Universidade Federal do Espírito Santo

GRADUATE PROGRAMME IN ENVIRONMENTAL ENGINEERING

ESTIMATING ASTHMATIC CHILDREN EXPOSURE AND DOSE TO AIR POLLUTANTS IN AN URBAN INDUSTRIALIZED AREA

Master's dissertation submitted as partial fulfilment of the requirements for the Master degree in Environmental Engineering at the Environmental Engineering Graduate Program in the Federal University of Espírito Santo.

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In memory of my dearest friend that always
wanted to walk when I was studying

I miss you buddy.

ABSTRACT

Asthma affects millions of people worldwide and there is substantial evidence that air pollution exposure is associated with asthma prevalence. For children, the impact is aggravated because their lungs are developing; they have higher ventilation rates and tend to be engaged in daily physical activities. All this contributes to higher doses (also per body weight) than adults have in the same exposed environment. In the Metropolitan Region of Vitoria (MRV), previous epidemiological assessments showed that asthma prevalence among children is higher than the national average. Furthermore, pollutants such as $PM_{2.5}$ and SO_2 impose different associated risks of respiratory symptoms. Nevertheless, to this day no study in MRV approached the exposure and dose of air pollutants at the individual level. Thus, in this work the author aims to address this gap in corroboration with the ongoing project 'ASMAVIX'. This study follows twenty-one children from three different neighborhoods (thus three campaigns) in their daily activities. To establish the methodology for exposure assessment a systematic review is proposed. The author observes drawbacks in 102 papers and approaches children exposure using the best practices found. The literature review also provides a list of opportunities, challenges, and recommendations for future studies to estimate exposure and the associations between air pollutants and asthma prevalence. In the concentration assessment of particles (PM_{10} and $PM_{2.5}$) and gaseous pollutants (NOx, NO_2, and SO_2) at children's home, school and pathway, the author uses the dispersion model CALPUFF, alongside with outdoor monitoring and personal samplers; all integrated with routine aspects of participants. PM_{10} and $PM_{2.5}$ indoor-outdoor (I/O) ratios are calculated (through indoor measurements) and gases I/O derives from literature. This research results support that the correct choice (or measurement of) indoor-outdoor ratios proved to be of significant importance in a holistic exposure assessment, especially for particulate matter. Pathway exposition showed little significance in this study approach, as revealed by sensitivity tests. The main environmental factors interfering in dosage are proximity to sources, and time spent indoors. Physiological key variables are the body mass index and ventilation minute. Thus, more research on I/O ratios on different environment and inhalation rates of children with asthma would benefit future analysis using the proposed method.

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1. INTRODUCTION

Asthma and air pollution

Asthma is a chronic airway inflammation and one of the most common respiratory diseases in children worldwide. It is characterized by wheezing, breathlessness, chest tightness, and cough and sputum production and affects 339 million people globally **(WHO, 2018)**. In Brazil, the prevalence of asthma in children and adolescents is among the highest in the world, **Solé et al. (2014)** estimated an overall total of 22.742 cases for children between 6 to 7 and 35.892 cases between 13 to 14. As for the Metropolitan Region of Vitória (MRV), **Castro et al. (2007)** claim that 15% of all respiratory cases of children (<6y) are due to asthma. Epidemiological studies indicate that environmental factors might contribute to asthma exacerbation, incidence and prevalence, being one possible cause the exposure to air pollution **(GUARNIERI; BALMES; FRANCISCO, 2015)**.

The pathway from air pollution to asthma attacks starts with the total personal exposure, defined as the person getting into contact with a pollutant at a certain location during a specified period. Later, the number of contaminants entering the body during a time interval (named dose) initiates a series of oxidative and radical damage, also influenced by dietary factors **(GILLILAND et al., 1999)**. While studies point out that some air pollutants are not associated with asthma, e.g. Na (sodium) and Cl (chlorine) **(PENTTINEN, 2007; STANEK et al., 2011)**, others shown clear negative connection, e.g. NO_x (nitrogen oxides) **(BOWATTE et al., 2018; JADAAN; KHREIS; TÖRÖK, 2018)**. For instance, in **Hasunuma et al. (2016)** study, an odds ratio[a] of 1.20 was associated with asthma prevalence in children exposed to 50.9 – 136.8 ppb of NOx (1 ½ year mean). Another study suggests that for each increase of 5.7 ppb on average of NO_2, the OR for asthma increased by 1.83 **(GAUDERMAN et al., 2005)**. In **Pénard-Morand et al. (2010)** study, authors found an odds ratio of 1.28, 1.21 and 1.26 between modelled annual mean of PM_{10}, CO and SO_2, respectively, and lifetime asthma.

To estimate the personal exposure, it is necessary to know the concentration that subjects are susceptible in numerous microenvironments (e.g. at school, neighborhood, home). Their total exposure is described in Equation 1 **(MÖLTER, 2012)**.

[a] OR: A measure that indicates the odds of an outcome given a particular exposure, compared to the odds of the same outcome occurring in the absence of that exposure.

$$E_i = \sum_{j=1}^{n} C_j t_{ij} \qquad Eq.1$$

where E_i is the total exposure of the subject i; C_j the pollutant concentration in the microenvironment j and t_{ij} the time spent by the person in the environment j.

To estimate the dose of a subject in terms of inhaled pollutant mass, **Correia et al. (2020)** suggests an equation (Equation 3) that uses the pollutant concentration $[i]$ (μg/m^3) in the microenvironment, the subject inhalation rate $[IR]$ (m^3/h) and the time spent at each microenvironment T_{ME} (hours). Another approach is given by **Morawska et al. (2013)** that suggests the Chronic Daily Intake (CDI) (Equation 4), given in mg/(kg.day), as a measure. The CDI is estimated using the average exposure concentration $[\bar{E}]$ (which is the sum of $[i]$ during the time spent in each microenvironment), the inhalation rate, uptake fraction $[UP]$ (the amount of pollutant that deposits in the lungs) and the person body weight $[BW]$.

$$D_i = \sum_{ME=1}^{n} [i] * IR * T_{ME} \qquad \text{Eq. 3}$$

$$CDI = \frac{[\bar{E}] * IR * UP}{BW} \qquad \text{Eq. 4}$$

Air pollutants dispersion models as an assessment tool

If knowing the concentration field of air pollutants, decision-makers would be able to plan the urbanization in order to reduce the impact of local sources and estipulate vulnerable regions of asthma exacerbation cases **(FRIDELL et al., 2014; LEVY; GRECO; SPENGLER, 2002; SCHUENEMAN; WILLIAMS; EDMISTEN, 1968)**. There are several ways to measure and estimate pollutants concentration in an urban-industrialized environment, including *in-loco* methods, such as fixed-site monitoring stations, residential samplers, and remote sensing, and mathematical tools, such as land-use regression models, proximity to roads, and dispersion models **(KHREIS et al., 2017).** According to **Mölter (2012)**, dispersion model and land use regression models are the main types of indirect exposure assessment tools in epidemiological studies.

Land use regression models use Geographical Information System (GIS) to estimate the concentration of pollutants inside different radius (or buffer zones) from monitoring stations through multivariate linear regression of land-use variables **(MÖLTER, 2012)**. They often depend on a large air quality monitoring network **(BASAGAÑA et al., 2012; MINET; GEHR; HATZOPOULOU, 2017; WU et al., 2017)** and estimates spatial-average values, not accounting

for temporal variations **(MÖLTER, 2012)**. Nevertheless, they are largely employed in epidemiological studies **(KHREIS, H.; NIEUWENHUIJSEN, 2017)**, and recent advances have been made to overcome its drawbacks **(HOEK, 2017)**.

Dispersion models, on another hand, refer to mathematical tools that use the meteorological field, topography, and emission data to estimate the concentration of air pollutants at receptor locations or at grid points. Their estimations are given based on either Eulerian or Lagrangian Gaussian approach. The advantage of employing dispersion models is that they are an alternative to expensive long campaigns and sampling equipment. Moreover, other mathematical tools do not offer the spatial-temporal cover given by the dispersion models and their capability of addressing multiple scenarios of emission in air quality assessment studies **(BATTERMAN; BURKE; et al., 2014; DELFINO, 2009)**. For those reasons, dispersion models turn out to be recommended by environmental protection agencies (EPA), such as U.S. EPA, as air quality assessment tools **(GAFFRON; NIEMEIER, 2015)**.

Even though dispersion models presents many advantages compared to other methodologies they have been rarely employed in epidemiological studies **(MAANTAY; TU; MAROKO, 2009)**, mainly due to the fact that it would require a multidisciplinary team of scientists.

ASMAVIX project and the context of this work

The ASMAVIX Project aims to investigate the association between air quality and symptoms of asthma in children living in the city of Vitória, ES - Brazil. The project is conducted by two complementary research groups: (1) health group and (2) air quality group.

The health group is made up of researchers from the Health Sciences Center, in the Federal University of Espírito Santo (UFES) and aims the health monitoring of children and adolescents with asthma in order to obtain longitudinal data necessary for the search for possible causal associations. Data collection is being made directly in contact with individuals as well as their parents or guardians. A comprehensive collection of covariates is also being performed, including analysis of genes that, in other populations showed association with the onset or severity of the disease.

The air quality group is made up of researchers from the Graduate Program in Environmental Engineering of the Technological Center in UFES and aims the monitoring and modelling of air pollutants of interest (PM_{10}, $PM_{2.5}$, CO, SO_2, O_3, and NOx) to which the investigated population is exposed. In this way, two distinct but complementary sub-projects are being conducted in parallel.

Scientific papers published so far on asthma and air pollution in the MRV are the result of ecological studies or descriptive studies concerning the general population or specific population subgroups **(CASTRO et al., 2007, 2011; DE FREITAS et al., 2016; NASCIMENTO et al., 2020; NASCIMENTO et al., 2017; SERPA et al., 2014)**. Such studies are not ideal to accurately evaluate the association between exposure and response and the causative relationship between asthma and exposure to airborne pollutants **(CASTRO et al., 2011)**. In contrast, the ASMAVIX project is collecting direct health data by following a specific group of children and adolescents during the long term. Furthermore, no past study addressed exposure using dispersion modelling and an integrated approach with the studied group (subjects) pathway and routine habits.

Therefore, the main goal of this master thesis is to estimate the exposure to ambient PM_{10}, $PM_{2.5}$, NO_X, SO_2, and CO of children and adolescents using the CALPUFF dispersion model as an air quality assessment tool and determine the dose of inhaled air pollutants by the children and adolescents under the scope of the ASMAVIX project.

2. OBJECTIVES

2.1 General objective

This work aims to estimate the exposure and dose to ambient air pollutants of children living in an urban-industrialized environment.

2.2 Specific objectives

- To assess the challenges, opportunities, drawbacks and best practices of air pollution exposure of asthmatic children by using dispersion models;

- To gather/assume children routine throughout the day, including time spent in school, outdoors and at home;

- To assess exposure by integrating the temporal-spatial concentrations of PM_{10}, $PM_{2.5}$, NO_X, NO_2 and SO_2 and children routine;

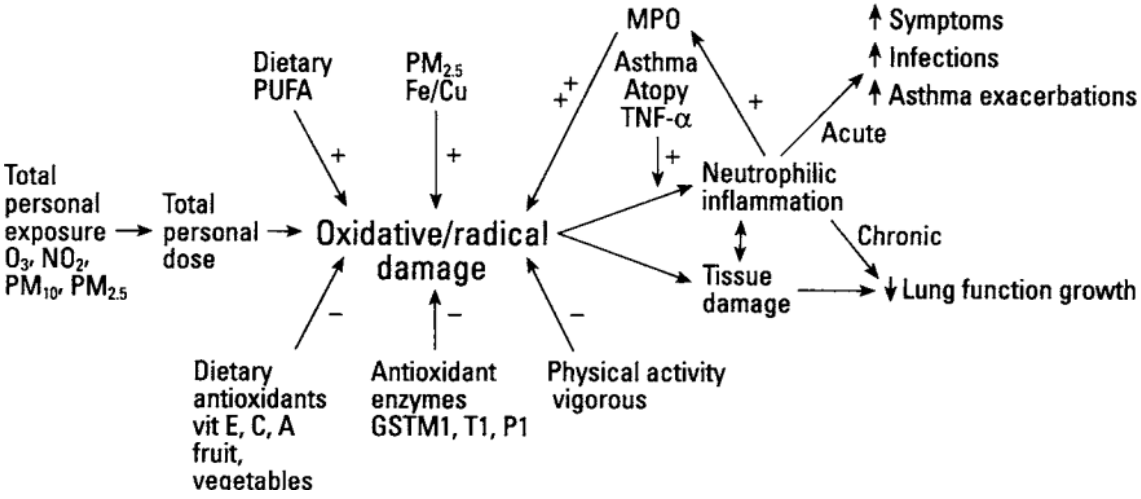
- To calculate the dose of PM_{10}, $PM_{2.5}$, NO_X, NO_2 and SO_2 per body weight of children, and indicate key environmental and physiological factors of influence;

3. LITERATURE REVIEW

3.1 Asthma importance and the need for a holistic approach

According to the 2018 World Health Organization report, **WHO (2018)**, asthma affects 339 million people worldwide and is one of the most common disease in children. Studies point out that some air pollutants have shown a clear association with asthma symptoms and children are the most susceptible group due to their physiological characteristics **(BATESON; SCHWARTZ, 2008)**, therefore they becoming the focus of epidemiologic research. **Gilliland et al. (1999)** study (**Figure 1**) show the health impacts pathway that some air pollutants can cause in children. The study claims that air pollution is one of the factors that influence asthma exacerbation episodes. Alongside, a series of genetic, dietary, and environmental factors play their role. To this day, discussion remains among scientists on how portioned the contribution for each factor is.

Figure 1. Pathways for the biologic impact of ozone, nitrogen dioxide, PM_{10} and $PM_{2.5}$ in the respiratory health of children.



Source: **(GILLILAND et al., 1999)**

An important confluence involved in air quality and health research is the definitions of air pollutant concentration, exposure and dose, explained by **Table 1**. The ability of concentration assessment tools in health studies restrain to the estimation of air pollution at community and individual levels. However, the integration of these tools results with exposure models/methods makes it possible to establish associations between air pollution and asthma.

Table 1. Definitions applicable in this dissertation

Air Pollution		
Concentration	**Exposure**	**Dose**
Amount of air contaminant present in the atmosphere as a function of mass, particle number or other, per volume of air	The person getting into contact with a pollutant at a certain location during a specified period	Amount of an air contaminant entering the body. It depends on lung volume, breathing pattern and type of pollution exposed

Adapted from: **(MÖLTER, 2012)**

In **Guarnieri; Balmes; Francisco (2015)** review, the authors investigated the effects of several pollutants in asthma exacerbation and new-onset asthma through results of clinical studies. Pollutants of interest were particulate matter (PM); gases (ozone –O_3, nitrogen dioxide – NO_2, sulfur dioxide – SO_2), and mixed traffic-related air pollution (TRAP), which is defined as air pollution that comes from the emissions of motor vehicles that result from fossil fuel combustion. From a biological perspective, TRAP appears as the most dangerous once it can suppress regulatory T cells (Treg) increasing asthma severity. While short-term exposures to $PM_{2.5}$ and PM_{10} (particles with less than 2.5 and 10 micrometers of aerodynamic diameter, respectively) are associated with asthma symptoms, long-term exposure of coarse fractions (the difference between PM and PM_{10} + $PM_{2.5}$) is correlated with the decrease in lung function. Gaseous pollutants also play a role in asthma exacerbation. Ozone and nitrogen oxides may induce airway inflammation, airway responsiveness, and decrements in lung function. Sulfur dioxide may cause bronchoconstriction. The authors pointed out some research gaps that still need attention, including the effect of short-term (1h) and long-term (days) exposure to pollutants. Other gaps are the asthma exacerbation due components of particulate matter; the epigenetic pathway of NO_2 alone, methods for personal monitoring and the cumulative effect of exposure to a mixture of pollutants.

Among sources of air pollutants in urban centers, those that are traffic-related received much attention over the last years. The idea of vehicular fleet continually increasing worldwide raises the question of the effect on exposure, especially of children, to this type of pollution. In **Khreis; Nieuwenhuijsen (2017)** review, the authors investigated the exposure assessments methods to estimate concentrations of TRAP pollutants and its correlation with childhood asthma. The authors compared the pros and cons of air quality assessment tools that can provide information on exposure, including 1) proximity to roads, 2) fixed-site monitoring stations, 3) residential

samplers, 4) remote sensing, 5) land-use regression models, and 6) dispersion models. They classified dispersion models as a 'very good' assessment tool due to its spatial-temporal resolution. Although dispersion models also carry some hypothesis, they are still considered reliable to estimate air pollutant concentrations in urban-industrialized environments **(PÉNARD-MORAND; ANNESI-MAESANO, 2008)**. However, they are not often used by health scientists as it would need a multidisciplinary approach to address exposure **(GAFFRON; NIEMEIER, 2015; MAANTAY; TU; MAROKO, 2009)**.

Another important aspect concerns indoor exposure since most children spend time inside their homes or schools. Due to the children mobility throw-out the day and the importance of ventilation inside indoor spaces, a strong approach to exposure assessment should be time-and-space-averaging; To estimate the indoor pollution from outdoor concentrations, a probabilistic model derived by **Dimitroulopoulou et al. (2006)** is advised. Another approach is the use of indoor/outdoor (I/O) ratios based on literature data. Several studies addressed the I/O ratio at schools for the pollutants under investigation **(BLONDEAU et al., 2005; CARRION-MATTA et al., 2019; CHALOULAKOU; MAVROIDIS, 2002; CHITHRA; SHIVA NAGENDRA, 2018; DIAPOULI et al., 2008; PALLARÉS et al., 2019; SALONEN; SALTHAMMER; MORAWSKA, 2019; STRANGER; POTGIETER-VERMAAK; VAN GRIEKEN, 2008; TRIANTAFYLLOU et al., 2008)**. Generally, the I/O ratio of gaseous pollutants is smaller than a unit in school environments, while for particles it is often the contrary **(BLONDEAU et al., 2005)**. Factors that studies point to influence the air quality inside schools are ventilation, occupants activity, clothes and shoes carrying outside particles, and smoking **(LEUNG, 2015)**. Some authors also focused in the I/O ratio of pollutants for car travelling **(ABI-ESBER; EL-FADEL, 2013; CHAN; CHUNG, 2003; CORREIA et al., 2020; WEICHENTHAL et al., 2015)**. For those studies, the travel speed, route location and type of vehicle most influenced the I/O. At home, more data that are complex are involved as more sources of air pollutants can be found (e.g., cooking, tobacco smoke, and pets). As far as the I/O ratio goes, variable ranges can be found for each pollutant under investigation **(BOZKURT et al., 2015; CAO et al., 2005; CHEN; ZHAO, 2011; MORAWSKA, L. et al., 2013; MORAWSKA; SALTHAMMER, 2003)**.

One issue of using the I/O is the conditions where the study took place. In locations isolated from outside sources, indoor concentrations can proof to be significantly higher than outdoors **(PAGEL et al., 2016, 2018)**. Meteorological events (e.g. raining) can also trap pollutants indoors **(BO et al., 2017)**. Thus, studies that are similar to the region and indoor environment of

application are preferable and sensitivity analysis advised, otherwise the I/O is not a strong assessment measure for certain pollutants **(CHEN; ZHAO, 2011)**.

3.2 Remarks

As shown by **Section** Error! Reference source not found., the risk and exposure assessment of sthmatic children to air pollution is not simplistic. It requires a multidisciplinary team to measure-or-model pollutants in indoors and outdoors spaces, collects children routine habits and performs a source-specific or pollutant-specific analysis of dose. Due to its spatial-temporal representativeness power to estimate the concentration of atmospheric pollutants, dispersion models are recommended. Thus, in **Section 4** the author performs a systematic review to understand how studies use this tool and if there is or not an integration with source apportionment tools such as receptor models in epidemiological research.

4. THE ROLE OF DISPERSION AND RECEPTOR MODELS IN ASTHMA RESEARCH - A SYSTEMATIC REVIEW

Work submitted to Environmental Research; Impact Factor: 5.02 (2018). **Qualis CAPES:** A1

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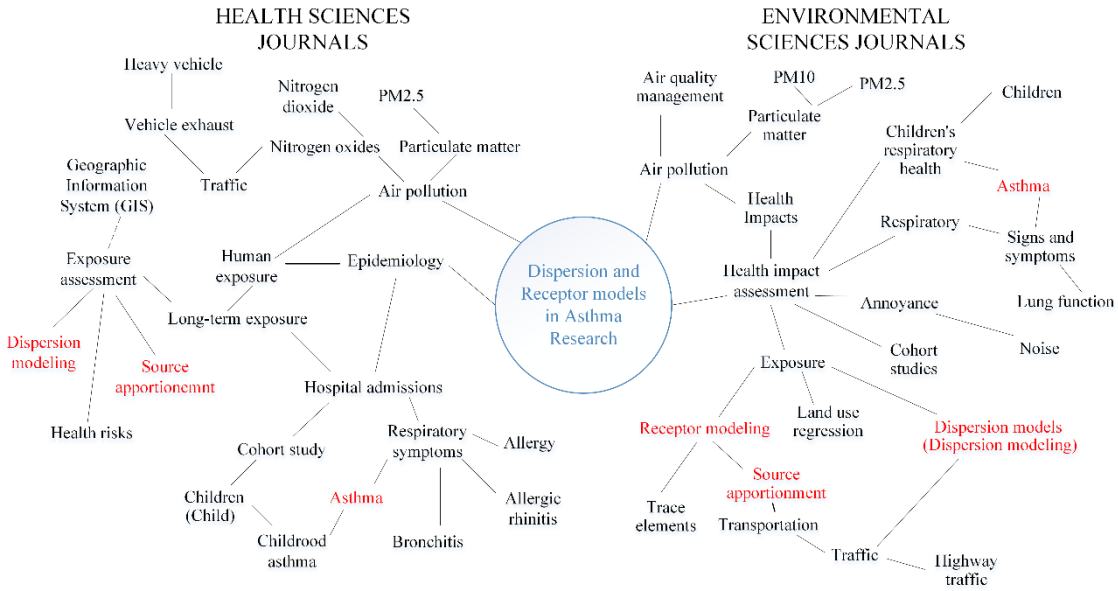
Graphical Abstract



Abstract

Asthma affects millions of people worldwide and there is substantial evidence that air pollution is associated with this disease prevalence. In addition to the methodological aspects of collecting medical data on asthma, air pollutant exposure can also be determined following different strategies. One of these strategies regards the use of dispersion models (DM) which presents the advantage of giving spatially distributed outdoor pollutants concentration or receptor model (RM) that gives the source apportionment of specific chemical species among particulate matter and volatile organic compounds (VOCs). However, the use of DM or RM in asthma research requires a multidisciplinary approach involving experts on air quality and respiratory diseases. This work is to provide a systematic literature review on the role of DM and RM in air pollution and asthma research over the years, their limitations, and the most important findings. We reviewed 102 papers to found that DM are mostly used to estimate air pollution levels outside the subject's home, school or workplace, however very few papers addressed the subject's routines or indoor/outdoor relationships. RM, on the other hand, are employed in regions where asthma incidence/prevalence is known as high or where a dispersion model has been previously used for this assessment. Results support that traffic (vehicle exhaust) and NOx are the most targeted source and pollutant, respectively. Few studies addressed VOCs or modeled more than one or a few sources and fewer investigated source apportionment. The associations between crucial air pollutants and asthma reported in different studies have been proved conflicting even in those using similar methodology in data collection and exposure assessment. Finally, this review provides a list of opportunities, challenges, and recommendations for future studies to address better the associations between air pollutants and asthma prevalence.

Keywords: Asthma; Air pollution; Exposure; Source Apportionment; Models coupling; Health;

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List of Abbreviations

BC – Black Carbon

CMB – Chemical Mass Balance

DM – Dispersion Model

EC – Elemental Carbon

ED – Emergency Department

FEV – Forced Expiratory Volume

FVC – Forced Vital Capacity

GINA – Global Initiative for Asthma

GPS – Global Position System

HR – Hazard Risk

ISAAC – International Study of Asthma and Allergies in Children

OC – Organic Carbon

OR – Odds Ratio

PAH – Poly Aromatic Hydrocarbons

PCA – Principle Component Analysis

PM – Particulate Matter

PMF – Positive Matrix Factorization

RM – Receptor Model

RR – Relative Risk

TRAP – Traffic Related Air Pollution

UFP – Ultrafine Particles

VOC – Volatile Organic Compounds

WHO – World Health Organization

4.1 Introduction

According to **WHO (2018)**, asthma affects 339 million people worldwide. It is characterized by a chronic inflammatory process of the airways that could lead to airflow obstruction and respiratory symptoms **(GINA, 2019)**. In developing countries like Brazil, for instance, the prevalence of asthma in children and adolescents is among the highest in the world **(SOLÉ et al., 2014)**. One of the possible causes of asthma exacerbations is air pollution.

Exposure to air pollutants can occur in indoor and outdoor environments. In indoor environments, the pollutant concentrations are a result of indoor sources as well as infiltration from outdoor pollutants, especially in rather warm countries where the natural ventilation system is more commonly employed. Therefore, the estimation of the outdoor concentration of pollutants is essential for clinical studies involving the effects of air pollutants on asthma exacerbation. There are mainly two ways of estimating outdoor air pollutants concentration: direct measurements and mathematical models. The advantage of mathematical models is that, once the model is validated for a specific region, it can provide the spatial distribution of concentration while measurements are generally carried out at scarce locations. Among the studies on asthma exacerbation due to exposure to ambient air pollutants, some have employed dispersion models to understand the role of ozone (O_3) **(BORREGO et al., 2007; DELFINO, R.J. J et al., 2014; FRIDELL et al., 2014; TSUI et al., 2018)**, particulate matter (PM), mainly PM_{10} **(MENDOLA et al., 2016; PÉNARD-MORAND; RAHERISON; CHARPIN; KOPFERSCHMITT; LAVAUD; CAILLAUD; ANNESI-MAESANO, 2010)** and $PM_{2.5}$ **(BATTERMAN; GANGULY; et al., 2014; JIŘÍK et al., 2017; LEVY; GRECO; SPENGLER, 2002)**, nitrogen oxides (NO_x) **(GUTTIKUNDA, S.K. et al., 2015; HASUNUMA et al., 2016; PUKLOVÁ et al., 2019)**, carbon monoxide (CO) **(BATTERMAN; BURKE; et al., 2014; DELFINO et al., 2014; PENNINGTON et al., 2018)**, sulfur dioxide (SO_2) **(KOIWANIT et al., 2016; MILANDO; MARTENIES; BATTERMAN, 2016; PASCAL et al., 2013)** and volatile organic compounds (VOC) **(CHARPIN, D. et al., 2009; SPADARO; RABL, 1999)**. An even more limited number of studies explored the contribution of different sources **(**for instance, **Batterman et al. (2014a); Galvis et al. (2015); Ganguly et al. (2015), Guttikunda et al. (2015); Guttikunda and Goel (2013); Khafaie et al. (2017) and C.W. Milando et al. (2016)**).

The support that dispersion models can provide to health studies is restrained to the estimation of concentrations at community and individual levels. However, the integration of the dispersion model results with exposure models/methods makes it possible to establish associations between air pollution and asthma. For instance, a dose inhaled by an individual in terms of pollutant mass

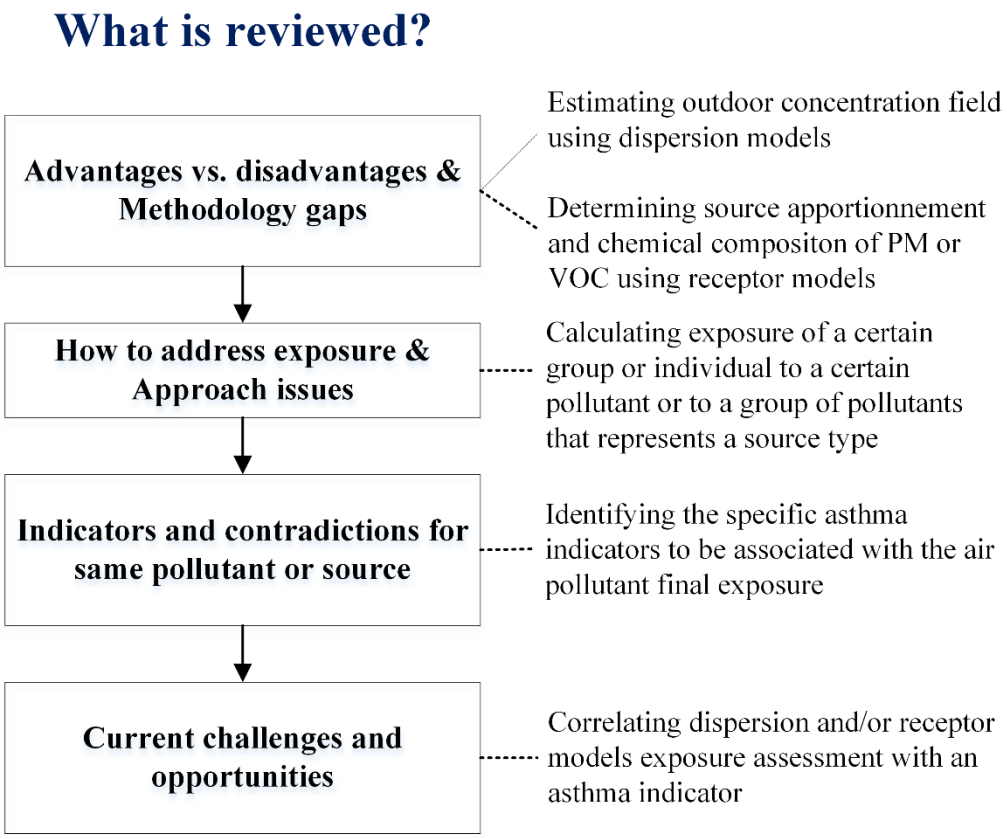
can be estimated based on the concentration to which a subject is exposed throughout a day at different microenvironments, or during their commute to school and home, subject inhalation rate (which depends on other variables) and the time spent at each microenvironment. In this sense, the dispersion models can supply the spatial-temporal variation of pollutants concentration in a given region. Despite the advantages of the use of dispersion models, studies present two recurrent drawbacks: not addressing indoor exposure (making estimations outside the place of interest and assuming an indoor/outdoor ratio of 1) and focusing on one or few specific sources (e.g, traffic).

Another mathematical approach, other than dispersion models, called receptor modeling consists in estimating the source apportioning of particulate matter or volatile organic compounds by chemically characterizing the pollutant and assessing sources contribution to the subject's exposure. Studies have proved that receptor-based studies provide a size-resolved toxicity analysis **(HALONEN 2009; OSTRO et al., 2016; ROHR et al., 2014)** thus discrediting the concept of PM mass alone being associated with adverse airway response **(HABRE et al., 2018; MORISHITA et al., 2006)**. The primary cost of this approach is the extensive sampling campaign that must precede the analysis and technical expertise required.

This present work intends to review the knowledge acquired on using dispersion and receptor models in asthma research, as authors recommend their use to estimate outdoor concentrations and specific source impacts in air pollution exposure assessment studies **(CHARPIN, D. et al., 2009; DELFINO et al., 2009; KHREIS, H.; NIEUWENHUIJSEN, 2017; PÉNARD-MORAND; ANNESI-MAESANO, 2008)**. This review also aims to present and discuss the use of coupled receptor modelling and dispersion models in asthma assessment, for the two following reasons: 1) RM can assist dispersion model results **(MONTICELLI et al., 2020)** and 2) identifying specific chemicals in air pollutants and contributing sources may lead to a better understanding of their relationship with asthma **(ZHAO et al., 2007)**. Note that this review does not intend to compare several exposure assessment tools as **Jerrett et al. (2005)** because the significant points claimed in the authors critique remain valid. This review also does not aim to compare specific models or focus on one specific source pollution as in **Favarato et al. (2014), Khreis and Nieuwenhuijsen (2017),** and **Pénard-Morand and Annesi-Maesano (2008)**.

The methodology to perform this systematic literature review and the overall bibliometric results are fully described in the **Appendix II** of this dissertation. Briefly, the authors used the ProKnow-C methodology, develop by **Ensslin et al. (2010)**, and compiled the results and discussions of one hundred and two papers within the topic of interest. This work follows the reasoning illustrated in **Figure 2**.

Figure 2. Study-design



4.2 Exposure assessment using dispersion models

There are numerous dispersion models presented in the literature to assess pollutants exposure. The choice of a model varies among countries and types of sources of interest. Whereas USEPA recommended models (e.g. AERMOD and CALPUFF) have been applied for USA cities **(BATTERMAN; GANGULY; et al., 2014; GALVIS et al., 2015; GANGULY; BATTERMAN; BRAKEFIELD-CALDWELL, 2012; ISAKOV et al., 2014; LEVY; NISHIOKA; SPENGLER, 2003; LEVY; GRECO; SPENGLER, 2002; MAANTAY; TU; MAROKO, 2009)**, other alternative models have been used for European cities and for the rest of the world (e.g. EPISODE, ADMS and AirViro) **(GRUZIEVA et al., 2013, 2017; IDAVAIN et al., 2019; MELÉN et al., 2008; MODIG; FORSBERG, 2007; NORDLING et al., 2008; OFTEDAL et al., 2009; SCHULTZ, A.A.; SCHAUER; MALECKI, 2017; SOMMAR et al., 2014)**. Because more than half of the studies investigated Traffic-Related Air Pollution (TRAP), dispersion models specifically advised for this source have been employed (e.g. CALINE4 and RLINE) **(BATTERMAN; BURKE; et al., 2014; DELFINO et al., 2014; DELFINO et al., 2009; FRANKLIN; FRUIN, 2017; GANGULY et al., 2015; GAUDERMAN et al., 2005;**

MCCONNELL et al., 2010; PENNINGTON et al., 2017, 2018; PERSHAGEN et al., 1995; SHANKARDASS et al., 2009).

Multiple applications were found among studies. **Fridell et al. (2014)** investigated the health impact of cleaner emissions by altering vehicles burning fuel in emission inventories. The authors coupled a large-scale dispersion model (EMEP) and a small scale one (TAPM) with projected emissions scenarios as a novelty. They further applied exposure-response functions found in the literature to estimate a new number of asthma cases. **Idavain et al. (2019a)** employed dispersion models to characterize children's level of exposure to specific pollutants not usually addressed (e.g., phenol and formaldehyde), emitted from oil shale industries. To associate exposure and health effects, authors employed logistic regression analysis and differentiated results by high-polluted areas versus non-polluted areas. **Milando et al. (2016)** proposed a framework integrating dispersion model results, alternative scenarios and health impacts estimated through health impact functions that give the number of asthma cases attributable to pollutant exposure and allow the use of user-defined local concentration-response functions. **Levy et al. (2002)** engaged the CALPUFF model to investigate the health impacts changes in subpopulation groups due to $PM_{2.5}$ emission abatement in selected power plants. In order to address health outcomes, morbidity, and mortality, concentration-response functions were employed. They concluded that distinguishing subpopulations could help studies to understand the benefits of emission control strategies. Recently, **Castell et al. (2018)** showed the advantages of data fusion between a dispersion model (EPISODE) and low-cost sensor nodes to show real-time information on outdoor air pollution so citizens could be aware of their NO_2 daily exposure levels and policy-makers could support targeted mitigation strategies. This process of assimilating multiple databases can provide more steady, precise and valuable information if compared to the individual data by each base.

In order to estimate exposure, studies model and integrate pollutants concentration at subjects specific locations in time, such as at home (e.g**., Idavain et al. (2019) ; Pennington et al. (2017); J.N. Sommar et al. (2014))**, school or work place (e.g., **D. Charpin et al.(2009); Khafaie et al. (2017)**), or mentioned a time-averaged function considering the subject routine (e.g., **Bougas et al. (2018); Gruzieva et al. (2017)**). To the best of our knowledge, no study using dispersion models considered the exposure during the subject pathway between indoor locations.

Some studies estimate concentration outside subjects home/school address and assumed an indoor/outdoor ratio of one, while literature indicates that this is not often the case **(BOZKURT et al., 2015; CARRION-MATTA et al., 2019; MORAWSKA, L. et al., 2013; PALLARÉS et al., 2019; SALONEN; SALTHAMMER; MORAWSKA, 2019)**. Indoor air quality research

suggests that people spend most of their time (60 to 90%) inside closed spaces **(CHITHRA; SHIVA NAGENDRA, 2018; FABIAN et al., 2012; JOHNSON et al., 2018; MORAWSKA, L. et al., 2013)**. This shows the importance of correctly estimating the indoor concentrations, which are a function of indoor sources and outdoor concentrations, among other variables. In addition to this drawback, some studies account only for one particular source or a group of sources that might result in underestimating the real concentrations to which the targeted population is exposed. To overcome this drawback without increasing the modeling complexity of having to estimate multiple source emission, authors often employ background concentrations derived from local air quality monitoring (e.g., **Malmqvist et al. (2018)**) or mesoscale models (e.g., **Khreis; De Hoogh; Nieuwenhuijsen, 2018)**).

Dispersion models are expected to be validated prior to their use in a specific region. Conventional approaches resort to correlation coefficients, like the Pearson correlation, while others recommend further statistics towards a complete valuation **(CHANG; HANNA, 2004; HANNA; CHANG, 2012)**. This review was concerned with papers that provide such analysis in order to obtain a proper insight into dispersion models applications. From the 72 papers reviewed regarding the use of dispersion models to assess the correlation between asthma and air pollution, only 38 (52%) showed to have validated the used model.

Validation often occurs by comparing estimates with measurements. Based on that approach, sixteen studies only addressed correlation coefficients **(BATTERMAN; BURKE; et al., 2014; BORREGO et al., 2007; CARRERAS; CHELLINI; BLANGIARDO, 2012; DELFINO et al., 2009; GRUZIEVA et al., 2017; HENDERSON et al., 2011; KHREIS, H.; DE HOOGH; NIEUWENHUIJSEN, 2018; LINDGREN et al., 2013; MALMQVIST et al., 2018; MELÉN et al., 2008; MODIG et al., 2009; NORDLING et al., 2008; RANCIÈRE et al., 2017; REUNGOAT et al., 2005; SMARGIASSI et al., 2009; ZMIROU et al., 2002)**. Eight studies mentioned that validation was carried out in previous work; however, in only six of these studies it is was possible to trace the validation methodology **(DELFINO et al., 2014; GRUZIEVA et al., 2017; GUTTIKUNDA; GOEL, 2013; KLÆBOE et al., 2000; SCHULTZ, et al., 2016; SHANKARDASS et al., 2009)** and in two it was not **(CHARPIN, D. et al., 2009; PERSHAGEN et al., 1995)**. Five papers opted for calibrating model results with measurements rather than validating **(ALCOCK et al., 2017; BELLANDER et al., 2001; MENDOLA et al., 2016; PENNINGTON et al., 2018; TONNE et al., 2010)**. One study provided a comparison of the measured and modeled mean concentration for a specific season **(MODIG; FORSBERG, 2007)** and another study made monthly average comparisons of dispersion models results

(GUTTIKUNDA et al., 2015). At last, one study state the modeling results agreed with the time series of observed data **(ISAKOV et al., 2014)**.

Five studies employed several statistical tools, such as Fractional Bias, Normalized Mean Square Error, Correlation Coefficients, and Index of Agreement. Those corresponded to 7% of studies that employed dispersion model and 14% of the 38 with validation procedures **(CASTELL et al., 2018; GALVIS et al., 2015; HASUNUMA et al., 2016; HOOGH et al., 2014; OFTEDAL et al., 2009)**. **Figure 3** shows the models that underwent a validation procedure.

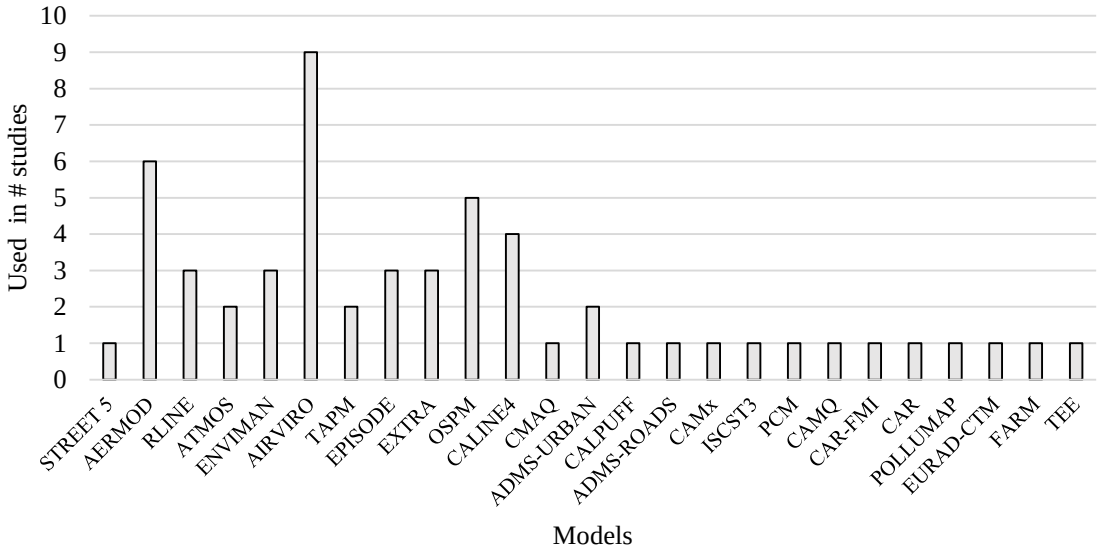


Figure 3. Variety and frequency of dispersion models used in asthma studies

4.3 Exposure assessment using receptor models

From the 17 papers that used receptor models, eight opted for the Positive Matrix Factorization (PMF) model **(DUCRET-STICH et al., 2013; HALONEN et al., 2008; HALONEN et al., 2009; HAMMOND et al., 2008; LI et al., 2016; MORISHITA et al., 2006; OSTRO et al., 2016; ROHR et al., 2014)**. Other four papers applied Principle Component Analysis (PCA) **(HABRE et al., 2018; PENTTINEN, 2007)** or Chemical Mass Balance (CMB) **(KALAIARASAN et al., 2017; PENNINGTON et al., 2018)**. Three studies applied more than one receptor model **(ANDERSEN et al., 2007; KRALL et al., 2017; SAHU et al., 2011)** and two applied methodologies that resemble conventional receptor models **(GENT et al., 2009; ZHAO et al., 2007)**. All receptor models solve mass balance equations, and the difference is given by the factor profile, i.e. while the majority of models create these factors from input data, the CMB receptor model works with prearranged profiles of sources emission and pollutant

speciation **(STANEK et al., 2011)**. The PCA model is often used as a pre-treatment of the factor profiles in order to reduce their correlation.

Two main applications were found among studies. The first is a complementary approach to a previous epidemiological study using dispersion modeling or monitoring stations, where authors explored the source apportionment of a region in which the association between air pollution and asthma was previously addressed (e.g., **Hammond et al. (2008); Morishita et al. (2006)**). The second approach gives a source-specific or pollutant-specific analysis of the risks for a given asthma outcome, using receptor model results and regression model analysis (e.g., **Gent et al. (2009); Halonen et al. (2009); Krall et al. (2017)**).

Stanek et al. (2011) review study pointed to sodium (Na) and chlorine (Cl), from sea origin, as having no positive association with asthma medication use, and sulfur (S), potassium (K) and zinc (Zn), from long-range transport, as having a negative effect on decreasing the Peak Expiratory Flow (PEF) in asthmatic adults. On the other hand, sulfate ion (SO_4^{2-}) appears to be associated with a decreased systolic blood pressure. and the PM emissions from road dust/soil/crustal sources appear to be associated with increased respiratory symptoms among children and adults with asthma. In another two studies, **Halonen et al. (2009)** and **Halonen et al. (2008)** showed that particle Accumulation mode and Aitken mode could present a higher percentage of change in cause-specific respiratory hospital admissions due to asthma for interquartile increases and different lag-response if compared to coarse fractions.

Many receptor models possess their own statistical validation procedure, such as chi-square (chi^2), minimum uncertainty (Q min), and percent mass resolved (%mass) **(BROWN et al., 2015; PAATERO et al., 2014; USEPA, 2004)**. However, not all studies presented these parameters, while it is well known that they should always be included in the discussion (e.g., **Andersen et al. (2007); Ducret-Stich et al. (2013); Halonen et al. (2009); Kalaiarasan et al. (2017);** and **Morishita et al. (2006)**).

A procedure that showed to provide better results is the pre-treatment of the species in which threshold limits for the signal to noise ratio (S/N) and the correlation between elements are used to improve source apportionment **(HAMMOND et al., 2008; KRALL et al., 2017; ROHR et al., 2014; SAHU et al., 2011; ZHAO et al., 2007)**. **Figure 4** gives the receptor models used in the investigated literature that presents validation or pre-treatment procedure.

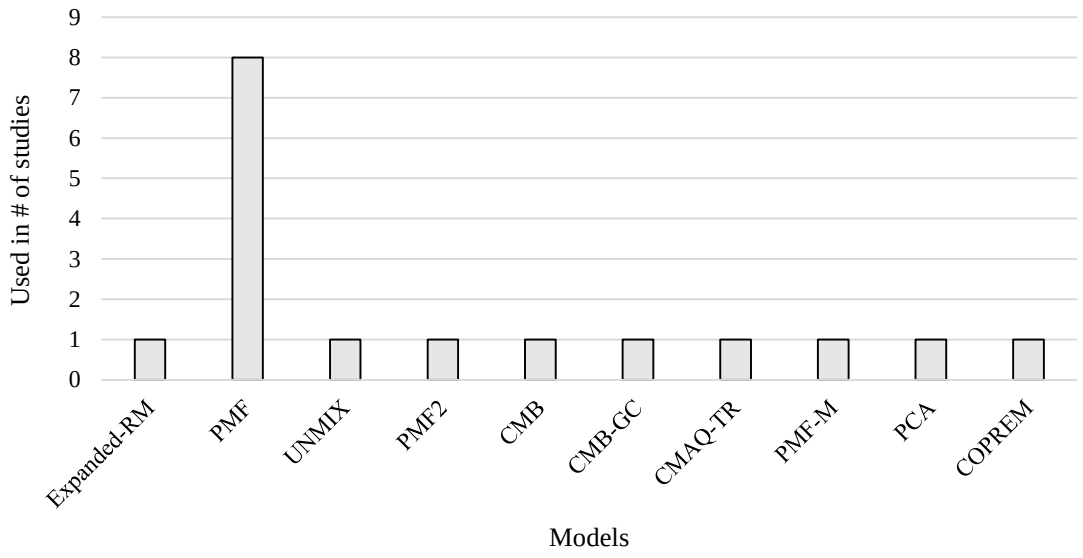


Figure 4. Variety and frequency of receptor models used in asthma studies.

4.4 Exposure assessment using coupled models

Four studies used dispersion models for source apportionment purposes. **Galvis et al. (2015)** and **Milando et al. (2016)** employed the AERMOD model for source apportionment using the 'sources grouping' function. Their results could be used for establishing new control strategies for major emitters. Neither study showed a comparison of the source apportionment using dispersion and receptor models, however, some mention previous studies results **(GUTTIKUNDA, S.K. et al., 2015; GUTTIKUNDA, S.K. K; GOEL, 2013)**.

Although those readings show the capacity of dispersion models for source apportionment, they still are not a 'coupled' approach. Neither are studies that only compare the results of both models (e.g. **Ganguly et al. (2015)**) or mention source apportionment results from previous research (e.g. **Khafaie et al. (2017)**). Only two studies used the coupled models strategy. The strategy was used for the following applications:

- Complete air quality and source apportionment data where/when monitoring was not available **(KRALL et al., 2017)**;
- Calibration of $PM_{2.5}$ dispersion model (RLINE) results with receptor model outcomes (CMB-GC) **(PENNINGTON et al., 2018)**.

4.5 Sources of interest

Sixty-five emission sources were the focus on the 102 papers analyzed. **Table 2** gives the sources grouping employed to construct **Figure 5** in which is presented the yearly trend of essential

sources. TRAP was the primary source of concern among studies and it appears in all years (except 2003 and 2019). Although papers point out that such source is capable of triggering asthma **(GRUZIEVA et al., 2013, 2017; MCCONNELL et al., 2010; MODIG et al., 2009; NORDLING et al., 2008; PERSHAGEN et al., 1995; RANCIÈRE et al., 2017; SCHULTZ et al., 2016; STANEK et al., 2011; ZMIROU et al., 2002)** others are not so conclusive **(CARRERAS; CHELLINI; BLANGIARDO, 2012; LINDGREN et al., 2013; OFTEDAL et al., 2009; SONNENSCHEIN-VAN DER VOORT et al., 2012)**. Due to the importance of this particular source (TRAP) and the contradicting findings, special attention is given further in the text.

Stationary sources/Industries were also a recurrent group of sources appearing in the papers alongside with anthropogenic activity. Between industries, the most frequent were power plants **(GUTTIKUNDA; JAWAHAR, 2014; LEVY; NISHIOKA; SPENGLER, 2003; LEVY; GRECO; SPENGLER, 2002; MILANDO; MARTENIES; BATTERMAN, 2016)**, petroleum-related **(IDAVAIN et al., 2019; PASCAL et al., 2013; SMARGIASSI et al., 2009)** or ironworks-related **(HAMMOND et al., 2008; MORISHITA et al., 2006; PASCAL et al., 2013)** plants. Some studies claim that indoor cooking and tobacco consumption might present higher risks for asthma recipients than outdoor air pollution **(SONNENSCHEIN-VAN DER VOORT et al., 2012; ZHAO et al., 2007)**. Many authors did not investigate all sources of influence in the region and, therefore, could be underestimating the population exposition or attributing the health impact unfairly, as stated by **Batterman et al., (2014b)**; and **Snyder et al. (2014)**.

Table 2. Sources grouping used in this review

Group	Sources
Traffic-Related (TRAP)	Streets, Motor vehicle emissions, Diesel vehicle emissions, Gasoline vehicle emissions, Road dust, Traffic, Motor vehicle, Urban road dust, Traffic exhaust, Tire & Brake wear, Vehicle, Paved road dust
Stationary/Industries	Power plants, Petrochemical, Ironworks, Rail yards, Industries, Oil shale industry areas, Kiln, Steel industry, Heavy industry, Petroleum refineries, Metal processing, Oil combustion refineries, Iron/steel manufacturing, Coal, Metals
Background	Regional, Long-range transport, Urban dust, Dust
Anthropogenic activity	Landfills, Civil construction, Chlorine-based cleaning, Cooking, Environmental tobacco smoking, Combustion sulfate, Oil, Ships, Municipal waste incinerators, House heating, Waste incineration, Automotive electroplating, Oil combustion, Construction site, Railway, Sulphur, Airport, Local combustion, Heavy fuel oil
Natural	Forest fire, Soil, Vegetative burning, Soil and crustal, Salt, Biomass burning, Mineral dust, Sea salt, Biomass, Crustal, Soil dust, Marine source emissions
Secondary formation	Secondary sulfate, Secondary nitrate, Secondary photochemistry
All sources	When the study specifies multiple sources of interest

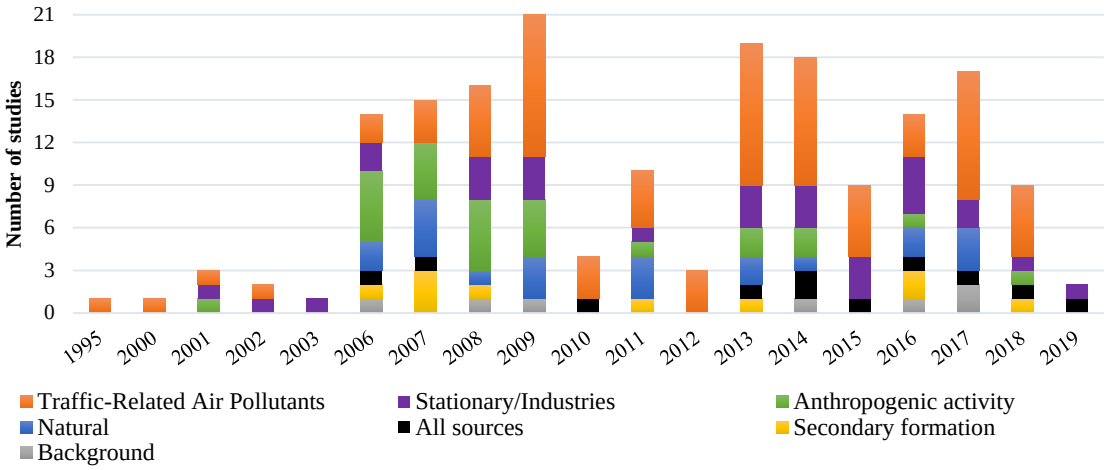


Figure 5. Temporal variability of main sources of interest among reviewed studies

Traffic-Related Air Pollutants

The increasing amount of vehicles in cities is a concern, especially in terms of air pollution and population exposure **(PÉNARD-MORAND et al., 2010)**. It is, therefore, rational that TRAP is extensively investigated in asthma research. However, as we aim to show, the methodological steps used in the exposure estimation approach may lead to errors in the analysis, compromising studies comparison **(GAUDERMAN et al., 2005; GRUZIEVA et al., 2017)**.

Fifteen studies were selected to be further investigated due to their contradictory findings. The goal here is to explore the methodological approach of such papers to find points in common and divergences in order to clarify their outcomes.

Points in common:

- All studies applied dispersion models or mentioned results from previous studies;
- None employed receptor models to refine exposure results;
- All evaluated outdoor air pollution;
- All evaluated urban scenarios;

Divergences:

- Two studies did not employ regression analysis to establish the relationship between exposure and asthma **(PERSHAGEN et al., 1995; ZMIROU et al., 2002)**;
- Two studies did provide validation for the model used for exposure assessment **(CARRERAS; CHELLINI; BLANGIARDO, 2012; MCCONNELL et al., 2010)**;

- Two studies did not seek support in air pollution monitoring **(CARRERAS; CHELLINI; BLANGIARDO, 2012; GRUZIEVA et al., 2017)**;
- One study did not employ a standard questionnaire (i.e ISAAC) to collect information about asthma symptoms at home **(LINDGREN et al., 2013)**;
- Three studies used hospital visits as a source of data **(LINDGREN et al., 2013; PERSHAGEN et al., 1995; ZMIROU et al., 2002)**;
- Different ages of interest were found, even among children (considered <18 years old in this review);
- Only one study focused not exclusively in TRAP **(NORDLING et al., 2008)**;
- Different pollutants of interest were also investigated within studies;

According to the review carried out by **Khreis and Nieuwenhuijsen (2017)**, those are divergences frequently found that reduce comparability. Whereas some claim that TRAP does not increase risk of asthma symptoms in their studies **(CARRERAS; CHELLINI; BLANGIARDO, 2012; OFTEDAL et al., 2009)**, others present physiological evidence of airway response to TRAP **(GRUZIEVA et al., 2017; ZMIROU et al., 2002)**. Exposure estimation may be erroneous due to geocoding error **(GANGULY et al., 2015; JACQUEMIN et al., 2013)**, and activity patterns **(CARRERAS; CHELLINI; BLANGIARDO, 2012)**. Airway response, on the other hand, can be incorrect if not counting for lag-response **(CHIEN; CHEN; YU, 2018; GENT et al., 2009)** or home environment, such as in-home tobacco consuming **(SONNENSCHEIN-VAN DER VOORT et al., 2012)**. However, it is also possible that the effect of TRAP in children is related to genetics **(MELÉN et al., 2008)**. All in all, future studies need to reduce the gap between methodologies in order to increase comparability and thus make results more conclusive.

Stationary/Industries

Stationary sources are regarded as sources fixed in a location that, differently from TRAP, are less subjected to daily variations in their emissions (e.g., stacks of industrial plants). They are simpler to model using dispersion models, as the required information is often described in inventories, however, they are complicated for receptor models due to the chemical speciation required to distinguish emissions and sources collinearity problem.

Idavain et al. (2019) found evidence that children living as close as 5 km of oil shale industrial sites might develop health outcomes more often than those living far away (>20 km). Volunteers of the clinical study of **Bergstra et al. (2018)** reported high blood pressure (adults) and respiratory symptoms (children) which was associated with the presence of heavy industry in the East

Vlissingen region, Netherland (in the study characterized by coal-based power plants, harbors for coal storage, a plastic recycling industry, a phosphorus chemical industry, an oil refineries and an aluminum smelter). In another study, the cost of the asthma attacks associated with coal-fired power plant emissions was estimated as USD 4.6 billion **(GUTTIKUNDA, S.K. K; JAWAHAR, 2014)**.

All in all, targeting industry emissions proved to be advantageous as mitigating strategies showed to reduce asthma-related impacts in more than one study **(KOIWANIT et al., 2016; LEVY; GRECO; SPENGLER, 2002; MALMQVIST et al., 2018)**.

4.6 Pollutants of interest

Studies using dispersion and receptor models to provide air quality data to be associated with asthma are summarized below according to their pollutants of interest. However, in some cases it was suitable to present more than one pollutant concomitantly.

Particulate matter (PM_{10})

Four studies evaluated PM_{10} exclusively, three of them applied dispersion models, AERMOD **(KHAFAIE et al., 2017)**, CALPUFF **(HENDERSON et al., 2011)** and PolluMap **(KÜNZLI et al., 2009)** and one applied the PMF receptor model **(DUCRET-STICH, R E et al., 2013)**. All studies investigated air pollutant exposure and asthma response in adults.

Henderson et al. (2011) suggested that respiratory symptoms are associated with higher levels of exposure, and significant risk (odds ratio OR 1.16) was associated with a 30 μg/m³ increase. **Khafaie et al. (2017)** claim that a standard deviation increase of PM_{10} concentration was associated with 3.71% lower values of %Forced Vital Capacity (FVC). **Künzli et al. (2009)** suggested different responses achieved with changes in traffic-related PM_{10} (hazard risk HR 1.30), regional PM_{10} (HR 1.0), secondary PM_{10} (HR 1.44), and total PM_{10} (HR 1.07).

With a different approach, **Spadaro and Rabl (1999)** estimated €1.56 spent per bronchodilator usage in adults for every kilogram of PM_{10} in the atmosphere and a total cost of €15.4 per kilogram, considering several endpoints of Life Cycle Assessment methodology. They used the ISC dispersion model for short-range application and Harwell Trajectory model and EMEP model for the long-range.

Due to the different use of methodologies, different cultures, and locations, among other reasons, it is hard to establish a clear comparison. For instance, **Pascal et al. (2013)** study in France used

the ADMS 4, dispersion model. Their results showed a 0.84 Relative Risk (RR) of hospital admission for asthma associated with PM_{10} (i.e. no effect) while the similar study of **Andersen et al. (2007)** (same time-length, the age considered, data collection), however employing the receptor models PCA and COPREM in Denmark, found an association of 1.077 (RR). Also, **Pénard-Morand et al. (2010)** found robust associations of lifetime asthma with PM_{10} (OR 1.28) using STREET5 dispersion model, while **Puklová et al. (2019)** using the EMEP dispersion model found that PM_{10} is not associated, having an OR of 0.79 for symptoms prevalence and 0.86 with lifetime asthma. Between the two previously mentioned works, the significant difference was associated with different sources of interest, as **Pénard-Morand et al. (2010)** focused on TRAP while **Puklová et al. (2019)** opted to include all sources.

The age factor also influences the results. **O. Gruzieva et al. (2013)**, using the DM AirViro, showed that non-allergic asthma associations with PM_{10} were higher on eight years old (OR 3.8) than four years old (OR 1.6) children. **Henderson et al. (2011)** used CALPUFF and claims that physician visits due to asthma had a higher association with PM_{10} for 20-30 years old subjects (OR 1.42) than to 80 years old (OR 0.78).

Other outcomes from PM_{10} exposure investigated in dispersion modeling studies were the associations with asthma symptoms (OR 0.876, DM: OSPM) **(CARRERAS; CHELLINI; BLANGIARDO, 2012)**; asthma attacks (OR 0.98, DM: AirViro) and doctor diagnosis (OR 0.30 to 0.64, DM: AirViro) **(IDAVAIN et al., 2019)**, and with new-onset asthma (hazard risk HR 1.35, DM: CALINE4) **(MCCONNELL et al., 2010)**.

Fine particulate matter ($PM_{2.5}$)

Thirteen studies evaluated $PM_{2.5}$ exclusively, four employed dispersion models **(GANGULY et al., 2015; GANGULY; BATTERMAN; BRAKEFIELD-CALDWELL, 2012; GUTTIKUNDA; JAWAHAR, 2014; KRALL et al., 2017; PENNINGTON et al., 2017)** and eight applied receptor models **(HAMMOND et al., 2008; KALAIARASAN et al., 2017; MORISHITA et al., 2006; OSTRO et al., 2016; ROHR et al., 2014; SAHU et al., 2011; ZHAO et al., 2007)**.

In **Morishita et al. (2006)**, the authors used the receptor model PMF. They found that the most significant contribution to $PM_{2.5}$ levels in Detroit – USA, came from coal combustion and secondary sulfate aerosol, characterized by high percentages of sulfate, selenium, elemental and organic carbon. In **Hammond et al. (2008)** study, also carried in Detroit – USA but using PMF2, more than 97% of $PM_{2.5}$ sources derived from secondary sulfate and motor vehicle combustion.

In both studies, the source apportionment was conducted due to the high childhood hospitalization rates related to asthma. In New York City, the **Rohr et al. (2014)** PMF results suggest that regional and salt sources are associated with asthma symptoms. Furthermore, sulfate, potassium and organic carbon showed positive associations with cough/wheeze symptoms. However, in another study carried out in eight USA cities, also through PMF RM, the soil source (including suspended road dust) was associated with the highest relative risk (4.5%) for asthma. Furthermore, elemental carbon, organic carbon, and zinc presented the highest excess risk (>0.5%) **(OSTRO et al., 2016)**. This supports the claim of **Krall et al. (2017)** that heterogeneity of $PM_{2.5}$ between cities due to exposition, chemical composition, and sources drive differences in asthma response. In another example, through the ATMoS dispersion model, **Guttikunda et al. (2015)** showed that the difference in the concentration of $PM_{2.5}$ between two cities in India proved relevant, once the one with lower air quality showed almost three times more the estimated cases of asthma attacks than the higher one.

Studies that focused on $PM_{2.5}$ alongside with other pollutants presented some reasons why this particular pollutant is extensively targeted in asthma research. **Koiwanit et al. (2016)** used the AERMOD model and stated that decreasing $PM_{2.5}$ levels in cities by controlling emissions could contribute to a great reduction of the incidence of asthma symptoms. In **Delfino et al. (2014)** study, through CALINE4 results, the authors showed that $PM_{2.5}$ was the only pollutant to be associated with asthma morbidity in either warm or cold seasons. The authors found a relationship between warm and cold seasons with the associated percent change (%change) in pediatric asthma hospital encounters. During Lag 1 to Lag 7 episodes, the %change for $PM_{2.5}$ ranged from 4.21 to 7.87 in the warm season and from 1.04 to 16.16 in the cold season.

At last, **Halonen et al. (2008)** receptor model study (with PMF) showed that children and elderly have different respiratory responses to $PM_{2.5}$, having infants a delayed effect and older people a more immediate effect. Overall, the %change in hospital emergency room visits due to asthma differ with age and lag response. While for 'Children' the associated %change with $PM_{2.5}$ ranged between -0.06 to 2.56 (Lag 0 to Lag 5), 'Adults' range was from -1.79 to 1.46 and 'Eldery' from -0.24 to 3.09. **Halonen et al. (2009)** later supported that particle fraction effect increase in the warm season regarding respiratory admission in hospitals.

Just as PM_{10}, in **Idavain et al. (2019a)** results, $PM_{2.5}$ appeared to have no association with asthma diagnosis (OR 0.94) and asthma attacks (OR 0.91), However, **McConnell et al. (2010)** suggested a high hazard risk for new-onset asthma (HR 1.66). The major difference between studies was the source of interest as **Idavain et al. (2019)** modelled oil shale industry areas emission with AirViro

DM and **McConnell et al. (2010)** interest was TRAP (DM: CALINE4). An different indicator, excess risk (ERi %) for asthma emergency visits was investigated by **Ostro et al. (2016)** using PMF who found it to be 1.2 to 1.4 (Lag 0 to Lag 2) for total $PM_{2.5}$ mass, with a maximum value of ERi to be 4.5 for the soil source and Lag 2.

Nitrogen oxides (NO_X)

Nitrogen oxides were the most recurrent pollutants in this review. As markers of TRAP, the most investigated emission source in the literature, they received special attention in asthma studies in recent years. A total of eighteen studies investigated NO_X or NO_2 alone **(BOUGAS et al., 2018; CASTELL et al., 2018; FRANKLIN; FRUIN, 2017; GAUDERMAN et al., 2005; KHREIS, H.; DE HOOGH; NIEUWENHUIJSEN, 2018; KLÆBOE et al., 2000; LINDGREN et al., 2013; MCCONNELL et al., 2010; MELÉN et al., 2008; MODIG et al., 2009; MODIG; FORSBERG, 2007; OFTEDAL et al., 2009; PERSHAGEN et al., 1995; RANCIÈRE et al., 2017; REUNGOAT et al., 2005; SHANKARDASS et al., 2009; SOMMAR et al., 2014; TONNE et al., 2010)**.

Among their findings, **Modig et al. (2009)** claim that adults between 20-44 years are susceptible to asthma development if exposed to increased levels of NO_2, the authors used the DM AirViro, Enviman, and TAMP. Some studies using DM have not found associations between NOx or NO_2 and asthma **(OFTEDAL et al., 2009; SOMMAR et al., 2014)**. **Franklin and Fruin (2017)** recommended that disturbance by noise should be included in epidemiological studies since adjusted regression models showed increased associations between TRAP and lung function. This recommendation is in accordance with **Modig and Forsberg (2007)** results, in which high levels of NO_2 estimated with AirViro, Enviman, and TAMP were associated with peaks in annoyance by vehicle exhausts. At last, **McConnell et al. (2010)** suggested that the associations with new-onset asthma and measured NO_2 (HR 2.17) were higher if compared to other pollutants such as PM_{10} (HR 1.35), $PM_{2.5}$ (HR 1.66) and O_3 (HR 0.76). However, this scenario changes if non-freeway TRAP at home and school is accounted for, increasing the PM association.

In **Andersen et al. (2007)** study, using PCA and COPREM, a receptor model that unifies USEPA CMB and PMF receptor models, the associations between NO_2 and hospital admissions due to asthma was compared with associations of CO, PM, PM fractions of PM sources and same outcome. They found significant associations for NO_2 (RR 1.128), higher than PM_{10} (RR 1.077), and CO (RR 1.104). If compared to the association between PM_{10} sources and asthma hospital

admissions, NO_2 appears only behind the 'Vehicles' source contribution (RR 1.2003), and ahead of the other five sources (secondary, biomass, crustal, oil and sea salt).

Eight studies employed the odds ratio analysis, and their results point to both none and positive associations between NOx and NO_2 with asthma. In **Charpin et al. (2009)**, using STREET5, the authors found an OR for exercise-induced asthma and NO_2 of 1.05 and NOx 1.25. The association was stronger for one-year exposure (OR 1.37 for NO_2 and 1.32 for NOx), and lower for lifetime asthma (OR NO_2 1.09 and NOx 1.08) in children. For the latter (lifetime asthma), **Puklová et al. (2019)** found no associations (OR 0.86 for NO_2), and the prevalence of current asthma OR with NO_2 was around 0.93 in children, being EMEP the DM. Their results differ from the association of prevalence found in **Hasunuma et al. (2016)** for NOx, which was OR 1.20 for adults, being USEPA ISC the DM used. Other results from this study were the no association with asthma incidence (OR 0.75) and stronger for persistency (OR 3.32). The major difference between **Charpin et al. (2009)** and **Puklová et al. (2019)** was the study region and, therefore, background concentrations. Between **Puklová et al. (2019)** and **Hasunuma et al. (2016)**, the age and pollutant factors may influence the results.

Other factors also were shown to influence the outcome. For instance, in **Modig and Forsberg (2007)**, the population that reported constant lightweight vehicle traffic outside their homes had higher OR (up to 1.38) of reporting asthma symptoms and for heavyweight vehicles OR 2.38. These results corroborate with **Pedersen et al. (2013)** work in which the area of exposure addressed by the ADMS-Urban DM also appeared to change the OR value. On the other hand, two other studies point to gender differences. **Modig et al. (2009)** showed differences for males increased OR of onset asthma and NO_2 and females increase for incident asthma per 10 $\mu g/m^3$ increase in concentration. **Delfino et al. (2009)** using CALINE4 for dispersion of TRAP showed higher OR for hospital encounters due to asthma related to TRAP NOx for females (OR 1.136) compared to the entire population (OR 1.097).

Three studies have shown that age is an essential factor. **Gruzieva et al. (2013)** support that OR were higher for the association between non-allergic asthma and NOx, with differences between 4 years old (OR 2.4) and eight years old children (OR 2.6). Their exposure assessment used the AirViro DM. In **Halonen et al. (2008)**, the authors showed using PMF that the %change expected in asthma emergency room visits for children (-0.09 to 10.9, Lag 0 to Lag 5), adults (-1.14 to 3.7, Lag 0 to Lag 5) and elderly (-0.09 to 4.82, Lag 0 to Lag 5) differ. At last, **Schultz et al. (2016)** (DM: AirViro) observed minor levels of Forced Expiratory Volume (FEV1) and Forced Vital Capacity (FVC), two pulmonary measures related to asthma, between 0-1 years old (FEV1 -15.8

mL and FVC -10.7 mL), 1-8 years old (FEV1 12.6 mL and FVC -10.8 mL), and 8-16 years old (FEV1 -9mL and FVC -19.5mL). Other studies also have shown a decrease in FEV1 and FVC with NOx or NO_2 exposure **(BOUGAS et al., 2018; FRANKLIN; FRUIN, 2017; JACQUEMIN et al., 2013)**.

In conclusion, the pair NOx or NO_2 showed to be more positively associated with asthma than negatively. As **Gauderman et al. (2005)** pointed out, for each 5.7 ppb (10.72 µg/m³) increase in average NO_2 modeled with CALINE4 there was a correspondent increment of 1.83 in the OR for asthma symptoms, with similar results during summer (OR 1.55) and winter (OR 1.50). Furthermore, reducing levels appears to have the opposite effect decreasing the number of asthma cases **(KOIWANIT et al., 2016; MALMQVIST et al., 2018)**.

Carbon Monoxide (CO)

No study investigated carbon monoxide alone, although nineteen studies included this pollutant in the analysis **(ANDERSEN et al., 2007; BATTERMAN; BURKE; et al., 2014; BATTERMAN; GANGULY; et al., 2014; BORREGO et al., 2007; CARRERAS; CHELLINI; BLANGIARDO, 2012; CHARPIN, D. et al., 2009; DELFINO et al., 2014; DELFINO et al., 2009; GENT et al., 2009; HALONEN et al., 2008; HALONEN et al., 2009; ISAKOV et al., 2014; MAANTAY; TU; MAROKO, 2009; MENDOLA et al., 2016; PÉNARD-MORAND; RAHERISON; CHARPIN; KOPFERSCHMITT; LAVAUD; CAILLAUD; ANNESI-MAESANO, 2010; PENNINGTON et al., 2018; SNYDER et al., 2013; SPADARO; RABL, 1999; TSUI et al., 2018)**. Among these studies, **Snyder et al. (2013)** suggest that CO should be considered as a marker of traffic volume and **Charpin et al. (2009); Delfino et al. (2014);** and **Mendola et al. (2016)** found a clear association of this pollutant with asthma.

Delfino et al. (2009) found out that for one increment per interquartile range in CO concentration there was an increased hazard risk of asthma symptoms (DM: CALINE4). They were higher for females (HR 1.1) and children (HR 1.158) to TRAP than the whole sample (HR 1.073). In a similar study, **Delfino et al. (2014)** found that a higher %change in pediatric asthma hospital encounters is more likely during cold seasons compared to warm seasons. The results varied according to lag day response. During the warm season, the Lag 0 indicator was -3.29% and Lag 7 3.29%. For the cold season, results varied even more, with Lag 0 indicator equals to -1.44% and Lag 7 13.20%.

Halonen et al. (2008) (RM: PMF) also studied the %change in hospital visits due to asthma. However, their separation criterion was the age factor instead of a season. The results pointed to a higher sensibility to CO by children (%change -1.85 to 4.30, Lag 0 to Lag 5), followed by elderly (-0.42% to 3.68%, Lag 0 to Lag 5) and adults (-2.12% to 0.89%, Lag 0 to Lag 5). Another study to investigate the association via hospital admission was carried out by **Andersen et al. (2007)**. They found a relative risk of 1.104 for the study population group.

At last, two studies used the same indicator, odds ratio, to establish a connection between CO and asthma. However, while **Pénard-Morand et al. (2010)** found stronger associations (for instance OR 1.29 for exercise-induced asthma, OR 1.21 for lifetime asthma and OR 1.45 for asthma in the last year), **Carreras et al. (2012)** result point to a slightly non-association (OR 0.968). They both had similar methodologies and were interested in the same source (TRAP). However, the studies were carried out in different countries in Europe (France and Italy, respectively) and used different dispersion models (STREET 5 and OPSM, respectively).

Sulfur Dioxide (SO_2)

Only four studies investigated sulfur dioxide alone, being all interested in industrial emissions **(MILANDO; MARTENIES; BATTERMAN, 2016; PASCAL et al., 2013; SCHUENEMAN; WILLIAMS; EDMISTEN, 1968; SMARGIASSI et al., 2009)**. **Smargiassi et al. (2009)** stated that hourly daily SO_2 peaks might play a more important role than daily averages. In their results using AERMOD, an OR of 1.01 to 1.42 was found for hospital admissions related to SO_2 depending on exposure metric. For emergency department (ED) visits, the association was minor, OR 1.04 to 1.10.

Milando et al. (2016) used concentration-response functions derived from previous studies in their exposure assessment (DM: FRESH-EST and AERMOD) to find results of asthma hospitalizations (6 to 13 cases), ED visits (9 to 196 cases), and asthma exacerbations (5.692 to 51.681 cases) in low (0.001 ppb daily 24h averaged) and high concentration (0.005 ppb daily 24h averaged) scenarios of SO_2.

Schueneman et al. (1968) study shows that twice as many asthma attacks are expected in high sulfating areas. According to their results, concentrations of 80-200 ppb of SO_2 could increase asthma attacks by 18%. Regarding confounders such as sex and age, **Pascal et al. (2013)** report that hospitalizations occurred for both sex, and children were most affected.

Other studies that present clear associations between asthma and SO_2 are **(ALCOCK et al., 2017; PÉNARD-MORAND et al., 2010)**. In **Pénard-Morand et al. (2010)**, OR association between SO_2 and exercised induced asthma was 1.27, asthma in the last year 1.29, and lifetime asthma 1.26. **Alcock et al. (2017)** found a relevant increase in the mean change to asthma rate of +159.64 and +101.64 for increments in the SO_2 3rd and 4th quintiles (1.18 ppb and 1.46 ppb), respectively.

VOC

Volatile Organic Compounds (VOC) were scarcely investigated in asthma studies that applied dispersion or receptor models. Only a few papers addressed these pollutants **(CHARPIN, D. et al., 2009; MENDOLA et al., 2016; MENTESE et al., 2015; PÉNARD-MORAND et al., 2010; SPADARO; RABL, 1999)**, mainly benzene or other Polycyclic Aromatic Hydrocarbons (PAH).

Penard-Morand et al. (2010) found higher associations per interquartile range increases for benzene alone than other VOC, for exercise-induced asthma (OR 1.32 benzene, OR 1.20 VOC), asthma in the last year (OR 1.36 benzene, OR 1.19 for VOC), and lifetime asthma (OR 1.25 benzene, OR 1.17 VOC). According to **P. Mendola et al. (2016)** the compounds benzene, ethyl benzene, m-xylene, o-xylene, p-xylene, and toluene were the most dangerous to asthmatics, while most PAH does not appear to increase risk. Furthermore, virtually all VOCs showed noteworthy interactions with asthmatics.

Other

Other pollutants that were frequently investigated are: Ozone (O_3) **(ANDERSEN et al., 2007; BORREGO et al., 2007; DELFINO et al., 2014; FRIDELL et al., 2014; GENT et al., 2009; TSUI et al., 2018)**, Black Carbon (BC), Organic Carbon (OC), and Elemental Carbon (EC) **(DUCRET-STICH et al., 2013; GALVIS et al., 2015; HASUNUMA et al., 2016; ISAKOV et al., 2014; SNYDER et al., 2013)**, and Ultrafine Particles (UFP) **(DELFINO et al., 2014; HABRE et al., 2018; LI et al., 2016)**.

Ozone daily averages were found to be confidently associated with asthma morbidity in warm seasons **(DELFINO et al., 2014)**. This corroborates with **Borrego et al. (2007)** results that found higher levels of O_3 during summer due to its derivation from photochemical reactions. **Rohr et al. (2014)** source apportionment study evaluated adjusting results for O_3 as a confounding agent. They achieved different positive association between cough and potassium element. However, overall results remained consistent.

Carbon groups (EC/OC/BC) were employed to distinguish traffic-related sources (e.g. **Ducret-Stich et al. (2013);** and **Snyder et al. (2013)**). **Hasunuma et al. (2016)** found no significant association of asthma incidence in children to personal exposure of EC. OC had a positive (between RR of 1.0 and 1.02) connotation with respiratory Emergency Department (ED) visits in **Krall et al. (2017)** study.

Habre et al. (2018) show that people exposed to UFP derived from airport activities had more acute systemic inflation. Their study also claims that it is necessary to investigate the multiplicity of UFP sources in urban regions to comprehend this pollutant role in asthma exacerbation better.

4.7 Discussion: challenges, opportunities and recommendations

Even though dispersion models present many advantages compared to other methodologies when the target sis to estimate spatially distributed air pollutants concentration, they have been rarely employed by health scientists **(MAANTAY; TU; MAROKO, 2009)**, mainly due to the required multidisciplinary technical expertise **(GAFFRON; NIEMEIER, 2015)**. Also, dispersion modeling may be time-consuming and involve computational power, which could limit an optimal strategy due a possible scenario limitation **(MILANDO; MARTENIES; BATTERMAN, 2016)**. However, with the continuous advance in technology, this drawback seems to be of less importance.

Stanek et al. (2011) reviewed receptor models-based studies. The authors investigate several health responses to apportioned sources or particular trace elements. A significant difficulty found was the high correlation of PM constituents, which made it problematic for the receptor model to attribute sources contribution, also making it problematic to attribute one episode of asthma, for instance, to a particular element. The rationale is that the impact of a highly correlated pollutant could be due to its corresponded actual toxic agent or mixture. In this case, grouping elements has been the solution found.

Challenges found in this present review refer to methodological steps that were either ignored, not mentioned or must be improved in the reported studies. They correspond to:

- *Validation procedures* – Around 42% of papers did not mention a validation procedure for modeling results, which compromise its use for health exposure assessment once it is not possible to determine if the model is capable of predicting concentrations correctly. Not only that, but studies should explore further statistical tools than correlation coefficients.

- *Chemical speciation* – Reviewed studies suggest that the composition of particulate matter (of all sizes) possesses a more important role than PM mass in asthma exacerbation; the chemical composition of Volatile Organic Compounds (VOC) also showed to be of importance. Therefore, it is advised that studies should address speciation techniques to relate air pollution to asthma better;
- *Lag-response and control population* – Not all authors employed lag-response functions in their exposure impacts assessments or established a control population. However, studies suggest that immediate and long-term exposure response to air pollutants might be different, especially according to the age factor. Moreover, different associations were found up to 5 days after exposure.
- *Standard health impact assessment* – Different functions were observed to express the relationship between air exposure and asthma. Several studies employed the odds ratio (OR) or other sorts of regression analysis. Although they all serve the purpose, a standard approach could facilitate studies comparison. In this sense, concentration-response functions appear to be the easiest to use, such as relative risk by $\mu g/m^3$ of pollutant increment.

The opportunities for future investigations revealed by this present study refer to methodological aspects that were not fully explored by receptor or dispersion models in asthma research. They include:

- *VOC and UFP exposure* – Only a few reviewed studies investigated the health effects of VOC or UFP in asthma response. It was showed that some VOC compounds, such as benzene and xylenes, may be dangerous than others, and that UFP can penetrate more in-depth in the respiratory system. These are pollutants commonly found in industrial regions. Therefore, a further effort could be given for a complete comprehension of VOC/UFP role in asthma research;
- *Indoor exposure* – Around 7% of studies showed concern for indoor air pollution assessment. This topic is essential because personal and family habits inside the house, schools, and work places are suggested to affect asthma response. It is also uncertain how much of these pollutants do enter indoor environments or are already present in high concentrations due to indoor sources, which would give different indoor-outdoor concentration ratio (I/O). All added, misrepresentation of impacts might take place in such conditions;

- *Rural areas* – Similar to indoor environments, rural areas were also barely explored by studies as fewer sources of interest are found. However, they present opportunities to study background pollution and specific sources impact;
- *Models coupling* – Only two studies out of one hundred and two employed a coupled approach using dispersion and receptor models. Thus, we can affirm that the spatial-temporal capacity of dispersion models to estimate air pollutants exposure and the unique assessment of receptor models to apportion sources, together, have not yet been explored at the fullest.
- *Data fusion* – The employment of data fusion techniques has not been explored at its most, having only one paper addressing it. This present a chance to provide real-time local information and exposure assessment and more effort must be driven in such direction;

A final flowchart was elaborated as a recommendation for best practices following this review. **Figure 6** could be used as a reference for future studies that employ either receptor or dispersion models in asthma research.

Starting with the methodology, either dispersion-based or receptor-based studies should explore hospital visits and standard questionnaires, such as ISAAC **(ASHER, 1998; ASHER et al., 1995; ASHER et al., 2010; SOLÉ et al., 2014)**, for data collection of asthma events. It is important at this stage to declare the control population, whichever being from a non-polluted area or establishing the percentages among confounders. Moreover, air pollution monitoring is highly advisable not only due to the applications that follow the results and discussion sections but also for exploring recent approaches, such as data fusion.

Dispersion modeling should be conducted to explore all significant sources in the region. However, the use of a specific dispersion model for estimating TRAP exposure is an option. Other practices employ background concentrations when modeling atmospheric pollutants dispersion and rely on GPS systems to avoid geocoding errors and track subjects' pathway between indoor spaces (outdoors). Receptor modeling, on the other hand, should give chemical speciation of compounds under analysis alongside with the pre-treatment techniques. The choice between which receptor model to use derives from background information possessed.

In the results section, it is essential that studies address model validation procedures and incorporate more than just correlation coefficients. It is also advisable to provide the total number of asthma cases, differentiating by seasonal aspects. To report associations, Odds Ratio is

considered more reliable than the *p*-value **(PANAGIOTAKOS, 2008)**. Results from DM and RM also should be distinguished by season. In dispersion-based studies, the visualization of concentration maps helps to characterize the region.

Further exploring sources contributions might enhance the discussion. Lastly, models coupling can be achieved with the practices of excluding sources contributions from monitoring results and enhance DM correlations or ungrouping RM collinear sources with source apportionment outcomes from DM. Receptor models could be used to calibrate DM results as well.

It is recommended that results incorporate lag-response, especially if applying regression models. Moreover, the activity pattern of the population under study should be weighed (i.e., concentration versus time spent at home or outdoors). If possible, studies should include indoor exposition as well. At last, model coupling provides the chance to give species and source-oriented concentration-response results, which further improves the discussion of asthma-related to air pollution.

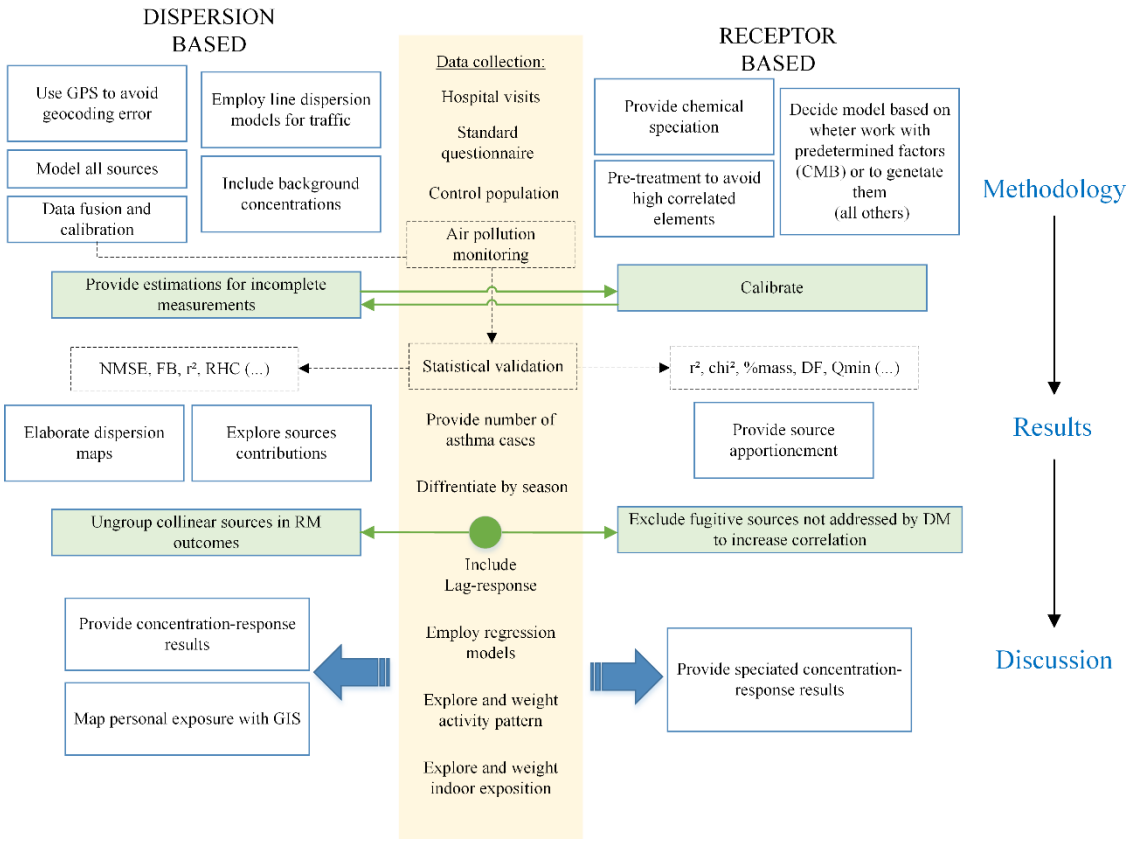


Figure 6. Flowchart with the best practices found within studies.

5. HOLISTIC ESTIMATION OF CHILDREN EXPOSURE AND DOSE TO AIR POLLUTANTS IN AN URBAN INDUSTRIALIZED ENVIRONMENT

Work to be submitted in Science for the Total Environment. **Impact Factor:** 5.58 (2018). **Qualis CAPES:** A1

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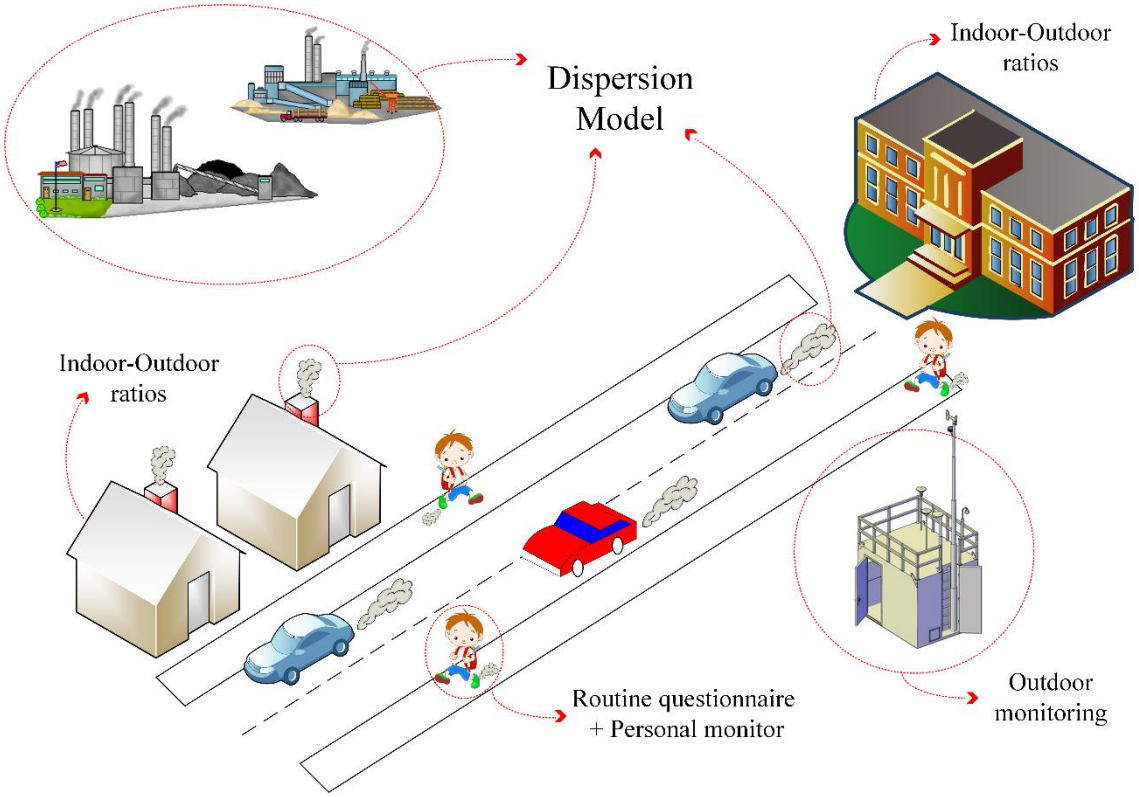
Graphical Abstract



Abstract

BACKGROUND: Several studies reported the exposure to atmospheric pollutants and how it presents risks for asthma prevalence; however, few have addressed indoor air pollution or subjects routine. **OBJECTIVE:** This work aims to test a holistic approach to estimate the exposure and dose of children and adolescents with asthma to ambient PM_{10}, $PM_{2.5}$, NO_X, SO_2, and CO in an urban industrialized area. **METHODS:** We employed dispersion modelling to estimate concentrations at homes, schools and pathway of twenty-one children. To represent differences between indoor and outdoor environments, we used indoor-outdoor (I/O) ratio and performed a sensitivity test to this parameter. Questionnaires were used to obtain subjects routines during campaigns. For NO_2, we compared the exposure outcomes using different methods, including a passive sampler and a fixed monitoring station. **RESULTS:** The results indicate that the dispersion model provides higher exposure spatial representativeness than a single monitoring station, as standard deviation are closer to those results obtained with personal monitors. The correct choice (or measurement of) indoor-outdoor ratios proved to be of significant importance in a holistic exposure assessment, especially for particulate matter. Results suggest that the main environmental factors interfering in dosage are proximity to sources and time spent indoors, and physiological factors are body mass index and ventilation minute. **CONCLUSIONS:** Our work provides insights into the importance of a holistic approach to estimate asthmatic children exposure and dose in urban environments. More research on I/O ratios for different environments and inhalation rates of children with asthma would benefit future analysis using the proposed method.

Keywords: Dispersion model; Asthma; Air pollution; Exposure; Dose; Health;

5.1 Introduction

Asthma is a chronic airway inflammation and one of the most common respiratory diseases in children worldwide. It is characterized by wheezing, breathlessness, chest tightness, and cough and sputum production **(WHO, 2018)**. Epidemiological studies indicate that environmental factors might contribute to asthma exacerbation, incidence and prevalence, being one possible link the exposure to air pollution **(GUARNIERI; BALMES; FRANCISCO, 2015).**

The pathway from air pollution to asthma attacks starts with the total personal exposure, which is defined as the person getting into contact with a pollutant at a certain location during a specified period **(WHO, 2005).** Later, the amount of contaminants entering the body during a time interval (named dose) initiates a series of oxidative and radical damage, also influenced by dietary factors **(GILLILAND et al., 1999; ROMIEU et al., 2008)**. Studies point out that some air pollutants have shown a clear negative effect, and children are the most susceptible group due to their physiological characteristics **(BATESON; SCHWARTZ, 2008)**, therefore they become focus of epidemiologic research. For instance, in the population-based study of **Hasunuma et al. (2016)**, an odds ratio (OR) of 1.20 was associated with asthma prevalence in children exposed to 50.9 – 136.8 ppb of NOx considering a $1^{1/2}$ year mean. In **Khreis; De Hoogh; Nieuwenhuijsen (2018)** population-based study, authors estimated that 18% of annual asthma cases of children was attributed to NO_2 levels (15.41 µg/m^3 annual mean) and 29% to NOx (25.68 µg/m^3 annual mean), using a full-chain health impact assessment model. In **Pénard-Morand et al. (2010)** cohort study, authors found an odds ratio of 1.28, 1.21 and 1.26 between PM_{10}, CO and SO_2, respectively, and children lifetime asthma, considering annual mean concentration modelled at schools location.

Although results of aforementioned studies (and other similar) are relevant, their methodology either addresses the population with and without an outcome in function of past exposure (case-control) or the opposite way differentiating the initial population between exposed and unexposed looking towards future outcomes (cohort). Thus, they do not consider exposure and the outcome at the same time (cross-sectional). However, it is imperative to assume that physiological, daily routine and environmental factors influence exposure cumulative value. Furthermore, to calculate the dose studies must address inhalation rates, age, gender, weight, health status, and levels of activity (running, walking, sleeping/resting, biking etc.) **(USEPA, 1997b)**. In addition, few are the studies that address a time-weighted approach in which authors account for the amount of time people spent in each microenvironment during the day e.g., **Mcconnell et al. (2010); Pershagen et al. (1995); Rancière et al. (2017); Yamazaki et al. (2014).** Even less include indoor exposure, e.g. **Borrego et al. (2007); Hasunuma et al. (2016); Hrubá et al. (2001); Zmirou et al. (2002)**. As a result, there is a gap in the literature for studies using a holistic approach of exposure assessment at individual level. Our present work aims to address this gap

with an all-inclusive estimation of the exposure and dose of asthmatic children to common air pollutants of an urban-industrialized environment.

5.2 Materials and Methods

5.2.1 Region of interest and participants selection

The Metropolitan Region of Vitoria (MRV) includes five municipalities (1447 km^2) of the state of Espirito Santo, Brazil, and has a population of 1.7 million people. MRV is located on a coastal area and has complex terrain and meteorological conditions **(SALVADOR et al., 2016)**. The most significant anthropogenic sources of atmospheric pollutants are steel and pelletizing industries and traffic, as shown by multiple source apportionment studies **(GALVÃO et al., 2018, 2019, 2020; GALVÃO; REIS; SANTOS, 2020; MONTICELLI et al., 2020; SANTOS et al., 2017)**.

Previous epidemiological approaches conducted in the MRV indicate that asthma prevalence in children is higher than the national mean **(SERPA et al., 2014)**. In the ecological study of **Castro et al. (2007)**, authors claim that respiratory diseases in children are connected to social factors and intensified by local air pollution sources. Two recent ecological studies show that an increase in the interquartile range of $PM_{2.5}$ (corresponding to 4.2 $\mu g/m^3$) consequently lead to 3.8% higher risk of hospital admission due to a respiratory condition **(NASCIMENTO et al., 2017)**. Furthermore, children from 0 to 12 years old exposed to SO_2 had a higher association (Relative Risk, RR: 1.28) with acute respiratory events followed by PM_{10} (RR: 1.14) **(NASCIMENTO et al., 2020)**.

From an exploratory point of view, studies indicate that the population of MRV, specifically children, is subjected to a high risk of asthma prevalence due to local air pollution levels. However, as ecological studies, they are applicable only at the population level, that is, data cannot be assumed true for individual-level **(MUNNANGI; BOKTOR, 2019)**.

To establish causal relationships, a new study is proposed; in which a sectional observation approach provide a chance to overlook at the exposure of children with and without asthma in MRV at the same time. For this present contribution, asthmatic participants were selected based on the criteria described in **Table 3**.

We performed three monitoring campaigns, with the supervision of asthmatic patients by trained physicians, in the neighborhoods of Andorinhas (‘Campaign 1’), Maruipe (‘Campaign 2’) and Itararé (‘Campaign 3’). According to the last census report (2010), key differences between neighborhoods are population, economic status, and overall Human Developing Index (HDI). Maruipe has HDI of 0.88, the highest between the three, and 0.23% of MRV municipality

population. Itarare and Andorinhas share similar population mean income: approximate the minimum wage, however very distinguish populations (Itarare: 0.47% and Andorinhas: 0.64% of MRV citizens). The selection of these neighborhoods was based on the fact that they are located close to the University Health Sciences Center and the local public health unities often work in collaboration the researchers which increases the likeability of local citizens to participate in the study.

Table 3. Selection criteria for participants of this study

Inclusion criteria	Exclusion criteria
a. Age between 8 and 14 years; b. Living in the neighborhoods monitored; c. Diagnosed with asthma by a certified medical doctor or institution; d. Confirmed diagnosis of 'moderate/light asthma' by a medical doctor participant in this project; e. Capable of filling their diary; f. Parental approval	a. Severe asthma; b. Children with controlled asthma who have not used any medicine in the last 12 months; c. Locomotion difficulties; d. Chronic diseases;

5.2.2 Air quality assessment

Air quality monitoring

We placed a mobile monitoring station inside the neighborhoods of interest to monitor PM_{10}, $PM_{2.5}$, NOx, NO_2, and SO_2 (See **Figure 7**). The station, here named after the project 'ASMAVIX', is a full operation and automatic monitoring site, equipped with sensors to detect gaseous pollutants and particulate matter. The sampling procedures of criteria pollutants were consistent with US EPA, Federal Equivalent Method following Title 40, Part 53 of the Code of Federal Regulations. Details of the station set-up (equipment and detection limits) are disclosed in the **Supplementary Material**.

Figure 7. Distribution of houses and schools in the region of interest

Experimental data were used to estimate indoor-outdoor (I/O) ratios for particulate matter. The school indoor air pollution assessment occurred before children follow up. However, the authors judged that the values of PM indoor air quality obtained are of significant relevance. Experimental work was also conducted at two homes; indoor sampling occurred at least one meter away from doors and windows to avoid highly ventilated spots. In addition, the sampling equipment (described below) was placed at average children's high as to simulate indoor concentrations experienced. All samplings occurred in the living room, the most spacious microenvironment. Both houses were in front of streets with not much traffic, similar to other participants' houses. The authors could not obtain details on the building age. The experimental data to estimate indoor-outdoor (I/O) ratios for particulate matter at school was taken from **(VELASCO, 2020)**. For the full description of the equipment set-up and routine collection, plus composition analysis of $PM_{2.5}$ and PM_{10} at schools, the reader is referred to **(VELASCO, 2020)**. Each room sampled had windows on the corner and used ceiling fans for mechanical ventilation, with capacity for twenty children. The building age is twenty-seven years old.

Equipment details, for both experimental works, used in each microenvironment is given in the **Supplementary Material**. Briefly, the indoor measurements at homes and school were carried out by using the LAS – Dust Monitor 1.109, calibrated to operate at 1.2 L/min (±5%). This laser aerosol spectrometer is a compact portable device that was built for continuous measurement (1 min steps) of airborne particles as well as for measuring the particle count distribution. It

possesses an integrated gravimetric filter on which all particles are collected after the optical measurement and thus are available for further analysis. This "Dual-Technology" is unique and patent-registered by Grimm Aerosol Technik, Germany. The author used the hour 1-min mean in contrast to outdoor measurements (1-hour mean) to estimate PM_{10} and $PM_{2.5}$ indoor-outdoor ratios. **Table 4** shows the period of the experimental design in each campaign.

Table 4. Sampling period by campaign

	Outdoor monitoring (PM_{10}, $PM_{2.5}$, NOx, SO_2, CO)	**Indoor monitoring (PM_{10}, $PM_{2.5}$)**
Campaign 1 (spring)	2/11/2019 to 17/11/2019	School classroom: 30/09/2019 to 07/10/2019
Campaign 2 (summer)	4/12/2019 to 19/12/2019	-
Campaign 3 (summer)	5/02/2020 to 19/02/2020	House 1: 05/02/2020 to 12/02/2020 House 2: 12/02/2020 to 19/02/2020

Air quality modelling

The dispersion modelling was performed using the California Puff Model (CALPUFF), version 7.1.2, level 150618, developed by **Scire et al., (2000b)**, and the Calpuff View 8.6.1 interface. This model has been widely used for estimation of species concentration in multiple environments, and presents good results in urban regions **(HOLNICKI; KAŁUSZKO; TRAPP, 2016)**. Furthermore it provided decent statistical values in an application on the study region as shown in **Monticelli et al. (2020)**. This model has been previously applied in asthma research **(HENDERSON et al., 2011; LEVY; GRECO; SPENGLER, 2002)**. At last, although CALPUFF has been removed from the status of preferred model for long-range applications by the USEPA, its recommendation for use in the near field (< 50km) as an alternative model for situations involving complex terrain and complex winds **(USEPA, 2017),** such as the study region, has not changed.

CALPUFF input data consists of sources emission, meteorology and terrain plus land use information. In 2019, the local environmental agency released an updated version of the atmospheric emission inventory for the MRV **(IEMA, 2019)**. It contains information of emissions from several industry segments, vehicular fleet, logistics, and civil construction. This updated version had many improvements if compared to the previous one, of 2010, including the use of USEPA Data Attribution System, D.A.R.S **(USEPA, 1997a)**. **Table 5** provides the total emission estimated for PM_{10}, $PM_{2.5}$, NOx, and SO_2, which are the pollutants of interest in the present work.

All sources described in the inventory were included except 'Civil construction', which were based on construction sites in operation in 2015 that are likely to have already been concluded, and 'Ships' as the main emissions occur far from the neighborhoods of interest to present a significant contribution considering that East winds are not typical in the region. Another aspect was the implementation of residential, commercial and secondary roads emission grouped as an urban area source for each municipality of MRV. All road sources had their emissions scaled by a weekly-diurnal cycle extracted from the inventory. **Figure 8** shows the final implementation in CALPUFF model. The MESOPUF II scheme was used to model the chemical transformation of SO_2 and NOx.

Table 5. Total emission of atmospheric pollutants by source type in MRV.

Sectors	**PM_{10} (kg/h)**	**$PM_{2.5}$ (kg/h)**	**NOx (kg/h)**	**SO_2 (kg/h)**	**CO (kg/h)**
Landfill	6.34	1.77	4.82	0.41	4.14
Civil construction	31.24	3.42	n.a	n.a	n.a
Fuel distribution	n.a	n.a	n.a	n.a	n.a
Food industry	11.20	10.34	17.61	2.91	25.56
Mineral products industry	84.66	43.77	65.84	24.71	192.67
Chemical products industry	6.07	3.72	16.08	3.68	8.88
Mining-steel industry	568.04	369.75	4176.71	3973.37	19832.23
Logistics	52.91	44.24	364.07	180.83	182.83
Others	45.97	39.36	990.31	315.14	245.53
Total	**806.42**	**516.37**	**5635.44**	**4501.05**	**20491.84**

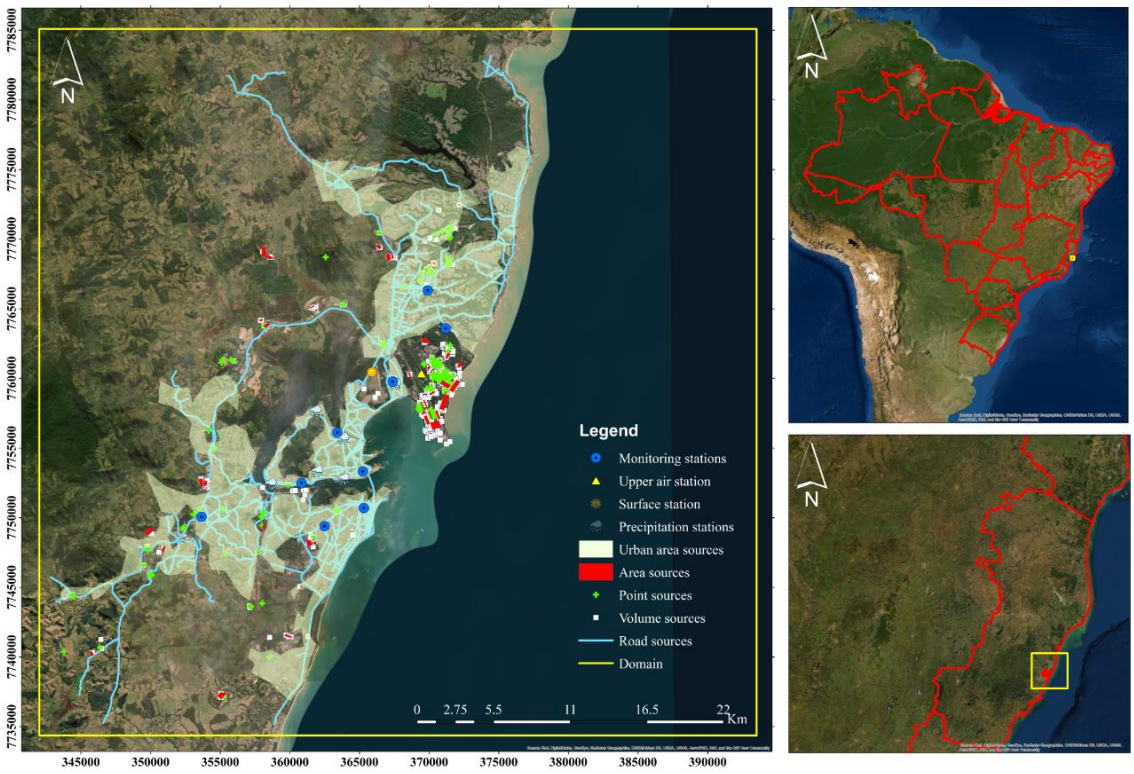


Figure 8. Sources distribution in the modelling domain

We gathered surface data from the meteorological station located at the closest Airport (SBVT, 83649). Downloaded data sets were from the Brazilian National Institute of Space Research (INPE) meteorological agency databases. Few hourly observations needed interpolation, and the data was considered of good quality for modelling applications with more than 90% of available observations **(USEPA, 2000)**. Previous works acknowledged this station to best represent the wind conditions for the modelling domain **(GALVÃO et al., 2019; MONTICELLI et al., 2020; SALVADOR et al., 2016)**.

The author used reanalysis data from the National Centers for Environmental Prediction database **(NCEP; NOAA; COMMERCE, 2019)** for upper air observations. These NCEP FNL (Final) files correspond to operational global analysis and forecast data based on 0.25-degree-by-0.25-degree grids available every six hours. Data was extracted data for i) geopotential heights (1000mbar, 975 mbar, 950 mbar, 900mbar, 800mbar, 700mbar, 600mbar, 500mbar, 400mbar and 300mbar); of ii) relative humidity; iii) temperature; iv) wind speed in the 'U' and 'V' directions. From the latter, authors used a simple mathematical manipulation presented in **Stull and Newtonian (2015)** to estimate the wind velocity and direction for the various layers.

We opted to custom the land-use file provided by the state environmental agency (IEMA), updated in 2015 (https://geobases.es.gov.br/links-para-mapes1215), to build the output of the CTGPROC pre-processor of CALMET. This was achieved through the use of a Geographical Information System (GIS) software and MS Excel to rearrange the data in an organized format

readable by MAKEGEO. The land-use categories legible by the CALMET system were matched with local fauna and soil, according to their description provided by **(SCIRE et al., 2000)**. Terrain data was extracted from the 3 arc-seconds for global coverage (~90 meters) Shuttle Radar Topography Mission (SRTM) **(USGS, 2018)**.

In **Section 4** we have suggested some of the best practices regarding the assessment of air pollution exposure using dispersion modelling. Here, we included ozone background for chemical reactions of SO_2 and NOx. Furthermore, the MRV emission inventory used GPS to locate sources, thus avoiding geocoding errors. Validation criteria corresponded to those described in **(CHANG; HANNA, 2004; HANNA; CHANG, 2012)**.

5.2.3 Exposure assessment

Equation 5 was used to estimate children's exposure to air pollutants. This method centers in the microenvironment assessment perspective, reviewed by **(BRANCO et al., 2014)**. Thus, information about children's location during the day, plus literature data on air quality at indoor environments was needed for a correct calculation.

$$E_i = \sum_{j=1}^{n} (C_j t_{ij}) * (\frac{I}{O})_j \quad \text{Eq.5}$$

where E_i is the total exposure of the subject i; C_j the outdoor pollutant concentration in the microenvironment j, t_{ij} the time spent by the person in the environment j and $(\frac{I}{O})_j$ the Indoor-Outdoor ratio in microenvironment j.

Children pathways

At total, the pair coordinates of twenty-one children's home location and nine schools were used as discrete receptors within a 3 km x 4 km. One drawback identified by **Section 4** is the non-inclusion of children's pathway between indoor spaces during exposure assessment. This is included in the present work under the hypothesis that, although the travel-time may be short, the closeness of the pathways to major traffic lanes could increase their exposure and relative dose to certain pollutants, e.g., NO_2 as discussed by **Ragettli et al. (2014, 2015)** or $PM_{2.5}$ and PM_{10} as showed by **Correia et al. (2020)**. Children travelling time was obtained through questionnaire and/or Google Earth Pro. We used the shortest path between the school and their homes, also obtained with Google Earth Pro, to represent their daily pathways.

A questionnaire was used (See **Supplementary Material**) to collect children routine and home information. Key evidence addressed in this questionnaire are (*i*) whether and when the children have been outdoors (outside their home and school); (*ii*) ventilation type at home and (*iii*) time spend in their pathways between indoor spaces.

I/O ratios

Another drawback pointed out by **Section 4** is not addressing indoor concentrations properly. For this, indoor-outdoor (I/O) ratios were collected in literature for gases (see **Table 6**). For particulate matter, I/O ratios were based on indoor monitoring at two houses and in two school classrooms, as previously discussed. Outdoor concentrations used were from 'ASMAVIX' station.

It should be noted that mean values do not capture peaks in hour exposition. For instance, during entrance hours (when the children first enter an indoor space), the I/O ratio employed for PM_{10} and $PM_{2.5}$ raise due to the expected personal-cloud effect **(BO et al., 2017; MORAWSKA, L. et al., 2013)**. In addition, because of the gas-cooking, during lunchtimes it is also expected to raise the I/O ratios of NOx and NO_2 at school and homes, as observed by **Dėdelė and Miškinytė (2016)**. Therefore, a sensitivity test to address this issue and dependency of values used in exposure assessment has been performed.

Table 6. Indoor-outdoor ratios selected for this study.

	School microenvironment*			**Home microenvironment***			**Vehicle microenvironment***		
	I/O min	**I/O mean**	**I/O max**	**I/O min**	**I/O mean**	**I/O max**	**I/O min**	**I/O mean**	**I/O max**
PM_{10}	2.21**	3.47**	4.28**	1.62**	2.70**	2.99**	0.70	0.76	1.32
$PM_{2.5}$	5.15**	10.21**	13.81**	2.34**	5.03**	5.85**	0.27	0.81	1.20
NOx	0.69	1.28	1.86	1.10	1.40	1.70	0.28	0.38	1.00
NO_2	0.88	1.12	1.40	1.10	1.40	1.70	0.02	0.90	1.30
CO	0.38	0.67	0.95	1.00	2.45	3.90	0.12	0.48	3.80
SO_2	0.20	0.25	0.30	0.20	0.39	1.00	0.50	1.00	1.50

*References**: (BLONDEAU et al., 2005; BOZKURT et al., 2015; CHALOULAKOU; MAVROIDIS, 2002; CHAN; CHUNG, 2003; CORREIA et al., 2020; DĖDELĖ; MIŠKINYTĖ, 2016; DIAPOULI et al., 2008; DIMITROULOPOULOU et al., 2006; MEIER et al., 2015; STRANGER; POTGIETER-VERMAAK; VAN GRIEKEN, 2008; WEICHENTHAL et al., 2015)**; **from monitoring data.

Measurements of personal exposure

To further assist in the exposure calculation, also serving for comparative purposes between indirect and direct methods as suggested by **Branco et al. (2014)**, children carried a personal

monitor of NO_2, SO_2 and O_3, the Ogawa Passive Sampler (https://ogawausa.com/), which is one of the only known methods of passive simultaneous monitoring of more than two components in the air. The first advantage of Ogawa Sampler is to have two chambers with the same configuration where is possible to place two different kinds of collection filter pads. The second is that the Ogawa Sampler can be reused; only the pre-coated collection filter pad is expendable. They have been employed in other studies **(CYRYS et al., 2012; KHREIS, H.; DE HOOGH; NIEUWENHUIJSEN, 2018; MADSEN et al., 2007)** over the years and provided good insights of exposure. **Table 7** provides details of the exposure assessment using Ogawa monitors.

Table 7. Sampling routine with personal monitors

	Period	**Filters change every**	**Total exposition time**
Campaign 1	02 – 17/11/2019	5th day at 8am	7200 minutes
Campaign 2	04 – 19/12/2019	5th day at 8am	7200 minutes
Campaign 3	05 – 19/02/2019	7th day at 8am	10140 minutes

5.2.4 Dose assessment

The questionnaire to subjects' families contained enquiries on their activity patterns. Physiological characteristics were obtained by tests conducted by trained physicians. The dose was estimated using **Equation 6**.

$$ADD = \frac{(C*IR*EF)}{BW*AT} \quad \text{Eq.6}$$

where ADD corresponds to the children's mean daily dose (µg day/kg), C is the contaminant concentration (µg/m^3), IR the intake rate (m^3/day), EF is the exposure factor (days), BW the body weight (kg) and AT the average time (days).

A key factor in dose calculation is the correct estimation of the intake rate (or inhalation rate). For this, we used literature data found to fit best the children of the project. There are a few studies that estimate this factor in the age of interest **(BROCHU; BOUCHARD; HADDAD, 2014; BROCHU; BRODEUR; KRISHNAN, 2011; BROCHU; DUCRÉ-ROBITAILLE; BRODEUR, 2006; KAWAHARA et al., 2011, 2012)**. However, they do not consider children with asthma in their studies. Asthmatic children have a multiplicity of respiratory conditions that differ them from non-asthmatic subjects, including Tidal Volume (TV), a measure of how much air inhaled in a normal breath, minute volume (amount of gas inhaled or exhaled by lungs in a minute) and breathing rate **(SANTUZ et al., 1997)**.

Linn et al. (1992) carried out the only study mentioned in **(USEPA, 1997b)** to address asthmatic subjects, including children in elementary school years. They studied 13 children, and found mean

inhalation rates for slow, medium and fast activity levels of 1.20 m^3/h, 1.20 m^3/h and 1.50 m^3/h, respectively, having a 99th percentile IR of 2.40 m^3/h. Therefore, we opted to use the values of 0.45 m^3/h for sleeping hours and 1.20 m^3/h for active hours of the participants of our work. We considered their sleeping hours to be between 10pm and 6am, for morning and integrate attendance to school, and 10pm to 8am for afternoon attendance. During weekends, we considered to be 10pm to 8am. Any of these intervals were changed if daily journal indicated otherwise.

5.3 Results

5.3.1 Children's profile

Table 8 gives the summary of responses regarding the questionnaires proposed to participants. Children in 'Campaign 1' were in general older than children in 'Campaign 2' and 'Campaign 3'. They travelled the shortest paths between school and homes all by walking. As for the ventilation system at their homes, the majority of participants use ceiling fan at night and open windows. Children in 'Campaign 2' travelled longer distances to school. Differently from 'Campaign 1', no child studied full-term (considering full-term as 9 hours and half term as 4 hours) and there was an equal distribution between morning and afternoon school-hours. In their homes, all subjects let the windows open during the day and half of them at night. None had air conditioning at home; five use ceiling fan for mechanical ventilation and one rely on natural ventilation. For those that have the ceiling fan, the majority uses it at night for sleep. Some 'Campaign 3' subjects travelled by vehicles between their homes and school. At home, the majority uses the ceiling fan for mechanical ventilation both day and night, and two subjects use air conditioning during sleep hours with windows shut. In all the houses, the windows are open during the day and for only five at night.

In conclusion, it is possible to affirm that subjects of each campaign are similar in each category analyzed, including their home environment and ventilation, which are key variables in indoor exposure. The category where they differ most is pathway distance and travelling time.

Table 8. Profile of participants of this study

	Campaign 1 (n = 6)			Campaign 2 (n = 6)			Campaign 3 (n = 9)		
	Mean	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**
Age (years)	11	10	13	10.7	8	13	10.6	8	14
Weight (kg)	42.0	25.6	54.8	43.0	26.8	64.4	42.8	23.9	70.9
Body mass index (kg/m^2)	18.6	13.4	26.3	19.2	14.6	26.2	19.6	15.2	24.9
Pathway distance (m)	308	170	550	1317	200	2500	1220	24	3200
Commute time (min)	4	2	8	15	2	32	5	1	10
Morning attendance	2			3			5		
Afternoon attendance	3			3			3		
Full-time attendance	1			0			1		
Goes by walking	6			5			5		
Goes by vehicle	0			0			1		
Goes by bus or van	0			1			3		
AC + Fan at home	2			0			2		
Ceiling fan at home	4			5			7		
None	0			1			0		
AC or fan ‘on’ during the day	0			0			0		
AC or fan ‘on’ during the night	1			1			1		
AC or fan ‘on’ day and night	5			3 (2 none)			7 (1 none)		
Windows open during the day	6			6			9		
Windows open during the night	4 (2 closed)			3 (3 closed)			5 (4 closed)		
Does it have pets	2 (4 not)			4 (2 not)			4 (5 not)		

5.3.2 Air quality in the region of interest

Compliance with WHO guidelines

Table 9 shows the statistical analysis of outdoor monitored data in the ASMAVIX station. The 24h mean for fine particulate matter ($PM_{2.5}$) during the entire period was below the 2005 WHO guideline (25 µg/m^3 – 24h mean) except for two days when this reference value was exceeded. For the PM_{10}, the 24h mean concentrations were below WHO guideline (50 µg/m^3 – 24h mean), without exceptions.

For gaseous pollutants, starting with SO_2, there were no days in which the 24h mean surpassed the WHO guideline (20 µg/m^3), with hourly maximum value of 71.83 µg/m^3. For NO_2, the hourly WHO guideline, 200 µg/m^3, was not reached. One explanation might be that during the period of analysis the common wind direction in the region were in North and Northeast quadrant. These winds transport pollutants, such as NO_2 and SO_2, from the major industrial complex away from ASMAVIX station location.

Table 9. Statistics of the measurements from outdoor monitoring stations

values in (µg/m^3)	ASMAVIX station (18/09/2019 - 28/02/2020)			
	$PM_{2.5}$	**PM_{10}**	**SO_2**	**NO_2**
Period 24h mean	3.88	15.63	7.17	8.16
24h Stand. Dev.	3.78	6.21	2.53	3.65
Hour – Min	1.00	1.00	0.07	0.16
Hour – Max	60.00	367.00	71.83	37.53
1st Quartile	2.00	8.00	5.34	4.94
3rd Quartile	6.00	20.00	8.07	9.82

Dispersion modelling results

The 'ASMAVIX', 'Enseada', and 'City center' stations were used for validating the dispersion modelling due to their proximity to neighborhoods of interest. 1h, 24h and weekly mean concentrations were compared as previous research have shown that in urban regions dispersion models not always perform well for short-time periods **(HOLNICKI; KAŁUSZKO; TRAPP, 2016)**. See **Supplementary Material** for statistical results.

For 'Enseada' and 'City center' stations location, there was a improvement in the statistical evaluation if increased the average time. The best results were found for NOx and NO_2, followed by SO_2 and particulate matter. The outcomes have not met the criteria of > 0.75 for the Pearson correlation coefficient in most cases until taken the weekly average. In general, the dispersion model overestimates mean concentration if compared to measurements, mainly due to peaks of concentration in specific hours, except for SO_2 (which underestimates occur).

As for 'ASMAVIX' station comparison, there was also an improvement in the statistical evaluation for longer averaging times. The best results were found for NOx and NO_2 as well. This creates higher reliability when further comparing values of exposure against the Ogawa passive sampler readings. Sulfur dioxide, on another hand, was poorly represented, and its concentration values underestimated. This might have been due to the presence of a local source not included in the emission inventory. For all other pollutants, the model overestimated the mean 1h, 24h and week values, yet still below reference values.

The concentration spatial heterogeneity inside the two-kilometer buffer of the 'ASMAVIX' station was investigated using dispersion model results. We analyzed the concentrations of $PM_{2.5}$ and NO_2 (two pollutants of major interest in epidemiology) at 8am, 12pm and 5pm of a typical school day, and the differences to which concentration children are exposed in their pathways.

Results clearly shows 'zones' of a higher concentration, mainly if near the major roads (See **Figure 9**). In contrast, the zone close to 'ASMAVIX' monitoring station appears to be in a zone of lower concentration during some parts of the day (also depending on wind conditions). Children are more exposed in their pathways during rush hours and as their path approaches major roads and intersections, a peak in concentration values follows.

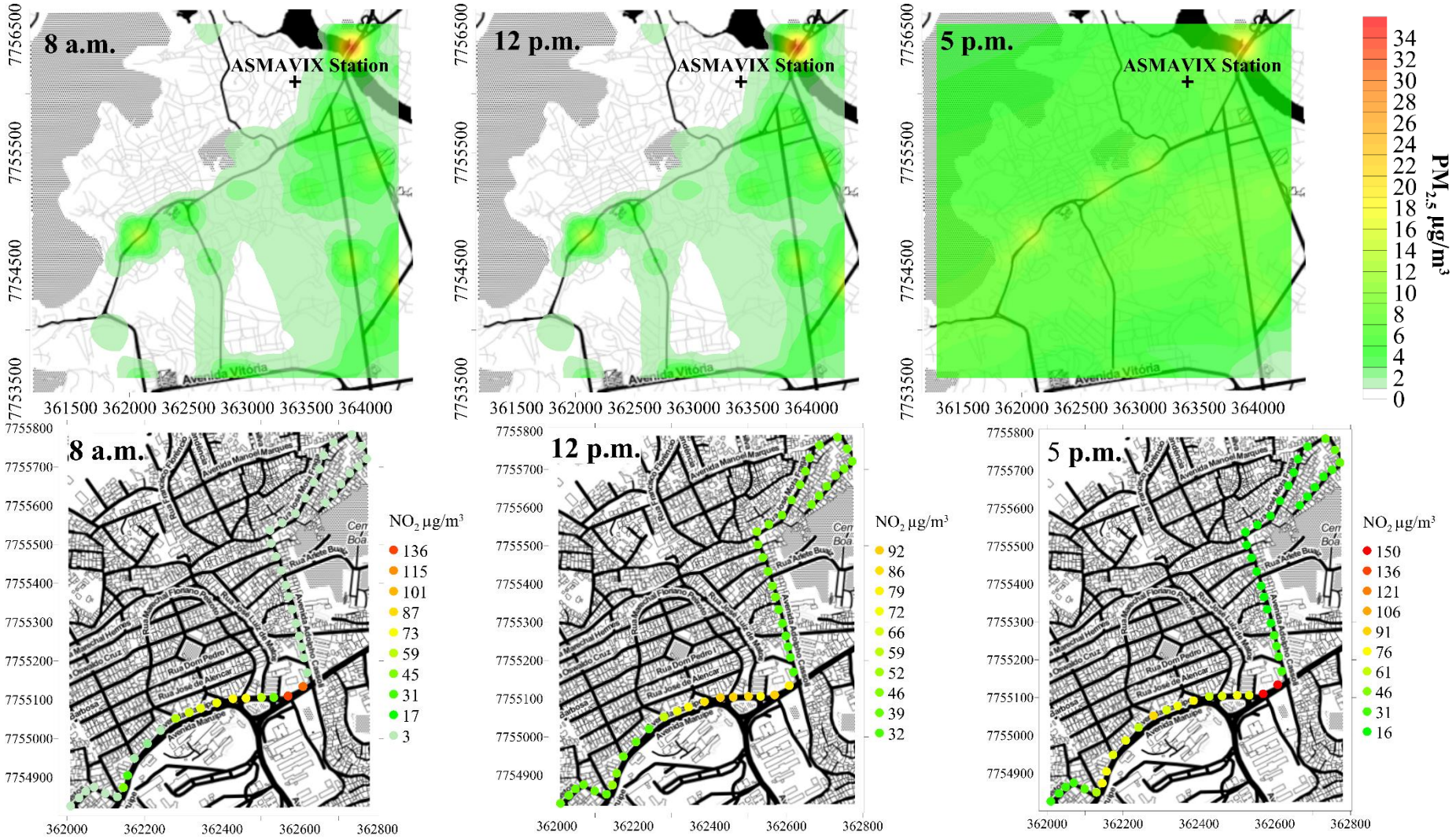


Figure 9. $PM_{2.5}$ spatial concentrations distribution around the ASMAVIX station and NO_2 variation at a typical pathway at 8am, 12pm, 5pm.

5.3.3 Mapping total exposure

Indoor-Outdoor ratios and hours spent outdoors

Figure 10 shows that PM_{10} and $PM_{2.5}$ indoor-outdoor ratios have significant differences between pollutants, however similarities amid indoor spaces. To estimate exposure and perform the sensitivity test, authors used the mean hourly values and the 1st and 3rd quartiles (see **Table 6**).

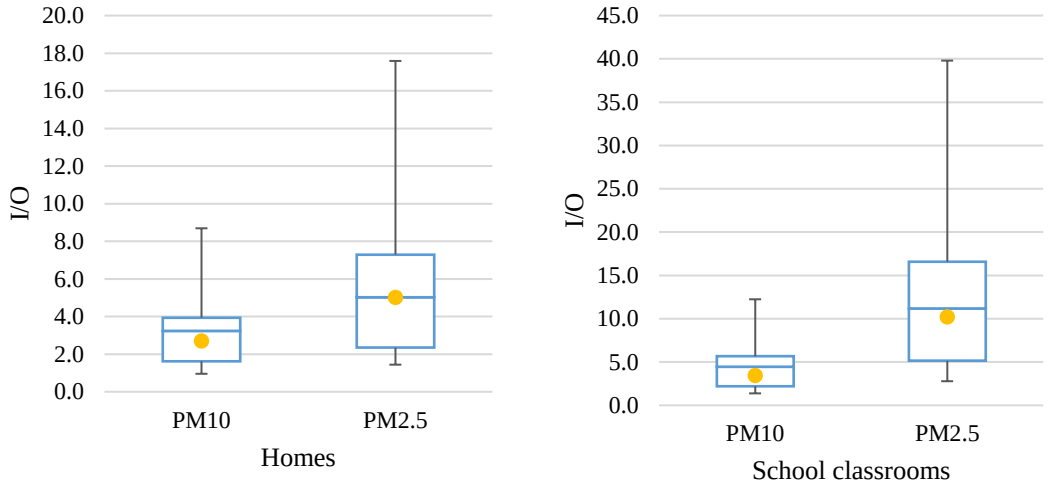


Figure 10. Indoor-outdoor ratios variation of particulate matter between microenvironments monitored.

Data obtained from the two monitored houses shows a mean hourly value of 2.70 I/O ratio for PM_{10} with a standard deviation of 2.30. Minimum and maximum values were 0.67 and 29.9, with the standard error of 0.13. In the school environment, the hourly mean I/O was 3.47, above the observed inside homes. The minimum and maximum values stand further apart, 0.83 and 17.1, as in the home environment. The interquartile range (IQR) of I/O inside houses for PM_{10} was 1.37 and at school 2.07. In both spaces, the I/O of PM_{10} were lower than $PM_{2.5}$ I/O. At last, the hours in which the mean I/O was less than unity inside homes at least once were midnight, 2 am, 3 am, 5 am, 10 am, 12 pm, 2 pm, 3 pm, 5 pm, 7 pm, 10 pm and 11 pm, with 22 occurrences between 322 or 6.8% of hours. For the school environment, the hourly mean I/O for PM_{10} was below the unity in 3 out of 288 valid hours (1%). These last results express that in the majority of the days, the indoor concentration of coarse particles is higher than outdoors in both spaces.

$PM_{2.5}$ data shows higher IQR than PM_{10}, of 8.66 at school and 3.51 inside houses. Mean I/O was also superior to PM_{10}, being 5.03 inside houses and 10.21 at school. For the later environment, minimum and maximum values are one order of magnitude apart, 2.36 and 31.7. Thus, one can infer that in the school environment the concentration of fine particles was always at least more than double than outdoors for the sampling period. Inside homes minimum and maximum I/O

were 0.9 and 36.1. The I/O mean hour values were lower than one four times in 254 valid hours (1.5%), happening at 6 am, 8 am, and twice at 2 pm.

Table 10 gives the mean amount of time spent in each microenvironment considering each campaign. We can conclude that their routine is similar. To perceive a more significant difference one would have to consider the variation and take the extreme values, such as one child from 'Campaign 1' spending 84.2% of its time at home compared to one 'Campaign 3' kid spending 66.2%.

Table 10. Amount of time in each microenvironment by campaign.

% (± SD)	Outdoor	Indoor (home)	Indoor (school)
Campaign 1 (384h)	9.5% (± 6.2%)	76.2% (± 8%)	14.3% (± 2.2%)
Campaign 2 (384h)	9.4% (± 5.6%)	75.7% (± 4%)	15.0% (± 2.3%)
Campaign 3 (360h)	9.1% (± 4.9%)	71.9% (± 5.7%)	16.0% (± 3.6%)

Exposure results

To illustrate children's exposure during the monitoring period, two mean values were used as reference, the daily exposure (**Figure 11**) and the week exposure (see **Supplemental Material**). **Figure 11** shows the results separately by each campaign using dispersion model outcomes. For all pollutants, there is a pattern of crescent exposure between campaigns. This appears to be because most children of 'Campaign 3' live and study close to major roads, which are the nearby emission sources to subjects' houses and school. As seen in **Table 8**, 'Campaign 1' subjects pathways to schools is shorter. Thus, their exposure when commuting is reduced by the time spent outdoors compared to other children. Besides, they are north of major roads. As a result, wind conditions for the monitoring period favor the transport of pollutants away from the neighborhood. 'Campaign 2' is a middle-term, with children spending more time outdoors, thus reducing exposure of pollutants with I/O higher than one, however, living in a higher concentration area than 'Campaign 1' subjects.

The upper and lower limits in the Box-Plot charts displayed in **Figure 11** indicate that even living in the same neighborhood, children can experience different exposures to each pollutant investigated. For participants of 'Campaign 1', the one with lower outdoor hours (14.3 hours) had the second-highest exposures for particulate matter (fine and coarse). On the other hand, subjects with outdoor time ranging from 29.3 hours to 83.4 hours had similar exposures for these pollutants. The subject living closer to major roads had the highest exposures to all pollutants, except for SO_2. For this pollutant, the child that stayed more outdoors had greater exposure.

In the second campaign, the child that went to school by van (vehicle) had higher exposure values if compared to other participants, and was the most exposed to NO_2 and NOx. For other pollutants, higher exposures were found for those spending less time outdoors. Our analysis also shows that school location is important. Two receptors, for instance, lived 75 m apart from each other, so experienced almost the same indoor concentration at home. However, their schools location differs. As a result, one participant experienced higher exposures for particulate matter, but lower for gases. In another case, the school and home of a subject were no more than 200 m apart, and although spent more time indoors, was not the one with the highest exposure to $PM_{2.5}$ and PM_{10}. In 'Campaign 3', the total exposure was more homogeneous between participants, although the mean hour-daily exposure had higher IQR if compared to the first and second campaigns. The highest exposure to SO_2 was found for the child that spent more time outdoors. The lowest exposition to particulate matter for the second subject that spent more time outdoors.

In conclusion, it is possible to affirm that there are two relevant aspects in exposure: 1) time spent outdoors (or indoors) and the concentration variation at the urban microscale (<2km), in this case related to the proximity of receptors (home and schools) to major roads and the position of these sources to receptors considering wind regime.

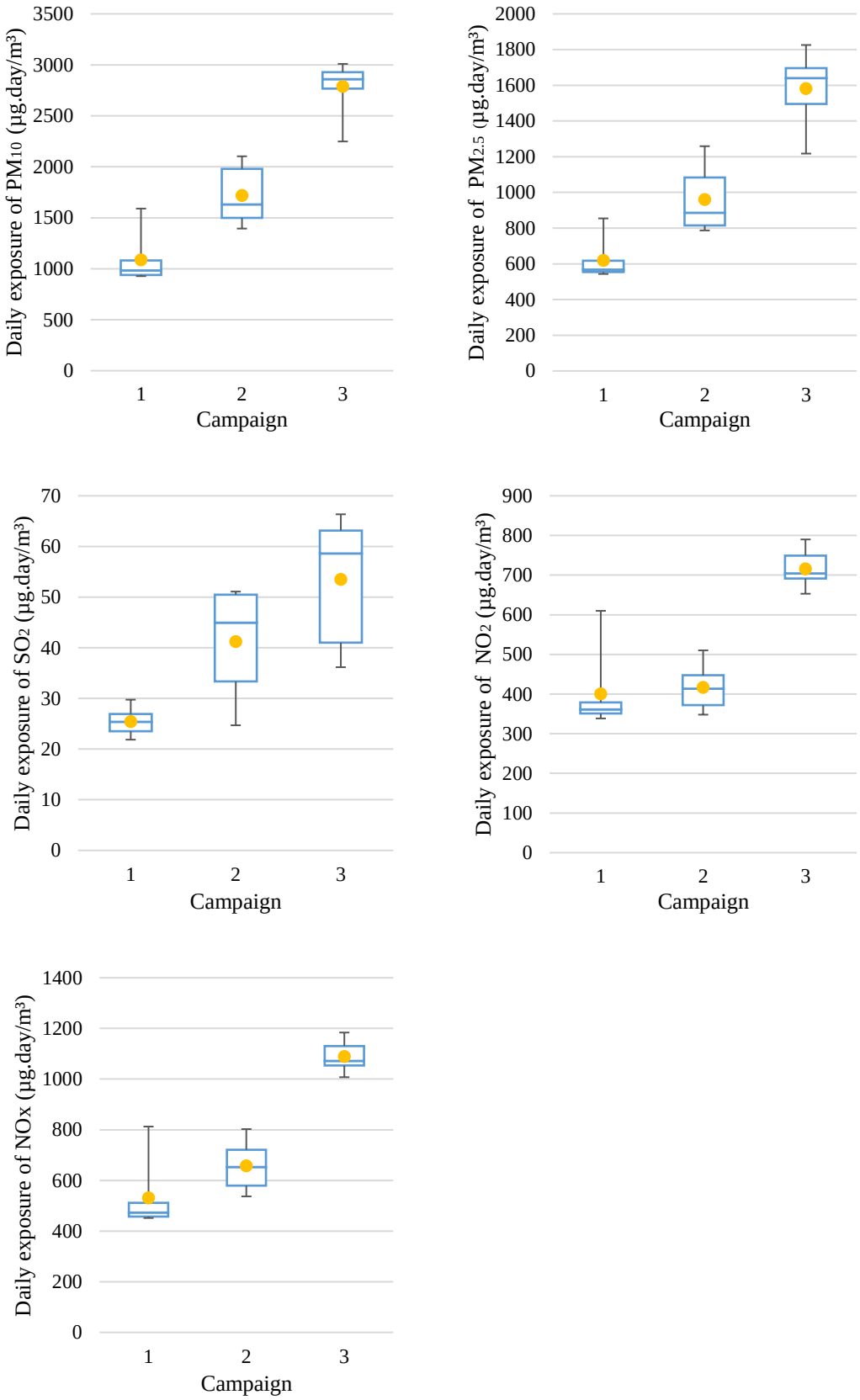


Figure 11. Box-plot of children daily exposures

Sensitivity analysis of exposure

For comparison purposes, the base scenario (S0) corresponds to results from the previous section, in which authors employed mean values of I/O and included the children pathways in the exposure analysis. Questions to be answered are: 'what is the effect of I/O on results?'; 'is the pathway important to the total exposure?'; 'what happens if indoor concentrations are ignored?'

In order to answer these questions, five scenarios were analyzed: Three scenarios include children's pathway, however with three different values of I/O ratio (maximum (S1) and minimum (S2) values shown in **Table 6** and unity (S3)). Two scenarios do not include children's pathway (I/O equal to mean values in **Table 6** and there is no pathway time (S4), and I/O ratio is equal to unity and no pathway time (S5)). Scenarios S1 and S2 intend to answer how strong the exposure results rely on the mean I/O ratio used. Scenarios S3, S4 and S5 are based on common drawbacks to estimate exposure in approaches found in the literature.

Table 11 indicates that the inclusion of children's pathway had little effect in the total exposure of each campaign. The I/O ratios proved to be a valuable information for a complete exposure assessment. The analysis indicates that the non-inclusion of a proper I/O can cause overestimation of exposure for pollutants, such as SO_2. Likewise, it can decrease the exposure of other pollutants that are commonly found in higher concentrations inside homes, e.g. particulate matter.

S1 and S2 results demonstrate that children of 'Campaign 1' and 'Campaign 3' had higher sensitivity to I/O ratio change. This is expected considering that 'Campaign 2' school-kids were the middle term in the exposure analysis, staying not as much indoors as subjects of 'Campaign 1' but also in a zone of lower concentrations than 'Campaign 3' students.

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Table 11. Results from sensitivity analysis of I/O ratios and pathway exposure.

	% of the change in exposition	Campaign 1				
		PM_{10}	**$PM_{2.5}$**	**SO_2**	**NO_2**	**NOx**
S1	I/O set to max	12.6%	20.9%	95.8%	20.4%	22.9%
S2	I/O set to min	-37.7%	-51.4%	-32.0%	-20.0%	-23.0%
S3	I/O equal to 1	-61.8%	-81.2%	140.7%	-24.7%	-25.7%
S4	no pathway	0.5%	0.9%	-1.6%	0.0%	0.1%
S5	S3 + S4	-61.8%	-81.2%	140.6%	-24.7%	-25.8%
	% of change in exposition	Campaign 2				
		PM_{10}	**$PM_{2.5}$**	**SO_2**	**NO_2**	**NOx**
S1	I/O set to max	13.0%	22.0%	86.2%	19.2%	22.8%
S2	I/O set to min	-36.2%	-50.3%	-28.2%	-18.8%	-22.7%
S3	I/O equal to 1	-60.3%	-80.7%	107.9%	-22.3%	-23.3%
S4	no pathway	2.1%	3.7%	0.7%	0.1%	0.3%
S5	S3 + S4	-60.4%	-80.7%	110.7%	-22.4%	-23.5%
	% of change in exposition	Campaign 3				
		PM_{10}	**$PM_{2.5}$**	**SO_2**	**NO_2**	**NOx**
S1	I/O set to max	13.6%	22.4%	94.5%	20.4%	23.6%
S2	I/O set to min	-37.6%	-51.3%	-30.9%	-20.4%	-23.4%
S3	I/O equal to 1	-62.6%	-82.0%	114.8%	-24.0%	-25.1%
S4	no pathway	0.4%	0.7%	-1.0%	-0.2%	0.1%
S5	S3 + S4	-62.7%	-82.1%	114.6%	-24.3%	-25.4%

5.3.4 Comparison with personal monitor

Literature shows particular interest in children exposure to NO_2 in urban centers, due to the association with road sources and asthma **(GAUVIN et al., 2001; LAWSON et al., 2011; PEREZ et al., 2012)**. **Table 12** shows the mean exposure to NO_2 of children at each campaign combining data obtained from measurements using a personal monitor, dispersion model and monitoring station. See **Supplemental Material** for each child particular analysis.

Table 12. Validation of exposure results for NO_2

Method µg hour/m^3 ± (SD)	**Campaign 1**		
	Week 1 **(02/11 to 07/11)**	**Week 2** **(07/11 to 12/11)**	**Week 3** **(12/11 to 17/11)**
Ogawa sampler	13.36 (± 4.98)	10.87 (± 3.04)	15.02 (± 6.41)
Monitoring station	9.05 (± 0.25)	11.41 (± 0.40)	14.73 (± 0.53)
Dispersion model	16.78 (± 5.86)	17.22 (± 5.56)	20.24 (± 5.75)
Method µg hour/m^3 ± (SD)	**Campaign**		
	Week 1 **(04/12 to 09/12)**	**Week 2** **(09/12 to 14/12)**	**Week 3** **(14/12 to 19/12)**
Ogawa sampler	11.16 (± 4.87)	8.17 (± 2.62)	12.84 (± 3.74)**
Monitoring station	8.56 (± 0.22)	7.17 (± 0.14)	7.15 (± 0.10)
Dispersion model	18.16 (± 2.08)	17.52 (± 3.50)	16.27 (± 2.93)
Method µg hour/m^3 ± (SD)	**Campaign 3**		
	Week 1 **(02/11 to 07/11)**	**Week 2** **(07/11 to 12/11)**	-
Ogawa sampler	***	13.74 (± 2.45)	-
Monitoring station	13.47 (± 0.27)	12.90 (± 0.29)	-
Dispersion model	18.16 (± 2.08)	33.54 (± 2.00)	-

**SD without outliers: 10.36; ***loss of material.

The outcomes presented in **Table 12** indicate that for most cases, especially in week one and three of the first and second campaign, the dispersion model exposure mean approaches the personal monitor results. For the third campaign, the exposure results using only the measurements from the monitoring station provided better estimations. In all cases, dispersion model outcomes are higher than outdoor monitoring. With a better validation, exposure results using dispersion model could be even closer to personal sampling.

Although mean exposures differ, the standard deviation of exposure results by personal monitor is best captured by using the dispersion model. As it is perceived in each campaign, the monitoring station alone provides little variance in exposure between children (in the same week). This is because it does not address the spatial variation in the field concentration since all values come from a singular measurement place. Dispersion modelling values captures this variance well, due to the spreading of receptors located in the neighborhoods of interest and the ability to estimate concentration in such multiplicity of locations.

5.3.5 Dose calculation

Table 13 shows the results of the mean total dose, that is, if adding all hourly doses of children and later averaging by a specific category We have categorized by body mass index (BMI) following the paper of **(CONDE; MONTEIRO, 2006)** that adapted critical point values for underweight, overweight and children with obesity for Brazil reality. Because of the weight distribution, subjects that have higher BMI have a lower dosage if experiencing the same exposure as children with BMI within the regular range. In the **Supplemental Material,** we further analyze the hour mean dose by subject and the dose contribution of each microenvironment for 'Campaign 1', 'Campaign 2', and 'Campaign 3'. These revealed that on particular cases, the time spent indoors influenced more the dose per kilogram than BMI, and that the home environment was responsible for the higher portion of dose inhaled.

Table 13. Dose calculation results for participants of this study.

Campaign	BMI	n. of children	Averaged value of total dose (µg/kg) by BMI category				
			PM_{10}	$PM_{2.5}$	SO_2	NO_2	NOx
1 (16 days)			**411.78**	**238.59**	**10.13**	**157.35**	**201.56**
	Regular	5	441.19	254.27	10.69	169.17	216.44
	Obesity	1	264.75	160.21	7.33	98.22	127.19
2 (16 days)			**651.17**	**370.72**	**20.20**	**160.58**	**259.79**
	Regular	3	765.72	438.15	28.65	199.61	322.12
	Overweight	3	536.62	303.28	11.76	121.54	197.46
3 (15 days)			**982.77**	**575.34**	**24.14**	**242.56**	**374.11**
	Regular	4	1247.35	713.80	32.36	319.99	491.04
	Overweight	5	771.11	464.57	17.57	180.62	280.56

At last, the significant drop in the inhalation rate (from 1.2 to 0.45) during sleep hours considerably reduced the total dose of participants. Since the authors employed the same IR for all children, the 1.2 m^3/h value might be a factor subjected to sensitivity as well. For instance, when applying the predictive models of **Greenwald et al. (2016, 2019)** using as input the heart rate (HR) and Forced Vital Capacity (FVC), sex and age of subjects (collected during physicians

visits), the inhalation rates found were between 0.25 to 0.88 m^3/hr. Some of these values are lower than expected resting inhalation rates (if children is laid down) **(USEPA, 1997b)**.

5.4 Discussion and Conclusions

A holistic methodology was applied to estimate the exposure and dose of children to air pollutants in an urban-industrialized environment. Pollutants commonly found in cities are addressed. A comparison of exposure assessment using dispersion models, a monitoring station and a personal monitor is provided for NO_2. **Physick et al. (2011)**, who conducted a similar study using adults subjects, argue that using outdoor monitoring data and a theoretical estimation of indoor concentrations provided better exposure results than air quality modelling integrated with any of three methods to estimate I/O used. However, our results point out that the use of dispersion models results in higher variability of exposure values – agreeing with the variability of personal monitors outcomes - if compared to a method relying solely on the monitoring station. If the dispersion model presents good statistical results in the validation process, we recommend it over a single monitoring station measurement, as supported by review papers **(KHREIS et al., 2017; WATSON; BATES; KENNEDY, 1988)** and validated by our results.

From the holistic investigation, the exposure results revealed higher sensitivity to I/O ratios used than to children's pathway. Depending on the case, researchers can ignore the pathway in exposure assessment to reduce the study complexity and redirect the focus to what matters most. Regarding particulate matter I/O ratios, our values differ from literature data, and are above normally reported ones. **Massey et al. (2012)** found mean I/O ratios at home for PM_{10} of 0.97 and 1.01 for $PM_{2.5}$ in roadside areas and 0.92 (PM_{10}) and 0.94 ($PM_{2.5}$) in urban areas. Age of the building varied between 5 to 50 years and some families had smoking habits. **Meier et al. (2015)** differentiate I/O levels in houses with parents smoking and without. For PM_{10} and $PM_{2.5}$ in no-smoke houses, I/O ratio varied from 0.62 to 0.78 (PM_{10}) and 0.64 to 0.87 ($PM_{2.5}$). **Chen and Zhao (2011)** show papers that reported mean I/O of less than 0.5 to 31.4 in the experimental results analyzed for $PM_{2.5}$. Nevertheless, the majority of studies had I/O in the range of 0.7 to 3, as also reported by **Bo et al. (2017)**. For PM_{10} **Chen and Zhao, 2011)** showed that experimental data of large-scale studies report I/O ratios from 0.5 to 2.3, below what was found in the schools and houses of this present contribution. Between factors that could cause this difference, one is the natural ventilation effect as in the two houses sampled the windows are open during the day and mechanical ventilation is mainly used at night. The second is that the occupancy factor, as reported in **Pallarés et al. (2019)** occupied school classrooms have higher I/O due to resuspension of particles and intrusion (particles in occupants clothes).

Our results indicate that the BMI is an important physiological parameter influencing the dose of air pollutants per body weight. On particular cases, the time spent indoors and, consequently, the

indoor-outdoor ratio showed to influence more the results over BMI factor. **Chalvatzaki et al. (2020)**, results supports that the school indoor environment have a higher contribution to the total dose for PM_{10}. However, in our study the home microenvironment was more responsible.

Another important parameter for dose calculation is the range of inhalation rates, which were not fully explored due to difficulties in obtaining such data. In **Scungio et al. (2020)**, the authors explore the differences in sub-micron particle dose calculation if using direct (measured) or indirect (modelled) data on particle concentration, inhalation rates and time activity pattern. Our study correlates better to 'M2' scenario in which results were the most proximate to a full-field calculation and only the inhalation rate was assumed. Their study also shows significant difference in dose if taken outdoor and indoor exposure. At last, results of **Scungio et al. (2020)** infer that assumed inhalation rates impacted less the results than wrong routine (time activity pattern) consideration.

This study found some limitations that we recommend for future research. First is the need for more published data on hourly values of I/O ratios of air pollutants (or methods to estimate this exchange). Second is the need for more published data on inhalation rates during multiple activities for asthmatic children. To detail the holistic investigation further, it would require knowledge over children academics routine (when and how much time they spent in each school microenvironment), the respective indoor monitoring of such places, plus children activity level if they are outside school or home (e.g., leisure or extracurricular activities).

Acknowledgements

This study is part of a larger project called 'ASMAVIX' in which a multidisciplinary team of medical and air quality researchers focus on finding the correlation between air pollution exposure and asthma indicators in an urban industrialized metropolitan area in the southeast region of Brazil. The national ethics committee has approved the project under the registration number CAAE: 09214519.1.0000.5071 on 01/09/2019.

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6. CONCLUSIONS

This is the first study to address MRV children exposure and dose to air pollutants from the individual level. To achieve this goal, the author used dispersion modelling, indoor measurements, personal samplers, routine questionnaire and data collected by trained physicians. Thus, a holistic approach is given.

One of the core results of this dissertation is the systematic review that derived the methodology to calculate children exposure. The review of 102 papers showed consistent drawbacks in literature that should be avoidable. The author also suggests a list of opportunities, challenges, and recommendations for future studies that estimate the associations' between air pollutants exposure and asthma prevalence, specifically directed to the use of dispersion and receptor models.

The second core result is the estimation of MRV children exposure and dose to PM_{10}, $PM_{2.5}$, NOx, NO_2, and SO_2. A crescent mean exposure outcome was observed between campaigns. Dispersion modelling proved to match better the exposure variation obtained with personal samplers, result attributed to the spatial concentration variation between children's location throughout the day. Environmental factors that proved relevant were proximity to sources and the correct estimation of Indoor-Outdoor ratios (or simply indoor concentrations). In dose assessment, an important factor was children Body Mass Index, and another variable that calls for more attention is the inhalation rate (minute ventilation) between asthmatic children during different activities. This type of data is scarce in literature and compromises a precise assessment.

6.1 Recommendation for future studies

- Improve the emission inventory by upgrading sources to 2019 panorama, adjusting emissions, and paying visits to the neighborhoods for investigating local relevant sources;

- Improve CALPUFF modelling by performing sensitivity tests of default parameters, with the inclusion of more meteorological data/stations and complex scenarios (i.e., dry/wet deposition);

- Use simultaneous data of indoor-outdoor monitoring in schools and houses, instead of I/O ratios, for all pollutants in comparison with literature data; alternatively, use probabilistic or mass-balance models to address indoor exposure.

- Use the recommended (new) questionnaire acquire data on children's routine and GPS to track children's pathways, thus providing a new assessment of exposure and dose;

- Validate exposure of other pollutants than NO_2 and SO_2 by using different personal measuring techniques;

- Conduct a source apportionment study using dispersion modelling and receptor modelling to estimate the exposure and dose to specific compounds of particulate matter (and sources contribution);

- Estimate the association between exposure and dose results with asthma symptoms for children of the ASMAVIX project;

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ZMIROU, D. et al. Five Epidemiological Studies on Transport and Asthma : Objectives , design

and descriptive results. **Journal of Exposure Analysis and Environmental Epidemiology**, v. 12, n. 3, p. 186–196, 2002.

8. APPENDIX I: GLOSSARY

THE ROLE OF DISPERSION AND RECEPTOR MODELS IN ASTHMA RESEARCH - A SYSTEMATIC REVIEW

SUPPLEMENTAL MATERIAL I

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8.1 Indicators

In this section, the indicators mentioned in the review paper will be defined to better comprehend the link between air pollution exposure and the related outcome. Because it will be given short definitions, for further information the authors strongly advise other readings **(ANDRADE, 2015; NOJIMA; TOKUNAGA; NAGAMURA, 2018; PANAGIOTAKOS, 2008; SZUMILAS, 2010)**.

- ***Odds Ratio (OR)***

  Represents the odds of an event, estimated by the ratio of the outcome frequency given a particular exposure and the frequency of the outcome happening in the absence of that exposure. The formula is as it follows:

$$OR = \frac{x/y}{w/z}$$

  where, x represents the number of exposed cases, y the number of unexposed cased, w the number of exposed non-cases, and finally z the number of unexposed non-cases.

- ***Hazard Risk (HR)***

  The hazard risk analysis was used in **DELFINO et al. (2009); KÜNZLI et al. (2009)** and **MCCONNELL et al. (2010)** studies. It is derived from the employment of Cox proportional hazard model which can be described as:

$$h_{ijl}(t) = h_{0s}(t) \,.\, u_{ij} \,.\, \exp(\beta X_{ijl} + \delta^T Z_{ijl})$$

where, l represents a subject, i community, j the school; thus $h_{ijl}(t)$ represents the hazard function at age t, $h_{0s}(t)$ the baseline hazard function in stratum s, u_{ij} denotes the community and school random effects; X_{ijl} pollution exposure understudy and Z_{ijl} possible confounders.

- ***Relative Risk (RR)***

  Represents the prospect of occurrence of the outcome after the exposure (in this case to atmospheric pollutants), in comparison to the prospect of the occurrence in a reference or control group of individuals. The formula is as it follows:

$$RR = \frac{a/b}{c/d}$$

  where, a represents the number of outcomes in exposed cases, b the total number of exposed cased, c the number of outcomes in unexposed cases, and finally d the total number of unexposed cases.

- ***Excess Risk (ERi)***

  The excess risk analysis was used in **OSTRO et al. (2016)** study. It derived from the estimated Odds Ratio and described as:

$$ERi = 100.(OR - 1)\ per\ IQR\ increment$$

  where, IQR refers to the pollutant interquartile-range.

8.2 Medical terms

In this section, the medical terms mentioned in the review paper will be defined for better understanding of the outcome. For further information the authors strongly advise other readings **(DHARMAGE; PERRET; CUSTOVIC, 2019; GINA, 2019; SÁ-SOUSA et al., 2014)**.

- ***Forced Vital Capacity (FVC)***

  Is the total amount of air exhaled during the Forced Expiratory Volume test;

- ***Forced Expiratory Volume (FEV)***

  Is a measure that indicates the amount of air a person can exhale when performing a forced breath; It can differ between the 1st, 2nd and 3rd seconds of the forced breath (FEV1, FEV2 and FEV3);

- ***Lifetime asthma***

Altough papers present numerous definitions (see **Sá-Sousa et al. (2014)**), the most dopted is “ever had asthma”;

- ***Non-allergic asthma***

  Asthma symptoms not triggered by allergic factors; It replaces the terminology of “extrinsic” and “intrinsic” asthma **(ROMANET-MANENT et al., 2002)**.

- ***New-onset asthma***

  This definition appeared soly on **McConnell et al. (2010)** study, in which the authors claimed that “children with physician-diagnosed asthma reported on a yearly questionnaire during 3-years follow-up were defined to have new-onset asthma”.

- ***Exercise-induced asthma***

  Defined as the asthma symptoms triggered after exercising.

- ***Incident asthma***

  This definition appeared sole on **Modig et al. (2009)** study in which the authors adopted the same criteria of definition for **onset asthma**, which was a negative followed by a positive answer in to the questions “have you had an attack of asthma during the last 12 months?”, “are you currently taking any medicine for asthma”, “do you have or have you ever had asthma?” and “have you ever had asthma diagnosed by a doctor?”. The difference is that for **incident asthma** the reporting age at onset of asthma symptoms was also used.

- ***Current asthma***

  Altough papers present numerous definitions (see **Sá-Sousa et al. (2014)**), the most dopted is “ever diagnosed with asthma by a health professional” and the most common element for diagnosis was “wheeze in the last 12 months”;

- ***Asthma incidence***

  Measure of new cases against the total population sampled. It corresponds to the probability os asthma symptoms occur in a certain period.

- ***Asthma prevalence***

  Measure of the existent cases of asthma in a given population at certain period.

- ***Asthma persistency***

  This definition appeared sole on **Hasunuma et al. (2016)** study in which the authors adopted the same criteria of "participants who had 'asthma' at the ages of both $1^{1/2}$ and 3 years were defined as patients with persistent asthmatic symptoms".

- ***Asthma morbidity***

  It refers to the condition of being symptomatic or unhealthy due to asthma; For further details on the difference between "morbidity" and "mortality" on epidemiology, please refer to **Hernandez and Kim (2020)**.

- ***Asthma mortality***

  It refers to the number of deaths caused by asthma exacerbations; For further details on the difference between "morbidity" and "mortality" on epidemiology, please refer to **Hernandez and Kim (2020)**.

9. APPENDIX II: REVIEW METHODOLOGY

THE ROLE OF DISPERSION AND RECEPTOR MODELS IN ASTHMA RESEARCH - A SYSTEMATIC REVIEW

SUPPLEMENTAL MATERIAL II

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9.1 ProKnown-C

ProKnown-C: Knowledge Development Process and Constructivist Method was the proposed methodology to carry out the search for papers and review criteria. Developed by **Ensslin et al., (2010)**, ProKnown-C consists of several steps of an integrated systematic review. The first step is the papers retrieving through search engines. In this work, the keywords 'asthma' and 'air pollution' were set as beginning point in SCOPUS database. The search resulted in 7217 documents that were then partitioned to include only 'articles', 'in-press', 'online' or 'reviews', also English written in the subject areas of 'environmental sciences' and 'engineering', with source type limited to 'journals'. A final number of 1522 papers were then exported to Mendeley software. Complementary research was done in SCOPUS, PubMed and Science Direct, however employing the keywords 'dispersion model' and 'asthma' and later 'receptor model' and 'asthma'. The results were also exported to Mendeley. In Mendeley software, the authors conducted a second search for all papers that mentioned either 'dispersion model' or 'receptor model' and 'asthma'. A total of 163 papers were then exported to a separate folder to be analysed.

After eliminating repetitive papers, the authors made another exclusion based on title and abstract reading. In the abstract reading phase, we divided those papers that had asthma as a key topic and mentioned the pollutant or exposure model used. From 163 papers, 102 passed the criteria. The final selected papers passed through a final screening process where the authors evaluated the main sources understudy, dispersion and/or receptor model used and other key aspects of their

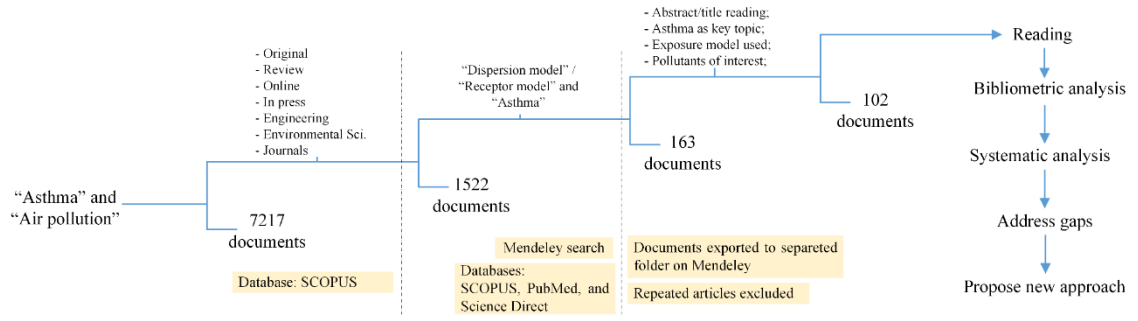
methodology, addressed by **Table 14**. The general flowchart of this review is summarized in **Figure 12** and the final papers selected (complete systematic review table) on online supplemental material.

From the search engines used, SCOPUS returned the most satisfactory results as we excluded fewer papers in the abstract reading phase. Other databases provided studies that only mentioned keywords but were not strict to the main topic of this review.

Table 14. Topics addressed in the screening process.

Section	Information retrieved
General info	The title, DOI, Authors, Year of publication
Abstract criteria	Review or research paper, asthma as a key topic, pollutants studied, main sources studied
Methodology aspects	Key topic, Dispersion model used, Receptor model used, Air quality monitoring, Validation process, Exposure or Response model used, Data collection (hospitals or questionnaires), Target age (Child < 18years), Outdoor or Indoor, Period, Urban or Rural, Country (or city) and Cohort
Compelling arguments	Selection of three discussing points to be addressed

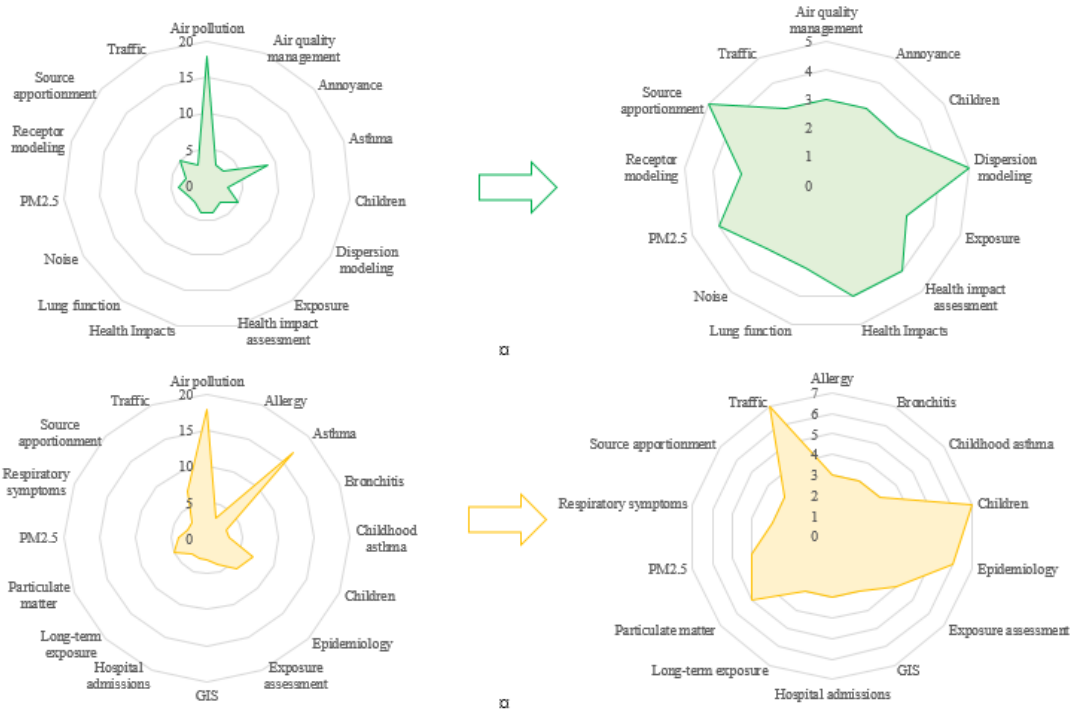
Figure 12. Flowchart of this study systematic review.



The authors created a 'radar of interest' to illustrate the most used keywords in asthma research applying dispersion or receptor models. It also shows a perspective of journals destination for papers published (**Figure 13**). To build this radar of interest, we considered only keywords that appeared more than twice in all the 102 papers addressed. Furthermore, we divided the journals

into two major categories: ‘Environmental Sciences Journals’ and ‘Health Sciences Journals’ based on their subjects of interest. A second radar was created excluding the words ‘asthma’ and ‘air pollution’ for a detailed perspective.

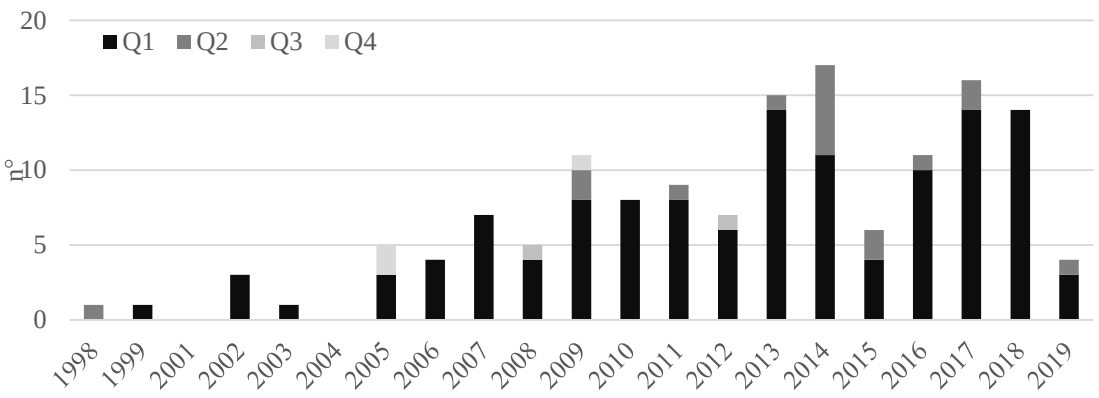
Figure 13. Radar of interest compiling recurrent keywords of this review (on the left without keywords “air pollution” and “asthma”). Environmental Sciences Journals in green; Health Sciences journals in yellow.



9.2 Data quality

The authors organized the distribution of the initial 163 papers according to the year of publication and their journal impact factor measured by Scientific Journal Rankings (SJR) (**Figure 14**). The complete table of journals destination is found in the online supplemental material.

Figure 14. Pre abstract reading papers in this study qualified by Scopus quartile classification (SJR).



It is possible to see that has been an unsteady increase of studies employing dispersion or receptor models in asthma research, especially after 2005, but also that papers are published in high impact journals (Q1). Notice that the year of 2019 only covers those papers published up to January of the same year.

9.3 Overall results

From the 102 papers analysed, five were review studies, four of them discussing dispersion models **(FAVARATO et al., 2014; JERRETT et al., 2005; KHREIS, H.; NIEUWENHUIJSEN, 2017; PÉNARD-MORAND; ANNESI-MAESANO, 2008)** and one discussed the use of receptor model **(STANEK et al., 2011)** in asthma research. The majority of studies focused on NOx atmospheric pollutants (63%), mainly because they are Traffic-Related Air Pollutants (TRAP), which is the major source found under investigation (i.e **(DELFINO et al., 2009; HASUNUMA et al., 2016; OFTEDAL et al., 2009; REUNGOAT et al., 2005)**). At total, thirty three studies had NOx and TRAP as focal points. Twelve studies did not discussed the results relationship with asthma, but rather addressed methodological approaches or mentioned the use of DM and RM in cohorts **(BELLANDER et al., 2001; CASTELL et al., 2018; DUCRET-STICH et al., 2013; DUCRET-STICH et al., 2013; GANGULY et al., 2015; GANGULY; BATTERMAN; BRAKEFIELD-CALDWELL, 2012; ISAKOV et al., 2014; KLÆBOE et al., 2000; MÖLTER, A. et al., 2010a; REUNGOAT et al., 2005; SNYDER, M. et al., 2014; SNYDER et al., 2013)**. More than half (56%) of studies further investigated other Respiratory Diseases (RD).

Filtering for the main topics of this review, seventy two papers used dispersion models and seventeen applied receptor models. One paper did not state the DM used clearly. Nine studies mentioned but did not use either RM or DM, though they applied different techniques, such as Land Use Regression (LUR) analysis **(ANDERSSON et al., 2011; AYRES-SAMPAIO et al., 2014; DUCRET-STICH et al., 2013; EZE et al., 2018; MÖLTER, A. et al., 2010b; SONNENSCHEIN-VAN DER VOORT et al., 2012; TSUI et al., 2018)** or integrating monitoring stations observed values **(GAFFRON; NIEMEIER, 2015; MENTESE et al., 2015)**. Only one research appeared to have employed DM (CMAQ-TR) and RM (various) together **(KRALL et al., 2017)**. However, seven studies have mentioned source apportionment results, being three from previous research **(GANGULY et al., 2015; GUTTIKUNDA, S.K. et al., 2015; KHAFAIE et al., 2017)**, and four conducted the source discretization via dispersion models **(BATTERMAN; BURKE; et al., 2014; GALVIS et al., 2015; GUTTIKUNDA; GOEL, 2013; MILANDO; MARTENIES; BATTERMAN, 2016)**. One study used a receptor model results to calibrate the dispersion model estimates **(PENNINGTON et al., 2018)**.

For data collection, a vast majority of studies have monitored the air pollutants of interest (76%) alongside with DM or RM estimations. Ninety five papers addressed outdoor pollution exposure and only seven indoor air pollution **(BORREGO et al., 2007; HASUNUMA et al., 2016; HRUBÁ et al., 2001; KALAIARASAN et al., 2017; MENTESE et al., 2015; ZHAO et al., 2007; ZMIROU et al., 2002)**. The greater part of papers also evaluated urban scenarios (98%) and only few on rural locations **(DUCRET-STICH et al., 2013; DUCRET-STICH et al., 2013; HENDERSON et al., 2011; PEDERSEN et al., 2013; PUKLOVÁ et al., 2019; SCHULTZ et al., 2016; SPADARO; RABL, 1999)**. Thirty two studies opted to use hospital visits to characterize asthma episodes while fourty four employed questionnaires (i.e ISAAC, **(STRACHAN et al., 2017)**). Nine papers employed both approaches **(BELLANDER et al., 2001; BERGSTRA; BRUNEKREEF; BURDORF, 2018; BORREGO et al., 2007; BOUGAS et al., 2018; GAUDERMAN et al., 2005; KHAFAIE et al., 2017; KÜNZLI et al., 2009; PERSHAGEN et al., 1995; ZMIROU et al., 2002)**. Twelve papers were interested in the effect of air pollution in Adults (> 18 years), 55 on Children (< 18 years) and 29 in all ages.

Figure 15 summarizes the overall results of this review and **Figure 16** gives the global distribution of studies. From the latter, it is possible to perceive that countries like Siri Lanka (n° cases = 5727 in 2006) or Fiji (n° cases = 153 in 2012) have a high rate of deaths by asthma per 100000 inhabitants compared to others; however no study employing either dispersion or receptor models in exposure assessment was found. The same goes for countries that have a considerable number of cases but large populations, like Brazil (n° cases = 1949 in 2015) or Argentina (n° cases = 333 in 2015). On the other hand, it is also observable that developed countries (and India) lead the asthma studies applying DM or RM. There is a concentration of studies in United States of America (USA, n° cases = 3289 in 2015) and France (n° cases = 714 in 2014). The city where most studies were based on is Detroit – USA (nº = 9). The complete list of deaths by asthma by country used is found in the online supplemental material and the numbers were extracted from **WHO (2018)**.

Figure 15. Overall results of this review.

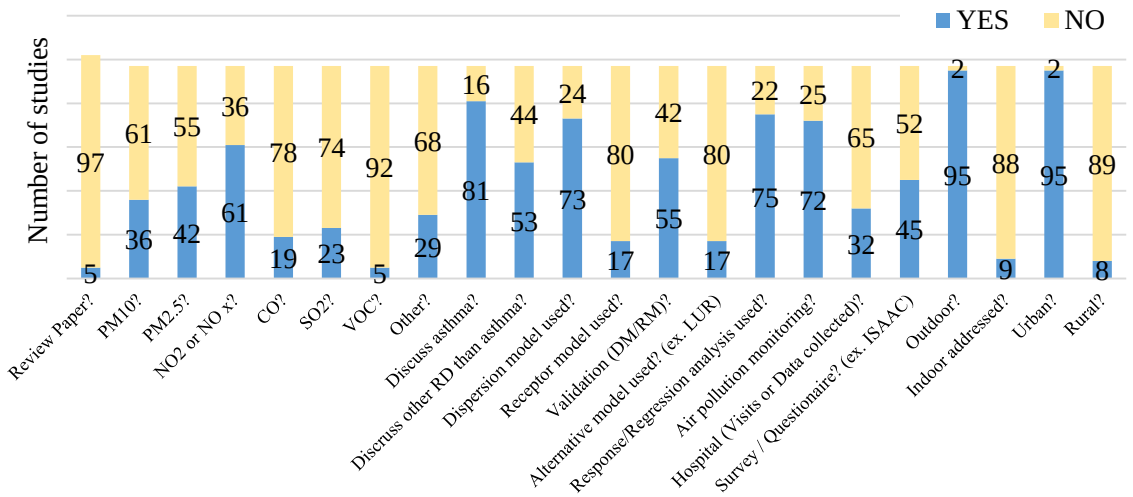
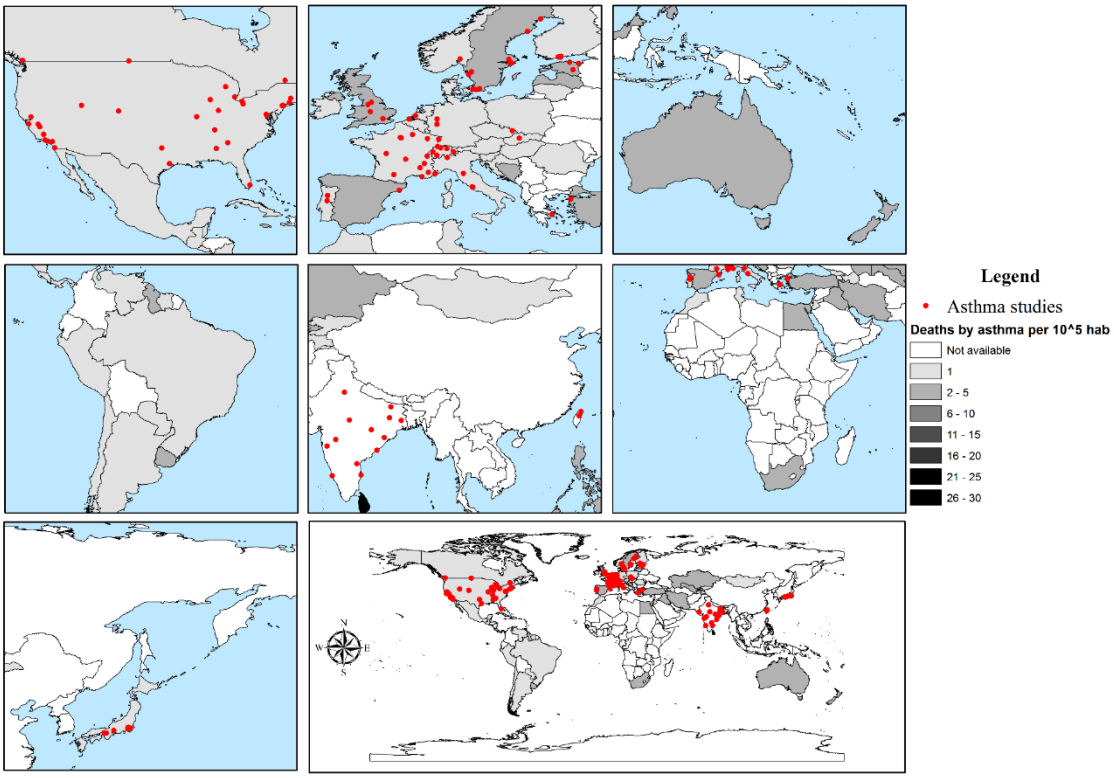


Figure 16. Global distribution of studies found in this review in contrast with deaths by asthma worldwide.



10. APPENDIX III: SUPPORTING INFORMATION

HOLISTIC ESTIMATION OF CHILDREN EXPOSURE AND DOSE TO AIR POLLUTANTS IN AN URBAN INDUSTRIALIZED ENVIRONMENT

SUPPLEMENTAL MATERIAL

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10.1 Questionnaire

a) Name:_____

b) Age / Weight:_____

c) School's name:_____

☐ Morning ☐ Afternoon ☐ Integrate

Questions to assist the Indoor-Outdoor ratio assessment:

a) Do you have air conditioner in your house/school? _____

b) If d) is YES does it stay on during day hours? _____

c) If d) is YES does it stay on during night hours? _____

d) Do you have a ceiling fan in your house/school? _____

e) If g) is YES does it stay on during day hours? _____

f) If g) is YES does it stay on during night hours? _____

g) Are the windows at your home/school open during daytime? _____

h) Are the windows at your home/school open during nighttime? _____

i) Do you have any pets? _____ If YES, which? _____

j) Are there any carpets/rugs at your house? _____ If YES, where? _____

Questions to assist the routine assessment:

k) After school you spend more your time at home or outside? _____

l) How do you go to school? _____

m) How long does it take to make the travel (in minutes)? _____

n) *Have you stayed outside home and school today? _____

o) *If d) is YES, have gone outside your neighborhood? _____

p) *If d) is YES, during which period of the day and for how long?

☐ Morning ☐ Afternoon ☐ Integrate

☐ 1 h – 2 h ☐ 3 h – 4 h ☐ 5 h – 6 h ☐ More

Questions revised:

We have made the questions simpler for subjects to answer, however it created complications in the exposure assessment due to overlapping responses with incompatible hours outside home/school. Therefore, we recommend the substitution of questions n), o) and p) by q) to v).

q) Outside school hours, do you do extracurricular, sports, or other activities? _____

r) If d) is YES, which days?_____, during which hours?_____ where?_____

s) Do you stay at some family relative during the week regularly?

t) If f) is YES, which days?_____, during which hours?_____ where?_____

u) *Have you stayed outside home and school today?

v) *If h) is YES, during which hours?

*(Reports gathered every week)

Questions recommended:

Apart from questions q) to v) it is also advised to add more questions about the school environment, such as:

w) When is the recreation time and where children most spend it (i.e., yard, inside rooms)?

x) What are children's class time schedule?

And to assist the dose assessment, questions about:

y) How much hours do you sleep during the week and weekends?
z) When you usually go to sleep?

10.2 Equipment used in Outdoor/Indoor air quality assessment and sampling location

Table 15. Design of the ASMAVIX monitoring station.

Parameter	Method name or published reference	Analytical technique and Instrument	Detection-limit	Precision
PM_{10}	Continuous	Beta ray attenuation (Spirant™ BAM 1100)	3.6 µg m^3	0.1 µg m^3
$PM_{2.5}$	Continuous	Beta ray attenuation (Spirant™ BAM 1100)	3.6 µg m^3	0.1 µg m^3
PM_{10}	Noncontinuous	Gravimetric (Airmetrics Mini-Vol TAS samplers)	0.1 µg m^3	10 µg m^3
$PM_{2.5}$	Noncontinuous	Gravimetric (Airmetrics Mini-Vol TAS samplers)	0.1 µg m^3	10 µg m^3
O_3	Continuous	Non-dirpersive UV absorption (Serinus 10 Ozone Analyser)	0.5 ppb	0.5 ppb
SO_2	Continuous	UV fluorescence (Serinus 50 Sulfur Dioxide Analyser)	0.3 ppb	0.5 ppb
NO_x and NO_2	Continuous	Chemiluminescence (Serinus 40 Oxides of Nitrogen Analyser)	0.4 ppb	0.4 ppb

Table 16. Equipment of the indoor monitoring campaign

Parameter	Method name or published reference	Analytical technique and Instrument	Detection-limit	Precision
PM_{10}	Continuous	Gravimetric and light scattering (Aerosol spectrometer and dust monitors model 1.109 LAS)	10 µg	10 µg a minimum of 1 mg dust
$PM_{2.5}$	Continuous	Gravimetric and light scattering (Aerosol spectrometer and dust monitors model 1.109 LAS)	-	10 µg a minimum of 1 mg dust
NO_2	Passive membrane	Passive membrane Ogawa	n.a.	n.a.

Figure 17. Indoor sampling location

10.3 Spatial heterogeneity analysis

The closest station to 'ASMAVIX' site is 'Enseada'. This station is owned by the local environmental agency (IEMA) and is the closest to the neighborhoods of interest apart from 'ASMAVIX' site. In this section, we demonstrate the differences between them by estimating the spatial heterogeneity of pollutants concentrations using the coefficient of divergence (COD) (**Equation 9**) **(SAHA et al., 2019; WILSON et al., 2005)**.

$$COD_{fh} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(\frac{x_{if}-x_{ih}}{xi_f+x_{ih}}\right)^2} \quad \text{Eq.9}$$

where i index represents the time interval, f, h the index for the site duo under comparison, and x the pollutant concentration at given time and location. The coefficient of divergence varies between 0 and 1, in which a lower level represents the higher spatial similarity between sites. If COD = 0 the concentrations are identical in both location, and COD = 1 highly different. As a reference **(WILSON et al., 2005)** considers a value of COD > 0.2 representatives for spatial heterogeneity.

Results returned values of COD equal to 0.32, 0.12, 0.31, 0.44, 0.19 and 0.26 for $PM_{2.5}$, PM_{10}, SO_2, NO, NO_2 and NOx, respectively. This implies that all pollutants, except PM_{10} and NO_2 (the latter for a small percent) had spatial differences during the shared monitoring period of 18/09/2019 to 28/02/2020. However, even with higher spatial homogeneity than other pollutants, there are differences in pollution levels of NO_2 and PM_{10} between 'ASMAVIX' and 'Enseada' sites. Both can be explained by the proximity of 'Enseada' site to a major road (< 20 m) if compared to 'ASMAVIX' (< 340 m). Not only has this closeness subjected 'Enseada' site to higher exposition to traffic NO_2 but also more traffic dust. In addition, 'Enseada' station is located on the central line of dispersion from air pollutants coming from industrial sites **(GALVÃO et al., 2019)**.

10.4 Dispersion model validation

Table 17. Statistical validation analysis of dispersion model results (part one)

	#1h Average	PM_{10}[a]	$PM_{2.5}$[a]	SO_2[a]	NO_2[a]	NO_X[a]
Enseada – From 01/06/2019 to 28/02/2020	FAC2	**0.44**	**0.37**	**0.30**	**0.49**	**0.49**
	R[b]	0.05	0.09	0.35	0.24	0.28
	VG	4.64	5.68	28.33	**3.15**	**3.16**
	NMSE	**3.53**	**1.56**	**2.26**	**2.74**	**2.19**
	MG	**1.01**	0.70	2.31	**0.93**	**0.93**
	FB	**-0.44**	**0.32**	**0.11**	**-0.47**	**-0.40**
	#24h Average	PM_{10}[a]	$PM_{2.5}$[a]	SO_2[a]	NO_2[a]	NO_X[a]
	FAC2	**0.50**	**0.60**	**0.64**	**0.74**	**0.79**
	R[b]	0.08	0.05	0.54	0.71	0.71
	VG	**2.05**	**2.13**	**1.98**	**1.41**	**1.36**
	NMSE	**0.98**	**0.56**	**0.50**	**0.50**	**0.43**
	MG	**0.80**	1.65	**1.25**	0.70	**0.76**
	FB	**-0.59**	**0.52**	**0.08**	**-0.50**	**-0.44**
	#Week Average	PM_{10}[a]	$PM_{2.5}$[a]	SO_2[a]	NO_2[a]	NO_X[a]
	FAC2	**0.64**	**0.56**	**0.54**	**0.89**	**0.89**
	R[b]	-0.15	-0.11	0.63	**0.78**	0.70
	VG	**1.72**	**2.20**	**2.14**	**1.25**	**1.22**
	NMSE	**0.53**	**0.69**	**0.31**	**0.27**	**0.23**
	MG	**1.03**	2.09	1.40	**0.76**	**0.81**
	FB	**-0.13**	**0.65**	**0.14**	**-0.36**	**-0.29**

[a]values in bold and gray passed the criteria of **(HANNA; CHANG, 2012)**

[b]**(CHANG; HANNA, 2004)** suggest the use of Spearman correlation because of the lognormal distribution nature of air pollutants concentration measured at fixed sites.

Table 18. Statistical validation analysis of dispersion model results (part two)

	#1h Average	PM_{10}[a]	SO_2[a]	NO[a]	NO_2[a]	NO_X[a]
City center – From 01/06/2019 to 28/02/2020	FAC2	**0.40**	0.22	**0.55**	**0.55**	**0.55**
	R[b]	0.19	0.17	0.46	0.31	0.06
	VG	5.63	153.11	**2.56**	**2.57**	**2.56**
	NMSE	**4.28**	**4.33**	**1.14**	**1.47**	**1.21**
	MG	**0.57**	3.62	**1.22**	**1.22**	**1.22**
	FB	-0.91	**0.63**	**-0.06**	**-0.12**	**-0.08**
	#24h Average	PM_{10}[a]	SO_2[a]	NO[a]	NO_2[a]	NO_X[a]
	FAC2	**0.36**	**0.44**	**0.89**	**0.89**	**0.90**
	R[b]	0.30	0.27	0.74	0.71	0.67
	VG	**3.06**	4.49	**1.25**	**1.23**	**1.23**
	NMSE	**1.67**	**1.37**	**0.19**	**0.21**	**0.18**
	MG	**0.42**	2.01	**1.05**	**0.97**	**1.01**
	FB	-0.91	**0.63**	**-0.06**	**-0.13**	**-0.09**
	#Week Average	PM_{10}[a]	SO_2[a]	NO[a]	NO_2[a]	NO_X[a]
	FAC2	**0.55**	**0.41**	**0.88**	**0.88**	**0.88**
	R[b]	0.20	0.31	0.72	0.69	0.62
	VG	**1.81**	4.38	**1.22**	**1.22**	**1.21**
	NMSE	**0.80**	**0.92**	**0.22**	**0.15**	**0.17**
	MG	**0.56**	2.25	**1.05**	**0.95**	**1.00**
	FB	**-0.63**	0.68	**-0.08**	**-0.12**	**-0.10**

[a]values in bold and gray passed the criteria of **(HANNA; CHANG, 2012)**

[b]**(CHANG; HANNA, 2004)** suggest the use of Spearman correlation because of the lognormal distribution nature of air pollutants concentration measured at fixed sites.

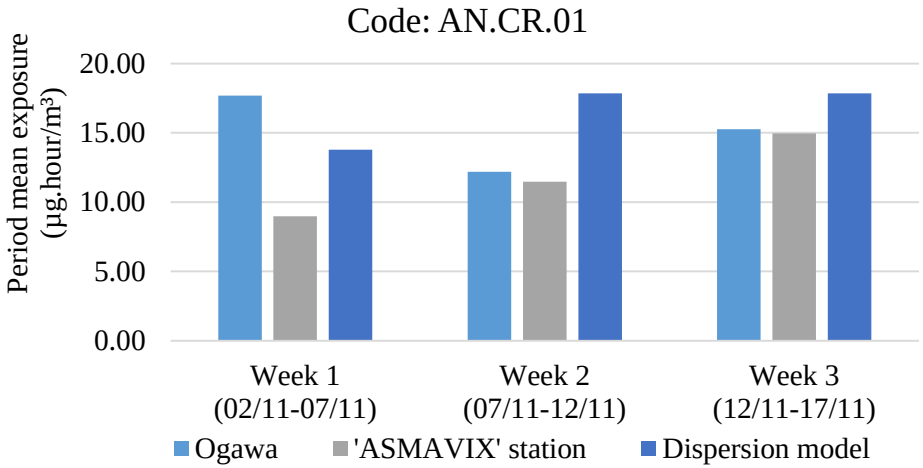
Table 19. Statistical validation analysis of dispersion model results (part three)

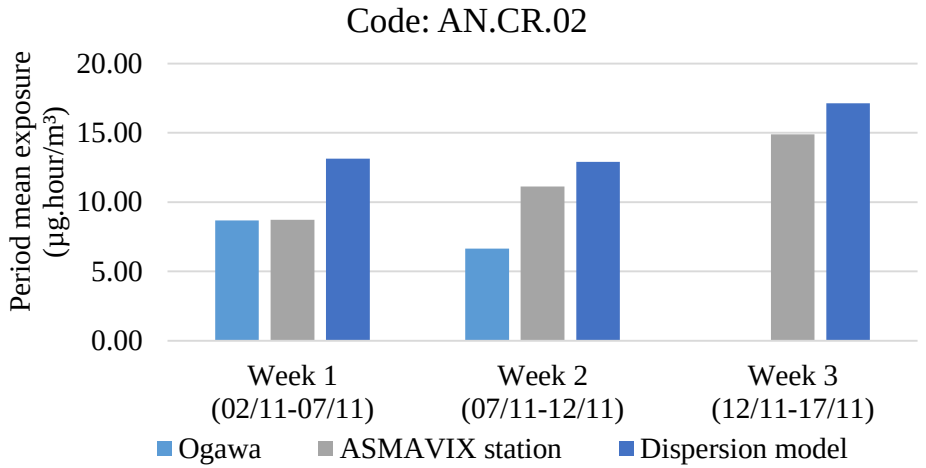
	#1h Average	$PM_{2.5}$[a]	PM_{10}[a]	SO_2[a]	NO[a]	NO_2[a]	NO_X[a]
ASMAVIX – From 18/09/2019 to 28/02/2020	FAC2	**0.39**	**0.44**	0.11	**0.56**	**0.56**	**0.56**
	R[b]	-0.04	0.00	0.23	0.48	0.32	0.31
	VG	7.10	5.66	7465.70	**2.61**	**2.61**	**2.61**
	NMSE	**3.66**	**2.98**	**2.85**	**1.31**	**1.82**	**1.66**
	MG	**0.87**	**0.94**	12.08	**0.91**	**0.91**	**0.91**
	FB	**-0.31**	**-0.45**	0.98	**-0.35**	**-0.41**	**-0.39**
	#24h Average	PM_{10}[a]	$PM_{2.5}$[a]	SO_2[a]	NO_2[a]	NO_X[a]	CO[a]
	FAC2	**0.48**	**0.63**	0.20	**0.76**	**0.70**	**0.73**
	R[b]	-0.12	-0.08	0.41	0.70	0.68	0.67
	VG	**3.53**	**2.04**	22.23	**1.38**	**1.40**	**1.38**
	NMSE	**2.34**	**0.88**	**1.48**	**0.44**	**0.43**	**0.42**
	MG	0.59	**0.70**	4.41	**0.76**	**0.72**	**0.73**
	FB	**-0.53**	**-0.43**	0.98	**-0.34**	**-0.41**	**-0.39**
	#Week Average	PM_{10}[a]	$PM_{2.5}$[a]	SO_2[a]	NO_2[a]	NO_X[a]	CO[a]
	FAC2	**0.46**	**0.54**	0.21	**0.92**	**0.79**	**0.83**
	R[b]	-0.06	-0.33	0.43	**0.86**	**0.80**	**0.81**
	VG	**2.61**	**1.91**	6.57	**1.24**	**1.35**	**1.31**
	NMSE	**1.30**	**0.71**	**1.20**	**0.24**	**0.30**	**0.28**
	MG	0.50	0.61	3.29	0.68	0.64	0.65
	FB	**-0.64**	**-0.51**	0.93	**-0.41**	**-0.46**	**-0.45**

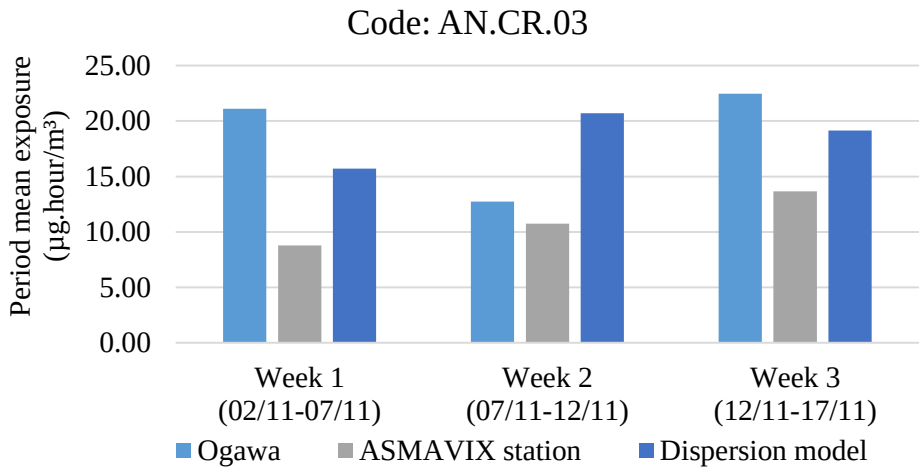
[a]values in bold and gray passed the criteria of **(HANNA; CHANG, 2012)**

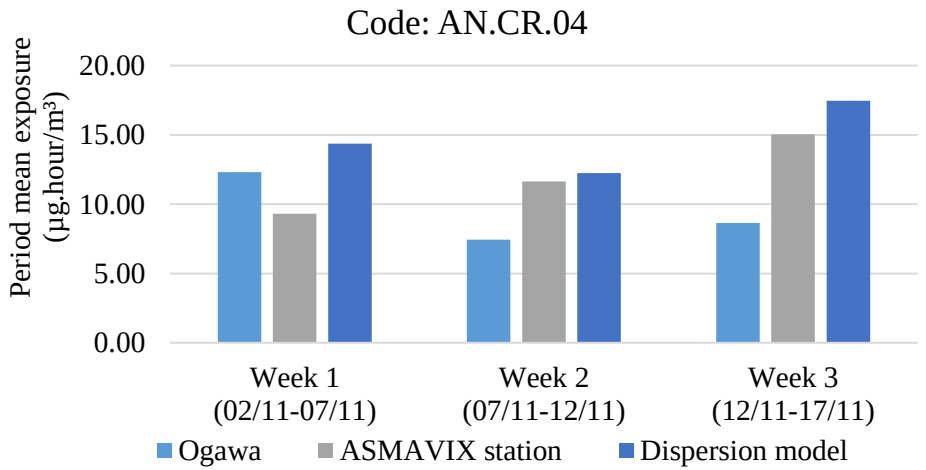
[b]**(CHANG; HANNA, 2004)** suggest the use of Spearman correlation because of the lognormal distribution nature of air pollutants concentration measured at fixed sites.

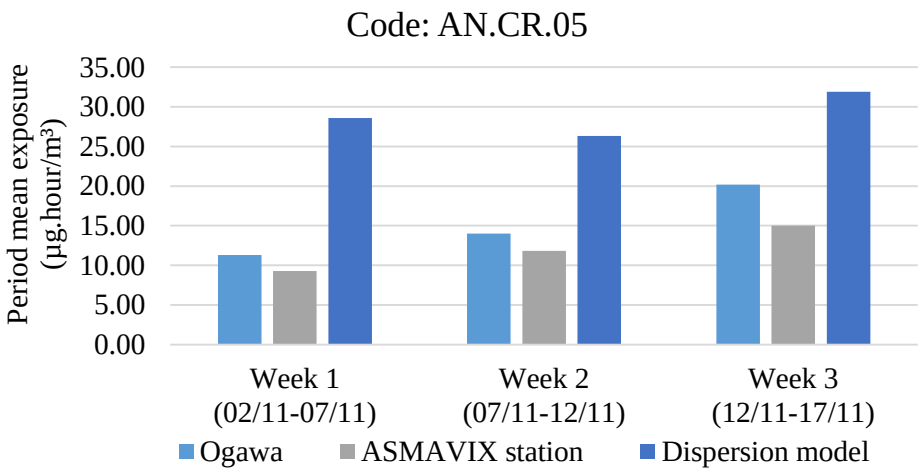
10.5 Supplementary exposure results

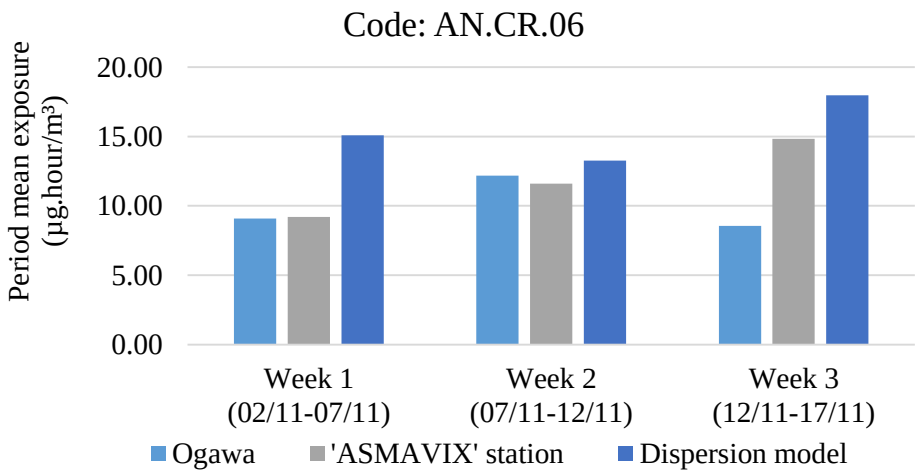









Code: AN.CR.05
Period mean exposure (µg.hour/m³)
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Week 1 (02/11-07/11)
Week 2 (07/11-12/11)
Week 3 (12/11-17/11)
Ogawa
ASMAVIX station
Dispersion model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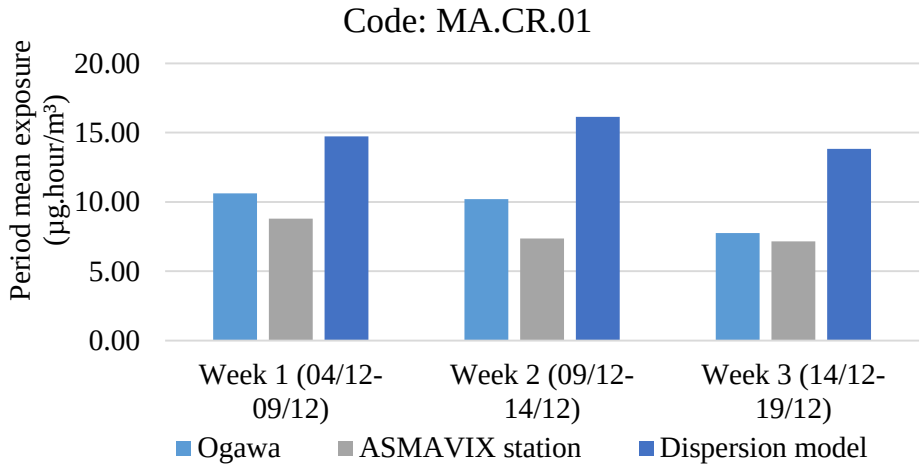
15.00
10.00
5.00
0.00
Week 1 (02/11-07/11)
Week 2 (07/11-12/11)
Week 3 (12/11-17/11)
Ogawa
'ASMAVIX' station
Dispersion model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Period mean exposure (µg.hour/m³)
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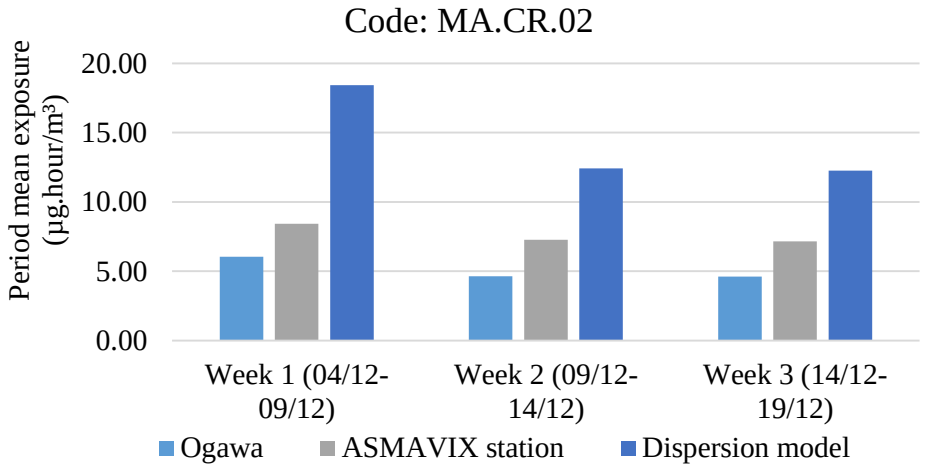
15.00
10.00
5.00
0.00
Week 1 (04/12-09/12)
Week 2 (09/12-14/12)
Week 3 (14/12-19/12)
Ogawa
ASMAVIX station
Dispersion model


Code: MA.CR.02
Period mean exposure (µg.hour/m³)
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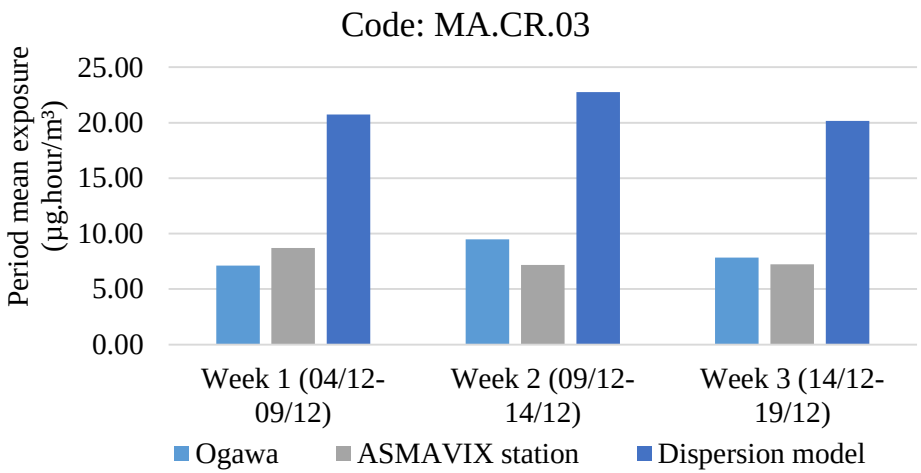
10.00
5.00
0.00
Week 1 (04/12-09/12)
Week 2 (09/12-14/12)
Week 3 (14/12-19/12)
Ogawa
ASMAVIX station
Dispersion model


Code: MA.CR.03
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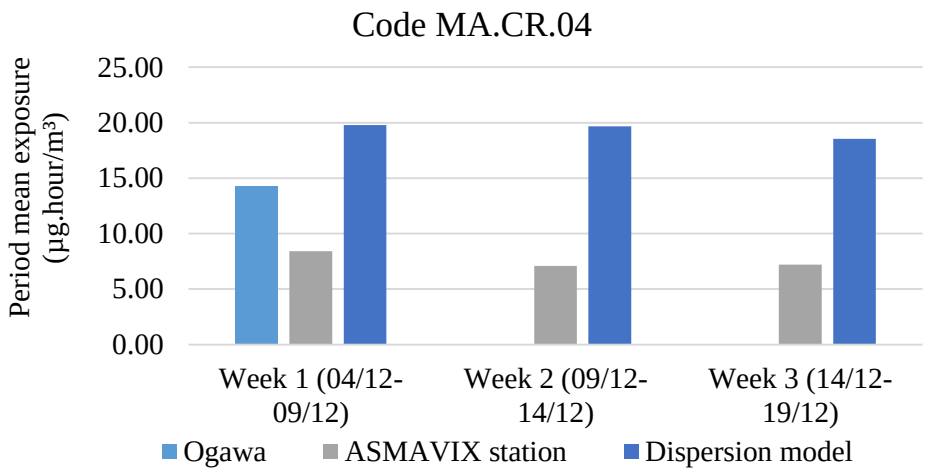
20.00
15.00
10.00
5.00
0.00
Week 1 (04/12-09/12)
Week 2 (09/12-14/12)
Week 3 (14/12-19/12)
Ogawa
ASMAVIX station
Dispersion model


Code MA.CR.04
Period mean exposure (µg.hour/m³)
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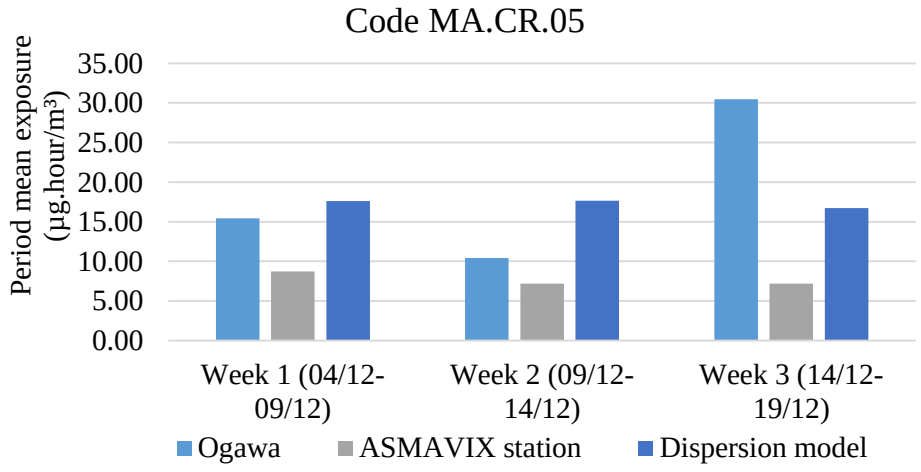
20.00
15.00
10.00
5.00
0.00
Week 1 (04/12-09/12)
Week 2 (09/12-14/12)
Week 3 (14/12-19/12)
Ogawa
ASMAVIX station
Dispersion model


Code MA.CR.05
Period mean exposure (µg.hour/m³)
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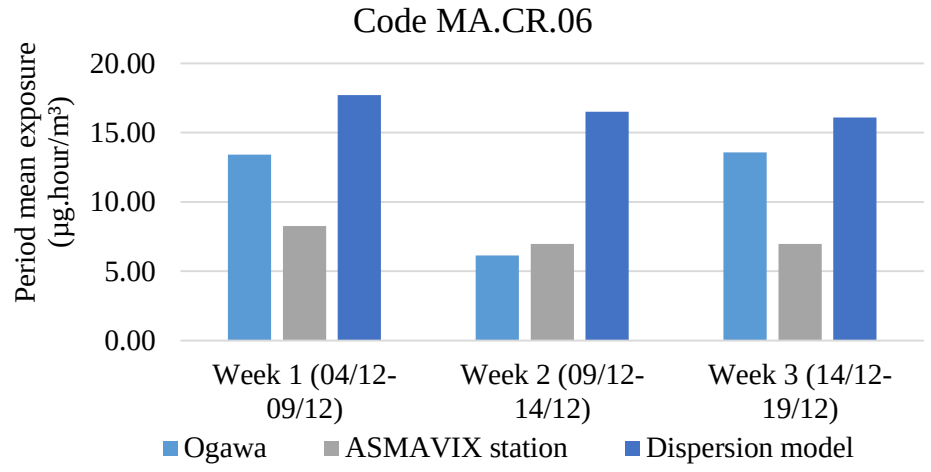
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Week 1 (04/12-09/12)
Week 2 (09/12-14/12)
Week 3 (14/12-19/12)
Ogawa
ASMAVIX station
Dispersion model


Code MA.CR.06
Period mean exposure (µg.hour/m³)
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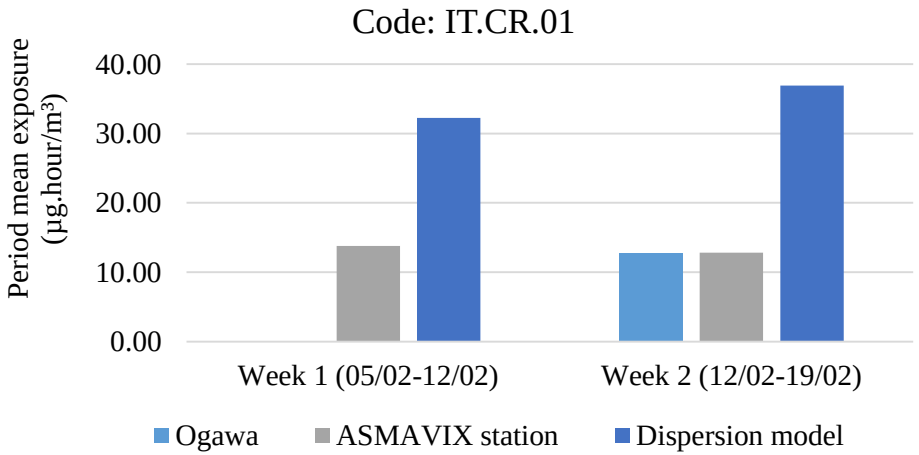
10.00
5.00
0.00
Week 1 (04/12-09/12)
Week 2 (09/12-14/12)
Week 3 (14/12-19/12)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.01
Period mean exposure (µg.hour/m³)
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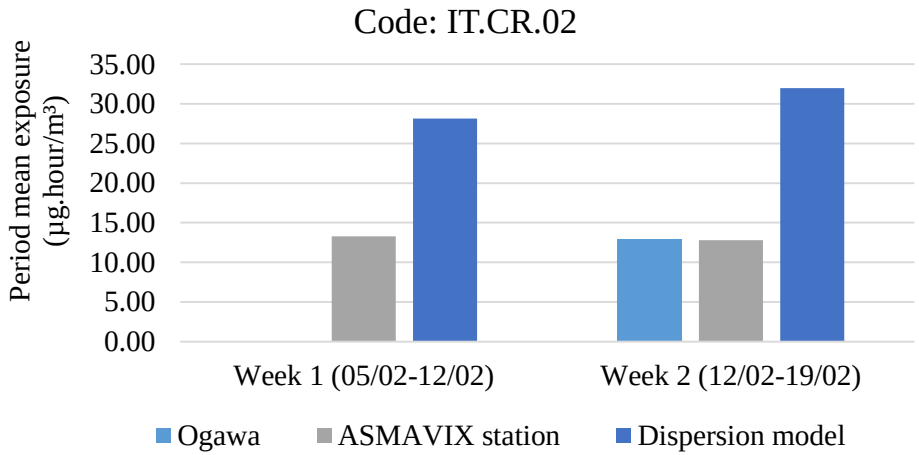
30.00
20.00
10.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.02
Period mean exposure (µg.hour/m³)
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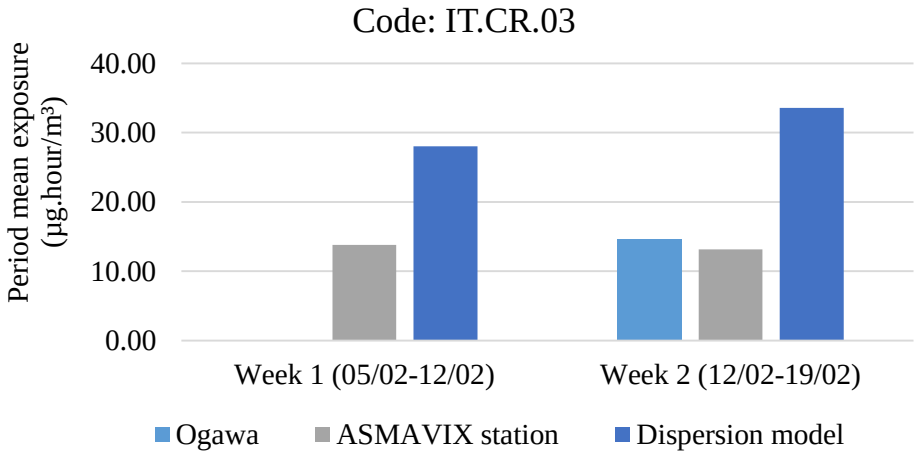
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.03
Period mean exposure (µg.hour/m³)
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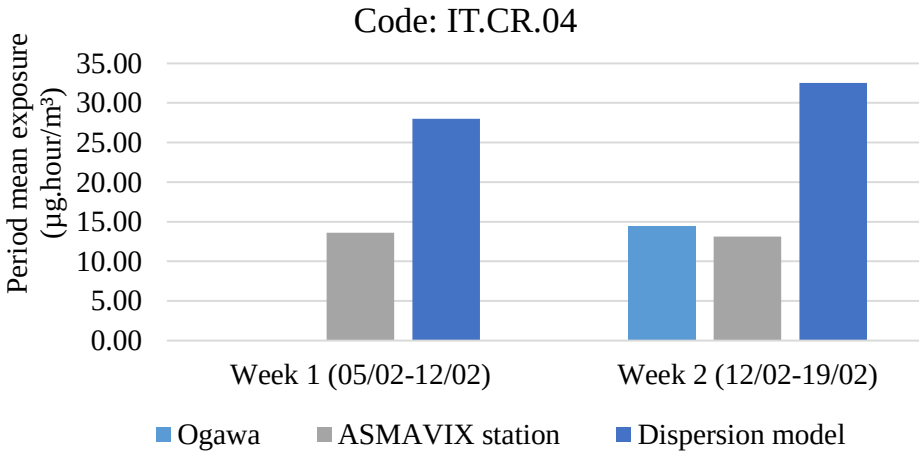
30.00
20.00
10.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.04
Period mean exposure (µg.hour/m³)
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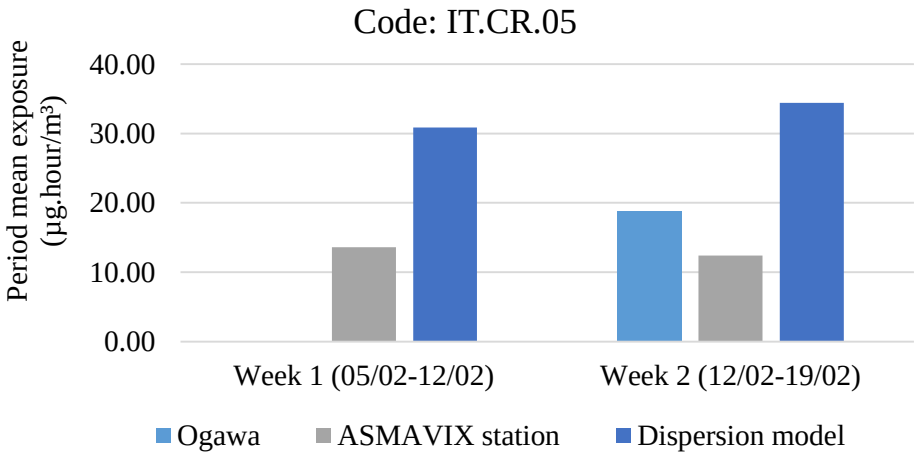
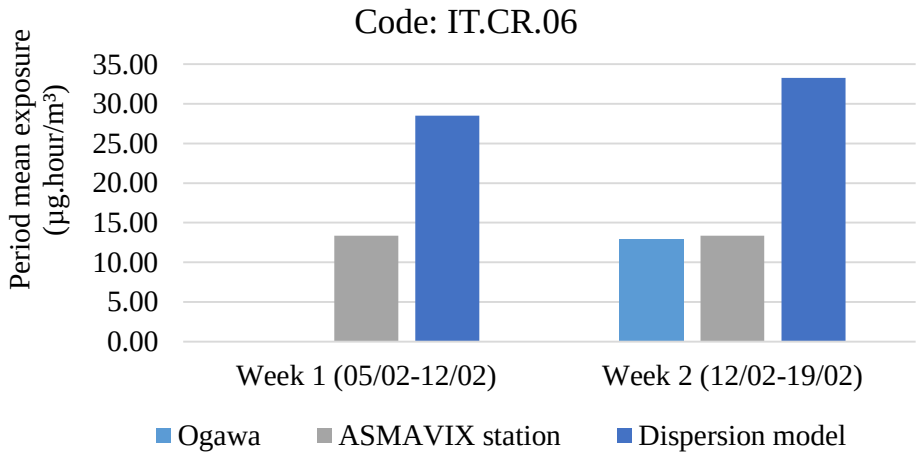
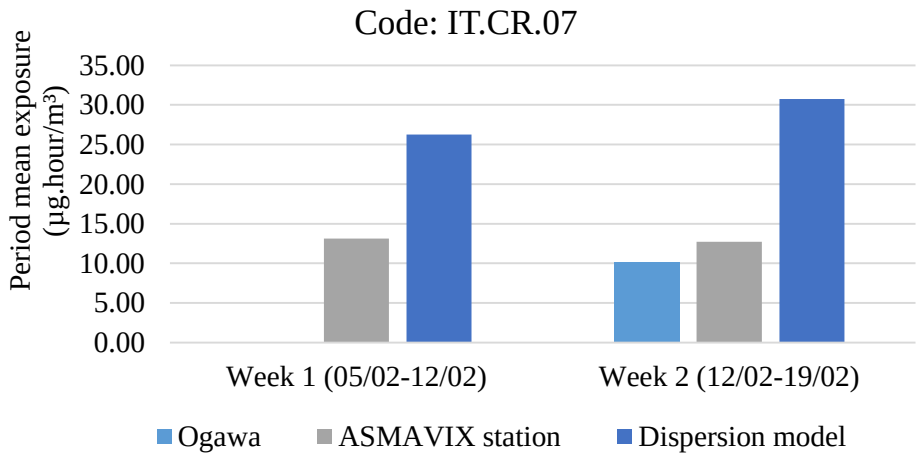
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.05
Period mean exposure (µg.hour/m³)
40.00
30.00
20.00
10.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.06
Period mean exposure (µg.hour/m³)
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.07
Period mean exposure (µg.hour/m³)
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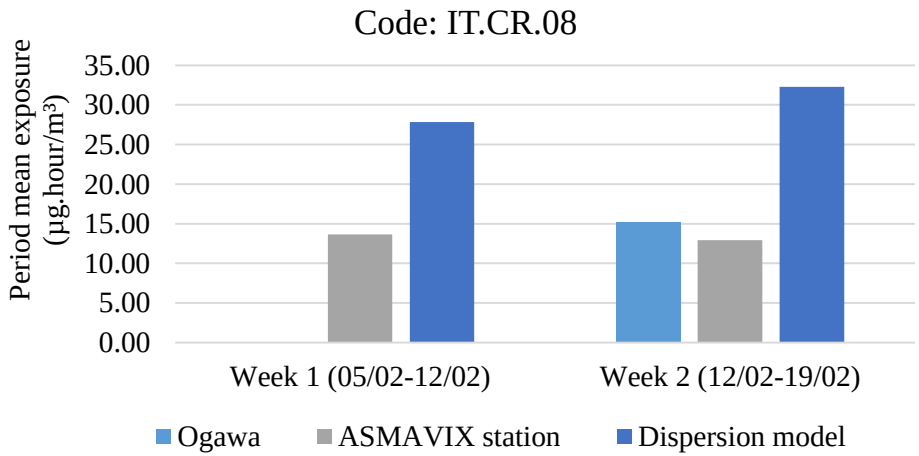
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model


Code: IT.CR.08
Period mean exposure (µg.hour/m³)
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30.00
25.00
20.00
15.00
10.00
5.00
0.00
Week 1 (05/02-12/02)
Week 2 (12/02-19/02)
Ogawa
ASMAVIX station
Dispersion model

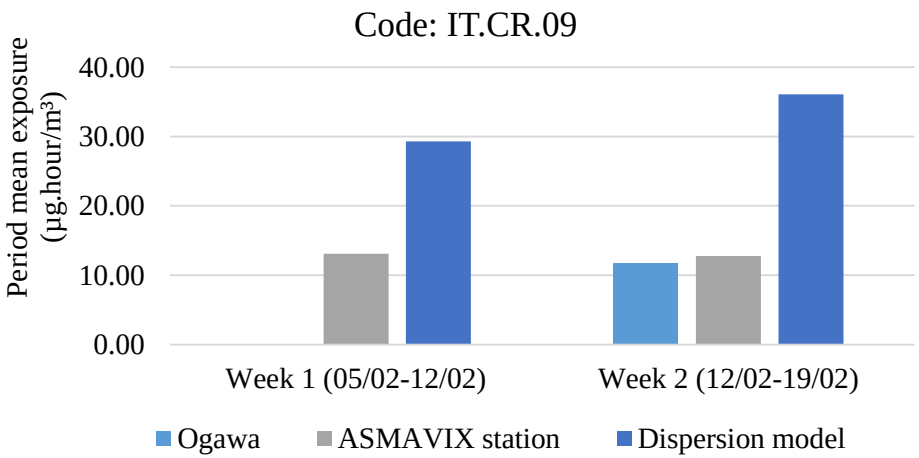

Figure 18. Children hour-mean exposure during the sampling period

Table 20 Week exposure between children in campaign 1

(µg.week/m³)	PM_{10}	$PM_{2.5}$	SO_2	NO_2	NOx
AN.CR.03					
w1	4653.89	2980.37	129.08	2075.58	2672.33
w2	4232.74	2511.84	172.55	1323.10	2239.76
w3	6004.17	3436.88	174.50	2696.57	3451.72
AN.CR.05					
w1	8691.80	4617.83	161.79	3641.48	4473.89
w2	6344.41	3421.65	95.23	1632.76	2936.50
w3	10407.97	5630.45	174.30	4483.88	5590.23
AN.CR.06					
w1	4619.12	2609.19	188.22	1927.88	2444.60
w2	4308.66	2393.27	92.81	1500.49	1941.53
w3	6581.67	3688.58	149.14	2521.46	3232.31
AN.CR.01					
w1	4629.18	2849.07	117.55	1777.86	2302.83
w2	4140.79	2213.39	99.05	1113.76	1950.70
w3	7225.14	4193.15	133.26	2525.03	3251.94
AN.CR.02					
w1	4214.57	2650.18	120.10	1705.29	2210.67
w2	4103.17	2385.34	128.97	1491.08	1920.52
w3	6528.37	3792.05	125.52	2417.13	3113.16
AN.CR.04					
w1	5245.42	3017.78	147.37	1806.88	2297.20
w2	4712.81	2577.93	89.25	1395.08	1810.20
w3	7781.59	4493.26	145.23	2410.70	3118.60

Table 21 Week exposure between children in campaign 2

(µg.week/m³)	PM_{10}	$PM_{2.5}$	SO_2	NO_2	NOx
MR.CR.01					
w1	7708.07	4398.24	77.54	1799.78	2830.48
w2	7221.05	3943.48	77.36	2008.27	2843.69
w3	7377.82	4249.07	485.60	1964.85	3227.62
MR.CR.05					
w1	8197.72	3909.44	129.22	2155.87	3332.44
w2	8728.26	5016.11	161.49	2130.84	3121.44
w3	10028.23	6378.89	526.76	2460.16	4064.20
MR.CR.06					
w1	8227.35	4247.55	128.60	2112.41	3459.01
w2	6475.92	3187.36	223.84	2147.69	3204.41
w3	8890.94	5601.93	458.42	2217.82	3694.62
MR.CR.03					
w1	11161.36	5648.33	224.59	2519.71	4068.73
w2	10035.02	5444.23	147.17	2744.82	3996.95
w3	12049.34	6920.24	426.05	2898.90	4774.89
MR.CR.02					
w1	10630.81	5436.44	82.37	2201.27	3416.94
w2	7130.96	3576.84	77.99	1669.42	2415.69
w3	7438.33	4028.31	234.85	1698.12	2756.60
MR.CR.04					
w1	11039.20	6122.22	95.89	2349.03	3901.15
w2	10462.00	6495.10	92.87	2380.80	3683.56
w3	12149.28	7522.27	308.97	2562.51	4287.66

Table 22 Week exposure between children in campaign 1

(µg.week/m³)	PM_{10}	$PM_{2.5}$	SO_2	NO_2	NOx
IT.CR.02					
w1	12467.77	6621.01	293.94	3367.20	5890.63
w2	14692.65	7782.77	249.39	4693.28	6512.98
w3	6568.11	3856.64	403.82	2301.96	3236.78
IT.CR.09					
w1	14169.38	7871.41	347.89	3535.72	6280.46
w2	19718.82	11480.59	213.54	5237.45	7464.77
w3	9313.34	5701.55	433.84	2531.32	3615.20
IT.CR.08					
w1	14816.44	8386.59	356.27	3412.60	6013.34
w2	18493.36	11294.22	208.14	4592.70	6670.30
w3	9569.98	5925.34	315.10	2362.41	3396.19
IT.CR.04					
w1	14277.29	7876.53	358.42	3414.30	5974.05
w2	18219.08	10740.46	216.71	4667.78	6696.38
w3	9008.52	5360.52	315.41	2358.50	3379.08
IT.CR.05					
w1	15197.82	8024.22	361.26	3699.38	6418.35
w2	17587.40	9433.32	303.17	4939.53	6901.24
w3	9426.49	4966.75	318.63	2595.30	3640.35
IT.CR.07					
w1	14640.87	8759.51	202.03	3189.55	5655.76
w2	18844.36	11849.90	190.19	4418.62	6279.02
w3	10446.56	6775.09	214.56	2186.97	3176.52
IT.CR.03					
w1	13719.35	7347.90	205.79	3351.62	5868.39
w2	16794.38	8770.30	195.93	4883.46	6701.02
w3	8504.43	4611.76	213.37	2324.80	3235.18
IT.CR.01					
w1	15713.89	8675.60	188.08	3791.50	6632.93
w2	19804.25	10614.60	204.31	5664.84	7724.51
w3	9620.26	5317.82	150.14	2393.28	3397.91
IT.CR.06					
w1	14414.83	7755.96	292.18	3408.16	5858.98
w2	20064.15	11943.44	207.94	4865.72	6905.09
w3	10302.00	5737.49	264.33	2449.74	3490.48

10.6 Supplementary dose results

If considering the mean dose at every hour of the campaigns, the intake of 'Campaign 1' children would be 0.69 µg/kg to 1.58 µg/kg for PM_{10}, 0.41 µg/kg to 0.93 µg/kg for $PM_{2.5}$, 0.02 µg/kg to 0.04 µg/kg for SO_2, 0.81 µg/kg to 2.13 µg/kg for CO, 0.26 µg/kg to 0.65 µg/kg for NO_2 and 0.33 µg/kg to 0.82 for NOx µg/kg. More interesting to note is that the participant with more weight (54.8 kg) was not the one with the lowest dose for $PM_{2.5}$, being, in fact, the second-heaviest child that spent more time indoors. For pollutants PM_{10}, $PM_{2.5}$ and SO_2 the lightest participant (25.6 kg) had higher doses per body mass kilogram if compared to others. For CO, NO_2, and NOx, the second lightest had the higher dose count and spent 11.5 hours more indoors.

For 'Campaign 2', the mean intake period was 1.22 µg/kg to 2.34 µg/kg for PM_{10}, 0.68 µg/kg to 1.31 µg/kg for $PM_{2.5}$, 0.02 µg/kg to 0.09 µg/kg for SO_2, 1.31 µg/kg to 2.71 µg/kg for CO, 0.30 µg/kg to 0.64 µg/kg for NO_2 and 0.49 µg/kg to 1.05 for NOx µg/kg. Exposing participants to the same analysis aforementioned reveals that the heaviest and lightest children (64.4 kg and 26.8 kg, respectively) were the ones with upper and lower extreme dosages of PM_{10}, $PM_{2.5}$, NO_2 and NOx. For SO_2 and CO the second-heaviest participant with less time outdoors had lower doses. The subject with the highest dose of CO per body mass kilogram lived in the region of higher ground, considered a concentration hotspot by model results.

The mean intake period for 'Campaign 3' participants was 1.35 µg/kg to 4.41 µg/kg for PM_{10}, 0.74 µg/kg to 2.64 µg/kg for $PM_{2.5}$, 0.03 µg/kg to 0.12 µg/kg for SO_2, 1.51 µg/kg to 5.41 µg/kg for CO, 0.35 µg/kg to 1.06 µg/kg for NO_2 and 0.53 µg/kg to 1.63 for NOx µg/kg. For this particular campaign, and except for SO_2, the heaviest and lightest children were the ones with lowest and highest dose uptake per body mass, respectively. Similar to 'Campaign 2', the second heaviest children that spent more time indoors was the one with a lower dose of SO_2.

MICROENVIRONMENT CONTRIBUTION TO OVERALL DOSE – CAMPAIGN I

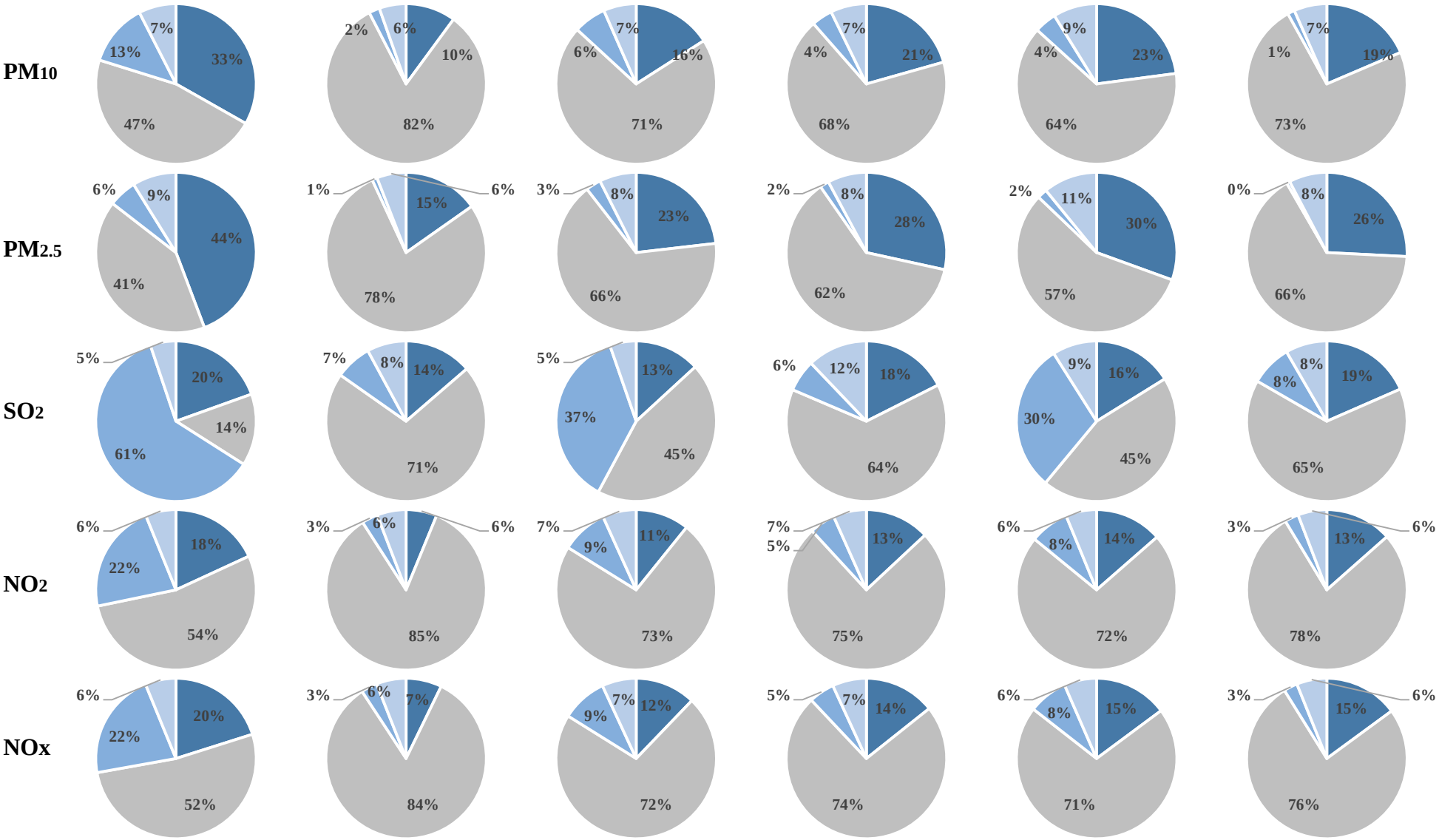

Figure 19. Microenvironment contribution to total dose in first campaign (rows = same pollutant, columns = same children)

MICROENVIRONMENT CONTRIBUTION TO OVERALL DOSE – CAMPAIGN II

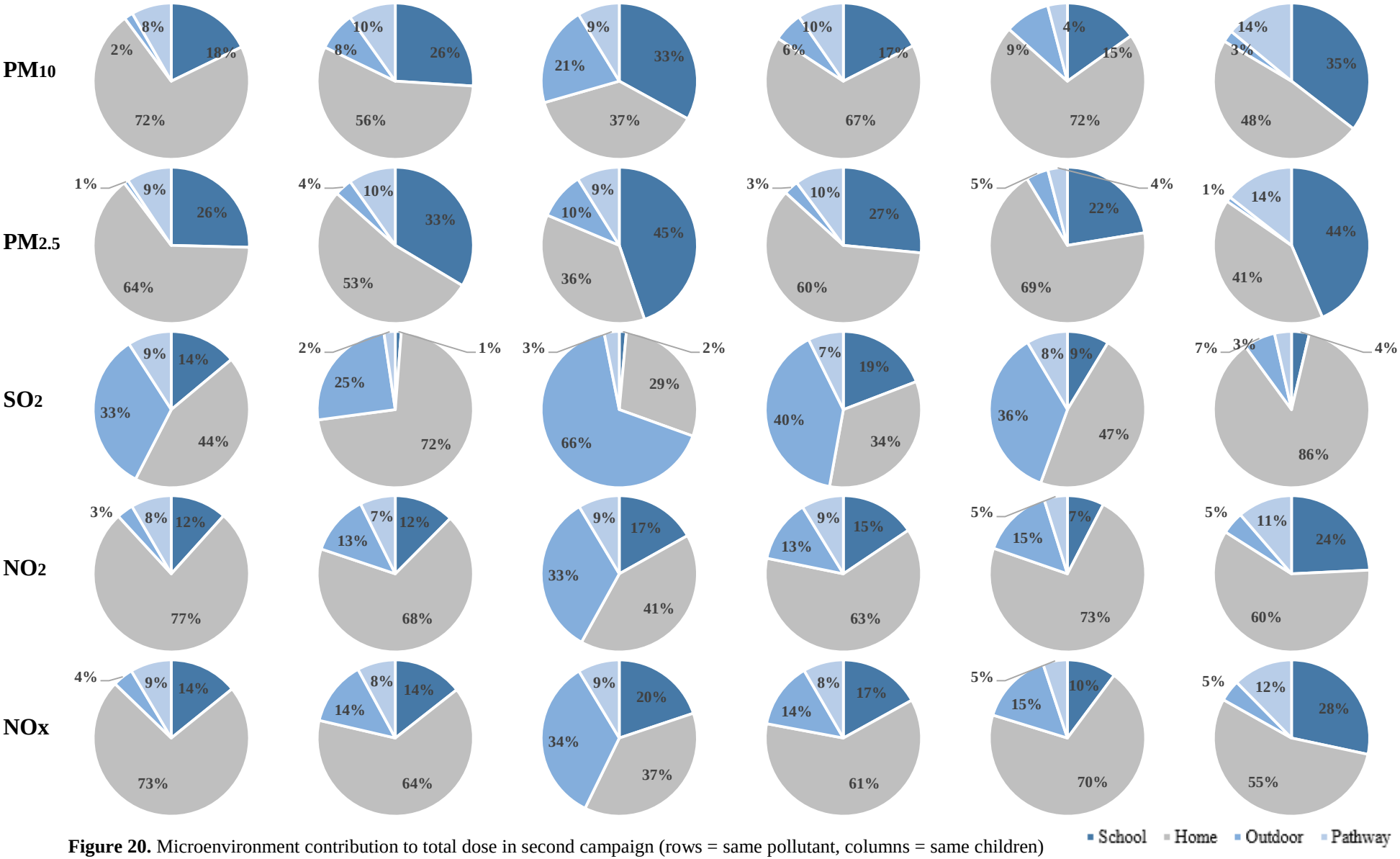

Figure 20. Microenvironment contribution to total dose in second campaign (rows = same pollutant, columns = same children)

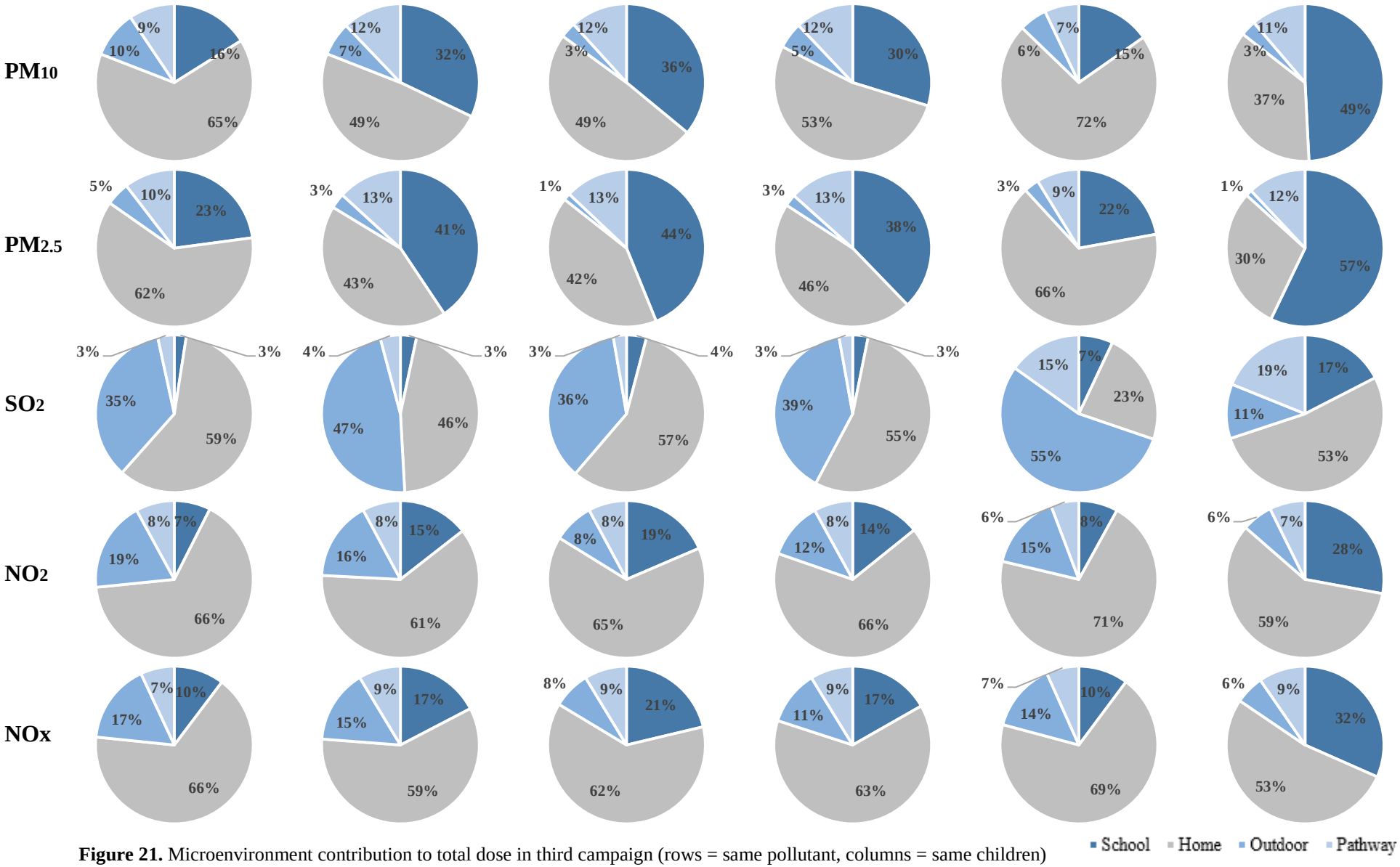

Figure 21. Microenvironment contribution to total dose in third campaign (rows = same pollutant, columns = same children)

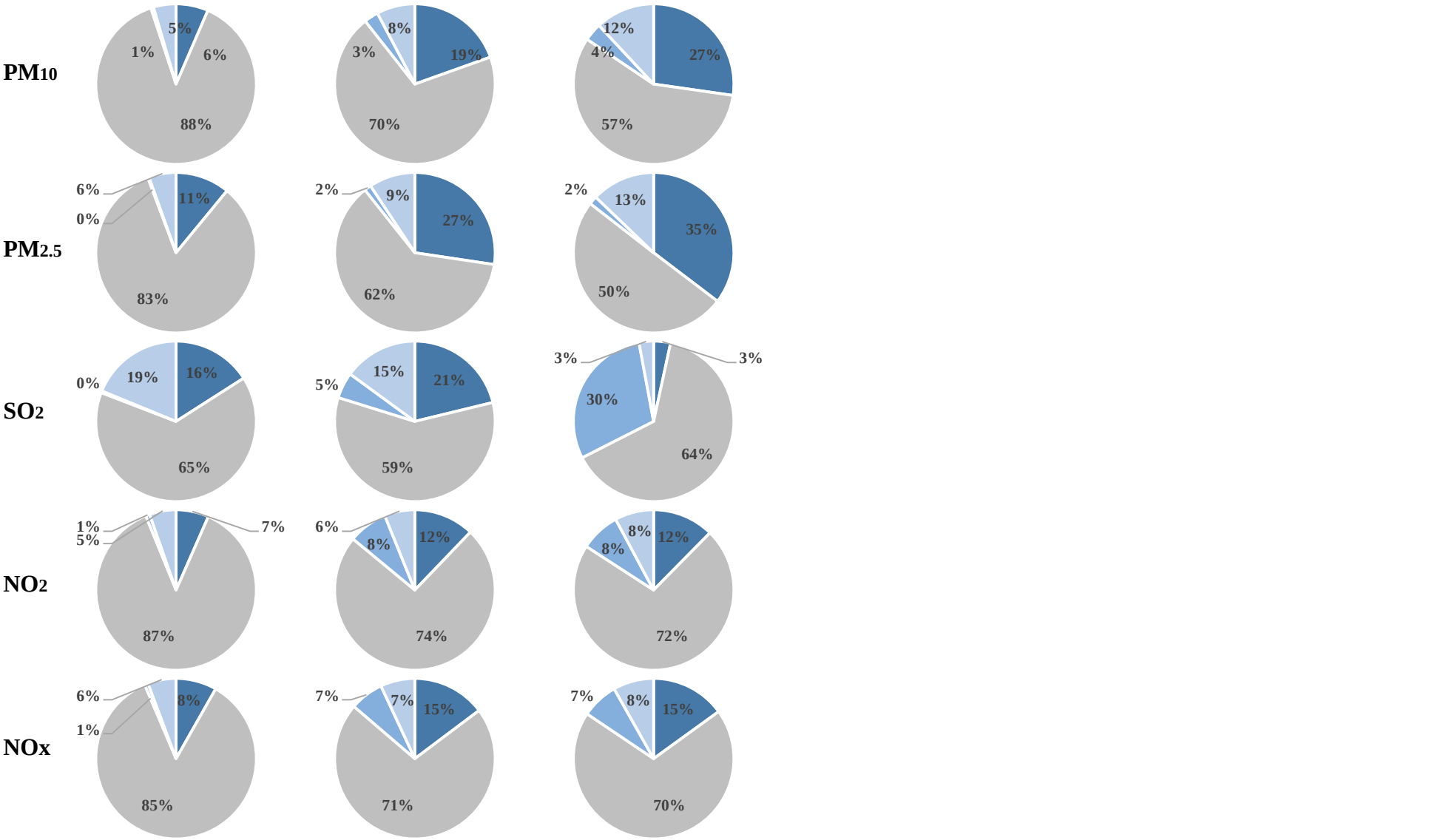

Figure 22. Microenvironment contribution to total dose in third campaign (rows = same pollutant, columns = same children)