Methods to assess $PM_{2.5}$ exposure from indoor sources in epidemiological studies: a review

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0. Layman´s Summary

Of all air pollutants, particles with a diameter of less than or equal to 2.5 µm ($PM_{2.5}$) have the greatest scientific evidence of adverse health effects, including respiratory, cardiovascular, nervous system effects, cancer, and mortality. Epidemiological studies are an invaluable and very important tool to establish the toxicity and effects of $PM_{2.5}$ on human health. Most epidemiological studies have measured or modelled ambient concentrations of $PM_{2.5}$ to estimate human exposure. However, humans spend most of their time indoors, where almost all exposure to air pollutants takes place.

Indoor $PM_{2.5}$ concentration is a mixture of both ambient and non-ambient particles. The ambient component refers to all the particles generated outdoors that infiltrate into the indoor environment through, for example, ventilation. Nonambient particles refer to all those particles that are produced directly indoors or by human personal activities. Many human activities can be sources of indoor $PM_{2.5}$, although the most important are smoking, cooking, and heating. Outdoor and indoor $PM_{2.5}$ sources are different, so the particle's composition, toxicity, and human health effects may also be distinct. Therefore, it is important to treat exposure to outdoor- and indoor-generated $PM_{2.5}$ as two separate exposures to investigate their effects in epidemiological studies.

To separate indoor- and outdoor-generated $PM_{2.5}$ exposure, researchers have used tracer compounds whose production occurs almost exclusively outdoors and infiltrate into indoor environments, a method called source partitioning. However, the separation between indoor- and outdoor-generated $PM_{2.5}$ implies many logistical challenges for epidemiological research since it often entails a great economic cost for the researchers to carry out measurements in each of the residences or indoor environments. It can also be inconvenient for the participants. This is why most of the studies that measure indoor $PM_{2.5}$ concentrations do so in small study populations or for short periods of time. Having small study populations limits the ability of epidemiological studies to draw valid results.

In this literature review, we aimed to evaluate the approaches and techniques used to assess indoor-generated $PM_{2.5}$ exposure in epidemiological studies of respiratory health effects, pointing out their strengths and limitations. We identified a total of 29 epidemiological studies that carried out measurements of indoor $PM_{2.5}$ concentrations, of which only 5 applied methods to separate indoor- and outdoor-generated particles. All studies that applied source partitioning methods used sulphate or iron as tracer compounds, had small study populations, and studied short-term exposures. The results of studies applying source partitioning methods highlight the importance of investigating the specific relationship between indoor-generated $PM_{2.5}$ and respiratory health outcomes, as well as distinguishing it from outdoor sources.

1. Introduction

Numerous epidemiological studies have documented the relationship between air pollution and health. Among all the fractions of particulate matter (PM) in air pollution, fine PM ($PM_{2.5}$ or particles with aerodynamic diameters less than or equal to 2.5 μm) shows the most substantial and consistent scientific evidence for relationships between short-term or long-term exposure and health [1]. $PM_{2.5}$ is associated with multiple adverse health outcomes, including respiratory, cardiovascular, and nervous system effects, cancer, and increased total mortality [1,2]. However, most epidemiological evidence is derived from studies that capture only the effect of ambient $PM_{2.5}$, usually assessing exposure through outdoor monitoring stations or outdoor modelling. These studies do not address the health impact of nonambient fine PM.

People spend most of their lives in indoor microenvironments with an estimated 87% of time spent inside buildings [3], so these environments mediate human exposure to both outdoor- and indoor-generated particles. Since air exchange rates in indoor microenvironments have been reduced in modern buildings and the ambient concentration of $PM_{2.5}$ started to decrease in recent years [4], the contribution of indoor $PM_{2.5}$ sources to personal exposure will become increasingly important. $PM_{2.5}$ was found to be one of the most harmful non-biological indoor air pollutants, associated with the largest number of DALY losses, and responsible for most chronic health effects in homes without smoking [5]. Additionally, it has been reported that $PM_{2.5}$ from indoor sources may be the dominant fraction of integrated daily residential exposure, with nearly 30% of the disease burden from PM exposure attributable to indoor-generated particles [6]. In this assessment, the assumption is made that $PM_{2.5}$ from indoor and outdoor sources have similar health effects, which is controversial. A pilot study suggested that indoor-generated fine PM may be more toxic and bioactive compared to fine PM from outdoor sources [7].

Personal exposure to $PM_{2.5}$ includes ambient and nonambient components, both of which can differ in composition/size and produce different types of health effects or, at least, involve different sources that would be desirable to identify in order to implement cost-effective measures to reduce or prevent exposure [8]. It has been shown that there is usually a low-to-moderate correlation between indoor-generated and outdoor PM concentrations [9–12]; thus, studies that show a relationship between variations in health endpoints and outdoor PM cannot provide any information regarding the possible health effects of indoor-generated PM. Epidemiological studies with an appropriate characterization of particles from indoor sources are required to determine the health effects of indoor-generated $PM_{2.5}$, as well as its composition-specific toxicity.

Two approaches can be used to assess the risks associated with indoor-generated $PM_{2.5}$: risk assessment and epidemiological studies. The former approach is based on exposure data from human exposure studies, where exposure is determined by modelling or

conducting direct measurements of indoor $PM_{2.5}$ concentrations. Exposure data is then used in conjunction with exposure-response relationships derived from experimental or analytical toxicological and epidemiological studies to perform risk characterization. The most serious disadvantage of this approach is that it generally uses exposure-response relationships derived from outdoor settings [5,13], assuming that exposure to indoor-generated and outdoor-generated $PM_{2.5}$ are equal in terms of toxicity ($PM_{2.5}$ is said to be equitoxic). In addition, source variability, as well as temporal and personal variability of particles from indoor sources, are not considered.

In contrast, epidemiological studies of the effects of indoor-generated $PM_{2.5}$ need to assess exposure produced indoors and relate it to an outcome of interest in the studied population. In this way, compositional toxicity dependencies, indoor sources, and temporal or personal variability can be properly addressed. However, epidemiological studies are often limited by cost and feasibility constraints imposed by indoor exposure assessment and the inability to directly measure indoor-generated particles because outdoor sources also contribute significantly to indoor PM concentrations. Therefore, most studies attempting to investigate the health effects of indoor particulate matter are generally limited to small cohorts or perform exposure characterization based on more approximate exposure assessment methods, such as exposure indicators [14]. In this review, we do not address the well-described exposure indicator literature but focus on the more challenging PM monitoring/modelling approaches. In Supplement 1 we briefly discuss the large body of evidence of exposure indicators.

It is important to treat indoor-generated $PM_{2.5}$ as a distinct and separate exposure from outdoor-generated particles or other indoor-produced pollutants to ensure proper assessment of its related human health risks. Quantitatively assessing exposure to fine PM from indoor sources is a challenging task. Because of this, the present review aims to evaluate the current approaches and techniques used in epidemiological research to assess exposure to $PM_{2.5}$ from indoor origin, summarizing their strengths and limitations. We focused only on epidemiological studies reporting quantitative exposure measurements of the fine fraction of PM in indoor environments. Specifically, we restrict our literature search to direct (personal exposure monitoring) or indirect (exposure modelling techniques and indoor concentration measurements) exposure assessment methods, which represent better estimates for personal exposure than exposure indicators [15,16]. Since respiratory outcomes are the most common health effects of fine particulate matter exposure reported in the literature, this review was limited to epidemiological studies assessing respiratory health. Including all possible health outcomes was not feasible due to time constraints.

In this paper, we first describe our literature search (Section 2), followed by a background section including a summary of the fundamentals of exposure assessment methods to indoor air pollutants (Section 3). Section 4 gives a short overview of $PM_{2.5}$ indoor sources, levels observed in indoor microenvironments, and existing general

challenges to its exposure assessment. In Section 5, we present a review of the exposure assessment approaches applied in the identified epidemiological studies of respiratory health.

2. Methods

Only articles written in English and published in peer-reviewed journals about the association between indoor $PM_{2.5}$ exposure and respiratory health outcomes were included in this literature review. The literature search was performed using the electronic databases PubMed, Google Scholar, and Web of Science. Potentially relevant studies were identified and screened for retrieval using the following keywords: "indoor PM2.5", OR "PM2.5 indoor environments", OR "indoor fine particulate matter", AND "health effects", OR "asthma", "COPD", OR "lung cancer" OR "respiratory health", OR "epidemiological study", OR "cohort". In addition, we complemented the search using the most relevant references of the identified articles.

3. Exposure assessment to indoor particulate matter

In epidemiological studies, exposure assessment is a major component with the same importance as outcome assessment. Exposure in relation to particulate matter is generally expressed in terms of air concentration ($\mu g/m^3$) and can be defined as the PM concentration near the breathing zone during a certain period (concentration x time) [11]. To represent an individual's total exposure to PM, we must consider all the microenvironments that contributed to breathable air for the individual and the time spent in those microenvironments. In other words, exposure is a function of both space and time and most studies report average exposures in a certain setting (e.g., 12- or 24-hour-averages).

Exposure to total $PM_{2.5}$ ($T_{PM2.5}$) is constructed from ambient $PM_{2.5}$ ($A_{PM2.5}$) and nonambient $PM_{2.5}$ ($NA_{PM2.5}$) [8]. Nonambient $PM_{2.5}$ is in turn made up of indoor-generated $PM_{2.5}$ and $PM_{2.5}$ generated from personal activities in any type of setting ($PA_{PM2.5}$, also referred to as "personal cloud" [8]):

$$T_{PM2.5} = A_{PM2.5} + NA_{PM2.5}$$

$$NA_{PM2.5} = IG_{PM2.5} + PA_{PM2.5}$$

Ambient $PM_{2.5}$ ($A_{PM2.5}$) are fine particles that are emitted (primary PM) or formed (secondary PM) in the ambient atmosphere. Indoor $PM_{2.5}$ ($I_{PM2.5}$) includes all fine particulate matter found indoors and can be divided into $PM_{2.5}$ that is emitted or formed indoors ($IG_{PM2.5}$) and PM from an ambient origin that infiltrates indoors depending on ventilation and infiltration conditions ($AI_{PM2.5}$) [8]. Thus, the indoor $PM_{2.5}$ concentration is given by:

$$I_{PM2.5} = IG_{PM2.5} + AI_{PM2.5}$$

It is important to note that neither $IG_{PM2.5}$ nor $AI_{PM2.5}$ can be directly measured, so they must be derived from mass balance equations using other measurable quantities. The indoor $PM_{2.5}$ ($I_{PM2.5}$) concentration can also be expressed through mass balance equations in equilibrium conditions as follows [17]:

$$I_{PM2.5} = \frac{Pa}{a+k} A_{PM2.5} + \frac{Q}{V\,(a+k)}$$

where $I_{PM2.5}$ is the indoor $PM_{2.5}$ concentration (μg/m^3), $A_{PM2.5}$ is the ambient $PM_{2.5}$ concentration (μg/m^3), P is the penetration efficiency (unitless), a is the air exchange rate (h^{-1}), k is the decay rate (h^{-1}), Q is the indoor sources strength (μg/h), and V is the volume of the indoor environment (m^3).

The penetration efficiency of $PM_{2.5}$ (P) can be defined as the fraction of ambient $PM_{2.5}$ that is not removed from ambient air when it enters indoor environments.

From the above equation, $PM_{2.5}$ indoor concentrations can be solved for its two components [(8,17)]:

$$AI_{PM2.5} = \frac{Pa}{a+k} A_{PM2.5} = F_{INF}\, A_{PM2.5}$$

$$IG_{PM2.5} = \frac{Q}{V(a+k)}$$

where F_{INF} is the infiltration factor and describes the fraction of outdoor air that infiltrates indoors and remains suspended [17]. Thus, F_{INF} is a function of penetration rates (P) and decay rates (k). P can be defined as the fraction of ambient $PM_{2.5}$ that is not removed from ambient air when it enters indoor environments, and k describes the particle loss processes by diffusion or sedimentation.

To determine the effects of indoor-generated $PM_{2.5}$, epidemiological studies must measure indoor and outdoor concentrations of $PM_{2.5}$ or directly measure personal exposure in indoor environments. The challenging task is the separation of indoor $PM_{2.5}$ concentrations or personal exposure measurements into its indoor-generated and outdoor-generated components. Measurements of the indoor source strength (Q) have rarely been done due to the difficulty of accurately measuring the emission rate of each indoor source. Similarly, the estimation of other indoor concentration parameters such as penetration efficiency and decay rates is a complicated task due to the influence exerted by other factors, like indoor and outdoor temperature, humidity, building characteristics, and wind speed [18]. Therefore, studies usually must rely on source partitioning methods that estimate F_{INF} to calculate the fraction of $PM_{2.5}$ generated outdoors and derive the indoor-generated component from the total indoor $PM_{2.5}$ concentration (estimation of F_{INF} using a tracer method is discussed in more detail in Section 5 of this review):

$$IG_{PM2.5} = I_{PM2.5} - AI_{PM2.5}$$

There are direct and indirect methods for exposure assessment and measurement of indoor $PM_{2.5}$ concentrations [2,11]. Direct approaches refer to those methods where exposure is measured through a monitoring device, such as Personal Exposure Monitors (PEM), or through biomarkers of exposure. PEMs are worn by study subjects and record detailed exposure data as the individual remains in a given microenvironment, generally through filter-based mass measurements or light scattering instruments [11]. When combined with time-activity data, they can provide detailed exposure information from indoor sources. However, PEMs usually represent a great burden for the participants and entail a high cost for the researchers; thus, serving only to evaluate short-term effects and within limited sample sizes. Currently, there is no biomarker that can be used in epidemiological studies to reflect $PM_{2.5}$ exposure, although it is a topic under investigation [19,20].

Indirect approaches make use of modelling techniques and other measurable quantities to derive or estimate personal exposure. Microenvironmental monitoring measures the concentration of $PM_{2.5}$ indoors and, along with time-activity data, can be used to determine integrated exposures for the time spent in each microenvironment and identify sources. To reliably reflect personal exposure, microenvironmental measurements must have a homogeneous distribution in time and space during the measurement period [15]. Both microenvironmental monitoring and time-activity data are input information for modelling exposure techniques.

Exposure models with varying levels of complexity are fitted using two general approaches: time-series and time-average [15]. In the former, microenvironmental exposures are estimated sequentially over time. For the time-average approach, the estimates of exposure are calculated for the time spent on average in each microenvironment. Modelling techniques can be further classified into deterministic and stochastic models [16]. While deterministic models (also known as physical models) mathematically describe the relationship between sources and PM concentration based on prior knowledge of pollutant properties, stochastic models (also known as statistical models) are based on the measured concentration of a representative sample of microenvironments which are regressed by certain variables [16].

4. $PM_{2.5}$ indoor levels and sources: challenges for exposure assessment

Indoor PM emissions can be sporadic, episodic, or continuous, and are site and time specific. Smoking, cooking, and heating constitute the most important $PM_{2.5}$ indoor sources. Simoni et al. showed that homes with a smoker had about 33 $\mu g/m^{-3}$ higher 48-hour average $PM_{2.5}$ concentrations, with a reported 48-h average increment of 0.2 $\mu g/m^3$ for each smoked cigarette [21]. Coal, wood, or other biomass fuel combustion for cooking or heating are also recognized as important sources of fine PM [2,22], with the largest peaks of indoor $PM_{2.5}$ concentrations found to be during cooking activities

[23,24]. Other known indoor sources of $PM_{2.5}$ are human movement [25], burning candles or incense [26], cleaning activities like vacuuming and sweeping [(8,27], usage of printers, fax machines, or photocopiers [(28)], and the application of anti-insect products, cleaning agents or cosmetics [29,30].

Indoor PM shows large spatial (within and between indoor environments) and temporal variability and may have higher concentration levels than outdoor PM, even in non-smoking households [31]. Morawska and Salthammer reported in a review of 14 representative studies that for naturally ventilated buildings in the absence of known indoor sources, the median value of the indoor to outdoor concentration ratio (I/O ratio) of $PM_{2.5}$ was 0.91, ranging from 0.54 to 1.08, showing the significant contribution of outdoor air as a source of indoor particles. In contrast, when known indoor sources were present I/O ratios ranged from 1 to 2.4, with a median value of 1.21 [25]. Furthermore, a study conducted in four European countries differentiating between the outdoor- and indoor-generated components of the $PM_{2.5}$ indoor concentration found that the contribution of indoor sources in non-smoking households represented 20-30% of the total indoor levels, with reported indoor- and outdoor-generated concentrations of 3–5 µg/m3 and 6-20 µg /m3, respectively [32].

The assessment of exposure to $PM_{2.5}$ generated indoors is complex in part because it has not been established which physical or chemical properties are responsible for its toxicity. $PM_{2.5}$ also represents a mixture of pollutants, unlike other well-known criteria gaseous pollutants like carbon monoxide (CO). CO is a widely distributed odourless and colourless gas mainly formed from anthropogenic emissions of incomplete combustion of carbonaceous material like coal, wood, natural gas, petrol, and kerosene [33]. Similar to fine PM, indoor concentrations of CO are the result of infiltration of ambient CO and the presence of nonambient combustion sources [34]. However, as its toxicity is not source-specific, the distinction between indoor and outdoor CO sources is not important for the study of health effects and both types of sources contribute to a relevant total exposure. Thus, exposure to CO can be assessed in epidemiological studies with a highly specific internal dose metric like carboxyhaemoglobin (COHb) or through personal monitoring analytic methods that estimate total personal exposure [34].

The concentration, sources, and characteristics of indoor particles are also highly indoor-specific and can vary within and between microenvironments. Carrying out activities that generate indoor $PM_{2.5}$ usually results in a heterogeneous distribution of particles throughout space [25], so it would be important to consider whether $PM_{2.5}$ concentration measurements in a specific compartment of a microenvironment (such as the living room in a residence) constitutes a relevant estimate of exposure. As already noted in section 3, microenvironmental monitoring is only a reliable estimate of exposure if $PM_{2.5}$ is well-mixed indoors. If this does not happen, the exposure could be underestimated or overestimated, and the effect estimates are likely biased to the null (classical error model) [35].

Although the residence represents the indoor microenvironment where people spend most of their time [3], sources of residential $PM_{2.5}$ can differ from those found in other microenvironments also relevant for health (e.g., schools, vehicles, hospitals, etc.). Therefore, exposure-response relationships are subject to the assumption that all indoor environments are well represented by the microenvironment in which the concentration measurements are made (usually the residence). In this case, the use of time-activity data becomes of utmost importance to estimate exposure levels relevant to the time spent in each environment. Additionally, the variability of emission factors between sources of the same type is substantial. For example, $PM_{2.5}$ emissions from indoor cooking can vary between developed and developing countries, where the type of stove used is different (fuel or wood stoves vs electric stoves). The fine particles produced can also vary according to the cooking style, type of food cooked, type of oil used, and cooking temperature [36].

5. Indoor $PM_{2.5}$ exposure assessment methods in epidemiological studies of respiratory health

We identified 29 studies that performed quantitative measurements of $PM_{2.5}$ in indoor environments to determine the effects of indoor fine PM on respiratory health endpoints. Tables 1 and 2 show the key study design characteristics of the identified epidemiological studies evaluating associations with respiratory health of short-term (n=20) and long-term exposure (n=9). Short-term exposure studies were primarily designed as panel studies and had, on average, a smaller sample size than long-term studies (median sample size of 46 and 150, respectively). Most studies have been published from 2010 onwards and have been conducted mostly in North America (n=17, 58.6%) and Europe (n=8, 27.6%), with a minority carried out in Asia (n=4, 13.8%) and without representation from studies performed in South America or Africa. Finally, the majority of the selected studies evaluated respiratory outcomes in vulnerable populations, such as children or older adults with asthma or COPD.

Tables 3 and 4 list the exposure assessment methods for short- and long-term effects epidemiological studies, respectively. Of the identified studies, nearly all conducted measurements of indoor $PM_{2.5}$ concentrations at the participants' residence (n=28); with only one study performing measurements in a different indoor microenvironment (i.e. hospital, Ma et al. [37]). Of the places where the measurements were made inside the residences, the living room was the most common (n=20, 69.0%), followed by the bedroom (n=10, 34.5%), and only four studies made measurements in another room (e.g., kitchen or farm workplace). Six studies also reported conducting personal exposure monitoring (PEM) and 13 collected time-activity data.

5.1 Epidemiological studies using source partitioning methods

Only five epidemiological studies performed source partitioning of indoor concentrations between indoor-generated and outdoor-generated $PM_{2.5}$ [38–42]

(Table 3). All of them used a tracer element without indoor sources as a method to estimate the infiltration factor (F_{INF}) and the application of deterministic models to derive the fraction of $PM_{2.5}$ from indoor sources using mass balance equations. One of these studies also applied a stochastic model to complement the estimates (Koening et al. [40]).

The use of a tracer element to estimate the fraction of outdoor-generated $PM_{2.5}$ is based on the assumptions that such an element primarily comes from outdoor sources, indoor and personal activity sources are practically negligible, and the physical behaviour of the element is similar to that of other outdoor $PM_{2.5}$ constituents [43]. A tracer compound allows the estimation of F_{INF} without having to measure the penetration efficiency (P), air exchange rate (a), and decay rate (k) of $PM_{2.5}$ for each indoor setting, which would be unfeasible in epidemiological studies. However, the costs of carrying out filtered-based measurements to identify tracer compounds are still high enough to prevent their application in epidemiological studies of long-term exposure since we did not find any long-term studies using this method.

It should be noted that the use of a tracer element (sulphur or iron in our identified studies) could also add uncertainty to indoor $PM_{2.5}$ exposure estimates. The largest fraction of sulphur-bound particles is in the sub-micron particle size range compared to PM which is more concentrated in larger particle sizes. Because of this, penetration and decay rates of PM, and thus infiltration rates, may be different from that of PM-bound sulphur, leading to potential misclassification [32].

The Vancouver Panel Study (Ebelt et al. [38], Wilson and Brauer [39]) was the first to investigate the association between ambient and nonambient $PM_{2.5}$ with lung and cardiovascular function in 16 adults with COPD. Total personal exposures for $PM_{2.5}$ and sulphate were measured for each participant and, together with time-activity data describing the amount of time spent outdoors, the ambient exposure fraction was calculated from the measured ambient concentration at five central stations within the study area. Sulphate was used as a tracer compound of the outdoor-generated $PM_{2.5}$ since it has practically no indoor or personal activity sources [43,44] and, thus, the total personal exposure to sulphate can be assumed to come entirely from outdoor sources. The nonambient component was calculated as the subtraction of the total exposure minus the ambient component. Unlike the other studies, this study used PEM and time activity data instead of indoor air monitoring concentrations to estimate the nonambient exposure. Furthermore, the study excluded a major indoor source of $PM_{2.5}$ by not including participants who smoked or lived in smoking households, so the results mainly reflect the effect of other major indoor sources than smoking or personal activities performed in outdoor or indoor settings.

The other three studies reporting source partitioning also applied deterministic models to differentiate the indoor-generated ($IG_{PM2.5}$) and outdoor-generated ($AI_{PM2.5}$)

components of indoor $PM_{2.5}$ concentration ($I_{PM2.5}$) (Table 3). Koening et al. [40] and Habre et al. [41] applied mass balance equations to estimate the infiltration factor of the residences of each of the children with asthma who were included in their studies. Sulphate was used as a tracer method of outdoor sources in the mass balance model. In addition, Koening et al. fitted a predictive model to estimate F_{INF} since the measurements of sulphate using a radiance nephelometer were only valid for a subsample of the residences. The predictive model applied was developed in a previous study [45] and considered residence indicators such as the type of dwelling, the use of air cleaners, and surrogates of home ventilation conditions. The authors reported a good agreement between estimates of F_{INF} using the sulphate-tracer method and the predictive model. Compared to the others, the study by Chi et al. [42] was the only epidemiological study differentiating between exposure to particles of indoor origin and those generated outdoors that was carried out in a non-first-world country and used a different tracer element: iron. It has been demonstrated that iron, and not sulphate, is a better indicator of particulate matter from outdoor sources in China in relation to the existence of different anthropogenic $PM_{2.5}$ sources in this country [46].

Air monitoring at a personal level or measurement of indoor $PM_{2.5}$ concentrations limits the applicability of source partitioning methods at larger scales and for long-term exposures, as it is labour-intensive and expensive. This is evidenced by the small sample size of the identified studies that applied these methods, which were small-scale panel studies with sample sizes ranging from 16 to 75. Therefore, the major disadvantage of source partitioning methods, and of all indoor $PM_{2.5}$ studies in general, is low statistical power due to small sample size. An underpowered study implies problems in the veracity of the results because the probability of finding a genuine true result is low (high rate of false negatives) and the probability that a significant finding is true is decreased (low Positive Predictive Value or PPV) [47]. In addition, external validity may also be compromised as findings tend to be less replicable [47,48].

Another challenge for source partitioning methods is the high temporal and spatial variability of indoor $PM_{2.5}$ concentrations, and how to capture this information to reduce error in exposure determination without losing feasibility. The level of complexity of mass balance models could become large enough to prevent their application in an epidemiological setting if the input information required is too detailed. For example, indoor concentrations of $PM_{2.5}$ and the contributions from indoor or outdoor sources can vary greatly throughout the year depending on the season. In winter and autumn, where ventilation rates are typically lower, indoor sources may be more important for total indoor $PM_{2.5}$ concentration than in spring and summer [49]. The temporal variability could also be affected by human activity: at night when people are asleep and static for long periods, indoor particle concentrations are usually lower than during the day [24]. These aspects can be addressed in part in the study design phase, conducting

the research only in a certain season, and collecting time-activity data to develop relevant exposure estimates.

In the identified studies with reported source partitioning, there is consistent evidence of differential effects and degrees of toxicity between fine PM from indoor and outdoor sources (Table 5). The studies conducted in Canada [38,39] found that the association estimates with different health outcomes were of greater magnitude for particles of ambient origin than for nonambient exposures. In the same line, Koening et al. [40] saw that $PM_{2.5}$ of outdoor origin was more potent per unit mass than particles of indoor origin for the development of airway inflammation. However, they also observed that $PM_{2.5}$ of indoor origin was associated with decrements in lung functions, indicating that the potential effects of indoor- vs outdoor-generated particles differed for different health endpoints. Another study conducted on children with asthma also found a difference in asthma-related symptoms: while PM from indoor sources was significantly associated with odds of more severe wheezing, PM from outdoor sources was associated with odds of more severe cough [41]. Finally, Chi et al. reported that outdoor-generated $PM_{2.5}$ was associated with increased blood pressure levels and with decreased pulmonary function in healthy elderly adults, whereas $PM_{2.5}$ from indoor sources was linked with decreased pulmonary function in COPD patients [42]. Therefore, the results of these studies suggest that health effects may vary between indoor and outdoor particles, depending on health outcome, population, and type of indoor source.

5.2 Epidemiological studies not using source partitioning methods

In the studies that did not report source partitioning methods (n=24), indoor $PM_{2.5}$ concentration was used as a proxy for exposure to indoor-generated $PM_{2.5}$. Some studies attempted to differentiate the effects of outdoor and indoor PM using different methods. 14 addressed the issue at the study design phase (e.g., limiting the inclusion of smokers or choosing populations with high levels of in-home combustion) [37,50–62], and eight did so in the statistical analysis [63–70], either with multiple-exposure models (i.e., adjusting the relationship between indoor $PM_{2.5}$ and health endpoints for outdoor concentrations) or adjusting the relationship between indoor $PM_{2.5}$ and health endpoints for questionnaire-based indicators (i.e., smoking, cooking, and residential behaviours). Finally, two did not mention performing any restrictions or adjustments in relation to the indoor concentrations [71,72]. The decision to take any of the above approaches depended largely on the study question and the aims of the research.

Studies that took the total concentration of indoor $PM_{2.5}$ for the analysis of respiratory effects assumed that there was no difference between indoor- and outdoor-generated particles in terms of toxicity and type of health outcome analysed. Kim et al. conducted a randomized intervention study to evaluate the efficacy of air purifiers with High-Efficiency Particulate Air (HEPA) filters in reducing indoor levels of $PM_{2.5}$ and the consequent effect on respiratory function in asthmatic children [71]. Because this study

was focused on reducing total levels of indoor fine PM, it was not necessary to distinguish between indoor and outdoor sources. The birth cohort study carried out by Raaschou-Nielsen et al. aimed to study the long-term relationship of indoor air pollutants with bronchial hyperresponsiveness measured through wheezing symptoms in infants [72]. In this study, the interest in indoor $PM_{2.5}$ was to obtain an estimate of total exposure, rather than treating indoor- and outdoor-generated $PM_{2.5}$ as distinct exposures.

Limiting the study population by indoor sources was the most used method to differentiate between indoor and outdoor sources in studies using only indoor concentrations as exposure metric; however, this approach does not resolve the controversial assumption of assuming equitoxicity between outdoor-generated particles and indoor-generated $PM_{2.5}$. For example, several studies limited the study population to non-smokers living in smoker-free homes [51,54,56–59,61], thus giving priority to the analysis of the effects of outdoor-generated $PM_{2.5}$ found indoors and assumed little or no effect from other $PM_{2.5}$ indoor sources. In contrast, Butz et al. [50] and Peng et al. [60] limited their study population to children residing in smoking households to assess the health impact of air cleaners reducing $PM_{2.5}$ from second-hand tobacco smoke (SHS).

Adjusting effect estimates for outdoor $PM_{2.5}$ concentrations could be an effective method to capture exposure-response relationships of indoor-generated $PM_{2.5}$ provided that outdoor concentrations constitute a good proxy of exposure to outdoor-generated PM that infiltrated indoors, that is that the correlation between $\boldsymbol{AI_{PM2.5}}$ and outdoor concentrations is high, and that outdoor-generated $PM_{2.5}$ is an important contributor to total indoor $PM_{2.5}$ concentrations. If indoor concentrations are statistically independent of ambient concentrations, then the relation between indoor $PM_{2.5}$ and the health outcome of interest cannot be confounded by ambient concentrations [8]. Using measurements made right outside the indoor location under study or modelling techniques will be better than using central site concentrations due to high geographic variability. In the same way, adjusting for indicators of indoor exposure (for example, hair nicotine) will be effective if the indicator reflects a true exposure to the indoor source.

Studies that did not perform source partitioning were also limited by the cost, feasibility, and participant burden limitations of indoor air and personal monitoring methods, although to a lesser extent than source partitioning studies. Indication of this is that the study samples were generally higher and that all the long-term exposure studies did not perform source partitioning. These studies added uncertainty to the exposure assessment of indoor-generated $PM_{2.5}$ since they did not make a straightforward distinction between outdoor and indoor sources.

6. Conclusions

Not many epidemiological studies of respiratory health effects have performed indoor $PM_{2.5}$ monitoring, compared to the large number of research conducted with exposure indicators. Even fewer studies have applied source partitioning methods to separate indoor- and outdoor-generated particles. Current source partitioning methods are a complicated task that involves several logistical challenges to large-scale epidemiological studies, particularly those of long-term exposure. The five studies that applied source-partitioning were all short-term exposure studies in small study populations. The results from studies that did apply source partitioning methods underscore the importance of investigating the specific exposure-response relationship for $PM_{2.5}$ originated indoors and distinguishing it from that of outdoor sources. While undeniably useful in addressing research questions based on identified indoor sources, studies using exposure surrogates or indoor concentrations alone are not enough to fill the gap of knowledge that still exists about the potential human health impact of indoor-generated $PM_{2.5}$. Therefore, more research is needed to establish the specific degree and type of PM toxicity from indoor sources in epidemiological studies, especially applying larger sample sizes and involving different populations. Source partitioning methods using trace elements from outdoor sources represent a reliable way to estimate a subject's exposure to indoor- and outdoor-generated $PM_{2.5}$, with a reduction of exposure measurement errors.

Table 1. General characteristics of the reviewed epidemiological studies assessing short-term exposure to indoor $PM_{2.5}$

Authors	Year	Type of study	Country	Population	Sample size	Outcomes
Balmes et al.	2014	Cross-sectional	USA	Adults with asthma and rhinitis	302	Respiratory symptoms and lung function (FEV1)
Chi et al.	2019	Panel study	China	COPD patients and healthy spouses	75	Resting BP, PEF and FEV1
Delfino et al.	2004	Panel study	USA	Children with asthma	19	Lung function (FEV1)
Ebelt et al.	2005	Panel study	Canada	Patients with COPD	16	Lung function (FEV1, change in FEV1), systolic and diastolic BP, SVE, HR, HR variability.
Habre et all.	2014	Panel study	USA	Children with asthma	36	Daily asthma caught and wheeze scores
Hartog et al.	2009	Panel study	Finland, Greece, Netherlands and UK	Adult patients with asthma or COPD	135	Lung function (FVC, FEV1, PEF)
Isiugo et al.	2019	Panel study	USA	Children with asthma	44	Lung function (FEV1, FVC, FEV1/FVC, FEF)
Jansen et al.	2005	Panel study	USA	Adult patients with asthma or COPD	16	FE_{NO}, lung function (FEV1), BP, SaO_2, and pulse rate.
Karottki et al.	2014	Cross-sectional study	Denmark	Adults	78	MVF, lung function, biomarkers related to inflammation, monocyte activation and the prediabetic marker HbA1c.
Karottki et al.	2015	Panel study	Denmark	Elderly adults	48	MVF, lung function, biomarkers related to inflammation, monocyte activation and the prediabetic marker HbA1c.
Kim et al.	2020	Randomized intervention study	Korea	Children with asthma	26	Daily PEFR
Koenig et al.	2005	Panel study	USA	19 asthmatic children	19	eNO, and lung function (FEV1, FVC, MEF)
Ma et al.	2008	Panel study	Japan	Hospitalized children with asthma	19	PEF and wheezing
Maesano et al.	2019	Cross-sectional study	France	Adults (farmers)	109	Asthma, COPD, early airway obstruction
Osman et al.	2007	Cross-sectional study	UK	Patients with COPD	148	Respiratory-specific health status (St. George's Respiratory Health Questionnaire)
Simoni et al.	2002	Cross-sectional study	Italy	Adults	383	Asthmatic symptoms and PEF variability
Simoni et al.	2004	Cross-sectional study	Italy	Adults	1091	Acute respiratory illness, asthmatic symptoms, irritant symptoms, PEF variability
Trenga et al.	2006	Panel study	USA	Children with asthma and elderly adults	74	Lung function (FEV1 and PEF in adults, MMEF, PEF, FEV1, and symptoms in children),
Weichenthal et al.	2012	Randomized intervention study	Canada	Adults	37	Lung function, BP, and endothelial function
Wilson and Brauer	2006	Panel study	Canada	Patients with COPD	16	Lung function (FEV1, change in FEV1), systolic and diastolic BP, SVE, HR, HR variability

COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in the first second; FVC=forced vital capacity; PEF=peak expiratory flow; FEF= forced expiratory flow; MEF=maximal expiratory flow; MMEF=maximal midexpiratory flow; FE_{NO}=fractional exhaled nitric oxide; SaO_2=oxygen saturation; BP=Blood pressure; MVF=microvascular function; eNO=exhaled nitric oxide; HR=Heart rate.

Table 2. General characteristics of the reviewed epidemiological studies assessing long-term exposure to indoor $PM_{2.5}$

Authors	Year	Type of study	Country	Population	Sample size	Follow-up	Outcomes
Butz et al.	2011	Randomized intervention study	USA	Children with asthma	126	6 months	Asthma symptom-free days (difference between baseline and follow-up)
Gurley et al.	2013	Birth cohort study	Bangladesh	Children	257	2 years	Incidence of acute lower respiratory infection (ALRI)
Hansel et all.	2013	Longitudinal cohort study	USA	Patients with COPD	84	6 months	Respiratory symptoms, rescue medication use, and COPD exacerbations
McCormack et al.	2009	Longitudinal cohort study	USA	Children with asthma	150	6 months	Respiratory symptoms, rescue medication use, acute health care use
McCormack et al.	2011	Longitudinal cohort study	USA	Children with asthma	150	6 months	Respiratory symptoms, rescue medication use, acute health care use
Neas et al.	1994	Longitudinal cohort study	USA	Children	1237	2 years	Cumulative incidence of respiratory symptoms, lung function (FVC, FEV1, FEV1/FVC, FEF25-75%, FEF25-75%/FVC)
Peng et al.	2018	Randomized intervention study	USA	Children with asthma	75	6 months	Asthma symptom-free days (difference between baseline and follow-up)
Raaschou-Nielsen et al.	2010	Birth cohort study	Denmark	Children	378	18 months	Number of days with wheezing symptoms
Walker et al.	2022	Randomized intervention study	USA	Children	461	1 years (2 winter seasons)	LRTI

FEV1=forced expiratory volume in the first second; FVC=forced vital capacity; FEF25-75%=forced mid-expiratory flow at 25-75% of FVC; BP=Blood pressure; SVE=supraventricular ectopy; HR=Heart rate; LRTI=lower respiratory tract infections

Table 3. Exposure assessment methods described in epidemiological studies of short-term exposure to indoor $PM_{2.5}$

Authors	Year	Exposure measurements	Instrument	Measurement period	Measurement season	Source partitioning	Time-activity data	Restriction of indoor sources
Balmes et al.	2014	Indoor-residence (kitchen, living room), outdoor-residence and central station	Nephelometer (DustTrak)	1 monitoring session of 3 min	Spring and summer	No	No	No, but hair nicotine was used as a covariate in multi-exposure models.
Chi et al.	2019	Indoor-residence (living room) and outdoor-residence	SKC sampling systems with Teflon filter	1 monitoring session of 5 days	Winter and spring	Yes, iron-tracer method	No	Yes, not smoking was an inclusion criterion for healthy spouses. Smoking status was used as a covariate.
Delfino et al.	2004	PEM, indoor-residence (living room), outdoor-residence and central station	Passive nephelometer (Personal dataRAM) and Harvard Impactors with Teflon filters	1 monitoring session of 2 weeks	Spring and fall	No	Yes (amount of time spent outdoors/indoors)	Yes, inclusion criteria included no active smoking or passive exposure to tobacco smoke at home.
Ebelt et al.	2005	PEM and concentrations at 5 central site stations	Harvard Impactors	7 monitoring sessions of 24 hours	Spring and summer	Yes, sulphate-tracer method	Yes (amount of time spent outdoors/indoors)	Yes, inclusion only of non-smokers living in non-smoking households.
Habre et all.	2014	Concentrations at indoor-residence (living room) and central site station	Nephelometer (DustTrak) with Teflon filters (indoor), Modified Harvard Impactors (outdoor)	2 monitoring sessions of 2 weeks	All year	Yes, sulphate-tracer method	No	Yes, exclusion criteria for the presence of a smoker in the residence.
Hartog et al.	2009	Concentrations at indoor-residence (living room), outdoor-residence and central cite station	Harvard Impactors	1 monitoring session of 1 week	All year	No	No	Yes, selection of non-smokers living in non-smoking households.
Isiugo et al.	2019	Concentrations at indoor-residence (bedrooms) and outdoor-residence	Teflon filters with a single-stage Personal Modular Impactor (SKC)	2 monitoring sessions of 48 hours	All year	No	No	No, but UVPM was measured (PM2.5 emitted from smouldering organics such as smoking cigarettes and burning fireplace wood)
Jansen et al.	2005	PEM and concentrations at indoor-residence (living room), outdoor-residence and central cite station.	$MPEM_{10}$ (personal exposure) and Harvard Impactors	1 monitoring session of 12 days	Winter	No	Yes (amount of time spent outdoors/indoors, household behaviours)	Yes, inclusion only of non-smokers.
Karottki et al.	2014	Concentrations at indoor-residence (living room) and at a central cite station.	Fluoropore Membrane PTFE filters	1 monitoring session of 2 days	Winter	No	Yes (household behaviours)	Yes, inclusion only of non-smokers.

PEM=personal exposure monitor; $MPEM_{10}$ =Marple Personal Environmental Monitors for PM10; PTFE=Polytetrafluoroethylene; TEOM=Tapered-element oscillating microbalance, UVPM=ultraviolet absorbing particulate matter

Table 3. Exposure assessment methods described in epidemiological studies of short-term exposure to indoor $PM_{2.5}$ (CONT.)

Authors	Year	Exposure measurements	Instrument	Measurement period	Measurement season	Source partitioning	Time-activity data	Restriction of indoor sources
Kim et al.	2020	Concentrations at indoor-residence (living room)	PurpleAir light scattering sensor	1 monitoring session of 7 weeks	Fall	No	No	No
Koenig et al.	2005	PEM and concentrations at indoor-residence (living room) and outdoor-residence.	Harvard Impactors, Radiance nephelometers, and Harvard personal environmental monitors	1 monitoring session of 10 days	Winter and spring	Yes, sulphate-tracer method and recursive mass balance model	Yes (amount of time spent outdoors/indoors)	No
Ma et al.	2008	Concentrations at indoor-hospital (2 rooms and a hall), outdoor-hospital (entrance), and central cite station near hospital.	TEOM (central cite), dust monitor with a laser diode light scattering device (indoor and outdoor).	7 monitoring sessions of 24 hours	Winter	No	No	No, but the study only included children under long-term hospitalization.
Maesano et al.	2019	Concentrations at farm-residence (living room/bedroom) and farm-workplace (granary/stable)	AEROCET 531S device	1 monitoring session of 2 min	Spring	No	No	No, but smoking status, presence of pets, moulds, and wood heating were included as covariates.
Osman et al.	2007	Concentrations at indoor-residence (living room) and at a central cite station.	DustTrak light scattering monitor	1 monitoring session of 12 hours	Winter and spring	No	No	No, but smoking status was included as a covariate.
Simoni et al.	2002	Concentrations at indoor-residence (living room)	Dorr Oliver-type preselector	2 monitoring sessions of 1 week	Winter and summer	No	Yes (amount of time spent outdoors/indoors)	No, but stratified analysis by smoking status.
Simoni et al.	2004	Concentrations at indoor-residence (living room)	Dorr Oliver-type preselector	3 monitoring sessions of 1-week	Winter and summer	No	Yes (amount of time spent outdoors/indoors)	No, but smoking status was included as a covariate
Trenga et al.	2006	PEM and concentrations at indoor-residence (living room), outdoor-residence and central cite station.	Harvard Impactors (indoor and outdoor-residence), Harvard Personal Environmental Monitor	26 monitoring sessions of 5-10 days	All year	No	No	Yes, inclusion only of non-smokers.
Weichenthal et al.	2012	Concentrations at indoor-residence (living room) and at a central cite station.	Harvard cascade impactors	1 monitoring session of 3 weeks	Winter	No	No	No, but daily average number of cigarettes smoked indoors was included as covariate.
Wilson and Brauer	2006	PEM and concentrations at 5 central site stations	Harvard Impactors	7 monitoring sessions of 24 hours	Spring and summer	Yes, sulphate-tracer method	Yes (amount of time spent outdoors/indoors)	Yes, inclusion only of non-smokers living in non-smoking households.

PEM=personal exposure monitor; $MPEM_{10}$ =Marple Personal Environmental Monitors for PM10; PTFE=Polytetrafluoroethylene; TEOM=Tapered-element oscillating microbalance, UVPM=ultraviolet absorbing particulate matter

Table 4. Exposure assessment methods described in epidemiological studies of long-term exposure to indoor $PM_{2.5}$

Authors	Year	Exposure measurements	Instrument	Measurement period	Measurement season	Source partitioning	Time-activity data	Restriction of indoor sources
Butz et al.	2011	Indoor-residence (living room and bedroom)	MSP impactors (MSP Corp.)	2 monitoring sessions of 7 days	All year	No	Yes (amount of time spent outdoors/indoors)	Yes, inclusion of only children residing with a smoker.
Gurley et al.	2013	Indoor-residence (bedroom)	Berkeley Air monitoring device	1 monitoring session per month of 24 hours	All year	No	No	No, but study was conducted in a low-income urban community.
Hansel et all.	2013	Indoor-residence (bedroom, living room)	MSP impactors (MSP Corp.)	3 monitoring sessions of 1-week	All year	No	Yes (household behaviours)	Yes, inclusion of former smokers only. Assessment of SHS exposure by air/hair nicotine (confounding variable).
McCormack et al.	2009	Indoor-residence (bedroom) and central site station	MSP impactors (indoor) and PartisolPlus sequential air sampler (outdoor)	3 monitoring sessions of 3 consecutive days	All year	No	Yes (household behaviours)	No, but ambient PM was included as a covariate.
McCormack et al.	2011	Indoor-residence (bedroom) and central site station	MSP impactors (indoor) and PartisolPlus sequential air sampler (outdoor)	3 monitoring sessions of 3 consecutive days	All year	No	Yes (amount of time spent outdoors/indoors, household behaviours)	No, but ambient PM was included as a covariate.
Neas et al.	1994	Indoor-residence (bedroom)	Harvard Impactors	2 monitoring sessions of 1-week	Winter and summer	No	No	Yes, inclusion of children residing in never-smoking households
Peng et al.	2018	Indoor-residence (living room and bedroom)	MSP impactors (MSP Corp.)	2 monitoring sessions of 7 days	All year	No	No	Yes, inclusion of only children residing with a smoker.
Raaschou-Nielsen et al.	2010	Indoor-residence (living room)	KTL PM2.5 cyclone and a BGI400 pump	3 monitoring sessions of 1-week	All year	No	No	No
Walker et al.	2022	Indoor-residence (kitchen)	DustTrak light-scattering monitor	1 monitoring session of 6 days	Winter	No	Yes (household behaviours)	Yes, inclusion only of children residing in households that use a wood stove as primary heating source.

SHS=second hand smoking

Table 5. Effect estimates observed in epidemiological studies of respiratory health effects using source partitioning

Study	Exposure	Health outcome	Type of effect estimate	Effect estimate	95% CI
Chi et al.	Indoor-generated PM2.5	FEV1	Percentage deviation for IQR increase	-0.5%	(-0.9%, -0.1%)
	Outdoor-generated PM2.5	PEF	Percentage deviation for IQR increase	-3.7%	(-7.1%, -0.3%)
	PM2.5 indoor concentration	FEV1	Percentage deviation for IQR increase	-1.7%	(-2.9%, -0.5%)
Vancouver Panel Study (Ebelt et al., Wilson and Brauer)	Ambient PM2.5	FEV_1 (ml)	Effect estimates for IQR increase	-14.42	(-40.22, 11.38)
		ΔFEV_1 (ml)	Effect estimates for IQR increase	-28.93	(-54.55, -3.30)
	Nonambient PM2.5	FEV_1 (ml)	Effect estimates for IQR increase	10.97	(0.21, 21.73)
		ΔFEV_1 (ml)	Effect estimates for IQR increase	4.01	(-6.32, 14.33)
Habre et al.	Indoor-generated PM2.5	Asthma caught symptoms	OR for a SD increase	1.2	(0.88, 1.64)
		Asthma wheeze symptoms	OR for a SD increase	1.55	(1.05, 2.28)
	Outdoor-generated PM2.5	Asthma caught symptoms	OR for a SD increase	1.27	(0.90, 1.77)
		Asthma wheeze symptoms	OR for a SD increase	1.13	(0.75, 1.72)
	PM2.5 indoor concentration	Asthma caught symptoms	OR for a SD increase	1.22	(0.91, 1.63)
		Asthma wheeze symptoms	OR for a SD increase	1.57	(1.09, 2.26)
Koening et al.	Indoor-generated PM2.5	eNO	Change per 10 $\mu g/m^3$ estimated PM2.5	No use of ICS: 3.29 Use of ICS: -4.94	No use of ICS : (-1.14, 7.73) Use of ICS : (-10.94, 1.06)
	Outdoor-generated PM2.5	eNO	Change per 10 $\mu g/m^3$ estimated PM2.5	No use of ICS: 4.98; Use of ICS: -0.19	No use of ICS : (0.28, 9.69) Use of ICS : (-3.77, 7.12)

FEV1= forced expiratory volume in the first second; PEF=peak expiratory flow; ΔFEV_1 = change in FEV1; eNo= Exhaled nitric oxide; IQR=interquartile range; SD=standard deviation; ICS: inhaled corticosteroid

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Supplement 1. Exposure indicator epidemiological studies

There is a large body of literature reporting health effects from indoor sources based on exposure questionnaire indicators for smoking, second-hand tobacco smoke (SHS), fuel-burning while cooking, or other in-home combustion process; although biomarkers have also been applied to assign exposure (e.g., nicotine in hair or urine for second-hand tobacco smoke) [1–6]. The use of exposure surrogates has the advantage of allowing larger study samples and greater statistical power, as well as longer follow-up periods for long-term effects. This is because exposure surrogates have greater accessibility and affordability, are simpler to administer, more cost-effective, and warrant a lower participant burden compared to quantitative methods. However, if the aim is to determine the health effects of $PM_{2.5}$ from indoor sources, exposure indicators entail certain disadvantages and risks for an accurate evaluation of exposure.

First, exposure indicators are not specific to a certain type of pollutant. While it is well established that smoking, cooking, and candle/incense burning are some of the largest sources of indoor $PM_{2.5}$ [7–9], these sources often produce a complex mixture of pollutants that can act separately or synergistically to affect human health. The use of exposure surrogates may lead to the attribution of health effects to $PM_{2.5}$ that are actually produced by other particles or compounds, with an under- or overestimation of the effect estimates (confounding bias). For example, carbon monoxide (CO) is another highly toxic pollutant present in the gas phase of tobacco smoke [10] and its chronic inhalation at doses corresponding to SHS has been associated with effects on the neurological, respiratory, and cardiovascular systems [11,12]. The evaluation of a mixture of pollutants can also be an advantage, depending on the study question to be analysed. Second, questionnaire-based indicators are more prone to exposure misclassification and recall bias. In general, self-reported exposure tends to underestimate real exposure, and correlations between questionnaire-based exposure indicators and quantitative exposure measurements can be highly variable and dependent on the exposure definition and time since exposure [13]. Even if the misclassification of exposure is random and not systematic, when the magnitude of the actual relationship between exposure and the health effect is small, inaccurate exposure assessment can lead to a statistical error type 2, in which the conclusion would be that such a relationship does not exist when in fact it does. Finally, there are indoor sources of $PM_{2.5}$ that simply cannot be determined using exposure indicators and that contribute to the potential risk to human health from indoor $PM_{2.5}$. Examples of this are the fine particles that come from resuspension by human indoor activities and whose exposure can only be estimated using modelling methods [14,15].

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