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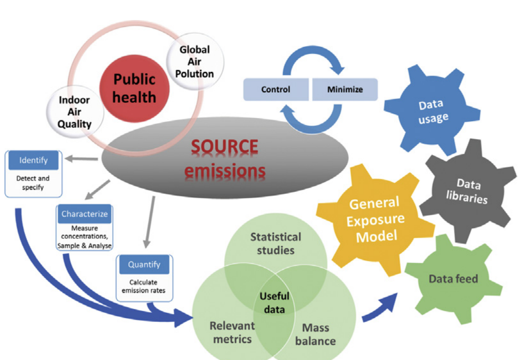
HIGHLIGHTS

- The majority of the inhalation exposure occurs in built environments.
- Indoor particle emissions have very limited regulations and are not well known.
- Indoor exposures are reduced by decrease of both outdoor and indoor air pollution.
- Particle emission sources should be documented in an emission library.
- Model development is dependent on high quality field measurements.

GRAPHICAL ABSTRACT



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ABSTRACT

Poor air quality is a leading contributor to the global disease burden and total number of deaths worldwide. Humans spend most of their time in built environments where the majority of the inhalation exposure occurs. Indoor Air Quality (IAQ) is challenged by outdoor air pollution entering indoors through ventilation and infiltration and by indoor emission sources. The aim of this study was to understand the current knowledge level and gaps regarding effective approaches to improve IAQ. Emission regulations currently focus on outdoor emissions, whereas quantitative understanding of emissions from indoor sources is generally lacking. Therefore, specific indoor sources need to be identified, characterized, and quantified according to their environmental and human health impact. The emission sources should be stored in terms of relevant metrics and statistics in an easily

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accessible format that is applicable for source specific exposure assessment by using mathematical mass balance modelings. This forms a foundation for comprehensive risk assessment and efficient interventions. For such a general exposure assessment model we need 1) systematic methods for indoor aerosol emission source assessment, 2) source emission documentation in terms of relevant a) aerosol metrics and b) biological metrics, 3) default model parameterization for predictive exposure modeling, 4) other needs related to aerosol characterization techniques and modeling methods. Such a general exposure assessment model can be applicable for private, public, and occupational indoor exposure assessment, making it a valuable tool for public health professionals, product safety designers, industrial hygienists, building scientists, and environmental consultants working in the field of IAQ and health.

1. Aerosols and their impact on human health

The air that we breathe contains a diverse mixture of gaseous and particulate matter (PM) pollutants released from natural and anthropogenic sources (Streets et al., 2009; Karagulian et al., 2015). In modern society, people spend 80 to 90% of their time indoors, where the quality of air is driven by pollutant source and loss mechanisms, including indoor emission sources in close proximity to occupants, outdoor pollutants that are transported indoors *via* ventilation and infiltration, pollutant deposition to indoor surfaces, and filtration, among others (*e.g.* Hussein et al., 2013).

Air pollution was ranked as the sixth highest risk factor attributable to Disability-Adjusted Life-Years (DALYs) in 2016 (GBD, 2017a). In 2015, over 90% of the world's population was breathing unhealthy air, with the majority of the disease burden carried by middle- and low-income countries (Landrigan et al., 2018; HEI, 2017). However, developed countries also carry their part of the disease burden attributed to poor air quality. According to the European Environmental Agency (EEA), ambient air $PM_{2.5}$ ($D_{50} \leq 2.5$ μm) concentrations alone caused *ca.* 400,000 premature deaths in the EU-27 (EEA, 2018). The World Bank (2016) estimated that air pollution in 2013 cost the global economy more than \$5 trillion in welfare losses. There is a common agreement that air pollution is globally still at an unacceptably high level and more stringent emission regulations are needed (HEI, 2017; WHO, 2016; The World Bank, 2016; OECD, 2014; IEA, 2016). For example, in the U.S., the benefits/costs ratio in air pollution regulations issued between 2004 and 2014 were economically at least four times more beneficial than the regulation expenses, being the most economically beneficial of all federal regulations (OMB, 2015). However, worldwide current regulations are mainly implemented for outdoor emissions, while there are mainly guidelines for indoor emissions (Harrison et al., 2011).

Disease burden due to ambient air pollution exposure is mainly associated with PM_{10} ($D_{50} \leq 10$ μm), $PM_{2.5}$, ozone (O_3), and nitrogen oxide (NO_X) pollutants where $PM_{2.5}$ is considered the most harmful component for human health (Landrigan et al., 2018; GBD, 2017a, 2017b; Butt et al., 2017; EEA, 2018; HEI, 2017; WHO, 2016; Lehtomäki et al., 2018). Air pollution causes a wide range of diseases (*e.g.* Thurston et al., 2017; Guxens et al., 2018; Bowe et al., 2018). Both short-term (few hours to weeks) and long-term (years to decades) $PM_{2.5}$ exposure is associated with respiratory and cardiovascular illnesses (Brook et al., 2010). For a short-term exposure, Achilleos et al. (2017) found a 0.89% increase in all-cause respiratory mortality per 10 μg m^{-3} increase in $PM_{2.5}$, and for long-term $PM_{2.5}$ exposure, the theoretical minimum for No-Observable Adverse Effect Level (NOAEL) ranges from 2.5 to 5.9 μg m^{-3} (GBD, 2017b). This is clearly lower than the WHO air quality guidelines for $PM_{2.5}$ of 25 μg m^{-3} for a 24-h mean and 10 μg m^{-3} for the annual mean (WHO, 2016).

An aerosol is a dynamic system where different compounds can be in gas, liquid, or solid phase depending on their thermodynamic equilibrium (*e.g.* Seinfeld and Pandis, 2016). Ambient PM is a complex mixture of inorganic elements from crustal or anthropogenic sources, water-soluble ions (acids, alkalines and salts) forming secondary inorganic aerosols, carbonaceous aerosols including organic carbon (OC) and elemental carbon (EC), organic compounds such as polyaromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), secondary organic aerosols (SOAs), and inhalable biological matter, including bacteria, fungi, and pollen (Nozière et al., 2015; Pernigotti et al., 2016; Liang et al., 2016; Mukherjee and Agrawal, 2017). In urban areas, the majority of PM emissions originate from local anthropogenic sources, such as traffic, industry, domestic fuel burning, and other combustion-related emissions (Karagulian et al., 2015; Liang et al., 2016), along with long-range transport of $PM_{2.5}$ (*e.g.* Lehtomäki et al., 2018).

Even though PM is a complex mixture of primary and secondary particles and condensates, epidemiological studies often focus on health effects of $PM_{2.5}$ or PM_{10} mass concentrations, regardless of their chemical composition, biological activity, or particle morphologies. This is mainly due to outdoor air quality measurement standards set in the 1990s (McClellan, 2002). However, there is increasing evidence that PM_1 ($D_{50} \leq 1$ μm) or ultrafine particulate matter (UFP; $D_{50} \leq 0.1$ μm) might have stronger associations to health effects at similar mass concentration (Seaton et al., 1995; Peters et al., 1997; Oberdörster, 2001; Donaldson et al., 2001; Nel, 2005; Politis et al., 2008; Chen et al., 2017). Chemical reactions, such as oxidation in ambient air, can change the compositions of the gaseous and PM pollutants and affect their toxicity (*e.g.* Shiraiwa et al., 2012). For example, Tyler et al. (2016) showed that freshly generated diesel and gasoline engine exhaust UFPs are inherently more toxic than PM that has lost surface-adhered volatile gases by aging.

2. Inhalation exposure to indoor aerosols

Asikainen et al. (2016) estimated that 78% of the total annual disease burden of indoor exposures in the EU was caused by $PM_{2.5}$, corresponding to a loss of 2 million DALYs annually. It was found that approximately 62% of the annual DALYs of indoor exposure was caused by the transport of outdoor $PM_{2.5}$ to the indoor environment *via* ventilation and 16% by indoor sources. Thus, according to this study, reducing outdoor concentrations is the most efficient way to make indoor air healthier. However, Chen and Zhao (2011) reviewed $PM_{2.5}$ pollutant indoor/outdoor (I/O) ratios measured in North America and Europe and found that it varies from 0.8 to 3.4, suggesting that indoor particle emission sources can still significantly contribute to indoor air pollution.

Many studies report indoor particle concentrations in residences (Bari et al., 2015; Secrest et al., 2017; Li et al., 2017), work environments (Moitra et al., 2015; Viitanen et al., 2017), public areas (Morawska et al., 2017; Chang et al., 2017), schools (Salthammer et al., 2016), or public transportation (Cepeda et al., 2017). However, quantitative particle releases from specific emission sources are seldom reported (Abadie and Blondeau, 2011), even though aerosol physics-based mathematical tools for indoor source characterization have been well established for decades (*e.g.* Nazaroff, 1989). Mass (or material) balance models account for the interplay between particle source processes that act to increase concentrations in an indoor space (*e.g.* emissions) and loss processes that act to reduce indoor concentrations (*e.g.* ventilation, deposition, and filtration).

The publicly available indoor air pollutant emission database PANDORA contains *ca.* 9000 pollutant emission rates coming from 600 indoor sources (gaseous and PM), but particle emission rates are given only for a limited number of sources: a candle or incense burning, cooking, spray use, printing, household cleaning, and wood combustion in a conventional masonry heater (Abadie and Blondeau, 2011; LaSIE, 2017). Similarly, *ca.* 2000 microbial volatile organic compound emissions from 1000 species are well documented in a public database (Lemfack et al., 2018). Detailed inventories of particle emission rates, which are strongly size-dependent, are clearly lacking and urgently needed. Recently, Koivisto et al. (2017) identified requirements for emission source characterization, which allows for predicting the source impact on the environment and human health. They established a first draft for an emission library for quantitative material releases from products containing manufactured nanomaterials.

Identification of emission sources forms a foundation for an effective indoor exposure control. The concentrations at the source are poorly diluted and can be removed or enclosed efficiently. Indoor personal exposure levels can be reduced by i) reducing outdoor ambient air concentrations, ii) removing indoor sources, iii) reducing product and process emissions by safe-by-design and building architecture, iv) applying engineered emission controls such as local exhaust ventilation systems, v) using high efficiency filter media in ventilation systems and portable air purifiers, vi) administrative changes of work organization, and vii) using personal protective equipment (PPE). Considering the emission control, emission source identification and detailed physio-chemical characterization of pollutants from molecular length scales (<3 nm) to >10 μm is critical (*e.g.* Nozière et al., 2015; Rönkkö et al., 2017). Without knowledge of source behavior, strength, and emitted chemicals, bioaerosols and other particles, it is challenging to efficiently implement safety actions as the listed above. Emission source identification is needed for the development of safer products or providing better guidance for product use before launching them to markets. For example, Sung et al. (2017) shows that a safe-by-design action reduces printer emissions by 40% and Jensen et al. (2015) demonstrated how working practices in sanding techniques affects the particle emission rate. The impact of risk management measures (RMMs) on air quality levels can be estimated by using mathematical mass balance models if emission sources and RMMs efficacies are known. This can be used to select or even design efficient RMMs for specific exposure scenarios.

3. Mathematical models for estimating indoor aerosol exposure

Indoor air quality (IAQ) can be assessed empirically and directly by suitable sampling. However, measurements are not always possible to perform to the required extent, and therefore may not provide sufficient information about the determinants of exposure. In the case of limited, or even completely missing empirical data, IAQ and exposure determinants can be alternatively assessed by means of mathematical models. Important exposure determinants that such models should include are source strengths, dispersion of pollutants, and particle removal rates by exposure and emission controls. Indoor exposure models can provide insight into exposure levels across a range of environmental conditions, facilitating efficient answers to 'what if' questions and can also be useful tools in understanding the dynamic behavior of aerosols under controlled conditions.

If implemented correctly, models can improve understanding of personal exposure, which so far has been mostly based on epidemiological studies solely based on ambient air monitoring data. For example, indoor exposure models can provide input data for epidemiological studies, which has been challenging because measurements in indoor environments on a population-representative scale have thus far not been feasible. In addition, indoor exposure models can be used for total personal exposure assessment in different and mixed daily exposure scenarios, including kindergarten/school/workplace, home, mall, transit, and outdoors (Hussein et al., 2015). A full daily personal exposure assessment is needed to understand which environments have most significant contribution to inhalation intake, dose, and health effects.

Exposure models consist of four main components describing:

- The source term (gas and PM emissions) and transformation of pollutants during release to the surroundings.
- Loss and transformation processes as described by the general dynamic equation for aerosol particles (mass balance) and chemical reactions (energy balance).
- The exposure controls reducing emissions from the source (*e.g.* local ventilation), preventing dispersion of pollutants (*e.g.* process chamber), reducing concentrations (*e.g.* portable air purifier), and use of PPE.
- A lung deposition model for estimating regional deposition of particles in respiratory tract during inspiration and expiration.

Different exposure model categories include mathematical mass balance models, knowledge-based models, and statistical models of exposure determinants (AIHA, 2009). Compared to knowledge-based or statistical models, mathematical mass balance models are transparent, have a physical concept to simplify reality, and may include physical processes, such as transformation of pollutants (*e.g.* particle coagulation). Most physical indoor air models are based on the general dynamic equation (Gelbard and Seinfeld, 1979), which describes the time rate of change of an indoor pollutant concentration by including sources, sinks (deposition, filtration), room-to-room airflows (interzonal airflows), air exchange with the outdoors, and transformation processes (*e.g.* Nazaroff, 1989; Kephalopoulos et al., 2005; Howard-Reed and Polidoro, 2006; Abadie and Blondeau, 2011). Importantly, the use of such models enables for generalization of the results across diverse indoor environments and exposure scenarios.

The general dynamic equation can be simplified according to user needs. Common simplifications are a single-compartment model for rooms with fully mixed air (Hewett and Ganser, 2017) and a two-compartment model where a concentration gradient near the source is described using a virtual volume with limited air exchange with a far-field zone (also known as a Near-Field/Far-Field (NF/FF) model; Hemeon, 1955; Nicas, 1996; Ramachandran, 2005; Jayjock et al., 2011; Ganser and Hewett, 2017; Jensen et al., 2018). Single- and two-compartment models can be useful especially in predictive top-down exposure modeling where a limited amount of information is available about the environmental characteristics.

Two-compartment models are especially useful for evaluating exposures when the occupant is in close spatial proximity to the source, *e.g.* cooking and human movement-induced dust resuspension (*e.g.* Wu et al., 2018). In such cases, the buoyant human thermal plume plays an important role in governing the transport of particles between the NF and FF (Rim and Novoselac, 2009; Licina et al., 2017; Göhler et al., 2018). Multi-compartment models, such as CONTAM, can be applied when the indoor environment (*e.g.* I/O and interzonal pressure differentials) and ventilation system characteristics (*e.g.* volumetric airflow rates and HVAC run-time) are known for a particular building. However, measurements of interzonal airflows between compartments, HVAC run-times, and long-term variations in ventilation rates are severely lacking (Liu et al., 2018; Touchie and Siegel, 2018; Alavy et al., 2018).

Regardless of the modeling approach, the emission source is the most critical parameter considering exposure to indoor generated aerosols. The particle emission source is usually described with i) a worst-case assumption - all used material is emitted and becomes airborne, ii) using a concept of dustiness index (mg kg^{-1}; *e.g.* Schneider and Jensen, 2009 and demonstrated in Levin et al., 2014), iii) by direct measurements in chamber and/or field studies. The particle emissions from powder handling are dependent on the material characteristics and properties (*e.g.* density, mechanisms and extent of aggregation and agglomeration, particle size distribution, moisture content), as well as external parameters (which can be mathematically represented by *e.g.* a handling energy factor) that are currently arbitrary and mostly qualitative values. Some studies have shown a correlation between dustiness and personal exposure to dust (Breum et al., 2003; Heitbrink et al., 1990; Brouwer et al., 2006; Ribalta et al., 2019). However, accurately connecting source parameterization concepts to measured concentrations and exposure has been shown to be challenging. As an example, in a paint factory, Koivisto et al. (2015a) demonstrated that the dustiness index did not predict the airborne respirable particle mass-concentrations during a pouring process very well. Better knowledge of the sources and their behavior, as well as more research on potentially useful concepts for representative source parameterization is needed for more accurately predicting exposure levels and mass flows of pollutants (Koivisto et al., 2017).

The RMMs and PPE properties are relatively well studied due to regulations. Fransman et al. (2008) developed an exposure control efficacy library, which contains 433 efficacy values for six RMM groups: enclosure, local exhaust ventilation, specialized ventilation, general ventilation, suppression techniques and separation of the worker. Goede et al. (2018) revised recently the exposure control efficacy library, but still more studies are needed to understand their workplace performances and append the library to cover modern RMMs (*e.g.* Yu and Kim, 2013; Mølgaard et al., 2014; Koivisto et al., 2015b). Moreover, a change from pure mass-based to aerosol dynamic modeling covering the entire nano- to μm-scale size-range would require a considerable improvement of the RMM test procedures and documentation.

4. Status of exposure assessment tools under REACH

The Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation implemented by the European Chemical Association (ECHA) demands that manufacturers or importers must determine the appropriate risk management measures and prevent excessive exposure by all relevant exposure routes (EC, 2006). Since June 2018, this is applied to all chemicals that are manufactured or imported in quantities over 1 metric ton per year within the European Union. Exposure assessment/exposure scenarios are needed on substances manufactured/imported >10 t/a and are classified as hazardous according to EU classification, labelling and packaging criteria for environmental, occupational, and consumer exposure scenarios (ECHA, 2016a). Such a task is not possible to overcome only with measurements, and therefore exposure assessment relies on mathematical exposure modeling.

ECHA accepts the use of both deterministic models, *e.g.* ConsExpo, and empirical models that are not necessary physical models, such as Stoffenmanager® (Marquart et al., 2008) and the Advanced REACH Tool (ART; Fransman et al., 2011). Empirical models are based on dimensionless exposure modifying factors to calculate an exposure score, which are further converted either to an exposure value (mg m^{-3}) by using calibration factors based on occupational exposure measurements (*e.g.* Schinkel et al., 2011). These exposure modifying factors are not always clearly described (*e.g.* the ART v1.5, Stoffenmanager® v8.0, EASE v2.0, EMKG-EXPO-TOOL, MEASE; see Savic et al. (2016) and its references), which makes the models typically more challenging to evaluate. For example, Koivisto et al. (2018a) found that the general ventilation multipliers were not correctly calculated by Cherrie (1999) in Stoffenmanager® and by Cherrie et al. (2011) in the ART. However, despite the direct error in the NF/FF ratios ranged from 0.8 to 2.8, the consequence of the error was difficult to assess due to subsequent calibration of the tools with measured exposure data and the empirical modeling approach.

The uncertainties in mechanistic or conceptual models can be seen in their poor predictive capability, which is why occupational exposure assessment substances of very high concern should rely on measured exposure levels. Comparison of modeling results using the ART and Stoffenmanager® with measurements has shown that the predicted exposure levels 90% confidence interval limits are typically two orders of magnitude or more (Lamb et al., 2015; Landberg et al., 2017, 2018; Savic et al., 2017; van Tongeren et al., 2017; Spinazzè et al., 2017; Lee et al., 2018a, 2018b). Due to modeling uncertainties, ECHA recommends using measurement data in exposure assessment of substances of very high concern (ECHA, 2016b). Properly applied physical mass-balance models appear to be stronger tools for case-specific exposure assessments (Table 1). Recent developments have demonstrated the use of the initial development of such tools including uncertainty analysis in the exposure and hazard assessments along product life-cycles as background for decision support and regulatory use (Tsang et al., 2017; Hristozov et al., 2018; Pizzol et al., 2019).

5. Current needs in aerosol exposure risk assessment and management

Aerosol exposure measurements form the foundation for understanding the exposure determinants. Measurements are needed to identify and characterize pollution sources, exposure model parameterization, performance testing and calibration, development of default exposure scenarios, and for better understanding of RMMs. This usually requires spatial concentration and size distribution measurements (ventilation air or outdoor air, Near-Field, Far-Field, and breathing zone) where exposure determinants can be solved if high quality contextual information is available regarding activities, material uses, and emission controls. Development of inexpensive and small sensors, such as shown by Crilley et al. (2018), are needed both for source and exposure identification and can be used to understand dispersion of pollutants in different indoor environments. Dispersion of pollutants is

Table 1
Ratios of predicted concentrations and measured concentrations. An update of Jayjock et al. (2011).

Scenario description	Study	Ratio of predicted and measured value
8 scenarios: Iron foundry, Dry wall finishing, weighing and transferring, mixing and cleaning	Arnold et al. (2017)	GM[a] 1.46, GSD 1.89[b]
6 scenarios: welding at two different environments (total particulate, Fe, Mn)	Boelter et al. (2009)	GM 1.08, GSD 1.25
17 test in emission rooms with volumes of 203, 169, and 8 m^3: Dry wall joint compound sanding using various tools.	Jones et al. (2011)	GM 1.08, GSD 2.54
7 Pouring scenarios at paint factory (500 kg and 25 kg sacks)	Koivisto et al. (2015a)	GM 1.01, GSD 2.32
Medical laser-generated particulate matter exposures at operating room and treatment room.	Lopez et al. (2015)	Modeled NF concentrations were between 170 and 340 μg m^{-3}, while measured were up to 246 μg m^{-3}.
Packing of inorganic fertilizer into 25 kg and 600 kg bags.	Ribalta et al. (2019)	M[c] 0.88, SD[d] 0.25 M 0.82, SD 0.12

[a] Geometric mean (GM).
[b] Geometric standard deviation (GSD).
[c] Mean (M).
[d] Standard deviation (SD).

needed to select the model design, such as number of model segments and air exchange between the segments. Closure studies are needed for indoor environments relating observations of individual particle characteristics to total concentrations, environmental parameters and activity patterns. However, comprehensive exposure assessment studies with such information are scarce. This is probably because comprehensive particle measurements standardization was recently developed (see *e.g.* CEN FprEN 17058:2018 E for occupational nanomaterial exposure assessment and Zhao et al. (2018) for I/O measurements). However, measurements and analyses not only need to be standardized, but also simple, feasible and to some extent, cost-efficient. Automated procedures are needed to limit time and user bias; otherwise, long-term studies are not economically feasible.

5.1. Measurement of relevant particle properties

There is a wide range of sampling techniques capable of providing information on the health relevant aerosol physical properties (*e.g.* mass, size, surface area, structure, charge, radioactivity), chemical aspects (molecular composition, solubility, elemental contents) and biological features (species, microbial viability, allergens, *etc.*). Nevertheless, for many important particle characteristics there is still a substantial need for new instrumentation to obtain data with high specificity, at high time resolution and at reasonable cost. In addition, the rapid development of new measurements techniques over the last decades have not been followed by a similar advancement in standardization, control and calibration of the instruments. Thus, variability between instruments may be considerable. Inter-calibration and harmonization of measurement procedures have been developed further in atmospheric research than in research of indoor environments through well-coordinated large research networks that allow comparison between field stations at different locations around the globe. Hence, experimental assessment of air quality and emissions in the built environment could probably benefit from an increased use of methodologies developed for calibration and quality control in atmospheric science.

High time resolution, on the scale of minutes, is often required to enable source identification, not least in indoor environments where temporal variability may be considerable. Aerosol morphological parameters can be determined *in-situ* by measuring the relationship between particle electrical mobility and mass (McMurry et al., 2002). Such measurements can be conducted by pairing a mobility sizer with an aerosol particle mass analyzer or centrifugal particle mass analyzer (*e.g.* Johnson et al., 2013, 2014; Rissler et al., 2012, 2014; Wang et al., 2015). This measurement technique enables for determination of size-resolved aerosol effective densities, dynamic shape factors, and fractal dimensions. However, *in-situ* assessment of the morphology of aerosols produced by indoor emission sources is very limited.

On the other hand, high spatial resolution is needed to assess distinct physico-chemical properties. There are currently rapid advancement in detection technologies that facilitates this research. Combined with energy dispersive X-ray detection, electron microscopy can serve to classify and categorize airborne collected particles according to their source (Schuetz, 1989, Scheuvens et al., 2011) and or effects, *e.g.* radiative properties (Lieke et al., 2011). The derived information from electron microscope data can be converted into quantifiable relevant metrics and assessed on a statistical basis (Weinbruch et al., 2018; Kandler et al., 2011). Current advancements in image analyses of transmission electron microscope images make it possible to derive primary particle size and specific surface area of nanoparticle aggregates (Bourrous et al., 2018) and nanoparticle structure relating to their composition (Malmborg et al., 2019); online aerosol detection with mass spectrometry enables analysis of increasingly complex chemistry (Nozière et al., 2015; Butler et al., 2018); and the revolution in molecular biology and genome sequencing have opened completely new opportunities to study biological aerosols (Mbareche et al., 2017). Long, insoluble fibers can to date only be identified by using combined methods in microscopy and spectroscopy (Kling et al., 2016). Considering regulatory nanofiber counting to comply with existing recommended provisional limit values, there is an urgent need to develop and validate both particle sampling and electron microscopy image analysis techniques (Koivisto et al., 2018b; Brostrøm et al., in review).

5.2. Measurement of biologically relevant particle properties

Commonly used exposure/dose limit values are derived from NOAELs (*e.g.* Hristozov et al., 2016, 2018; Koivisto et al., 2016; Tsang et al., 2017; Pizzol et al., In Press), integrated exposure-response functions (IERs; GBD, 2017b; Pope 3rd et al., 2018), human equivalent dose-responses (*e.g.* a daily no significant risk dose level; Thompson et al., 2016), and micro-organisms infectivity potency (Teunis et al., 2008; Hamilton et al., 2017). The majority of the exposure/dose-response studies rely on mass, even though it is known to be only a rough indicator for a biologically effective dose of the complex mixture of airborne particles; especially in the work environment (*e.g.* Kuempel et al., 2014; Braakhuis et al., 2016; Noël et al., 2017; Fadeel et al., 2018). Other biologically relevant metrics, such as number and surface-area, needs to be considered as well, depending on the aerosol particle properties. For example, the total particle BET surface area (cm^2) instilled in rats and mice lungs was recognized to correlate well with polymorphonuclear neutrophilia (PMN) for low solubility and low toxicity particles as well as some transition metal oxides (Schmid and Stoeger, 2016). PMN is a strong indicator for lung inflammation and forming acute phase response protein that cause plaque formation in the blood vessels causing cardiovascular diseases (Saber et al., 2014; Thompson et al., 2018). Koivisto et al. (2016) used the relation of surface area dose and PMN influx to predict first order estimates of workers risk suffering pulmonary inflammation during an 8-h exposure. This is a potential technique to predict exposure risks of low solubility low toxicity particles and transition metal and metal oxide particles by assessing inhaled surface area doses. Such relations between exposure and health effects needs to be derived for different pollutants and their relevant health effects in order to select the best methods for on-line risk monitoring techniques.

Microbial pollution in indoor air is traditionally estimated based on total bacterial and fungal concentrations present in the air measured as colony-forming units (CFU) m^{-3} by cultivation of air samples on non-selective agar (ACGIH, 1986). Although this can be used as indication of air quality, human pathogens, capable of causing illness even in low concentrations, may still be present. Identification of potential pathogens that could pose a health risk upon exposure and investigations of microbial diversity may therefore be crucial for assessment of health effects. Specific pathogens can be measured as CFU m^{-3} by cultivation on selective medium or as genomic copies m^{-3} by using molecular-based methods such as qPCR. Although, the latter lacks the ability to differentiate between infectious and non-infectious organisms, it is often used for assessing exposure to non-culturable and slow-growing microorganisms *e.g.* viruses (*e.g.* Uhrbrand et al., 2011, 2017a, 2017b). Bioaerosol diversity can be assessed as relative genomic abundance m^{-3} of air by sequencing when viability is not important (*e.g.* Madsen et al., 2015; Fang et al., 2018), while MALDI-TOF identification can used be to quantitatively study the diversity of culturable bacteria and fungi as CFU m^{-3} (*e.g.* Uhrbrand et al., 2017a; Madsen et al., 2016).

5.3. Assessment of particle emission rates

Currently, the source emission rate testing standards and guidelines for airborne pollutants are designed mainly for gaseous emissions (European Communities, 1991; ASTM, 1997, 2001). Particle emission source characterization methods exists for well-controlled chamber studies (*e.g.* Rauert et al., 2014; Morgeneyer et al., 2015; Torkmahalleh et al., 2017; Boor et al., 2017), as well as for measurements performed in built environments, such as residential houses (He et al., 2004; Hussein et al., 2005), classrooms (*e.g.* Bhangar et al., 2014), and occupational environments (Koivisto et al., 2014, 2018c). However, guidelines and standard methods for particle source characterization are needed for assuring quality of the emission rate assessment and sampling and characterization of the physio-chemical properties of the released particles. For bioaerosols, methods should be able to quantitatively detect and discriminate between specific human pathogenic and non-pathogenic micro-organisms (*e.g.* Uhrbrand et al., 2017a). Size-resolved particle emission rates are needed for mass flow analysis, and because there is no clear consensus of relevant metrics, for particle hazard assessment (EN ISO 28439; CEN FprEN 17058:2018 E). Procedures for determination of aerosolization of fungal spores using a particle-laboratory field emission cell has been developed and used for controlled human exposure assessments (Kildesø et al., 2003; Meyer et al., 2005).

5.4. Particle emission source descriptors and ontology

Reliability of an exposure assessment model depends on user inputs. Thus, an ontology including all descriptors needs to be designed so that the users can identify the processes and sources with reasonable accuracy. This requires agreement on emission rate assessment in biologically relevant metrics, measurement of particle properties, ontology and descriptors for the processes causing emissions. A Danish EPA (Miljøprojekt nr. 1800, Christensen et al., 2015) and the EU FP7 SUN project (PF7, EC-GA No. 604305) developed a preliminary structure for an particle emission library for articles and products containing nanomaterials (Table 2). The emission library development continues in the EU Nano Safety Cluster task force (https://www.nanosafetycluster.eu/) by developing an ontology of the parameters used to describe particle emission sources and revising the library format so that it meets the requirements for both human and environmental risk assessment. Harmonized ontology is needed for both source, *i.e.* process, and the emissions reporting. The GRACIOUS project (EU H2020, EC-GA No.760840) will continue the work by developing rules for source read-across extrapolation for products containing nanomaterials.

5.5. Exposure modeling

A comprehensive indoor exposure model compromising both gaseous and particle emissions from outdoors *via* ventilation, passive sources (*e.g.* building materials), and processes (*i.e.* indoor activities) can be used to understand most relevant exposure determinants. Outdoor exposure levels can be estimated from regulatory environmental measurements and by using atmospheric air pollution models (*e.g.* Hvidtfeldt et al., 2018; Jensen et al., 2017). The model can be combined with the emission library and exposure control library where the user can select correct parameters for describing indoor activity emissions. Such models exist for gas pollutants, such as *e.g.* PANDORA, MOEEBIUS or CONTAM, but models combined with comprehensive particle emission library are needed.

In model development, comprehensive aerosol measurements are needed for model performance testing, calibration, and understanding parameterization of different exposure scenarios for top-down modeling. Default exposure scenarios need to cover parameters such as building properties, sources, emission controls, and activities. Currently, personal or environmental exposure modeling exclude gas-particle interactions mainly because the source emission compositions are rarely well defined (Hopke, 2016), and detection techniques of atmospheric organic compounds suffer limitations (Nozière et al., 2015). However, when the information becomes more available, there are relatively simple models applicable to estimate the phase of chemical species in an aerosol using mass balance models (*e.g.* Liu et al., 2013; Liagkouridis et al., 2014). Such processes are needed to estimate the uptake of semi-volatile compounds, such as PAHs, where particles effect on the semi-VOCs uptake. In addition, it is clear that in many indoor environments, it is likely that photochemically formed aerosol components are readily available and may strongly contribute to the aerosol mass and number as well as various removal processes.

5.6. Parameterization of dispersion model

The model needs to be parameterized by respecting the user needs and available information with respect to the current exposure assessment standards. For example, the consumer exposure assessment

Table 2
Structure of the emission library designed in the SUN project. Colors indicate different descriptor groups.

Descriptor	Description	Descriptor group
Study	Reference	
Process	Process overview	
Process details	Description of process(es)	**Process descriptors**
Process rate (g s^{-1})	Material production, use, or removal rate	
Matrix	General description of the matrix	
Matrix details	Description of the matrix	
NM	NM composition	
NM vendor	NM manufacturer or supplier	
NM product name	NM name	
NM concentration (wt%)	NM concentration in the matrix	**Material descriptors**
NM state	State of ENM(s): pristine, embedded into matrix, surface bound, incorporated, impregnated, dispersion, surface bound, …	
MN PP size (nm)	NM primary particle size or NM dimensions	
Other information for materials and methods		
Released fragments	Description of released fragments	**Emission descriptors**
Fragments density (g cm^{-3})	Density of released particles	
Notes	Relevant information regarding uncertainties, assumptions, and boundary conditions	
S (units s^{-1})	Emission rates where units can be number, surface area, or (respirable) mass.	**Emission rates** described with log-normal distribution parameters
GMD (μm)	Geometric mean diameter	
GSD	Geometric standard deviation	
$D_{p,i}$	Geometric mean diameter of size channel i	
dS_i (units s^{-1})	Emission rate of channel i	**Emission rates** measured values
$d\log(D_{p,i})$	Logarithmic (10-based) width of size channel i	
Expected effect levels, limit values	*e.g.* OEL, NOAEL (units m^{-3}), IER (units m^{-3}), dose-response (units g^{-1} bw^{-1}), where bw is body weight.	**Hazard descriptors**

should follow the ECHA R.15 recommendations where the room volume is 20 m^3 and the air exchange is 0.6 h^{-1}. Model complexity can always be reduced with parametrization, which is a benefit of multi-compartment models with complex ventilation designs. Nymark et al. (in preparation) designed a default parameterization for an exposure assessment along a Cooper-like stage-gate idea-to product launch scheme as part of the EU H2020 caLIBRAte project (www.nanocalibrate.eu). In their proposal, the parameterization complexity of the source and dispersion model increases accordingly the knowledge of the product and exposure situation; the less information available, the more conservative the exposure prediction is. Such an approach can enable material producers or product users to predict conservative estimates for worst-case material/application users for top-down exposure estimates, and *vice versa*, estimation of exposure levels in well-defined conditions.

Top-down exposure assessment is required when a material producer or importer assesses human exposure risks of material use in unspecified exposure scenarios. For such assessment, default personal exposure scenarios (*e.g.* pouring filler in a mixing tank) are needed, which can be analogous to OECD emission scenario documents that form the basis for estimating the concentration of chemicals in the environment (OECD, 2017). Default parameterization of the ventilation and interzonal airflows in indoor exposure scenarios needs to be based on measured values (U.S. EPA, 1994; Liu et al., 2018). Currently, in ECHA R.14 and R.15 guidance, parameterization of the models is based on mutual agreement rather than measured values even though the data is available (see Tables 3 and 4 for interzonal airflows and ventilation rate in occupational settings and residences, respectively). Facilitating exposure scenario development requires systematic measurement and reporting methods, such as the Industrial Hygiene Exposure Scenario Tool (IHEST), which is freely available and guides the exposure assessor through the collection and documentation of these details (Arnold et al., 2017). Further, it can be used to assess the critical exposure determinants used in mass balance models.

5.7. Regulatory exposure assessment

The U.S. EPA (2009) provides comprehensive guidance for a model development and evaluation for a regulatory decision-making. Well-documented and generally accepted models may be required if modeling results are used in an expert witness's scientific testimony. In the USA, the *Daubert* standard is widely used to assess whether expert witnesses scientific testimony is methodologically valid (*Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 1993; Raul and Dwyer, 2003). The standard provides five criteria that may be used to assess the validity of the methodology:

1) Is applicable and has been tested.
2) Has been subjected to peer review and is generally accepted.
3) The rate of error is known and acceptable.
4) The existence and maintenance of standards and controls concerning the operation.
5) Is generally accepted in the relevant scientific community.

In regards to human exposure assessment, Jayjock et al. (2011) challenged the NF/FF model for these criteria in the context of an industrial hygienist providing a testimony for gaseous pollution exposure assessment. The conclusion was that when the NF/FF model fulfils the *Daubert* criteria and when it is used within its stated limitations, it simulates adequately the conditions. Later studies support this conclusion (Hofstetter et al., 2013; Earnest and Corsi, 2013; Arnold et al., 2017). Based on 63 case studies, the NF/FF model is shown to have good predictive power for PM exposure assessment as well when high quality input values can be derived or are available (Table 1; Jayjock et al., 2011). The single-compartment model has similarly been demonstrated to accurately predict exposures in well-mixed rooms and detailed knowledge of emission rates and ventilation rates (Arnold et al., 2017; Arnold et al., In Press). This provides strong indication that properly designed and used models based on mathematical mass balance are applicable for regulatory decision-making as well as juridical procedures when representative measured exposure data is not available. Similarly, as Jayjock et al. (2011) evaluated the NF/FF model regulatory acceptance and recommended reviewing the exposure assessment tools used under REACH regulation.

5.8. Impact on society

On a global scale air quality needs to be improved healthier for humans and environment. Indoor air consisting of outdoor aerosols and indoor aerosol emissions is a dominant exposure route for humans. The impact of indoor sources on IAQ becomes increasingly more important as buildings become more airtight, ventilation air is recirculated and new materials, products, and processes are being introduced (McDonald et al., 2018). A holistic understanding of the emission sources and dispersion of particles is needed for IAQ assessment and management. Currently, there is no mandatory particle emission labelling for products or processes that people use in their everyday life. This is one reason why determinants for IAQ are not well known. Systematic mapping and reporting of the emission sources is needed for effective

Table 3
Default parameterization of the interzonal flows in occupational exposure scenarios.

Source/location	Study	Number of measurements	Face velocity/volume flow through NF volume.	Comments
Inter-zonal ventilation (β)				
Indoor workplaces	Baldwin and Maynard (1998)	55 work areas within 27 different factories	12 m min^{-1} (0.04–0.72 m min^{-1}) GM[a] 3.6 m min^{-1}, GSD[b] 1.96	
Indoor workplaces	Berry and Froude (1989)	16 workers in 6 workplaces	12 m min^{-1} (6–94 m min^{-1})[c]	
Offices	Thorshauge (1982)	12 different offices	3–24 m min^{-1}	
Naturally ventilated industrial building with heat sources	Wang et al. (2016)	4 locations	18–90 m min^{-1}	
Rooms ranging from 79 to 1137 m^3	Keil and Zhao (2017)	From 5 to 8 experiments in 12 rooms	4.0 m min^{-1} (0.33–15.6 m min^{-1})	Effect of worker motion, room volume, and general ventilation was studied
Simulation in industrial environment	Keil (2015)	34 (mid-room) and 27 (side of room)	GM 2.14 m^3 min^{-1}, GSD 1.81 (mid-room) 1.19 m^3 min^{-1}, GSD 1.54 (side of room)	Robot arm simulating the work

[a] Geometric mean (GM).
[b] Geometric standard deviation (GSD).
[c] Averages of static and personal measurements and excluding fume cupboard face velocity when used.

Table 4
Default parameterization of general ventilation and interzonal flows in consumer exposure scenarios.

Source/location	Study	Number of measurements	GM[a] (h^{-1})/Range	GSD[b]
General ventilation rates (Q_{FF})				
HouseDB database	Jayjock and Havics (2018)	603	0.39	1.8
Japan	Shinohara et al. (2011)	26	0.38–1.4	
Residence, summer, occupied	Liu et al. (2018)	8-weeks of continuous measurements	0.47	1.6
Residence, winter, occupied		5-weeks of continuous measurements	0.33	1.3
Inter-zonal ventilation (β)				
HouseDB database	Jayjock and Havics (2018)	603	0.51	2.05
Danish bedrooms	Bekö et al. (2010, 2011)	500	0.46	2.08
Danish residences	Bekö et al. (2016)	5	0.36–1.67	
Swedish bedrooms	Bornehag et al. (2005)	390	0.31–0.47	
Basements and garages at Boston	Dodson et al. (2007)	45	1.1	
Japan	Shinohara et al. (2011)	26	0.42–1.6	

[a] Geometric mean (GM).
[b] Geometric standard deviation (GSD).

mitigation for air pollution in residences, public domains, and occupational environments. One potential measure might be an emission index label for products, which is based on the fraction of material released per amount of processed material (mg kg^{-1}). A measure for product emissions is needed to make people aware of their role in a clean ambient environment.

Emission libraries combined with mass balance models is applicable for finding biologically relevant components for human health trough epidemiological studies. A properly designed mass balance model with well characterized sources, emission controls, and activities fulfils requirements for regulatory exposure assessment and would be applicable for all particles from natural or incidental sources, as well as for manufactured nanomaterials. Such tools would be widely applicable for atmospheric research, epidemiological and toxicological studies, industry at both occupational hygiene and safe product development, and public health and environmental professionals to understand exposure determinants. Accuracy in exposure/risk assessment is needed to assure a lower probability of underestimating or overestimating the human health hazards associated with product use. The advantage of not underestimating exposure/risk are obvious considering the precautionary principle, but the societal costs of overestimating and overregulating risk could also be grave.

6. Conclusions

Investment in good air quality is an efficient way to increase quality of life in both developed and developing countries. The most effective approach to improve air quality is to prevent the emissions at the source. This requires knowledge of the materials, processes, and activities that cause emissions. The best approach to identify aerosol emission sources are systematic measurements, which are recorded into an emission library and made widely available for scientific and administrative uses. When the pollution components and particle properties are sufficiently characterized, their impact on human health and the environment can be estimated; thus enabling efficient risk control actions. Currently, there exist mass balance models for estimating mass flows and dynamic transformations of gases and aerosols and libraries that comprise mainly gaseous emissions (*e.g.* PANDORA) and exposure controls in work environments. Emission libraries for aerosol particles are currently just emerging. For top-down modeling, we need exposure scenarios to understand the potential impact of the sources to IAQ. Good modeling methods based on mathematical mass balance have been designed decades ago, which should be taken into efficient use (*e.g.* MOEEBIUS). The current need is to improve the model parameterization such that it reflects better the reality, which requires high quality release rate data and exposure measurements for model testing. Good knowledge of size-resolved particle and gas emission sources in combination with well parameterized mass balance models give us comprehensive picture of factors influencing our atmospheric environment.

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