Poland C [2010]. Asbestos, carbon nanotubes, and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura inflammation and mesothelioma. Part Fibre Toxicol 7:1-17.
18. Lines 139-143: I'm not sure I understand this paragraph. A majority of the literature on CNT toxicology has not addressed whether CNT induce toxicology and pathology associated with pathogenic fibres (the Fibre Paradigm). However, the studies which have addressed this question do show that CNT that are long, relatively straight and more easily dispersed induce mesothelial responses (proliferation, fibrosis and inflammation) that are indicative of fibre-induced responses. Poland et al., Murphy et al. This is backed up by an in vitro study which shows that long CNT induce frustrated phagocytosis and pro-inflammatory signaling in macrophages Brown et al. In comparison entangled CNT did not induce any of the in vivo or in vitro responses described above.
19. Line 143: add a new sentence: "However, standard method of assessing workers exposure to airborne particles involved measuring mass concentration of health

related fraction of particle in the breathing zone and their chemical composition except for fibres where the number concentration is determined by microscopy.”

20. Line 160: insert “ROS-formation capacity can also be measured [Sauvain JJ, Deslarzes S, Riediker M. Nanoparticle reactivity toward dithiothreitol. Nanotox 2008; 81(3):273-284. e-published ahead of print on: 25 July 2008.] This ROS-forming capacity (or the consequences of the oxidative damage) may be linked to the functional surface groups: Setyan A, Sauvain JJ, Guillemin M, Riediker M, Demirdjian B, Rossi MJ. Probing functional groups at the gas-aerosol interface using heterogeneous titration reactions: a tool for predicting aerosol health effects? Chemphyschem, 2010; 11(18): 3823-3835.”
21. Lines 164-170: replace with “NIOSH recommended exposure limits (RELs) for titanium dioxide [NIOSH 2011] and draft REL for carbon nanotubes and nanofibers [38] are some of the few examples. The vast heterogeneity of nanomaterials limits the number of specific OELs that are likely to be developed in the near future. Thus, there is a need to develop a risk assessment prioritization strategy [Wolfgang 2004; EU 2004], as well as methods for utilizing the best available data. For example, interim OELs could be developed more expeditiously by a tiered risk assessment process, depending on the amount of data available, including comparative potency analyses using dose-response data from animal studies of specific nanoparticles within categories of nanomaterials with similar properties and modes of action [Kuempel et al. 2007; 2]. Examples of various approaches used in developing interim OELs from various organizations for some nanomaterials can be found in Ref [2].” Refs: NIOSH [2011]. Current Intelligence Bulletin 63. Occupational Exposure To Titanium Dioxide. Department Of Health And Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2011–160; Wolfgang L, editor [2004]. Industrial Application of Nanomaterials – Chances and Risks. VDI Technologiezentrum, Dusseldorf, Germany; Kuempel ED, Geraci CL, Schulte PA [2007]. Risk assessment approaches and research needs for nanomaterials: An examination of data and information from current studies. In: Simeonova PP, Opopol N, Luster MI, eds. Proceedings of the NATO Advanced Research Workshop on Nanotechnology – Toxicological Issues and Environmental Safety, in Varna, Bulgaria, 12-17 August 2006. The Netherlands: Springer.
22. Lines 172-173: We may need to group nanomaterials as there are too many individual specific nanomaterials to consider.
23. Line 174: Additional question: How can the hazard information effectively be communicated along the supply chain? Do MSDS provide valuable information? If no, how can the quality of MSDS be improved?
24. Line 174: insert “This is a good question, as it implies that nanomaterials can be classed into different hazard categories. Of course, the big issue remains: Which criteria to apply.”
25. Line 176: insert “There is tons of information and recommendations in the above mentioned NanEx study.”
26. Line 184, “amount of time they remain airborne”: Better: “…, which may significantly influence their dusting behaviour …”

27. Line 185, “seems likely that particle size”: The deposition rate of particulates inhaled into the human lung is clearly depending on the particle size.
28. Line 193: replace “very few” with “some”
29. Line 193, “few workplace measurements”: A review article commissioned by VCI on exposure measurement/assessment will be published shortly. 250 references have been identified, but only about 25 are considered as being highly relevant accordingly.
30. Lines 194-198: It would be useful to include a brief summary of the best studies of nanomaterials exposures in the workplace. This is a bit misleading since each of these exposure metrics is defined, and instruments are available to measure each of these. Issues include limit of detection and whether the metric selected is the best predictor of hazard. Also, these metrics are correlated, and may be inter-convertible. ISO [39] (and Maynard) have recommended collecting data using each of these metrics until the best dose metric is resolved for a given nanomaterial.
31. Line 206: add “..[2], although the scientific literature on the biological modes of action for other types of particles (including the nanoscale “ultrafine” particles) and fibers provides useful preliminary data of relevant metrics to monitor and control exposures to nanomaterials.”
32. Line 208-209: replace sentence with “ISO [39] has developed exposure measurement strategies for nanoaerosols in the workplace, which include options for measuring p metrics including mass, number, and surface area concentrations. The ISO guidance includes a list of occupational sources of nanoaerosols, considerations before and during sampling, and “readily available instruments and techniques” for nanoaerosol exposure monitoring. The document concludes that despite limitations in each of the available measurement methods, it is currently feasible to: (1) identify the sources of nanoparticle emissions and (2) estimate the size-selective mass, particle number, or surface area concentration of collected samples. In addition, some characterization of nanoparticles is possible. ISO [39] notes that field observations are essential to link the exposure monitoring results to the workplace conditions in order to better identify and control potential exposures to workers.”
33. Line 207: List of papers – Workplace measurements:

- Song, Y., Li, X., and Du, X. (2009). Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma. European Respiratory Journal 34, 559-567.
- Phillips, J. I., Green, F. Y., Davies, J. C. A., and Murray, J. (2010). Pulmonary and systemic toxicity following exposure to nickel nanoparticles. American Journal of Industrial Medicine 53, 763-767.
- Methner MM, Birch ME, Evans DE, Ku BK, Crouch K and Hoover MD, Identification and characterization of potential sources of worker exposure to carbon nanofibers during polymer composite laboratory operations, J Occup Environ Hyg, 4(12), D125-130, 2007.
- Han, J. H., Lee, E. J., Lee, J. H., So, K. P., Lee, Y. H., Bae, G. N., Lee, S. B., Ji, J. H., Cho, M. H., and Yu, I. J. (2008). Monitoring multiwalled carbon nanotube exposure in carbon nanotube research facility. *Inhal Toxicol* **20,** 741-9.

- Bello, D., Wardle, B., Yamamoto, N., Guzman deVilloria, R., Garcia, E., Hart, A., Ahn, K., Ellenbecker, M., and Hallock, M. (2009). Exposure to nanoscale particles and fibers during machining of hybrid advanced composites containing carbon nanotubes. *Journal of Nanoparticle Research* **11** 231-249.
- Bello, D., Hart, A. J., Ahn, K., Hallock, M., Yamamoto, N., Garcia, E. J., Ellenbecker, M. J., and Wardle, B. L. (2008). Particle exposure levels during CVD growth and subsequent handling of vertically-aligned carbon nanotube films. *Carbon* **46,** 974-977.
- Fujitani, Y., Kobayashi, T., Arashidani, K., Kunugita, N., and Suemura, K. (2008). Measurement of the physical properties of aerosols in a fullerene factory for inhalation exposure assessment. *J Occup Environ Hyg* **5,** 380-9.
- Yeganeh, B., Kull, C. M., Hull, M. S., and Marr, L. C. (2008). Characterization of airborne particles during production of carbonaceous nanomaterials. *Environ Sci Technol* **42,** 4600-6.
- Tsai, S.-J., Ada, E., Isaacs, J., and Ellenbecker, M. (2009). Airborne nanoparticle exposures associated with the manual handling of nanoalumina and nanosilver in fume hoods. *Journal of Nanoparticle Research* **11** 147-161.
- Methner, M. M. (2008). Engineering case reports. Effectiveness of local exhaust ventilation (lev) in controlling engineered nanomaterial emissions during reactor cleanout operations. *J Occup Environ Hyg* **5,** D63-9.
- Demou, E., Peter, P., and Hellweg, S. (2008). Exposure to manufactured nanostructured particles in an industrial pilot plant. *Ann Occup Hyg* **52,** 695-706.
- Bello, D., Wardle, B. L., Yamamoto, N., deVilloria, R. G., Garcia, E. J., Hart, A. J., Ahn, K., Ellenbecker, M. J., and Hallock, M. (2009). Exposure to nanoscale particles and fibers during machining of hybrid advanced composites containing carbon nanotubes. Journal of Nanoparticle Research 11, 231-249.
- Demou, E., Stark, W. J., and Hellweg, S. (2009). Particle emission and exposure during nanoparticle synthesis in research laboratories. Annals of Occupational Hygiene 53, 829-838.
- Fujitani, Y., and Kobayashi, T. (2008). Measurement of aerosols in engineered nanomaterials factories for risk assessment. Nano 3, 245-249.
- Liao, C. M., Chiang, Y. H., and Chio, C. P. (2009). Assessing the airborne titanium dioxide nanoparticle-related exposure hazard at workplace. Journal of Hazardous Materials 162, 57-65.
- Park, J., Kwak, B. K., Bae, E., Lee, J., Kim, Y., Choi, K., and Yi, J. (2009). Characterization of exposure to silver nanoparticles in a manufacturing facility. Journal of Nanoparticle Research 11, 1705-1712.
- Plitzko, S. (2009). Workplace exposure to engineered nanoparticles. Inhalation Toxicology 21, 25-29.
- Robichaud, C. O., Uyar, A. E., Darby, M. R., Zucker, L. G., and Wiesner, M. R. (2009). Estimates of upper bounds and trends in nano-tio2 production as a basis for exposure assessment. Environmental Science & Technology 43, 4227-4233.
- Tsai, S. J., Ada, E., Isaacs, J. A., and Ellenbecker, M. J. (2009). Airborne nanoparticle exposures associated with the manual handling of nanoalumina and nanosilver in fume hoods. Journal of Nanoparticle Research 11, 147-161.

- Tsai, S. J., Ashter, A., Ada, E., Mead, J. L., Barry, C. F., and Ellenbecker, M. J. (2008). Control of airborne nanoparticles release during compounding of polymer nanocomposites. Nano 3, 301-309.
- Tsai, S. J., Hofmann, M., Hallock, M., Ada, E., Kong, J., and Ellenbecker, M. (2009). Characterization and evaluation of nanoparticle release during the synthesis of single-walled and multiwalled carbon nanotubes by chemical vapor deposition. Environmental Science & Technology 43, 6017-6023.
- Bello, D., Wardle, B. L., Zhang, J., Yamamoto, N., Santeufemio, C., Hallock, M., and Virji, M. A. (2010). Characterization of exposures to nanoscale particles and fibers during solid core drilling of hybrid carbon nanotube advanced composites. International Journal of Occupational and Environmental Health 16, 434-450.
- Evans, D. E., Ku, B. K., Birch, M. E., and Dunn, K. H. (2010). Aerosol monitoring during carbon nanofiber production: Mobile direct-reading sampling. Annals of Occupational Hygiene 54, 514-531.
- Gohler, D., Stintz, M., Hillemann, L., and Vorbau, M. (2010). Characterization of nanoparticle release from surface coatings by the simulation of a sanding process. Annals of Occupational Hygiene 54, 615-624.
- Huang, C. H., Tai, C. Y., Huang, C. Y., Tsai, C. J., Chen, C. W., Chang, C. P., and Shih, T. S. (2010). Measurements of respirable dust and nanoparticle concentrations in a titanium dioxide pigment production factory. Journal of Environmental Science and Health Part a-Toxic/Hazardous Substances & Environmental Engineering 45, 1227-1233.
- Jankovic, J. T., Hollenbeck, S. M., and Zontek, T. L. (2010). Ambient air sampling during quantum-dot spray deposition. International Journal of Occupational and Environmental Health 16, 388-398.
- Johnson, D. R., Methner, M. M., Kennedy, A. J., and Steevens, J. A. (2010). Potential for occupational exposure to engineered carbon-based nanomaterials in environmental laboratory studies. Environmental Health Perspectives 118, 49-54.
- Lee, J. H., Lee, S. B., Bae, G. N., Jeon, K. S., Yoon, J. U., Ji, J. H., Sung, J. H., Lee, B. G., Lee, J. H., Yang, J. S., Kim, H. Y., Kang, C. S., and Yu, I. J. (2010). Exposure assessment of carbon nanotube manufacturing workplaces. Inhalation Toxicology 22, 369-381.
- Methner, M., Hodson, L., Dames, A., and Geraci, C. (2010). Nanoparticle emission assessment technique (neat) for the identification and measurement of potential inhalation exposure to engineered nanomaterials-part b: Results from 12 field studies. Journal of Occupational and Environmental Hygiene 7, 163-176.
- Methner, M. M. (2010). Effectiveness of a custom-fitted flange and local exhaust ventilation (LEV) system in controlling the release of nanoscale metal oxide particulates during reactor cleanout operations. International Journal of Occupational and Environmental Health 16, 475-487.
- Sahu, M., and Biswas, P. (2010). Size distributions of aerosols in an indoor environment with engineered nanoparticle synthesis reactors operating under different scenarios. Journal of Nanoparticle Research 12, 1055-1064.
- Tsai, S. J., Huang, R. F., and Ellenbecker, M. J. (2010). Airborne nanoparticle exposures while using constant-flow, constant-velocity, and air-curtain-isolated fume hoods. Annals of Occupational Hygiene 54, 78-87.

- Wang, Y. F., Tsai, P. J., Chen, C. W., Chen, D. R., and Hsu, D. J. (2010). Using a modified electrical aerosol detector to predict nanoparticle exposures to different regions of the respiratory tract for workers in a carbon black manufacturing industry. Environmental Science & Technology 44, 6767-6774."

    And additional sentence: "There is also a lack of portable and personal instruments."

34. Line 219: insert a new sentence as follows: "Samples can also be collected directly onto transmission electron microscopy grids with a thin carbon film for direct TEM analysis. Samples are collected using thermal or electrostatic precipitation methods."
35. Line 221: add at the end ", and there remains a paucity of data on workers' personal exposures"
36. Line 231: insert a new paragraph as follows: "Other measurement strategies published include:

- BSI guidance - Guide to assessing airborne exposure in occupational settings relevant to nanomaterials 6699 (2010).
- BASF tiered approach - BASF's tiered type approach to an exposure assessment of nanoscale aerosols in the workplace (2010).
- Brouwer D et al. From workplace exposure air measurement results toward estimates of exposure? Development of a strategy to assess exposure to manufactured nano-objects. Journal of Nanoparticle research 11, 1867-1881 (2009)."

37. Line 251, "effectively controlled": What are the criteria for evaluating effectiveness of controls? This is a key issue and topic for t his paper – the need to develop hazard and risk framework to evaluate whether exposures are being effectively controlled.
38. Lines 261-262: Expand paragraph. Surely these lists are of some value?
39. Lines 264-265: I think that there are many processes to consider and so we may need to prioritise on the basis of either tonnage of nanomaterial produced, potential for toxicity or on the basis of procedures that are considered to result in the highest exposures.
40. Lines 267-268: Not necessarily true. The common respirable cyclone and other instruments can provide some indication about whether exposures are occurring above background. Also, there is lot of effort in developing low cost, portable nanoparticle monitoring devices. This topic may deserve a small subgroup to explore the utility of what is currently available.
41. Line 273: Add a section on exposure modeling Schneider et al, 2011) (see end of document), in line with the QSAR approach in hazard assessment. As workplace air measurements of manufactured nanoparticles are relatively expensive to conduct, models can be helpful for a first tier assessment of exposure. A conceptual model was developed to give a framework for such models. The basis for the model is an analysis of the fate and underlying mechanisms of nanoparticles emitted by a source during transport to a receptor. Four source domains are distinguished; that is, production, handling of bulk product, dispersion of ready-to-use nanoproducts, fracturing and abrasion of end products.
42. Lines 274-275: change this question as follows: "*How can exposures in varying scales of industrial operation best be assessed in a tiered approach?*"

This conceptual exposure model was used as starting point for exposure banding and converted into an online tool called Stoffenmanager Nano (http://nano.stoffenmanager.nl), tested and reviewed by a number of companies. During the development of the Stoffenmanager Nano tool, the precautionary principle was applied to deal with the uncertainty regarding hazard and exposure assesment of Manufactured Nano Objects. Reference: Stoffenmanager Nano version 1.0: a web-based tool for risk prioritization of airborne manufactured nano objects. Birgit van Duuren-Stuurman, Stefan R Vink, Koen J M Verbist, G A Henri Heussen, Derk H Brouwer, Dinant E D Kroese, Maikel F J van Niftrik, Erik L J P Tielemans, Wouter Fransma. Ann.Occup. Hygiene (accepted for publication)

43. Line 276: Other issues:

- Instruments can have different parameters set-up (e.g. bin size), can cover different range of sizes and can measure different type of size (e.g. mobility diameter vs aerodynamic diameter or geometric surface area vs active surface area).
- How can data from real-time instruments be interpreted?
- Which statistical tools should be used to interpret data from real-time measurements?
- How can instruments be calibrated for the measurement of nanoparticles? What are the performance and limitation of real-time instruments and characterization methods?

44. Line 291: add "Such findings identify populations for focused risk communication and risk mitigation guidance."
45. Line 305, "known methods to decrease toxicity": Could you give an example?
46. Lines 316-317: Again we may need to divide nanomaterials into groups and prioritize as to answer this question for very nanomaterial and every exposure scenario would be enormous.
47. Lines 319-320: Why not now? Based on previous paragraph, it sounds like this information is already available.
48. Lines 325: insert "We, a group of French speaking specialists, proposed last year in a anses report (corresponding peer-review publication in review) a Control Banding (CB) approach that is based on only a few fundamental physico-chemical properties of the nanomaterials occurring in companies. It accounts for the presence of already existing hazard and exposure data. It is flexible and thus allows to integrate newly generated (toxicity and exposure) data. The CB approach has three steps: 1) Analyse hazard and exposure information, attribute control bands and define an action plan. 2) Implement: Set up the control measures and start the routines as defined in the action plan. 3) Check and correct: regularly monitor workplaces, review knowledge and control measures. Correct the control bands or action plan when needed. Reference for this (experts in alphabetical order followed by anses staff): *Ostiguy C, Riediker M, Triolet J, Troisfontaines P, Vernez D,* Bourdel G, Thieriet N, Daguet I, Cadene A, Lassus M. Development of a specific Control Banding Tool for Nanomaterials. Request N°2008-SA-0407 relating to Control Banding, Report of Expert Committee (CES) on Physical Agents. Anses, French Agency for Food, Environmental and Occupational Health & Safety. Maisons-Alfort Cedex – France. December 2010."
49. Lines 328-331: change sentence as follows "The WHO guidelines for protecting workers health from potential risks of nanomaterials can provide a range of

options for occupational risk management of nanomaterials starting from semi-qualitative (such as Control Banding), quantitative models and finishing with traditional quantitative (such as those built around Occupational Exposure Limits) approaches."

50. Lines 336-357: Note: These added topic areas for each question suggest some possible regrouping of questions, and also identify which steps of the risk assessment process may have the greatest data needs.