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The new WHO air quality guidelines for PM_{2.5}: predicament for small/medium cities

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ABSTRACT

The Global Burden of Disease estimated that approximately 7.1 million deaths worldwide were related to air pollution in 2016. However, only a limited number of small- and middle-sized cities have air quality monitoring networks. To date, air quality in terms of particulate matter is still mainly focused on mass concentration, with limited compositional monitoring even in mega cities, despite evidence indicating differential toxicity of particulate matter. As this evidence is far from conclusive, we conducted PM_{2.5} bioaccessibility studies of potentially harmful elements (PHE) in a medium-sized city, Londrina-Brazil. The data was interpreted in terms of source apportionment, the health risk evaluation, and the bioaccessibility of inorganic contents in an artificial lysosomal fluid. The daily average concentration of PM_{2.5} was below the WHO guideline, however, the chemical health assessment indicated a considerable health risk. The in vitro evaluation showed different potential mobility when compared to previous studies in large-sized cities, those with 1 million inhabitants or more (Curitiba and Manaus). The new WHO guideline for PM_{2.5} mass concentration puts additional pressure on cities where air pollution monitoring is limited and/or neglected, because decision making is mainly revenue- and not socio-economical-driven. Given the further emerging evidence that PM chemical composition is as, or even more, important than mass concentration levels, the research reported in the paper could pave the way for the necessary inter- and intra-city collaborations that are needed to address this global health challenge.

Keywords: Fine particles; aerosol chemical composition; Bioaccessibility of heavy metals; Urban area.

41 1. INTRODUCTION

42 Air pollution has received attention in recent decades due to its adverse impact on eco-systems and human health.
43 The global burden of disease (GBD) study estimated that approximately 7.1 million deaths worldwide were related to air
44 pollution in 2016 (Landrigan et al., 2018; WHO, 2021), of which 543 000 (just shy of 8%) were that of children under five
45 years of age, but less than 1% for the ages between 5 and 15 years. It is evident that the more vulnerable groups are at high-
46 risk, even at low exposure levels (Chen et al., 2018; Klepac et al., 2018; Landrigan et al., 2018; WHO, 2018). In addition,
47 99% and 89% of deaths related to household and ambient air pollution, respectively, occurred in low-and middle-income
48 countries in 2015 (Landrigan et al., 2018). Although air quality has improved in high-income countries, the contrary can be
49 said for low- and middle-income countries, due to urbanisation and economic development.

50 Because of the growing evidence that burden of disease is strongly associated with ambient and household air
51 pollution exposure, the World Health Organization (WHO) launched its latest latest Air Quality Guidelines (AQG) in
52 September 2021, after a thorough evidence-based review. For PM_{2.5} the former update (dated to 2005) was based mainly on
53 two studies (Dockery et al., 1993; Pope et al., 2002), whereas the 2021 update was based on 25 studies (Chen & Hoek, 2020)
54 which concluded that PM_{2.5} exposure poses a moderate to strong health risk. The review concludes that the lowest level of
55 long-term exposure associated with mortality, was between 3 and 6.7 µg m⁻³, with a mean of 4.2 µg m⁻³ and a sensitivity
56 analysis value of 4.9 µg m⁻³, leading to the long-term AQG level of 5 µg m⁻³ annual mean concentration of PM_{2.5} (WHO,
57 2021). Moreover, mortality due to circulatory, non-malignant respiratory diseases and lung cancer showed even higher
58 relative risks than the all-cause of death, and there may be a higher relative risk in the lower levels of exposure (Chen &
59 Hoek, 2020). With the 2005 WHO update, it was estimated that a reduction of air pollutant levels would avoid 3.4 million
60 deaths (47.8%) (Evangelopoulos et al., 2020) where the new 2021 update (WHO, 2021) predicts a decrease of 5.6 million
61 (79.5%).

62 Even so, scientific reports highlight that only a limited number of cities have PM_{2.5} sources and components
63 consistently measured (Lelieveld et al. 2015). In addition, the authors point out that most information about air pollution is
64 related to megacities and/or capital cities due to their political relevance or industrial complexity. To estimate air quality in
65 rural locations, towns and smaller cities, atmospheric chemistry and transport models are used (Lelieveld et al., 2015) by
66 reason of a lack of monitoring data. Due to the complexity of PM_{2.5} emissions and the impact of diverse local and long-range
67 transport sources on the levels and chemistry of these airborne particles, reliable monitoring should be carried out frequently
68 and/or continuously across all areas (Martins et al., 2018).

69 However, the air quality guidelines (AQG) of the World Health Organization (WHO) is still based on the exposure-
70 response functions that rely on PM_{2.5} mass concentration, implicitly treating all fine particles as equally toxic without regard
71 of their sources and/or chemical composition (Lelieveld et al., 2015). The main exposure route for PM_{2.5} is through inhalation
72 by which potentially toxic, carcinogenic, and genotoxic compounds in the aerosol can become partially or totally soluble in
73 the lung fluid. This fraction, called the bioaccessible fraction, can then pass through the blood barrier and thus be taken up in
74 the blood stream, causing systemic health effects such as increasing the relative risk to a stroke (Nascimento et al., 2012;
75 Fisher et al., 2019). During the last decade researchers documented the importance of the chemical composition of PM_{2.5} and
76 identified compounds of specific health importance (Pope et al., 2009; Canova et al., 2012; Cao et al., 2012; Langrish et al.,
77 2012; Sorensen et al., 2012; Wu et al., 2012). Specifically, metals have been associated with adverse effects, such as
78 respiratory, neurological, reproductive and carcinogenic effects (Kurt-Karakus, 2012; Liu et al., 2015; Fang et al., 2018).
79 Some metals such as Fe, Cu and Mn have the capacity to generate reactive oxygen species (ROS), which can cause damage
80 to DNA and cellular functionality through the oxidation of proteins and lipids associated with oxidative stress (Angelé-

81 Martínez et al., 2014). To that end, the pulmonary bioaccessibility of these metals are of importance to establish exposure
82 risk.

83 In vitro studies using artificial biological fluids have the advantage of producing rapid and inexpensive results
84 compared to in vivo studies, in addition to the worldwide concern over animal cruelty and the difficulties associated with
85 human studies. Artificial pulmonary fluids seek to mimic the lung environment, presence of macrophages and pulmonary
86 surfactants. Artificial Lysosomal Fluid (ALF) currently presents the closest composition to the more acidic lung
87 environment, simulating phagocytosis conditions when inflammatory conditions prevail (Midander et al., 2007).

88 The new WHO guidelines put all countries on the spot, asking them to take action, not only in monitoring levels but
89 reducing the health risks associated with it. By means of an extensive characterization of fine particles in a medium sized
90 middle-income city, the present paper aims to call into question why and how to guide efforts to reduce air pollution
91 emissions to the new WHO guidelines levels, using Londrina, Brazil as a case study. To estimate the toxic and carcinogenic
92 potential of potentially harmful elements (PHEs) present in inhaled PM, we conducted lung bioaccessibility tests using ALF.
93 Although bioaccessibility data, using artificial lung fluids, are available in a limited number of papers, very few studies were
94 conducted in medium size cities (those with 1 million inhabitants or less) all over the world (Mbengue et al., 2015; Coufalík
95 et al., 2016; Hernández-Pellón et al., 2018; Expósito et al., 2021). To provide data on such a middle-sized city, we
96 investigated the long-term trend of PM_{2.5} in Londrina, Brazil. Londrina has a population of around 569,733 inhabitants
97 (IBGE, 2019), similar to some important cities worldwide, as shown in Table 1. This research presents the results of almost
98 2 years of daily PM_{2.5} monitoring. We report mass, black carbon and elemental concentrations (used for source
99 apportionment). Using an in vitro approach, the pulmonary bioaccessibility in ALF simulated lung fluid, were determined
100 and resident's health exposure risks estimated.

101
102 Table 1 - Worldwide cities population estimate in 2018.

Country	Region/City	Population	Ref.	Country	Region/City	Population	Ref.
USA	New Mexico/ Albuquerque	560.218	(USCB, 2019)	Italy	Genoa	580.097	(Istat, 2018)
USA	Maryland/ Baltimore	602.495	(USCB, 2019)	Spain	Málaga	571.026	(INEbase, 2018)
USA	Arizona/ Tucson	545.975	(USCB, 2019)	China	Mongolia/ Wuhai	532.900	(NBSPRC, 2019)
UK	Glasgow	615.070	(ONS-UK, 2017)	China	Tibet/ Lhasa	559.400	(NBSPRC, 2019)
Germany	Dortmund	585.813	(IT.NRW, 2013)	China	Yunnan/ Nujiang	534.000	(NBSPRC, 2019)

103

104 2. MATERIALS AND METHODS

105

106 2.1. SAMPLING SITE DESCRIPTION AND PM_{2.5} SAMPLING PROCEDURES

107 The study site is located at the Historical Museum of Londrina, Paraná state, Brazil (Figure S1 - coordinates
108 23°18'29"S 51°09'35.1"W, and at 608 m asl). The museum is situated in the central part of the city where traffic density
109 between 746 and 1,300 vehicles per hour are experienced during peak times. The Central Bus Station, which is responsible

110 for transporting approximately 45 million commuters per year, is in close vicinity. The 400 buses in the fleet are on average
111 five years old and run on S500 and S10 diesel fuel (500 and 10 ppm of Sulphur) (CMTU, 2015; IPPUL, 2016).

112 Londrina area is about 1,652 km² with a population of 569,733 inhabitants registered in 2018 (IBGE, 2019). It has
113 almost 400,000 vehicles of which 59% are light vehicles, 18% motorcycles, and 15% heavy duty vehicles (DENATRAN,
114 2019). The main Gross Domestic Product (GDP) of the metropolitan region of Londrina are mainly services (40%),
115 agriculture and livestock (23%), industry (19%), and administration/education (18%) (IBGE, 2017). Londrina has a
116 subtropical climate with temperature highs of 24°C (December to March) and lows of 16 °C (May to August).

117 Twenty four-hour PM_{2.5} continuous mass sampling was carried out from September 2014 to February 2015 and
118 from June 2015 to July 2016, using an inertial low volume Harvard impactor sampler (Marple et al., 1987) operated at 10 L
119 min⁻¹ and collecting particulates on 37 mm polycarbonate filters. The impactor was positioned at 2 m height and field blanks
120 were kept for both campaigns to reduce filter handling and transport errors.

121 PM_{2.5} mass concentration was determined using gravimetry by determining weight differences before and after
122 sampling, using a microbalance and an electrostatic charge eliminator. Black Carbon (BC) mass concentration was obtained
123 using a transmissometer SootScan OT21 (Magee Scientific) at an 880 nm wavelength (infrared), the meteorological data of
124 the city was obtained in the National Institute of Meteorology website database (INMET, 2016).

125

126 2.2. SOURCE APPORTIONMENT

127 In order to determine the sources of the pollutant over time and season, the elemental profile of each filter had to be
128 determined. The elemental concentrations were obtained by non-destructive X-ray Fluorescence Spectrometry, using a
129 Minipal-4 (PANalytical. Almelo. The Netherlands) equipped with a thermo-electrically cooled Silicon Drift Detector (SDD).
130 The optimum tube voltage and current were determined based on reference standards (Micromatter. Seattle. WA. USA) and
131 validated by the measurement of a certified reference material from NIST (2783 air particulate on filter media). The best
132 spectra and calibration curves were obtained using a He-atmosphere with 600 s of acquisition time under two conditions: a
133 tube voltage of 30 kV. and a current of 0.3 mA with the limit of detection in brackets in ng m⁻³ for Cr (0.39), Cu (0.32), Fe
134 (0.69), Mn (0.35), Pb (0.81), Ti (0.35), K (1.3) and Zn (0.5); a tube voltage of 9 kV and a current of 1.0 mA for Al (0.53), Si
135 (2.3), S (1.4), Ca (0.39), Cl (1.9), and Mg (9.0). The limit of detection (LOD) was calculated as three times the inverse of
136 instrumental sensitivity multiplied by the square root of the background noise signal from the measure of ten blank filters
137 divided by the measurement time.

138 In order to determine the PM_{2.5} sources in the region of interest, two methods were applied, Firstly, enrichment
139 factor analysis (EF), which enables the identification of anthropogenic elements, and secondly, principal component analysis
140 (PCA), a receptor modelling method.

141 The EF analysis was applied as described in previous studies (Godoi et al., 2006, Polezer et al., 2018) using
142 Equation 1 (Molnar et al., 1993; Hoornaert et al., 2004). Al is used as the crustal reference element, and average crustal
143 elemental concentrations were obtained from literature (Mason, 1966). An element with an EF value close to one (below 10)
144 is considered to be of natural origin and values higher than 10 is indicative of anthropogenic sources at play (Liu et al.,
145 2003).

146

$$147 \quad EF = \frac{\frac{X_{experimental}}{RE_{experimental}}}{\frac{X_{crustal}}{RE_{crustal}}} \quad \text{Equation 1}$$

148

149 Where $X_{\text{experimental}}$ is the concentration of the element under assessment on the filter, $RE_{\text{experimental}}$ is the concentration of the
150 chosen reference element (Al) on the filter, X_{crustal} is the concentration established for the element under assessment in
151 nature, and RE_{crustal} is the concentration established for the RE nature. As described by Polezer et al. (2018), the PCA was
152 performed with a Varimax rotation of the coordinates system, where the principal components were related to specific
153 sources due to the high loadings of specific variables. This was followed by absolute principal component analysis (APCA).
154 The combination of these two methods provides a quantitative chemical profile of sources instead of the known qualitative
155 factor loading matrix as in PCA, a method previously applied successfully in aerosol studies (Echalar et al., 1998; Maenhaut
156 and Cafmeuyer, 2002). The method was applied using the SPSS 16.0 software[®]. The variables data was composed of PM_{2.5}
157 mass, BC and elemental concentration.

158

159 2.3. HEALTH RISK EVALUATION

160 Ambient airborne particulates are complex chemical mixtures made up of primary and secondary particles, each of which
161 is prone to further chemical ageing due to atmospheric processes such as adsorption and absorption. The resulting product is
162 a polydisperse system with complex toxic and carcinogenic potential due to its diverse chemical and biochemical character.
163 To assess the impact on health, two health risk assessment procedures were performed. Firstly, the toxic and carcinogenic
164 risk was assessed using the elemental composition and the web-based Risk Assessment Information System (RAIS)
165 (<https://rais.ornl.gov>). Secondly, in-vitro studies were performed to determine the pulmonary bioaccessibility.

166

167 2.3.1 Toxic and carcinogenic risk assessment

168 The elemental profile of the PM_{2.5} samples was subjected to a chemical health risk assessment using the RAIS, which is
169 based on a method created by the United States Environmental Protection Agency (USEPA, 1989; USEPA, 2009) as
170 described by Godoi et al. (2013). The RAIS models the Carcinogenic Risk (CR) and non-carcinogenic risks (Hazardous
171 Quotient - HQ) of adverse health effects that may occur through ingestion with the pollutant based on the equations 2 and 3
172 presented below. The input parameters used to model the CR and HQ risks are: C - Concentration of contaminant in air
173 ($\mu\text{g}/\text{m}^3$); ET: Exposure Time (hours/day); EF: Exposure Frequency (days/year); ED: Exposure Duration (years); RfCi:
174 Chronic Inhalation Reference Concentration (mg/m^3); IUR: Chronic Inhalation Unit Risk ($1 (\mu\text{g}/\text{m}^3)^{-1}$); LT: Lifetime (years).
175 CR is the probability of an individual to develop cancer over a lifetime in relation to the population exposed to the
176 pollutants, where values in excess of 10^{-4} are considered a significant risk to develop cancer. An $\text{HQ} < 1$ indicates there is no
177 significant risk of non-carcinogenic effects occurring, with a probability that tends to increase as the value of HQ increases
178 (USEPA, 1989; Hu et al., 2011; USEPA, 2009).

179

$$180 \quad \text{HQ} = \frac{\left(\frac{C \times \text{ET} \times \text{EF} \times \text{ED}}{24 \times 365 \times 1000 \times \text{ED}} \right)}{\text{RFC}_i} \quad \text{Equation 2}$$

181

$$182 \quad \text{CR} = \text{IUR} \times \left(\frac{C \times \text{ET} \times \text{EF} \times \text{ED}}{24 \times 365 \times \text{LT}} \right) \quad \text{Equation 3}$$

183

184 For Cr (VI) exposure, 40% of the total Cr obtained was used (Swietlik et al., 2011). The other elemental concentrations
185 were used as total elemental concentration. Other parameters for the calculation were: exposure duration of 40 years,
186 exposure frequency of 350 days per year, exposure time of 24 hours per day (the average exposure of resident obtained in
187 the chemical risk users guide (RAIS, 2020), and a lifetime of 76 years (IBGE, 2018). These values were deemed

188 representative of describing the exposure duration and frequency of the population of the urban area of the city under
189 investigation.

190

191 2.3.2 Bioaccessibility analysis

192 The percentage bioaccessibility of each studied element (Cu, Pb, and Mn) in PM_{2.5} was obtained by the element mass
193 concentration solubilized in a simulated lung fluid, artificial lysosomal fluid (ALF) in relation to total mass concentration as
194 determined by XRF. To simulate the inhalation of air pollution process, PM_{2.5} collected on filters were subjected to an in
195 vitro test (Colombo et al., 2008), whereby each filter was incubated at 37 °C with agitation at 40 cycles per minute for 1 hour
196 in ALF with a solid:liquid ratio between 1/16,000 and 1/30,000 g mL⁻¹. There after the supernatant was analysed by graphite
197 furnace atomic absorption spectrometer (GFAAS) (model AA 6800. Shimadzu. Japan).

198 A method blank was obtained by treating a field blank filter to the same procedure as the PM_{2.5} filters. The instrumental
199 settings and chemical modifiers employed were the same as those used in previous work and can be found in Polezer et al.
200 (2020). The limits of detection obtained were 0.4, 2.9 and 0.3 µg L⁻¹; and the limits of quantification were 1.5, 9.8 and 1.2
201 µg L⁻¹ for Cu, Pb, and Mn, respectively. The accuracy and repeatability of the analytical methods were evaluated by the
202 analysis of the ALF previously spiked with known amounts of each element (Cu, Pb, and Mn) and the recovery tested. The
203 recovery of the spiked ALF solution for different levels of the calibration curve was 91% to 109% for Cu, 82% to 108% for
204 Pb and 84% to 104% to Mn. Likewise, the repeatability values of spiked samples were within the acceptable range, RSD
205 <10% (European Commission, 2002).

206

207 3. RESULTS AND DISCUSSION

208 3.1. PM_{2.5} MASS CONCENTRATION, BC AND ELEMENTAL CONTENT

209 The results obtained for PM_{2.5} 24-hour mass concentrations (µg m⁻³), BC concentration (µg m⁻³), and elemental
210 profiles (ng m⁻³) during the two sampling campaigns are reported in Table 2. The chemical elements are ordered from the
211 highest concentrations to the lowest. Three hundred and seven PM_{2.5} samples were collected of which 268 were analysed for
212 BC and 172 for elemental concentration. The sum of the average BC and total elemental concentrations constituted 37% of
213 the PM_{2.5} mass, corresponding to 16% and 21%, respectively.

214 The mean mass concentration of PM_{2.5} of 4.4 µg m⁻³ was below either the former (WHO, 2006) and the new (WHO,
215 2021) World Health Organization (WHO) annual guidelines level, respectively 10 µg m⁻³ and 5 µg m⁻³ (the most restrictive
216 current guideline). The 24-hour mean guideline was exceeded one day in the former WHO guideline (25 µg m⁻³), whereas 6
217 days exceeded the new value (15 µg m⁻³) within a year in 2015, that is more than the 99th percentile permitted exceedance of
218 3 days. The mean PM_{2.5} mass concentration found is also below 12.9 µg m⁻³ (11.0 – 16.2 µg m⁻³), the mean PM_{2.5} in Brazil
219 for the 1990 – 2016 period (Ritchie and Roser, 2019). Brazil is one of the most populated countries and it is among the most
220 important emerging economies (Brazil, Russia, India, China – BRICs) and classified as a middle-income country (MIC). It is
221 interesting to note that the mean PM_{2.5} mass concentration in Brazil is well below the average of 48.9 µg m⁻³ (45.0 – 55.5 µg
222 m⁻³) observed for MICs during the same period (Ritchie and Roser, 2019).

223 The mean PM_{2.5} mass concentrations reported here for Londrina were also lower than other medium-sized cities
224 around the world. Ribeirão Preto, São José dos Campos, Piracicaba, Guaratinguetá, Taubaté, middle-size cities located in the
225 São Paulo state of Brazil, presented annual averages from 10 to 15 µg m⁻³ (CETESB, 2019). In Denver (EUA), for example,
226 the values found were between 5.7 and 6.5 µg m⁻³ (Clements et al., 2014), while in Genoa (Italy), 22.3 µg m⁻³ was reported

227 by Ariola et al. (2006). In several medium-sized cities in Southern Spain (with populations ranging from 250 000 to 700 000
 228 inhabitants), PM_{2.5} varied from 18 to 37 µg m⁻³ (Amato et al., 2014).

229

230 Table 2 - Average and standard deviation of PM_{2.5} mass concentration (µg m⁻³), BC (µg m⁻³), and elemental concentration
 231 (ng m⁻³), enrichment factor and chemical health risks (Hazard Quotient (HQ) and Carcinogenic Risk (CR) of samples
 232 obtained during the two sampling campaigns.

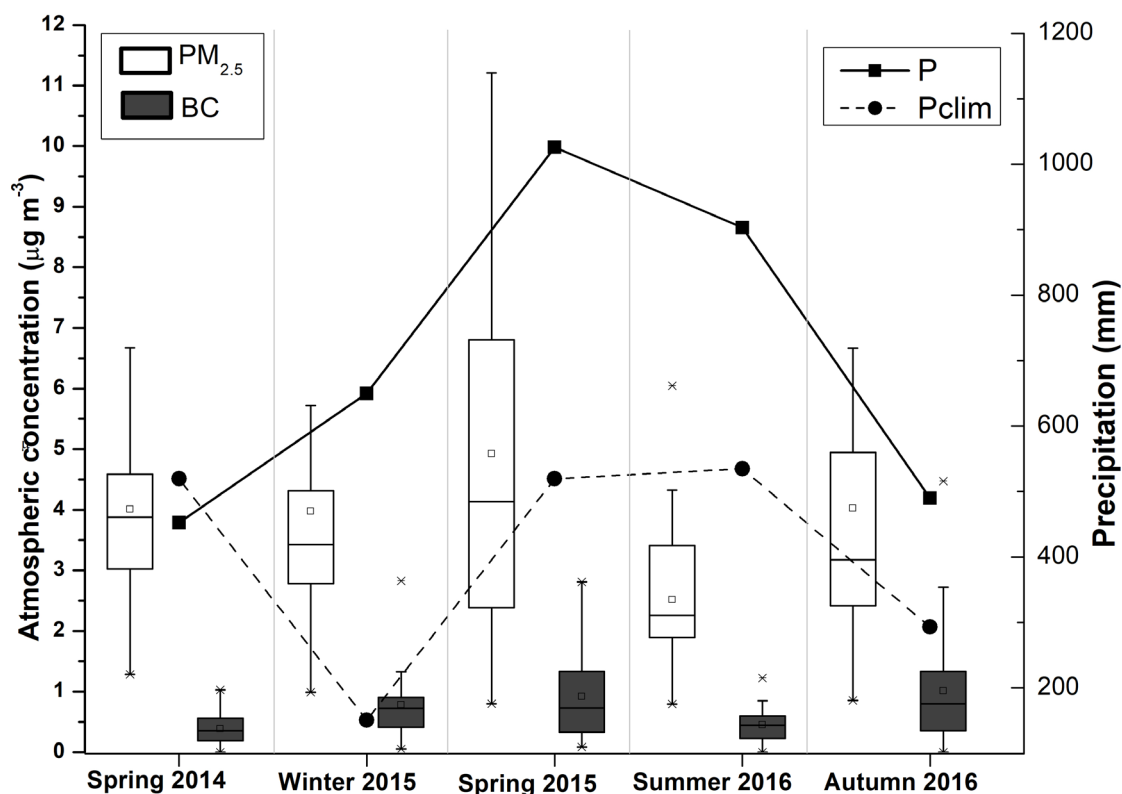
	Concentration			Enrichment factor	HQ	CR (10 ⁻⁵)
	Mean	S.D.	Median			
PM_{2.5}	4.4	3.8	3.5			
BC	0.7	0.7	0.5			
Mg	285	90	281	19		
S	227	157	188	920		
Si	151	98	119	1		
Fe	57	47	40	1		
Ca	56	19	54	2		
K	49	87	0.1	1		
Mn	26	11	23	40	0.50	
Al	25	28	13	0.2	0.005	
Cu	12	6.2	10	310		
Sr	7.0	2.3	7	33		
Co	4.9	1.7	4.6	319	0.24	2.3
Ti	4.1	4.5	2.7	1		
Pb	4.0	5.7	0.1	327		0.002
Cr	1.0	1.0	0.9	19	0.001	3.0
Zn	0.50	1.4	0.1	4		
Total risk					0.75	5.3

233 *Risk for Cr⁶⁺ was obtained assuming that it constitutes 40% of total Cr.

234

235 A previous study done in Londrina (Beal et al., 2017), measured PM_{2.5} mass and BC concentrations during winter
 236 and summer periods (one month). These were conducted at the Federal University of Technology -Paraná (UTFPR), which
 237 is a semi-urbanized residential region with agricultural fields in close vicinity, light and heavy-duty traffic and is situated
 238 about 4 km from our sampling site. Beal et al. (2017) report average PM_{2.5} and BC concentrations of 7.7 µg m⁻³ and 1.6 µg
 239 m⁻³ in September 2013, 4.4 µg m⁻³ and 0.9 µg m⁻³ in December 2013, and 10.3 µg m⁻³ and 1.8 µg m⁻³ in August 2014,
 240 respectively. For comparison purposes, our temporal data is also displayed in Figure S2, showing the monthly mean and
 241 variation for both BC and PM_{2.5} mass concentrations across the two campaigns. Although the PM_{2.5} mass concentrations
 242 (Beal et al., 2017) are mostly higher (41%) than the average value reported in our study, comparing on a month by month
 243 basis (even though different years) there seems to be a fair correlation for the September and December concentrations.

244 According to Ritchie and Roser (2019) there was a general decrease in PM_{2.5} mass concentration in Brazil since the
 245 1990s, however, from 2015 there seems to be an increase again (~10%). The data has been obtained from fixed monitoring
 246 stations (only 10 of the 27 states are monitored) of which none are close to the Parana State. In fact, the Brazilian
 247 Government only announced the launching of monitoring air pollution in the remaining states in June 2019. Even if it
 248 becomes a reality, when the data from these stations become available, it has to be said that it will not account for local hot
 249 spots and therefore the value of these local studies is obvious.



251 Figure 1. Boxplots of PM_{2.5} and BC mass concentrations, precipitation of the sampling period (P) and historic precipitation
 252 (Pclim) in Londrina among seasons of the sampling campaign between October 2014 and February 2016. Boxplots show the
 253 median, 25th and 75th percentile, and average (□).
 254

255 This tendency is not observed in this data, displaying a decrease on average compared to the Beal et al. (2017)
 256 study, albeit not directly comparable (Figure 1). One plausible explanation for this is the precipitation, the main natural
 257 process whereby airborne PM are removed from the atmosphere. The rainfall during the campaign was significantly higher
 258 than the historic rainfall data for the city, but it has to be noted that there is no direct correlation on a month-to-month basis,
 259 and one has to conclude that it cannot be the prime reason for the lower concentrations observed. The BC concentration in
 260 our study is also similar to background values (roof top measured) reported in Londrina (Krecl et al., 2018). Comparing the
 261 Beal et al. (2017) campaign with our study it is evident that location, and therefore different sources of pollution and
 262 meteorological conditions, seems to be the main reasons for the differences observed.

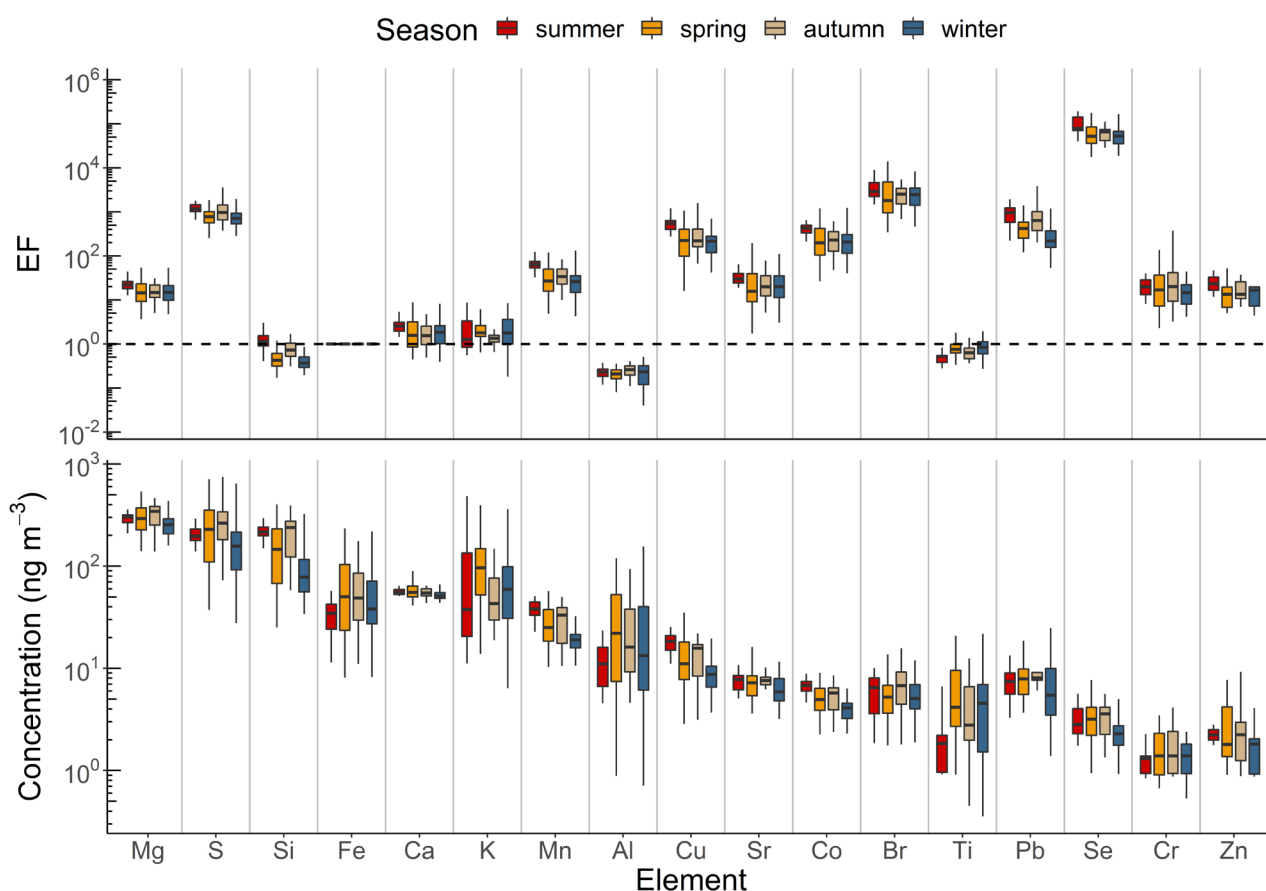
263 The elemental profiles and the corresponding enrichment factors (EFs) are displayed in Figure 2. It is seen that Mg,
 264 Ca, Sr, and Co do not vary significantly across the four seasons and crustal elements (Al, Fe, Si, Ca) seem to vary the most,
 265 generally speaking. The Beal et al. (2017) paper also report large variations in Al concentrations, but interestingly their
 266 concentrations were an order of magnitude higher in comparison with this study, pointing towards the different sources
 267 influencing the chemical character of the PM. In their case it may well be that the higher Al concentration is due to
 268 resuspension of dust due to the dryer weather.

269 Pb and Mn were similar to those found in Albuquerque, New Mexico (USA), and probably mostly associated with
 270 road dust (Kavouras et al., 2015). Beal et al. (2017), however, reported four times higher concentrations for Pb, both from
 271 the Londrina and Maringa (~100 km west to Londrina) sites. In Cuiaba (Brazil), an agricultural city with around 600,000
 272 inhabitants (Santanna et al., 2016), and in the harbour city of Genoa (Italy) much lower values were found for Mn, although

273 Pb in Genoa presented similar concentrations (Bove et al., 2014). Similar Al and Fe concentrations are reported in Denver,
 274 EUA (Clements et al., 2014) and is probably associated with industrial and vehicular (abrasion and fuel consumption)
 275 emissions. While in Cuiaba and Genoa, Fe and Al concentrations were higher than in this study (Bove et al., 2014; Santanna
 276 et al., 2016).

277 Londrina presented higher Cr levels on the other hand than observed in Albuquerque (Kavouras et al., 2015) and at
 278 the Londrina site of the Beal et al. (2017) study, whilst in Cuiaba Cr levels were similar (Santanna et al., 2016). The Zn
 279 levels were higher than that reported in Denver, and lower than Cuiaba and Genoa (Bove et al., 2014). The relatively high
 280 (above 10) EFs for the PHEs (here referring to those with toxic/carcinogenic and/or reactive oxidative generating
 281 properties), Cu, Cr, Pb, Zn, and Co, not only informs on sources but predicts that significant health risks upon inhalation is
 282 plausible.

283



284 Figure 2 – Comparison of mean enrichment factors (top), and element concentrations (bottom) among different seasons.
 285 Boxplots show the median, 25th and 75th percentile. EF = 1 line is also shown as reference.

286

287 3.2. SOURCE APPORTIONMENT

288 The enrichment factor (EF) and absolute principal component analysis (APCA) of PM_{2.5} and its contents were performed
 289 for Londrina in order to obtain the source apportionment. The EF results displayed in Table 2 and illustrated temporally in
 290 Figure 2 indicate that the elements Al, Si, Fe, Ca, K, Zn, and Ti (EF close to 1) could be ascribed to resuspension of soil as
 291 they are crustal related. The remaining chemical elements were enriched in relation to the crustal reference (i.e. EF > 10)
 292 (Liu et al., 2003), indicating that they probably were generated by anthropogenic sources. Pb and S had the highest EFs
 293 pointing to PM being highly enriched with these elements.

294 After the EF analysis, the data group consisting of PM_{2.5} mass, BC and the elemental concentrations were subjected
295 to APCA analysis, in which the variables and samples containing more than 30% of missing data (below the quantification
296 limits) were excluded. Then the variables selected to compose the data group for APCA analysis were PM_{2.5}, BC, Mg, Al,
297 Si, Cu, Pb, Fe, Ti, Mn, and S concentrations.

298 Table S1 contains the Pearson correlation of the data set selected for APCA analysis. As expected, the typical
299 crustal correlations that both Al and Si displayed with Fe and Ti, were observed and is probably representative of the
300 resuspended soil or road dust contribution. It is known that road dust could make up a substantial portion of airborne
301 particulate matter and this also seems to corroborate with the correlation between PM_{2.5} mass concentration and these four
302 crustal elements. The slightly higher correlation between Fe and PM_{2.5} mass could be the contribution from vehicle wear and
303 tear (Srimuruganandam and Nagendra, 2012). PM_{2.5} mass and BC were correlated to Al and Fe, indicating the contribution
304 of fuel combustion and soil (Viana et al., 2008). For the S correlation one would not see the realistic correlation unless you
305 take away the soluble sulphates, which will be correlated with Na, NH₄⁺ and potentially K.

306 Applying APCA to the chosen variables, 12 principal components were initially identified, which were reduced to
307 four after Varimax rotation, contributing 86% of the total cumulated variation (%CPC). The rotated principal components
308 with the loadings of each variable are shown in Table S2. Loadings below 0.3 were ignored. The four principal components
309 were assigned to four different PM_{2.5} sources, based on the loadings of variables (BC, Mg, Al, Si, Cu, Pb, Fe, Ti, Mn, and S
310 concentrations) and in concordance with published literature (Song et al., 2006).

311 The APCA was followed by a linear regression analysis between PM_{2.5} mass concentration and the factor scores
312 matrix of the four selected principal components. This enabled the prediction of the relative PM_{2.5} mass concentration
313 contribution of each sample for each principal component. The average mass concentration of PM_{2.5} (%AVG PM_{2.5} mass)
314 attributed to each principal component could then be determined, allowing source apportionment. Both the %AVG PM_{2.5}
315 mass and absolute average concentrations for each principal component are presented in Table S2.

316 The first principal component (PC) presented the highest contribution (36%) to the data set variance, as well as the
317 %AVG PM_{2.5} mass. This component is associated with transport emissions, namely diesel vehicle, high loading of BC and
318 low loading of S associated with diesel combustion (Brito et al., 2010, Herich et al., 2011; Andrade et al., 2012; Sharma et
319 al., 2021), and resuspended road dust (high loadings of Al, Fe, Ti, and Si, corroborating with the low EF values indicative of
320 natural sources such as sediments) (Viana et al., 2008; Srimuruganandam and Nagendra, 2012), as well as a high loading of
321 Mg which had a high EF value, indicative of an anthropogenic source (Song et al., 2006). Brake lining dusts are associated
322 with markers Mg, Fe, and to a lesser extent Al, Cr, Mn, Ca, and Na, indicating a possible source reason for Mg's presence in
323 this PC (Srimuruganandam and Nagendra, 2012). The percentage AVG PM_{2.5} mass associated with this PC suggests that
324 65% of the PM_{2.5} mass can be apportioned to diesel vehicles and/or resuspended road dust.

325 The second component corresponding to a strong soil signature due to the high Al, Si, Fe, and Ti loadings
326 (Srimuruganandam and Nagendra, 2012; Chow et al., 2015; Sharma et al., 2021), represent 5.3% of the PM_{2.5} mass
327 concentration. The third component showed high Cu and Mn loadings and could be attributed to industrial sources such as
328 metallurgical activities (Yang et al., 2013; Qi et al., 2016; Sharma et al., 2021) which totalled 1.5% of PM_{2.5} mass. The
329 fourth component had a high loading of Pb and S, an industrial source, possibly smelting of metals, contributing to 1.2% of
330 PM_{2.5}. Londrina has several recycling industries, for example battery recycling that could contribute to this component.
331 Unfortunately, no specific source could be assigned to the remaining 24% of PM_{2.5} mass concentration, using APCA
332 analysis, suggesting that other sources different from that identified in the PC contributes either to PM_{2.5} budget in Londrina.

333 The limited number of source apportionment studies of PM_{2.5} in medium/small-sized cities worldwide makes
334 comparison difficult (some results are summarized in the Table 3). Comparing the data from the studies listed in Table 3, it
335 is noted that the PM_{2.5} levels varied greatly (2 to 37 µg m⁻³). This was mirrored by an equally wide variation in types of
336 sources allocated, as well as the percentage contribution to the PM_{2.5} budget. The major contributors were from road
337 transport sources, such as emissions from vehicle exhausts, wear and tear, and road dust resuspension (4 – 68%) and crustal
338 or soil sources (4 to 28%). The industrial sources presented in the studies, including our study, are of such diverse nature that
339 a general comparison is not possible, suffice to say that it varied from as low as 1.5% to as high as 36%. Several other
340 sources are reported, such as biomass and oil burning, maritime and sea salt emissions, and undetermined sources. This
341 variance in source apportionment and contribution has also been reported for larger urban conurbations (Putaud et al., 2004,
342 2010; Hand et al., 2012; Snider et al., 2016; Hama et al., 2021), further emphasising the importance of monitoring at local
343 level.

344

345

346 Table 3 – PM_{2.5} mass concentration (µg m⁻³) and estimated percentage of sources in brackets when available, for medium sized cities with source apportionment studies.

City	Pop. (1,000)	PM _{2.5} (µg m ⁻³)	Sources (% of PM _{2.5})								Reference
Albuquerque (USA)	800		Automobile (4-12)			Road dust (5-15)	Biomass burning (32-43)	Sulphate (9-48)	Nitrate (7-34)		Kavouras et al., 2015
Cuiaba (Brazil)	600	2-20	Urban	Soil dust	Fire	Biogenic					Santanna et al., 2016
Spain	250-700	18-37	Vehicle /traffic (10-63)	Mineral (4-12)	Metallurgy (0-19)	Road dust (6-31)	Sulphate (4-34)	Nitrate (0-11)	Sea salt (0-31)	Oil (0-20)	Amato et al., 2014
Genoa (Italy)	580	12.6-14	Road transport (35-38)		Energy/industry (33-36)	Others (14-18)	Maritime (14-16)				Bove et al., 2014
Denver (USA)	650	5.7-6.5	Vehicle (6-15)	Crustal/road dust (13-28)		Road salt (7-8)	Sulphur (46-62)				Clements et al., 2014
São Jose do Rio Preto (Brazil)	450	10.88		Crustal	Industrial combustion	Biomass burning					Franzin et al., 2020
Londrina (Brazil)	570	4.4	Diesel Vehicle /Road Dust (68)	Soil (5.3)	Industrial (1.5)	Battery recycling (1.2)					Present study

347 3.3. HEALTH RISK EVALUATION

348

349 3.3.1. Chemical assessment

350 The results obtained from the elemental health risk assessment (RAIS) are presented in Table 2. The sum of the
351 non-carcinogenic risks (HQ) observed for Mn, Co, Al and Cr (VI) was 0.75, with Mn and Co contributing to 50 % and 24 %
352 of the risk, respectively. Although below unity, this is still important to consider. The total carcinogenic risk ($CR = 5 \times 10^{-5}$,
353 meaning a 5 in 100,000 chance to develop cancer during lifetime) observed, indicates a moderate risk according to the US
354 EPA. The maximum daily values found for HQ was 1.53 while for CR was 9.9×10^{-5} (almost 1 in 10,000 chance to develop
355 cancer during lifetime), and 21.7% of the days investigated for non-carcinogenic risk were above the unit risk of health
356 effects.

357 Moreira et al. (2018) present personal monitoring data, sampling fine particles and their trace elements during
358 typical workdays (about 9 hours of sample collection during travel to and from work) to assess personal exposure of workers
359 in Londrina. The hazard quotient (HQ) calculated, considering the reference dose, ranged from 0.15×10^{-03} to 1.38 for all
360 volunteers, indicating potential non-carcinogenic effects. Moreira et al. (2018) found $PM_{2.5}$ average level of $12.3 \mu g m^{-3}$
361 (maximums of $20 \mu g m^{-3}$ and $100 \mu g m^{-3}$ during non-peak and peak-time hours respectively) during a working day trial
362 including one bus ride commute. In our study, 24-hour samples were collected, resulting in an obvious lowering of the
363 average due to lower night-time traffic density.

364 So, we can infer that although the 24-hour data indicates a non-carcinogenic risk below the dose reference of
365 observed outcomes, the dose exposure during work/day activities and high pollution days may pose a significant risk. In
366 addition, the great variability in the concentration of $PM_{2.5}$ composition throughout the exposure time indicates that a
367 responsible and correct health risk evaluation should be performed with epidemiological studies that consider both
368 concentrations and responses in health of the population.

369

370 3.3.2. Bioaccessibility

371 The bioaccessibility of Cu, Mn, and Pb in ALF was calculated as the ratio of the ALF-soluble concentration and the
372 total sampled concentration of the elements in $PM_{2.5}$, expressed as a percentage. Boxplots, to provide insight on the
373 distribution of the spread of data (the average is indicated by the square symbol), are presented in Figure S3.

374 Cu presented the highest bioaccessibility average (59%) and variability in the results (38 – 97%). A similar study
375 developed in two large Brazilian capitals (about 2 million inhabitants) obtained averages of 56% in Curitiba associated with
376 traffic source, and 31% in Manaus associated with Thermal Power Plants (TPP) sources (Polezer et al., 2019). Wiseman and
377 Zereini (2014) reported Cu bioaccessibility after 24-hour ALF-incubation of 80% during a study performed in Frankfurt
378 (730.000 inhabitants in the city and 2.3 million in the urban region). They indicated that the main source of Cu was vehicle
379 traffic, probably originating from brake lining attrition and rubber tire degradation (Midander et al., 2007; Sysalová et al.,
380 2012; Wiseman and Zereini, 2014). The lower bioaccessibility average of Cu in Londrina could indicate that the primary Cu
381 source in Londrina is obviously different than that of Frankfurt. This finding was confirmed by the APCA, where we found a
382 96% correlation with industrial sources and no correlation with vehicular emissions, although Cu bioaccessibility in Londrina
383 was much more similar to Curitiba than Manaus. These results give rise to the hypothesis that source apportionment at local
384 level is crucial to build air pollution inventories that could inform decision making and result in responsible and sustainable
385 health interventions. Besides that, deleterious effects of Cu on human health are generally associated with the rare Wilson's
386 disease, a hereditary disorder of the homeostasis regulation process of Cu leading to a high concentrations of Cu in body

387 tissues (WHO, 1998). It has been recently observed that anthropogenic Cu has the most potential of all of the transition
388 metals to induce the formation of reactive oxygen species (ROS), generating oxidative stress in the body (Becker et al.,
389 2005; Godoi et al., 2016, Charrier & Anastasio, 2015). Differential leaching is also observed in this study, where even
390 though the Cu had a lower concentration than either Mn or Fe (both with concentrations two and five times higher), it had a
391 much higher bioaccessibility than Mn (the latter three time lower). Indicating yet again the importance of Cu content and
392 hazard health risk exposure.

393 The lowest average bioaccessibility in Londrina was observed for Mn (17%). Similar values were obtained in the
394 Curitiba and Manaus study with an average of 15% for Mn bioaccessibility with sources related to limestone/ceramic/cement
395 kilns and TPP respectively (Polezer et al., 2019), while the study conducted in Frankfurt observed 52% of bioaccessibility
396 for Mn (Wiseman and Zereini, 2014). It seems that the Mn traffic related emissions in Frankfurt had a higher soluble fraction
397 in relation to the Mn from industrial processes in Londrina, Curitiba and Manaus. Mn is an essential nutrient with the level
398 of its absorption controlled by the body homeostasis regulation system (firstly by metabolised in the liver and potentially
399 excreted before entering the circulation system) (Mehvar, 2018). For example, generally, up to 95% of ingested Mn is
400 retained in the liver, and 5% is absorbed into the circulatory system (WHO, 1999). However, the respiratory exposure route
401 can deliver this element to the circulatory/systemic system before it passes through metabolisms and excretion, enabling a
402 higher amount of Mn that could reach for instance the brain. Consequently, long-term respiratory exposure to high levels of
403 Mn has been associated with a syndrome similar to Parkinson's disease, with progressive neurodegenerative damage (WHO,
404 1999; Chen et al., 2015). Crossgrove and Zheng (2004) reported that the neurotoxicity of Mn may be associated with its
405 interaction with iron (Fe) homeostasis, leading to high Fe deposition in the brain, which generates cellular oxidative stress
406 and neural damage. Then besides the low bioaccessibility of Mn found in Londrina samples, the concentration of Mn (second
407 highest between transition metals) and its possible interaction with Fe (highest concentration between transition metals)
408 could produce health risks to the population upon exposure.

409 Pb is a toxic element and it has the ability to accumulate in the hard tissues (e.g., bones and teeth), with a half-life of
410 about 20 years, and it can cause severe and sometimes irreversible damage in the nervous system from fetuses to adults
411 (ATSDR, 2019). In the present study the Pb bioaccessibility average was 42%, compared to an average of 57% in Curitiba
412 (traffic source), 71% in Manaus (associated with the TPP's), and 84% in the Frankfurt study (related to traffic sources)
413 (Wiseman and Zereini, 2014). A similar study developed in Nanjing (8 million inhabitants) indicated that the bioaccessibility
414 of Pb is between 66% and 78%, when the metallurgic smelters are in operation together with coal combustion power plants;
415 and 61% when only coal combustion power plants are in operation, showing that the emissions of metallurgical operations
416 have a higher Pb bioaccessibility (Li et al., 2016).

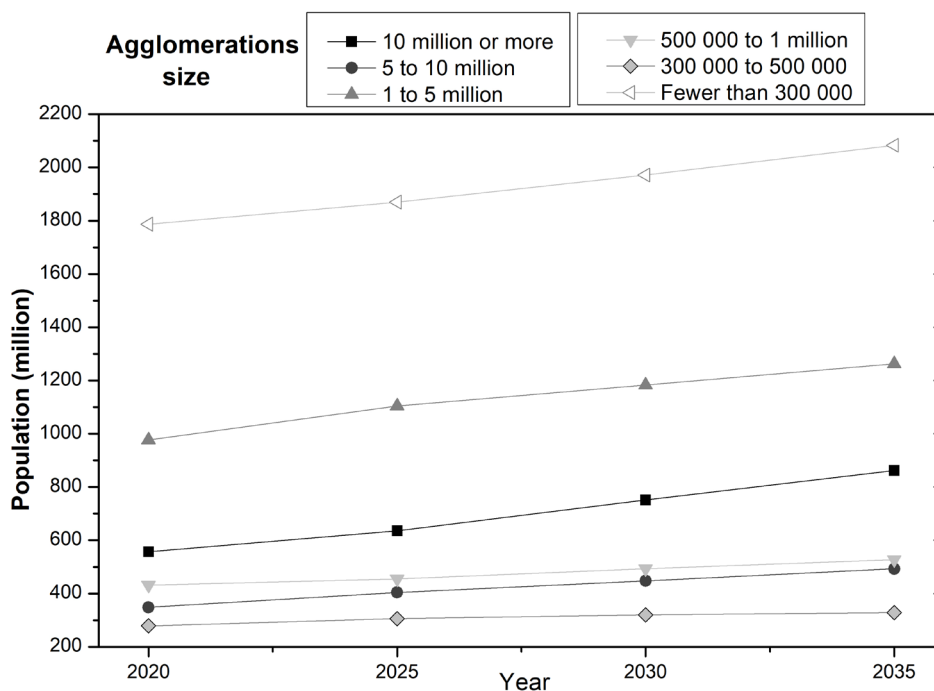
417 These data suggest that population health in Londrina is at risk to be adversely affected by PM_{2.5} inhalation, due to
418 high elemental concentrations, as well as bioaccessible fractions of PHEs (Cu, Pb, Mn). The data further confirms the
419 hypothesis that without local monitoring and analysis, an informed risk assessment in terms of population health cannot be
420 made.

421 422 3.4. WORLD URBAN DEVELOPMENT AND AIR POLLUTION IN PERSPECTIVE

423 Sustainable and responsible urban development is co-dependent on air quality. At least two goals of the 2030
424 Agenda for Sustainable Development recognize the importance: SDG3 - Ensure healthy lives and promote wellbeing for all
425 at all ages, and SDG11 - Make cities and human settlements inclusive, safe, resilient, and sustainable (UN, 2020). Clearly,
426 air pollutant inventories, specifically of PM_{2.5} (including its composition and levels), in small- and medium-sized cities of

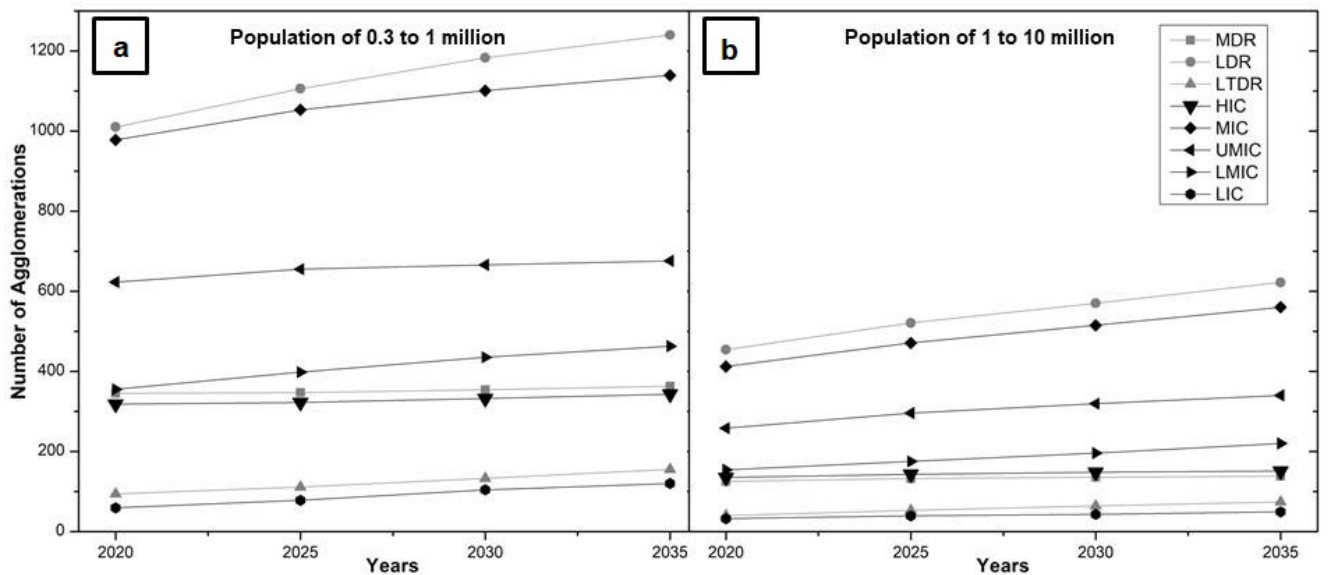
427 middle/low-income countries, are greatly beneficial as a tool to formulate policies to improve the well-being and quality of
428 life for those most at risk (Landrigan et al., 2018).

429 According to the report by the World Urbanization Prospects of the United Nations (UN, 2018) about 57%, 2.4
430 billion people, of the urban world population live in a city with less than 1 million inhabitants (Figure 3). Each
431 agglomeration (city, metropolitan areas, conurbations, etc.) in the world was ranked by its population size (the number of
432 inhabitants) and the number of people living in each category was summed to give the total number of populations by
433 agglomeration size. For instance, in the most populated countries in the world, China, India, and USA, this percentage is
434 52.0%, 54.1%, and 43.5%, respectively (UN, 2018). The largest growing rate, 20 million residents per year in average, is
435 predicted in cities with fewer than 300,000 inhabitants and those with more than 10 million (Fig. 3), followed by those with
436 populations larger than 1 million inhabitants (19 million inhabitants per year in average).
437



438
439 Figure 3: Sum of the world population that lives in each agglomeration size. (UN, 2018)

440
441 It is important and necessary to manage the air pollution health risk not only in large cities but also in medium- and
442 small-sized cities, the most prevalent type of urban settlements in all the geographic regions of the world (Figure 4). This is
443 especially of importance taking into account that in the next few years the number of small/medium size cities is expected to
444 rise most in the Less Developed Regions, Middle-income, Lower-middle-income and Low-income countries (which are also
445 the countries most at risk of the effects of climate change which goes hand in hand with air pollution) (USEPA, 2021;
446 Manisalidis et al., 2020).



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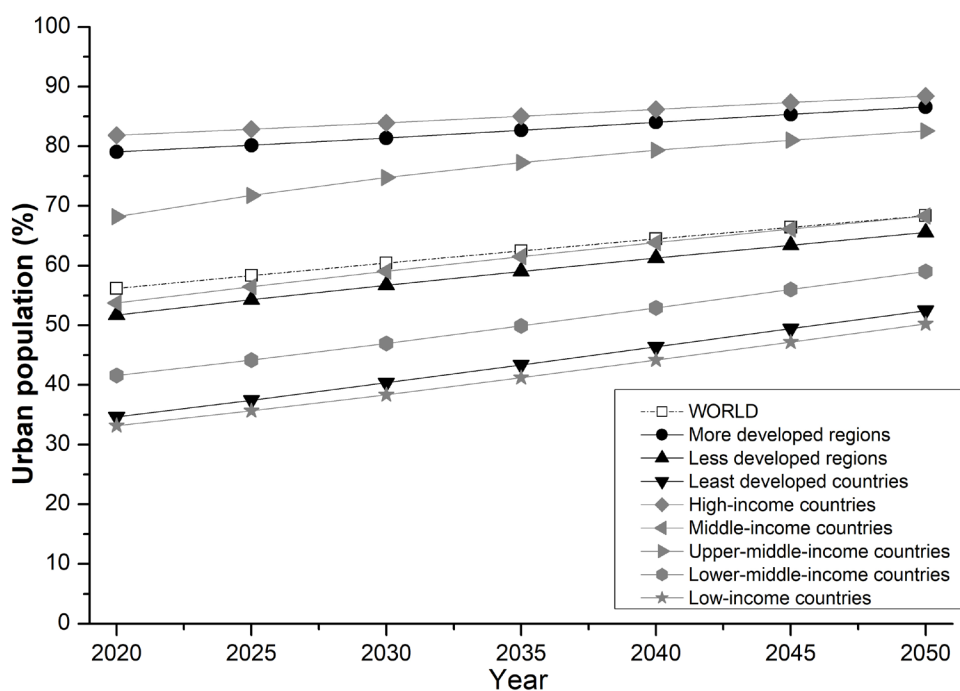
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Figure 4: Number of agglomerations (cities proper, urban agglomeration, or metropolitan area) by population size (a- from 0.3 to 1 million inhabitants. b- from 1 to 10 million inhabitants) in the world. The used classifications are based on country development by the United Nations (MDR: more developed regions; LDR: less developed regions; LTDR: least developed regions; in gray) and the economic development by the Word Bank (HIC: high-income countries; MIC: middle-income countries; UMIC: upper-middle-income countries; LMIC: lower-middle-income countries; LIC: low-income countries; in black).

Therefore, as the world continues to grow and urbanize (Figure 5), the proportion of the population exposed to urban air pollution will increase, further exacerbated by the fact that urbanization is predicted to be 2 to 2.5 times higher in the low- and middle income countries, exactly where the air pollution management and control is more limited. Although the growing role of technologies such as Satellite Observations and Chemical Transport Modeling to evaluate the global burden of PM_{2.5} exposure, the ground and air-craft-based observations produce specific detailing in inventory information that are not noted from satellite (Snider et al., 2016). For instance, the chemical composition of PM_{2.5} ranges more than one order of magnitude between populated sites (Polezer et al., 2019; Snider et al., 2016), being dependent on several local particularities such as social-economic development models (Gouveia et al., 2021; Polezer et al., 2019), and climate and geographic characteristics (Hand et al., 2012), and source contributions (Cepeda et al., 2017; Evans et al., 2021), that lead to specific and unique aerosol mixtures. Consequently, the improvement of the global health PM_{2.5} risk factor, providing a better understanding of the role of the chemical components in this global health challenge to assess health effects, needs additional local observations of this pollutant all over the world, and more so in the low and medium size sites (Hand et al., 2012; Putaud et al., 2004, 2010; Lippman, 2014; Bell et al., 2007).



469 Figure 5: Proportion of population living in urban areas in the world and categorized by development regions and economic
 470 status of the countries.

471

472 Finally, beyond the need to determine the specific features of air pollution, it is also necessary to investigate the
 473 local population characteristics such as social conditions, access to medical care, genetics, age, sex, and behavior (Pope et al., 2020; West et al., 2016; Pope et al., 2009). A recent study by Shi et al. (2020), applying a longitudinal nationwide open
 474 cohort population-based study in the United States of America (all above 65 years from 2000 to 2016), investigated the
 475 annual mean PM_{2.5} concentrations associated with zip codes and the first hospital admissions for Parkinson's disease,
 476 Alzheimer's disease, and Related Dementias. The health model adjustment considered, besides the usual possible confounds,
 477 also age, sex, race, zip code, medical eligibility (indicating level of socio-economic status), level of education, population
 478 density, previous smoking, median home value, owner-occupied housing, and median household income. It was possible to
 479 obtain Hazard Ratios relating the hospital admissions for both outcomes with 5 µg m⁻³ change, and strong evidence of
 480 linearity with PM_{2.5} concentrations less than 16 µg m⁻³ was found. Moreover, it was found that subgroups of women, white
 481 people, and more urbanized populations were more susceptible for hospital admissions for Parkinson's and Alzheimer's
 482 diseases, and Related Dementias.
 483

484

485 4. CONCLUSIONS

486 As in any city, air quality in Londrina is determined by the balance between pollutant emissions sources and the
 487 capacity to disperse and remove those air pollutants. We found that a substantial health risk is present even at pollutant
 488 concentrations below the new updated WHO AQGs, highlighting the general unspoken hypothesis that no level of PM_{2.5} is
 489 safe. The important statement to be made is that high levels of anthropogenic metals, including Cu, Pb, and Mn, are critical
 490 factors compounding the health risk of the population of Londrina.

491 The differential bioaccessibility of the PHEs in PM_{2.5} observed during this study is of particular importance, not
 492 only for the Londrina population, but also in the wider global context, as absolute concentrations did not reflect necessarily
 493 in the degree of mobility of the elements. As this differential behavior is chemistry dependent, which in turn is source

494 dependent, the true health risk can only be determined by performing local ground-based studies. It is therefore, not
495 unrealistic to expect a wide spectrum of pathologies at different locations. The fact that the disease burden due to poor air
496 quality is most prone in low- to middle-income countries and that the indiscriminate use of atmospheric chemistry and
497 transport models to estimate the local/regional air quality of medium-sized cities underestimate the real impact of air
498 pollution on the population, provides a basis for urgent global action to empower these countries to monitor effectively and
499 widely. Lastly, in view of the predictions of increased urbanization, growth of small- and medium-sized cities, and increased
500 numbers of agglomerations (especially in the Less Developed and Low Income Countries) in the near future, local
501 authorities will need to take action urgently to protect their citizens from the additional burden on population health.

502

503 **Declarations**

504

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508

509 **Declaration of competing interest**

510 The authors declare that they have no known competing financial interest or personal relationship that could have appeared
511 to influence the work reported in this paper.

512

513 **Availability of data and material**

514 Data available within the article or its supplementary materials

515

516 **CRediT authorship contribution statement**

517 **Gabriela Polezer:** Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing. **Sanja**
518 **Potgieter-Vermaak:** Conceptualization, Data Curation, Writing - Review & Editing, Visualization. **Andrea Oliveira:**
519 Validation, Investigation, Writing - Review & Editing. **Leila D. Martins:** Methodology, Investigation, Writing - Review &
520 Editing. **Jéssica C. Santos-Silva:** Software, Writing - Review & Editing. **Camila A. B. Moreira:** Software, Writing -
521 Review & Editing. **Theotonio Pauliquevis:** Formal analysis, Writing - Review & Editing. **Ana F. L. Godoi:** Resources,
522 Writing - Review & Editing. Yara Tadano Resources, Writing - Review & Editing. **Carlos I. Yamamoto:** Resources,
523 Writing - Review & Editing, Funding acquisition. **Ricardo H. M. Godoi:** Conceptualization, Writing - Review & Editing,
524 Supervision, Project administration, Funding acquisition.

525

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