Aerosol and Air Quality Research, 16: 1452–1463, 2016

ISSN: 1680-8584 print / 2071-1409 online
doi: 10.4209/aaqr.2015.09.0536

Personal Exposure and Dose of Inhaled Ambient Particulate Matter Bound Metals in Five European Cities

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ABSTRACT

The objective of the current study is the determination of the personal exposure and dose of ambient particulate matter-bound metals in human tissues at five European cities. The accumulation in human body of lead (Pb), arsenic (As) and cadmium (Cd), in five European cities (Athens, Seville, Rome, Frankfurt and Zabrze) was calculated using an exposure and dose assessment model, ExDoM, and a pharmacokinetic model, PBPK. The study subjects are adult Caucasian non-smoker males. It was calculated that the highest dose of particulate matter is received from a resident of Seville, due to the higher ambient PM_{10} levels in the city compared to the other sites. First, the current study showed that the European Union thresholds of particle-bound Pb, Cd and As concentrations were not exceeded in the cities under study. As regard the dose of Pb and As the higher dose is calculated for Athens and Seville, respectively. The highest dose of Cd is found at Zabrze, due to the high industrial activity in the city. It was calculated that after one day of exposure, the highest accumulation of Pb occurred in blood, muscles and bones. Furthermore, the highest deposition of Cd occurred in the lungs and intestines and for As in the lung and muscles. The heavy metals intake, calculated in this study, was very low in comparison with the recommended WHO levels for heavy metals intake from all types of exposure (inhalation, ingestion).

Keywords: Human exposure; Human metal dose; Exposure modelling; PBPK model; Respiratory tract model.

INTRODUCTION

Urbanization and population growth, have led to densely populated cities with high elevated anthropogenic gaseous and particulate matter emissions. As a result, the levels of particulate matter are elevated in big cities and due to human activity they are enriched with heavy metals. Many epidemiological studies (Pope, 2000; Brunekreef, 2005; Davidson, 2005) studied the risk of health impacts of particulate matter to human health.

How dangerous atmospheric particulate matter is for human health depends mainly on its size and on its chemical composition. The wide range of particles sizes and their complex chemical composition and morphology makes the relation between them and health impacts a complex process (Solomon, 2011). The airway dimensions and the breathing pattern of the individuals play also an important role on how deep particles penetrate in the human lungs and where they deposit. Soluble particles, dissolve and their components are transferred via blood to other human tissues (WHO, 1999). Accumulation of particulate matter compounds, like heavy metals, to human organs is related with the cause of serious diseases (Jarup, 2003).

In the urban atmosphere many heavy metals bound with particulate matter are present. The current study focus on toxic metals associated with ambient particulate matter such as lead (Pb), cadmium (Cd) and arsenic (As). Many studies focus on these metals because Pb, Cd and As are in the list of the ten chemicals of major public health concern (WHO, 2010), Pb is characterized as possibly carcinogenic to humans (WHO, 2006), Cd is characterized as carcinogenic to humans (WHO, 2006) and As associated with an increased risk of cancer (Chiou *et al.*, 1995). These three heavy metals can be characterized as being road-specific, so high concentrations of them are found in big cities (Hildemann *et al.*, 1991). Moreover, the major part of these metals is in the fine mode (Espinosa *et al.*, 2001; Samara *et al.*, 2005; Pérez *et al.*, 2008).

The objective of this study is to determine the deposition of heavy metals in the human body from the inhalation of particle-bound metals, which are present in the atmosphere. The exposure model Exposure Dose Model (ExDoM; Aleksandropoulou and Lazaridis, 2013) is used for the estimation of the deposited dose and retention of aerosol particles-bound metals (Pb, Cd, As) in the respiratory tract (RT) of human body and a pharmacokinetic PBPK model (Chalvatzaki *et al.*, 2014; Chalvatzaki *et al.*, 2015) is also applied to estimate the movement of metals from the blood into the tissues as a blood-flow-limited model.

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METHODS

Cities under Study

In order to estimate the exposure of residents of different European cities to atmospheric particle-bound metals, data from five different studies were evaluated. The studies selected from the literature meet the following criteria: (1) the studies had to be performed at big European cities and in different geographical parts of Europe; (2) The studies had to include not only the chemical composition of particulate matter, but also the size distribution of the heavy metals analyzed, in order to determine their deposition fraction in different parts of the human respiratory tract. The studies that were selected took place in Athens (Karanasiou *et al.*, 2007), Rome (Canepari *et al.*, 2008), Seville (Álvarez *et al.*, 2004), Frankfurt (Zereini *et al.*, 2005) and Zabrze (Rogula-Kozłowska *et al.*, 2013).

Athens, the capital of Greece, is a densely populated city of about 4 million residents with some industries in its greater metropolitan area. The measurements (Karanasiou *et al.*, 2007) were performed from June to July 2001, at a central avenue of Athens, Patission, at 21m height above street. The site is affected by the heavy traffic of the avenue (37,000 cars day-1, Thomaidis *et al.*, 2003).

Rome, capital of Italy with population about 2.7 million, has not heavy industrial activity (Perrino *et al.*, 2008). The sampling in Rome (Canepari *et al.*, 2008), took place, in April 2006, at an urban background site, which is influenced by the traffic of a near located urban street and a parking lot. The site is at the area of the University of Rome «La Sapienza» and the duration of the measurements was 15 days.

Seville, the fourth largest city of Spain, is one of the most populated cities of Spain with some industrial activity concentrated in industrial parks. In Seville (Álvarez *et al.*, 2004), samples were collected, in duration of 18 months, in 24 different sites, including urban, traffic, suburban and industrial sites. The data provided by the authors are average values of all sites.

Frankfurt, the fifth largest city in Germany, is characterized by heavy traffic. Zereini *et al.* (2005) selected a street with heavy traffic (32,500 vehicles day^{-1}) to collect samples for analyzing the chemical composition of ambient particulate matter. Three different samples were taken during the period of August 2001–July 2002.

Zabrze, a city in Silesia in southern Poland, is smaller than the rest of the selected cities in the current work with population about 200,000, but is a city with big interest in terms of air pollution. In this area there is high concentration of particulate matter due to the presence of old steel works, cokeries and coal mines. The measurements (Rogula-Kozłowska *et al.*, 2013) were done at an urban background site during the period of January to March 2008.

There are a limited number of studies in the scientific literature including size distribution data of ambient particulate matter and bound metals simultaneously. Therefore the data used in the current study were obtained at different time periods and from different sites in urban areas in Europe. The main objective was to calculate the human exposure and dose of PM_{10} and bound metals in different urban areas in Europe.

Exposure Scenario

The activity pattern and the breathing parameters of the subject studied, influence the personal exposure and dose. The subject is considered to be a male, adult, Caucasian, resident of the cities under study who works 8h outdoors. The daily timetable of the person is the following: Resting (indoors) 12 p.m. to 8 a.m., light exercise (outdoors - urban environment) 8 a.m. to 4 p.m., sitting awake (indoors) 4 p.m. to 12 p.m. It is considered that the subject is nose breather and no smoker. The ventilation rates that were used as input data for resting, light exercise and sitting awake are 0.45, 1.5 and 0.54 $m^3 h^{-1}$ (reference values for adult Caucasian males; ICRP, 1994a), respectively.

Exposure and Dose Assessment Using the ExDoM Model

An exposure and dose assessment model for simulating the dynamics of respirable particulate matter in human airways was developed by Aleksandropoulou and Lazaridis (2013). The estimation of the human dose is based on the Human Respiratory Tract Model (HRTM) of the ICRP (ICRP, 1994a). The RT is divided in five regions, the extra thoracic airways ET1 (anterior nose) and ET2 (posterior nasal passages), the thoracic BB (bronchial), bb (bronchiolar) and the alveolar interstitial AI. Within each region of the lung, exposure is influenced by the inhalability, and the deposition is calculated after accounting for the filtering effect of the preceding airways.

For high wind speed (> 1 m s^{-1}), the inhalability (nasal and oral) of particles is calculated according to the ICRP (1994a):

$$Inhalability = 1 - 0.5\left(1 - \left[7.6\times10^{-4}\times d_{ae}^{2.8} + 1\right]^{-1}\right) + 1.0 \times 10^{-5}\times u^{2.75}\times\exp\left(0.055\times d_{ae}\right) \quad (1)$$

where, dae (μm) is the aerodynamic particle diameter and u (m s^{-1}) is the wind speed.

For low wind speed (< 1 m s^{-1}) the logistic function proposed by Menache *et al.* (1995) is used for the estimation of nasal inhalability:

$$Inhalability_{nasal} = 1 - \left[1 + \exp\left(13.56 + 0.4343\times\log\left(d_{ae}\right)^{-4.88}\right)\right]^{-1} \quad (2)$$

whereas the function proposed by Brown (2005) is used for the estimation of oral inhalability:

$$Inhalability_{oral} = (1 + 0.44)\times\left[1 + 0.44\times\exp\left(0.0195\times d_{ae}\right)\right]^{-1} \quad (3)$$

The ExDoM is implemented for the estimation of the exposure and dose of an adult Caucasian male exposed to PM-bound metals at indoor and outdoor environments in

different European countries. The PM exposure and the deposition, dose, clearance and finally retention of aerosol particles in the respiratory tract, the gastrointestinal tract (GI) tract and their absorption to blood are assessed based on a ‘‘realistic’’ exposure scenario, according to a typical time schedule of an individual.

The individual’s dose rate (H; μg h^{-1}) is calculated as:

$$H = \sum BC_i n_{i,j} \quad (4)$$

where C_i is the exposure concentration (μg m^{-3}) for particles in the size fraction i, B the ventilation rate of the exposed individual (m^3 h^{-1}), and $n_{i,j}$ the deposition fraction in region j of the respiratory tract for particles in the size fraction i. The Σ is the sum of dose rate of all particles (fine and coarse particles) in a specific region of the respiratory tract. Then, the mass of particles in each compartment of the RT, during and after exposure to particles and their fraction, is transferred to the GI tract, lymph nodes and blood is estimated taking into account the mechanical movement of particles between compartments and their absorption into blood is estimated by the expression:

$$\frac{dR_j}{dt} = \sum \left[m_{k,j} R_k - (m_{j,k} + s) \times R_j \right] + H_j \quad (5)$$

where, m is the mechanical movement rate of particles from compartment k to j ($m_{k,j}$) or the opposite ($m_{j,k}$), s is the rate of absorption into blood, R is the retained mass after time t in compartments j, and H_j is the instantaneous dose applied to the compartment j at time t.

Based on the ICRP absorption to the blood is dependent on the chemical form of the particles. The absorption behavior of particles is classified in three main categories: Type F (fast), M (moderate) or S (slow). Particle absorption in blood for PM_{10} was assumed to be moderate in the simulations while for particles-bound metals it is based on the ICRP recommendations. Particle absorption in blood was moderate, fast and slow for PM_{As}, PM_{Pb} and PM_{Cd}, respectively (ICRP, 1994a, b).

In addition, the absorption to the blood occurs only in four regions (ET2, BB, bb and AI) of the respiratory tract. In the ET1 region no absorption to the blood occurs (ICRP, 1994a).A detailed description of the ExDoM can be found in Aleksandropoulou and Lazaridis (2013) The output (lung dose, blood dose and GI_tract dose) from the ExDoM model was used as input for PBPK model.

Physiologically Based Pharmacokinetic Model

A physiologically based pharmacokinetic (PBPK) model for inhaled PM-bound metals in humans is also developed. The PBPK model was developed to describe the movement of metals from the blood into the tissues as a blood-flow-limited model.The model is applicable for the prediction of the kinetics and metabolism of As, Pb and Cd in the human body. The PBPK model is based on the studies of Chou *et al.* (2009) and Sharma *et al.* (2005) for As and Pb, respectively. The Cd pharmacokinetics was modelled using the formulation proposed in Kjellstrom and Nordberg model (Kjellstrom and Nordberg, 1978). The PBPK model structure (Fig. 1(a)) contains compartments for the lung, liver, kidney, GI tract, skin, muscle, fat tissues, heart, brain and remaining body tissues. Model parameters were obtained from the scientific literature. To implement the model, the following parameters are required: Tissue/Blood partition coefficients for the various tissue groups (adopted from Liao *et al.* (2008) for As and from Sharma *et al.* (2005) for Pb), elimination rate constants (adopted from Liao *et al.* (2008)), whereas biochemical constants for metabolism and first-order rate constants for As were derived from Chou *et al.* (2009). The physiological constants (blood flow rates and tissue volumes) were obtained from ICRP (2003) and Lenz (2010). A thorough description of the model parameters are given in Chalvatzaki *et al.* (2014).

The behaviour of As and Pb (j) in each tissue group (i) can be described by a set of first-order differential equations (Sharma *et al.*, 2005; Chou *et al.*, 2009):

$$\frac{dA_{i,j}}{dt} = Q_i \left(C_{a,j} - C_{v,i}^j \right) - \text{Metabolism}_{i,j} - \text{elimination}_{i,j} \quad (6)$$

$$C_{v,i}^j = \frac{C_{i,j}}{P_{i,j}} \quad \text{for As} \quad (7)$$

$$C_{v,i}^j = 0.55 \times Cp_{ven,i} + 0.45 \times Cp_{ven,i} \times \left(1 + \frac{BIND}{KBIND + Cp_{ven,i}} \right) \quad \text{for Pb} \quad (8)$$

where $A_{i,j}$ is the dose of chemical j in tissue group (i) (mg or μmol), Q_i is the blood flow rate to tissue group i (h^{-1}), $C_{a,j}$ is the arterial concentration (mg L^{-1} or μmol L^{-1}) of chemical j, $C_{i,j}$ is the concentration of chemical j in tissue group i (mg L^{-1} or μmol L^{-1}), and $P_{i,j}$ is the tissue i/blood partition coefficients for chemical j, $Cp_{ven,i}$ is the lead concentration in venous blood plasma flow out from the *i* organ or tissue (mg L^{-1}), *BIND* is the maximum capacity of erythrocytes to bind lead (mg L^{-1}) and *KBIND* is the half-saturation constant, useful in partitioning of lead between blood and blood plasma (mg L^{-1}).

The dose of metals in tissues depends mainly on the tissue/blood partition coefficient and blood flow to the tissue. The tissue/blood partition coefficient is related with the retention in tissues. High tissue/blood partition coefficients imply high dose in tissues while tissues that receive a high blood flow (e.g., muscle during light activity) may achieve high dose of metals even though the tissue partition coefficient is low.

The methylation of arsenite (As(III)) takes place mainly in the liver and kidney according to Michaelis–Menten kinetics (Chou *et al.*, 2009):

$$Metabolism_{liver} = \frac{V_{\max,liver}^{3+\to MMA} \times C_{liver}^{3+}}{K_{m,liver}^{3+\to MMA} + C_{liver}^{3+}} + \frac{V_{\max,liver}^{3+\to DMA} \times C_{liver}^{3+}}{K_{m,liver}^{3+\to DMA} + C_{liver}^{3+}} \quad (9)$$

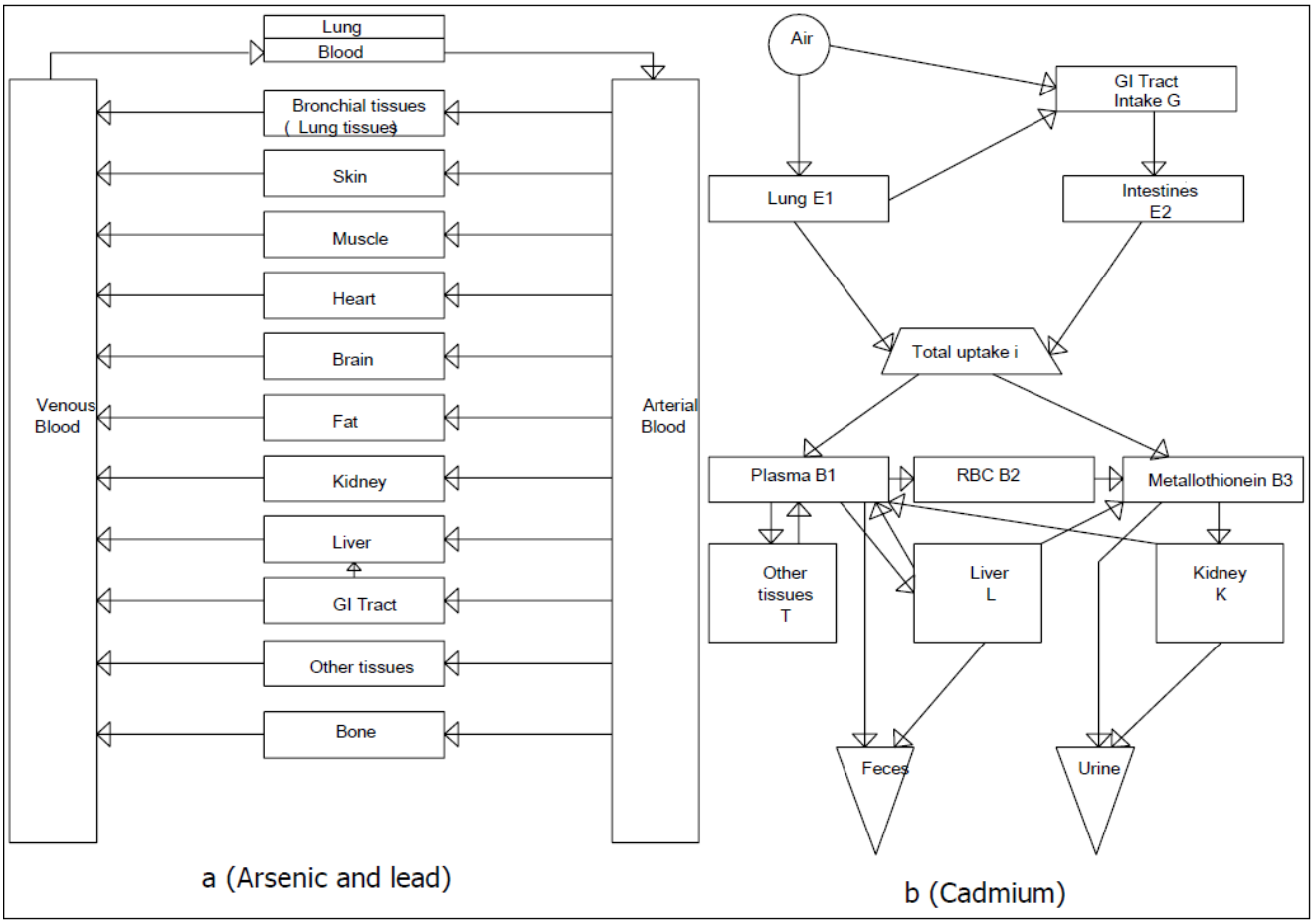

Fig. 1. (a) A typical Physiologically-Based PharmacoKinetic (PBPK) model structures for Arsenic (AS) and lead (Pb) (adapted from Chou *et al.*, 2009 for As and from Sharma *et al.*, 2005 for Pb); (b) A schematic representation of the eight-compartment kinetic model for the metabolism of cadmium in human tissues (adapted from Kjellström and Nordberg, 1978).

$$Metabolism_{kidney} = \frac{V_{\max,kidney}^{3+\to MMA} \times C_{kidney}^{3+}}{K_{m,kidney}^{3+\to MMA} + C_{kidney}^{3+}} + \frac{V_{\max,kidney}^{3+\to DMA} \times C_{kidney}^{3+}}{K_{m,kidney}^{3+\to DMA} + C_{kidney}^{3+}} \quad (10)$$

where, $V_{\max,liver}^{3+\to MMA}$ is the maximum reaction rate for As(III) methylated to methylarsenic acid (MMA) in liver (μmol h^{-1}), $V_{\max,liver}^{3+\to DMA}$ is the maximum reaction rate for As(III) methylated to dimethylarsenic acid (DMA) in liver (μmol h^{-1}), $V_{\max,kid}^{3+\to MMA}$ is the maximum reaction rate for As(III) methylated to MMA in kidney (μmol h^{-1}), $V_{\max,kid}^{3+\to MMA}$ is the maximum reaction rate for As(III) methylated to DMA in kidney (μmol h^{-1}), C_{liver}^{3+} is the concentration of As(III) in liver (μmol L^{-1}), C_{kid}^{3+} is the concentration of As(III) in kidney (μmol L^{-1}), $K_{m,liver}^{3+}$ is the Michaelis–Menten constant for As(III) in liver (μmol L^{-1}) and $K_{m,kid}^{3+}$ is the Michaelis–Menten constant for As(III) in kidney (μmol L^{-1}).

As regards cadmium (Cd), due to its long half-life time in humans, the PBPK formulation is different from typical PBPK formulations as shown in Fig. 1(b). The Cd pharmacokinetic model compared to typical PBPK models contains different number of compartments and uses a different set of equations. The transport of Cd between the compartments was assumed to follow first-order exponential functions. The Cd pharmacokinetic model is a linear eight-compartment (depicted in Fig. 1(b)) kinetic model, largely based on human data, which can be divided into four parts with different functions: absorption and uptake, transport and distribution, excretion, retention and accumulation.

Input Data

Available data in the scientific literature, on ambient metal concentrations of PM_{10} levels including Pb (all five cities), Cd (Athens, Rome, Seville and Zabrze) and As (Seville, Rome, Zabrze) were used.

The calculation of the deposition of heavy metals in different human body organs was accomplished with the use of ExDoM and PBPK models. ExDoM needs specific input data in order to calculate the deposition of particles in the RT, the GI tract and their absorption to blood. Input data for ExDoM are: particles concentration, size distribution, density, shape factor and exposed subject's characteristics

like breathing type and pattern. Furthermore, the results of ExDoM model are input data for the PBPK model. In the case of Cd it is not necessary to use the ExDoM model, as the applied PBPK model for Cd calculates the deposition of particles in the lung, the GI tract and their absorption to blood.

An important factor that influences the inhalability of PM_{10} and is input parameter for the ExDoM model is the wind speed. For each city, the yearly average wind speed was used in the calculations.

Data for the concentrations of PM_{10} and particulate matter-bound metals were used from the studies selected (Table 1). The highest PM_{10} levels were occurred in Zabrze followed by Frankfurt, Seville, Rome and Athens. In this classification it must be taken into consideration that $PM_{8.8}$ were measured in Athens and not PM_{10} as in the rest of the cities. Cadmium particles concentration was more elevated in Zabrze (1.2 ng m^{-3}) and Athens (0.8 ng m^{-3}) in relation with Seville (0.5 ng m^{-3}) and Rome (0.3 ng m^{-3}). In Zabrze this occurs due to the intense industrial activity in the city. Lead particles concentration was higher in Athens (77.1 ng m^{-3}) and Zabrze (40.6 ng m^{-3}), respectively, with Frankfurt (33.0 ng m^{-3}), Seville (14.0 ng m^{-3}) and Rome (9.6 ng m^{-3}) following. The elevated levels of Pb in Athens are result of the vehicular traffic which is the main emission source of Pb in Athens (Thomaidis *et al.*, 2003). In the increased Pb levels in Athens contributes the presence of vehicles which used still leaded gasoline at the period of the sampling, while in the other four cities the measurements were done after the ban of leaded gasoline. Arsenic particles concentration was notably higher in Seville (3.4 ng m^{-3}) and Zabrze (3.0 ng m^{-3}) with large difference from Rome (0.3 ng m^{-3}), where the concentration is almost 8 times lower. The emission sources of Pb and As are mainly vehicle emissions and re-suspended road dust, whereas the emission sources of Cd and a part of As are industrial activity (Thomaidis *et al.*, 2003). Main sources of As particles are combustion processes, iron and steel industry, timber industry,waste treatment and disposal facilities (Maggs, 2000). For these reasons, As and Cd levels are elevated in Zabrze that has industrial activity and are lower in Rome, where the industries are far from the city centre.

The European Union thresholds of particle-bound Pb, Cd and As inhalation were not reached by the mean values for the sampling period in none of the cities under study Threshold value for Pb concentration averaged over a calendar year, in the PM_{10} fraction, is 500 ng m^{-3} according First Daughter Directive (1999/30/EC). Target values for Cd and As concentrations averaged over a calendar year, in the PM_{10} fraction, are 5 ng m^{-3} and 6 ng m^{-3}, respectively.

US-EPA has created the Integrated Risk Information System (IRIS), a program that evaluates information on health effects that may result from exposure to environmental contaminants. For the inhalation of heavy metals, such as As and Cd, exist specified risk levels. Risk is presented as the probability of formation of cancer of 1 in 10,000 (E-4 risk level), 1 in 100,000 (E-5 risk level) or 1 in 1,000,000 (E-6 risk level), (U.S. EPA., 1986). For exposure in As particles, concentration close to 2×10^{-3} μg m^{-3} t is E-5 risk level and close to 2×10^{-4} μg m^{-3} - is E-6 risk level. Taking into consideration the mean concentrations of arsenic particles for the sampling periods, shown on Table 1, the probability of cancer formation due to inhalation of As is 1 in 100,000 in Seville and Zabrze and 1 in 1,000,000 in Rome. Regarding Cd, the mean exposure concentrations for the sampling periods in all the cities studied,is below or close to 6×10^{-4} μg m^{-3} that is E-6 risk level.

The indoor particle concentration (for fine and coarse modes) was calculated using the indoor/outdoor ratio for naturally ventilated buildings in the absence of indoor sources. Morawska and Salthammer (2003) concluded that, for naturally ventilated buildings in the absence of indoor sources, I/O ratios for PM_{10} and $PM_{2.5}$ ranged from 0.5 to 0.98 and 0.54 to 1.08, respectively. Therefore, for fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$) indoor/outdoor ratio an average ratio equal to 0.8 and 0.5, respectively, was adopted.

One of the most important factors, determining the deposition of particulate matter in the human respiratory tract is their size. In the ExDoM model, it is necessary to use the size distribution of the particulate matter as an input parameter. The determination of concentrations and size distribution of heavy metals in the PM_{10} fraction was performed using data obtained from gravimetric measurements. In Athens (Karanasiou *et al.*, 2007), the samples were collected with a six stage Andersen cascade impactor, with cut-off diameters (at 50% efficiency collection) 0.35 μm, 0.62 μm, 1.2 μm, 1.8 μm, 3.6 μm and 8.8 μm (Fig. 2(a)). In Rome (Canepari *et al.*, 2008) (Fig. 2(b)) and Zabrze (Rogula-Kozłowska *et al.*, 2013) (Fig. 2(c)), a 13-stage impactor (DLPI DEKATI Ltd) was used with cut-off diameters (at 50% efficiency collection) 0.030 μm, 0.060 μm, 0.108 μm, 0.17 μm, 0.26 μm 0.40 μm, 0.065 μm, 1 μm, 1.6 μm, 2.5 μm, 4.4 μm, 6.8 μm and 10 μm. A cascade impactor with cut-off diameters (at 50% efficiency collection) 0.6 μm, 1.3 μm, 2.7 μm, 4.9 μm and 10 μm was used to collect samples in Seville (Álvarez *et al.*, 2004) (Fig. 2(d)). An eight-stage Andersen impactor was selected for the

Table 1. Ambient concentrations of PM_{10}, $PM_{PB,}$ PM_{As} and PM_{Cd} in Athens (Karanasiou *et al.* 2007), Rome (Canepari *et al.*, 2008), Seville (Álvarez *et al.*, 2004), Frankfurt (Zereini *et al.*, 2005) and Zabrze (Rogula-Kozłowska *et al.*, 2013).

City	PM_{10} (μg m^{-3})	PM_{Pb} (μg m^{-3})	PM_{As} (μg m^{-3})	PM_{Cd} (μg m^{-3})
Athens[1]	19.11	0.0771	-	0.0008
Rome	27.98	0.0096	0.0004	0.0003
Seville	41.8	0.0140	0.0034	0.0005
Frankfurt	36.43	0.0330	-	-
Zabrze	38.52	0.0406	0.0030	0.0012

[1] $PM_{8.8}$.

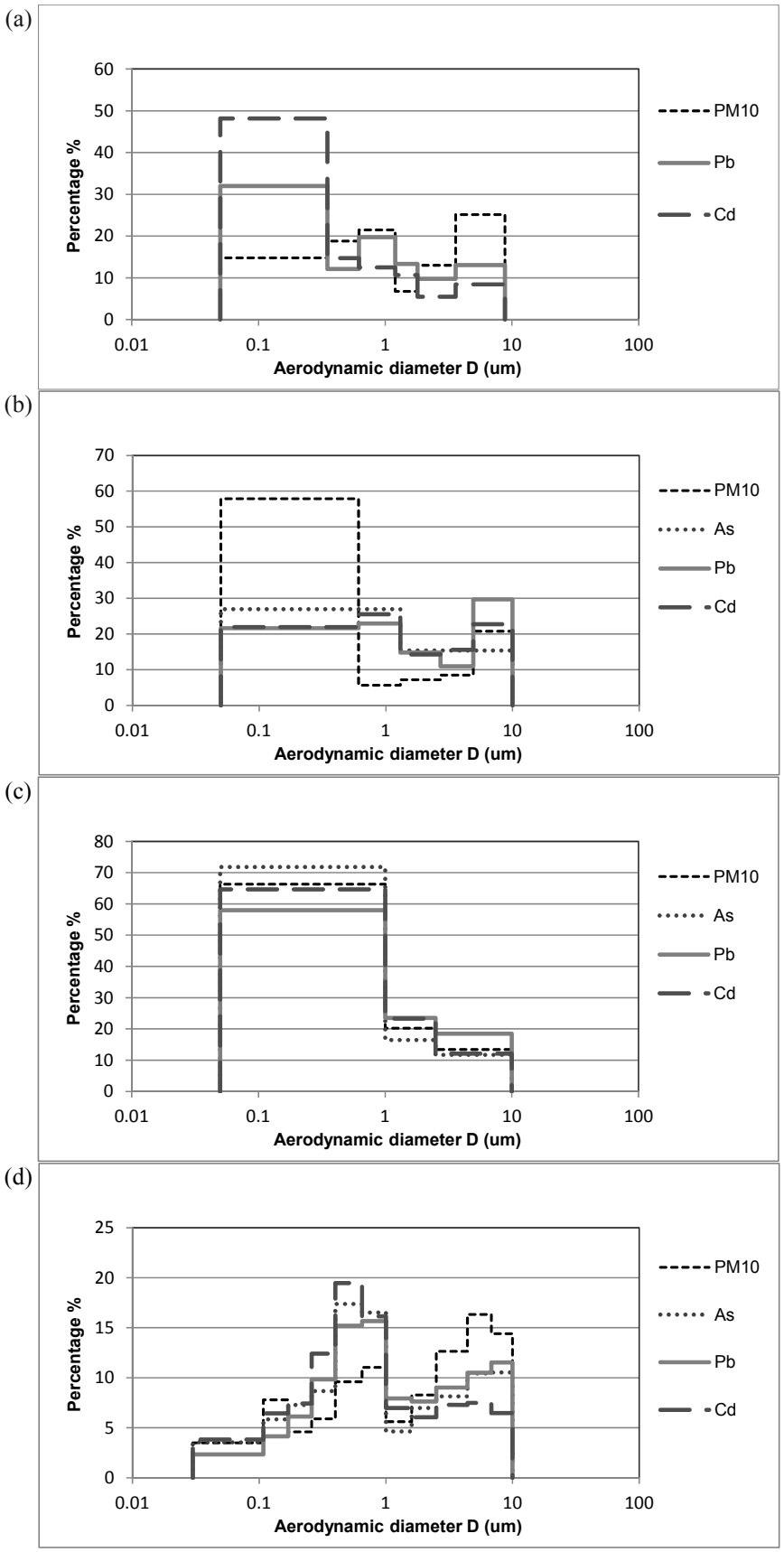

Fig. 2. PM_{10}, PM_{Pb} and PM_{Cd} size distribution in (a) Athens (adapted from Karanasiou *et al.*, 2007) (b) Rome (adapted from Canepari *et al.*, 2008), (c) Zabrze (adapted from Rogula-Kozłowska *et al.*, 2013) (d) Seville (adapted from Álvarez *et al.*, 2004) and (e) Frankfurt (adapted from Zereini *et al.*, 2005).

(e)

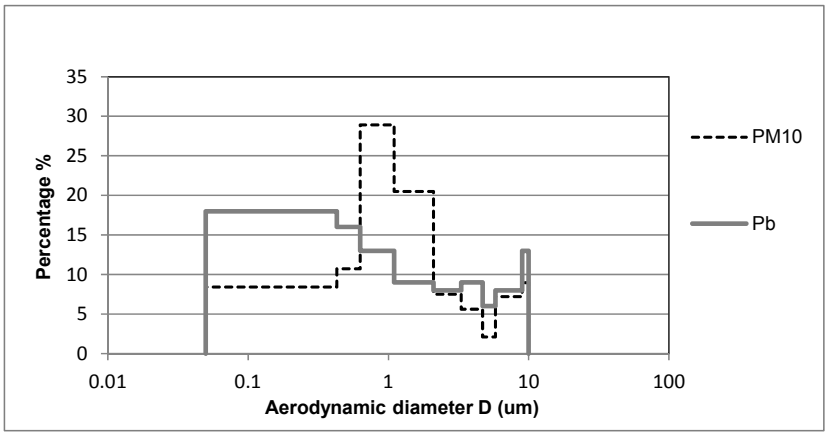

Fig. 2. (*continued*).

Table 2. Percentages of PM_{10} being in the fine and coarse fraction in the five European countries (Athens, Rome, Seville, Frankfurt and Zabrze).

City	PM_{10}		PM_{Cd}		PM_{As}		PM_{Pb}	
	Fine	Coarse	Fine	Coarse	Fine	Coarse	Fine	Coarse
Athens[1]	62%	38%	86%	14%	-	-	77%	23%
Rome[2]	57%	43%	79%	21%	71%	29%	69%	31%
Seville[3]	71%	29%	83%	17%	88%	12%	87%	13%
Frankfurt[4]	69%	31%	-	-	-	-	56%	44%
Zabrze[2]	87%	13%	88%	12%	88%	12%	82%	18%

[1] Fine: $PM_{1.8}$, Coarse: $PM_{8.8\text{-}1.8}$, [2] Fine: $PM_{2.5}$, Coarse: $PM_{10\text{-}2.5}$, [3] Fine: $PM_{2.7}$, Coarse: $PM_{10\text{-}2.7}$, [4] Fine: $PM_{2.1}$, Coarse: $PM_{10\text{-}2.1}$

Table 3. Particulate matter deposited dose in human respiratory tract and in 4 regions of the respiratory tract (ET2, BB, bb, AI) in five European countries after 24 h exposure scenario, calculated by the ExDoM model. The retention of particles in the respiratory tract and the amount of material transferred to the GI tract and absorbed in blood were calculated using a moderate clearance.

	PM				
City	Cumulative deposited dose to respiratory tract (μg)	Cumulative deposited dose in 4 regions of the respiratory tract (μg)	Retention in respiratory tract (μg)	Blood (μg)	GI Tract (μg)
Athens	1.73E+02	1.18E+02	4.05E+01	8.42E+00	6.93E+01
Rome	2.81E+02	1.88E+02	5.98E+01	1.31E+01	1.15E+02
Seville	3.56E+02	2.66E+02	1.33E+02	2.14E+01	1.11E+02
Frankfurt	3.22E+02	2.19E+02	7.75E+01	1.57E+01	1.26E+02
Zabrze	2.74E+02	2.04E+02	9.79E+01	1.62E+01	8.98E+01

sampling in Frankfurt (Zereini *et al.*, 2005) (Fig. 2(e)) with cut-off diameters (at 50% efficiency collection) 0.43 μm, 0.63 μm, 1.1 μm, 2.1 μm, 3.3 μm, 4.7 μm, 5.8 μm, 9 μm and 10 μm.

Table 2, shows the percentage of particle mass and metals that are in the fine and coarse modes. From the measurement campaigns the majority of the particle mass and metal mass are in the fine fraction. Specifically, in Seville (Fig. 2(d)) 84% of arsenic particles, 75% of lead particles and 67% of cadmium particles are in the $PM_{1.3}$ fraction and in Zabrze (Fig. 2(c)) 72% of arsenic particles, 58% of lead particles and 65% of cadmium particles are in the PM_1 fraction. These data agree with other studies in the literature (Espinosa *et al.*, 2001; Samara *et al.*, 2005; Pérez *et al.*, 2008) which studied the size distribution of Pb, As and Cd and concluded that the majority of particle-bound metals are in PM_1 fraction.

RESULTS AND DISCUSSION

Calculation of the Dose of Particulate Matter-Bound Metals Using the ExDoM Model

The exposure and dose assessment model, ExDoM, was used to evaluate the dose from the inhalation of particulate matter and particle-bound metals. In Table 3 the deposition of PM_{10} in the RT, GI tract and blood is shown. Between the European cities studied in the current study, the highest dose in the respiratory tract has a resident in Seville (3.56×10^2 μg), Frankfurt (3.22×10^2 μg), Zabrze (2.74×10^2 μg), Rome (2.81×10^2 μg) and Athens (1.73×10^2 μg), respectively for the pre-described 24 h exposure scenario.

Similar classification follows the PM_{10} deposit in blood with 2.14×10^1 μg in Seville, 1.62×10^1 μg in Zabrze, 1.57×10^1 μg in Frankfurt, 1.31×10^1 μg Rome and 8.42×10^1 μg in Athens. These classifications are in agreement with the concentration of PM_{10} in the different European cities as the internal PM_{10} dose is proportional to the ambient PM_{10} concentration. A proportion of the particles deposited, remain in the RT. Specifically 50% of the particles in Seville, 48% in Zabrze, 35% in Frankfurt, 32% in Rome and 34% in Athens deposited in the RT. It is observed that the percentage of deposition in blood is similar in the different cities (7–8%). Regarding GI tract the highest dose receives a citizen of Frankfurt 1.26×10^2 μg, with Rome (1.15×10^2 μg), Seville (1.11×10^2 μg), Zabrze (8.98×10^1 μg) and Athens (6.93×10^1 μg) following. The deposition in the GI tract is related with the ambient concentration of coarse particles (Table 2) because coarse particles are mainly deposited in the upper respiratory tract regions and transferred to the trachea by the mucociliary escalator and swallowed to the GI tract (Aleksandropoulou and Lazaridis, 2013).The greater the percentage of coarse particles the greater the transport of particles from the respiratory tract to GI tract and more specifically the percentage of particles transported to the GI tract correspond to: 61% in Rome; 59% in Athens; 57% in Frankfurt; 44% in Zabrze and 42% in Seville.

The deposition of PM_{Pb} in the lungs, GI tract and blood is shown in Table 4. Due to the fast absorption behavior of Pb (ICRP, 1994a) only a very low percentage, below 0.5% in all the cities, remains in the respiratory tract. The majority of particles deposited to RT are transferred to blood: with 87%, 80%, 75%, 73% and 71% of the deposited particles to RT transferred to blood for residents of Seville, Athens, Zabrze, Frankfurt and Rome, respectively. The deposition in the RT follows the same classification in respect to the ambient concentrations. Therefore, in the city with the higher concentration of Pb, Athens, there is calculated also the higher deposition in blood. In the GI tract, the deposition classification from the higher dose to the lower is Athens (8.51×10^{-2} μg), Frankfurt (6.05×10^{-2} μg), Zabrze (5.59×10^{-2} μg), Rome (1.51×10^{-2} μg) and Seville (1.15×10^{-2} μg).

Table 5 presents the deposition of PM_{As} in the RT, GI tract and blood. Only for Rome, Seville and Zabrze were found data for PM_{As} concentration and their corresponding size distribution. The highest deposition in the RT and blood occurs for a resident of Seville where there is the highest As ambient concentration in respect to the cities studied, and follows Zabrze and Rome. Rome has very low As ambient concentration due to the absence of industrial activity. For a resident in Rome 34% of the As particles deposited in the respiratory tract retained there after one day, whereas the percentage of deposited As particles in the respiratory tract that retained there after one day for a resident of Seville is 65% and 51% for a resident in Zabrze. This difference occurs because the percentage of particles being in the coarse mode is higher in Seville, compared with the other two cities. The percentage of the deposition in blood is similar in the three cities and ranges from 7–9% of the initial deposited particles in the RT.

Table 4. Lead particles deposited dose in human respiratory tract and in 4 regions of the respiratory tract (ET2, BB, bb, AI), retention of particles in the respiratory tract, particles transferred to the GI tract and absorbed in the blood, (fast clearance), in five European countries after 24 h exposure scenario, calculated by the ExDoM model.

	PM_{Pb}				
City	Cumulative deposited dose to respiratory tract (μg)	Cumulative deposited dose in 4 regions of the respiratory tract (μg)	Retention in respiratory tract (μg)	Blood (μg)	GI Tract (μg)
Athens	5.87E-01	4.48E-01	2.04E-03	3.60E-01	8.51E-02
Rome	7.88E-02	5.37E-02	2.12E-04	3.82E-02	1.51E-02
Seville	1.14E-01	9.41E-02	4.96E-04	8.18E-02	1.15E-02
Frankfurt	3.27E-01	2.26E-01	8.95E-04	1.64E-01	6.05E-02
Zabrze	3.23E-01	2.33E-01	1.02E-03	1.75E-01	5.59E-02

Table 5. Arsenic particles deposited dose in human respiratory tract, in 4 regions of the respiratory tract (ET2, BB, bb, AI) and retention in five European countries after 24 h exposure scenario, calculated by the ExDoM model. The retention of particles in the respiratory tract surfaces and the amount of material transferred to the GI tract and absorbed in blood were calculated using a moderate clearance.

	PM_{As}				
City	Cumulative deposited dose to respiratory tract (μg)	Cumulative deposited dose in 4 regions of the respiratory tract (μg)	Retention in respiratory tract (μg)	Blood (μg)	GI Tract (μg)
Athens	-	-	-	-	-
Rome	3.54E-03	2.34E-03	7.86E-04	1.66E-04	1.38E-03
Seville	2.79E-02	2.34E-02	1.52E-02	2.09E-03	6.09E-03
Frankfurt	-	-	-	-	-
Zabrze	1.97E-02	1.50E-02	7.74E-03	1.23E-03	6.07E-03

Application of a PBPK Model for Calculating the Dose of Metals in the Human Body

A physiologically-based pharmacokinetic (PBPK) model is furthermore used for the determination of internal dose in several pre-selected anatomical compartments. The body is subdivided into various compartments representing specific organs or homogeneous groups of tissues linked and irrigated by blood vessels (Yang *et al.*, 2010). The output (lung dose, blood dose and GI_tract dose) from the ExDoM model was used as input for PBPK model. In particular, PBPK model was developed to describe the movement of metals from the blood (ExDoM results) into the tissues.

Estimations of particle-bound metals dose in the human body were performed for arsenic (As), lead (Pb) and cadmium (Cd) of an adult Caucasian male. Among the European cities studied, the highest dose in the human body for As, Pb and Cd was found in Seville (Spain), Athens (Greece) and Zabrze (Poland), respectively due to higher ambient concentration in these countries (see Figs. 3(a), 3(b) and 4). In particular, during the period of PM_{Pb} measurements in Athens (Greece)

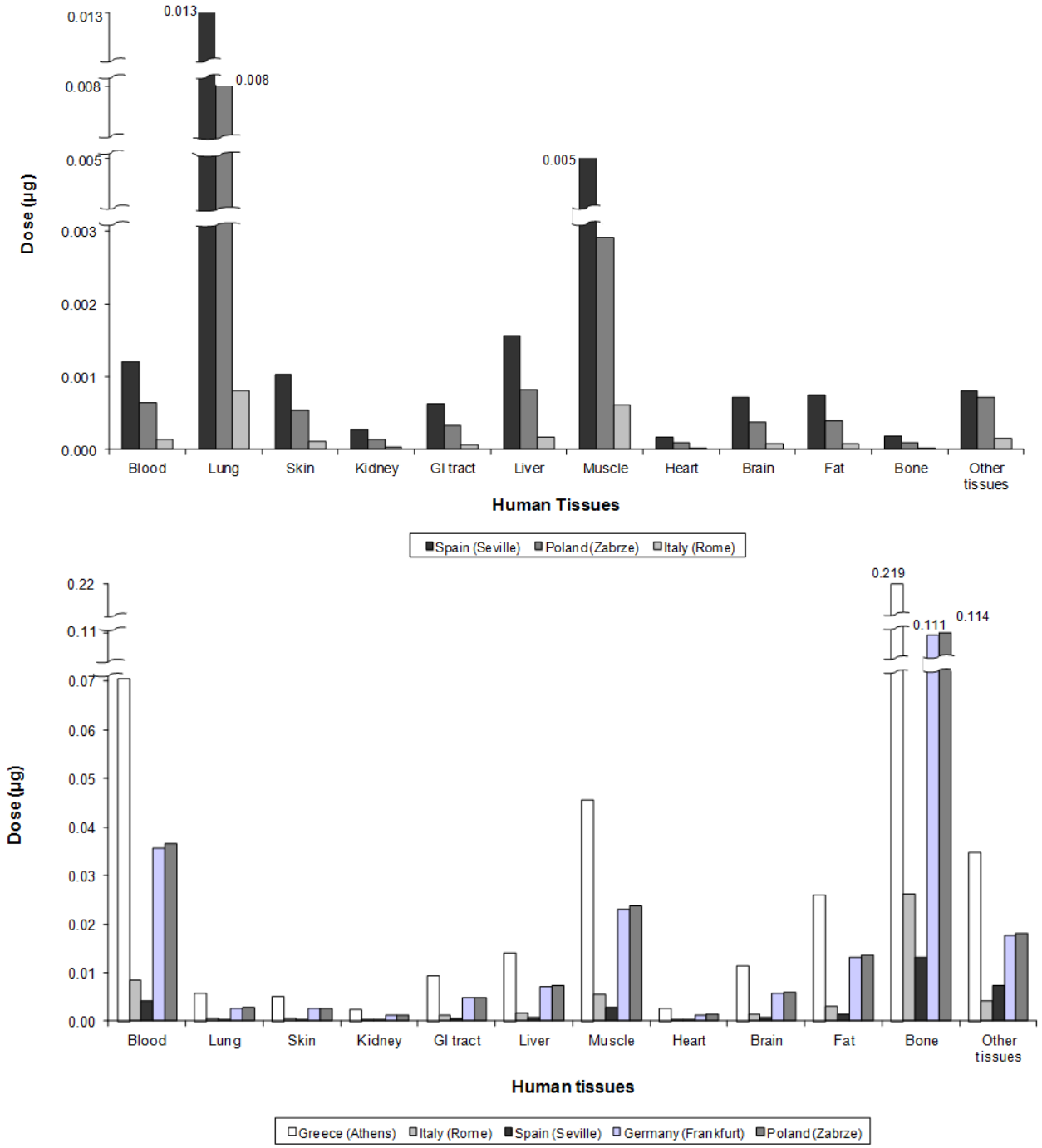

Fig. 3. Internal Dose in human tissues provided by the PBPK model in conjunction with the ExDoM for adult Caucasian males (nose breather) of five European countries (after an 24 h exposure scenario of (a) Arsenic (As) (b) Lead (Pb).

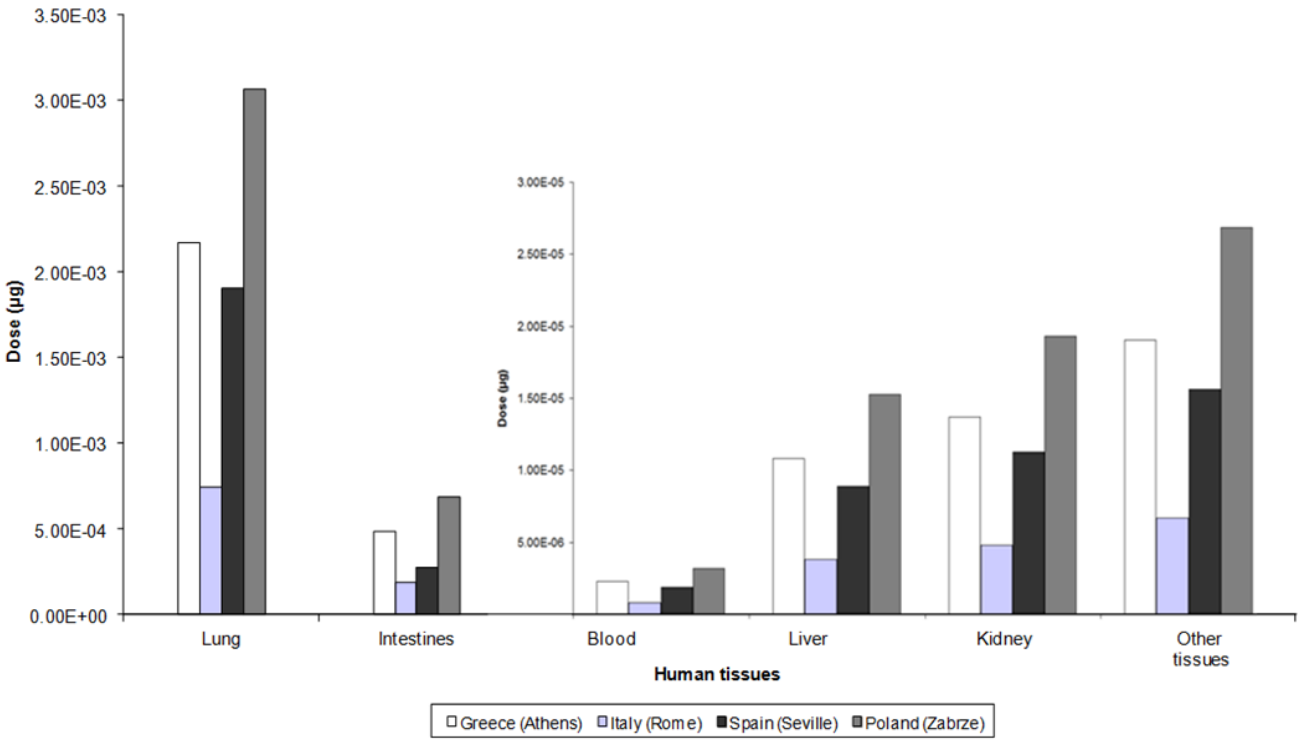

Fig. 4. Cadmium Dose provided by the kinetic model proposed in Kjellström and Nordberg (1978) for adult Caucasian males (nose breather) of four European countries after a 24 h exposure scenario, in (a) Lungs and intestines (b) Blood, liver kidney and other tissues.

by Karanasiou *et al.* (2007), leaded gasoline for older vehicles lacking catalytic converters was still available. Therefore, emissions from those vehicles are responsible for high concentrations of PM_{Pb} in Athens (Greece). In addition, PM_{cd} measurements in Zabrze (Poland) by Rogula-Kozlowska *et al.* (2013) were done in a winter heating season, when the emissions from combustion of fossil fuels for energy production (especially municipal) result to high PM_{10} concentrations (38.52 µg m^{-3}). Rogula-Kozlowska *et al.* (2013) reported that the combustion of low-quality coal in domestic furnaces (municipal emission) is the source of Cd in Zabrze in winter.

It is observed in Fig. 3(a) that after one day of exposure to PM_{AsIII} (particle-bound arsenite), the major accumulation occurs in the lung, muscles and liver (1.53×10^{-2} µg in the lung, 3.27×10^{-3} µg in the muscles and 3.27×10^{-3} µg in the liver for a resident of Seville, where there is the highest ambient measured As concentration). This result is in agreement with the study by Chou *et al.* (2009), where it was found that the highest dose is present in lungs and liver tissues after chronic exposure to Arsenic. For $PM_{Pb,}$ it is observed in Fig. 3(b) that the major accumulation occurs in the bone, blood and muscles whereas as regard PM_{Cd} (see Fig. 4) the highest dose is present in the lungs (3.07×10^{-3} µg in Zabrze), due to the slow absorption to the blood and intestines (6.89×10^{-4} µg in Zabrze) at the end of first day. In Athens the Pb accumulation in bones is 2.19×10^{-1} µg, in blood 7.05×10^{-2} µg and in the muscles 4.56×10^{-2} µg. According to WHO (2007) inhalation of cadmium can cause chronic obstructive airway disease. For Pb, the major accumulations occur in bone due to the high tissue/blood partition coefficient, in blood due to fast absorption and in muscle due to high blood flow. For Cd, because of its slow absorption from the human body, in addition to the calculation of its deposition after 24 h, the deposition of Cd after 800 h was also calculated. It was observed that after 800 h the major accumulation occurs in the other tissues, kidney and liver. This estimation comes in agreement with WHO (2007) that states that the majority of Cd inhaled is retained in the kidneys and liver with half life in these organs about 10–20 years. The conclusions are also in agreement with the study by Kjellstrom and Nordberg (1978). Furthermore, the WHO has recommended a provisional tolerable intake at 7 µg kg^{-1} Cd kg^{-1} (body weight)/week (WHO, 1993) from all types of exposure (inhalation, ingestion). The body weight of an adult Caucasian male was considered to be 73 kg in the current study and therefore the weekly allowable intake was 511 µg. In the European cities weekly intake for Cd ranged from 0.05 to 0.10 µg which are considerably lower than the recommended value. Likewise, the weekly allowable intake for Pb was calculated, from the provisional tolerable weekly intake of 25 µg kg^{-1} body weight, recommended by FAO/WHO (1999), to be 1.825 µg per week. In the current study, weekly intake for Pb ranged from 1.18 to 9.61 µg which is lower than the recommended value.

CONCLUSIONS

In the current study, the dose of particles-bound metals

in human body of an adult Caucasian male in five European countries during 24-h exposure scenario was calculated. The ExDoM in conjunction with a PBPK model was applied to determine the dose in the human body. The models are capable of studying human exposure under variant exposure conditions and for particles bound-metals. The models have been implemented using a typical exposure scenario and real measurement data. The model results showed that the highest dose in the human tissues for As and Cd was found for Italian (resident in Rome) and Polish (resident in Zabrze) male, respectively, whereas as regard Pb the highest dose was found for Greek (resident in Athens) male because ambient particles-bound metal concentrations at these cities were more elevated during the measurement periods. Therefore, elevated particulate matter-bound metals concentrations result in elevated dose in human tissues. Nowadays, with the removal of lead from gasoline and the use of new technologies, there have been some changes in vehicle emissions which will result to lower exposure and dose. Finally, the use of PBPK model can become a key component of human health effect of particulate matter-bound metals. With the use of the PBPK modelling it is possible to estimate the contaminant burden (dose) of organs and thereby potential health effects from human exposure to particulate matter-bound metals. In the cities studied, the heavy metals concentrations were below the EU thresholds and as a result the inhaled intake of Pb and Cd (not available for As) were both lower than the recommended WHO values for heavy metals intake from all sources.

ACKNOWLEDGMENTS

The present study was funded by the European Union 7th framework program HEXACOMM FP7/2007-2013 under grant agreement N° 315760.

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Received for review, September 8, 2015
Revised, December 1, 2015
Accepted, December 1, 2015