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GUIDANCE

Guidance on information requirements and chemical safety assessment.

Appendix R14-4 Recommendations for nanomaterials applicable to:

Chapter R.14 Occupational exposure estimation

Appendix R14-4: Recommendations for nanomaterials

1. INTRODUCTION

This appendix has been developed in order to provide advice to registrants preparing their registration dossiers for nanomaterials (NM). The content of the appendix implements the advice provided by the REACH Implementation Project on Nanomaterials 3 (RIP-oN 3) on exposure assessment and risk characterization.

The final report of the project contains a large amount of information including applicability of the methods, research gaps etc. This appendix implements only the agreed outputs (i.e. the recommendations for guidance update).

For further information (e.g. research & development requirements or reasoning for the advice provided for guidance, the reader can refer to the final report of RIP-oN3. (http://ec.europa.eu/environment/chemicals/nanotech/index.htm).

2. RECOMMENDATIONS ON OCCUPATIONAL EXPOSURE ESTIMATION ARISING FROM RIP-oN 3 for NANOMATERIALS

2.1. General remarks

2.1.1. Consideration in relation to measurement of inhalation exposure to nanomaterials

2.1.1.1. Preamble

Measurement of exposure to nanomaterials provides particular challenges. These have been highlighted in several publications (e.g. Brouwer 2009, 2010). They include discrimination from background particles, collection and analysis of size information, effective high spatial and temporal variability, choice of metrics and measurement instruments, and measurement of high aspect ratio nanomaterials. The state of knowledge on these issues is continuing to develop. Further information on current approaches is provided in BSI 6699/3 (2010), OECD (2009).

2.1.1.2. Discrimination from background nanoparticles

Typical urban air contains anywhere between 10,000 to 40,000 particles/cm^3 which come from a variety of sources including, industrial pollution, traffic and domestic emissions.

In industrial settings, evidence of measurement problems relating to background aerosols has been reported in several studies (e.g. Kuhlbusch *et al.*, 2004, 2006; Demou et al., 2008; Park *et al.,* 2009). Specifically identified sources include heating units, fork lift trucks and vacuum cleaners.

These background number concentrations are dominated by particles smaller than1000 nm and much of the distribution is typically in the range 10 to 300 nm. The presence of this

ambient particulate creates problems when attempting to measure emissions of engineered nanoparticles from nanomaterials sources.

Three strategies have been reported (including combinations) to address these issues with varying degrees of success. The first is to take time series, or time differentiated measurements with associated log of events, typically including activities such as pre-operation of reactor, to determine a plausible relationship between events and levels.

A second approach is to take parallel samples with the same instrumentation in an area where it is expected that there is only background aerosol present, i.e. there is no expected contribution from the source (e.g. Kuhlbusch *et al.* 2004, 2006). This is sometimes called the "far field" and can be outside, or at another point in the production building/laboratory. For this type of approach, care is required that there is no contribution from the sources of interest, or from other background sources in the far field sample.

A third approach is to collect physical samples of the aerosol for off-line analysis to confirm that the peak concentrations observed correspond to an identified NM, either by composition (elemental analysis of the primary material or impurity) or morphology or both, for example by Scanning Electron Microscopy (SEM)/ Transmission Electron Microscopy (TEM) and Energydispersive X-ray Spectroscopy (EDAX) analysis (e.g. Methner et al., 2010; Brouwer *et al.*, 2009).

While all of these approaches have utility, all must be applied with care to ensure that no confounding effects, such as a change in the far field background with time, corrupt the data. Combination approaches have been described and are generally more successful. Brouwer et al. (2009) used a combination of these approaches as the basis of a semi-formal decision logic to determine whether nano-objects were present in the workplace air. This required an exceedance of a predetermined near-field/far field ratio (in the reference ratio 1.05 was used), that changes in concentration or size distribution corresponded to observed activities and that the chemical composition of the sample (in the near and far field) matched that expected. The obvious limitation of the method in the light of the dynamic response, detection limits and the measurement uncertainty of the applied measurements is in its ability to detect statistically significant deviations in the ratio. Currently available sampling and analytical methods might also have insufficient sensitivity to assess very low levels required when in due course in many cases OELs/DNELs for nanomaterials may be substantially lower than current OELS/DNELs(e.g. NIOSH (2005) for TiO_2)).

2.1.1.3. Measurement of size distribution

Measurement of size distribution is clearly an important parameter. The size information may be obtained through a number of instrumental routes. It is unlikely that the size distribution of aerosols measured in the workplace is the same as the size distribution of the primary material. Evidence is that distributions are not log normal (as might be expected for laboratory generated samples) but more complex, sometimes but not always bi-modal.

Various reasons have been suggested for this. One is that the smaller mode represents primary particles and the larger mode either agglomerates or aggregates of these materials or agglomerates in combination with background particles, following scavenging by these particles. Given the irregular nature of the distribution in most cases, it is inappropriate to summarise the distribution by a single set of parameters such as median and diameter and geometric standard deviation.

Devices which measure size distribution such as the SMPS (Scanning Mobility Particle Sizer/ Stepped Mobility Particle Sizer) and Fast Mobility Particle Sizer (FMPS) provide a particularly data rich output. These devices produce count data in several size bins either collected in parallel (in the case of the FMPS) or in a very close time sequence (in the case of the SMPS). There are several ways in which this data might be used. The simplest approach is to inspect

the complete size distribution. This is particularly useful in assessing single events or single changes (e.g. the implementation of a control measure, or the comparison between an aerosol and a background). However, this type of analysis is difficult to quantify as multimodal distributions cannot be easily described and compared by summary statistics such as the geometric mean and standard deviation.

An alternative is to sum the total counts to provide a single number. However this approach looses the size information and so it is of limited value. In the reviewed studies, several authors (e.g. Fujitani *et al*., 2008; Bello 2008, 2009) have grouped (integrated) the size distribution into several discrete size ranges e.g. < 10 nanometres, < 100 nm , < 1000 nm etc. and examining the size ranges compared their respective time series to support the development of the background discrimination strategies or understanding of the particle formation dynamics, for each. This can be highly effective in looking at how different parts of aerosol distribution change with time.

2.1.1.4. Maximum relevant size

Use of size dependent-health related criteria is common practice in measurement of occupational exposure (CEN 1993, ISO, 1995). From the preceding section it is clear that the size distribution of aerosols which are present in workplaces where nanomaterials are synthesised or used typically have a broad distribution. An important issue to consider is whether it is appropriate to impose an upper size limit of the particles to be collected or measured in order to characterise exposure to NM. One option would be to exclude all particles with physical dimensions greater than 100 nm, providing methods where available. This would allow estimation of human exposure to “nanoparticles” as formally defined in ISO/TS 27687:2008 ISO 2008

Evidence from the studies reviewed suggests that emissions are rarely in the form of single nanoparticles (this is not to exclude this possibility entirely). In most cases the measurements indicated that where nanoparticles were present, they were in an aggregated or agglomerated form or were associated with other materials including background particles. In the main studies reviewed, the selected strategies were to maximise the information available by looking at a wide particle size range (and thus not operate with a 100nm cut-off). The implicit assumption in that is that agglomerates, aggregates and other combined particles are at least potentially relevant NM exposures. The relevance of these agglomerated forms, including potential for dissolution, or dissagregation, needs to be considered also from the toxicological perspective in the risk characterisation.

Many devices used do already have a maximum measurable particle size. For example several of the condensation particle counters (CPCs) have a cut-off (maximum size) of 1000 nm which is achieved by including an impactor in the inlet. This can be to protect the instruments’ detection system or because of decreasing detection efficiency beyond that size. There is a rationale to standardise that, particularly if emphasis is given to (total) number concentration as a parameter. Otherwise, two instruments, with different maximum sizes will give different results. However, this is not a health based selection criterion.

One approach could be to use the respirable convention as an upper size limit (CEN 1993, ISO, 1995).). This would have the advantage of being biologically relevant and would provide coherence with current practice in occupational exposure assessment. Use of the respirable convention has been recommended by several authors (e.g. Schneider and Jensen, 2008). Respirable concentrations have been measured in several of the reviewed studies (e.g. Peters et al., 2009; Han *et al*., 2008).

In general however, given the current state of knowledge, the practice adopted in the reviewed studies, assessing multiple parameters with multiple instruments, seems correct. Where the maximum (and indeed minimum) size limits of an instrument and the instrument response function are known, this should be clearly stated.

2.1.1.5 Effect of high spatial and temporal variability

In occupational settings it is common that airborne concentrations are higher and closer to the source worker (near-field) than at some distant point (far-field). High spatial variability has been reported in the studies reviewed. Demou *et al*. (2009) reported both high and low spatial variability in different settings. Plitzco (2009) reported "genuine nanoparticles" emitted from a reactor that agglomerated in a very short time and immediately led to a lowering of the number concentration. Seipenbusch *et al*. (2008), as part of the FP6 project NANOTRANSPORT, investigated the evolution in time of a nanoparticle (NP) aerosol released into a particle-free atmosphere and in the presence of a pre-existing background aerosol and demonstrated rapid agglomeration and scavenging by the background aerosol.

High spatial and temporal variability emphasise the need for measurements of exposure in workplaces that are based on personal sampling, i.e. by using a sampling device located in the breathing zone of the worker being assessed. Studies have generally shown that personal exposure is higher compared to exposure as measured in the general environment of a workplace. This is partly because the worker is usually closer to the source than static environmental monitors are able to be placed but also due to the activities undertaken by the worker himself, and the extent to which these modify the exposure levels. This may be particularly relevant for NM due to high transport, agglomeration and scavenging rates.

Measurements of workplace air concentrations will not adequately represent personal exposure. Therefore a preferred approach is the use of personal sampling devices. However given the current lack of such a device, measurements strategies which encourage (even limited) comparison between workplace air concentrations and personal exposure are recommended.

2.1.1.6 Metrics

There are three main metrics, all of which could have some utility in measuring exposure to nanoparticles. These are: i) mass concentration (units mg/m^3); ii) number concentration (units n/m^3) and; iii) surface area concentration units (m^2/m^3). A case may be made for the use of any of these metrics under certain circumstances.

The metric used to assess exposure to nanomaterials should be that which most closely links to any potential health effect. Analysis indicates that no single metric (or method) for monitoring nano-aerosol exposure will suit all nanomaterials. Rather, there will be occasions where particle number, surface area and mass concentration measurements or their combination will play an important role in evaluating potential impact.

Instrumentation is available to measure each of these metrics but there are identified practical issues in the selection and use of metrics. For mass, a key issue is a lack of sensitivity towards the nanoparticles of interest. Measurement of number concentration is in contrast highly sensitive. However, measuring particle number concentration in isolation can be misleading. In all particle number concentration measurements, the integration limits over which a particular instrument operates are critical to the reported results. Real-time measurements of surface area concentration are technically feasible but there is very limited practical experience with these instruments. The results obtained need to be carefully interpreted and the limitations and boundaries carefully examined. Issues to consider include the effect of initial aerosol charge, the composition of the material, how aggregates are dealt with (in particular where both external and internal surfaces are available) and the effect of extreme particle shape.

An ideal approach is to choose a metric which is correlated with the health effect of concern, can be relatively easily measured and be both measurable and sensitive enough to detect differences in the probable ranges encountered. Which then, is the best metric for nanoparticles and is this even a sensible question to ask? Useful preliminary questions might

be “what types of nanoparticles are we interested in?” and “what is the health effect we are trying to correlate with?”

2.1.1.7. Assessment of high aspect ratio nanomaterials

Exposure to fibrous aerosols is assessed by measuring the number (concentration) of fibres in the air with a specific shape and composition (WHO, 1997). Critical to the method is definition of a fibre, specifically a respirable fibre. WHO defines a respirable fibre as an object with length greater than 5 x 10^{-6} m (5000 nm) a width less than 3 x 10^{-6} m (3000 nm), and a length to width ratio (aspect ratio) greater than 3:1. It relies on manual counting of fibres by optical microscopy according to a set of counting rules governing size (as above), number of areas (graticules) scanned, number of fibres scanned, number density of fibres on the collection substrate, and how to deal with “bundled” or overlapping fibres. The scope of application of the WHO method is broad, as indicated in the following statement: “The method […] is applicable to the assessment of concentrations of airborne fibres in workplace atmospheres most commonly personal exposures - for all natural and synthetic fibres, including the asbestos varieties, other naturally occurring mineral fibres and man-made mineral fibres” (WHO, 1997).

Several high aspect ratio nanomaterials (HARN) could fall within this scope. It has been suggested that fibre counting could be an appropriate method to assess exposure to HARN (BSI 6699-2:2007; BSI, 2007). However concerns have been raised regarding the applicability of the WHO for HARN, specifically for CNT. Optical microscopy would not detect individual CNT although it could detect bundles of CNT. The higher magnification required would require SEM/TEM which would increase the counting time substantially.

It is known that optical microscopy is less sensitive than SEM/TEM to very fine fibres and therefore underestimates the total number of fibres collected. SEM/TEM will measure these very fine fibres which would not be observed by optical microscopy leading to larger counts in what would be an equivalent sample. This would lead to difficulties in making comparisons with limit values for fibres set using optical microscopy.

Han *et al.* (2008), used an approach based on the WHO method and report fibre concentrations. The extent to which WHO counting rules were applied is not clear. However it is noted that all the fibres reported were shorter than the WHO definition and so by strict application of the fibre counting rules the count would be zero. Bello *et al*. also collected onto a filter for EM analysis, but no fibres were identified. Han *et al*. made measurements of total carbon using a portable aethalometer. Other investigators used CPC, optical particle counter (OPC) and SMPS to try to detect although these devices prove no morphological information. A recent review on options for CNT detection and analysis (SWA, 2010a) concluded that the Electrical Low Pressure Impactor (ELPI) spectrometer may have some utility in this respect. Various off line measurement approaches reviewed by Tantra *et al*. (2007) concluded that none were immediately appropriate for measurement of occupational exposure. Currently there is no consensus on the most appropriate approach.

Assessment of fibre concentration is likely to be relevant to some high aspect ratio nanomaterials in terms of their exposure. The presence of fibres is only likely to be detected by electron microscopy. Application of the WHO approach has not yet been validated for any types of high aspect ratio nanomaterials. No specific guidance can be given at this time regarding quantitative assessment of bundles or clumps of high aspect ratio nanomaterials. However, their presence should be noted in any assessment.

2.1.1.8. Available instruments

There are a number of instruments available which measure the metrics discussed. The instruments have been described in a number of publications. Table R14-4.1 overleaf is taken from ISO/TR 27628:2007 (ISO, 2007) and describes the main types of instruments which are

currently available along with the metric which they are most often used to measure. This table is not inclusive of all of the commercial instruments which are available but nonetheless provide good general descriptions of the instrument types and purpose. Similar tables can be found in other publications (e.g. BSI 2007, ISO 2008) where further descriptions of these instruments can be found.

Table R14-4.1 Main instruments available for exposure assessment and metric measured (reproduced from ISO, 2007).

Metric	Devices	Remarks
Mass	Size selective personal sampler	No current devices offer a cut point of 100 nm. Off-line gravimetric or chemical detection is necessary. Mass may also be derived from size distribution measurements (see below).
	Size selective static sampler	The only devices offering a cut point around 100 nm are cascade impactors.
	TEOM®	Sensitive real-time monitors such as the Tapered Element Oscillating Microbalance (TEOM®) may be useable to measure nanoaerosol mass concentration on-line, with a suitable size selective inlet.
	SMPS	Real time size-selective (mobility diameter) detection of number concentration. Data may be interpreted in terms of aerosol mass concentration, only if particle shape and density are known or assumed.
	ELPI	Real time size-selective (aerodynamic diameter) detection of active surface-area concentration. Data may be interpreted in terms of mass concentration if particle charge and density are assumed or known. Size-selected samples may be further analyzed off-line.
Number	CPC	CPCs provide real time number concentration measurements between their particle diameter detection limits. Without a nanoparticle pre-separator, they are not specific to the nanometre size range (no suitable pre-separators are currently available).
	SMPS	Real time size-selective (mobility diameter) detection of number concentration.
	ELPI	Real time size-selective (aerodynamic diameter) detection of active surface-area concentration. Data may be interpreted in terms of number concentration. Size-selected samples may be further analyzed off-line.
	Optical Particle Counter	These are insensitive to particles smaller than approximately 100 nm - 300 nm in diameter, and therefore unsuitable for nanoparticle monitoring.
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on size-specific aerosol number concentration.
Surface area	SMPS	Real time size-selective (mobility diameter) detection of number concentration. Data may be interpreted in terms of aerosol surface-area under certain circumstances. For instance, the mobility diameter of open agglomerates has been shown to correlate well with projected surface area (Rogak *et al.*,1993)]
	ELPI	Real time size-selective (aerodynamic diameter) detection of active surface-area concentration. Active surface-area does

		not scale directly with geometric surface-area above 100 nm. Size-selected samples may be further analyzed off-line.
	SMPS and ELPI used in parallel	Differences in measured aerodynamics and mobility diameters can be used to infer particle fractal dimension, which can be further used to estimate surface-area.
	Diffusion Charger	Real-time measurement of aerosol active surface-area. Active surface-area does not scale directly with geometric surface-area above 100 nm. Note that not all commercially available diffusion chargers have a response that scales with particle active surface-area below 100 nm. Diffusion chargers are only specific to nanoparticles if used with an appropriate inlet pre-separator
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on particle surface-area with respect to size. TEM analysis provides direct information on the projected area of collected particles, which may be related to geometric area for some particle shapes.

2.1.1.9. Data analysis

Guidance for exposure data requires the use of summary statistics such as the mean and the 90th percentile. Many of the instruments suggested for use are real time devices which can either provide an instantaneous spot measurement or can be used to average over a set period. In some cases, summary statistics can be derived directly from the device. If this is not feasible then multiple measurements should be taken over appropriate fixed sampling periods to enable these statistics to be calculated. In these cases, the duration of the averaging period should be recorded.

2.1.1.10 Strategy

In this context, measurement strategy includes selection of instruments, how they are used and what samples are taken (incl. where and when/timing). Currently, there is no single consensus view on the most appropriate method for assessing exposure to nanomaterials. As indicated earlier in this report, there is unlikely to be a universal strategy due the many differing purposes for which measurements may be made. In studies published thus far, the purpose seems to have been primarily for identification of emission sources, quantification of same, or for the evaluation of the effectiveness of control approaches.

Initial approaches, for example that described by Brouwer *et al.* (2004), suggest a multi-instrument approach in an attempt to capture all relevant metrics and characteristics. In this study, based on the assessment of ultrafine welding fumes, the authors suggest a multi-instrument approach in which CPCs are used to identify potential sources of emissions (and background sources), an SMPS or ELPI is used to characterise size distribution and how this varies as a function of time or space combined with SEM or TEM analysis of samples collected on filters to characterise the physical or chemical form of the aerosol.

The authors recognise that each of the measurement methods has its drawbacks, but when used in combination they “may give full insight into the presence of ultrafine particle aerosols in the workplace”. They recommend however that the use of static samplers at fixed locations hampers the interpretation of the results for personal exposure of ambulatory workers and, even for workers who are positioned at fixed workstations, the interpretation will be “very inaccurate”.

BSI 6699-2 describes a three step process (BSI, 2007). The first step would involve identifying the source of nanoparticle emissions using a CPC which provides acceptable capability for this purpose, taking due consideration of any background. In the second stage aerosol surface area

measurements should be conducted with a portable diffusion charger and aerosol size distributions should be determined with an SMPS or ELPI using static (area) monitoring.
Lastly, personal sampling using filters or grids suitable for analysis by electron microscopy or chemical identification should be employed, particularly if measuring exposures to specific nanoparticles is of interest. Electron microscopy can be used to identify the particles, and can provide an estimate of the size distribution of the particle of interest.

In the US, the National Institute for Occupational Safety and Health (NIOSH) has developed a multi-stage strategy (NEAT) with an initial assessment by CPC and OPC, plus electron microscopy and elemental identification (Methner et al. 2010). The document was developed by the NIOSH team to provide specific advice on how to use the many available techniques in a coherent way. The approach described by these authors comprises three main steps. These are:

1. Identify potential sources of emissions. The recommendations are that this initial assessment should involve reviewing processes, work flow etc. to gain an understanding of where engineered nanomaterials may be used and including physical chemical properties such as size, shape, composition etc. Once the potential sources of the emissions have been identified the teams should conduct a walkthrough survey, determine the frequency and duration of each operation, determine the presence and absence of local exhaust ventilation and determine the process points where the containment is deliberately breached e.g. opening the system for product retrieval or for cleaning.

2. Conduct particle number concentration sampling. Critical to this is determining the influence of background particle concentration, e.g. by making measurements with CPC or OPC before processing or handling of nanomaterial begins. Potential incidental nanoparticles sources identified included heat sources, vacuum pumps, gas heating units, fork lift trucks etc. The authors also carried out measurements of background particle number concentration after the active processing or manufacturing took place. The average of the background number concentration before and after the task is then subtracted from the measurements made during the task. The authors identified a number of problems with their approach which could include e.g. the background particle number concentrations could remain elevated after a particular task indicating that release had occurred. Once background particle number concentrations had been determined process or task specific measurements are made with the CPC and OPC simultaneously at locations near to the suspected emissions source. Airborne particle number concentrations are then determined and compared to background to determine if an emission of nanomaterials occurred.

3. Collect filter based samples. A pair of filter based air samples (in this case 37mm open face cassettes) were collected at the process task locations and or from workers engaged in the process. (Note that these open faced cassettes would not be size selective in nature). The authors comment that analysis of these samples by electron microscopy allows the determination of particle size range and degree of agglomeration of the aerosol collected. The authors indicate that one of the samples is analysed for airborne mass concentration and the other sample analysed by electron microscopy. For particle characterisation (e.g. size, shape, morphology etc.) by TEM or SEM using measurements specified in NIOSH methods 4702, 4704 or other equivalent methods. The analysis of the air samples using TEM with energy dispersive x-ray spectrometry can provide information on elemental composition.

If measurements obtained with CPC and OPC indicate that engineered nanomaterial is emitted and workers are present then personal (breathing zone) samples should be collected using the two filter strategy. One further option is to use size selection in the collection of filter based samples, e.g. the use of a cyclone to collect the respirable fraction.

The approach described is the basis of the programme of work which is reported in Methner *et al.* (2010).

One noticeable difference between this approach and that suggested by other authors is the lack of any real time collection of size information, e. g. with an SMPS or similar device. Rather the approach is dependent on collection of samples for off-line analysis to determine particle size.

The approach described by Methner *et al. (*2010) is very similar and has clearly influenced the approach suggested in guidance by OECD in their document ENV/JM/MONO(2009)16 *Emission Assessment for the Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance (OECD 2009).* Currently available guidance is reviewed in this document. Also it is clear that the apparent lack of use of sophisticated real time size information gathering equipment provides a "relatively simple" approach towards assessing exposure to engineered nanomaterials. It is maybe less challenging both in terms of timescales between collection of the sample and subsequent analysis and also the usability of this method by e.g. small to medium enterprises without access to sophisticated TEM equipment.

Brouwer *et al. (*2009) describe a strategy which has been developed within the EU sponsored NANOSH (EU FP6 contract NMP4/CT/2006/032777) project. This is a harmonised approach for measurement strategy, data analysis and reporting. In addition to time activity concentration profiles this approach enables a first step to estimate the potential for exposure to manufactured nano objects more quantitatively.

The sampling strategy developed for the NANOSH field studies was based on a mixture of scientific desirability and practical feasibility for all the partners. With respect to the instrumentation, size distributive particles concentration devices, e.g., SMPS model 3080 (TSI, USA) with a differential mobility analyzer (DMA) and a CPC model 3025 (TSI, USA) or ELPI (Dekati, Finland) formed the basis for workplace air measurements. In addition, near-real-time active surface area concentration was measured by either of the two different types of DCs i.e., LQ1 (Matter Engineering, Switzerland), or an Aerotrak 9000 (TSI, USA). The former device measures the active surface area concentration, whereas the latter one mimics the active surface area of the lung- deposited particles (Asbach et al., 2009B). In addition, particle number concentrations were measured by CPC (TSI, model 3025). The measurement devices were located next to the work station with instrument inlets (tubing) in the workers' breathing zone.

For characterization, samples on TEM grids were collected by (electrostatic) precipitators, e.g., the Nanometer Aerosol Sampler 3089 (TSI, USA).

Key element of this study was the development of a "decision logic" to estimate the likelihood of exposure to manufactured nanomaterials. A preliminary ''decision logic'' was developed to take advantage of the array of measurement results and to assist the evaluation of the results with respect to exposure to manufactured nano objects. First, for a case-by-case comparison, the average concentration during a defined period of activity should be statistically different ($p<0.05$) from either a period of non-activity (''near-field background''), or from a concentration at a ''far-field'' background position during the activity. In addition, the difference should be equal to or larger than 5%, i.e., a ratio of activity–non-activity >=1.05. Second, the characterization of the samples during the activity should indicate the presence of primary particles<100 nm or agglomerates, and the EDX elemental analysis should confirm the (elemental) identity of the objects or agglomerates similar to the manufactured nanomaterials MNM. Ideally, there should be a confirmation, that the particle size distribution (or the mode) as determined by SMPS or ELPI, is different from the background. Finally, the observations during the measurements should be evaluated, especially with respect to other sources that might generate nano- sized aerosols.

The issue of determination of background concentration was addressed in two ways, by comparison between near and far field and between periods of activity and non activity.

The decision logic as presented in this article offers guidance as regards how to proceed with data analysis. The NANOSH approach formulates decision criteria explicitly e.g. statistical significance and substantiality of difference and gives a framework to combine the different types of results. In the case that an application of decision logic shows evidence that the increment of concentration during the activity is associated with manufactured nano objects it is still unclear what the relevance of this observation might be in view of a risk assessment. The authors conclude that it can be stated that workplace air measurements still are not able to generate data for the quantitative assessment of exposure. However these studies can contribute to a better understanding of the potential for the exposure for different types of exposure situations. This contribution can be more effective and powerful if the design of measurement strategies, the data analysis and reporting are compatible.

2.2. Advice concerning specific sections of the guidance document

2.2.1. Types and routes of exposure

Types and routes of exposure are described in Section R.14.2. Inhalation exposure can be described by the concentration of the substance in air and the duration and frequency of exposure. It is generally expressed in ppm (parts per million) or amount per unit air volume inhaled, averaged over the duration of the relevant task or shift (e.g. mg/m^3 8hr Time Weighted Average (TWA)). For measurement of exposure to nanomaterials, information in relation to number concentration (especially for fibres) (i.e. $n/m^{3)}$ and surface area concentration are also considered to be of benefit (i.e cm^2/m^3).

2.2.2. Exposure estimation with measurements and modelling approaches

The preferential hierarchy for exposure data is explained in Section R.14.4.1. In the case of nanomaterials (specially considering the limitations of modelled estimates for nanomaterials) the inclusion of date derived from simulations in the hierarchy is recommended. Considering this modification the hierarchy will be updated as follows:

- measure data including the quantification of key exposure determinants;
- appropriate analogous data, (including data derived from simulations) including the quantification of key exposure determinants;
- modelled estimates.

As an example of simulation studies, Gohler *et al.* (2010) measured emissions from a sanding simulation using polyurethane coating and architectural paint containing two types of nanoparticles. During the abrasion tests, no significant difference was detected between the number concentrations of released particles of the pure coatings and of the coatings that were dosed with additives. However, larger particles containing nanoparticles were observed.

The use of simulations has, thus to be included also in Table R.14-1 modified as follows (simulations added to “medium quality data”):

Table R14-4.2: Workplace exposure assessment rating criteria

Data characteristics	Comments & interpretation
High quality data	
Actual measurement data of high quality, e.g. personal exposure data (including that obtained by biological monitoring) that are representative of the scenario being	This form of data is likely to enable a decision on whether or not there is safe use. There may be a need for more information, if key activities in the exposure scenario are

described; which have been collected and analysed according to recognised (e.g. CEN or equivalent) protocols; and that are available as sets of raw data supported by information on key exposure determinants.	not covered by measurement data presented. Data confidence is high.
Medium quality data	
Analogous measurement data of a similar quality to the above and which describe exposures that derive from: • other substances having similar exposure characteristics[1] (e.g. volatility, dustiness) and/or • other comparable activities considered likely to provide a reliable estimate of exposure for the scenario in question.	This form of data is likely to enable a decision as to whether or not the use is safe. A conclusion that there is a need for more information may be appropriate when the estimated exposure levels are close to the DNEL.
Actual measured data of intermediate quality e.g. data that have been consolidated and where only basic statistics are available to support them; where data have been obtained using non-standard protocols; where data cannot be described as being fully representative of the exposure scenario; obtained from static sampling which can be shown to reasonably represent personal exposures, etc.	Data confidence is good and this should positively affect the interpretation of the data.
Data derived from simulations which mimic the task or activity under controlled conditions	
Medium to low quality data	
Predicted exposures derived from suitable models and using input criteria/values that are relevant for the scenario and are derived from generally accepted sources.	To reflect the increased uncertainty of data, this might lead to the conclusion that there is safe use only if the exposure level is clearly lower than the DNEL. With Tier 1 modelled data in the region of the DNEL the safety of use is less certain.
Actual data of lesser quality, e.g. where data are only available from compliance monitoring or static sampling; where limited information on key exposure determinants is available.	Data confidence remains acceptable, particularly when the exposure assessment is derived from an extensive range of sources.
Analogous data of intermediate quality, e.g. conforming to the definition for actual data contained in above, but where only basic statistics are available to support them	Exposure data derived from compliance monitoring are often biased towards high-end exposures. This in-built bias should be

[1] The judgement on similarity must be provided in the CSR.

or where data points may be insufficient to suggest representativeness. **Low quality data**	taken into consideration.
Exposure data arising from sources not addressed in any of the above classes. For example, this may include data obtained from non-appropriate static sampling; circumstances where input data for models are inadequately defined or some biological monitoring data which have been used to predict airborne exposure levels.	Cannot be used to reach the conclusion that there is safe use. The conclusion that there is a need for more information, and/or interaction steps is the preferred option. The conclusion that the use is not safe may otherwise be indicated. Data confidence is questionable and these data alone cannot usefully be used to describe risk. However, such data can be useful in helping to interpret those scenarios for which some exposure data may be deficient and in guiding decisions on the scope and type of additional information needed

Additionally, the use of simulation studies replicating the task or activity of concern should be taken into account when considering the use of measured data (Section R.14.4.4).

Regarding the selection and interpretation of measured data (Section R.14.4.5) it should be noted that measurement of exposure to nanomaterials provides particular challenges. These have been highlighted in several publications (e.g. Brouwer 2009, 2010). They include discrimination from background particles, collection and analysis of size information, effective high spatial and temporal variability, choice of metrics and measurement instruments, and measurement of high aspect ratio nanomaterials. The state of knowledge on these issues is continuing to develop. Further information on current approaches is provided in BSI 6699/3 (2010), OECD (2009) and in Section 2.2.1 of this appendix.

Finally when considering the use of estimation tools (Section R.14.4.7) it should be noted that these tools have not yet been validated for use with nanomaterials. If the output of the model is used to estimate exposure for NMs, this should preferably be supported by measured data. There should be a clear description in the CSR of the uncertainties associated with the estimated values and the consequences for the risk characterisation.

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