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# Characterization of Human Health Risks from Particulate Air Pollution in Selected European Cities

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**Abstract:** The objective of the current study was to estimate health risk indexes caused by the inhalation of particulate matter (PM) by adult males and children using data sampled in three European cities (Athens, Kuopio, Lisbon). Accordingly, the cancer risk (CR) and the hazard quotient (HQ) were estimated from particle-bound metal concentrations whilst the epidemiology-based excess risk (ER), the attributable fraction (AF), and the mortality cases were obtained due to exposure to PM<sub>10</sub> and PM<sub>2.5</sub>. CR and HQ were estimated using two methodologies: the first methodology incorporated the particle-bound metal concentrations (As, Cd, Co, Cr, Mn, Ni, Pb) whereas the second methodology used the deposited dose rate of particle-bound metals in the respiratory tract. The indoor concentration accounts for 70% infiltration from outdoor air for the time activity periods allocated to indoor environments. HQ was lower than 1 and the cumulative CR was lower than the acceptable level (10<sup>-4</sup>), although individual CR for some metals exceeded the acceptable limit (10<sup>-6</sup>). In a lifetime the estimated number of attributable cancer cases was 74, 0.107, and 217 in Athens, Kuopio, and Lisbon, respectively. Excess risk-based mortality estimates (due to outdoor pollution) for fine particles were 3930, 44.1, and 2820 attributable deaths in Athens, Kuopio, and Lisbon, respectively.

**Keywords:** particulate matter; health risks; dose; respiratory tract; metals; cancer risk; mortality

## 1. Introduction

Air pollution can cause respiratory and cardiovascular diseases [1–6] such as bronchitis, cardiac arrhythmia, lung inflammation, lung fibrosis, deep vein thrombosis, and lung cancer [7–10]. Particulate matter (PM) and other pollutants such as O<sub>3</sub> and NO<sub>2</sub> are responsible for these adverse health effects. The WHO project “Health Risk of Air Pollution in Europe” (HRAPIE) focuses on quantifying air pollution caused health impacts [4]. Epidemiological methods have been proposed for air pollution health risk assessment [4]. Recent application of these methods has shown substantial health effects also in areas with low pollution levels [11]. In addition, Pope et al. [12] pointed out that the relation of PM<sub>2.5</sub> level and life expectancy is stronger during a low pollution period. Health impacts and the associated risk of the exposed subjects are necessary to investigate as they involve everyday life

exposure to ambient contaminants. Hoek et al. [5] suggest that additional research is required in order to examine the health effects of air pollution on susceptible subjects (e.g., obese).

According to the World Health Organization [6] PM was responsible for 3 million premature deaths globally in 2016. However, Héroux et al. [4] pointed out that mortality due to PM exposure was reduced by 20% between 2000 and 2010. Pope et al. [12] asserted that a decrease of PM<sub>2.5</sub> level by 10 µg/m<sup>3</sup> increased life expectancy by 0.61 year. Furthermore, Hoek et al. [5] found little evidence between long-term exposure to coarse particles and mortality, whereas, Romanazzi et al. [13] indicated that exposure to coarse particles is associated with pro-inflammatory and cytotoxic effects. Several studies [13–18] estimated the effect of PM on human health as well as the associated impact from the chemical composition [13–16,18,19]. Accordingly, metal components such as As, Cd, Co, Cr (VI), and Ni were investigated due to their carcinogenic health risk. Rogula-Kozłowska et al. [20] pointed out that the most hazardous components of PM are polycyclic aromatic hydrocarbons (PAH) and metals. Bello et al. [21] suggested that the majority of metals are toxic and may cause significant health effects such as several types of cancer. In addition, Carpenter and Bushkin-Bedient [22] proposed that exposure to a carcinogen during childhood can lead to an elevated cancer risk in later life. Therefore, investigation of metal concentrations, their impact on human health, and age of the exposed subject is of major importance due to their carcinogenic and toxic effects.

It is well established that natural sources emit mainly coarse particles (>2.5 µm) while anthropogenic sources emit particles mainly in the fine/ultrafine region (<2.5 µm) [23]. Common anthropogenic sources that release heavy metals in the ambient air are emissions from vehicles, industry, domestic emissions, and weathering of buildings [24]. In addition, the chemical composition of PM varies from city to city and depends on many factors such as geography, season, climate, and combustion sources [10]. It is therefore crucial to conduct a risk assessment analysis to estimate the effect of PM on human health and in different environments to map the potential risk from exposure to airborne particles.

The aim of the present study is to apply several available scientific approaches to characterize health risks caused by population exposures to airborne particulate matter. Specifically, we (i) calculate particle bound metal cancer risks and non-cancer toxicity hazard quotients; (ii) estimate the resulting numbers of cancer cases by city; (iii) calculate epidemiology-based estimates of all-cause cardiopulmonary and lung cancer mortalities; (iv) compare and discuss the estimates obtained from the alternative approaches; and (v) estimate and discuss the differences in body-weight adjusted metal dose rates between adults and children. The current work is a follow-up study of the work presented by Chalvatzaki et al. [25].

## 2. Material and Methods

### 2.1. Study Areas and Field Measurements

A methodology for assessment of the health risk due to air pollution was applied in three selected European cities: Athens metropolitan area (Greece), Kuopio (Finland), and Lisbon metropolitan area (Portugal) with populations of 3,754,000, 117,000, and 2,811,000, respectively. Simulations were performed for both adult males and children who were considered residents in the under study sites where experimental data for PM concentrations and particle-bound metal concentrations were adopted from the literature [25–28]. Health risk indexes were estimated using the data implemented in Chalvatzaki et al. [25] to obtain the deposited dose to the human respiratory tract and the results (deposited dose rate) from the application of the exposure dose model 2 (ExDoM2; [29]) are used as input. The methodology was applied to two age groups: adult males and children. Model simulations (using ExDoM2) for children were performed separately for a 5- and a 10-year old child and the average deposited dose rate was used in subsequent calculations. The equations of International Commission on Radiological Protection (ICRP) [30,31] were used by ExDoM2 for the calculation of deposition fractions.

Sippula et al. [28] performed field measurements in Kuopio during 2010 for 2–3 weeks sampling in each season. Average values of PM were used by Chalvatzaki et al. [25] and hence in the current study. In particular, Sippula et al. [28] used a Harvard high-volume cascade impactor (HVCI) for collection of particles into different size categories (<0.2  $\mu\text{m}$ , 0.2–1  $\mu\text{m}$ , 1–2.5  $\mu\text{m}$ , and 2.5–10  $\mu\text{m}$ ). Almeida et al. [26,27] performed field measurements in Lisbon using a Berner Impactor (Hauke LPI 30/0.06/2) during 2001 for 3 days in each season (again average values were used). The Berner Impactor (Hauke LPI 30/0.06/2) collected particles in different size categories (0.0625–0.125  $\mu\text{m}$ , 0.125–0.25  $\mu\text{m}$ , 0.25–0.5  $\mu\text{m}$ , 0.5–1  $\mu\text{m}$ , 1.0–2.0  $\mu\text{m}$ , 2.0–4.0  $\mu\text{m}$ , 4.0–8.0  $\mu\text{m}$ , 8.0–16.0  $\mu\text{m}$ ). The values of the range (8.0–16.0  $\mu\text{m}$ ) were not used by Chalvatzaki et al. [25] and hence in the current study. Finally, field measurements in Athens were performed from November 2014 to May 2015 using a low pressure Berner cascade impactor which collects particles in different size categories (0.0255–0.062  $\mu\text{m}$ , 0.062–0.11  $\mu\text{m}$ , 0.11–0.173  $\mu\text{m}$ , 0.173–0.262  $\mu\text{m}$ , 0.262–0.46  $\mu\text{m}$ , 0.46–0.89  $\mu\text{m}$ , 0.89–1.77  $\mu\text{m}$ , 1.77–3.4  $\mu\text{m}$ , 3.4–6.8  $\mu\text{m}$ , 6.8–13.35  $\mu\text{m}$ , and >13.35  $\mu\text{m}$ ). Herein, the values from stages 6.8–13.35  $\mu\text{m}$  and >13.35  $\mu\text{m}$  were not used (as well as in Chalvatzaki et al. [25]). Detailed description of the field measurements in the study areas can be found in Chalvatzaki et al. [25] for Athens, in Sippula et al. [28] for Kuopio, and in Almeida et al. [26,27] for Lisbon.

The present study used data from different periods for each city and hence no comparison between the three cities was performed but our study aims to apply several available scientific approaches to estimate health risks caused by exposure to particulate matter in several residential areas.

## 2.2. Health Risk Assessment Methodology for Particle-Bound Metals

The present study implements a methodology which is based on the risk assessment guidance provided by the US EPA [32,33]. Accordingly, non-carcinogenic health risks are evaluated by the hazard quotient (HQ) whereas the carcinogenic health risks are evaluated by the cancer risk (CR).

The hazard quotient is given as [32,33]:

$$HQ = CDI/RFD \quad (1)$$

where  $CDI$  is the chronic daily intake (mg/kg/day) and  $RFD$  is the reference dose (mg/kg/day). An  $HQ < 1$  indicates no significant (acceptable) risk, and  $HQ > 1$  suggests that the non-carcinogenic effect is likely to appear [32,33] whilst a high chronic risk is denoted for  $HQ > 10$  [34,35]. It should be noted that the value of 10 is very high for ambient areas and is used for electronic-waste recycling sites [34,35]. Two methodologies were used to estimate the daily intake. The US EPA [32,33] based Methodology 1 incorporates the concentration of particle-bound metals and the inhalation rate to obtain chronic daily intake ( $CDI$ , mg/kg) as shown in Equation (2). The second methodology uses the deposited dose rate of particle-bound metals in the human respiratory tract that was first estimated from the application [25] of a dosimetry model (ExDoM2; [29]) and then Equation (3) used as given by Lyu et al. [15].

$$CDI = \frac{C_a \times IR \times ET \times EF \times ED}{BW \times AT} \quad (2)$$

$$CDI = \left( DF \times 10^{-6} \right) \times \frac{ET \times EF \times ED}{BW \times AT} = (C_a \times IR \times DE) \times \frac{ET \times EF \times ED}{BW \times AT} \quad (3)$$

where  $C_a$  is the contaminant concentration (mg/m<sup>3</sup>),  $IR$  is the inhalation rate (m<sup>3</sup>/h),  $ET$  is the exposure time (h/day),  $EF$  is the exposure frequency (days/year),  $ED$  is the exposure duration (years),  $BW$  is the body weight (kg) of the exposed subject,  $AT$  is the averaging time (days), and  $DF$  is the deposition flux or the deposited dose rate (ng/h) of the particle-bound metal in the human respiratory tract. Equation (3) demonstrates that  $DF$  is obtained as the product of the contaminant concentration, the inhalation rate, and the deposition fraction ( $DE$ ) of the particle-bound metal in the respiratory tract. Therefore, the two equations differ only in the use or not of  $DE$ . This implies that for cases

where  $DE \approx 1$  the two methodologies give similar results whereas for cases where  $DE < 1$  the second methodology provides results lower than that of the first methodology.

The advantage of using the deposited dose rate in the second methodology is that it takes into account the deposition of particles in the human respiratory tract. As Rissler et al. [36] found, the probability of particle deposition in the human respiratory tract is essential for its toxic effects. Furthermore, the authors highlighted the variability of deposition between different subjects (adults/children) therefore it is important to examine the impact of particle deposition in the calculations. As our results suggest, the second methodology results in lower estimates because it takes into account the mechanisms of particle deposition. The main mechanisms of particle deposition are: impaction, sedimentation, and diffusion. Brown [37] proposed that particle deposition in the respiratory tract is minimal in the range 0.1–1.0  $\mu\text{m}$  because particles in this size range are small for sedimentation/impaction and large for diffusion.

Reference values for the inhalation rate for adult males and children (average values of 5 and 10 year olds) were adopted according to ICRP [30]. For example, IR for adult males for light exercise, sitting (rest) and sleep was set equal to 1.5, 0.54, and 0.45  $\text{m}^3/\text{h}$ , respectively [30]. Average IR was implemented in Equation (2) according to the daily activity pattern which was used in Chalvatzaki et al. [25]. Likewise, an average value was adopted for  $C_a$ . The indoor concentration was considered to be 70% of the outdoor air (due to infiltration) for the time activity periods allocated to indoor environments. The exposure time (ET) and exposure frequency (EF) were set equal to 24 h/day and 350 days/year respectively whilst the exposure duration (ED) was considered equal to 24 years for adults and 6 years for children based on the US EPA [38]. Body weight (BW) was considered to be 73 kg for adults and 25.5 kg (average values of 5 and 10 year old children) for children [39]. Moreover, according to the US EPA [38] the averaging time (AT) can be considered equal to 8760 days for adults and 2190 days for children ( $ED \times 365$  days/year) for non-carcinogens while for carcinogens it can be considered equal to 25,550 days (70 years  $\times$  365 days/year) for both adults and children.

The reference dose (RFD) is given as [38]:

$$RFD = RFC \times (IR_d/BW) \quad (4)$$

where  $IR_d$  ( $\text{m}^3/\text{d}$ ) is the daily inhalation rate estimated based on ICRP [30] and the daily activity pattern which was used in Chalvatzaki et al. [25] while  $RFC$  ( $\text{mg}/\text{m}^3$ ) corresponds to a reference concentration and is provided by US EPA [40]. Specifically, RFC is equal to  $1.5 \times 10^{-5}$ ,  $1.0 \times 10^{-5}$ ,  $6.0 \times 10^{-6}$ ,  $1.0 \times 10^{-4}$ ,  $5.0 \times 10^{-5}$ ,  $2.0 \times 10^{-5}$ ,  $2.0 \times 10^{-4}$   $\text{mg}/\text{m}^3$  for As, Cd, Co, Cr (VI), Mn, Ni, and Pb respectively [40].

The cancer risk (CR) represents the probability for an individual developing cancer and was estimated by [32,33]:

$$CR = CDI \times CSF \quad (5)$$

where  $CSF$  is the cancer slope factor ( $\text{mg}/\text{kg day}$ ) $^{-1}$ . The US EPA [38] considers values of  $CR < 10^{-6}$  acceptable; however, the cumulative CR for all potential carcinogenic contaminants must preserve values  $< 10^{-4}$  [13,41,42].

Finally, the cancer slope factor ( $CSF$ ) is estimated as [38]:

$$CSF = IUR \times \left( \frac{BW}{IR_d} \right) \times 10^3 \quad (6)$$

where  $IUR$  ( $\mu\text{g}/\text{m}^3$ ) $^{-1}$  is the inhalation unit risk and is provided by US EPA [43]. Particularly, IUR is equal to  $4.3 \times 10^{-3}$ ,  $1.8 \times 10^{-3}$ ,  $9 \times 10^{-3}$ ,  $1.2 \times 10^{-2}$ ,  $2.6 \times 10^{-4}$  ( $\mu\text{g}/\text{m}^3$ ) $^{-1}$  for As, Cd, Co, Cr (VI), and Ni, respectively [43].

We estimated the cancer incidences (number of new cancer cases) (I) per lifetime (70 years) in the three cities based on the CR as followed:

$$I = N \times CR \quad (7)$$

where  $I$  is the cancer incidence (cases),  $N$  is the number of people in the target city, and  $CR$  is the cancer risk probability estimated in this work.

### 2.3. Health Risk Assessment Methodology for $PM_{10}$ and $PM_{2.5}$

The relative risk (RR) for all-cause mortality associated with short-term exposure to  $PM_{10}$  was calculated using the equation provided by Ostro [44]. The relative risk is the probability of health effects (e.g., all-cause mortality, lung cancer mortality) occurring in a population exposed to a level of air pollution higher than that considered as background without any anthropogenic pollution ( $10 \mu\text{g}/\text{m}^3$  for  $PM_{10}$ ; [44]).

The relative risk (RR) for all ages due to all-cause mortality was estimated by [44]:

$$RR = \exp[\beta(X - X_0)] \quad (8)$$

where  $X$  is the annual mean concentration of  $PM_{10}$  ( $\mu\text{g}/\text{m}^3$ ),  $X_0$  is the baseline concentration of  $PM_{10}$  ( $10 \mu\text{g}/\text{m}^3$ ), and  $\beta$  is the coefficient of the risk function (0.0008; 95% confidence interval (CI): 0.0006–0.0010).

In addition, the relative risk for cardiopulmonary and lung cancer mortality (age >30 years old) associated with long-term exposure to  $PM_{2.5}$  was calculated by [44]:

$$RR = [(X + 1)/(X_0 + 1)]^\beta \quad (9)$$

where  $X$  is the annual mean concentration of  $PM_{2.5}$  ( $\mu\text{g}/\text{m}^3$ ),  $X_0$  is the baseline concentration of  $PM_{2.5}$  ( $3 \mu\text{g}/\text{m}^3$ ), and  $\beta$  is the coefficient of the risk function. The coefficient  $\beta$  is equal to 0.15515 (95% CI: 0.0562–0.2541) for cardiopulmonary mortality while for lung cancer mortality  $\beta$  is equal to 0.23218 (95% CI: 0.08563–0.37873).

The functions of Ostro [44] were adopted because: (1) they are particularly handy for numerical applications, (2) the more recent developments especially in the Intergrated Exposure Response (IER) function [45,46] and subsequent GEMM [47] reflect also substantial uncertainties, (3) only the Burnett et al. [45] version (of the IER functions) has been published at a level that can readily be reapplied; comparison of Ostro [44] with it shows that Ostro's function for cardiopulmonary mortality (the most significant mortality component) is roughly double, and (4) in the next iteration of IER the threshold (TMERD) was brought down from  $5\text{--}6 \mu\text{g m}^{-3}$  to  $2\text{--}3 \mu\text{g m}^{-3}$ , which is very close to the value applied by Ostro.

Once the relative risk (RR) is determined, the attributable fraction (AF) is estimated as [44]:

$$AF = (RR - 1)/RR \quad (10)$$

The AF estimates the proportion of deaths from a disease (e.g., lung cancer) which could be avoided if PM levels were reduced to  $10 \mu\text{g}/\text{m}^3$  and  $3 \mu\text{g}/\text{m}^3$  for  $PM_{10}$  and  $PM_{2.5}$ , respectively [44]. Equations (8)–(10) estimate the RR and AF due to outdoor air pollution. The RR estimates are presented as excess risk ( $ER = RR - 1$ ) later on.

The attributable deaths (AI) were calculated using AF and background mortality ( $I$ ) in the target cities [48]:

$$AI = AF \times I \quad (11)$$

where  $AI$  is the number of deaths attributable to exposure and  $I$  is the total number of deaths in the target population. Age-adjusted estimates calculated from annual national mortality data for 2015 were obtained from the WHO [49]. The country level estimates for the selected cities were calculated by multiplying country levels deaths with the fractions of the country's population living in the under study city.

### 3. Results and Discussion

#### 3.1. Ambient Concentration and Deposited Dose Rate of Particle-Bound Metals

Tables 1 and 2 list the PM concentrations and particle-bound metal concentrations respectively for each city. In addition, Tables 3 and 4 give the deposited dose rate of the particle-bound metals for adult males and children respectively. The values of Tables 1 and 2 represent the measured concentrations by experimental techniques in the under study sites [25–28] whereas the values in Tables 3 and 4 correspond to the modeled results obtained from the use of the dosimetry model ExDoM2 for adult males [25] and children respectively. The values suggest that the deposited dose rates were 1.7–1.9 times higher per body weight in children.

**Table 1.** Mass concentration ( $\mu\text{g}/\text{m}^3$ ) of outdoor particulate matter (PM) in each city [25–28].

Athens		Kuopio		Lisbon	
PM <sub>1.77</sub>	PM <sub>6.8</sub>	PM <sub>2.5</sub>	PM <sub>10</sub>	PM <sub>2</sub>	PM <sub>8</sub>
11.1	19.6	6.2	10.3	21.3	36.6

**Table 2.** Outdoor concentration ( $\text{ng}/\text{m}^3$ ) of particle-bound metals in each city [25–28].

	Athens (PM <sub>6.8</sub> )	Kuopio (PM <sub>10</sub> )	Lisbon (PM <sub>8</sub> )
As	2.87	0.21	0.46
Cd	-	0.07	-
Co	3.53 *	0.09	0.67
Cr	2.39	0.34	23.75
Mn	14.96	4.19	-
Ni	7.47 *	7.12	-
Pb	6.01	1.56	-

\* unpublished data from the same sampling period.

**Table 3.** Deposited dose rate ( $\text{ng}/\text{h}$ ) of particle-bound metals in the human respiratory tract for adult males [25].

	Athens		Kuopio		Lisbon	
	Average	min–max	Average	min–max	Average	min–max
As	1.45	0.50–2.60	0.07	0.02–0.13	0.18	0.06–0.32
Cd	-	-	0.02	0.01–0.04	-	-
Co	1.64	0.55–2.97	0.06	0.02–0.11	0.40	0.12–0.75
Cr	1.03	0.31–1.89	0.21	0.07–0.37	10.60	3.29–19.46
Mn	7.46	2.60–13.38	2.36	0.81–4.22	-	-
Ni	3.31	1.12–5.97	1.96	0.55–3.68	-	-
Pb	1.70	0.61–3.02	0.64	0.20–1.16	-	-

**Table 4.** Deposited dose rate ( $\text{ng}/\text{h}$ ) of particle-bound metals in the human respiratory tract for children (average values of 5- and 10-year old children).

	Athens		Kuopio		Lisbon	
	Average	min–max	Average	min–max	Average	min–max
As	0.85	0.31–1.49	0.04	0.01–0.08	0.11	0.04–0.19
Cd	-	-	0.02	0.01–0.03	-	-
Co	0.98	0.35–1.73	0.04	0.01–0.06	0.25	0.08–0.44
Cr	0.64	0.21–1.15	0.12	0.05–0.21	6.53	2.19–11.72
Mn	4.35	1.62–7.64	1.42	0.51–2.49	-	-
Ni	1.97	0.71–3.48	1.33	0.38–2.46	-	-
Pb	1.04	0.39–1.82	0.40	0.13–0.71	-	-

PM concentrations were the highest in Lisbon ( $36.6 \mu\text{g}/\text{m}^3$  and  $21.3 \mu\text{g}/\text{m}^3$ ) followed by Athens ( $19.6 \mu\text{g}/\text{m}^3$  and  $11.1 \mu\text{g}/\text{m}^3$ ), and Kuopio ( $10.3 \mu\text{g}/\text{m}^3$  and  $6.2 \mu\text{g}/\text{m}^3$ ) (Table 1). The mass percentage for fine particles ( $\text{PM}_{2.5}$  for Kuopio;  $\text{PM}_{2.0}$  for Lisbon, and  $\text{PM}_{1.77}$  for Athens) is higher than for coarse particles ( $\text{PM}_{2.5-10}$  for Kuopio;  $\text{PM}_{2.0-8.0}$  for Lisbon, and  $\text{PM}_{1.77-6.8}$  for Athens) for all cities. In particular, the mass percentage for fine particles is equal to 56%, 58%, and 60% in Athens, Lisbon, and Kuopio, respectively. Bigger cities are expected to preserve higher ambient PM concentrations compared to smaller cities due to increased anthropogenic activities. Additionally, Querol et al [50] emphasized that variations in PM concentrations may be observed between countries (e.g., Mediterranean and Scandinavian countries) with different climatologic and geographical patterns. Likewise, International Agency of Research on Cancer (IARC) [51] emphasized that  $\text{PM}_{10}$  concentrations in southern Europe are higher than that of north-western Europe. Regarding the concentrations of particle-bound metals higher concentrations in Athens were obtained for Mn ( $14.96 \text{ ng}/\text{m}^3$ ) followed by Ni ( $7.47 \text{ ng}/\text{m}^3$ ) among the measured metals. Similarly, Ni ( $7.12 \text{ ng}/\text{m}^3$ ) and Mn ( $4.19 \text{ ng}/\text{m}^3$ ) preserved elevated concentrations in Kuopio whilst a substantially higher concentration of Cr ( $23.75 \text{ ng}/\text{m}^3$ ) was measured in Lisbon compared to the rest of the particle-bound metals that were measured in this site. Herein, the average deposited dose rates given (Tables 3 and 4) were used for the calculation of the Hazard Quotient and Cancer Risk. Originally, the deposited dose rates were estimated based on an hourly variation due to the different microenvironment (outdoor, indoor) and physical activity of the exposed subject (sleep, sitting awake, light activity) according to the daily activity pattern which was used by Chalvatzaki et al [25] in the ExDoM2. The same daily activity pattern was used for adult males and children to examine the effect of age on the deposited dose rate. Accordingly, it was observed that the deposited dose rate for adult males is higher compared to the deposited dose obtained for children, a characteristic that is associated with the higher inhalation rate of adults. In addition, the maximum rate corresponds to the period when the subject (both adults and children) was exposed to the outdoor environment doing light exercise whereas the minimum rate was obtained when the subject was sleeping indoors. These results were associated with the lower concentration in the indoor environment (absence of indoor sources) and the lower inhalation rate during sleep.

### 3.2. Hazard Quotients and Cancer Risks

#### 3.2.1. Hazard Quotients

The hazard quotient (for non-carcinogenic health risks) obtained for the measured seven metals in the three cities were estimated for adults and children respectively (Tables 5 and 6). Accordingly, the cumulative *HQ* (or hazard index) was lower than the limit of 1 in all examined cases except for Athens when the first methodology was used. Thus, the present results indicate no significant risk from inhalation exposure to these metal compounds although a higher risk exists for Athens if the first methodology is taken into account.

**Table 5.** Hazard quotient for adult males estimated from both methodologies for each metal and city.

City	Metal	Methodology 1 (US EPA)	Methodology 2 (Lyu et al. [15])
Athens	As	$1.47 \times 10^{-1}$	$9.32 \times 10^{-2}$
	Cd	-	-
	Co	$4.51 \times 10^{-1}$	$2.64 \times 10^{-1}$
	Cr	$1.83 \times 10^{-2}$	$9.92 \times 10^{-3}$
	Mn	$2.30 \times 10^{-1}$	$1.44 \times 10^{-1}$
	Ni	$2.87 \times 10^{-1}$	$1.60 \times 10^{-1}$
	Pb	$2.31 \times 10^{-2}$	$8.20 \times 10^{-3}$
Cumulative		1.16	$6.79 \times 10^{-1}$

Table 5. Cont.

City	Metal	Methodology 1 (US EPA)	Methodology 2 (Lyu et al. [15])
Kuopio	As	$1.06 \times 10^{-2}$	$4.52 \times 10^{-3}$
	Cd	$5.06 \times 10^{-3}$	$2.11 \times 10^{-3}$
	Co	$1.18 \times 10^{-2}$	$9.87 \times 10^{-3}$
	Cr	$2.59 \times 10^{-3}$	$1.99 \times 10^{-3}$
	Mn	$6.43 \times 10^{-2}$	$4.55 \times 10^{-2}$
	Ni	$2.73 \times 10^{-1}$	$9.47 \times 10^{-2}$
	Pb	$5.99 \times 10^{-3}$	$3.07 \times 10^{-3}$
	Cumulative	$3.73 \times 10^{-1}$	$1.62 \times 10^{-1}$
Lisbon	As	$2.34 \times 10^{-2}$	$1.13 \times 10^{-2}$
	Cd	-	-
	Co	$8.55 \times 10^{-2}$	$6.50 \times 10^{-2}$
	Cr	$1.82 \times 10^{-1}$	$1.02 \times 10^{-1}$
	Mn	-	-
	Ni	-	-
	Pb	-	-
	Cumulative	$2.91 \times 10^{-1}$	$1.79 \times 10^{-1}$

Table 6. Hazard quotient for children estimated from both methodologies for each metal and city.

City	Metal	Methodology 1 (US EPA)	Methodology 2 (Lyu et al. [15])
Athens	As	$1.47 \times 10^{-1}$	$9.42 \times 10^{-2}$
	Cd	-	-
	Co	$4.51 \times 10^{-1}$	$2.72 \times 10^{-1}$
	Cr	$1.83 \times 10^{-2}$	$1.07 \times 10^{-2}$
	Mn	$2.30 \times 10^{-1}$	$1.45 \times 10^{-1}$
	Ni	$2.87 \times 10^{-1}$	$1.64 \times 10^{-1}$
	Pb	$2.31 \times 10^{-2}$	$8.64 \times 10^{-3}$
	Cumulative	1.16	$6.95 \times 10^{-1}$
Kuopio	As	$1.06 \times 10^{-2}$	$4.96 \times 10^{-3}$
	Cd	$5.06 \times 10^{-3}$	$2.66 \times 10^{-3}$
	Co	$1.18 \times 10^{-2}$	$1.00 \times 10^{-2}$
	Cr	$2.59 \times 10^{-3}$	$2.05 \times 10^{-3}$
	Mn	$6.43 \times 10^{-2}$	$4.72 \times 10^{-2}$
	Ni	$2.73 \times 10^{-1}$	$1.10 \times 10^{-1}$
	Pb	$5.99 \times 10^{-3}$	$3.30 \times 10^{-3}$
	Cumulative	$3.73 \times 10^{-1}$	$1.81 \times 10^{-1}$
Lisbon	As	$2.34 \times 10^{-2}$	$1.17 \times 10^{-2}$
	Cd	-	-
	Co	$8.55 \times 10^{-2}$	$6.83 \times 10^{-2}$
	Cr	$1.82 \times 10^{-1}$	$1.09 \times 10^{-1}$
	Mn	-	-
	Ni	-	-
	Pb	-	-
	Cumulative	$2.91 \times 10^{-1}$	$1.89 \times 10^{-1}$

Likewise,  $HQ$  for each metal was lower than the acceptable level ( $HQ < 1$ ) for all cases involved and again no significant toxic effect is expected. Megido et al. [52] reports values of  $HQ$  equal to 0.063 and 0.027 for As and Co respectively which is close to the ones presented in this study for As (0.023 methodology 1; 0.011 methodology 2) and Co (0.086 methodology 1; 0.065 methodology 2).

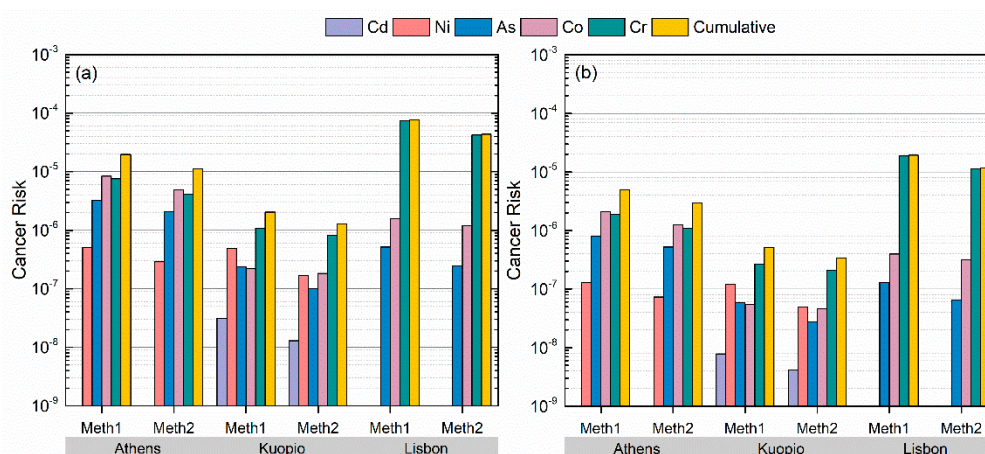


Methodology 1 provides slightly higher estimates (1.2–2.9-fold, mean 1.8 fold) compared to the second methodology. This observation induces a significant implication on the use of each methodology. Intrinsically, the second methodology includes the use of the deposited dose rate through the deposition fraction, which preserves values lower than 1, in the calculation of *CDI*. On the other hand, the first methodology considers only the ambient concentration of particles for the estimation of *CDI*. Therefore, the second methodology always results in lower estimates compared to the first methodology.

Additionally, using the first methodology to estimate the hazard quotient produced equal estimates for adults and children. The same observation is reported in Wang et al. [53] regarding inhalation exposure of heavy metals in fine particles. On the contrary, using the second methodology to obtain *HQ*, higher estimates corresponded to children compared to adults. Again, this characteristic is attributed to the deposition fraction that was considered in the second methodology. Several studies [36,54,55] asserted that the deposition fraction in children is higher than that in adult males, which in turn results in higher *HQ* (although the deposited dose rate is higher in adult males due to the higher inhalation rate). Lastly, cumulative *HQ* is expected to preserve higher estimates if exposure to metals via ingestion and dermal contact is considered.

### 3.2.2. Cancer Risks

The cancer risk (via inhalation) estimated for each metal in the three under study cities using both methodologies for adult males and children respectively is shown Figure 1a,b. Again, the results indicate that the first methodology provides higher estimates. Based on the US EPA [38] the exposure duration and averaging time was set equal to 24 and 70 years for adults, whilst, the corresponding values for children were 6 and 70 years [38]. Therefore, *CR* for children was lower due to the lower exposure duration. A similar finding is reported in Bello et al. [21] as well as in Wang et al. [53] regarding *CR* of inhaled  $PM_{2.5}$ -bound trace metals. However, both studies found that *CR* for children was higher than that for adults through ingestion exposure.



**Figure 1.** Cancer risk for (a) adult males and (b) children estimated from both methodologies for each metal and city.

Overall, lower estimates of cancer risk (for both methodologies) were obtained for Kuopio due to the lower metal concentrations (Table 2). However, differences apply within each city and the cancer risk for individual metal compounds ranges from values higher than the acceptable limit to values lower than  $10^{-6}$ .

Cancer risk levels for Cd and Ni obtained for all cities were lower than  $10^{-6}$ , suggesting low or acceptable risks. On the other hand, a  $CR > 10^{-6}$  was obtained for As in Athens, whilst, the cancer risk for Co and Cr was higher than the acceptable level in Athens and Lisbon. Note that the cancer risk for Cr in Kuopio using the first methodology is slightly higher than the acceptable limit ( $1.1 \times 10^{-6}$ ) and

that there are no available data (inhalation unit risk) for total or trivalent Cr. Therefore, the inhalation unit risk of hexavalent Cr was used although the total Cr was measured in these cities. The cancer risk of Cr in Lisbon ( $7.50 \times 10^{-5}$  methodology 1;  $4.21 \times 10^{-5}$  methodology 2) was at a similar level with the cancer risk ( $3.7 \times 10^{-5}$ ) obtained in an urban area in the center of Porto (Portugal) by Pinto et al. [16], where, the authors also used the inhalation unit risk of hexavalent Cr while the total concentration of Cr was measured in their study. Additionally, Megido et al. [52] reports a cancer risk for Co via inhalation at  $1.1 \times 10^{-6}$  in an industrial suburban station in Asturias (Spain).

Using population data from the target cities we calculated the estimates of cancer cases, showing a total of approximately 74 cancers in a lifetime in Athens, 0.11 cancers in Kuopio, and 217 cancers in Lisbon (Table 7). Cancer case estimates were dominated by Cr and Co.

**Table 7.** Cancer risk based estimates of cases per lifetime in the three cities.

	Cancer Cases per Lifetime (70 Years)					
	Methodology 1 (US EPA)			Methodology 2 (Lyu et al. [15])		
	Athens	Kuopio	Lisbon	Athens	Kuopio	Lisbon
As	12.2	0.020	1.5	7.7	0.008	0.7
Cd	-	0.003	-	-	0.001	-
Co	31.3	0.018	4.4	18.4	0.015	3.4
Cr	28.3	0.090	210.8	15.3	0.069	118.3
Ni	1.9	0.041	-	1.1	0.014	-
Cumulative	73.7	0.172	216.7	42.5	0.107	122.4

At the end, the cumulative cancer risk (both adults and children) in all three cities and for both methodologies was lower than the acceptable limit  $10^{-4}$  [38,41] as shown in Figure 1. Herein, the cancer risk was estimated considering only inhalation, whilst, the exposure to metals occurs also via ingestion and dermal contact. Therefore, the cumulative cancer risk is expected to be higher if ingestion and dermal contact are considered [13]. This observation is reported in Megido et al. [52] where the cumulative cancer risk via ingestion was higher than  $10^{-4}$  at an industrial suburban station in Asturias (Spain).

### 3.3. Excess Risk and Attributable Mortality

Excess risks and the attributable fractions for all-cause mortality were estimated for each city using  $PM_{10}$  data for Kuopio,  $PM_8$  for Lisbon, and  $PM_{6.8}$  for Athens (Table 8). Accordingly, the excess risks were estimated at 0.77%, 0.02%, and 2.2% for Athens, Kuopio, and Lisbon respectively. These results demonstrate that a higher excess risk was obtained for Lisbon and suggests that an individual in a group exposed to the corresponding PM concentration in Lisbon is more likely to present a health effect (all-cause mortality) than an individual in a group that is exposed to a background concentration of  $10 \mu\text{g}/\text{m}^3$  ( $PM_{10}$ ) by 2.2%. Similarly, the lower excess risk that corresponds to Kuopio (0.02%) indicates a safer ambient  $PM_{10}$  concentration for a recipient under the conditions measured in this site. Regarding the results for the attributable fraction, Table 8 indicates that 0.77%, 0.02%, and 2.11% of all-cause mortality could be avoided in Athens, Kuopio, and Lisbon respectively if  $PM_{10}$  concentration was reduced to  $10 \mu\text{g}/\text{m}^3$ . Again, higher AF was obtained for Lisbon which represents a higher risk for this case study. A similar finding was published in the city of Valladolid in Spain by Cardaba Arranz et al. [56], where, the authors found that 2% of all-cause mortality was attributed to particulate matter pollution.

Furthermore, ER and AF for cardiopulmonary and lung cancer mortality due to long-term exposure to  $PM_{2.5}$  ( $PM_{2.0}$  for Lisbon and  $PM_{1.77}$  for Athens) are listed in Table 8. The excess risk for cardiopulmonary mortality was found equal to 19%, 9.5%, and 31% for Athens, Kuopio, and Lisbon respectively whilst the attributable fraction suggests that cardiopulmonary mortality can be prevented by 15.8%, 8.7%, and 23.4% in Athens, Kuopio, and Lisbon respectively if fine particle mass concentration

preserves levels close to the background concentration of  $3 \mu\text{g}/\text{m}^3$ . Pokorski [57] who conducted a study during the period 2006–2011 found that percentages of 15% and 22% for cardiopulmonary mortality could be prevented in Lublin and Katowice respectively. Likewise, for lung cancer mortality *ER* in Athens, Kuopio, and Lisbon was found equal to 29%, 15%, and 49% respectively with % *AF* being equal to 22.7, 12.8, and 32.9 for Athens, Kuopio, and Lisbon, respectively (Table 8). Similar results are published in Pokorski [57] where the authors found that lung cancer mortality can be prevented by 23% and 32% in Lublin and Katowice respectively, whilst, Cardaba Arranz et al. [56] found that 26% of cardiopulmonary mortality and 36% of lung cancer mortality can be prevented in Valladolid if the ambient concentration was equal to  $3 \mu\text{g}/\text{m}^3$ . In addition, Evans et al. [58] proposed that the global fraction of mortality attributed to  $\text{PM}_{2.5}$  was 12.1% for cardiopulmonary disease and 16.8% for lung cancer. The authors also pointed out that the eastern Mediterranean and western Pacific regions had a greater *AF* of mortality associated with  $\text{PM}_{2.5}$  in comparison with African sub regions.

Furthermore, Table 8 indicates that the sum of deaths due to cardiopulmonary mortality and lung cancer are 3930, 44, and 2820 for Athens, Kuopio, and Lisbon respectively. The annual total mortality rate was approximately 1% in all the cities, ranging from the minimum value of 0.92% for Kuopio to maximum of 1.2% in Lisbon. Herein, the estimated deaths due to air pollution in Athens, Kuopio, and Lisbon represent ca. 0.1% of the total mortality in Athens and Lisbon and 0.04% in Kuopio.

**Table 8.** Percentages (%) of the excess risks (*ER*) and attributable fractions (*AF*) along with the number of attributable deaths for (a) all-cause mortality associated with short-term exposure to  $\text{PM}_{10}$ , (b) cardiopulmonary mortality and (c) lung cancer mortality associated with long term exposure to  $\text{PM}_{2.5}$  in each city. The corresponding confidence intervals (*CI*) are given in brackets.

	Athens		Kuopio		Lisbon	
(a) All-cause mortality ( $\text{PM}_{10}$ )						
ER (95% CI)	0.77	(0.58–0.96)	0.02	(0.02–0.03)	2.2	(1.6–2.7)
AF (95% CI)	0.77	(0.57–0.96)	0.02	(0.02–0.03)	2.1	(1.58–2.62)
Deaths (95% CI)	320	(236–398)	0.2	(0.2–0.3)	730	(546–905)
(b) Cardiopulmonary mortality ( $\text{PM}_{2.5}$ )						
ER (95% CI)	19	(6.4–33)	9.5	(3.4–16)	31	(10–55)
AF (95% CI)	15.8	(6.0–24.5)	8.7	(3.2–13.9)	23.4	(9.2–35.4)
Deaths (95% CI)	3450	(1311–5353)	38	(14–61)	2450	(962–3702)
(c) Lung cancer mortality ( $\text{PM}_{2.5}$ )						
ER (95% CI)	29	(9.9–52)	15	(5.2–25)	49	(16–92)
AF (95% CI)	22.7	(9.0–34.2)	12.8	(4.9–20.0)	32.9	(13.7–47.8)
Deaths (95% CI)	480	(190–721)	6.1	(2.3–9.5)	370	(155–540)
Sum of deaths (b+c)	3930		44.1		2820	

In this study we applied different methods for risk characterization: cancer risk (*CR*), hazard quotient (*HQ*), hazard index, attributable all-cause mortality, and cause specific mortality. Xiong et al. [59] discussed the strengths and weaknesses of these methods, pointing out that the hazard index and hazard quotients are merely indicators and are suitable for identifying a potential risk; they cannot be used for true quantification of the risks. Cancer slope-based risk estimates represent the probability of an individual developing cancer in a 70-year lifetime at a given chronic average daily intake level. While the risk estimate is quantitative and risks from multiple exposures can be summed up (additivity), the definition built on lifetime risk makes it somewhat difficult to interpret the risk magnitude in a normal decision making context. It is easier to interpret epidemiological risk assessment-based annual number of cases. Xiong et al. [59] pointed out that the numbers of cases are useful for risk comparisons, estimation of economic impacts, and setting priorities.

In our work the cancer slope factor-based estimates of cancer cases attributable to heavy metals were small. Excess risk-based estimates of deaths are substantially larger for all three mortality models. It is clear that the component specific cancer risk model lacks polycyclic aromatic hydrocarbons known

to be carcinogenic, as well as potentially carcinogenic components such as black carbon and secondary organics. It is important to develop the dose-based health risk modeling towards better comparability with epidemiological RR-based risk estimates. This would allow for taking advantage of the refined respiratory tract dose model features.

Comparing PM<sub>10</sub>-based all-cause mortality estimates with the PM<sub>2.5</sub>-based cause-specific mortalities the former produces smaller number of deaths for all cities. The PM<sub>2.5</sub>-based cause-specific mortality models for cardiopulmonary and lung cancer mortalities therefore totally dominate the overall effects. Only in Lisbon the all-cause mortality exceeded the lung cancer mortality estimate. It should be noted that the relative risk-based mortality estimates included baseline levels (10 µg/m<sup>3</sup> for PM<sub>10</sub> and 3 µg/m<sup>3</sup> for PM<sub>2.5</sub>). Any possible health or mortality effects under these were not accounted for.

The PM<sub>2.5</sub>-based mortality estimates, cardiopulmonary and lung cancer mortality are mutually exclusive and can therefore be summed together. The PM<sub>10</sub>-based all-cause mortality in principle contains the former ones and should not be added to the PM<sub>2.5</sub> estimates in order to avoid double-counting.

Cancer slope-based cancer risks potentially partly overlap with the mortality risks. However, the magnitude of the former ones is substantially smaller and thus any practical implications of potential double counting can be ignored. The cancer slope and hazard quotient-based risk estimates account for the respiratory tract deposition of particles. This methodology is very interesting and promising for future development. However at least in the current work it seems that merely focusing on PM<sub>2.5</sub>-attributed cause-specific mortality captures the magnitude of health risks in the adult populations.

In the case of the children, mortality is a substantially less relevant endpoint. It would be interesting to develop methods to study effects on e.g., respiratory infections, school absenteeism, and academic performance.

#### 4. Conclusions

Human health risks associated with exposure to particle-bound metals (cancer risk and hazard quotient) and particle mass concentrations (PM<sub>10</sub> and PM<sub>2.5</sub>) (excess risks and attributable deaths) were estimated in the current study. Ambient air quality data was obtained, human time-activity weighted exposures calculated, and respiratory tract doses were estimated in three selected European cities (Athens, Kuopio, and Lisbon). Due to the different sampling periods and locations no comparison between the three cities was performed but the data were used in order to retrieve the corresponding estimates for the health indexes and discuss their implications.

In particular, we applied several risk models and compared their results to evaluate non-carcinogenic, cancer, and mortality risks. It was found that the non-carcinogenic health risks (Methodology 2) are greater in children because the deposition fraction of children is higher than the deposition fraction of adults. On the other hand, the carcinogenic health risks (for both methodologies) were found to be higher for adults due to the higher ratio of exposure duration to averaging time.

The hazard quotient that represents the non-carcinogenic effects due to the inhalation of particle-bound metals was lower than the acceptable level (<1). Hence no significant risk is expected for all the cases investigated. In addition, the cumulative cancer risk was lower than the acceptable level (10<sup>-4</sup>). However, the cancer risk for some metals was higher than the acceptable level (10<sup>-4</sup>) thus a health risk is expected from exposure to these metals. Both the excess risk and attributable fraction (for PM<sub>10</sub> and PM<sub>2.5</sub>) were higher in Lisbon compared to Athens and Kuopio due to higher ambient concentrations measured in this city. In addition, the results have shown that the first methodology provides higher *CR* and *HQ* compared to the second methodology for all cases investigated.

The epidemiology-based lung cancer and cardiopulmonary mortality estimates were higher than the annual total cancers estimated from the toxicological life time cancer risks. In Athens and Lisbon the excess mortality rate caused by air pollution was approximately 0.1%, and in Kuopio 0.04%.

The background mortality level was 0.92% in Kuopio, 1.1% in Athens, and 1.2% in Lisbon. There are specific benefits in respiratory tract dose modeling, but at the moment it seems that the overall health impact is best captured—or at least dominated—by using PM<sub>2.5</sub> excess risk-based mortality models.

Although, PM concentrations for the cities under study do not exceed air quality standards the present study highlights that the health impacts from exposure to air pollution are still an important issue. Finally, implementation of several available scientific approaches to estimate health risks caused by exposure to airborne particulate matter is an important step for air pollution control and for mitigation of urban air pollution.

**Author Contributions:** E.C. conducted model calculations with ExDoM2, applied the methodology to estimate the health risk indexes and prepared the manuscript; S.E.C. contributed to the preparation of the manuscript; H.L. calculated the case estimates for background mortality, and cancers and mortality attributable to the exposures; S.M.A. analyzed input data for Lisbon and provided important suggestions; K.E. analyzed input data and provided data for Ni and Co for Athens; O.H. supervised the transformation of cancer risk probabilities to case estimates and the calculation of mortality estimates; M.L. supervised the preparation of the paper. All co-authors participated in writing the paper.

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