

Chapter 5

Monitoring Nanomaterials in the Workplace



Adrienne C. Eastlake, Luca Fontana, and Ivo Iavicoli

Abstract Increased engineered nanomaterial production, combined with widespread use and worldwide distribution, have increased the likelihood of occupational exposure. Considering that engineered nanomaterials have additional toxicological concerns relative to their larger material forms, there exists a clear need to develop, implement, and apply an adequate strategy for occupational risk assessment and management. Unfortunately, a thorough evaluation of pertinent engineered nanomaterial properties cannot be obtained using a single instrument or analytical technique. Therefore, it is recommended that the collection and characterization of engineered nanomaterials should be performed via a multifaceted approach involving the use of multiple complementary sampling tools and analytical methods.

Keywords Exposure assessment · Engineered nanomaterials · Occupational exposure · OECD three-tiered approach · NIOSH Nanomaterial Exposure Assessment Technique (NEAT 2.0) · Personal exposure

A. C. Eastlake
U.S. National Institute for Occupational Safety and Health, Cincinnati, OH, USA
e-mail: aeastlake@cdc.gov

L. Fontana · I. Iavicoli (✉)
University of Naples Federico II, Naples, Italy
e-mail: luca.fontana@unina.it; ivo.iavicoli@unina.it

5.1 Background

In recent years, the unique physicochemical properties of engineered nanomaterials (ENMs) have been widely exploited in numerous industrial and commercial sectors to improve the effectiveness of myriad consumer products and industrial applications [1]. Increased ENM production combined with widespread use and worldwide distribution have increased the likelihood of occupational exposure to ENMs. Although human exposure to ENMs may take place in any stage of a material's life cycle (from their synthesis and integration in the laboratory to their release during use or disposal of ENM-containing products), such exposures are more likely to occur in industrial facilities and/or research laboratories where ENMs are produced or handled in large quantities or over long periods of time [2]. Also, considering that ENMs have additional toxicological concerns relative to their larger material forms [3–13], there exists a clear need to develop, implement, and apply an adequate strategy for the occupational risk assessment and management of ENMs [14].

ENMs are generally considered chemicals in spite of the extraordinary classification challenges they create due to the diversity of sizes, shapes, chemical composition, and morphologies they can assume. Consequently, principles of ENM risk assessment and management traditionally used for chemicals may also be applicable to ENMs. The gold standard for chemical risk assessment and management was established by the US National Academy of Sciences [15]. According to this paradigm, the risk assessment process is based on four critical steps including hazard identification, dose–response assessment, exposure assessment, and risk characterization. Unfortunately, the application of this model to ENMs is especially challenging given limited toxicology data and few occupational exposure limits (OELs).

For example, occupational ENM monitoring can be conducted by assessing different metrics such as mass, number, and/or surface area concentration [16]. However, currently there is no international consensus on the most adequate metrics to be measured [17], although it has been suggested that ENM toxicity is closely related to surface area and number concentration, rather than mass dose [3, 18]. Moreover, the ability of ENMs to induce adverse effects has been associated with several intrinsic physical and chemical characteristics such as size, shape, and chemical composition [3, 9, 11, 19, 20]. Therefore, the development and implementation of an appropriate sampling strategy should directly measure different concentration-related metrics or, at a minimum, provide sufficient characterization of ENM physicochemical properties to allow for an accurate estimation of these dose metrics from mass-based measures of ENMs [21]. Unfortunately, a thorough evaluation of pertinent ENM properties cannot be obtained using a single instrument or analytical technique. Rather, collection and characterization of ENMs should be performed via a multifaceted approach involving the use of multiple complementary sampling tools and analytical methods [22, 23].

In the forthcoming sections, important occupational exposure assessment strategies are described to provide practical information useful for determining and characterizing ENM occupational exposure levels.

5.2 Organization for Economic Co-operation and Development

The Organization for Economic Co-operation and Development (OECD) is an intergovernmental organization with representatives from 34 countries that coordinate policies, areas of mutual concern, and work together to address international problems. Much of this work is performed through expert working groups and committees organized around topics of shared interest. The OECD Working Party on Manufactured Nanomaterials (WPMN) was established in 2005 to evaluate the safety of nanomaterials. A steering committee was formed to address the potential for human health and safety implications and to work toward creating a science-based and internationally harmonized standard [24].

5.3 OECD Three-Tiered Approach

The OECD WPMN performed a systematic comparison of 14 different published nanomaterial-specific exposure and measurement approaches (for use in the absence of OELs) and compared the similarities and key differences between these approaches [25]. This review indicated that most of the reviewed documents made use of a tiered assessment strategy. In addition, analysis of the reviewed approaches indicated that, to be valuable, an approach should be cost effective, based on current measurement methods, able to discern the ENM of interest, and capable of providing comparable results. The WPMN collated all information and created a three-tiered approach to form a comprehensive and consistent method to address gaps in the 14 methods reviewed. A summary of the OECD tiered method is provided in Fig. 5.1.

5.3.1 Tier One

5.3.1.1 Information Gathering

The aim of tier one is to gather as much information as possible about the occupational workplace under evaluation, such as processes involved and materials in use. All data gathered are then evaluated to determine if additional assessment work should be performed. Tier one can involve a walk-through of the facility to visually confirm the potential for specific tasks or processes to generate emissions, or it may consist of carefully reviewing policies and procedures related to activities involving the production or handling of ENMs. In addition, thorough characterization of materials used in the workplace (ENMs in particular) should be performed using a suite of laboratory analytical approaches as mentioned earlier. Information on the

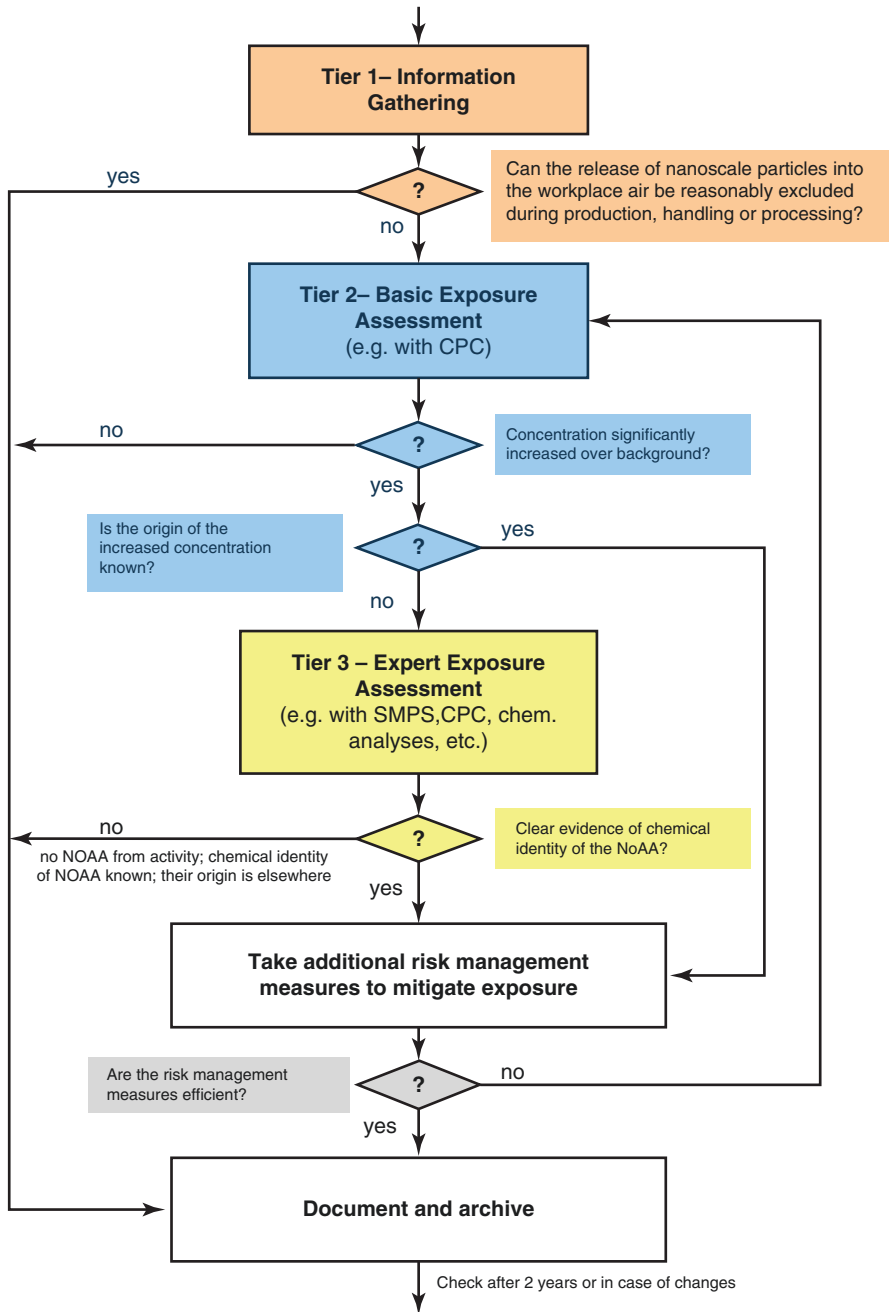


Fig. 5.1 OECD tiered approach flowchart. Reprinted from ‘Harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces’. Series on the Safety of Manufactured Nanomaterials,’ OECD. 2015, No. 55. ENV/JM/MONO(2015)19

hazard potential of a particular ENM should be evaluated. Risk management or control banding tools that allow for data collection and evaluation can be helpful at this point, e.g., Control Banding Nanotool, NanoSafer, and Stoffenmanager Nano [26–29]. If the hazard potential is high (i.e., exposure to a low concentration could lead to health effects), then tier two or tier three should be considered.

Following is a list of the minimum information typically required for effective use of risk management or control banding tools:

- Workplace information, such as type of workplace, processes, materials, production volume, and the presence of exposure control measures (such as general or local exhaust ventilation)
- ENM(s) of interest, information to include: particle structure, particle size, aspect ratio, and composition (such as powder or solid)
- Workplace activities, such as processes and tasks performed, processing of composites, presence of other processes in the workplace that could potentially effect measurement methods, and the presence or absence of ventilation

Once all data are collected and analyzed in tier one, it should be determined if there is the potential for the release of ENMs in the work environment. If the possibility for release of ENMs exists, then it is recommended to pursue tier two exposure assessment measurements.

5.3.2 Tier Two

5.3.2.1 Exposure Assessment

The aim of tier two is to determine whether an exposure to ENMs may occur. This aim is completed by making use of portable field equipment and knowledge of the material and processes gathered during tier one. As no single commercial instrument is currently capable of providing all information needed to adequately identify specific ENMs, multiple direct reading instruments (DRIs), such as condensation particle counters (CPC) or optical particle counters (OPC), are used in concert with off-line, collection-based sampling (e.g., filter-based collection). Off-line sampling media can be analyzed using electron microscopy to determine number concentration, composition, and morphological. Information gathered during tier one is essential to guide the planning and execution of the exposure assessment. It is important to select and use DRIs that are capable of measuring the ENM of interest. Tier one data will also provide input as to potential emission sources, sampling locations, and the duration of sampling required.

Background sampling should be performed to help separate process-related emissions from emissions attributable to ambient environmental conditions (e.g., nearby vehicle exhaust, neighboring industrial emissions, kitchen areas). As DRIs are unable to differentiate between the ENM of interest and naturally occurring and incidental sources, it is essential that concurrent background sampling is performed

to compare with any other sampling. Instead of making a recommendation as to how a background sample should be performed, the OECD method instead references several general methods recommended in the reviewed approaches. Some of these methods include: (1) measuring before and after processing or handling of ENMs (time variance approach); (2) measuring simultaneously in an area not affected by the processing or handling (spatial variance approach); (3) measuring in the same area where the ENM is handled or processed, but when no ENM is present; (4) or a combination of any of the above.

When DRIs are used in data log mode, it is important to note tasks and processes that take place over the entire duration of the operation evaluated, even events that might seem insignificant. This applies to DRI data collected to monitor both the processes/tasks and the background. During analysis of the data collected, any change in number or concentration can then be linked to specific activities, tasks, or processes that may have contributed to that change (i.e., a decrease based on local exhaust ventilation or an increase due to benchtop agitation/handling of a dry powder).

Based on input from subject matter experts, a minimum of 45 min of sampling is recommended for both the assessment and background [25, 30]. If possible, sampling during a specific task in addition to assessing full-shift will provide an understanding of the changes in aerosolized materials throughout the day. When sampling is complete, fluctuations in DRI data should be compared among sampling locations throughout the day. When the data indicate stable particle number concentrations for a contiguous duration, the mean and standard deviation for that stable concentration should be calculated and noted. The standard deviation for the background should be of the same order of magnitude or smaller than those obtained from the processes. If the standard deviation from the process is larger than that of the background, then it is recommended to subtract the average background from the process concentrations. If the difference of the concentrations between background and process data is more than three times the standard deviation for the background, then a tier three investigation should be conducted [30].

Data reporting requirements for tier two include:

- Instruments and metrics used
- Information on
 - Emission sources
 - Potential confounding factors (such as forklifts or motors)
 - Workplace activities performed throughout the day or process
- Concentration of DRI data reported over time
 - Analysis should indicate if process concentration is significant relative to background.
 - Trends should be evaluated and compared to workplace activity documentation.
- Off-line analysis data can be used to augment DRI data
 - Electron microscopy for ENM morphology and energy dispersive X-ray analysis for chemical identification

If tier two data indicate the location of an ENM concentration increased (exceeding three times the background standard deviation), then risk management actions should be pursued. These actions may include, for example, the installation and use of local exhaust ventilation. The effectiveness of any risk management action should be verified by repeating all tier two sampling and analyses to verify a decrease in exposure potential.

5.3.3 Tier Three

5.3.3.1 Expert Exposure Assessment

The aim of tier three is to build on the information gathered in both tier one and tier two, by determining if the potential for ENM exposure exists or if additional risk management actions need to be taken. In tier three, all appropriate exposure assessment techniques, equipment, and samplers should be used to identify the potential for occupational exposure.

In tier three, measurement methods may include instruments that are not easily operated or portable. These instruments may include, but are not limited to the following: surface area monitors, diffusion chargers, electrical mobility analyzers, and aerodynamic particle sizers. These instruments may require expert experience in order to use, analyze, and interpret the data obtained. As in tier two, DRI data must be collected in concert with off-line analysis to determine number concentration, composition, and morphological characteristics or mass concentration. Off-line analyses can also include mass analysis or collection and interpretation of surface wipe samples. Information gathered during tier one is essential to guide the overall planning and performance of the exposure assessment.

Data reporting requirements for tier three are the same as indicated for tier two. Additional DRIs are used in tier three, which may require additional data analysis and focus on particle sizes and ranges.

Data analysis requirements are indicated below:

- The average, maximum, and minimum data should be provided for the particle spectrum in addition to the particle size range (i.e., <100 nm or 1–400 nm).
 - This should include background and any other area locations sampled.
- If similar data were collected by different instruments, then any variability between instruments should be taken into consideration.
- When data are logged over a period of time, it is important to note every workplace event that may have caused an increase or decrease and interpret the data within the appropriate context.

If tier three data indicate an ENM concentration increase over background, then risk management actions should be taken in accordance with the hierarchy of controls. The effectiveness of any risk management action should be verified by

repeating all tier two and tier three sampling and analyses to verify a decrease in exposure potential.

5.4 United States National Institute for Occupational Safety and Health (NIOSH)

The NIOSH is the United States federal agency that conducts research and provides guidance and recommendations on occupational injury and illness. Since 2004, the NIOSH Nanotechnology Research Center has been performing research to:

- Increase the understanding of ENM worker hazards and health risks
- Identify and fill research gaps regarding ENM hazards
- Create and provide ENM guidance materials to inform a wide variety of audiences on hazards, risks, and appropriate risk management strategies
- Perform epidemiologic studies on ENM workers
- Assess and promote national and international risk management guidance

As part of ENM exposure assessment research, the NIOSH field team has performed over 120 exposure assessments since 2006. By collecting field data in a variety of facilities on many different ENMs, the NIOSH field team has been able to create a method that is both adaptable for a variety of facility types and flexible enough to be used for different types of materials.

5.5 United States NIOSH Approach: Nanomaterial Exposure Assessment Technique (NEAT 2.0)

The Nanomaterial Emission Assessment Technique (NEAT) was first published in 2010 to assist occupational safety and health specialists with the identification and measurement of ENMs in the workplace [31, 32]. In addition to the method, data were published on 16 field assessments that used the method [32, 33]. NEAT was included in the OECD review of tiered approaches. The original method focused on the use of DRIs to detect emissions from short-term tasks or processes. The collection of off-line filter-based samples was used, but the data obtained from these samples could not be compared to any existing ENM-specific OELs as they were not taken over a full-shift or in the worker's personal breathing zone (PBZ) (defined as a 30 cm hemisphere around mouth and nose). In addition, at this time, OELs did not exist for most ENMs. NEAT did not address the potential for the following: fluctuation of DRI data because of incidental or intermittent background particles; or, extended exposure to ENMs such as full-shift or performing multiple ENM tasks.

Based on ongoing NIOSH field team research, it was determined that the methods described in the NEAT method were focused on *emissions* as opposed to a comprehensive *exposure* assessment. Therefore, as the knowledge, experience, and

Table 5.1 Components of the Nanomaterial Exposure Assessment Technique (NEAT 2.0)

Collect basic workplace information	Design and implement the sampling plan	Risk assessment	Risk management
Work flows, staffing, and tasks Materials used Safety data sheets Literature review Anticipate and recognize hazards Other indicators of potential exposure situations	Full-shift and task-based integrated filter sampling for elemental mass and microscopy characterization. Direct reading instruments Evaluate ventilation and engineering controls	Evaluation of data: Background Engineering Controls Worker Practices Develop strategies to mitigate exposure potential based on results and utilizing the hierarchy of controls. Communicate potential occupational risks	Confirmation of continued risk control Additional measurements or controls may be required

Reprinted from ‘Refinement of the Nanoparticle Emission Assessment Technique into the Nanomaterial Exposure Assessment Technique (NEAT 2.0),’ Eastlake AC, Beaucham C, Martinez KF, Dahm MM, Sparks C, Hodson LL & Geraci CL. (2016) *Journal of Occupational and Environmental Hygiene*, 13:9, 708–717

measurement techniques progressed, it became possible to revise the emission-centered technique to focus on exposure assessment [4]. The Nanomaterial Exposure Assessment Technique (NEAT 2.0) is a series of codependent elements that are used to perform a comprehensive exposure assessment to characterize the potential for worker exposure to ENMs as opposed to focusing on task and process emissions [4]. A summary of the components of the NIOSH NEAT 2.0 is provided in Table 5.1.

The key component of NEAT 2.0 is the use of tandem off-line filter-based sampling. It is recommended that one of these samples be analyzed for mass and the other with electron microscopy. These samples are collected on filter media consistent with the type and composition of the ENM of interest. These samples are collected in the workers’ PBZ, area(s) close to the task or processes evaluated, and in a background (far field) area. The selected background area should be away from the task or processes evaluated and on a different ventilation system. PBZ samples can be collected full-shift for comparison with any existing OELs or shorter durations, such as for identifying exposures specific to a particular task [5, 6]. It should be noted that there are still relatively few OELs available for ENMs.

For three nanoparticles—titanium dioxide (TiO₂), carbon nanotubes (CNTs), and carbon nanofibers (CNFs)—NIOSH has completed a risk assessment and provided risk management guidelines, including detailed sampling and analysis guidance and recommended exposure limits (RELs), which are believed to be protective over a working lifetime [5, 6]. As of this writing NIOSH has a proposed REL for silver nanomaterials [7]. These RELs are expressed as the respirable fraction of mass per unit volume, over a full work shift:

- Ultrafine TiO₂: REL = 300 micrograms per cubic meter (µg/m³)
- Carbon nanotubes (CNTs) and carbon nanofibers (CNFs): REL = 1.0 µg/m³ as elemental carbon
- Silver nanomaterials: REL = 0.9 µg/m³

Comparing nanomaterial exposure levels to the OELs for larger forms of the material may not properly protect workers as studies have determined that ENMs may be more toxic than their larger material forms [3, 5–13, 20, 34]. Electron microscopy analysis should be used to confirm the presence of an ENM by matching its physico-chemical characteristics in a collected field sample with its characteristics in a known bulk sample. As existing analytical methods for elemental mass may not be specific to the ENM of interest, modifications to the collection process may need to be performed to obtain results (such as maximizing flow rates to collect sufficient mass).

DRI's are used to determine variations in number, mass concentration, and/or approximate size range of particles. As not all instruments are capable of determining the presence of all types of particles (such as due to high aspect ratio), this method recommends the use of a suite of DRI's together at the same locations where filter-based samples are collected (such as work process area and background). These instruments are used in data-log mode and, if accurate notes are taken detailing worker processes throughout the day, can provide insight into specific worker activities or tasks that contribute to an increase or decrease in particle concentrations or counts. These instruments typically include, but are not limited to, the following: (1) CPC; and/or (2) OPC.

5.5.1 Collect Basic Workplace Information

Initial characterization of the worksite consists of obtaining information on the work processes used, the workers, and the ENM of interest. Information can be obtained through a walk-through of the facility and interviews with workers. Current literature along with safety data sheets should be reviewed to determine safety and health data. It should be noted that information on many ENM-specific safety data sheets may not be accurate as they may provide information about the larger or bulk form of the material instead of information specific to the ENM, or they may lack critical information [35, 36]. Data on the ENM should be obtained such as physical aspects (e.g., size, shape, coatings) and state during use (e.g., slurry, dry powder, or composite).

The number of workers, the type of processes performed, and the workflow should be documented. Process flow diagrams should be reviewed, if available. In addition, existing ventilation systems and exposure control devices should be documented. All data should be evaluated to determine the potential for exposure hazards and emissions. If the potential for exposure exists, then a sampling plan should be designed and implemented.

5.5.2 Design and Implement the Sampling Plan

Based on data obtained in the initial worksite characterization, a sampling plan should be organized. The plan should focus on both task-based and full-shift

samples collected in both the surrounding area and PBZ to determine worker exposure. Tandem filter-based samples should be collected to allow for both mass and electron microscopy analysis. An array of DRIs can be used to support data provided by the filter-based samples. Surface wipe sampling can also be used to verify the spread of materials throughout the facility and to verify housekeeping practices are effective. Following the hierarchy of controls, both general and engineering control ventilation, administrative controls, and the use of any personal protective equipment (PPE) should be evaluated and documented.

5.5.3 Risk Assessment

Results of filter-based mass data should be compared with corresponding ENM occupational exposure limits, if available. For ENMs, such as carbon nanotubes and fibers that may include incidental materials that contribute to the mass results, such as carbon emitted from engines or combustion processes, it is important to subtract the mass of the background samples from other representative samples in order to determine the exposure potential of the ENMs. This is not necessary for ENMs that do not have environmental contributions, such as nanosilver or titanium dioxide. It is important to note that OELs for bulk or larger materials may not protect workers handling the same material in the nanoscale size range. Electron microscopy results can confirm the presence of the ENM in the location sampled. DRI data do not identify the specific type of particle (or ENM), but can document changes in particle number or concentration throughout the day. When these data are analyzed and compared with documentation of task and worker activities, they can indicate the potential for ENM release from specific tasks/processes or the effectiveness of ventilation or engineering controls. Recommendations for the use of specific engineering controls or changes in work practices should take into account all data obtained. NIOSH supports use of the hierarchy of controls and recommends the use of engineering and administrative controls before the use of PPE. PPE is the least preferred control method because it transfers the responsibility for personal safety from the employer to the employee, and there is considerable variability from one individual to the next in the use and fit of the PPE.

5.5.4 Risk Management

Once any recommended changes in work practices or engineering controls are implemented, it is recommended that subsequent sampling efforts be performed to confirm that the changes actually decrease the exposure potential as anticipated. Additional sampling should be performed annually or whenever changes are made to the process.

5.6 Other Sampling Techniques

Exposure assessments require the collection of information sufficient to determine the extent to which a worker is exposed to a particular chemical or condition during workplace activities [15]. To obtain data that most accurately represent exposure conditions, such assessments should involve the use of personal measurement devices that are able “to breathe together with the worker,” which ensures sampling of the environmental air within the worker’s PBZ [37]. Currently, comprehensive ENM exposure assessments require the use of multiple DRIs that can be impractical for personal sampling and allow only for a static measurement at a predetermined sampling position (usually located in an area near a suspected source of ENM emission) [18, 38]. Further, the expense of the most advanced characterization instruments often limits multiplexed sampling, which can be essential for distinguishing ENM emissions from background conditions.

As a result of these analytical limitations, most ENM occupational exposure literature data are provided by studies that use various combinations of DRIs designed to stitch together a more integrated picture of a particular exposure scenario (i.e., CPC, OPC, scanning mobility particle sizer, electrical low pressure impactor, micro-orifice uniform deposit impactor, diffusion chargers) [2, 16]. However, although a suite of DRIs may be placed as close as physically possible to the breathing zone of selected workers, they do not represent personal sampling. The limitations of fixed DRI sampling are especially apparent when workers move within and through the designated work environment. In some cases, the worker may move away from a DRI’s static sampling position, which can lead to the mischaracterization of a particular exposure scenario [37]. Recently, innovative samplers and monitors have been developed to overcome the limitations of static instrument positioning and allow for evaluation of individual exposure to airborne ENMs [37]. The use of these portable, small, and lightweight devices could represent an important step forward in the field of ENM exposure assessment, especially considering that both the OECD three-tiered approach and NEAT 2.0 recommend the use of both portable equipment and filter-based sampling.

5.6.1 Personal Monitors

Personal monitors are real-time devices that collect data on airborne ENM levels by measuring lung deposited surface area (LDSA) or particle number concentrations with high time resolution. Currently, five different monitors are available commercially. They are: (1) the Miniature Diffusion Size Classifier DiSCmini (Testo, Titisee-Neustadt, Germany, identical with miniDiSC); (2) the Aerasense NanoTracer (Oxility, Eindhoven, the Netherlands); (3) the Partector (Naneos, Windisch, Switzerland); (4) the Personal Ultrafine Particle Counter (PUFP C100 and C200, Enmont, New Richmond, OH; USA); and (5) the MicroAeth AE51 (AethLabs, San Francisco, CA, USA) [18, 38–46].

DiSCmini, NanoTracer, and Partector exploit the principle of unipolar diffusion charging to calculate the LDSA. Briefly, sampled particles are charged using a unipolar diffusion charger, which allows for the measurement of induced current. The induced current is directly proportional to the LDSA concentration [46]. In addition, the DiSCmini and NanoTracer are also capable of estimating the particle number concentration and the average particle diameter [18, 38]. The PUFPC100 and C200 models are water-based CPCs that measure particle number concentrations, while the MicroAeth AE51 is a portable aethalometer that is capable of measuring black carbon concentration [18, 38].

Some studies have used personal monitors to quantify occupational ENM levels and their effectiveness or applicability in routine environmental monitoring practices has been tested in several laboratory studies [2, 18, 38, 44]. In general, the accuracy and comparability of LDSA concentration measurements conducted with the DiSCmini, NanoTracer, Partector, and MicroAeth AE51 personal monitors is in the range of $\pm 30\%$. The accuracy of particle number concentrations determined by diffusion chargers can be lower since this metric is inferred by assuming parameters of the particle size distribution [18, 38, 45–48]. Although the accuracy of particle concentration measurements obtained from personal monitors falls short of more robust stationary reference instruments, the tradeoff is worth considering given that the data obtained in a worker's PBZ may provide a more realistic estimate of ENM inhalation exposure.

5.6.2 Personal Samplers

Personal samplers are instruments that collect particles using a substrate such as a filter or flat surface. Here, the emphasis is on collection and preservation of ENMs rather than their immediate detection and quantification. Substrates can be removed from personal sampling devices and characterized using sophisticated analytical techniques such as inductively coupled plasma mass spectrometry (ICP-MS); electron microscopic (scanning electron microscopy or transmission electron microscopy with chemical detectors) or Raman spectroscopy analyses to obtain information (mass, chemical composition, size, shape). Collectively, these techniques can provide a wealth of information about the ENM of interest. Several filter-based personal samplers are available: (1) the NanoBadge (Nano Inspect, Alcen group, Paris, France and French Alternative Energies and Atomic Energy Commission CEA, Grenoble, France); (2) the Nanoparticle Respiratory Deposition sampler (NRD, Zefon International, Ocala, FL, USA); (3) the handheld electrostatic precipitator (ESPnano, Spokane, WA, USA); (4) the Partector TEM (Naneos particle solutions GmbH, Windisch, Switzerland); (5) the Thermal Precipitator Sampler (TPS, RJ Lee Group, Monroeville, PA, USA); (6) the personal sampling system Personengelegenes Gefahrstoff-Probenahmesystem (PGP) (GSA Messgerätebau GmbH, Ratingen, Germany); and (7) a filtration badge and Raman spectrograph (StatPeel Switzerland) [2, 49–53].

In general, these instruments consist of a particle size-selective inlet, a filter cassette/net/grid, and a personal pump. Although they may not all be specific for nano-sized particles, their use may still be helpful in efforts to thoroughly characterize ENMs, particularly under real-world exposure scenarios. Currently, little information is available regarding the comparability of personal nanoparticle samplers to each other or to standard techniques [18, 38]. Additionally, these samplers usually use a low flow rate. Based on the subsequent analytical technique that has been chosen to characterize the sample, a low flow rate may require a long duration sample to obtain adequate sample for analytical detection. Alternatively, individual aerosol particle analysis is sensitive to oversaturation of the filter or substrate surface. When oversaturation occurs, attached or overlapping particles may confound results. Therefore, the use of a personal sampler device for ENMs requires consideration of the ENM particle number concentration, as well as the rate and duration of sampling [18]. Even under highly controlled situations, some trial and error may be necessary to adjust sampling variables to achieve optimal results. For some personal samplers, such as the partector TEM or the ESPnano, the instrument is capable of suggesting an optimal sampling duration to the operator.

5.7 Conclusions

Both the OECD tiered approach and NEAT 2.0 methods have considered the knowledge and contributions of many experts. Both methods rely on pre-assessment and final confirmation steps, but differ in recommended approaches. Within OECD, discussion regarding exposure assessment is based on the collection of airborne data from DRIs with the Tier 3 investigation triggered when the difference of the concentrations between background and process data is more than three times the standard deviation for the background. However, there is currently no consensus method on how to statistically analyze and report DRI data [54, 55]. The collection of filter-based samples is mentioned, but is not indicated as a key part of the assessment. In NEAT 2.0, integrated filter-based sampling is the key step in the exposure assessment process. Subsequent analysis of these samples is used to confirm the presence of the ENM of interest. In addition, both surface contamination and dermal exposures are noted. As DRIs are unable to effectively identify the presence or type of ENMs, they are used to support the integrated filter-based results, identify emission sources, and verify the efficacy of engineering controls. Although these methods may look similar, they are not (Table 5.2). OECD is a tiered approach, which takes the user through a stepwise process to perform both an exposure assessment and a complete risk evaluation. NEAT 2.0 is not a tiered approach, but leads the user through different codependent elements that support a comprehensive exposure assessment.

Overall, the data obtained using NEAT 2.0 may support a tiered approach to risk assessment. Given the diversity of ENM types and exposure scenarios, it is highly unlikely that a single instrument or technique will ever be capable of providing all

Table 5.2 Comparison between the OECD tiered approach and NEAT 2.0

OECD tiered approach	NEAT 2.0
Tier 1—Pre-assessment information gathering	Pre-assessment prioritization
Tier 2—Basic exposure assessment (area particle counters and EM samples)	Exposure Sampling (particle counters, EM samples, mass samples in personal breathing zone and area. Sometimes expanded into additional aerosol samples. Focus on integrated sampling with use of DRIs to identify emission sources.
Tier 3—Personal breathing zone samples, mass samples additional aerosol samples	Risk Management Summary
Confirmation	Confirmation

of the data needed for an adequate risk assessment. Further, new ENMs are introduced to workplaces and commerce with increasing frequency. Fortunately, new tools and analytical techniques are being developed to address challenges that ENMs pose workplace safety. Looking ahead, a critical role of the occupational safety professional will be to maintain awareness of current knowledge and recommended strategies regarding the identification and management of emerging workplace ENM risks.

5.8 Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention and of the other Institutions where the authors work. Mention of company or product does not constitute endorsement by NIOSH, CDC.

References

1. Leso V, Fontana L, Mauriello MA, et al. Occupational risk assessment of engineered nanomaterials: limits, challenges and opportunities. *Curr Nanosci.* 2017;13:55–78.
2. Iavicoli I, Fontana L, Pingue P, et al. Assessment of occupational exposure to engineered nanomaterials in research laboratories using personal monitors. *Sci Total Environ.* 2018;627:689–702.
3. National Institute for Occupational Safety and Health (NIOSH) (2009) Approaches to safe nanotechnology: managing the health and safety concerns associated with engineered nanomaterials; US Department of Health and Human Services, Centers for Disease Control and Prevention: Atlanta.
4. Eastlake AC, Beaucham C, Martinez KF, et al. Refinement of the nanoparticle emission assessment technique into the nanomaterial exposure assessment technique (NEAT 2.0). *J Occup Environ Hyg.* 2016;13:708–17.
5. National Institute for Occupational Safety and Health (NIOSH). Current intelligence bulletin 63: occupational exposure to titanium dioxide. Cincinnati, OH: U.S. Department of Health

- and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2011-160; 2011.
6. National Institute for Occupational Safety and Health (NIOSH). Current Intelligence Bulletin 65: Occupational Exposure to Carbon Nanotubes and Nanofibers. 2013. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2013-145; 2013.
 7. National Institute for Occupational Safety and Health (NIOSH). Revised Draft NIOSH Current Intelligence Bulletin: Health Effects of Occupational Exposure to Silver Nanomaterials. 2018. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH); 2018.. <https://www.regulations.gov/docket?D=CDC-2016-0001>. Accessed 12 Apr 2019
 8. Poland CA, Duffin R, Kinloch I, et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nanotechnol.* 2008;3:423–8.
 9. Grassian VH, O’shaughnessy PT, Adamcakova-Dodd A, et al. Inhalation exposure study of titanium dioxide nanoparticles with a primary particle size of 2 to 5 nm. *Environ Health Perspect.* 2007;115:397–402.
 10. Lam CW, James JT, McCluskey R, et al. Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation. *Toxicol Sci.* 2004;77:126–34.
 11. Oberdorster G. Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. *Inhal Toxicol.* 1996;8(Suppl):73–89.
 12. Shvedova AA, Kisin ER, Mercer R, et al. Unusual inflammatory and fibrogenic pulmonary responses to single-walled carbon nanotubes in mice. *Am J Physiol Lung Cell Mol Physiol.* 2005;289:L698–708.
 13. Shvedova AA, Fabisiak JP, Kisin ER, et al. Sequential exposure to carbon nanotubes and bacteria enhances pulmonary inflammation and infectivity. *Am J Respir Cell Mol Biol.* 2008;38:579–90.
 14. Oomen AG, Steinhäuser KG, Bleeker EAJ, et al. Risk assessment frameworks for nanomaterials: scope, link to regulations, applicability, and outline for future directions in view of needed increase in efficiency. *NanoImpact.* 2018;9:1–13.
 15. National Research Council (NRC). Risk Assessment in the Federal Government: Managing the Process. Washington DC: Committee on the Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences. National Academy Press; 1983.
 16. Iavicoli I, Leso V, Fontana L, et al. Characterization of inhalable, thoracic, and respirable fractions and ultrafine particle exposure during grinding, brazing, and welding activities in a mechanical engineering factory. *J Occup Environ Med.* 2013;55:430–45.
 17. Stefaniak AB, Hackley VA, Roebben G, Ehara K, Hankin S, Postek MT, Lynch I, Fu W-E, Linsinger TPJ, Thünemann A. Nanoscale reference materials for environmental, health, and safety measurements: needs, gaps, and opportunities. *Nanotoxicology.* 2013;7:1325–37.
 18. Asbach C, Alexander C, Clavaguera S, et al. Review of measurement techniques and methods for assessing personal exposure to airborne nanomaterials in workplaces. *Sci Total Environ.* 2017;603-604:793–806.
 19. Romero-Franco M, Godwin HA, Bilal M, et al. Needs and challenges for assessing the environmental impacts of engineered nanomaterials (ENMs). *Beilstein J Nanotechnol.* 2017;8:989–1014.
 20. Shvedova AA, Kisin E, Murray AR, et al. Inhalation vs. aspiration of single-walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress, and mutagenesis. *Am J Physiol Lung Cell Mol Physiol.* 2008;295:L552–65.
 21. Hull M, Kennedy A, Detzel C, Vikesland P, Chappell M. Moving beyond mass: the unmet need to consider dose metrics in environmental nanotoxicology studies. *Environ Sci Technol.* 2012;46(20):10881–2.

22. Groso A, Petri-Fink A, Rothen-Rutishauser B, et al. Engineered nanomaterials: toward effective safety management in research laboratories. *J Nanobiotechnol.* 2016;14:21.
23. Spinazzè A, Cattaneo A, Del Buono L, et al. Engineered nanomaterials: current status of occupational exposure assessment. *Italy J Occup Environ Hyg.* 2016;7:81–98.
24. Murashov VV, Engel S, Savolainen K, Fullam B, Lee M, Kearns P. Occupational safety and health in nanotechnology and organisation for economic co-operation and development. *J Nanopart Res.* 2009;11(7):1587–91. <https://doi.org/10.1007/s11051-009-9637-7>.
25. Organization for Economic Co-operation and Development (OECD). Harmonized tiered approach to measure and assess the potential exposure to airborne emissions of engineered nano-objects and their agglomerates and aggregates at workplaces. Series on the Safety of Manufactured Nanomaterials, No. 55. ENV/JM/MONO(2015)19; 2015.
26. Paik SY, Zalk DM, Swuste P. Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. *Ann Occup Hyg.* 2008;52:419–28.
27. Zalk DM, Paik SY, Swuste P. Evaluating the control banding nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. *J Nanopart Res.* 2009;11:1685.
28. NanoSafer. (2016) NanoSafer 1.1. <http://nanosafer.org/>. Accessed 2 Apr 2019.
29. Van Duuren-Stuurman B, Vink SR, Verbist KJ, et al. Stoffenmanager Nano version 1.0: a web-based tool for risk prioritization of airborne manufactured nano objects. *Ann Occup Hyg.* 2012;56:525–41.
30. Asbach C, Kuhlbusch TAJ, Kaminski H, et al (2012) Standard operation procedures for assessing exposure to nanomaterials, following a tiered approach. Nano GEM.
31. Methner M, Hodson L, Geraci C. Nanoparticle emission assessment technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials—part A. *J Occup Environ Hyg.* 2010;7:127–32.
32. Methner M, Hodson L, Dames A, et al. Nanoparticle Emission Assessment Technique (NEAT) for the identification and measurement of potential inhalation exposure to engineered nanomaterials—Part B: Results from 12 field studies. *J Occup Environ Hyg.* 2010;7:163–76.
33. Methner M, Beaucham C, Crawford C, et al. Field application of the Nanoparticle Emission Assessment Technique (NEAT): task-based air monitoring during the processing of engineered nanomaterials (ENM) at four facilities. *J Occup Environ Hyg.* 2012;9:543–55.
34. Warheit DB, Laurence BR, Reed KL, et al. Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats. *Toxicol Sci.* 2004;77:117–25.
35. Eastlake A, Hodson L, Geraci C, et al. A critical evaluation of material safety data sheets (MSDSs) for engineered nanomaterials. *Chem Health Saf.* 2012;19:1–8.
36. Hodson L, Eastlake A, Herbers R. An evaluation of engineered nanomaterial safety data sheets for safety and health information post implementation of the revised hazard communication standard. *J Chem Health Saf.* 2019;26:12–8.
37. EN (2012) Workplace Exposure – Terminology, EN 1540:2012–03. Beuth Verlag Berlin.
38. NanoIndEx Project. Assessment of personal exposure to airborne nanomaterials – a guidance document; 2016. http://www.nanoindex.eu/wp-content/uploads/2016/06/Nano_Brosch%C3%BCre.pdf. Accessed 12 Apr 2019.
39. Fierz M, Houle C, Steigmeier P, et al. Design, calibration, and field performance of a miniature diffusion size classifier. *Aerosol Sci Technol.* 2011;45:1–10.
40. Marra J, Voetz M, Kiesling H. Monitor for detecting and assessing exposure to airborne nanoparticles. *J Nanopart Res.* 2010;12:21–37.
41. Fierz M, Meier D, Steigmeier P, et al. Aerosol measurement by induced currents. *Aerosol Sci Technol.* 2014;48:350–7.
42. Ryan P, Son S, Wolfe C, et al. A field application of a personal sensor for ultrafine particle exposure in children. *Sci Total Environ.* 2015;508:366–73.
43. Hansen A, Rosen H, Novakov T. The Aethalometer—an instrument for the real time measurement of optical absorption by aerosol particles. *Sci Total Environ.* 1984;36:191–6.
44. Asbach C, Neumann V, Monz C, et al. On the effect of wearing personal nanoparticle monitors on the comparability of personal exposure measurements. *Environ Sci Nano.* 2017;4:233–43.

45. Todea A, Beckmann S, Kaminski H, et al. Accuracy of electrical aerosol sensors measuring lung deposited surface area concentrations. *J Aerosol Sci.* 2015;89:96–109.
46. Todea AM, Beckmann S, Kaminski H, et al. Inter-comparison of personal monitors for nanoparticles exposure at workplaces and in the environment. *Sci Total Environ.* 2017;605-606:929–45.
47. Viana M, Rivas I, Reche C, et al. Field comparison of portable and stationary instruments for outdoor urban air exposure assessments. *Atmos Environ.* 2015;123:220–8.
48. Bau S, Zimmermann B, Payet R, et al. A laboratory study of the performance of the handheld diffusion size classifier (DiSCmini) for various aerosols in the 15–400 nm range. *Environ Sci: Processes Impacts.* 2015;17:261–9.
49. Asbach C, Clavaguera S, Todea A. Measurement methods for nanoparticles in indoor and outdoor air. *Indoor and outdoor nanoparticles—Determinants of release and exposure scenarios*, vol. 48. Cham: Springer International Publishing; 2016. p. 19–49.
50. Cena L, Anthony T, Peters T. A personal nanoparticle respiratory deposition (NRD) sampler. *Environ Sci Technol.* 2011;45:6483–90.
51. Miller A, Frey G, King G, et al. A handheld electrostatic precipitator for sampling airborne particles and nanoparticles. *Aerosol Sci Technol.* 2010;44:417–27.
52. Fierz M, Meier D, Steigmeier P, et al. Miniature nanoparticle sensors for exposure measurement and TEM sampling. *J Phys Conf Ser.* 2015;617:012034.
53. Bieri R, Cattaneo S. (2018) Device for measuring the exposure to small particles, in particular nano tubes. United States patent US20180073985A1.
54. Houseman A, Virji MA, A Bayesian approach for summarizing and modeling time-series exposure data with left censoring. *Ann Work Expo Health.* 2017;61(7):773–83
55. Entink RHK, Fransman W, Brouwer DH. How to statistically analyze nano exposure measurement results: using an ARIMA time series approach. *J Nanopart Res.* 2011;13:6991–7004.

Current Topics in Environmental Health and Preventive Medicine

Series Editor

Takemi Otsuki
Kawasaki Medical School
Kurashiki
Okayama, Japan

Current Topics in Environmental Health and Preventive Medicine, published in partnership with the Japanese Society of Hygiene, is designed to deliver well written volumes authored by experts from around the globe, covering the prevention and environmental health related to medical, biological, molecular biological, genetic, physical, psychosocial, chemical, and other environmental factors. The series will be a valuable resource to both new and established researchers, as well as students who are seeking comprehensive information on environmental health and health promotion.

More information about this series at <http://www.springer.com/series/13556>

Takemi Otsuki • Mario Di Gioacchino
Claudia Petrarca
Editors

Allergy and Immunotoxicology in Occupational Health - The Next Step

 Springer

Editors

Takemi Otsuki
Department of Hygiene
Kawasaki Medical School
Kurashiki
Okayama
Japan

Mario Di Gioacchino
Department of Medicine and Aging
Science (DMSI)
University G. d'Annunzio of Chieti-Pescara
Chieti
Italy

Claudia Petrarca
Department of Medicine and Aging
Science (DMSI)
University G. d'Annunzio of Chieti-Pescara
Chieti
Italy

ISSN 2364-8333 ISSN 2364-8341 (electronic)
Current Topics in Environmental Health and Preventive Medicine
ISBN 978-981-15-4734-8 ISBN 978-981-15-4735-5 (eBook)
<https://doi.org/10.1007/978-981-15-4735-5>

© Springer Nature Singapore Pte Ltd. 2020

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

We published the second volume of this EHPM eBook series in 2017: *Allergy and Immunotoxicology in Occupational Health*. And this is a new eBook that, 3 years later, describes the next step.

As I wrote last time, the three editors will be working together in the Allergy and Immunotoxicology Scientific Committee (AISC) of the International Congress of Occupational Health (ICOH). The ICOH plenary meeting is held once every 3 years and will be held in Melbourne (Australia) in March 2021. Before that it was held in Dublin (Ireland) in 2018. In 2015 it was held in Seoul (Korea), and the previous eBook was published as a mid-term AISC activity between 2015 and 2018.

And this time, as a mid-term activity from 2018 to 2021, we decided to write this book again.

As in the previous case, we will also introduce new discoveries, following the previous case, regarding basic experimental systems related to allergy and immunotoxicity and immune abnormalities in respiratory disorders (pneumoconiosis) such as silica and asbestos. In addition, we talk about pesticide immunotoxicity—an old and new problem.

In addition, this time, a chapter was also set up on regulations on occupational medicine in relation to skin diseases and respiratory diseases. It does not specialize in occupational medicine at present, but also mentions immune reconstitution inflammatory syndrome.

In addition, taking into account clinical control and basic experiments, we devoted a number of chapters to nanomaterials to raise awareness of nanomaterials, which is a topic of recent times, as an AISC.

Readers of this book who are interested in ICOH, or who are already members of ICOH but did not know about AISC, should definitely stop by the AISC session at the 2021 meeting in Melbourne. I want you. During Dublin in 2018, I had many poster presentations with two symposiums and two oral presentation sessions. Participants from Europe also actively asked questions about basic aspects and controls in the field of occupational medicine. In addition, presentations from Africa were presented at the symposium.

In particular, from the viewpoint of allergy and immunotoxicity, there is a complex background to pay attention to in the basic occupational health activities and in the health care of workers. Therefore, it is necessary to study carefully on the issues of normal occupational health and health and also to understand the basics of allergology, immunology, and toxicology before responding. And it is also important to take precautionary measures, so further consideration of all AICS members will be important.

Among these perspectives, the eBook published in 2017 and the book *Allergy and Immunotoxicology in Occupational health: The Next Step* are intended to improve the health of readers, all researchers related to occupational health, and even workers. We hope to contribute to disease prevention.

Kurashiki, Japan
Chieti, Italy
Chieti, Italy

Takemi Otsuki
Mario Di Gioacchino
Claudia Petrarca

Introduction

This eBook highlights the importance of allergy and immunotoxicity, especially in occupational medicine. Examples of the substance include nanomaterials, pesticides, fibers, and particulate matter (silicic acid and asbestos). An important viewpoint is respiratory and skin diseases and their clinical regulation or prevention of health disorders due to allergies and immunotoxicity. This year, the second tier of the eBook, published in 2017 as *Allergy and Immunotoxicology in Occupational Health*, added the phrase “The Next Step” to the title. Also, the three editors are the same as the previous one, but all are active members of the Allergy and Immunotoxicology Scientific Committee (AISC) of the International Congress in Occupational Health (ICOH), and the previous book was ICOH 2015 and 2018 The Next Step will be published as an activity of the AISC during this year’s main competition and this year’s The Next Step. Many thanks to readers who are interested in occupational health and allergies and immunotoxicity.

Contents

1	Mechanisms of Action of Inhaled Particulates on Allergic Lung Inflammation	1
	Etsushi Kuroda	
2	Metal Nanoparticle Health Risk Assessment	17
	Luca Di Giampaolo, Claudia Petrarca, Rocco Mangifesta, Cosima Schiavone, Cinzia Pini, Alice Malandra, Francesca Bramante, Alessio Pollutri, Michele Di Frischia, and Mario Di Gioacchino	
3	Immune Toxicity of and Allergic Responses to Nanomaterials	37
	Yasuo Yoshioka, Toshiro Hirai, and Yasuo Tsutsumi	
4	Inflammation and Environmental (Ultrafine) Nanoparticles	47
	Francesca Larese Filon	
5	Monitoring Nanomaterials in the Workplace	57
	Adrienne C. Eastlake, Luca Fontana, and Ivo Iavicoli	
6	Immunotoxicity of Nanoparticles	75
	Claudia Petrarca, Rocco Mangifesta, and Luca Di Giampaolo	
7	Occupational Respiratory Allergic Diseases: Occupational Asthma	95
	Sasho Stoleski	
8	Occupational Respiratory Allergic Diseases: Occupational Rhinitis	115
	Sasho Stoleski	
9	Occupational Skin Diseases	129
	Dragan Mijakoski	

10	Expanding Concept of Immune Reconstitution Inflammatory Syndrome: A New View Regarding How the Immune System Fights Exogenous Pathogens	151
	Yumi Aoyama and Tetsuo Shiohara	
11	Workplace Risk Assessment in Occupational Allergology	171
	Dragan Mijakoski and Sasho Stoleski	
12	Pesticide and Immunotoxicology	183
	Tomoki Fukuyama and Risako Tajiki-Nishino	
13	Clinical Evaluation of Plasma Decoy Receptor 3 Levels in Silicosis	197
	Suni Lee, Shoko Yamamoto, Hiroaki Hayashi, Hidenori Matsuzaki, Naoko Kumagai-Takei, Tamayo Hatayama, Min Yu, Kei Yoshitome, Masayasu Kusaka, Yasumitsu Nishimura, and Takemi Otsuki	
14	Reduction of Antitumor Immunity Caused by Asbestos Exposure ..	215
	Naoko Kumagai-Takei, Suni Lee, Hidenori Matsuzaki, Megumi Maeda, Nagisa Sada, Min Yu, Kei Yoshitome, Yasumitsu Nishimura, and Takemi Otsuki	