

Commentary

Harmonization of Measurement Strategies for Exposure to Manufactured Nano-Objects; Report of a Workshop

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The present paper summarizes the outcome of the discussions at the First International Scientific Workshop on Harmonization of Strategies to Measure and Analyze Exposure to (Manufactured) Nano-objects in Workplace Air that was organized and hosted by the Netherlands Organization for Applied Scientific Research (TNO) and the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) (Zeist, The Netherlands, December 2010). It reflects the discussions by 25 international participants in the area of occupational (nano) exposure assessment from Europe, USA, Japan, and Korea on nano-specific issues related to the three identified topics: (i) measurement strategies; (ii) analyzing, evaluating, and reporting of exposure data; and (iii) core information for (exposure) data storage. Preliminary recommendations were achieved with respect to (i) a multimetric approach to exposure assessment, a minimal set of data to be collected, and basic data analysis and reporting as well as (ii) a minimum set of contextual information to be collected and reported. Other issues that have been identified and are of great interest include (i) the need for guidance on statistical approaches to analyze time-series data and on electron microscopy analysis and its reporting and (ii) the need for and possible structure of a (joint) database to store and merge data. To make progress in the process of harmonization, it was concluded that achieving agreement among researchers on the preliminary recommendations of the workshop is urgent.

Keywords: core information; database; exposure; harmonization; nanoparticles; strategy

INTRODUCTION

The number of workplace air measurement studies focused on the assessment of exposure to manufactured nano-objects (MNOs) [International Organization for

Standardization (ISO, 2008)] has increased substantially in the last few years (Brouwer, 2010; Woskie *et al.*, 2010). However, due to the diversity of exposure situations with respect to the life cycle of nanomaterials and the rate at which new technology and nanomaterials are introduced into the market, comprehensive characterization of exposure will remain a challenge in the near future. Therefore, it is

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acknowledged that data that will be generated in the future should be compatible with its multipurpose use for exposure scenario building, exposure modeling, or meta-analysis for risk assessment or epidemiology. Key conditions for such intended uses include harmonization of data collection, data analysis and reporting, and data storage.

Within the European Union Framework Program project ‘Nano Impact Net’, two initial workshops were organized (Bilthoven, The Netherlands, October 2009; Dublin, Ireland, September 2010) to discuss issues related to measurement strategy and sampling of manufactured nanoparticles for imaging analysis. The Netherlands Organization for Applied Scientific Research (TNO) and the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) elaborated on the results of the discussions and organized and hosted (Zeist, The Netherlands, December 2010) under the Partnership for European Research in Occupational Safety and Health (PEROSH) umbrella, the First International Scientific Workshop on Harmonization of Strategies to Measure and Analyze Exposure to (Manufactured) Nano-objects in Workplace Air. This workshop was considered the first in a series of harmonization workshops and organized in collaboration with University of Massachusetts, Lowell, and aligned with the US National Institute for Occupational Safety and Health (NIOSH) and Nano Impact Net initiatives and aimed to discuss state-of-the-art approaches on:

1. nano-specific features of measurement strategies (Measurement strategy),
2. analyzing, evaluating, and reporting of exposure data (Analyzing, evaluating, and reporting of exposure data), and
3. core information for (exposure) data storage (Core information for (exposure) data storage and pooling).

This paper summarizes the workshop participants’ reflections of the nano-specific issues related to the three identified topics and provides some preliminary recommendations for conducting and reporting nano exposure studies.

WORKSHOP ACHIEVEMENTS

About 25 key players in the area of occupational (nano) exposure assessment from Europe, USA, Japan, and Korea (Table 1) discussed the ‘nano-specific’ issues related to the topics guided by three position papers (The position papers can be downloaded from www.tno.nl/) that were prepared and

Table 1. List of workshop participants

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circulated among the participants prior to the workshop. The position papers described the state of the art and the challenges that are faced when developing harmonized strategies to measure and analyze workplace nanomaterial exposure. The results from the discussion for each of the three topics are described below.

Measurement strategy

In general, a measurement strategy can be described as a framework for the selection of relevant considerations associated with a measurement campaign (e.g. what substance will be measured, at which location, when, for how long, how many individuals to sample, how many samples per individual to collect, and by what methods, in particular, what exposure metrics will be measured). The objectives of a particular measurement campaign can vary broadly and may include exposure exploration and characterizations, risk assessment, epidemiology, exposure control measures and their effectiveness, and compliance with any occupational exposure limit or benchmark level. The actual measurement strategy should be designed to be consistent with the study objectives. For example, exposure characterization attempts to identify exposure pathways (transport processes of the contaminant from source to receptor). Exposure assessments primarily focus on the individual worker such as personal breathing zone samples collected over a full work shift for use

in compliance assessment, epidemiologic studies, or risk management. By contrast, exposure control studies focus on the efficacy of a control device. Therefore, there is a need to evaluate the impact of the measurement objectives on the various measurement considerations and to harmonize the strategy with respect to the various measurement objectives as much as possible.

Task-based static exposure assessment versus full-shift (personal) exposure assessment. This issue is not unique to 'nano' since in general, the rationale for task-based exposure assessment is that it allows for the evaluation of the contribution of specific tasks to overall exposure and thus helps focus control efforts on the major source/task contributions (Smith *et al.*, 1997; Ramachandran, 2008). The lack of easy-to-use portable devices and the often short duration of relevant 'nano' activities, combined with the topics addressed above, all promote the use of static sampling of specific tasks or for the entire shift where emission of MNO is likely. In case of full-shift sampling, source apportioning (i.e. contribution of other sources) is a key factor so that observational information and reporting contextual information are crucial. Task-based as well as shift-based approaches are useful and will generate data on real-time, shift-based, task-based, and peak concentrations. The most suitable approach will depend on the goal, activity, duration of the activity, and whether personal sampling can be conducted on the worker. For non-MNO's compliance, measurements would require personal full-shift samples since most occupational exposure limits are based on 8-h time-weighted average (TWA) concentrations. The (few) recommended exposure limits for specific MNOs', e.g. carbon nanotubes and titanium dioxide, proposed by NIOSH, are also 8-h TWA concentrations (NIOSH, 2010, 2011). For modeling purposes, however, task-based measurements are needed. Sampling emphasis should be on task exposures where samples are collected through the length of a task. In addition, auxiliary data and concurrent information should be collected on the amount of time (or estimates of the range of time) spent doing the task daily, so that daily exposures can be estimated. A common time base (e.g. 5 or 15 min) may also be defined or set as a convention for short-time task-based measurements (Nicas and Spear, 1993a, b). It was acknowledged that the definition of 'task' is very important and contextual information should be collected as well on task-based level. Observations and contextual information are necessary in defining the task and explaining variations in exposure levels within- and between-tasks (Virji *et al.*, 2009).

Tiered approach. Tiered-type approaches strategies are pragmatic decision schemes where in each successive tier information is collected at a more detailed level. After each tier, a decision can be taken either to stop further collection or to continue. The use of a tiered approach will likely be different for researchers and occupational hygiene (OH) practitioners. Presently, there are several proposed measurement strategies for MNO including the nanoparticle emission assessment technique (Methner *et al.*, 2010), the approach proposed by the British Standard Institution (BSI) (BSI, 2010), and the German Chemical Association (VCI) (Reuter *et al.*, 2011). All three suggest a tiered approach, starting with a relatively simple and limited set of measurements and/or gathering basic information on processes and jobs in a first tier followed by extended assessment in subsequent tiers. In general, a tiered approach is consistent with modern industrial hygiene practice. The decision criteria to enter the next tier are key factors for such approaches. Each tier will use different devices and will generate different degree of detail and specificity of data. Evaluation of the data may lead to revisit a certain percentage of the companies for the next tier assessment. Benchmarking of lower tier metrology (e.g. easy-to-use direct reading and offline analyses) and higher tier instrumentation are necessary.

Some of the unique characteristics of MNO that might affect the measurement strategy and the analysis of the generated data were discussed.

Particle size. It is acknowledged that particle size distribution is important to indicate the efficacy of particle intake into the respiratory tract and the location of particle deposition. In addition, particle size distribution of the number concentration can also be used to calculate other (health-relevant) metrics like surface area of the particles assuming smooth, compact spherical particles; however, errors in surface area estimates arise when the assumptions are not valid. Nano-sized aerosols are a subfraction of the respirable exposure as defined by the conventions on health-relevant size fractions. Currently, only a few (static or portable) time-integrated or real-time sampling devices can provide particle size-resolved measurements. In addition, primary MNO aerosols tend to coagulate, either homogeneously in case of relatively high concentrations ($>10^6$ p cm⁻³) or heterogeneously in case of low concentrations and relatively high 'background' aerosol concentrations (Schneider *et al.*, 2011). Subsequent to inhalation, fractioning or de-agglomeration may occur in body fluids; hence, the actual cut-off for 'nano-relevant' (aerosol) sizes has not been agreed up on. A harmonized

approach is needed to pool size-fractionated exposure data. Size-fractionated data measured with more sophisticated instrumentation should be summarized into size ranges compatible with those from less sophisticated instrumentation to broaden the pool of available data.

Metric. Since the toxicological significances of the various exposure metrics such as mass, particle number, surface area concentrations, and particle size (distribution) are not fully understood, it is agreed that a single exposure metric will generally not be sufficient to adequately characterize and quantify MNO aerosol exposure for all types of MNOs and all sampling objectives. In addition, the lack of specificity of the direct reading instruments and potential issues with loading and sensitivity of the analytical methods combined with the varying physical, chemical, and physicochemical properties of MNO preclude the idea of a single exposure metric. Even for non-MNOs, mass concentration has limited sensitivity in the case of gravimetric analysis and for short-time frames, therefore, it is useful to measure the chemical mass of MNO or MNO components, using 'wet chemistry' analytical techniques. Direct measurement of the surface area concentration, e.g. by using diffusion charging-based devices, is not always feasible or possible as in the case of fibers, highly porous (core-shell) nanoparticles, and highly irregular morphologies. Therefore, it seems that exposure is best characterized by multiple exposure characteristics (physical, chemical, and physicochemical characteristics and workplace factors) and thus should be described by a minimum set of metrics/information (e.g. direct monitoring results, additional offline analysis results, and observa-

tions) (Table 2). However, in some limited instances such as for implementing and intervention-based testing of the efficacy of control measures, one metric (e.g. particle number concentration) might be sufficient.

Distinction of MNO particles from background aerosols. Background nano aerosols from natural and incidental sources are ubiquitous and present major challenges for online characterization of MNO. Presently, the use of real-time instruments to characterize MNOs is greatly affected by lack of specificity for MNO. Adequate characterization of exposures to aerosols of manufactured nanomaterials cannot be accomplished without successfully distinguishing them from background aerosols, i.e. ambient particles and ultra-fine particles from sources in or outside the workplace. This often requires the use of a combination of several techniques, e.g. time-integrated sampling and offline analysis, and thoughtful consideration in the design of the sampling campaign and background aerosol characterization.

Background distinction is achieved by either by relatively simple approaches (by comparing near-field to far-field or before task to after task) measurements (Brouwer *et al.*, 2009) or by more comprehensive approaches such as calculation using an intrusion factor (Kuhlbusch *et al.*, in preparation). All approaches have drawbacks and it was concluded that not just one approach may suit all exposure scenarios. The most suitable approach will depend on the measurement objectives, the time frame of the measurements (e.g. activity-based or full-shift), availability of devices, and the actual situation (e.g. ventilation, other incidental sources of nanomaterial, etc.). It is unclear whether background

Table 2. Preliminary recommendations for measurement and data analysis

Topic	Preliminary recommendation
'Minimum' dataset	<ol style="list-style-type: none"> 1. Statistically representative number concentration, and particle size distribution OR particle number concentration with information about surface area OR particle number concentration for at least two size bins (<100 and > 100 nm) 2. A (qualitative) morphologic and element identification of the MNO 3. 'Wet' mass concentration of respirable fraction (if applicable)
Type	<ol style="list-style-type: none"> 1. Real-time task-based and peak measurements + time/task registration OR 2. Real-time measurements averaged over a shift (repeated sampling is to be encouraged.)
Background distinction	<p>The approach for background aerosol distinction should be clearly described and documented.</p> <p>Describe the presence of other sources of NPs, e.g. compressors, fork lifts, etc.</p> <p>Contrasting of statistically representative size distributions of background and process is encouraged.</p>
Data processing/analysis	<ol style="list-style-type: none"> 1. Check if data are (log)-normally distributed. 2. Look at (partial) autocorrelation and stationarity (e.g. autoregressive integrated moving average) 3. Calculate AM/GM and (G)SD and other summary statistics, e.g. 95% confidence interval, highest value, etc. using appropriate methods.

measurements should be subtracted from the task measurements or reported separately. Any subtraction would likely occur after a summary measure was calculated. Since the summary measures will usually be geometric means (GMs), this makes simple subtraction inadvisable. Background measurements can be collected simultaneously (from accepted location) and the background exposure time series can then be overlaid with MNO measurements time series for interpretation; however, simultaneous measurements may not be feasible due to instrumentation limitations. It was stated that instead of trying to get agreement among all the participants, the approaches used to characterize background should be clearly described and documented. The need to address the levels and composition of background exposure was also discussed as it may relate to long-term health effects. In some cases, the target organs/health effect mechanisms and the potency of the background particles may be similar to the health effects due to exposure to MNO, whereas in other cases, these may be different.

Analyzing, evaluating, and reporting of exposure data

Since measurements strategies for the assessment of exposure to MNO put emphasis on task-based evaluation of (size-resolved) aerosol concentrations, appropriate analysis of the results obtained from real-time instrumentation is a key factor. In addition, benchmarking of the performance of instruments is important since a gold standard is lacking. Appropriate statistical techniques were identified and their use discussed. Currently, details on the offline methods used to characterize integrated samples (e.g. according to morphology or elemental composition) are often lacking. Consistency in reporting of this type of information is recommended.

Time series. Real-time instrumentation used to monitor workplaces for nanomaterial aerosol concentrations have averaging times ranging from 1 s to 3 min. They generate a sequence of measurements over time (i.e. time-series data that are shown to have high autocorrelation). An average concentration for a full shift or a portion of the shift associated with a task can be obtained from a time series of real-time measurements by calculating a TWA over the duration of interest. However, it has been known that statistical methods for summarizing data that do not account for the autocorrelation structure can lead to erroneous conclusions for hypothesis testing or regression modeling as the standard errors are not appropriately computed. A time-series analysis meth-

od such as the autoregressive integrated moving average procedure in statistical packages [e.g. SAS and the free statistical environment R (R Development Core Team, 2011)] can be used to summarize or model time-series data. A foundation for the statistical analysis of such data can be found in Box and Jenkins (1970), and several examples of its application in the field of air pollution exist (e.g. Houseman *et al.*, 2002; deCastro *et al.*, 2008). When a simple autocorrelation structure is identified (e.g. first order autoregressive) and the data are deemed stationary, summary statistics including the arithmetic mean (AM) and GM and (geometric) standard deviation [(G)SD] may be calculated from linear mixed models specifying the appropriate correlation structure (Bello *et al.*, 2010). However, caution should be exercised as time-series data from a full shift are often non-stationary and the autocorrelation structure may be complex requiring expert statistical guidance. Conversely, it was recognized that the advanced statistical methods might be out of the scope of an OH practitioner, thus guidance should be developed for data analysis. Consultation with a statistician is necessary to develop guidance on methods for the different research and OH practice objectives.

Summary statistics. Although the GM and GSD are the most commonly used summary statistics, reflective of the dominance of right-skewed (lognormal) distributions, other summary metrics such as the AM or peak exposure may be relevant for different disease mechanisms (Smith and Kriebel, 2010). A wealth of information exists in the real-time data including peak exposures and patterns of exposure. Limited understanding of a biological basis for peak definition is problematic, but attempts should be made to extract more information from the real-time data. For example, exposure over a task, an agreed time-basis (see above), or shift can be evaluated and percentiles (e.g. 95th percentile) of the real-time distributions can be extracted.

Instrument comparisons. A research-driven need is intra- and inter-instrument comparison to assess agreement among instruments or calibrate one instrument to a 'gold standard'. A number of factors may affect the experimental set-up and data analysis to evaluate instrument agreement including the size ranges, averaging times, principles of operation, etc., of the instruments being compared; however, this discussion is limited to the appropriate statistical analysis for instrument comparison. Traditionally, the Pearson correlation coefficient or paired *t*-test has been used to assess agreement, neither of which adequately measure absolute agreement (White and van den Broek, 2004). The former only measures the

degree of association (precision), while the latter only measures the average difference (bias). Thus, a combination of approaches is needed to fully assess the desired agreement characteristics.

The concordance correlation coefficient (CCC) is an aggregate measure of agreement commonly used in the clinical sciences to compare instruments or methods (Lin *et al.*, 2002). The CCC can be calculated via the method of variance components (using linear mixed models) which allow for the incorporation of covariates that may affect the degree of agreement, as well as account for repeated measurements or longitudinal data (Carrasco *et al.*, 2009).

Integrated samples. Currently, there is no consistency in reporting of information from integrated samples of MNO analyzed by transmission electron microscopy (TEM) on morphology, shape, size, and energy-dispersive X-ray analysis. The characterization of MNO by electron microscopy (EM) is hampered by a lack of a counting convention; thus, EM and elemental analysis quantification in terms of numbers of (identified) MNO, magnification, numbers of fields addressed, counting method, etc., are subjective (operator dependent) and based on fragmented observation (only a portion of the sample is analyzed) rather than an objective quantification. Even with agreed upon counting rules, quantitative TEM analysis is very time consuming and therefore expensive and not suitable for routine analysis. The principle of operation for TEM (which measures physical size and can be traced to a primary standard) and a real-time device measuring particle size distribution (e.g. Scanning Mobility Particle Sizers) differ and therefore will not likely provide the ‘same’ size measurements.

Current development of samplers that enable homogeneous deposition of aerosols on a substrate will most probably be an important step toward quantification by EM (Azong-Wara *et al.*, 2009). Since size resolution during chemical analysis is not feasible, size fractionation will have to be on physical separation during sample collection [e.g. using (low pressure) impactors].

Development of a standard protocol, counting rules, or semi-automatic routines for EM analysis should be encouraged including the use of standard reference materials for sizing and characterizing particles. A tiered approach, e.g. screening by laser scanning microscopy, or tomography TEM followed by more detailed analysis of interesting sections was suggested. Table 3 lists recommended aspects of integrated samples collected on filters or grids to be addressed and reported. It should be noted that the American Society for Testing and Materials International (ASTM) Technical Committee D22 has a work item (ASTM WK28561—New Test Method for Airborne Carbon Nano tube Concentration in Ambient and Indoor Atmospheres as Determined by TEM Direct Transfer) on the preparation of samples for EM analysis (<http://www.astm.org/DATABASE.CART/WORKITEMS/WK28561.htm>).

Quantification with respect to particle number requires counting statistics and assumptions about distributions across the whole substrate. If a homogeneous distribution of the particles can be achieved, then the selection of a section to be analyzed would be less critical. The development of personal thermal precipitators would be very helpful (Azong-Wara *et al.*, 2009). In addition to particle counting, collection efficiency also affects accuracy of quantification.

Table 3. Preliminary recommendations for reporting electron microscopy results

Topic	Preliminary recommendations
Collection devices	Report use of specialized instruments like electrostatic or thermal precipitators or (TEM grids attached to) filters Address uniformity of deposition
Collection substrate	Specify filter (coating), TEM grid size, etc.
Selection of filter/grid section for analysis and magnification	Report location and method of selection Report different magnification levels, to provide information on loading, uniformity, representativeness of images, etc. Report number of fields, number of particles per field, minimum number of particles counted per bin, selection of fields (random) Report categories of morphology (free, agglomerates, and categories of shapes)
Quality control (QC) issues for TEM grids (artifacts such as CNTs and carbonaceous material)	Analyze background grids as reference Discuss QC issues
Miscellaneous	Energy-dispersive X-ray analysis If possible, reconstruct size distribution from TEM images to confirm real time instruments (e.g. Pfefferkorn <i>et al.</i> , 2010)

Core information for (exposure) data storage and pooling

It is acknowledged that comprehensive characterization of exposure data for numerous exposure situations will remain scarce in the near future and there is a need for data pooling in view of future development, calibration or validation of exposure models, or building exposure scenarios. A database should be developed to collate a substantial amount of nano exposure data from a diversity of locations and exposure scenarios. Conditions to achieve such a database with respect to its intended use were discussed (e.g. identification of the type of information that should be collected and stored, agreement upon database structure, and data sharing rules).

Core information. In conjunction with each set of measurement data, a set of contextual core information should be systematically collected and stored in such a database. The different clusters of core information as described in Table 4 (with a much longer list of variables for each of these clusters) have been based on and are in line with the proposal for core information for the storage and exchange of workplace exposure measurements on chemical agents by Rajan *et al.* (1997) and later elaborated on by Tielemans *et al.* (2002). Such a new nano exposure database will be based on the characteristics of existing databases, e.g. the Advanced Reach Tools database (www.advancedreachtool.com) and IFA's measurement data relating to workplace exposure to hazardous substances (MEGA) exposure database (www.dguv.de/ifa/en/gestis/mega). As nano-sized materials have distinctive characteristics, additional variables have been introduced based on the NANOSH dataset (NANOSH EU-project D2.2. Re-

port of results and implications of main study to measure nanoparticle concentrations in workplaces. Available through www.tno.nl/).

Multi-purpose use of a database. A nanomaterial exposure database should ideally be multifunctional and used for exposure modeling projects, epidemiological studies, compliance testing, etc. The lessons learned from developing other databases is that sharing data between existing databases and attempting to restructure and recode (i.e. reinterpret) the measurement data are a very difficult and time-consuming effort with the potential to compromise a successful outcome. This can be prevented by collecting and storing nanomaterial exposure data in a uniform and harmonized way rather than retrospectively trying to merge datasets that are collected and stored differently. An agreed upon database structure along with a harmonized measurement strategy can result in datasets that can have multiple uses.

Currently, most devices used for measuring concentrations of nanoparticles are stationary online devices capable of generating and storing multiple concentrations per minute. A full-shift measurement therefore consists of a large pool of data, instead of one single concentration per sampling period obtained from conventional time-integrated shift exposure measurements. As we would like to include all data points available, instead of one single average outcome, a different approach is necessary in comparison to conventional databases. In addition, due to lack of specificity of current real-time measurement devices, images from EM analysis of time-integrated samples should be employed and stored in databases. Information technology solutions should be explored to automatically process online measured exposure data to be able to control the averaging process and activity descriptions at all times.

As the industry moves to scale-up production, it is likely that methods of measuring nano exposure will evolve toward a more personal sampling approach with multiple activities and locations per sample, as is the norm with conventional exposure sampling for respirable particles, chemicals, or physical agents. However, database structure should be flexible in handling different types of exposure data and measurement strategies. In later stages of the database development, new insights may be incorporated into the database design, for instance, decision logic, exposure metrics, contextual information, and so on. Currently, IFA and TNO together with other PEROSH institutes are developing a database structure called Nano Exposure and Contextual Information Database. NIOSH is also developing an exposure database.

Table 4. Preliminary recommendations on core information that should be provided

The institute that collects the samples
The premise in which samples are collected
The location (inside the premise) in which the samples are collected
The worker who is being sampled or who is present during the stationary measurement
The sampling equipment and situation
An adequate description of the process and facility
The activity that is performed during the measurement (with specific exposure modifiers)
Exposure mitigation, e.g. exhaust ventilation, PPE, and other control measures that are in place during the measurement
Climate conditions during the measurement, e.g. temperature and relative humidity
The product (with active nano ingredient) that is handled during the activity
The measurement results that are derived from the measurement device

PPE, Personal Protective Equipment.

Data sharing issues: responsibility and ownership of the acquired data. Data sharing might be affected by legal, ethical, and other constraints. Terms of use should be composed for research institutes and third parties. Different user-specific rights may be awarded for entering, reading, reporting, and exporting data to different users. A disadvantage of open access input for a database is that no direct quality control is guaranteed. Collecting additional information in a later stage may be difficult.

Although the database (concept) is likely to be owned by the parties involved in the funding or maintenance of the database, the data itself will be made available for research use by the users. Rules have to be agreed upon to balance the rights of ownership of data and the obligation to keep business information confidential with the need to share the data for further analyses.

A suggestion was made to start data sharing within PEROSH and expand this to other Occupational, Safety and Health research institutes in the future. If data collection and reporting are harmonized, the data can be stored in separate databases allowing for easier merging at a later time. It was agreed that a joint working group should be established to discuss issues related to the preparation of a database and its structure consisting of PEROSH institutes and other interested parties in this database development.

Harmonization and standardization

During the workshop, the possible role of the Organization for Economic Co-operation and Development (OECD) and the ISO/Comité Européen de Normalization (CEN) in the process of formal harmonization of a measurement strategy was introduced and discussed.

The need for (future) standardization is clear, and many stakeholders are involved in these processes. Consequently, the processes are consensus driven and time consuming. It was acknowledged that EC Mandate 461 (European Commission DG Enterprise and Industry, 2010) has put pressure on the process of standardization (related to CEN) and that the experts in this workshop should anticipate drafting such a (preharmonized) document. In near future, the OECD Working Party on Manufactured Nanomaterials Steering-Group 8: Co-operation on Exposure Measurement and Exposure Mitigation (WPNM SG8) may serve as an excellent platform for harmonization.

Since the workshop, Bartley and Vincent (2011) have described the new draft European and International standard on sampling conventions prEN ISO/DIS 13128:2010, which is designed amongst other things to give a sampling convention for nanoparticles.

CONCLUSIONS

A broad variety of topics were addressed and many issues were discussed extensively during the workshop. The general consensus was that harmonization of strategies for measuring exposure to MNO and for the analysis of data are needed, and agreement among researchers in this area will be very helpful. No firm decisions were taken; however, based on the discussions among experts, preliminary recommendations [The recommendations of this manuscript are fairly in line with the recommendations reported by the EU-FP7 project NANEX (www.nanex-project.eu), Clark *et al.*, in preparation] were agreed upon for some of the topics as a gradual growth from current general practices including:

1. A multimetric approach to exposure assessment, a minimal set of data to be collected, and basic data analysis and reporting (Table 2).
2. A minimum set of contextual information to be collected and reported (Table 4).

Other issues that have been identified and are of great interest include:

1. Need for guidance on statistical approaches to analyze time-series data.
2. Need for guidance on EM analysis and its reporting (Table 3).
3. Need for agreement on generic and 'nano-specific' exposure terminology.
4. Need for and possible structure of a (joint) database to store and merge data.

To make progress in the process of harmonization, it was concluded that the next workshop to be held in the series should focus on the topics that are 'close to agreement', i.e. the preliminary recommendations listed in Tables 2–4, to achieve agreement among the researchers. In addition, the possibility of proposing and leading a new work item on Measurement Strategy to OECD WPNM SG8 should be explored.

IFA and TNO together with PEROSH partners will continue to build and populate a database. A working group will be established to further discuss the structure and contents of the database. In addition to PEROSH partners, others (e.g. NIOSH) are encouraged to participate in such a working group to ensure global consistency.

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