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The Nano Exposure Quantifier: a quantitative model for assessing nanoparticle exposure in the workplace

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Abstract

Exposure to manufactured nanomaterials (MNs) is a growing concern for occupational health and safety. Reliable methods for assessing and predicting MN exposure are essential to mitigate associated risks. This study presents the development of the Nano Exposure Quantifier (NEQ), a mechanistic model designed to assess airborne MN exposure in the workplace. By utilizing a dataset of 128 MN measurements from existing exposure studies, the model demonstrates its effectiveness in estimating MN exposure levels for particles smaller than 10 µm. The NEQ provides estimates in terms of particle number concentration accompanied by a 95% confidence interval (CI), enabling a comprehensive assessment of MN exposure. The NEQ includes 2 quantitative models: a simplified tier 1 model and a more comprehensive tier 2 model. Both tier 1 and tier 2 models exhibit robust performance, with correlation coefficients (*r*) of 0.57 and 0.62, respectively. The models exhibit a moderate level of error, as indicated by residuals' standard deviation of 4.10 for tier 1 and 3.90 for tier 2. The tier 1 model demonstrates a slightly higher overestimation bias (1.15) compared to the tier 2 model (0.54). Overall, the NEQ offers a practical and reliable approach for estimating MN exposure in occupational settings. Future validation studies will investigate the impact of initial calibration efforts, heteroscedasticity, and further refine the model's accuracy.

Key words: emission potential; exposure assessment; exposure modeling; modifying factors; nanoparticles; risk management

What's Important About This Paper?

This paper reports on the development of a user-friendly, quantitative, and evidence-based model, the Nano Exposure Quantifier (NEQ), for assessing manufactured nanomaterial exposure in the workplace. Due to its tiered approach, the model is well suited to assess the exposure risks and thus help implement the stepwise approach of the European Commission's Safety and Sustainability by Design framework.

Introduction

Manufactured nanomaterials (MNs) are materials with at least one dimension in the nanoscale range, typically between 1 and 100 nm. Due to their small size and unique physical and chemical properties, MNs have found widespread use in numerous industrial, commercial, and consumer products. As the use of MNs continues to grow in various industries, workers in these industries are increasingly at risk of exposure to these materials. There is a growing concern about the potential health risks of MN exposure (e.g. lung cancer, cardiovascular diseases, respiratory illness), prompting the need for accurate and reliable methods for predicting and assessing exposure in the

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workplace (Borm et al. 2006; Donaldson et al. 2005; Kermanizadeh et al. 2016). The exact prevalence of occupational diseases resulting from nanoparticle exposure is not well established. This is mainly due to the lack of long-term epidemiology studies on the health effects of nanoparticle exposure, as well as the difficulty in accurately measuring exposure to nanoparticles in the workplace (NIOSH 2009). Measuring airborne MNs can pose several challenges, primarily due to the need for specialized equipment and trained personnel to ensure accurate measurements. Moreover, the diverse nature, size ranges and exposure metrics of MNs demand various sampling methods and analytical techniques, further increasing the complexity of the process. Therefore, it may be worthwhile to use exposure models to estimate the level of exposure as a preliminary assessment.

In the past decade, several pragmatic control banding tools (CB; CB nanotool, Swiss Precautionary Matrix, IVAM Guidance, Stoffenmanager Nano 1.0, Nanosafer, ANSES CB Tool) (Zalk et al. 2009; Höck et al. 2013; Jensen et al. 2013; Cornelissen et al. 2011; Riediker et al. 2012) and other qualitative tools (e.g. NanoRiskCat) have been developed to assess and manage the potential risks associated with exposure to MNs in the workplace (Hansen et al. 2011). While these tools are useful in providing a screening of potential risks associated with workplace exposures to MNs, these tools do not provide quantitative estimates on the levels of exposure in the workplace. Conventional quantitative models, such as the Advanced Reach Tool (ART; Fransman et al. 2011), also have limitations in estimating exposure to MNs and may not provide adequate background for risk assessment. The ART model, while useful in predicting exposure to conventional chemicals (Spinazzè et al. 2017; Landberg et al. 2017), is not able to account for the unique characteristics of MNs, which can influence their dustiness and subsequently affect exposure levels (Bekker et al. 2016). Therefore, relying solely on such conventional models may not provide accurate estimates of MN exposure and could result in inadequate risk assessments (OECD 2021).

Overall, developing exposure models that accurately predict MN exposure in the workplace remains a challenge due to the limited availability of well-characterized exposure measurement data, necessary to develop and validate these models. This study aims to address this challenge by the development of the Nano Exposure Quantifier (NEQ): a quantitative and evidence-based model for assessing MN exposure in the workplace. The model was developed building upon prior methodological work in the field of exposure modeling, as detailed by Van Duuren-Stuurman *et al.*, (2012) and Kuijpers et al. (2017). Subsequent validation and calibration of the model were conducted using exposure measurement data collected through a standardized data template (Jimenez et al. in preparation), specifically tailored to capture workplace exposure measurements related to MNs. This approach facilitated the development of a tiered model for assessing inhalation exposure to MNs in the workplace.

Development of the mechanistic model

Conceptual model

The NEQ is based on the source-receptor conceptual framework described by Schneider et al. (2011), which provides a comprehensive understanding of the emission pathway of MNs from the source (e.g. manufacturing process) to the receptor (e.g. worker). As proposed by Fransman et al. (2011) and Marquart et al. (2008), factors that influence emission are the emission potential, which includes the substance emission potential (SEP) and the activity emission potential (AEP). The emission potential of a substance is determined by its characteristics, while the activity emission potential is determined by the nature of the activity being performed. Research on the SEP related to dustiness has concluded that the emission of nanoparticles is not determined by their specific type, but rather by physical and chemical factors such as coating and binding strength of the particles (Schneider and Jensen, 2009; Levin et al. 2015). Other factors that influence worker exposure include interventions on transmission (e.g. local controls, ventilation) and immission (e.g. separation, personal protective equipment).

The NEQ was developed to create a practical tool for calculating MN exposure, taking into account both near-field (within 1 m of the worker's breathing zone) and far-field (remainder of the working area) sources of exposure, the SEP, and the AEP. The NEQ also considers the impact of local control measures, general ventilation, segregation, and duration of the activities on MN exposure (Fig. 1). Immission factors such as personal protective equipment are not included in the model.

Model algorithm

The NEQ calculates the relative exposure based on a range of modifying factors (MFs) and underlying exposure parameters, reflecting particle number concentrations in the air. The selection of the modifying factors and exposure parameters was based on evidence found in the peer-reviewed literature (Kuijpers et al. 2017; Van Duuren-Stuurman *et al.*, 2012), expert judgment, and relations found in the exposure measurement data library.

In the model, relative exposure (E) is calculated using Equations 1–3 with: E = exposure score; t_h =

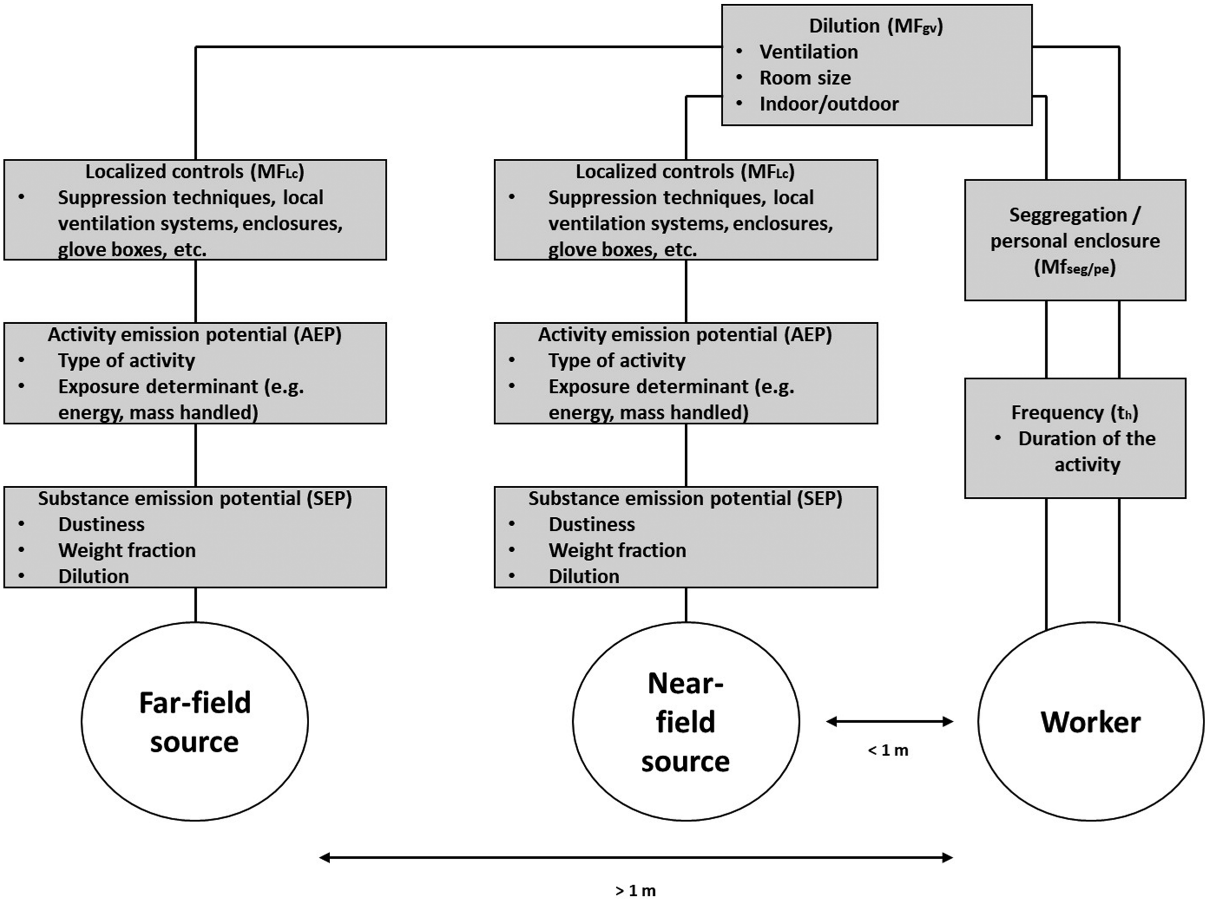

Fig. 1. Illustration of the NEQ model for inhalation exposure in the workplace. Adapted from Tielemans *et al.*, (2008).

duration of the performed activity (minutes/day); C_{nf} = concentration from near-field sources; C_{ff} = concentration from far-field sources; SEP = substance emission potential (intrinsic emission multiplier), AEP = activity emission potential (handling/task multiplier), $MF_{lc\_nf/ff}$ = multiplying factor for the use of local control measures in the near-field or far-field; $MF_{gv\_nf/ff}$ = multiplying factor for general ventilation in relation to room size for near-field or far-field sources; MF_{seg} = multiplying factor for segregation; MF_{pe} = multiplying factor for personal enclosure.

$$E = \left[C_{nf} + C_{ff}\right] \times \mathrm{MF}_{seg/pe} \times t_h \tag{1}$$

$$C_{nf} = \mathrm{SEP} \times \mathrm{AEP} \times \mathrm{MF}_{lc\_nf} \times \mathrm{MF}_{gv\_nf} \tag{2}$$

$$C_{ff} = \mathrm{SEP} \times \mathrm{AEP} \times \mathrm{MF}_{lc\_ff} \times \mathrm{MF}_{gv\_ff} \tag{3}$$

The NEQ model adopts a systematic approach to evaluate relative exposures to MNs by assigning baseline exposure values to the MN-specific activity parameters. These baseline exposure values, established in terms of particle number concentration (#/cm^3), are further refined through the application of multipliers assigned to parameters that influence airborne MN exposure. The NEQ was specifically designed to estimate total MN particle number concentrations in the range of 1 to 10,000 nm. This range was chosen to capture agglomerated nano-sized particles which often exceed the size of 100 nm. The choice of particle number concentrations as the primary metric was driven by the availability of this data within the exposure measurement library.

To develop the NEQ multipliers and baseline values, we relied on scientific studies, primarily drawing from the works of Van Duuren-Stuurman et al. (2012) and Kuijpers et al. (2017). Van Duuren-Stuurman et al. (2012) provided insights into the appropriate multipliers associated with different parameters influencing MN exposure, which served as the initial framework for our own set of multipliers. Furthermore, Kuijpers et al. (2017) provided essential data on particle number concentrations for different MN-related exposure activities. They normalized this data, derived from peer-reviewed exposure measurements by using a method that adjusted for differences in workplace conditions and measurement locations. These normalized particle number concentrations formed the foundation for establishing the NEQ baseline values, which were further refined through expert judgment and analysis of relationships found in the exposure measurement data library (see the section "Database development").

The NEQ follows a tiered approach for MN exposure assessment. The first tier is a conservative, minimal-information screening assessment. If this initial assessment raises concerns in specific areas, the second tier provides a more detailed evaluation requiring specific data, including energy levels for activities.

Source domains

The exposure parameters underlying the model's MFs are derived from 4 main sources of worker exposure during the lifecycle of nanomaterials, which are referred to as source domains in the model. These include synthesis of MNs (source domain 1), handling and transferring of bulk powdered MNs and dispersion of solid/granular intermediates, or ready-to-use MN-containing products (source domain 2), handling of liquid intermediate nano-products or application of liquid ready-to-use nanoproducts (source domain 3) and activities that result in the fracturing and abrasion of MN-containing end products (source domain 4).

Source domain 1—Synthesis of nanoparticles

In the model, source domain 1 (SD1) pertains to the emissions that occur during the MN synthesis phase, including any unintended releases during MN production and manufacturing, such as leaks or incidental exposures (excluding harvesting of the materials). During this phase, workers are potentially exposed to pristine MNs, and the level of exposure is directly affected by the production process. It was assumed that the emission potential does not vary between different types of MNs for the same synthesis process (Van Duuren-Stuurman et al. 2012). Therefore, in the tier 1 assessment, the emission potential solely consists of the AEP. The AEP is defined by the MN production process, which is categorized into 4 different groups in the model: gas-phase synthesis, mechanical reduction, chemical vapor condensation, and wet chemistry (Table S1).

Defining baseline values for the SD1 processes has posed challenges, as the tasks primarily involve controlling the closed production process (Van Duuren-Stuurman et al. 2012). Gas-phase processes (e.g. flame pyrolysis, laser ablation, and electro-spraying) have been identified as the only MN production methods that can result in direct inhalation exposure to primary MNs through reactor leaks (Aitken et al. 2004). For gas-phase synthesis methods, MN exposures ranging from 100,000 to 1,000,000 #/cm^3 have been reported (Leppänen et al. 2012; Mäkelä et al. 2009). Mechanical reduction has also shown relatively high exposure compared to the other synthesis processes with exposures up to 115,000 #/cm^3 (Koivisto et al. 2012). Wet chemistry and vapor condensation methods generally result in lower exposures. Wet-chemistry methods result in lower exposure by keeping MNs in the liquid medium, preventing dust generation. Similarly, vapor condensation forms MNs on substrates, minimizing airborne emissions (Kuijpers et al. 2017). The process of calcination involves heating a substance at high temperatures, typically to induce a chemical or physical transformation. Calcination is a closed process, that similarly to gas-phase synthesis processes can result in inhalation exposure to MNs through reactor leaks. An emission potential score of 80,000 #/cm^3 was assigned, based on exposure measurement results by Fonseca et al. (2018).

Source domain 2—Handling powder

Source domain 2 (SD2) covers the handling and transfer of bulk MN powders and the dispersion of intermediates or ready-to-use MN-containing products. In this domain, workers may be exposed to pure MNs, aerosols containing MNs, and incidentally free MNs. The level of exposure is influenced by various factors, including the type of activity, the dustiness of the MN powder, the concentration of the MN in the intermediate or MN-containing products and the mass handled.

In SD2, the AEP is determined by the activity being performed which was categorized into 5 different activity groups in the model: harvesting, dumping, mixing, cleaning (i.e. contaminated objects like a reactor), and transferring (Table S2). With regards to the activities, the tier 1 activities do not require information on the energy level nor the mass handled. For these baseline values, worst-case energy levels and mass handled were assumed. For example, for cleaning the mass handled was assumed to be 1 to 100 g and therefore the activity emission potential score of 30,000 #/cm^3 corresponds to 10,000 (cleaning high energy level * 3 (mass handled 1 to 100 g, Table S3). For dumping and mixing >1,000 g was assumed, and for transfer 100 to 1,000 g was assumed. Dumping and mixing are considered the highest exposure activities as they often involve handling amounts greater than 1 kg, whereas the other activities typically involve handling less than 1 kg (Kuijpers et al. 2017). In the second tier assessment, the AEP is refined with information on the mass handled and the energy level of the activity performed.

In this source domain, the SEP consists of the MN dustiness and MN concentration parameters, of which the categories are given in Table S3. Based on current understanding, it is believed that exposure modeling to MNs in this domain is comparable to the handling of solids in the generic exposure modeling, as nanoparticles tend to agglomerate or aggregate during these activities (Van Duuren-Stuurman et al. 2012).

Source domain 3—Liquid nano-products

Source domain 3 (SD3) pertains to the handling of liquid intermediate nanoproducts or the application of liquid ready-to-use nanoproducts. During these activities, workers may be exposed to liquid aerosols that contain MNs. The extent of exposure primarily depends on the nature of the task being performed, the concentration of the MN in the liquid, and the degree of dilution of the nanoproduct in water. In the tier 1 assessment, the AEP consists of the activity performed which is categorized into 5 different activity groups in the model: spraying, activities with open liquid surfaces and open reservoirs (e.g. stirring), spreading of liquid products (e.g. brushing/rolling), application of liquids in high-speed processes (e.g. pressure spraying) and transfer of liquid products (Table S4). In the tier 2 assessment, the activity groups are divided into subcategories with specific parameters such as the application rate, direction of the spray, and size of the open surface that determine the energy level of the activity (Table S4).

The SEP consists of parameters such as concentration and dilution, as outlined in Table S5. In tier 2, a more comprehensive assessment of dilution is necessary regarding the percentage dilution of the liquid nano-product, currently limited to water.

Exposure modeling to MNs in SD3 is expected to be similar to the handling of liquids in generic exposure modeling, as nanoparticles have been observed to agglomerate or aggregate during the activities involved (Van Duuren-Stuurman et al. 2012).

Source domain 4—Nano-embedded objects

Source domain 4 (SD4) focuses on activities that lead to the fracturing and abrasion of MN-containing end products. This exposes workers to pure matrix material, MN-embedded matrix material, and free MNs. Exposure varies based on the type of activity (manual/mechanical), the MN distribution (surface/bulk incorporated), and the MN weight fraction. The AEP includes 6 categories: (i) mechanical treatment resulting in substantial release (e.g. sanding, sawing, grinding), (ii) Mechanical treatment resulting in limited release (e.g. fine cutting, drilling), (iii) Mechanical breaking of objects (e.g. de-lumping, pulverization), (iv) Manual treatment resulting in limited release (e.g. hand sawing, hand sanding), (v) Manual treatment resulting in very limited release (e.g. hand drilling), and (vi) Manual breaking of objects (e.g. chiseling).

Tier 2 incorporates the MN location (surface bound/bulk incorporated), featuring surface-level (e.g. sanding) and body-level (e.g. drilling) activity subcategories (Table S6).

Both tiers account for the weight fraction of the MN in the end product when determining the exposure level (Table S7). According to Kuijpers et al. (2017), exposures from high-energy activities such as grinding, abrasion, and sanding were found to be the highest with particle number concentrations ranging from 4,000 to 250,000,000 #/cm^3. These activities often involve the use of high-speed machinery and tools that generate a large amount of dust. Pulverization, which involves the breaking or grinding of materials into smaller particles, typically generates larger particles than those produced during sanding or abrasive blasting. The resulting larger particles tend to settle more quickly, reducing the potential for inhalation and exposure to the dust.

Transmission factors for nanomaterials

As proposed by Van Duuren-Stuurman et al. (2012), transmission factors affecting MN exposure are similar to conventional particles. These factors include localized controls, particle dispersion in the room (near-field/far-field consideration), and source segregation. Local control measures are assumed to have similar efficacy for both nanoparticles and conventional particles, with some variations among specific control methods (Goede *et al.*, 2018).

In tier 1 assessment, transmission factors encompass local control types (e.g. wetting powder, local exhaust, containment, glove boxes/bags) and MN dispersion (Table S8). Dispersion is assessed in the near-field (within 1 meter of the worker's breathing zone) and far-field, influenced by room size and general ventilation type (Table S9, S10).

Tier 2 assessment adds control measures like segregation and personal enclosure. Segregation physically separates the MN source from workers, effectively reducing exposure. Personal enclosure considers workers operating in cabins with or without an independent clean air supply. The model assumes the same effectiveness for both nanoparticles and non-nanoparticles. However, for partial segregation, efficiency decreases, and variation increases significantly (Fransman et al. 2008), therefore, the model includes only categories for total segregation.

For tier 2 local controls, we used efficiency values from the Exposure Control Efficacy Library (ECEL) by Goede et al. 2024, supported by available data. When data were insufficient, we applied effectiveness values consistent with those in the ART model (Fransman et al. 2011).

Database development

Standardized exposure measurement template

An exposure database was created by collecting occupational exposure measurements for MNs from various published studies and own conducted experiments. A standardized data collection template from the EU-funded project GRACIOUS (GRACIOUS 2020) was used to ensure data quality and completeness. We conducted background correction on measurement data when not previously applied and background concentrations were available. Cases, where background levels exceeded measured particle numbers (n = 11), were set to a fixed value of 0.1, maintaining data integrity and allowing further analysis. For the calibration of the model, outliers were not included, ensuring that the results were based on representative data.

Missing data for model parameters such as room size, ventilation, and MN position were imputed based on expert judgment and informed by relevant literature. When possible, missing data were inferred from descriptions or schematics. Room size and ventilation rates were inferred from the study context (e.g. Dylla and Hassan, 2012) assumed a small laboratory, Tsai *et al.*, (2008) inferred room size from workroom images), and nanoparticle positioning was estimated based on the matrix type (e.g. Methner *et al.*, (2012) assumed body positioning in a polymer matrix).

To ensure scenario quality, independence, and reliability, we established selection criteria:

1. Studies utilized by Kuijpers et al. (2017) to establish NEQ baseline values were excluded to prevent bias.
2. Scenarios were considered of sufficient quality when they provided geometric mean measurements and complete parameter details, either directly or derivable from cited sources.

Extrapolation for nano-sized exposures (<10 μm)

The variation in the measurement range of direct reading devices, such as the Fast Mobility Particle Sizer (FMPS) and the DiscMini, introduces potential measurement uncertainty when comparing results obtained from different instruments, which measure different size ranges. For instance, the FMPS measures (nano)particle concentrations up to 542 nm, while the DiscMini measures up to 700 nm. To address this issue, we extrapolated the measurement results for each instrument up to 10 μm. To accomplish this, we consulted the scientific literature for size distribution plots across a range of particle sizes, from approximately 5 to 10,000 nm, for all relevant source domains. By using this information, we were able to estimate a typical particle number concentrations up to 10 μm for each of the source domains, which is the range of interest in our model. We used plotdigitizer (https://plotdigitizer.com/app), a web application, to extract particle number concentrations per particle size from size distribution plots. In cases where both an FMPS (range: 5.6 to 560 nm) and APS (range: 500 to 20,000 nm) were used, we summed the concentrations from both devices to obtain a 10-μm particle number concentration. If this was not possible, we calculated the percentage of particles in the size range captured by the measurement device and the percentage of particles in the size range that was not captured by the device, using the available typical particle size distribution data. We then extrapolated by:

$$(\text{Particle number concentration instrument}/ \\ \%\text{ of particles measured by instrument}) \times 100$$

Statistical methods

In this study, exposure concentrations (#/cm^3) were calculated for all scenarios using the entered measurement data. To validate model parameters against independent measurements, we included data for MNs with aerodynamic diameters below 10,000 nm.

It is important to note that the available data utilized in this study consisted of measurements obtained using instruments that captured total aerosols (liquid or solid), rather than individual MN particles. To ensure comparability, the weight fraction of MNs was not considered in the exposure calculations.

To assess the association between estimated and background-corrected measured particle number concentrations in tier 1 and tier 2 models, Pearson correlation coefficients were calculated. Prior to the analysis, the measurement data were log-transformed due to non-normal distribution. To quantify uncertainty, we computed 95% confidence intervals (CI) for estimated particle number concentrations by:

$$\text{CI} = \text{GMestimate} \pm 1.96 \times \text{SD error} \quad (4)$$

In a first attempt to refine the NEQ, the tier 1 and tier 2 models were calibrated using mixed-effect models (Equation 5), where γ_i is the estimated particle number concentration; β_0 is the intercept, β_1 is the fixed effect estimate and δ_i is the random effect from the scenario. The error terms σ^2_{bs} (between scenario variance) and σ^2_{ws} (within scenario variance), were used to calculate the model uncertainty factor (M) (Equation 6). This

Table 1. Summary statistics of the background corrected measurements (#/cm³) per activity in a source domain.

Source domain	Activity	GM (#/cm³)	GSD (#/cm³)	Min (#/cm³)	Max (#/cm³)	N
SD1	Calcination	1.09E+03	2.00E+00	6.81E+02	2.41E+03	3
	Chemical vapor condensation	6.04E+02	8.00E+01	1.00E-01	7.40E+03	6
	Gas-phase synthesis	4.39E+06	2.43E+01	3.50E+03	3.03E+07	7
	Mechanical reduction	3.08E+02	1.06E+03	1.00E-01	2.28E+04	3
	Wet chemistry	5.80E+05	3.07E+00	2.62E+05	1.28E+06	2
SD2	Dumping	6.68E+01	2.59E+01	1.00E-01	1.18E+04	23
	Mixing	3.15E+01	3.42E+03	1.00E-01	9.95E+03	2
	Transferring	1.73E+03	1.91E+00	9.51E+02	3.89E+03	5
SD3	Activities with open liquid surfaces and open reservoirs	4.68E+03	8.99E+00	5.21E+02	4.21E+04	3
	Spray application	5.55E+03	8.10E+02	1.00E-01	1.78E+08	12
	Transfer of liquid products	1.56E+02	3.64E+02	1.00E-01	4.11E+04	6
SD4	Mechanical breaking of objects	3.03E+00	5.28E+01	1.00E-01	1.60E+02	4
	Mechanical treatment resulting in substantial release (body level)	4.81E+04	2.50E+01	1.00E-01	7.37E+05	28
	Mechanical treatment resulting in substantial release (surface level)	1.03E+05	2.20E+00	1.81E+04	2.52E+05	24

GM, geometric mean; GSD, geometric standard deviation.

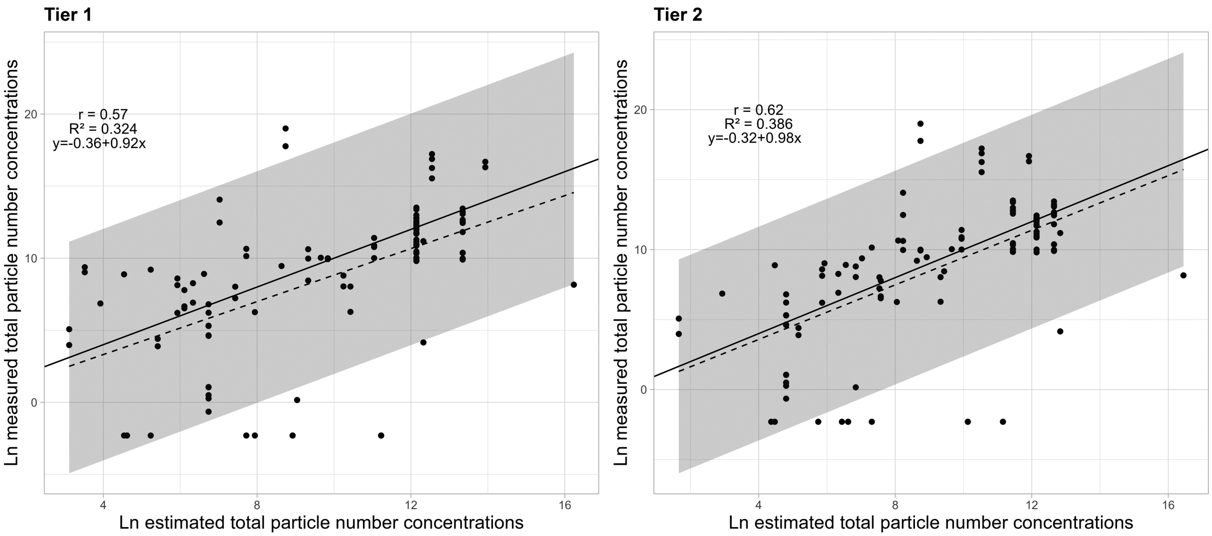

Fig. 2. Scatter plot of the natural logarithm of the measured vs. estimated total particle number concentrations with the reference line (solid), regression line (dashed), and 95% CI (gray) for the tier 1 and tier 2 models. A black reference line represents perfect agreement between the estimated and measured values.

uncertainty factor allows the NEQ to estimate the 90th percentile concentrations in addition to the GM.

$$\ln(\gamma_i) = \beta_0 + \beta_1 \times \ln(\mathrm{NEQ} - score_i) + \delta_i \quad (5)$$

$$\mathrm{M} = \mathrm{EXP}\left[1,285\sqrt{(\sigma_{\mathrm{bs}}^2 + \sigma_{\mathrm{ws}}^2)}\right] \quad (6)$$

All statistical analyses were performed using R Studio (version 2022.07.1).

Results

Summary statistics

The database comprises data from 24 exposure studies conducted in various industrial workplaces, with a total of 269 exposure measurements (Table S11). After applying the selection criteria, the final dataset included 128 exposure measurements from 14 exposure studies (Table S11). The final dataset includes only near-field measurements taken using direct reading instruments, such as CPC, SMPS, and FMPS, that provide continuous, real-time data on particle number concentrations. In terms of source domains, the majority of measurements were observed in SD4 (44%), followed by SD2 (24%), SD1 (16%) and SD3 (16%). Dumping (77%), spraying (57%), mechanical treatment resulting in substantial release (50%), and gas-phase synthesis (33%) and were the most prevalent activity categories within SD2, SD3, SD4, and SD1, respectively.

Table 1 provides summary statistics of the background corrected observed particle number concentrations for the different activities per source domain. The highest particle number concentration was observed for spray application in source domain 1 with a geometric mean of 5.55E+03 particles/cm³ (min: 1.00E-01#/cm³, max: 1.78E+08#/cm³), while the lowest concentration was observed for the mechanical breaking of objects in source domain 4 with a geometric mean of 3.03E+00 particles/cm³ (min: 1.00E-01 #/cm³, max: 1.60E+02 #/cm³).

Relationship measured and estimated particle concentrations

The relationship between the log-transformed measured and estimated particle concentrations was assessed for both the tier 1 and tier 2 models using both a linear model and correlation analyses.

The linear regression for tier 1 and tier 2 showed an intercept of respectively −0.36 ($P > 0.1$) and −0.32 ($P > 0.1$), and a slope for the estimated score of 0.92 ($P < 0.001$) and 0.98 ($P < 0.001$), respectively. A scatter plot was generated, showing a regression line along with 95% confidence intervals of the estimates, as calculated with (1), to visualize the uncertainty of the estimated relationship (Fig. 2). The plot illustrates a positive linear relationship between the natural logarithm of the estimated and measured total particle number concentrations. The tier 1 model demonstrates an R-squared value of 0.32, indicating that ~32% of the variance in the measured data is explained by the model. Similarly, the tier 2 model exhibited an R-squared value of 0.39, suggesting that approximately 39% of the variance in the measured data was explained by the model.

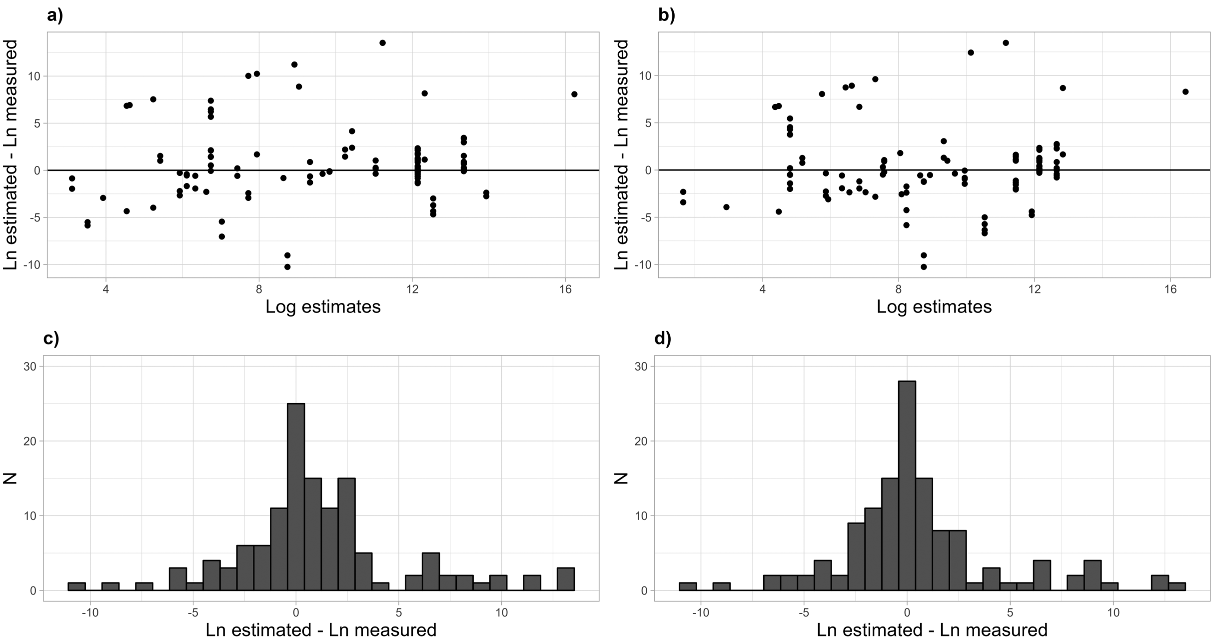

Fig. 3. Residuals plot and error distribution of the tier 1 (a,c) and tier 2 (b,d) model.

Table 2. Bias, model error, and the percentage of measurements observed within the 95% CI for the tier 1 and tier 2 models.

Tier	Bias	Model error (sd)	% < lower bound 95% CI	% > upper bound 95% CI
1	1.15	4.10	7.8	1.6
2	0.54	3.90	7.8	1.6

CI, Confidence interval; sd, standard deviation.

In addition to Fig. 2, 2 scatter plots were created to investigate the relationship between estimated and measured particle concentrations per source domain (SD) and activity level (Figs S1 and S2).

Residuals

An investigation of the model error or residuals was conducted to assess the accuracy of the estimated particle concentrations. Figure 3a,b indicated that the residuals meet the assumption of homoscedasticity, and Fig. 3c,d showed that the model errors followed roughly a normal distribution for both the tier 1 and tier 2 models which is an indication for random noise. However, especially for the tier 2 model a bias seems present.

Table 2 displays bias as mean error and the percentage of measurements within the 95% CI, calculated using (1) for both tier 1 and tier 2 models. In the tier 1 model, bias was 1.15, indicating a slight overestimation of exposures, with 7.8% estimates below the lower CI bound (compared to the expected 2.5%) and 1.6% above the upper CI bound. This suggests slightly larger tails in the distribution than expected (9.4% versus the expected 5%). The tier 2 model exhibited a bias of 0.54, also tending to overestimate exposures. Similar to the tier 1 model, 7.8% fell below the lower CI bound, and 1.6% exceeded the upper CI bound.

Both models had a model error (sd) of 4.10 for tier 1 and 3.90 for tier 2. These deviations from normality seem inconsequential given the dataset size (128), where a single data point represents almost 1% of the data, suggesting that these deviations result from a few aberrant data points.

Calibration

Table 3 presents the outcome of the model calibration using a mixed-effect model to elucidate the relationship between NEQ scores and measured particle number concentrations. The "empty model" represents the model without fixed effects, while the tier 1 and tier 2 models integrate NEQ scores as fixed effects and the exposure scenario as random effects.

Table 3. Results of the linear mixed effect models for calibration of the NEQ.

Model	N	β_0	β_1	σ^2_{bs}	σ^2_{ws}	Explained variance (%)	UF
Empty model	117	10.1	n.a.	9.30	2.30	n.a.	n.a.
NEQ Tier 1[a]	117	4.24	0.57	6.11	2.36	21.3	42.1
NEQ Tier 2[a]	117	3.68	0.65	5.23	2.46	28.5	35.3

[a]Model with NEQ scores as fixed effects and scenario as random effect; N, number of measurements used for calibration; β_0, Intercept; β_1, Fixed effect estimate; σ^2_{bs}, Between scenario variance; σ^2_{ws}, Within scenario variance; UF, Model uncertainty factor.

Introducing NEQ scores as fixed effects in the tier 1 model resulted in a between-scenario variance (σ^2_{bs}) of 6.11 and a within-scenario variance (σ^2_{ws}) of 2.36. The calibrated tier 1 model explained 21.3% of the variance, with an uncertainty factor (UF) of 42.1. The calibrated tier 2 model showed a between-scenario variance (σ^2_{bs}) of 5.23 and a within-scenario variance (σ^2_{ws}) of 2.46. This model explained 38.5% of the variance, outperforming the tier 1 calibrated model, with an uncertainty factor (UF) of 35.3.

Discussion

This study presented the development of a quantitative model for occupational exposure to MNs. The database used for validation and subsequent calibration of the model contains 128 measurements collected from existing exposure studies. The NEQ modifiers were developed with the use of previous studies (Fransman et al. 2011; Kuijpers et al. 2017; Van Duuren-Stuurman et al. 2012).

The findings of this study highlight the potential of the tier 1 and tier 2 models in estimating occupational exposure to MNs. Moreover, the significant Pearson correlation coefficients (0.57 for Tier 1 and 0.62 for Tier 2) indicate a positive and moderately strong relationship between the estimated and measured particle concentrations. Specifically, the tier 2 model exhibits a bias of 0.54 while the tier 1 model shows a bias of 1.15 indicating that the tier 1 model tends to be more conservative, leading to a higher proportion of overestimated values, which is to be expected since the simpler tier 1 model is developed to be more conservative compared to the tier 2 model. The residuals show a standard deviation of 4.10 for tier 1 and 3.90 for tier 2, which combined with the bias show the discrepancy between the models' predicted- and observed values. The calibrated tier 2 model outperformed the tier 1 model by explaining 28.5% of the variance compared to 21.3%. Additionally, the calibrated tier 2 model demonstrated a lower uncertainty factor of 35.3, indicating more precise estimates. However, assessing the performance differences between the original and calibrated models will require validation with new exposure measurement data, as planned in the forthcoming study by Vermoolen et al. (in preparation). Additionally, the number of measurements available to calibrate the model was limited, model uncertainty and explained variance might improve if more measurements are added to the calibration database in the future.

In this study, we encountered cases where the background levels exceeded the measured particle number concentrations. The presence of higher background levels can suggest the influence of external factors, such as airborne contaminants or interference sources, which may affect the accuracy of the measured particle number concentrations. These outliers (n = 11) were set to a fixed value of 0.1 and could have potentially introduced variability and influenced the results, with the exception of the calibration step, where these outliers were excluded.

It is important to acknowledge that certain factors that may influence MN exposure, such as particle coating and moisture content were not included in the current model for several reasons. Although particle coating has been recognized as a significant factor in determining dustiness (Schneider and Jensen, 2009; Levin et al. 2015) different dustiness levels have been observed for powders with hydrophilic and hydrophobic surfaces (Shandilya et al. 2019). This indicates that the presence of a coating does not consistently effect of increase or decrease in dustiness and, subsequently, exposure. Moisture content is another parameter that has been shown to impact MN exposure (Fransman et al. 2011) and is included in other exposure models, such as Stoffenmanager Nano 1.0 (Van Duuren-Stuurman et al. 2012). However, moisture content as well as coating are indirectly accounted for in the dustiness parameter. In addition, we found that the availability and accessibility of moisture content data is often limited making it difficult to include in this quantitative model. We use respirable mass-based dustiness data due to its standardization and availability. However, this may underestimate exposure to the smaller particles prevalent in nanomaterials. This method might underestimate the exposure to MNs, which often consist of numerous small particles contributing more to particle number than to mass. In addition to dustiness, repetition frequency significantly influences MN exposure (Koponen *et al*., 2015). The variation in exposure concentrations from repeating tasks is captured as a random effect in the mixed effect model and thus in the uncertainty factor which is used to calculate the 90th percentile. While the results demonstrate the models' promising potential, it is important to acknowledge certain limitations. First, the data collected may not fully represent all possible scenarios of MN exposure in occupational settings. The data collected might be biased toward certain industries or job tasks, such as fine chemical manufacturing, potentially limiting the generalizability of the findings to other occupational settings. It is important to note that approximately 16% of the measurements were categorized within SD3, indicating a slight underrepresentation of this particular domain. Moreover, certain activities such as cleaning in SD2 and spreading of liquid products in SD3 were not included in the final dataset. Additionally, the activities mixing in SD2 and mechanical reduction in SD1 are underrepresented in comparison to the other activities in this study. When assessing the performance of the tier 1 and tier 2 models across different source domains, it appears that the models perform most accurately for the activities within SD3 (as shown in Figs S1 and S2). For activities in SD1, the models tend to underestimate concentrations, which is primarily due to outliers such as for wet chemistry where the model's baseline is set to 5,000 #/cm^3, but measured values are much higher. However, with only 2 data points available for wet chemistry, we found this insufficient to warrant model adjustments. Additional data will be included in an upcoming validation paper. Also, both models tend to overestimate particle concentrations for dumping activities in SD2. This may be attributed to the wide variability observed in the "dumping" measurements. Specifically, with 23 measurements for dumping compared to only 2 for mixing and 5 for transferring, the extensive spread in dumping measurements contributes to the decreased performance for SD2 relative to SD3. This suggests a potential need to introduce additional parameters for dumping or reevaluate the chosen cutoff dump height of 50 cm. Future model validation incorporating data from currently underrepresented source domains will be essential to enhance the reliability and precision of modeling outcomes.

Second, due to the limited size of the database, we were unable to calibrate the model as has been done in previously developed models such as Stoffenmanager (Tielemans et al. 2008), ART, and AREAT (Franken *et al*., 2021). Calibration using a mixed effect model, which considers both between-worker and within-worker variation, would provide a more sophisticated approach to quantifying exposure values and characterizing model uncertainty. However, considering existing tools to estimate exposure to MNs in the workplace and the limited number of measurement data available, the NEQ has succeeded to characterize the model uncertainty. Calibration, accounting for worker variation, may be pursued in the future as more measurements become available.

Finally, it is important to note that the extrapolation process introduces inherent assumptions and potential uncertainties. The accuracy of the extrapolated particle number concentrations heavily relies on the reliability and representativeness of the available size distribution data and the assumptions made during the calculation. Therefore, it is crucial to further validate the extrapolated data with exposure measurements wherever possible and to continually improve the dataset as new data becomes available.

In the near future, new measurement data will be collected from both literature sources and measurements conducted at industry sites as part of ongoing EU projects. This data will be utilized for further validation and refinement of the model. It is worth noting that there is a scarcity of validation studies specifically focused on models estimating exposure to MNs. To our knowledge, there is only one OECD report available that assesses the performance of well-known models such as Nanosaferv1.1, Stoffenmanager Nano, GUIDEnano, and BIORIMA, among others (OECD 2021). Although the authors of the report do not refer to it as a "validation" due to the limited number of data points used for assessing the tools (around 50 measurements), Nanosafer demonstrated similar Pearson correlations to our model, ranging from 0.56 to 0.71 (OECD 2021). GUIDEnano demonstrated a nearly perfect correlation (r = 0.96), indicating its potential for effective exposure assessment. However, it is worth noting that GUIDEnano is a complex tool, potentially less user-friendly. Notably, the NEQ model requires fewer user inputs to estimate exposure concentrations in contrast to GUIDEnano. Furthermore, GUIDEnano necessitates information on the substance release rate, which may be unavailable to small and medium-sized enterprises (SMEs). The NEQ model provides added value compared to existing tools, offering promising performance while maintaining user-friendliness, making it suitable for SMEs with limited exposure assessment expertise. More details on its functions and usability will be available in Vermoolen et al. (in preparation). Overall, developing accurate MN exposure models is vital for occupational health and safety, given limited measurement data. Future research should consider material characteristics, including agglomerated MNs, for comprehensive risk assessment. Standardized data can improve model validation and applicability across workplaces. Further research is needed to address model limitations and understand MN exposure's health risks.

Conclusion

We developed a model, the NEQ, for estimating airborne MN exposure in occupational settings. Calibration of the model employed a comprehensive dataset of 128 MN exposure measurements, integrating within- and between-scenario variance to quantify model uncertainty and to be able to calculate 90th percentile exposure concentrations. Future evaluation studies are essential to further assess the model's performance, reliability, and accuracy, thereby testing its usability and robustness in diverse workplace environments.

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Conflict of interest

The authors declare no conflict of interest relating to the material presented in this Article. Its contents, including any opinions and/or conclusions expressed, are solely those of the authors.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *Annals of Work Exposures and Health* online.

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