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Burden of disease at the same limit of exposure to airborne polycyclic aromatic hydrocarbons varies significantly across countries depending on the gap in longevity

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ABSTRACT

Atmospheric polycyclic aromatic hydrocarbons (PAHs) disproportionately affect human health across the globe, and differential exposure is believed to drive the unequal health burden. Therefore, this study assessed and compared the burden of disease, in disability-adjusted life years (DALYs), at the same level (or limit) of exposure to atmospheric PAHs in nine countries. We calculated the DALYs per person-year per ng/m^3 of benzo[a]pyrene from ten cancers and thirty-four non-cancer adverse outcomes using published toxicity information and country-specific disease severity. Exposure duration was averaged over 30 years and we adjusted for early-life vulnerability to cancer. The DALYs per person-year per ng/m^3 of fifteen other individual PAHs was calculated using relative potency factors, and toxicity factors derived from quantitative structure-activity relationships. We found that even at the same level of exposure to PAHs, the incremental burdens of disease varied substantially across countries. For instance, they varied by about 2–3 folds between Nigeria and the USA. Countries having the lowest longevity had the highest DALYs per person-year per ng/m^3 of each PAH. Kruskal-Wallis test ($\alpha = 0.05$) showed that the variation across countries was significant. The post hoc tests detected a significant difference between two countries when the gap in longevity was > 10 years. This suggests that countries having very low average life expectancy require more stringent PAH limit. Linear or exponential function of average longevity gave valid approximation of the DALYs per person-year per ng/m^3 of benzo[a]pyrene or phenanthrene, respectively. Furthermore, we used global gridded surface benzo[a]pyrene concentrations and global population dataset for 2007, with spatial resolution of 0.1° × 0.1°, to calculate the contribution of differential exposures to the estimated DALYs per person-year. We found that in six out of nine countries, differential exposures to PAH contribute less to the estimated health loss than differential severities of the diseases. This indicates that the risk to health from PAHs may be underreported if the severities of the diseases in the countries are not considered.

1. Introduction

There is compelling evidence that exposure to airborne polycyclic aromatic hydrocarbons (PAHs) affects health. Several cancers and non-cancer adverse effects have been linked to PAHs inhalation exposure (USEPA, 2017a; WHO, 2010). Although the exposure concentration is believed to drive the risk to health of PAHs, population susceptibility and vulnerability may increase the severity of the health effects (Kiyohara et al., 2002; Shen et al., 2014). Susceptibility is often used interchangeably with vulnerability for subpopulations having disproportionate health burdens (Shen et al., 2014; Etchie et al., 2017). But, distinctions have also been made (Kottow, 2003; Bell et al., 2013).

Susceptibility is defined here as a state of being injured and predisposed to additional harm caused by PAHs, while vulnerability refers to a state of being intact but fragile (Kottow, 2003). For instance, subpopulations having pre-existing health problems such as lung cancer

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or cardiopulmonary disease suffer disproportionately from the same level and duration of exposure to PAHs due to susceptibility. Ethnic groups that are genetically predisposed to the adverse effects of PAHs are vulnerable. Similarly, some PAH-related health effects are gender or age-specific e.g. reproductive or developmental effects, respectively (USEPA, 2017a). People in such subgroups are also vulnerable. Vulnerability may also be due to socioeconomic status (less education, less income and lower occupational status), behaviors (e.g. smoking, drug or alcohol misuse), poor quality of drinking-water, inadequate nutrition or access to healthcare (Etchie et al., 2017). Indeed, vulnerability, but not susceptibility, may disproportionately increase even the exposure dose of PAHs (Bell et al., 2013).

Regulation of PAH in air is usually based on a target exposure limit that translates into an acceptable level of risk over a lifetime of exposure (WHO, 2000a, 2010). But, this single exposure limit may represent different burden of disease for countries having disparate proportions of susceptible/vulnerable subpopulation. This is particularly true for countries having considerably different baselines and onsets of the diseases related to PAHs. Thus, accounting for such differences may provide the basis for developing country-specific health-based target that is protective of the population.

In this study, we assessed and compared the incremental burdens of disease, in disability-adjusted life years (DALYs), from the same level (or limit) of exposure to sixteen PAHs in nine countries. We determined the gap in longevity where the variation was significant. We identified valid approximation of the incremental burden of disease per ng/m^3 of each PAH using information on the average life expectancy at birth. The average life expectancy at birth may be taken as a proxy indicator of a country's average level of susceptibility and vulnerability.

The countries we selected are Bangladesh, Brazil, China, India, Indonesia, Nigeria, Pakistan, Russia and the USA. They comprise more than half (56%) of the world's population (UN, 2017). They are among the top ten countries having the highest number of premature deaths or DALYs due to air pollution exposure, globally (Cohen et al., 2017). Eight of them are among the top ten countries emitting the largest amount of PAHs (Shen et al., 2013; Zhang and Tao, 2009). Thus, the countries accounted for about 60% of the global total PAHs emitted annually. They also comprise about 70% of the global deaths or DALYs due to ambient air pollution exposure (Shen et al., 2013; Cohen et al., 2017).

2. Methods

2.1. Sources of information

The information on PAH toxicity was obtained from a detailed systematic review of the toxicology of benzo[a]pyrene (USEPA, 2017a). The review provided human equivalent benchmark concentrations or doses ($BMC_{10[HEC]}$ or $BMD_{10[HED]}$), no-observable-adverse-effect-levels ($NOAEL_{[HEC]}$ or $NOAEL_{[HED]}$) or lowest-observable-adverse-effect-levels ($LOAEL_{[HEC]}$ or $LOAEL_{[HED]}$) for several cancer and non-cancer endpoints associated with benzo[a]pyrene. However, no information was obtainable for PAH-related lung cancer in the USEPA (2017a) toxicity dataset. Thus, for uniformity, we obtained toxicological inhalation unit risk (IUR) (upper bound) for PAH-related lung cancer disease of 2.0×10^{-5} per ng/m^3 of benzo[a]pyrene (Heinrich et al., 1994; WHO, 2000a) instead of the epidemiological IUR of 8.7×10^{-5} per ng/m^3 of benzo[a]pyrene (WHO, 2000a).

For each country, we collected information on the severity of each disease related to PAH – prevalence of the disease (P), number of deaths due to the disease (N), number of years of life lost from deaths due to the disease (YLL), number of years lived in disability (YLD) and average life expectancy (L) from the Global Burden of Disease (GBD) 2016 database (IHME, 2017). We also obtained information on the age and sex distributions of people in each country (P_F) from the United Nations Population Prospect (UN, 2017).

2.2. Estimation of incremental burden of disease per ng/m^3 of PAHs in the countries

2.2.1. Benzo[a]pyrene

Because our toxicity information was for benzo[a]pyrene, we first estimated the incremental burden of disease per ng/m^3 of benzo[a]pyrene exposure in each country. We used a unified method that assumes linear, no threshold, addition to background effects for both cancer and non-cancer disease endpoints. The method assumes that the adverse effects observed in a country are due to unknown factors and inhalation exposure to benzo[a]pyrene just adds to the overall effects, thereby aggravating existing disease condition (Pennington et al., 2002; Crawford-Brown and Crawford-Brown, 2012; Etchie et al., 2013, 2014, 2018a).

For each endpoint, i, we calculated the central estimate of IUR (IUR_c, per ng/m^3) from the central estimate of $BMC_{10[HEC]}$ (ng/m^3) using the algorithm (Etchie et al., 2018a):

$$IUR_C = \frac{0.1}{BMC_{10[HEC]}} \quad (1)$$

$BMC_{10[HEC]}$ estimate was obtainable for upper respiratory tract/pharynx cancer only. Therefore, for the other endpoints, we estimated the value of $BMC_{10[HEC]}$ from $NOAEL_{[HEC]}$ or $LOAEL_{[HEC]}$, (ng/m^3) using the following algorithms (Wignall et al., 2014):

$$BMC_{10[HEC]} = 1.96 \times NOAEL_{[HEC]} \quad (2)$$

$$NOAEL_{[HEC]} = \frac{LOAEL_{[HEC]}}{3.81} \quad (3)$$

We derived the $BMC_{10[HEC]}$ value for lung cancer endpoint from toxicological (upper bound) IUR of 2×10^{-5} per ng/m^3 of benzo[a]pyrene using the following equations:

$$BMC_{10[HEC]} = 1.83 \times BMCL_{10[HEC]} \quad (4)$$

$$BMCL_{10[HEC]} = \frac{0.1}{IUR} \quad (5)$$

where:

$BMCL_{10[HEC]}$ is the lower limit of $BMC_{10[HEC]}$.

The ratios in Equations (4) and (5) were derived from inhalation toxicity values for benzo[a]pyrene-related upper respiratory tract/pharynx cancer (USEPA, 2017a).

For health effects with just oral point-of-departure human equivalent dose (POD_{HED}: $BMD_{10[HED]}$, $NOAEL_{[HED]}$ or $LOAEL_{[HED]}$, expressed in mg/kg/day), we estimated the corresponding POD_{HEC} ($BMC_{10[HEC]}$, $NOAEL_{[HEC]}$ or $LOAEL_{[HEC]}$), using the following algorithms (Reichard et al., 2016) (see Supplemental Material Tables S2 and S3):

$$POD_{HEC} = \frac{POD_{HED} \times BW \times 10^6}{V \times BCF} \quad (6)$$

$$BCF = \frac{\%Bioavailabilitythroughinhalationroute}{\%Bioavailabilitythroughoralroute} \quad (7)$$

where:

BW is average body weight of people in the country (Walpole et al., 2012) (see Supplemental Materials (Table S1).
V is volume of air breathe per 24 h. For each country, the value of 'V' was calculated using the country-specific body weight and assuming a standard inhalation rate of 0.286 m^3/kg-day, for 24 h exposure (ECHA, 2008) (see Supplemental Materials (Table S1).
BCF is bioavailability correction factor = 2 (Naumann et al., 2009).

We utilized a subchronic to chronic duration conversion factor of 3.3 obtained from experimental observation (Lewis et al., 1990). We

did not however correct for exposure (subchronic to chronic) duration for reduced embryo/fetal survival or decreased ovulation rate because the exposure periods are sensitive developmental and reproductive windows which are more important to the initiation of the effects than lifetime exposure (USEPA, 2017a). In addition, we utilized a modifying factor (MF) of 1. The MF was chosen based on scientific discernment of the completeness of the database and the number of organisms studied, and could range from zero to ten (Pennington et al., 2002).

A limitation in calculating the burden of disease from chemical exposures using toxicological method is in relating the chemical's toxicity with the disease severity. They are often not identical. In fact, the toxic effects are usually precursors to the diseases (Crawford-Brown and Crawford-Brown, 2012). To overcome this limitation, we assessed the cause of the disease. We identified and choose diseases in the GBD database that matched the toxicity endpoints (see Supplemental Materials Table S4). For instance, we assumed that decrease in embryo/fetal survival linked to benzo[a]pyrene exposure may contribute to the background incidence of maternal abortion, miscarriage and ectopic pregnancy. Neurological changes due to benzo[a]pyrene inhalation were assumed to increase the baseline incidence of conduct disorders, idiopathic developmental intellectual disability and attention-deficit/hyperactivity disorder. Likewise, we linked benzo[a]pyrene-related decrease in ovulation rate, ovary weight and ovarian follicle count to female infertility. Decreased sperm motility, abnormal sperm and decreased intratesticular testosterone were related to male infertility.

We could not identify suitable disease outcome for cervical epithelial hyperplasia (USEPA, 2017a). Most mild cases are likely to regress than progress (Burd, 2003). However, if not properly treated, some cases may develop into cervical cancer. The probability of developing into cervical cancer in affected women was calculated as 0.01% per year (Burd, 2003; Chung et al., 2010; Holowaty et al., 1999; McCredie et al., 2008). Thus, the severity (i.e. $DALY_c$) of cervical epithelial hyperplasia was taken as 0.01% of that of cervical cancer (see Supplemental Materials Table S4).

Reduction in thymus weight, B-cells, IgA and IgM are other endpoints that may result from PAHs exposure (USEPA, 2017a). The thymus grows T cells that are important to adaptive immunity against antigens. Reduced thymus weight in infants could increase vulnerability to a range of diseases caused by bacteria, viruses or fungi (Grahame et al., 2014; IDF, 2017; Janeway et al., 2001; Pearse, 2006). Likewise, individuals having reduced count of B-cells, IgM or IgA may be more vulnerable to frequent bacterial infections. Such infections may include respiratory infections, diarrheal, meningitis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary sarcoidosis, dermatitis or otitis media (IDF, 2017; Makhoul et al., 2015). They may also be vulnerable to autoimmune diseases, and allergies such as asthma (Grahame et al., 2014). Hence, we choose relevant infectious diseases for reduced thymus weight, B-cells, IgM and IgA. Furthermore, reduced level of B-cells may also increase the risk of cancer by reducing immune surveillance that could have marked tumor cells for elimination (Goodson et al., 2015; Makhoul et al., 2015). Thus, we considered the additional risk of lymphoid cancer due to PAH inhalation in our calculation (see Supplemental Materials Table S4).

For each country, we calculated the disease severity, expressed in disability-adjusted life years per case of the disease ($DALY_{ci}$), using Equation (8).

$$DALY_{ci} = YLL_{ci} + YLD_{ci} \tag{8}$$

where:

$$YLL_{ci} = \frac{YLL_i}{N_i} \tag{9}$$

$$YLD_{ci} = \frac{YLD_i}{P_i} \tag{10}$$

YLL_{ci} and YLD_{ci} is YLL and YLD, respectively, per case of the disease.

N_i and P_i have been defined previously.

Some health outcomes have no YLL_c e.g. maternal abortion/miscarriage/ectopic pregnancy, neurological effects and infertility. Thus, the YLD_c for the health outcomes equaled $DALY_c$.

The incremental burden of disease per ng/m^3 of benzo[a]pyrene ($BoD_{B[a]P}$) was estimated using the following algorithm:

$$BoD_{B[a]P} = \sum_{i=1} \frac{E \times IUR_{Ci} \times DALY_{ci} \times P_{Fi}}{L} \tag{11}$$

where:

E is time weighted exposure in ng/m^3 of benzo[a]pyrene, averaged over 30 years.
IUR_{ci} and $DALY_{ci}$ have been defined.
P_{Fi} is the fraction of the population, differentiated by sex, in each country that is affected by that endpoint (see Supplemental Materials Table S1). If both sexes have equal likelihood of the effect, then $P_{Fi} = 1$. We did not differentiate by age, as the severity information has already accounted for the fraction of the population having the baseline disease problem in that country.
L is average life expectancy of people in the country (IHME, 2017) (see Supplemental Materials Table S1).

The time-weighted exposure concentration, E (ng/m^3) was calculated using the following algorithm (USEPA, 2009):

$$E = \frac{CA \times ET \times EF \times ED_n}{AT} \tag{12}$$

where:

CA is average concentration of benzo[a]pyrene assumed to be 1 ng/m^3
ET is exposure time (24 h/day) (USEPA, 2009).
EF is exposure frequency (365 days/year). We used year-round exposure frequency for nationwide exposure, assuming that a larger proportion of the population in the countries would spend the first thirty years of life within the country.
AT is averaging time = average life expectancy at birth (L) × 365 days × 24 hours/day.
ED_n is exposure duration for a period n.

We used n = 30 years for the non-cancer exposure concentration, while for that of cancer, we used n = 2, 14 and 14 years, respectively, for 0– < 2, 2– < 16 and > 16 years old, so as to integrate age-dependent adjustment factors (ADAF) of 10, 3 and 1, respectively, for early-life vulnerability to cancer (USEPA, 2017a).

2.2.2. Other (fifteen) PAHs

We calculated the DALYs per person-year per ng/m^3 of other (fifteen) PAHs, aside benzo[a]pyrene. We used relative potency factors (RPFs) (USEPA, 2010), and relative toxicity factors (RTFs) derived from quantitative structure-activity relationships (QSAR) (Di Toro et al., 2007), respectively. We estimated RTF for each PAH relative to benzo[a]pyrene (RTF_{PAH_i}) using Equation (13):

$$RTF_{PAH_i} = \frac{CTP_{PAH_i}}{CTP_{B[a]P}} \tag{13}$$

where:

CTP_{PAH_i} is chronic toxicity potential of other individual PAH, *i*, in water (mmol/L).
$CTP_{B[a]P}$ is chronic toxicity potential of benzo[a]pyrene in water (mmol/L).

Utilizing the target lipid model, Di Toro et al. (2007) showed that:

$$\log(CTP_{PAH}) = -0.155\log(K_{ow}) - \log(C^{*}_{L,i}) + 3.803 \quad (14)$$

where:

CTP_{PAH} is chronic toxicity potential of each PAH in water (mmol/L).
K_{ow} is octanol/water partition coefficient.
$C^{*}_{L,i}$ is final chronic value critical target lipid body burden for the test organism (e.g. 6.94×10^{-3} mmol/g octanol for *Pimephales promelas*) (Di Toro et al., 2007).

Therefore, the incremental burden of disease per ng/m^{3}of each PAH (BoD_{PAH_i}) was estimated as:

$$BoD_{PAH_i} = \left(RPF_{PAH_i} \times \mathrm{BoD}_{\mathrm{B[a]P}_C}\right) + \left(RTF_{PAH_i} \times \mathrm{BoD}_{\mathrm{B[a]P}_{NC}}\right) \quad (15)$$

where:

$\mathrm{BoD}_{\mathrm{B[a]P}_C}$ and $\mathrm{BoD}_{\mathrm{B[a]P}_{NC}}$ is the incremental burden of disease per ng/m^3 of benzo[a]pyrene from cancer and non-cancer effects, respectively.

2.3. Statistical comparison of the incremental burden of disease across the countries

We compared the incremental burdens of disease assuming the same levels (0.1, 1 and 10 ng/m^3) of exposure to the sixteen PAHs across the countries using Kruskal-Wallis test by ranks. The post hoc tests (Dunn and the Conover-Iman with Bonferroni correction of the significance level, $\alpha = 0.05$) were used for multiple pairwise comparisons. The statistical analysis was conducted using XLSTAT software (version 2018.5.53172).

3. Results

3.1. Incremental burden of disease per ng/m^3 of PAHs

The incremental burdens of disease, expressed in DALYs per person-year, per ng/m^3 of benzo[a]pyrene, in the nine countries are shown in Fig. 1. The estimates were derived from ten cancers and thirty-four non-cancer disease outcomes. Among all health outcomes considered, the burden of lung cancer disease dominated the overall burden of disease per ng/m^3 of benzo[a]pyrene. Lung cancer disease accounted for about 71–77% of the estimated burden of disease across the countries.

The large burdens of lung cancer disease per ng/m^3 of benzo[a]pyrene stemmed from a combination of large lifetime unit risk of lung cancer of approximately 1 case per 100,000 people and high disease severity ranging from 19 to 27 DALYs per case of lung cancer, across the countries. Although the estimated lifetime unit risk of benzo[a]pyrene-related reproductive effects in males (reduced testis weight, reduced sperm count, reduced sperm motility or abnormal sperm) of 5 excess cases per 100,000 persons is five times greater than that of lung cancer, the severity of male infertility is comparatively very small, a range of 5.5×10^{-3}–6.6×10^{-3} DALYs per case across the countries. Likewise, even though the severity of measles is the greatest among the health outcomes considered, a range of 76–84 DALYs per case across the countries, the lifetime unit risks of benzo[a]pyrene-induced immunological effects (reduced thymus weight and reduced count of B-cells of ~2–8 excess cases per 100 million people) are about three orders of magnitude smaller than lung cancer.

The United States Environmental Protection Agency (USEPA) considers decreased embryo/fetal survival as a very sensitive hazard of benzo[a]pyrene exposure (USEPA, 2017a). In fact, this endpoint was used to derive the inhalation reference concentration for benzo[a]pyrene (USEPA, 2017a). The USEPA reported a subchronic lowest-observable-adverse-effect-level human equivalent concentration ($\mathrm{LOAEL}_{[\mathrm{HEC}]}$) of 4.6×10^{-3} ng/m^3 for benzo[a]pyrene (USEPA, 2017a). This value was used to calculate the maximum likelihood

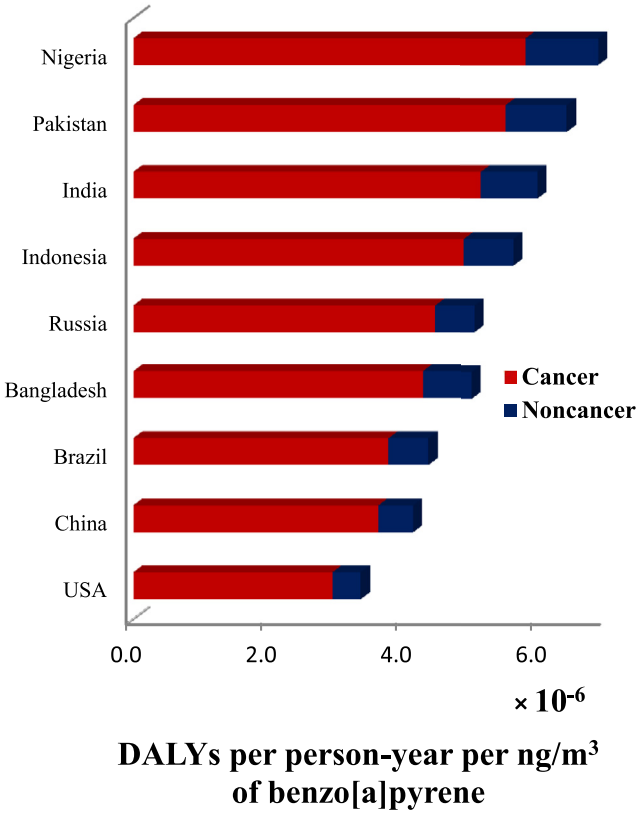

Fig. 1. Incremental burden of disease, expressed in disability-adjusted life years (DALYs) per person-year per ng/m^3 of benzo[a]pyrene, in nine countries.

(central) estimate of the inhalation unit risk (IUR_c) of the endpoint (please see Supplemental Material Table S3). The estimated IURc of 0.04×10^{-3} per ng/m^3 of benzo[a]pyrene implies an excess lifetime unit risk of 4 in every 100,000 population. The risk estimate was combined with the country-specific severity of maternal abortion/miscarriage/ectopic pregnancy of 0.11 DALYs per case (please see Supplemental Material Table S4) using Equation (11). Therefore, per ng/m^3 of benzo[a]pyrene, the estimated DALYs per person-year from maternal abortion/miscarriage/ectopic pregnancy ranged from 21×10^{-9} in the USA to 32×10^{-9} in Nigeria (please see Supplemental Material Table S4).

Estimates of the DALYs per person-year per ng/m^3 of the other fifteen PAHs were derived from cancer RPFs (USEPA, 2010) and non-cancer RTFs, respectively (see Supplemental Materials Table S6). Fig. 2 shows the estimated DALYs per person-year per ng/m^3 of fluoranthene or phenanthrene – a high molecular weight (HMW) or low molecular weight (LMW) PAH, respectively. The results for the other PAHs are not shown. Individually, HMW PAHs are more harmful than LMW PAHs. In fact, the toxicity of PAHs appears to increase with the number of aromatic rings (Ramírez et al., 2011). However, the biological response to a PAH depends not only on toxicity of the PAH, but also on the dose that gets to target tissues and the biological residence time (elimination half-life) of the PAH.

The tissue dose of PAHs may be influenced by the exposure concentrations (air concentration and ventilation rate) and the rate or percentage of absorption and distribution in the body (Gerde et al., 1997). In this study, we assumed equal air concentration of PAHs (1 ng/m^3) and utilized standard ventilation rate of 0.286 m^3/kg-day over 24-h exposure (ECHA, 2008). Thus, the ventilation rate for the countries would vary according to the average body weight of people in that country.

We accounted for differential rate of absorption and distribution of PAHs in the body using QSAR. The QSAR method was based on the

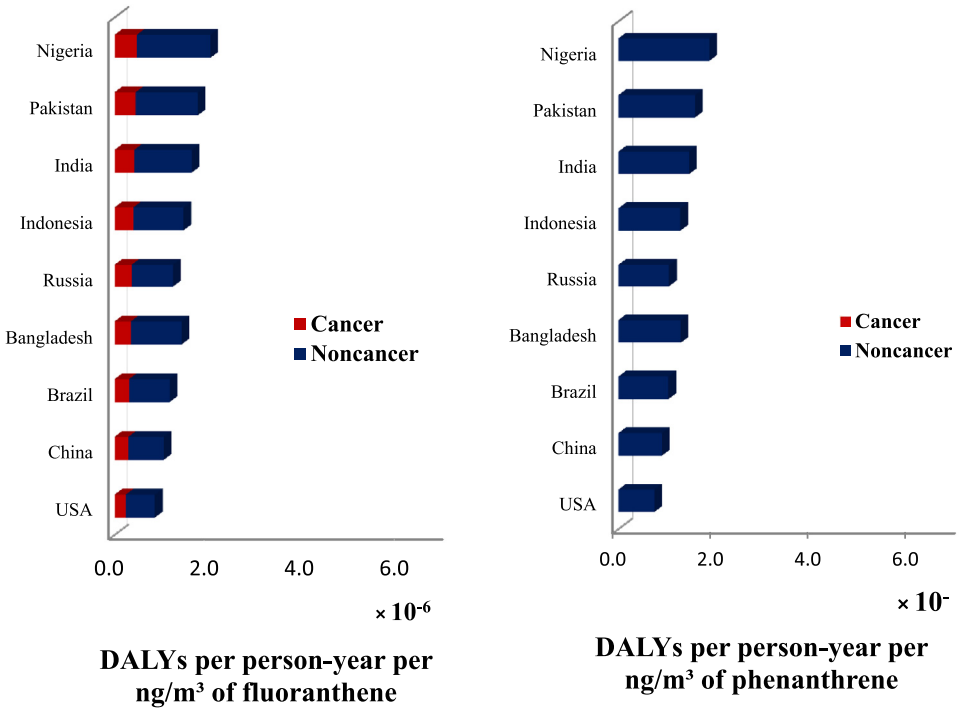

Fig. 2. Incremental burden of disease, expressed in disability-adjusted life years (DALYs) per person-year per ng/m^3 of fluoranthene or phenanthrene: a representative of high molecular weight (HMW) or low molecular weight (LMW) PAHs, respectively.

differential lipophilicity (octanol-water partitioning coefficients) and water solubility of each PAH in relation to benzo[a]pyrene. Based on the QSAR-approach, we calculated the non-carcinogenic, non-localized systemic RTFs for the sixteen PAHs. The values ranged from 2.7 (for Naphthalene) to 0.8 (for indeno [1,2,3-cd]pyrene or dibenzo[a,h]anthracene) (see Supplemental Materials Table S6). The estimated RTFs for LMW PAHs were larger than those of HMW PAHs. This suggests that LMW PAHs may have greater potency for non-carcinogenic, non-local, systemic effects than HMW PAHs. This is consistent with a previous report (Di Toro et al., 2007).

The HMW PAHs are typically bound to particles (Kim et al., 2013), and particle-bound PAHs must first desorb from their carrier particles into the mucus-lining layer before they can be absorbed through the epithelium into systemic circulation. Desorption of PAHs from particles has been shown to lower the rate of absorption by about 1000 fold compared to if they were present in the free gaseous state (Gerde et al., 1997). Furthermore, about 30% of PAHs bound to particles do not desorb from their carrier particles and therefore are not readily available for absorption into systemic circulation (Gerde et al., 2001; WHO, 2010). HMW PAHs are also more lipophilic than LMW PAHs: the more lipophilic a PAH is, the slower the rate of diffusion via the tracheobronchial and alveolar epithelia into the circulating system (Boström et al., 2002). Therefore, slow passage of HMW PAHs through the epithelia into systemic circulation may restrict their bioavailability for systemic effects, but may also result into very high-localized dose to the lungs, leading to greater risk of lung related diseases (Gerde et al., 1993). In contrast, the higher volatility, smaller molecular weight and lower lipophilicity of the LMW PAHs make them penetrates the portal of entry epithelia much more rapidly, thereby exposing deeper lying tissues and entering into the systemic circulation for distribution to distal body tissues.

We did not account for the differential half-lives of PAHs elimination from the body. The elimination half-life of a PAH refers to the time it takes to remove 50% of the PAH from the body (Benowitz, 1996). The reported half-lives of PAHs after inhalation exposure ranged from 6 to 35 h for LMW PAHs (Jongeneelen et al., 1990) and 6–34 weeks for HMW PAHs, depending on whether the PAH is adsorbed on particles or not (Wolff et al., 1989). When HMW PAHs are adsorbed on particles, the respiratory uptake rate is relatively slower because the particles are retained for a longer period of time in the respiratory tract (WHO, 2000b). Thus, because of the longer half-lives, HMW PAHs tend to accumulate in the body and are eliminated over a much longer period of time compared with LMW PAHs.

3.2. Variation in incremental burden of disease per ng/m^3 of PAHs across the countries

The estimated DALYs per person-year per ng/m^3 of each PAH varied substantially across the countries. For instance, it varied by about two to three folds between Nigeria and the USA (Figs. 1 and 2). Amongst the nine countries considered, the health burden per ng/m^3 of each PAH appears to be largest in Nigeria. Nigeria also had the highest estimated number of DALYs per case for most of the diseases (see Supplemental Materials Table S4).

The statistical comparison using Kruskal-Wallis test showed a significant variation ($\alpha = 0.05$) in the incremental burden of disease per ng/m^3 of each PAH across the countries (see Supplemental Materials Table S7). The post hoc tests – Conover-Iman test or Dunn's test, with Bonferroni adjustment – detected a significant difference between two countries when the gap in their average life expectancy was above 10 years. For instance, we detected a significant difference between the USA and Nigeria, China and Nigeria, USA and Pakistan or USA and India. The gap in longevity between these countries was 13.8 years, 11.6 years, 11.2 years or 10.3 years, respectively (IHME, 2017). The smallest difference with a statistical significance was observed between USA and India with 10.3 years gap in longevity. The difference in attributable burden of disease was 2.62×10^{-6} or 0.71×10^{-6} DALYs per person-year per ng/m^3 of benzo[a]pyrene or phenanthrene, respectively. However, Dunn's test (with Bonferroni correction) was less sensitive than Conover-Iman test. The former only detected a statistically significant between countries when the gap in longevity was above 11 years.

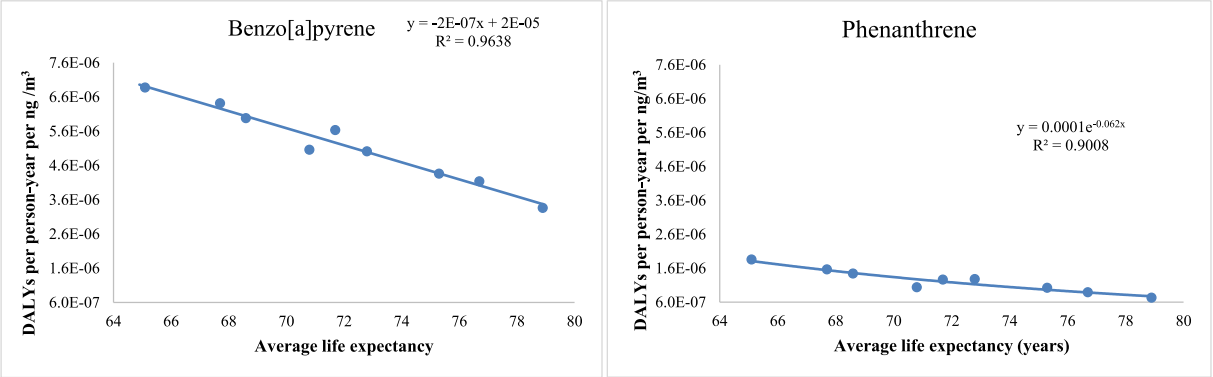

Fig. 3. Approximation of the incremental burden of disease expressed in DALYs per person-year per ng/m^3 of benzo[a]pyrene or phenanthrene from average life expectancy at birth.

A country's average life expectancy at birth has been taken as a proxy indicator of the country's overall health condition i.e. a measure of its average level of susceptibility and vulnerability. We attempted to see how a country's average life expectancy at birth could predict its regulatory limit for PAHs in air. Fig. 3 shows a linear or exponential approximation of the DALYs per person-year per ng/m^3 of benzo[a]pyrene or phenanthrene, respectively, from the average life expectancy at birth. The exponential function of phenanthrene may be due to the logarithmic scale of the QSAR model used to extrapolate the non-carcinogenic effects of phenanthrene from benzo[a]pyrene.

Model accuracy check was performed using the calculated and predicted datasets for seven other countries – Maldives, Mexico, South Africa, Sudan, Tajikistan, Uganda and Ukraine. The percentage mean absolute error (%MAE) or percentage root mean square error (%RMSE) for out-of-sample cross validation was 8.42% or 8.55% for benzo[a]pyrene, or 16.34% or 18.09% for phenanthrene, respectively. The maximum estimated error from the model performance evaluation was 0.69×10^{-6} or 0.46×10^{-6} DALYs per person-year per ng/m^3 of benzo[a]pyrene or phenanthrene, respectively. The error was primarily due to the morbidity effects not captured in the longevity metric. Thus, the "healthy" life expectancy, which computes morbidity effects, may have smaller errors than the average life expectancy, and may be a superior predictor of the excess burden of disease per ng/m^3 of PAH.

We used average life expectancy as the independent variable in the models, instead of the healthy life expectancy because information on the former is readily available for all countries (IHME, 2017). Nonetheless, estimates from the WHO (2018) shows that the lost "healthy" years is on the average about 8 years of healthy life, globally. This value is smaller than the statistically significant difference of > 10 years of life expectancy we obtained in our statistical analysis. Similarly, the maximum predicted error of 0.69×10^{-6} or 0.46×10^{-6} DALYs per person-year per ng/m^3 of benzo[a]pyrene or phenanthrene, respectively is also smaller than the statistically significant difference of 2.62×10^{-6} or 0.71×10^{-6} DALYs per person-year per ng/m^3 of the PAH, respectively.

4. Discussion

In real life, people are exposed to different concentrations of PAHs in air and for different durations. However, regulatory limit is usually set at a fixed (or target) PAH concentration in air that translates into an "acceptable level of risk" over a lifetime of exposure. For instance, the World Health Organization's air quality guideline for PAH is based on an excess lifetime cancer risk of 8.7×10^{-5} per ng/m^3 of benzo[a]pyrene (WHO, 2000a; 2010). This global air quality guideline assumes that all individuals would be affected equally by the same limit of exposure to PAHs. In other words, the severity of the effects from PAHs would depend only on the magnitude of the exposure. But, countries having very high baseline and early onset of cancer diseases, due to competing risk factors or genetic vulnerability, may have considerably higher excess burden of cancer at the same limit of exposure to PAHs. This statement holds true for the other health outcomes related to PAHs: respiratory, developmental, immunological and reproductive effects (USEPA, 2017a).

For the very first time, we have shown that the cancer and non-cancer burden of disease at the same limit of exposure to PAHs vary significantly across countries. The variation between two countries was significant when the gap in their longevity was above 10 years. This findings calls attention to the fact that countries having very low average life expectancy at birth require more stringent PAH exposure limit. To the best of our knowledge, this is the very first time the magnitude of the variation in the severity of the diseases at the same limit of exposure has been statistically assessed.

In the WHO Guideline for drinking-water quality, targets for waterborne contaminants were set at concentrations associated with a tolerable burden of disease of 1×10^{-6} DALYs per person-year (WHO, 2011; Gibney et al., 2013). Adopting similar level of risk to health from PAH as acceptable, the corresponding exposure limit for benzo[a]pyrene that would produce a tolerable burden of disease of 1×10^{-6} DALYs per person-year in the nine countries ranged from 0.15 ng/m^3 to 0.30 ng/m^3. The country-specific exposure limits for the fifteen other PAHs are shown in Table 1.

The WHO air quality guideline for PAH is based on benzo[a]pyrene equivalence (WHO, 2000a; 2010). We thus compare our country-specific values for benzo[a]pyrene with the global air quality guideline. Among the nine countries considered, Nigeria requires the most stringent exposure limits, owing to the high severity of the diseases related to PAHs (Table 1). This result is consistent with a recent report that ranked Nigeria among the top three countries having the highest per capita years of life lost (high death rates at young ages) from ambient air pollution exposure, globally (Lelieveld et al., 2018). The two other top ranked countries were Chad and Sudan (Lelieveld et al., 2018).

Using the average longevity in Chad or Sudan of 60.2 or 70.5 years, respectively (IHME, 2017), we predict a corresponding limit value of 0.1 ng/m^3 or 0.17 ng/m^3 of benzo[a]pyrene, respectively, based on a reference risk of 1×10^{-6} DALYs per person-year. Chad's exposure limit of 0.1 ng/m^3 of benzo[a]pyrene is slightly lower than the global recommended limit of 0.12 ng/m^3 of benzo[a]pyrene. Our result is consistent with a previous report which states that it would take a more stringent exposure limit of 0.1 ng/m^3 of benzo[a]pyrene to protect 97.5% of the world's population from the adverse effects of airborne PAHs (Shen et al., 2014).

Our value of 0.30 ng/m^3 of benzo[a]pyrene for the USA appears to be less stringent than the United States Environmental Protection Agency's screening level of 0.21 ng/m^3 of benzo[a]pyrene for residential ambient air (USEPA, 2017b). However, the differential burden

Table 1
Country-specific health-based guideline (ng/m^3) for sixteen PAHs in air, based on the attributable burden of disease of 10^{-6} (or 10^{-5}) DALYs per person-year.

Countries	PAHs															
	NAP	ACY	ACE	FLO	PHE	ANT	PYE	FLA	CHR	B[a]A	B[a]P	B[b]F	B[k]F	B[ghi]P	I[cd]P	D[ah]A
Nigeria	0.35 (3.5)	0.36 (3.6)	0.42 (4.2)	0.47 (4.7)	0.54 (5.4)	0.53 (5.3)	0.61 (6.1)	0.50 (5.0)	0.55 (5.5)	0.43 (4.3)	0.15 (1.5)	0.18 (1.8)	0.85 (8.5)	1.0 (10)	0.79 (7.9)	0.02 (0.2)
Pakistan	0.42 (4.2)	0.43 (4.3)	0.49 (4.9)	0.56 (5.6)	0.64 (6.4)	0.63 (6.3)	0.72 (7.2)	0.57 (5.7)	0.63 (6.3)	0.48 (4.8)	0.16 (1.6)	0.19 (1.9)	0.99 (9.9)	1.2 (12)	0.90 (9.0)	0.02 (0.2)
India	0.45 (4.5)	0.46 (4.6)	0.53 (5.3)	0.61 (6.1)	0.69 (6.9)	0.68 (6.8)	0.79 (7.9)	0.62 (6.2)	0.68 (6.8)	0.52 (5.2)	0.17 (1.7)	0.20 (2.0)	1.10 (11)	1.3 (13)	0.97 (9.7)	0.02 (0.2)
Indonesia	0.51 (5.1)	0.53 (5.3)	0.61 (6.1)	0.69 (6.9)	0.79 (7.9)	0.78 (7.8)	0.90 (9.0)	0.69 (6.9)	0.75 (7.5)	0.57 (5.7)	0.18 (1.8)	0.22 (2.2)	1.20 (12)	1.5 (15)	1.10 (11)	0.02 (0.2)
Bangladesh	0.51 (5.1)	0.52 (5.2)	0.60 (6.0)	0.69 (6.9)	0.78 (7.8)	0.77 (7.7)	0.89 (8.9)	0.71 (7.1)	0.78 (7.8)	0.61 (6.1)	0.20 (2.0)	0.24 (2.4)	1.20 (12)	1.5 (15)	1.1 (11)	0.02 (0.2)
Russia	0.63 (6.3)	0.64 (6.4)	0.74 (7.4)	0.84 (8.4)	0.96 (9.6)	0.95 (9.5)	1.10 (11)	0.82 (8.2)	0.88 (8.8)	0.65 (6.5)	0.20 (2.0)	0.24 (2.4)	1.40 (14)	1.8 (18)	1.3 (13)	0.02 (0.2)
Brazil	0.64 (6.4)	0.65 (6.5)	0.75 (7.5)	0.86 (8.6)	0.98 (9.8)	0.97 (9.7)	1.10 (11)	0.87 (8.7)	0.95 (9.5)	0.72 (7.2)	0.23 (2.3)	0.28 (2.8)	1.50 (15)	1.8 (18)	1.4 (14)	0.03 (0.3)
China	0.73 (7.3)	0.75 (7.5)	0.87 (8.7)	0.98 (9.8)	1.10 (11)	1.10 (11)	1.30 (13)	0.97 (9.7)	1.0 (10)	0.78 (7.8)	0.24 (2.4)	0.30 (3.0)	1.70 (17)	2.1 (21)	1.5 (15)	0.03 (0.3)
U.S.A	0.89 (8.9)	0.91 (9.1)	1.10 (11)	1.20 (12)	1.40 (14)	1.30 (13)	1.60 (16)	1.20 (12)	1.3 (13)	0.96 (9.6)	0.30 (3.0)	0.36 (3.6)	2.10 (21)	2.5 (25)	1.8 (18)	0.03 (0.3)
Global guideline								**2.0****			**0.12 (1.2)***					

NAP: naphthalene; ACY: acenaphthylene; ACE: acenaphthene; FLO: fluorene; PHE: phenanthrene; ANT: anthracene; PYE: pyrene; FLA: fluoranthene; CHR: chrysene; B[a]A: benzo[a]anthracene; B[a]P: benzo[a]pyrene; B[b]F: benzo[b]fluoranthene; B[k]F: benzo[k]fluoranthene; B[ghi]P: benzo[g,h,i]perylene; I[cd]P: Indeno[1,2,3-cd]pyrene; D[ah]A: Dibenzo[a,h]anthracene; * WHO (2000a,b, 2010); **Boström et al. (2002).

of disease at both exposure limits (0.30 and 0.21 ng/m^3 of benzo[a]pyrene) is statistically not significant at $\alpha = 0.05$. Furthermore, Boström et al. (2002) proposed a global exposure limit for fluoranthene of 2.0 ng/m^3. They derived their value assuming that the carcinogenic potency of fluoranthene is 20 times lesser than benzo[a]pyrene. Their value is substantially less stringent than our proposed range for fluoranthene of 0.47 ng/m^3 to 1.2 ng/m^3.

For regulatory purpose, we have calculated the excess burden of disease attributable to airborne PAHs assuming the same exposure limit across countries. But, the actual concentrations of atmospheric PAHs in the countries are very different. The global gridded surface benzo[a]pyrene concentration dataset for 2007, with spatial resolution of 0.1° × 0.1° (Shen et al., 2014), provided us the opportunity to assess the contribution of differential exposures to the overall burden of disease from benzo[a]pyrene in the countries. To account for differential exposures to the PAH across the countries, we combined the gridded surface benzo[a]pyrene concentrations with population count datasets for the same year and spatial resolution. We estimated population-weighted average exposure to benzo[a]pyrene and the associated burden of disease following standard method (Etchie et al., 2018b). Fig. 4 shows the per capita or population burden of disease due to benzo[a]pyrene inhalation in each country in 2007. The share of the burden of disease at the local sub-national level in the USA or China is shown in Fig. 5. Results for the other countries are in the Supplemental Materials Figure S1.

After integrating the differential levels of exposure in our estimations, India or China now ranked highest in terms of per capita or population burden of disease due to benzo[a]pyrene exposure, respectively. Also, except for the USA, no other country's locality averaged below the acceptable risk level of 1.0×10^{-6} DALYs per person-year. In six countries (USA, Brazil, Indonesia, Bangladesh, Nigeria and Pakistan) differential exposures to benzo[a]pyrene contributed less to the overall burden of disease due to benzo[a]pyrene inhalation than do differential severities of the diseases. This indicates that the risk to health from PAHs would be underreported in these countries if the severities of the diseases are not taken into consideration. Shen et al. (2014) made similar observation for the lung cancer risk.

The top four localities that had the greatest per capita burden of disease from exposure to benzo[a]pyrene in 2007 were all in India: Chandigarh, Delhi, Dadra and Nagar Haveli, and Sikkim. China's Henan had the highest population burden of disease from exposure to the PAH in 2007. The estimated burden of disease in Henan was 4700 DALYs, followed in a decreasing order by Delhi (2600 DALYs), West Bengal (2100 DALYs), Shandong (2000 DALYs) and Hebei (1700 DALYs). Furthermore, assuming all localities within each country complied with benzo[a]pyrene guideline of 0.1 ng/m^3, about 64–98% of the DALYs or 66–99% of the DALYs per person could have been avoided.

We could not compare our estimates of the burden of disease due to benzo[a]pyrene exposure with literature estimates because of differences in methodology. For instance, a recent study conducted in Nagpur, India gave estimates of the burden of disease from exposure to total (thirteen) airborne PAHs (Etchie et al., 2018a). Estimates for individual PAHs was not presented. Furthermore, most previous studies calculated only the lung cancer burden of disease, and utilized epidemiological upper-bound IUR estimate of 0.087 per μg/m^3 of benzo[a]pyrene (Geelen et al., 2009; Li et al., 2015; Zhou et al., 2015). However, for consistency with the other endpoints considered, we have utilized the toxicological central maximum likelihood IUR estimate of 0.011 per μg/m^3 in this study (Heinrich et al., 1994).

We considered 30 years exposure weighting and adjusted for early-life vulnerability to cancer in our estimation. Most previous studies considered full lifetime exposure weighting of 70 years, and did not state whether they adjusted for early-life vulnerability to cancer. Nonetheless, the studies reported that the lung cancer burden of disease due to benzo[a]pyrene exposure in USA, Netherland and China was 86, 96 and 12,000 DALYs per year, respectively (Geelen et al., 2009; Li

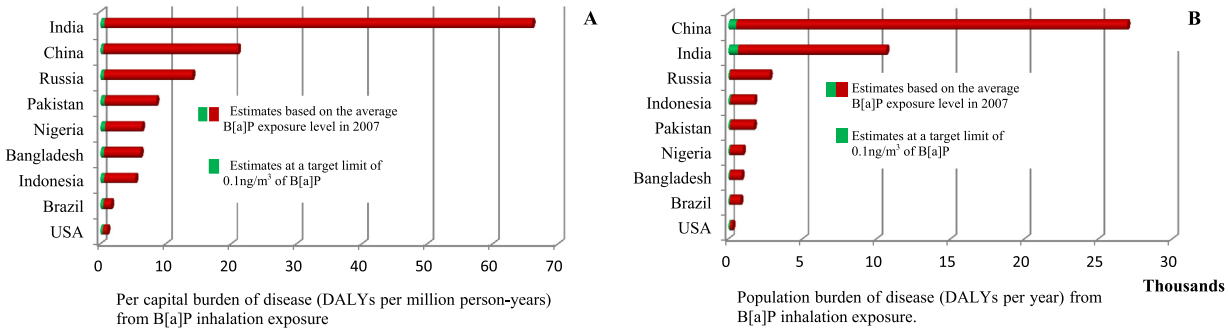

Fig. 4. Per capita (A) and population (B) burden of disease attributable to benzo[a]pyrene inhalation exposure in the nine countries in 2007.

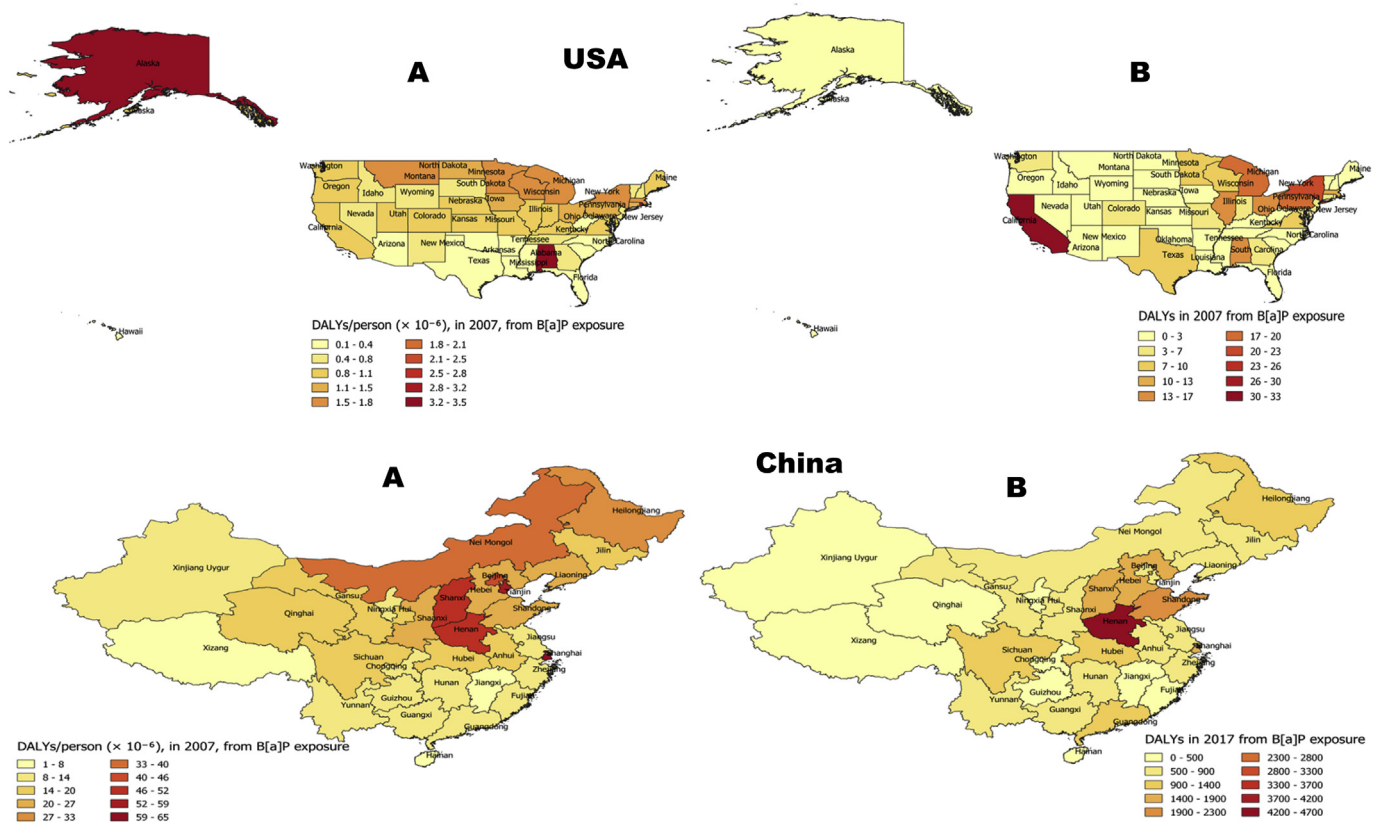

Fig. 5. The share of per capita (A) or population (B) burden of disease due to benzo[a]pyrene (B [a]P) inhalation exposure at the local sub-national level in the USA or China in 2007.

et al., 2015; Zhou et al., 2015). Our estimate for USA or China was 260 or 27,000 DALYs per year, respectively. Similarly, Etchie et al. (2018a) reported that the total burden of disease attributable to thirteen airborne PAHs exposure in an Indian district was 49,500 DALYs per year.

We note some limitations in this study. First, we did not account for the additional exposure due to vulnerability when calculating the contribution of differential exposures to the overall burden of disease from benzo[a]pyrene inhalation across the nine countries. For instance, people in lower socioeconomic position (less education, less income and lower occupational status) are very likely to live and work in areas nearer to emission hotspots e.g. near dense traffic corridors or industrial areas (Etchie et al., 2017). They are also more likely to indulge in unhealthy behaviors such as smoking and cooking with solid fuels, leading to additional exposure to the PAH and its health effects. Secondly, we did not consider the contribution of other main routes of exposure such as smoking, dietary intake and dermal absorption of the PAH that may modify the overall burden of disease due to PAH exposure. To identify suitable target limit for a PAH, the concentrations of its biomarker e.g. 1-hydroxypyrene (a metabolite of pyrene) in people urine are often correlated with the atmospheric concentration of the indicator PAH (benzo[a]pyrene). The regression equation could then be used to find the concentration of benzo[a]pyrene in the atmosphere equaling the NOAEL of 1-hydroxypyrene in the urine (Jongeneelen, 2001). However, because PAH profile can vary considerably in different environments and worksites, utilizing this method to set health-based limit for PAHs in ambient air has its shortcomings. In this study, we used the addition-to-background-effect approach, which is similar to the WHO's incremental lifetime unit risk of lung cancer approach (WHO, 2000a; 2010; Shen et al., 2014). However, we considered more health outcomes than just lung cancer in our risk estimation, and integrated the differential severities of the diseases in the countries.

Lastly, we did not consider the differential elimination half lives of PAHs when calculating the non-cancer RTFs. Weighting PAHs according to their biological half lives may alter our RTFs, which we used

to extrapolate the non-cancer, non-local, systemic effects of fifteen other PAHs from benzo[a]pyrene.

5. Conclusion

From this study, we reach the following conclusions:

1. There is significant variation in the excess burden of disease at the same limit of exposure to PAHs across countries. This is due to the differential severities of the diseases related to PAHs.
2. In some countries, the contribution of differential severities of diseases to the overall burden of disease from ambient PAH outweighs that due to differential exposures.
3. Countries having the lowest average life expectancy at birth had the highest burden of disease per ng/m^3 of PAH.
4. At the global exposure limit of PAH, a gap in longevity by above 10 years between two countries results in a significant difference in the excess burden of disease. This indicates that countries having very low average life expectancy may require more stringent PAH limit.
5. Linear or exponential function of the average life expectancy at birth gave valid approximation of the incremental burden of disease per ng/m^3 of benzo[a]pyrene or phenanthrene – a high or low molecular weight PAH, respectively.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ecoenv.2019.04.028.

Declaration of competing financial interests

None declared.

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