Exposure dose metrics, instrumentation, and operating procedures for occupational exposure assessment for nanomaterials and nanoparticles: a scoping review

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Keywords
engineered nanoparticles, inhalation exposure, measurement strategy, exposure assessment

How to cite this paper
Letsoalo MS, Masekameni MD, Andraos C, Gulumian M. Exposure dose metrics, instrumentation, and operating procedures for occupational exposure assessment for nanomaterials and nanoparticles: a scoping review. Occup Health Southern Afr. 2025; 31(1):12-24.
doi: 10.62380/ohsa.2025.31.1.2

ABSTRACT

Introduction: The rapid emergence of nanotechnology has resulted in the potential for workplace exposure to airborne particles in the nano-range, but consensus on exposure dose metrics hinders measurement strategies and evaluation. Thus, the association between exposure and adverse health outcomes is challenging to establish.

Aim: The aim of this scoping review was to describe current exposure dose metrics, instrumentation, and strategies for quantifying occupational exposure to nanomaterials and nanoparticles.

Methods: Peer-reviewed manuscripts and articles published from January 2008 to November 2024 about exposure dose metrics, instrumentation, and standard operating procedures for quantifying nanomaterials and nanoparticles in occupational settings were identified, using Google Scholar, PubMed, and ScienceDirect. Search phrases were (*"direct reading instruments"* OR *"exposure dose metric"* OR *"human risk assessment"*) AND (*"nanoparticles manufacturing"* OR *"occupational exposure assessment"* OR *"standard operating procedures for exposure assessments"*) AND *"sampling techniques"*.

Results: Five hundred peer-reviewed papers were identified,118 of which were included in the review. Most of the literature reviewed focused on inhalation as an exposure route. Mass concentration was the most commonly used exposure dose metric. The chosen exposure dose metric appeared to be influenced by the availability of the data collection instrument. Six real-time monitoring instruments were widely used: four particle sizers and two particle counters. Only one particle counter that was used measured three exposure dose metrics (concentration, mass, and size); the others measured only one exposure dose metric. The filter-based method was widely preferred for sampling. Various analytical methods were used to characterise nanomaterials and nanoparticles.

Conclusion: There is no consensus on exposure assessment methodology in the nanotechnology field, hindering the ability to compare exposure scenarios and to draw conclusions about associations between exposures and adverse health outcomes. Africa lags behind other continents in the use of exposure dose metrics other than particle mass concentration. A combination of real-time instrumentation, analytical methods, and exposure models is needed to provide an integrated exposure assessment methodology, and to standardise exposure quantification in the rapidly growing nanotechnology field.

INTRODUCTION

With the rapid emergence of nanotechnology, nanomaterials (NMs) are in high demand for applications to improve product strength and/or durability in cosmetics, food processing, pharmaceuticals, medical applications, etc. The International Organisation for Standardisation (ISO) and Organisation for Economic Co-operation and Development (OECD) refer to NMs as *"materials with any external dimension in the nanoscale or having an internal structure or surface structure in the nanoscale range"*.[1] Nanoparticles (NPs) are *"nano-objects with all external dimensions in the nanoscale range where the lengths of the longest and the shortest axes of the nano-objects do not differ significantly"*.[2]

Several studies have highlighted that the wide use of NMs and NPs could result in human exposure through dermal, inhalation, and/or ingestion, leading to toxic endpoints such as lung inflammation, permanent cell damage, organ injury, and oxidative stress.[3–5] Some NPs can cause infertility by reducing sperm counts and causing ovaries to undergo apoptosis.[6] Studies have highlighted that exposure to NMs and NPs has the potential to induce cyto-and-genotoxic effects, inflammation, and even cancer.[7,8]

There is a lack of consensus regarding the most appropriate single exposure dose metric for assessing exposure to NMs and NPs, which creates uncertainty about the type of instrumentation

and measurement strategies to use.[9,10] There is a need to investigate the use and value of all available exposure dose metrics.[11]

The objective of this scoping review was to describe dose metrics and instrumentation used in NM and NP exposure assessment, and standard operating procedures used to quantify NMs and NPs in occupational settings.

METHODS

A scoping review was conducted to acquire peer-reviewed literature addressing exposure dose metrics, instrumentation used in exposure assessment, and standard operating procedures on how to quantify exposure to NMs and NPs in occupational settings. Terms used in this paper are defined in Table 1.

The review was conducted within a larger study that received ethical approval from the University of the Witwatersrand Human Research Ethics Committee (ethics clearance certificate number HRECNMW23/02/04).

Search strategy

Three scholarly databases were searched, viz. Google Scholar, PubMed, and ScienceDirect, for scientific papers published from January 2008 to November 2024. The keywords/phrases that were used were *("direct reading instruments"* OR *"exposure dose metric"* OR *"human risk assessment"*) AND (*"nanoparticles manufacturing"* OR *"occupational exposure assessment"* OR *"standard operating procedures for exposure assessments"*) AND *"sampling techniques"*. Papers were included in the review based on the information in terms of the metrics, measurement strategies, and different instruments used as well as the data analysis.

Inclusion criteria

Only peer-reviewed papers published in English between January 2008 and November 2024 were included in this review. A team of four reviewed the papers in this scoping review. Although there was some research on this topic before 2008, studies on the potential health effects of exposure to NMs and NPs began to be published in 2008 (Figure 1).

Table 1. Definitions of key terms

Key term	Definition
Exposure assessment	The process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed[12]
Exposure dose metric	A concentration at a specific time point or total concentration integrated over time, e.g. particle mass, number, and surface area[13]
Particle mass concentration	The total mass of particles per unit volume of air (μg/m^3)[14]
Particle number concentration	The number of nanoparticles per unit of volume or mass[2]
Surface area	The total particle surface area per unit volume of media[15]
Particle size	The size of a particle in micrometres (μm) or nanometres (nm)[2]

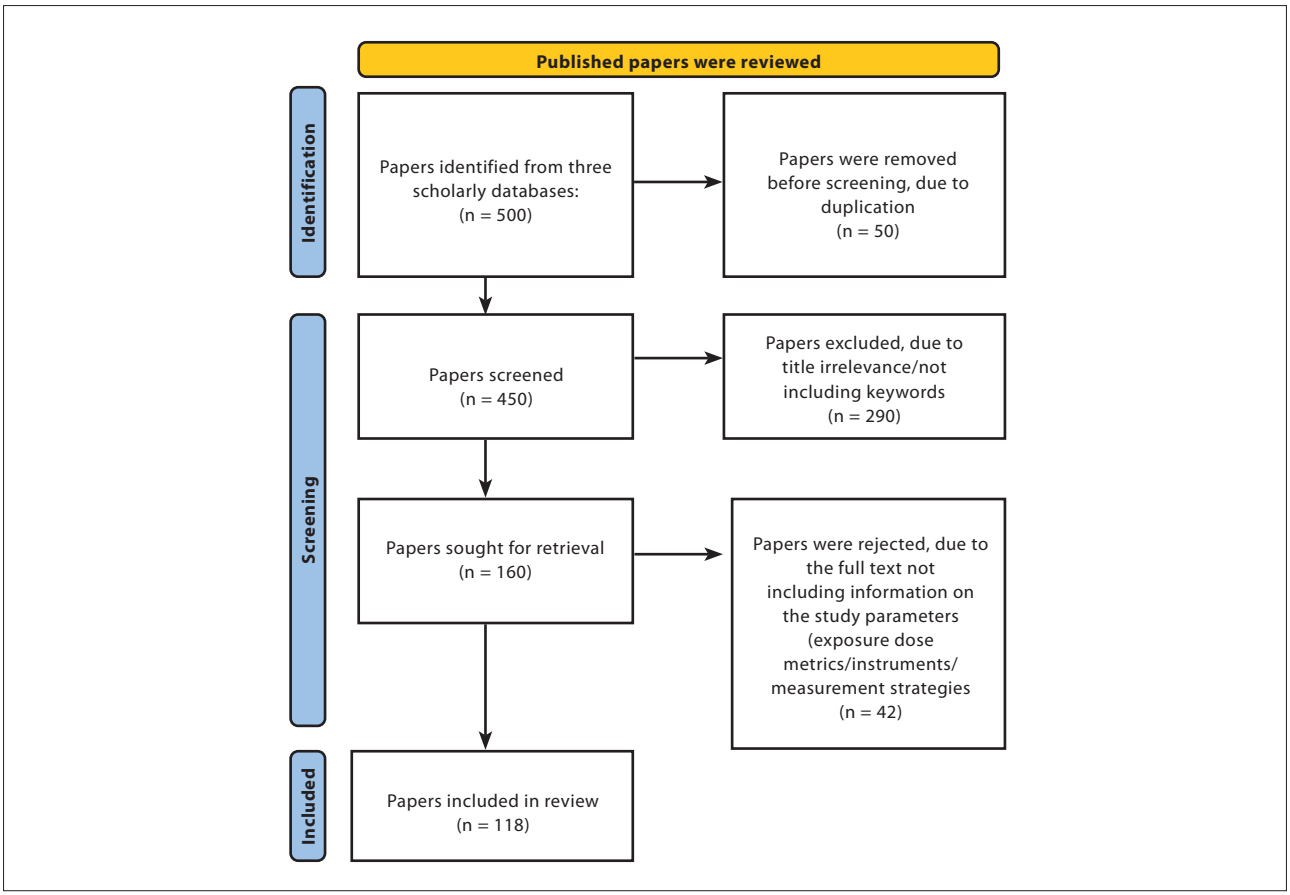

Figure 1. Selection of papers for scoping review

Data analysis

The criteria used to assess the quality of the information from the 118 published papers sourced were modified from the method published by Balshem et al. (2011),[16] as shown in Table 2.

RESULTS AND DISCUSSION

One hundred and eighteen English-language peer-reviewed papers that described studies on exposure assessment in occupational settings, and addressed inhalation as the exposure route for NMs and NPs, were selected for review.

Concentration metrics in exposure assessments (external dose)

External dose/environmental concentration refers to the concentration of the emissions of NMs/NPs in the microenvironment in which personnel conduct their activities. In 26 of the 118 papers reviewed (22.0%), a single exposure dose metric was described (see Supplementary Table S1). Fourteen of the 26 papers (53.8%) used particle mass concentration to quantify exposure and toxicity of NPs.[17–30] However, several authors showed that, given the negligible mass of NPs, this exposure dose metric is impractical.[31–39] Particle number concentration, volume, and surface area were the suggested exposure dose metrics to use.[26,38,40–49] Thirty-three (28.0%) of the articles reviewed reported the simultaneous use of two exposure dose metrics (particle number concentration, particle mass, or particle size) as exposure dose metrics for NMs and/or NPs during exposure assessments.[35,39,50–80] More than two metrics (particle number concentration, particle mass, surface area, and/or particle size) were used as exposure dose metrics in nine (7.6%) of the papers reviewed.[81–89]

Consensus on the most appropriate exposure dose metric to use for NP exposure assessment is necessary, as there is insufficient and inconsistent information regarding the correlation between particle number concentration, mass concentration, and surface area.[32,35,37]

Particle number concentration

Particle number concentration was reported to be the most informative metric to describe the exposure dose of NPs.[34,37,60,90,91] Some authors stated that although particle number concentration was a better exposure dose metric than particle mass concentration, size, and surface area, it may not be useful in the post-synthesis of NPs where particles are agglomerated. Particle number concentration was the commonly used metric used in studies in laboratory settings.

Only six of the 118 papers (5.1%) described using only particle number concentration as the exposure dose metric.[4,90,92–95] It has been reported that instrumentation that focuses solely on particle number concentration is relatively insensitive for NP exposure assessments.[4,91] Particle number concentration and surface area may present challenges, due to the heterogeneity and different shapes of particles.[34] In one paper, it was stated that it is difficult to separate ultrafine particles from background NMs or NPs using particle number concentration and size distribution measurements.[7]

Particle mass concentration

It is recommended that mass concentration be used as an exposure dose metric for exposure assessment of engineered nanomaterials (ENMs).[48,60,96–98] Fourteen of the 118 papers (11.9%) described using only particle mass concentration to quantify exposure to NMs and NPs.[17-30] Some researchers argued that, due to the physiochemical characteristics of NPs, the use of mass concentration does not accurately show the toxicological effects induced by exposure to NPs, making it difficult to characterise the exposure.[32,96] Thus, mass and chemical composition alone may not adequately describe the dose, because particles with the same chemical compositions can have different toxic mass doses dependent on properties such as particle size.[40] Nanoparticles account for a small percentage of the total mass concentration of particles, due to their size, so often the mass is negligible, but they account for a high percentage of the particle number concentration.[32,46] While it has been argued that mass concentration is unlikely to be the best exposure dose metric to assess exposure, it can be used while more accurate exposure dose metrics are being developed.[38]

Surface area

Several studies concluded that surface area is likely to be a better exposure dose metric than particle mass concentration to quantify exposure to NMs and NPs;[35,36,38,43,48,97] however, in only three was surface area alone used as an exposure dose metric.[43,99–101] This conclusion was based on the fact that surface area accounts for NPs with the same chemical composition, but of different sizes.[102] However, surface area changes with the shape of the particles, while particle number and mass concentration do not.[46] It has been argued that, due to the differences in particle composition and morphology of NPs, further research on surface area is needed before it is considered to be a reliable exposure dose metric.[103] It has also been argued that particle number concentration and surface area may be better exposure dose metrics than mass concentration when classifying exposure to NPs.[32] Other researchers have argued that surface area is potentially a better metric than particle number concentration concerning toxicity assessment, as the exposure dose is more important than the ambient air concentration.[35,46,104,105] The consensus is that, toxicologically, the surface area is likely to be the most appropriate exposure dose metric for inhaled, spherical NPs.[43]

Table 2. Assessment criteria used in the review

	Rating		
Assessment criterion	**High**	**Moderate**	**Low**
Number of metrics	Three or more (mass, particle number concentration, and surface area)	Two (mass and particle number concentration, OR particle number concentration and surface area, OR mass concentration and surface area)	One (mass, or particle number concentration, or surface area)
Instruments	Real-time measurements, sampling and offline analysis	Real-time measurements	Sampling and offline analysis
Measurement strategy	Adopted from known scientific body/programmes, e.g. OECD, ECHA	Adopted from other published papers	Authors' own strategy

ECHA: European Chemicals Agency, OECD: Organisation for Economic Co-operation and Development

Comparison of exposure dose metrics (external dose)

To improve the quantification of exposure to NPs, it is necessary to use a multi-metric approach, where all exposure dose metrics can be used, depending on the exposure scenario.[96] This approach is necessary to assess if NPs are released from different work activities and should form the basis of exposure assessment strategies.[32] It has been stated that particle number concentration and surface area provide biological information associated with exposure to NPs.[96,101] Of concern, is the lack of multi-metric use on the African continent, where only mass concentration is usually used to quantify exposure to ultrafine and respirable dust fractions, and then compared against mass concentration-derived occupational exposure limits.

Several papers reported that surface area and particle number concentration were useful to identify exposure, while mass was needed for risk characterisation as the instruments tend to be extremely sensitive to NPs emissions.[61,96,103,106] However, none of these exposure dose metrics can be used to measure dose in the lungs; they can only be used for external exposure.[46] Particle number concentration is not a commonly used parameter due to agglomeration, while mass concentration is dominated by the largest particles.[107] To date, no limitations have been identified regarding the multi-metric approach. It reduces measurement errors during exposure assessments, while ensuring that the associations between exposure and health outcome are discernible.

As recommended in all the papers, a combination of exposure dose metrics should be used for the exposure assessment of NPs. The European Chemical Agency (ECHA), under the European Union (EU), has recommended using more than a single metric.[33,60] As all exposure dose metrics are dependent on particle size, instruments used for exposure assessments must be sensitive in terms of the size-dependent response function per particle.[46] In one paper, it was emphasised that the best metric in terms of accuracy in representing exposure has not yet been identified, primarily due to the lack of comparability. A harmonised approach for data evaluation concerning metric, size range, etc. is missing, which hinders the ability to reach scientifically sound conclusions.[91]

A single metric may not be sufficient to characterise and quantify NP exposure for all types of ENMs adequately, due to poor correlation between the particle number and mass concentration, and insufficient data about surface areas related to NP exposure.[32,54]

From the scoping review, the preferred type of exposure dose metric was categorised according to geographical region. Most of the research on exposure dose metrics was conducted in Europe (58.4% of papers), followed by North America (28.7%), as shown in Figure 2. In Africa, only one study, by Masekameni et al. (2022),[108] investigated airborne exposure to silver and gold NPs in South Africa, using mass and particle number concentration as exposure dose metrics, which were then converted to particle mass concentration for comparison with occupational exposure limits.

Real-time monitoring instruments

Area measurements predominated in the papers reviewed. There was limited information regarding measuring exposures to NMs, especially personal exposures,[13] which is primarily due to the lack of availability of suitable instruments. Real-time instruments, which are practical and portable, aid in the ability to identify particle exposure in workplaces.[32,39] In 23 of the 118 papers reviewed (19.5%), it was stated that real-time instruments were used to assess exposure to NMs or NPs;[46,51,85,90,94,107–121] most of the studies (> 50%) were conducted in Europe. One study in Africa made use of real-time instrumentation, viz. the NanoScan Scanning Mobility Particle Sizer (SMPS), which was used to assess exposure to gold and silver NPs during synthesis activities in a South African research laboratory.[108]

Particle sizers

Scanning mobility particle sizer

The scanning mobility particle sizer (SMPS) measures particles of 2.5 to 1 000 nm and is often referred to as a reference instrument for measurements within the nano-range.[114,122,123] The instrument considers the number size distribution based on the electrical mobility diameter.[62,69] However, the instrument requires operating personnel

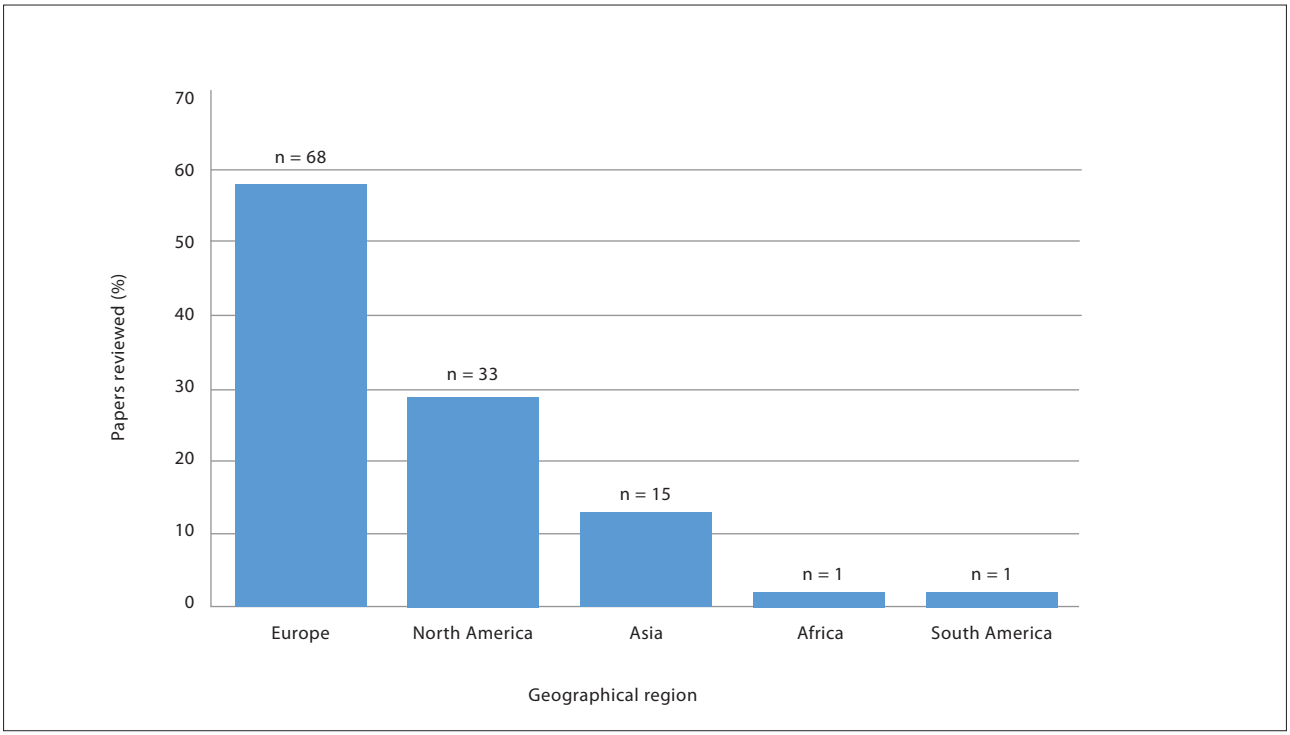

Figure 2. Papers included in the review, by geographical region

to be trained in aerosol measurement techniques.[107] Several variables need to be considered (scan time, airflow, impactor used, type of differential mobility analyser), and the size of the instrument makes it difficult to carry and operate in the workplace.[114] Nevertheless, SMPS data are considered to most accurately represent particle size concentration.[111]

Smaller, portable versions of the SMPS, such as the NanoScan SMPS, are used to measure particle number concentrations of 10 to 420 nm, in 13-size bins.[122,124,125] Its portability and the use of a non-radioactive charger make it suitable for workplace monitoring.[118,120] However, the 13 size fractions are an indication of the low sizing resolution, which translates into an overestimation of measured particle number concentration, due to particle size misclassification.[111,118,120] This misclassification makes SMPS unsuitable for occupational exposure assessments.[111] Another disadvantage is the complexity of the raw data from a NanoScan SMPS in comparison to that obtained from other types of SMPSs, especially since the multiple charge and diffusion loss corrections are already inherently included in the empirical data.[111]

The NanoScan SMPS is suitable for tier 2 studies, i.e. studies that focus on a basic exposure or release assessment, using a straightforward approach to determine if releases of, or exposure to, engineered nano-objects may occur. This requires a basic background exposure assessment to measure the concentration of NM or NP emissions for at least 45 minutes to determine if there is exposure (or not), using, for example, personal samplers to obtain real-time measurements throughout the entire work shift.[13,125] The NanoScan SMPS is discouraged for tier 3 studies, i.e. those that focus on obtaining as much information as possible about airborne nano-objects in the workplace, to a) determine if exposure to engineered nano-objects has the potential to occur, b) identify the level of exposure, and c) assess the need for additional risk management steps, which involve real-time instruments in addition to those used in tier 2 studies.[125] Real-time instruments are discouraged for tier 3 studies, because complex instruments and analytical methods are used in these studies to characterise both particle exposure and emission in terms of agglomeration, aggregation, morphology, and chemical composition.[13]

Aerodynamic particle sizer

Aerodynamic particle sizers (APSs) cover a broad range of aerosol sizes, as they measure the aerodynamic size distribution in the 0.52–20 µm range.[80,126]

Optical particle sizer

Optical particle sizers (OPSs) measure the particle number concentration for particles of 300–1 000 nm and comprise 16-size bins.[4]

Fast mobility particle sizer

The fast mobility particle sizer (FMPS) measures much smaller particles (5.6–560 nm in 32-size bins) and higher concentrations than the SMPS, providing better time resolution.[114] The disadvantage of the FMPS is that it cannot measure distributions of spherical particles with a geometric mean diameter > 200 nm.[64] One study highlighted that the FMPS tends to overestimate the total particle number concentration, by about three-fold, when particles are agglomerated.[120]

Particle counters

Optical particle counter

Particle counters are used to measure the particle number concentration of NPs.[122] The optical particle counter (OPC) is used to supplement filter-based sampling. It can measure emissions, but not characterise particle size distribution or measure the number of particles sized 10–100 nm.[31,113] For example, the optical aerosol Nanozen DustCount 9000 is used to measure real-time mass concentration, particle number concentration, and size distribution, and has 20 particle size channels.[127–129] It has a removable cassette that allows the collection of the aerosol on a 25-mm diameter particulate filter.[127,129]

Condensation particle counter

P-Trak is a condensation particle counter (CPC) used to measure the particle number concentration of 200–1 000 nm-sized particles.[129] The instrument is portable, easy to use, and less expensive than the SMPS.[120] Disadvantages are the lack of a comparable size distribution[120] and that it cannot be used in high-temperature environments, such as welding, smelting etc., because this can result in coincidence errors (where multiple particles are detected as a single larger particle).[32]

Comparison of real-time monitoring instruments

Real-time monitoring instruments are effective in assessing the efficacy of control measures and are the best instruments to measure exposure to NPs by inhalation.[46,130] The instruments are useful for studying variations in exposure by identifying peak emissions which, in turn, will indicate the activities/phases that are associated with peak emissions.[33,84,131] Exposure assessments can be conducted at any moment using real-time monitoring instruments, which assists in early warning systems.[112] Some researchers have stated that SMPSs provide size distribution information with better time resolution.[55]

The major limitation of the real-time monitoring instruments is their inability to differentiate NPs from background particles.[33] They are not capable of differentiating the physio-chemical properties of particles collected on filters. There are also differences in the sensitivities of the various instruments, e.g. the CPC can measure size particles of 1–3 µm, but those larger than 1 µm are easily lost due to inertial impaction (this does not affect NPs). The NanoScan SMPS tends to underestimate size distributions of particles > 100 nm.[132]

Another limitation of real-time monitoring instruments is the uncertainty related to the 30% deviation during the calibration of the instruments.[33,133] According to some authors, research should be conducted on both the uncertainties and the instruments' detection limits, to ensure reliable measurement data and enable comparison of results from different studies.[91] Most of the instruments are not suitable for non-spherical particles and tend to measure major deviations for agglomerated particles.[4] Environmental conditions can influence the results, e.g. in high-humidity environments, water droplets in the air may be counted by the OPC instrument.[119] Caution should be taken when using direct-reading results to derive mass-related values for exposure dose assessments.[33] Some authors indicated that the instruments often cannot be used for a wide spectrum of NPs.[45] Additionally, the relative performance of these instruments is limited to single exposure dose metrics.[134]

In summary, from the papers reviewed, it is clear that the comparability and variability of real-time monitoring instruments are not consistent, even when using instruments of the same model. Deviation errors, sensitivity, and detection limits of the same instruments varied between instruments made by different manufacturers. Real-time instruments that can provide data on particle number concentration, mass concentration, and particle size distribution would be valuable for conducting exposure assessments for NPs.

Instrumentation used for characterisation of nanomaterials/nanoparticles

The use of analytical methods for the characterisation of NMs/NPs is still preferred over the use of real-time instrumentation. In 29 of the 118 reviewed papers (24.6%), analytical methods and instrumentation for the characterisation of NM/NP were used.[17–30,43,44,93,100,131,135–140]

Filter-based sampling

A single-particle inductively coupled plasma mass spectrometer (ICP-MS) is used to quantify the number, concentration, and size of NPs, and it has been stated that this technique has high sensitivity and selectivity for elemental analysis.[19,20] Inductively coupled plasma optical emission spectrometry (ICP-OES) is the most common method used to identify the elemental composition of particles.[33,129]

Gravimetric analysis is used to measure the mass of particles; filters are weighed on a microbalance scale.[68,129] This sampling technique is not used to assess exposure to a single NP, but caters to large micro agglomerates and/or aggregates of NPs.[26,68] Gravimetric analysis can only be applied to NMs/NPs when used in conjunction with a size-selective sampler, designed to measure particles in the nano-range size.

Electron microscopy

Scanning electron microscopy (SEM) is used to detect size, shape, dimensions, elemental composition, and degree of agglomeration of NPs.[32,141] Compared to transmission electron microscopy (TEM), SEM provides sufficient data about a single particle and provides statistical analysis of the NPs, including physical and elemental composition data.[31,84,124,131,133] However, for elemental composition data, the SEM is coupled with energy-dispersive X-ray spectroscopy (EDS). Transmission electron microscopy uses image analysis software to obtain data on the NPs per volume of air, as well as morphological characteristics such as size, shape, and degree of agglomeration.[68,124] Similar to SEM, for elemental composition data, TEM is coupled with EDS. Additionally, TEM requires a small amount of sample – an advantage over SEM.[100]

Analytical inter-comparison of methods/techniques used for characterisation of nanomaterials/nanoparticles

The efficiency of the sampling is dependent on the filter's sufficient particle load.[31] Additionally, filter-based sampling allows for the analysis of the morphology and chemical content of the particles.[124] The method provides information about the characteristics that affect the toxicity of NPs.[142,143] Studies have highlighted that SEM and TEM techniques are accurate in identifying particle size distributions; however, statistically reliable results can only be obtained by counting the number of particles.[142,143]

One limitation of filter-based sampling is that the data are not readily available, as the filters need to be analysed in a laboratory.[144] Analytical methods to obtain statistically robust data about the shape, composition, and size distribution of NPs are time-consuming.[22,131] Another disadvantage is that gravimetric samplers cannot be used to detect small mass concentrations of NPs.[120,124] Gravimetric sampling is not ideal for obtaining information about changes in emissions of NPs throughout the work shift.[120] Overloaded filters will compromise TEM and SEM analysis.[31] While TEM and SEM provide information about the surface of a sample, they cannot be used to identify NPs embedded in a matrix, e.g. polymer fragments with carbon nanotubes.[33]

In conclusion, considering real-time monitoring instruments as well as analytical techniques used for the characterisation of NMs/NPs, it is evident that a single instrument cannot be used to measure all exposure dose metrics simultaneously; multiple instruments are required for exposure assessments. Instrumentation for the characterisation of NMs/NPs requires care when handling, and extensive training and experience in their use, and retrieval and analysis of the data.[26,31]

Internal dose and dose-response for exposure modelling

Ambient concentrations of NMs and NPs do not necessarily equate to the concentrations humans are exposed to, hence internal dose should also be considered.[145] In exposure models, the particle mass concentration as an input value is necessary to mimic exposure and provide the internal dose output. However, due to the negligible mass of NMs/NPs, it is necessary to convert particle number concentration to particle mass concentration. Dose exposure assessment is based on two methods: single- and multiple-path. Such methods are used for tracking the airflow and particle deposition in the lungs, providing output values in terms of lung surface area.[146] Understanding human exposure enables the improvement of experimental designs within exposure models, which predict not only exposure due to emissions, but also how exposure to NMs and NPs may translocate to different organs in the human body.[147]

Multiple-path particle dosimetry

Multiple-path particle dosimetry (MPPD) is used to model particle deposition ranging from nano-sized to coarse, and the clearance thereof from the lungs.[108,148,149] A paper describing a study on silver nanoparticles reported that (according to the model) the fraction of NPs that reaches the alveoli is about 5.5 times higher for 15-nm NPs than for 410-nm particles.[150] It has been suggested that the MPPD model can be used to relate human lung cytotoxicity and pulmonary inflammation to risk profiling.[151]

Single-path particle dosimetry (International Commission on Radiological Protection dosimetry model)

The International Commission on Radiological Protection (ICRP) dosimetry model is a single-method path model used to describe the deposition and retention of particles.[124,149] The model tends to predict the penetration of fewer particles into the respiratory regions than the MPPD model,[152] attributed to the single-path model using semi-empirical expressions based on experimental data, while the MPPD model is based on lung morphology.[18]

Comparison of exposure dose models

The MPPD model allows for the quantification of deposited particles within the different lung segments for both spherical and non-spherical NPs, and accounts for their uptake into the alveolar macrophages.[18,153] The MPPD model is readily available online and the particle dosimetry calculations are easy to apply.[146] Multiple-path particle dosimetry tends to overestimate exposure to NPs by not accounting for NP dissolution (interaction of NPs with the lung lining fluid), lung clearance, and ventilation changes that occur during exposure.[148] Accurate simulations require accurate estimates in terms of systemic absorption, clearance, and disposition, following the dissolution of NPs.[148]

Another limitation of exposure models is that they are dependent on the inhaled lung volume and the exposure concentration, and not the size of the particles inhaled.[146] Although MPPD and ICRP are both lung deposition models, the outcomes of the simulations

of the deposited particle concentrations vary significantly, e.g. the ICRP deposition curve was reported to have the highest deposition values for particles close to 10 nm, whereas the MPPD curve showed the highest values for particles larger than 60 nm.[46] Because the MPPD and ICRP are deposition models, they often report only on the deposition of the NMs/NPs, and not on any possible translocation (transport of the particles from the lungs to other regions of the human body) that may occur. The main differences between the MPPD and ICRP models are the breathing frequency and lung volume estimates used, which can lead to differences in outputs.[46] Despite the availability of the exposure models, the interpretation of the models is limited in the absence of actual human exposure data, and the estimation of exposure in work environments should take precedence.[147]

In summary, there are only a few studies on exposure dose of human absorption, which are not comparable.[145] The internal dose of NMs and/or NPs in the human body has been estimated using a variety of techniques and exposure models, which has led to variation in estimations.

Frameworks for occupational exposure assessments

To conduct reliable and robust exposure assessments, guidelines regarding the different measurement strategies are necessary, including how to implement those strategies and how to interpret and draw conclusions from the findings. This will also enable the reproducibility of exposure assessments, thus creating harmonisation and standardisation. The methods and guidelines form the basis for the efficient collection of NMs according to their size, composition, and shape, which is crucial in exposure assessments.[34,39] Currently, there is no single best method for measuring NMs/NPs, and the recommendation is to use a combination of methods/strategies.[154]

Measurement strategies

Measurement strategies for chemicals, which include easy-to-measure mass-based metrics suitable for exposure assessment, are well documented.[33] However, there are no globally established standard measurement strategies for NPs, other than those from country-specific harmonisation initiatives or those proposed by various international organisations.[83,145] Most of the published NP measurement strategies described similar exposure dose metrics but differences in the instrumentation used,[83] and omitted one aspect of the work activity.[83] Work activity accounts not only for the concentration of the contaminants in the environment, but also the length of time and type of tasks that expose employees to potential hazards. Thus, work activity represents work done by the worker and the possible exposure during work tasks.[83]

Recently, a tiered approach developed by bodies such as the OECD, the European Committee for Standardization (CEN), and the ECHA was recommended for exposure assessments relating to NPs.[3,83] The tiered approach is a risk-based approach to conducting an exposure assessment to determine whether exposure to NMs/NPs may occur, and if there is a need for risk management steps.[125] The approach involves tailoring the exposure assessment to the materials used, and work-based scenarios, to reduce uncertainty in the assessment of exposure while creating a balance regarding costs and effectiveness.[7,33,155] The tiered approach comprises three steps, viz. information gathering (literature search and review), basic exposure assessment (spot check measurements, using real-time monitoring instruments), and expert exposure assessment (labour-intensive, expensive tier).[45,51,108]

Currently, there is no harmonisation regarding the best analytical method for characterising exposure to NPs emitted from ENMs. The National Institute for Occupational Safety and Health (NIOSH) and the ISO have acknowledged that there are no established analytical methods to assess exposure to NPs using any exposure dose metric other than mass concentration.[33,115] The identification of emission sources of NPs, using quantitative assessments, is well-documented in the literature, e.g. comparing particle concentrations at the emission source with background concentrations to enable the implementation of measures for exposure mitigation.[31] One study highlighted that the ISO 2007 guidelines provide information about methods of characterisation, but not about analysis or interpretation of measurement results, considering differentiation between ENMs and other nano-sized particles emitted in the workplace environment. [33]

It is evident that no 'one-size-fits-all' approach can be followed in exposure assessments, especially as aspects of exposure dose metrics, measurement strategies, and measurement instruments are influenced by the exposure scenario. The use of a single exposure dose metric creates uncertainty about whether there is exposure or not. Due to some regulatory frameworks, dose is expressed in mg/m^3 (mass), but most of the instruments available for monitoring NPs (that measure particle number concentration) require conversion of particle number to particle mass concentration. Some studies have highlighted that the correlation between the particle number and mass concentration is not always consistent, and that there are insufficient data regarding the particle surface area related to NP exposure. This is because each exposure dose metric serves a unique purpose in an exposure assessment, and provides unique information, e.g. surface area provides information about lung deposition, whereas particle number concentration provides information about the number of particles in a specific volume. The multi-metric approach is recommended to provide an holistic overview. Such information can be used in various exposure assessment models that mimic human exposure, such as MPPD. These dose models can provide information regarding the deposition and retention of NPs, particularly those that are bio-accumulative (non-biodegradable).

Real-time monitoring is preferable over the use of analytical methods only, as it provides real-time information. However, considering background particles, the use of offline analyses, such as gravimetric analysis and ICP-MS, can assist in differentiating emissions associated with specific activities (exposure scenario) from those not associated with the exposure scenario. The use of offline analysis can provide information about the physiochemical characteristics and the possible toxicological effects of the NPs, which is essential in determining the potential health outcomes associated with exposure.

Last, considering that there is no harmonisation on the standard measurement strategies, we recommend the use of the tiered approach as cited by the OECD, CEN, and ECHA. The starting point of this approach is understanding the exposure scenario to inform the measurement strategy, and the instruments to use with the exposure dose metric of interest. This information is essential in the exposure assessment toolkit of quantifying exposure by characterising the exposure, rather than merely using the risk rating approach (e.g. low to high risk), which is often subjective and increases the level of uncertainty.

CONCLUSION AND RECOMMENDATIONS

In this paper, we have highlighted aspects of exposure assessment that influence the quantification of exposure, considering the exposure assessment toolkit, and showed that consensus about

exposure dose metrics, types of instruments, analytical methods, and measurement strategies remains unresolved within the nanotechnology fraternity. This hinders the ability to quantify exposures, as well as to draw conclusions about associations between exposure and adverse health outcomes.

The use of real-time instrumentation, in conjunction with offline analysis, can provide information on emitted NM/NP concentration fluctuations throughout the associated activities. This will decrease many uncertainties regarding the data recorded by instruments during exposure assessments. Exposure models such as MPPD mimic lung deposition and provide information on particle deposition and retention; however, they lack information on translocation. This information is important, given that NPs can translocate from the lungs during gaseous exchange to other organs of the body, due to their small size and non-biodegradability.

We compared the strengths and limitations of each NP measuring instrument, which should be considered when selecting an instrument for NP exposure assessments. There is a wealth of literature on standardised measurement techniques for particles outside of the nano-range size, but limited knowledge regarding measurement strategies and approaches for determining exposure to NMs/NPs. Quantification of exposure to NPs remains comparatively difficult. In the absence of a standardised strategy, we recommended that the measurement strategies proposed by the OECD, CEN, ECHA, and others be applied with caution. A multi-metric approach should be incorporated into a standardised measurement strategy that will be used in exposure assessments to protect human health.

Overall, we explored the use of different exposure dose metrics simultaneously during exposure assessments, considering that particle mass concentration is often negligible when referring to NMs/NPs. The use of real-time instrumentation, in conjunction with the methods of characterisation to assess exposure, provides a more integrated approach. There is an urgency to standardise methods/strategies to quantify exposure to NMs/NPs, considering the rapid growth of the nanotechnology field.

KEY MESSAGES

1. There is no consensus about appropriate exposure dose metrics to use for quantifying exposure to nanomaterials/nanoparticles (NMs/NPs).
2. The type of instrumentation used to assess exposure to NMs/NPs is dependent on the exposure dose metric of interest.
3. Exposure models allow for mimicking particle deposition and penetration in the human respiratory tract, which is essential for predicting deposition, retention, and clearance of NPs in the various regions of the respiratory tract.
4. Although there is literature describing standardised measurement approaches for particle sizes beyond the nano-range, measurement strategies/approaches for quantifying exposure to NMs/NPs remain underdeveloped.
5. There is a need for more exposure assessment studies on NMs and NPs on the African continent.

DECLARATION

The authors declare that this is their own work; all the sources used in this paper have been duly acknowledged and there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design of the study: MSL, MDM, CA
Data acquisition: MSL
Data analysis: MSL
Interpretation of the data: MSL
Drafting of the paper: MSL
Critical revision of the paper: MSL, MDM, CA, MG

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