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Health risk assessment for residents exposed to atmospheric diesel exhaust particles in southern region of Taiwan

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HIGHLIGHTS

- DEP dose and cancer risk estimates showed heterogeneously spatiotemporal difference.
- DNA damage biomarker and cancer incidence estimates had a positive association.
- Resident health risk from atmospheric DEP depending on measured data type.
- Health risk assessments of air pollution can guide adaptive mitigation strategies.

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ABSTRACT

Evidence shows a strong association among air pollution, oxidative stress (OS), deoxyribonucleic acid (DNA) damage, and diseases. Recent studies indicated that the aging, human neurodegenerative diseases and cancers resulted from mitochondrial dysfunction and OS. The purpose of this study is to provide a probabilistic risk assessment model to quantify the atmospheric diesel exhaust particles (DEP)-induced pre-cancer biomarker response and cancer incidence risk for residents in south Taiwan. We conducted entirely monthly particulate matter sampling data at five sites in Kaohsiung of south Taiwan in the period 2002–2003. Three findings were found: (i) the DEP dose estimates and cancer risk quantification had heterogeneously spatiotemporal difference in south Taiwan, (ii) the pre-cancer DNA damage biomarker and cancer incidence estimates had a positive yet insignificant association, and (iii) all the estimates of cancer incidence in south Taiwan populations fell within and slight lower than the values from previous cancer epidemiological investigations. In this study, we successfully assessed the tumor incidence for residents posed by DEP exposure in south Taiwan compared with the epidemiological approach. Our approach provides a unique way for assessing human health risk for residences exposed to atmospheric DEP depending on specific combinations of local and regional conditions. Our work implicates the importance of incorporating both environmental and health risk impacts into models of air pollution exposure to guide adaptive mitigation strategies.

1. Introduction

Growing evidence shows that there were significant associations among air pollution, oxidative stress, deoxyribonucleic acid (DNA) damage, and diseases (Klaunig and Kamendulis, 2004; Demirbag et al., 2005; Altindag et al., 2007). Lin and Beal (2006) indicated that mitochondrial dysfunction (e.g., DNA damage) and oxidative stress (e.g., production of reactive oxygen species (ROS)) were highly likely to pose aging related and human neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), and Huntington's diseases (HD). Thus, many aging related diseases, including cancer (Klaunig and Kamendulis, 2004), coronary artery disease (CAD) (Demirbag et al., 2005), human neurodegenerative diseases (AD, PD, ALS, and HD) (Lin and Beal, 2006), and rheumatoid arthritis (RA) (Altindag et al., 2007), were caused by DNA damage through ROS production and accumulation.

Kappos et al. (2004) indicated that per 10 μg m^{-3} $PM_{2.5}$ (particulate matter (PM) with aerodynamic diameter ≤ 2.5 μm)

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increase resulted in mortality up to 13–14% (95% CI: 4.2–23%) for all causes, 18–19% (95% CI: 5.8–33%) for cardiopulmonary disease, and 18–20% (95% CI: −8.4 to 60%) for lung cancer. Krewski et al. (2000) and Pope et al. (2002), however, indicated that the estimated mortality was 4.1–7.0% (95% CI: 0.8–11%) for all causes, 5.9–12% (95% CI: 1.5–17%) for cardiopulmonary disease, and 0.8–13.5% (95% CI: −8.7 to 23%) for lung cancer per 10 μg m^{-3} $PM_{2.5}$ increase. Several studies have performed the DNA damages by using several biomarkers, such as determinations of 1-hydroxypyrene (1-OHP), 8-hydroxydeoxyguanosine (8-OHdG or 8-oxodG), disease activity, DNA adducts and formamidopyrimidine glycosylase (FPG), through detecting tissues, plasma, and urine (Chuang et al., 2003; Altindag et al., 2007).

Here we focused on a highly industrialized (more than 60% of Taiwan heavy industries) and densely populated area, Kaohsiung, located in south Taiwan (Yuan et al., 2002; Wang et al., 2006). Kaohsiung is the second largest metropolitan area in Taiwan. Moreover, Kaohsiung is a densely populated region (nearly 2.78 million persons within a total area of 3000 km^2). Yuan et al. (2002) reported that the neighborhood of Kaohsiung has the worst ambient air quality in that the haze days of the Pollution Standard Index (PSI) greater than 100 was about 9–10% during 1999–2000. Several epidemiological studies have also evaluated the adverse health outcomes exposed to air pollutants for susceptible populations in south Taiwan (Chen et al., 1998; Cheng et al., 2006).

In the recent year, the chemical compositions, source identification, and their environmental impacts (e.g., visibility) of atmospheric aerosols were concerned inseparably (Yuan et al., 2002; Tsai and Chen, 2006a; Wang et al., 2006). The epidemiological studies of the human health outcomes have investigated, especially for cancer incidence among occupational and non-occupational populations. However, the issue of the adverse health effects (e.g., asthma, respiratory diseases, tumor incidence) caused directly (not epidemiological study) from atmospheric aerosols in the area was rarely addressed (Wang et al., 2006).

The most effective way to study the impacts of atmospheric air pollutant on human health is through a mechanistic modeling because it resolves some of the limitations associated with empirically based statistical techniques. These limitations include the lack of long-term and continuous air pollutant data. Because of a scientific consensus that air pollutants are occurring with associated human health consequences, public health research has focused on identifying and implementing effective mitigation and adaptive strategies.

The purpose of this study is to provide a probabilistic risk assessment model to quantify the atmospheric diesel exhaust particles (DEP)-induced pre-cancer biomarker response and cancer incidence risk for residents in south Taiwan. It is recognized that one of challenges for public health responses to air pollutants is the need for location-specific risk assessment. This study addresses this challenge by providing a unique way for assessing human health risk for residences posed by atmospheric DEP depending on specific combinations of local and regional conditions.

2. Materials and methods

2.1. Data sources

There are five selected sampling sites that are all located in Kaohsiung: (i) Meinung (Site M), (ii) Chiautou (Site C), (iii) Jenwu (Site J), (iv) Daliao (Site D), and (v) Linyuan (Site L). Several industrial and agricultural mixed areas are scattered in this study area (Fig. 1A). Fig. 1B gives the locations shown with the Universal Transverse Mercator (UTM) Grid System along with population densities. Among the five sites, Site M is considered as a less polluted small town with lower industrial and vehicle emissions compared to the other sites. The other four sites (Sites C, J, D, and L), however, are close to many industrial complexes with petrochemical and metal manufacturing plants in south Taiwan. Therefore, there were 60% of Taiwan's petrochemical plants and over 5000 factories located in this study area, emitting nearly 39.6 ktons of TSP and 17.4 ktons of PM_{10} in 1997 (CTCI Corporation, 1999).

All PM_{10} and $PM_{2.5}$ samples at each site were collected using personal environmental monitor (PEM, MSP corp.) and Harvard samplers (Air Diagnostics and Engineering) on a 24-h basis placed 3 m apart on the roof of a building about 10–15 m above ground. The air flow rate of PEM was settled at 10.0 ± 0.11 pm and used 37 mm diameter quartz (Pallflex 2500 QAT-UP) filter paper as sampling media. The sampling period covered September 2002–August 2003 with autumn (September–November), winter (December–February), spring (March–May), and summer (June–August) seasons. All 110 samples were collected for chemical and statistical analyses. The statistical analysis was based on chemical mass balance (CMB) modeling (Watson et al., 1991).

After sampling, each sample was weighed by an analytical balance (Mettler, Toledo AT261), and then water soluble ions (including F^-, Cl^-, NO_3^-, SO_4^{2-}, Na^+, NH_4^+, K^+, Mg^{2+}, and Ca^{2+}), carbonaceous contents (including organic carbon (OC) and elemental carbon (EC)), and metals (including Ag, Al, As, Ba, Ca, Cd, Co, Cr, Cs, Cu, Fe, Hg, K, Mg, Mn, Na, Ni, Pb, Rb, Se, Sr, Ti, Tl, V, and Zn) were analyzed by using Dionex DX-120 Ion Chromatograph, Heraeus CHN-O-Rapid elemental analyzer, and Agilent Model 7500 Inductively coupled plasma mass spectrometry, respectively (Tsai and Chen, 2006a; Wang et al., 2006). Details of the sampling program, chemical analysis protocols, and CMB modeling have been described in previously studies (Lai et al., 2003; Wang et al., 2006). Briefly, the CMB source apportionment technology can be described as follow equation

$$X_i = \sum_{j=1}^{J} F_{ij} S_j, \tag{1}$$

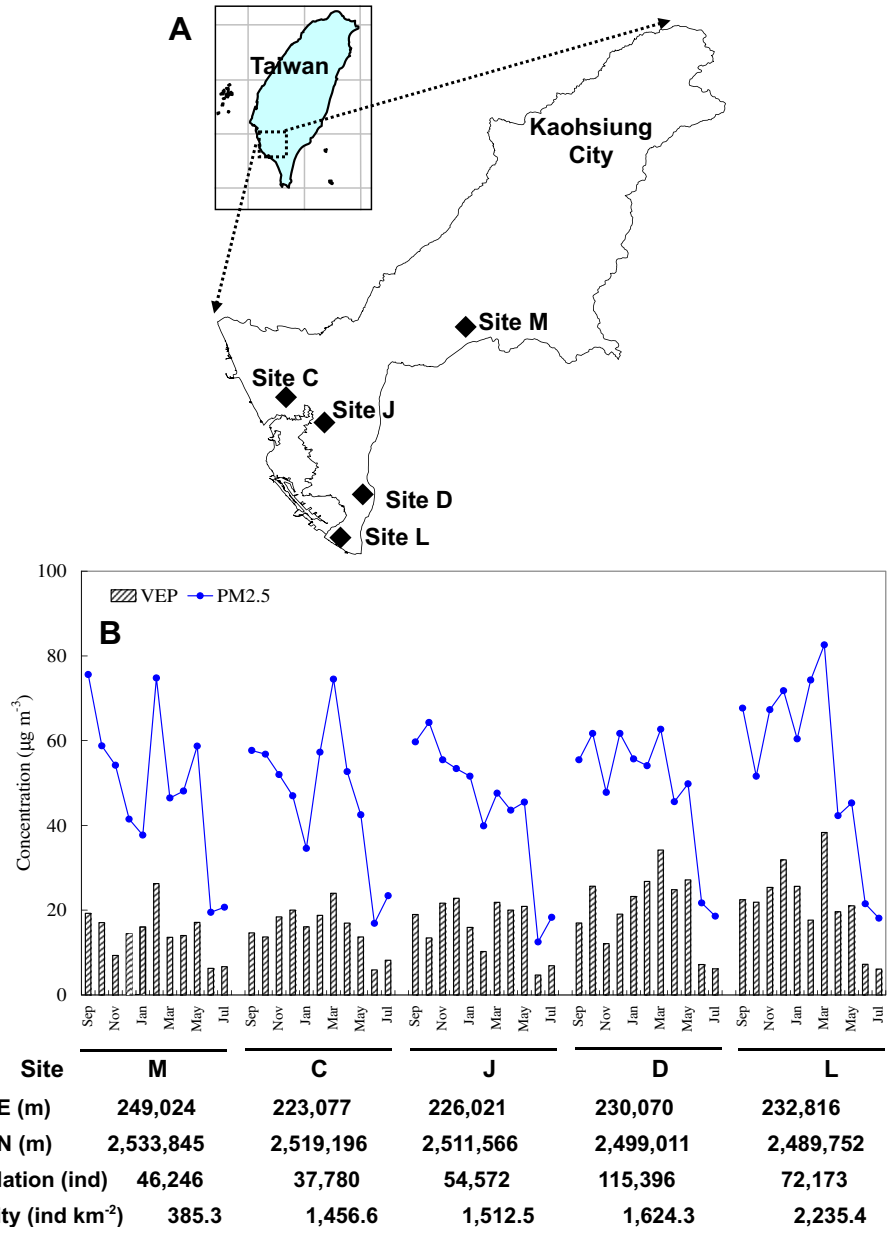
where X_i is the concentration of element i, F_{ij} is the fraction of element i in source j, S_j is the contribution of source j (Watson et al., 1991). Here, our observed data was collected with at least 2 consequence sampling days per month each site, except for August. Therefore, the sample size for each site was 22.

2.2. Problem formulation

Here we used the source apportionment technology to estimate the DEP contributory ratio from published $PM_{2.5}$ data measured in selected five sites in south Taiwan (Lai et al., 2003). Residents lived in the study area were more concerned, especially for elderly subgroup. Fortunately, we had enough information on monthly, seasonal, and annual $PM_{2.5}$ to estimate the human adverse effect of tumor incidence. We employed Crystal Ball® (Version 2000.2, Decisioneering, Inc., Denver, Colorado, USA) to perform the Monte Carlo (MC) simulation. All of the simulation frequencies were 10,000 iterations to ensure the stability of results. Lognormal distributions were fitted to the measured $PM_{2.5}$ data by maximizing the log-likelihood function.

2.3. Exposure assessment

Our exposure assessment model based on a monthly-basis vehicle contribution can be expressed as



Site	M	C	J	D	L
UTM-E (m)	249,024	223,077	226,021	230,070	232,816
UTM-N (m)	2,533,845	2,519,196	2,511,566	2,499,011	2,489,752
Population (ind)	46,246	37,780	54,572	115,396	72,173
Density (ind km^{-2})	385.3	1,456.6	1,512.5	1,624.3	2,235.4

Fig. 1. (A) Sampling sites and their related locations in Kaohsiung, Taiwan, (B) Measured $PM_{2.5}$ mass concentration, estimated vehicle contributions in five selected sampling sites. Sites M, C, J, D, and L present Meinung, Chiautou, Jenwu, Daliao, and Linyuan townships, respectively. The location information and demographic data for the selected sites are also shown.

$$D = \int_0^t (C \times f \times \mathrm{BR} \times d_\mathrm{F} \times \mathrm{ED})\mathrm{d}t, \tag{2}$$

where D is the estimated cumulative DEP dose (mg), C is the monthly basis vehicle contributions (VEP) obtained from CMB model (μg m^{-3}), f is the ratio of DEP to VEP (dimensionless), BR is the air breathed rate for adult (m^3 d^{-1}), d_F is the deposition fraction of $PM_{2.5}$ inhaled into human lung alveolar-interstitial (AI) region (dimensionless), and ED is the exposure duration (yr). Table 1 lists the parameters used in Eq. (1) for estimating DEP exposure dose.

2.4. Effect assessment

We reconstructed two dose–response profiles by fitting empirical four-parameter Hill equation model to the published data of DEP dose-DNA damage response (8-OHdG production) in lung cells, and DEP dose-tumor incidence response in lung organ (Ichinose et al., 1997),

$$R_i = R_{i,\min} + \frac{R_{i,\max} - R_{i,\min}}{1 + \left(\frac{\mathrm{ED}_{50}}{D}\right)^n}, \tag{3}$$

where $R_{i,\max}$ and $R_{i,\min}$ are the maximum and minimum value of selected response i, respectively, R_i is the estimated response i given DEP dose D, ED_{50} is the DEP cumulative dose yielding half of maximal response of $R_{\max}$ (mg), and n is a fitted slope or is referred to as the Hill coefficient which is a measure of cooperativity. A value of $n > 1$ indicates positive cooperativity.

We treated ED_{50} value in Eq. (2) probabilistically. Cumulative distribution function (CDF) of predicted response function for a given DEP dose could be expressed symbolically as a condition CDF,

Table 1
Parameters used in exposure model and fitted values in dose–response models.

Exposure model				
Parameter	Value	Distribution	Range	Reference
C: Monthly basis vehicle concentration (μg m^{-3})	Varied	Lognormal	Site-specific	This study
f: Ratio of DEP to VEP (−)	0.475	Normal	0.26–0.69	Chio et al. (2007)
BR: Air breathed rate (m^3 d^{-1})	20	Normal	18–22	Chio et al. (2007)
d_F: Deposition fraction (−)	0.324	Fixed value		Chio et al. (2007)
ED: Exposure duration (yr)	1	Fixed value		This study

Dose–response model[a]				
	Estimate	Std error	*t*-Value	*p*-Value
8-OHdG production (per 10^5 dG),[b] model $r^2 = 0.94$				
$R_{1,max}$ (fixed)	8.92			
Hill coefficient, *n*	1.787	0.375	4.762	0.005
ED_{50} (mg)	124.136	13.734	9.038	0.0003
$R_{1,min}$	2.645	0.319	8.282	0.0004
Tumor incidence (per 10^5 populations),[b] model $r^2 = 0.88$				
$R_{2,max}$ (fixed)	43.3			
Hill coefficient, *n*	1.338	0.834	1.604	0.207
ED_{50} (mg)	57.560	15.459	3.723	0.034
$R_{2,min}$	11.994	3.031	3.957	0.029

Abbreviation: VEP: vehicle exhaust particle (estimated by chemical mass balance model), DEP: diesel exhaust particle, ED_{50}: critical dose of yielding half effect.
[a] Oral bioavailability for DEP dose is 6% (assumed as same as the range of 5–7% for tin) (Bright and Richardson, 2006).
[b] Two dose–response data adopted from Ichinose et al. (1997).

$$P(R_i|D) = \Phi\left(R_{i,\min} + \frac{R_{i,\max} - R_{i,\min}}{(ED_{50}/D)^n}\right), \quad (4)$$

where $\Phi(\bullet)$ is the cumulative standard normal distribution.

We used TableCurve 2D (Version 5, AISN Software Inc., Mapletion, OR, USA) to optimize the dose–response profile with $p < 0.05$ significant level.

2.5. Risk characterization

Risk characterization is a process to provide an estimate of risk for the specific subpopulation under study. The risk at a specific DEP dose for increasing DNA damage production and tumor incidence responses can be calculated as the proportion of human lung cells and plasma expected to that DEP dose multiplied by the conditional probability of proposed responses.

A joint probability function (JPF) or exceedance profile describes the probability of exceeding the cumulative dose associated with related response R_i and can be expressed mathematically as

$$P(R_i(D)) = P(D) \times P(R_i|D), \quad (5)$$

where $P(R_i(D))$ is the probabilistic risks of response R_i for a certain cumulative dose D, $P(D)$ is the probability of DEP cumulative dose D in human lung, and $P(R_i|D)$ is the CDF of response R_i of having DEP cumulative dose D in human lung. This equation is based on the Bayes' Theorem (Tanner, 1993) in that $P(D)$ is the prior distribution of cumulative dose D and $P(R_i|D))$ may be referred to as a function of cumulative dose D. Their product is a joint probability function of response R_i for given cumulative dose D. The selected response R_i included DNA damage ($i = 1$) and tumor incidence ($i = 2$).

3. Results

3.1. $PM_{2.5}$ and vehicle contributions

Our results indicated that the ranges of measured $PM_{2.5}$ mass concentrations were 19.5–75.6, 16.9–74.5, 12.5–64.3, 18.6–62.7, and 18.1–82.6 μg m^{-3} for sites M, C, J, D, and L, respectively (Fig. 2A, C, E, G, I). The ranges of estimated contributions of vehicle exhaust particle (VEP) analyzed by CMB model were 6.3–26.3, 5.9–24.0, 4.7–22.8, 6.1–34.2, and 6.1–38.3 μg m^{-3} for sites M, C, J, D, and L, respectively. The ranges of contribution percentages of VEP were accounted for 17.2–42.2, 24.1–46.5, 20.9–45.9, 25.3–54.5 and 23.8–46.4% of $PM_{2.5}$ mass contributions in above five sites. Based on the probabilistic analyses of $PM_{2.5}$ exposures, we treated the measured data with three datasets on annual, seasonal, and monthly bases, respectively.

By comparison, there was no significant difference in peak values (or modes) of annual $PM_{2.5}$ concentrations among the five sites. Focusing on the upper limit of annual $PM_{2.5}$, which in Site L had the highest value ($\sim$100 μg m^{-3}) than other four sites. However, the patterns of the seasonal $PM_{2.5}$ showed significant difference at the five selected sites. In summer, most of the probability distributions of $PM_{2.5}$ were narrower and the upper values were always less than 30 μg m^{-3}, whereas $PM_{2.5}$ in Site D had a relative larger variation compared to other four sites. In autumn, Sites C and J had narrower $PM_{2.5}$ distributions, and the Sites M, D, and L had larger variations in $PM_{2.5}$ distributions. Among the $PM_{2.5}$ distributions of five selected sites, Sites M and J had similar pattern (autumn > spring > winter > annual > summer), whereas Sites D and L experienced another similar fashion (winter > autumn > spring > annual > summer) (Fig. 2A, C, E, G, I).

3.2. DEP dose estimates

Based on the analyses with annual data type, the estimated cumulative DEP doses were 14.05 (95% CI: 5.51–35.09), 15.52 (6.55–37.07), 15.78 (6.14–39.88), 19.17 (7.77–47.84), and 17.79 (6.86–44.78) mg for Sites M, C, J, D, and L, respectively (Fig. 2B, D, F, H, J). The highest annual DEP dose estimate occurred at site D due to the VEP contributive fraction in $PM_{2.5}$ (Fig. 2H). However, the cumulative DEP doses for Sites M, C, J, D, and L with monthly data type were 15.42 (10.23–21.74), 16.67 (11.00–23.60), 17.42 (10.98–25.99), 21.42 (14.22–30.48), and 22.87 (14.83–33.02) mg, respectively (Fig. 2B, D, F, H, J).

Overall, in view of all data types, our results indicated that the highest dose appeared at Site L resulting from the highest $PM_{2.5}$ and VEP contribution at this site (Fig. 2J). We could reduce the uncertainties of cumulative DEP dose estimation via higher data resolution. Moreover, results also showed that the median values with monthly data type in five sites had a slight higher trend compared to that with annually and seasonally data types (Fig. 2B, D, F, H, J).

3.3. Dose–response analysis

Fig. 3A shows the reconstructed dose–response relationship between DEP cumulative dose and associated DNA damage as 8-OHdG production. The results indicated that the estimated maximum and minimum values of DNA damage are 8.92 and 2.645 (per 10^5 dG), respectively (Table 1). The ED_{50} estimate and fitted Hill coefficient n were 124.136 ± 13.734 (mean ± se) mg and 1.787 ± 0.375, respectively, indicating the positive cooperativity for the selected endpoint. The dose–response profile of secondary endpoint with tumor incidence (per 10^5 populations) is shown in Fig. 3B. The minimum to maximum tumor incidence of the fitted model ranged from 11.994 to 43.3 (per 10^5 populations) (Table 1).

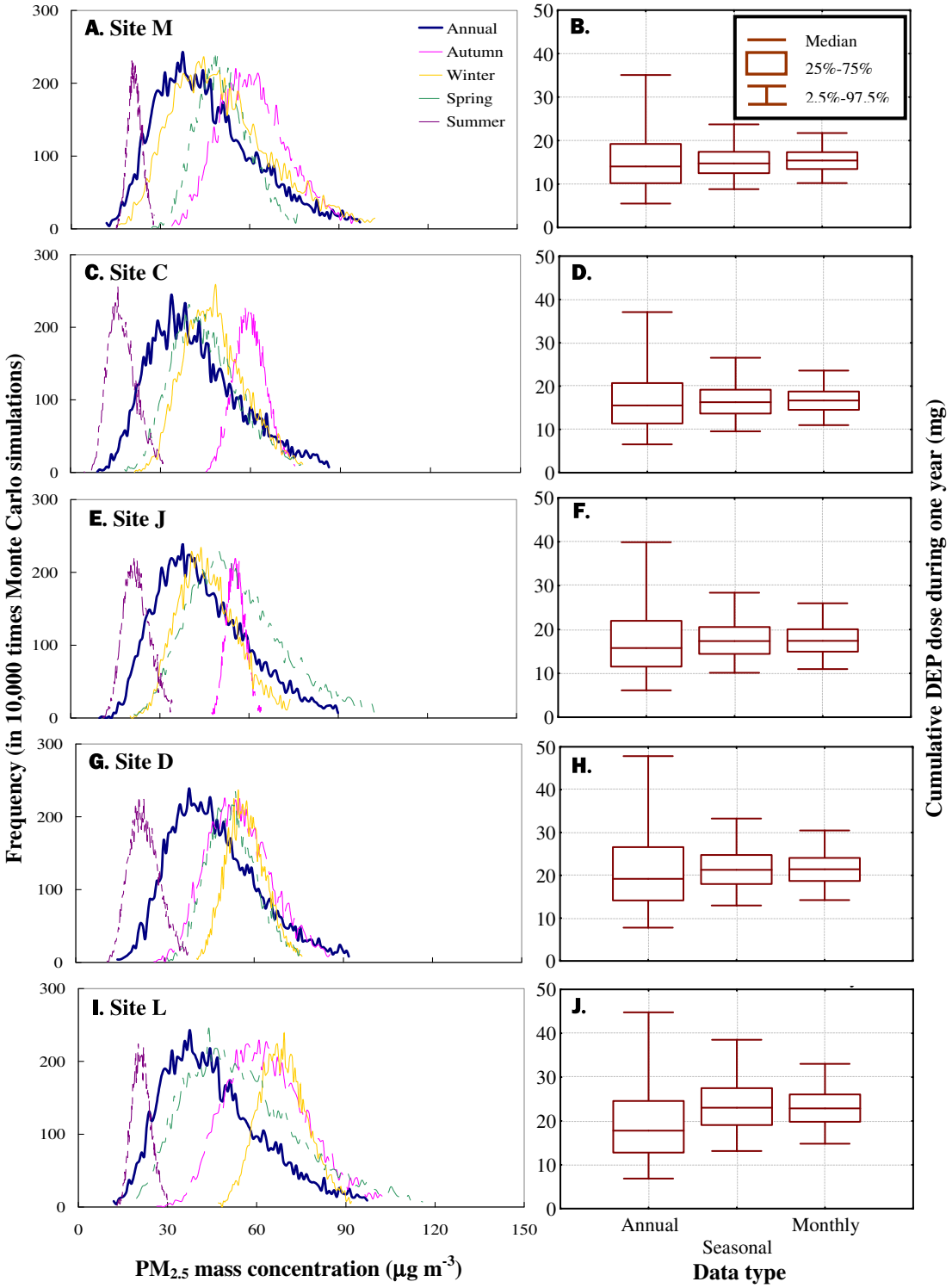


Fig. 2. Annual/seasonal $PM_{2.5}$ concentrations distributions and estimated cumulative DEP doses in selected sampling sites. (A, B) Site M, (C, D) Site C, (E, F) Site J, (G, H) Site D, and (I, J) Site L. Frequency distributions are presented in 10,000 time Monte Carlo simulations. Cumulative DEP doses estimated based on one year exposure.

The estimates of ED_{50} and n were 57.56 ± 15.459 mg and 1.338 ± 0.834, respectively (Table 1).

3.4. Risk estimates

Table 2 shows the risk estimates of DNA damage and tumor incidence effects at 10%, 50%, and 90% probabilities for five select sites based on monthly data type. In these two selected responses, results showed that there was a slowly increasing trend with the decreasing latitude of sampling site (from Sites M to L). The highest responses with DNA damage effect in Site L, the southernmost site in this study, at 10%, 50%, and 90% probabilities were 3.09 (2.96–3.30), 2.93 (2.85–3.08), and 2.83 (2.77–2.92) per 10^5 dG, respectively. However, the populations at Site L with tumor incidence

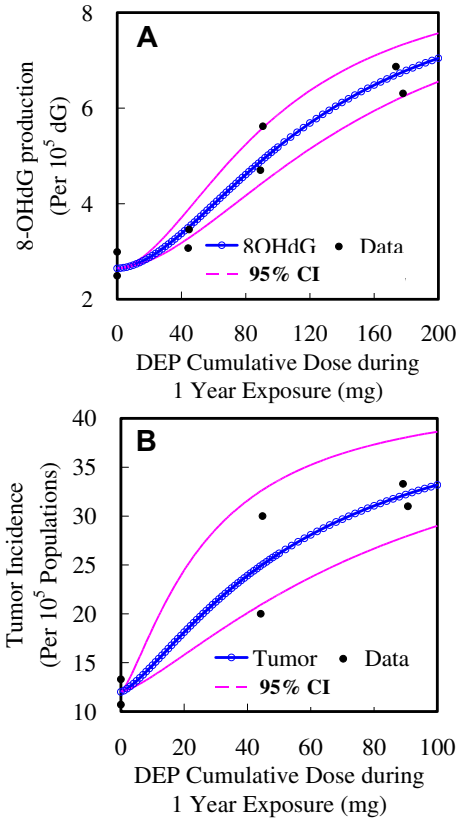


Fig. 3. Reconstructed dose–response profiles characterizing the relationships between selected effects and cumulative DEP dose. (A) 8-OHdG production, and (B) Tumor incidence.

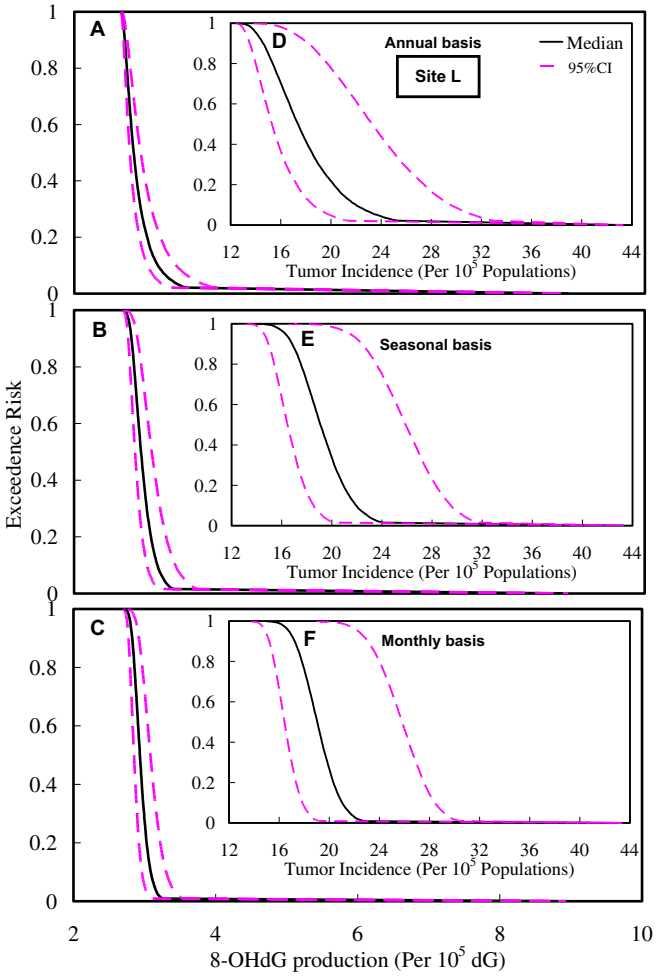


Fig. 4. Exceedance risk estimates of 8-OHdG production and tumor incidence in Site L with (A, D) annual, (B, E) seasonal, and (C, F) monthly basis data.

effect at 10%, 50%, and 90% probabilities were 21.03 (17.85–28.42), 19.04 (16.43–25.82), and 17.24 (15.20–23.07) per 10^5 populations, respectively (Fig. 4). For the other four sites, the risk profiles of the selected two endpoints were shown in Figs. S1–S4 (see Supplementary material).

The site-specific tumor incidence risk with different data types is shown in Fig. 5A–E. Our results showed that the upper bond (97.5%-tile) tumor incidence estimates at median risk (50%) were 22–26 per 10^5 populations (Fig. 5F). Fig. 5F also indicated that the higher tumor incidence occurred at the southerly site. The estimated site-specific DNA damage risk was shown in Fig. S5 (see Supplementary material). Overall, our risk estimates of DNA damage had the similar level (median value at 50% probability: 2.79–2.93 8-OHdG production per 10^5 dG) for the selected sites in Kaohsiung. The median tumor incidence risk, however, ranged between 16.57 and 19.04 per 10^5 populations at 50% probability.

Table 2
Risk estimates of DNA damage and tumor incidence effects at exceedance risk (ER) of 10%, 50%, and 90% probabilities at five selected sites.[a]

Site	ER_{10}	ER_{50}	ER_{90}
8-OHdG production (per 10^5 dG)			
M	2.86 (2.80–2.98)	2.79 (2.75–2.87)	2.74 (2.71–2.79)
C	2.90 (2.82–3.03)	2.81 (2.76–2.90)	2.75 (2.72–2.81)
J	2.93 (2.85–3.08)	2.83 (2.77–2.92)	2.75 (2.72–2.81)
D	3.03 (2.92–3.22)	2.90 (2.83–3.04)	2.81 (2.76–2.90)
L	3.09 (2.96–3.30)	2.93 (2.85–3.08)	2.83 (2.77–2.92)
Tumor incidence (per 10^5 populations)			
M	17.92 (15.66–24.16)	16.57 (14.77–21.95)	15.37 (14.00–19.74)
C	18.45 (15.05–22.67)	17.00 (15.05–22.67)	15.68 (14.20–20.33)
J	18.97 (16.38–23.09)	17.25 (15.21–23.09)	15.73 (14.23–20.42)
D	20.31 (17.33–27.53)	18.57 (16.10–25.14)	16.93 (15.00–22.57)
L	21.03 (17.85–28.42)	19.04 (16.43–25.82)	17.24 (15.20–23.07)

[a] Estimates calculated based on monthly basis monitoring data.

4. Discussion

4.1. Spatiotemporal variations of DEP exposures

This study adopted one year aerosol measurements and applied three different types of data sources to assess the human health risk posed by atmospheric DEP. We selected five sampling sites to perform the spatial variations for exposure groups in south Taiwan. Results showed that there was spatial heterogeneity existed in the sampled $PM_{2.5}$ mass concentrations in five selected sites. Sites D and L with the relative lower latitude regions in south Taiwan had major industrial parks and large quantity of vehicles, especially the diesel-powered trucks.

We showed that the DEP exposure dose strongly depended on the measured $PM_{2.5}$ mass and predicted VEP concentrations that are varied spatiotemporally. In details, there were three types of the temporal variations for $PM_{2.5}$ in five selected sites. Sites M and J had same trends, whereas Sites D and L showed the other similar pattern, indicating that we might designate two representative locations as north-Kaohsiung (sites M and J) and south-Kaohsiung regions (sites D and L), respectively. Moreover, the same patterns

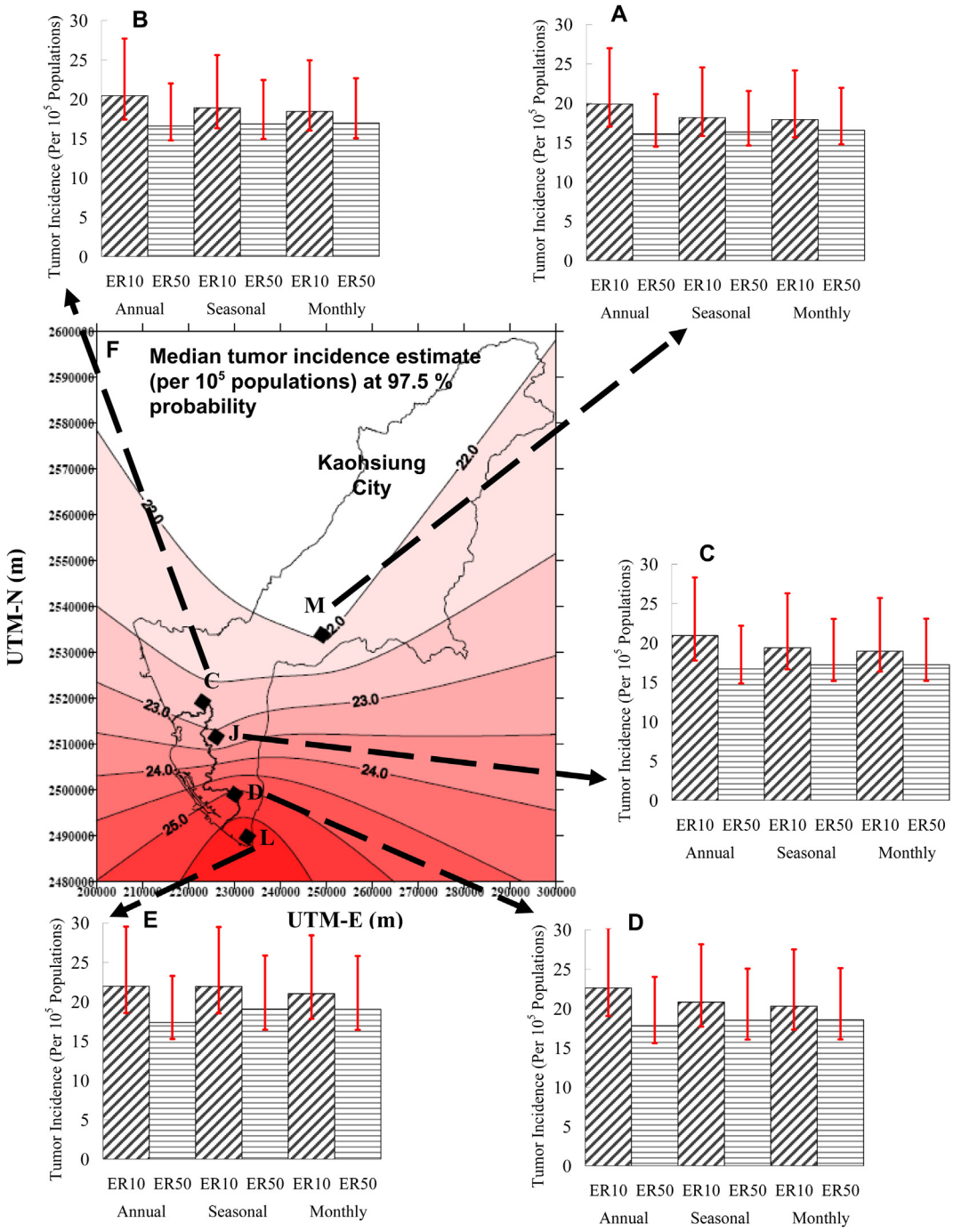


Fig. 5. Exceedance risk map of tumor incidences at most severity setting in Kaohsiung city. (A) Site M, (B) Site C, (C) Site J, (D) Site D, and (E) Site L. (F) Contour line map showing median tumor incidence estimates at 95%-tile probability.

from VEP concentrations were also found. Except for location reason, these sites had similar pattern on annual and seasonal peaks of $PM_{2.5}$ levels,. However, they were different for seasonal data type in Sites M and J, especially for spring and autumn shown in Fig. 2. Here if we did not have higher time-resolution data (monthly and seasonal bases), we would lost the correct $PM_{2.5}$ distribution for Sites M and J.

4.2. Linkage of selected health outcomes

This study selected two health outcomes, pre-cancer DNA damage biomarker 8-OHdG and cancer incidence, for populations posed by DEP exposure in south Taiwan. Ichinose et al. (1997) revealed that the production of 8-OHdG in lung DNA with DEP-treated mice showed a dose–response fashion. However, few studies pointed out that there was no positive causal association between DEP exposure and lung cancer mortality risk (Cox, 1997). Many studies supported that lung cancer might be caused by DEP exposure via DNA damage (Ichinose et al., 1997; Valavanidis et al., 2009). Recently, the background level of DNA damage has measured using more sensitive analytical techniques and showed nearly 0.5 and 1 lesions per 10^6 DNA nucleosides in lymphocyte cell line and human urine, respectively (Valavanidis et al., 2009). On the other hand, Iwai et al. (2000) indicated that the 8-OHdG level had a

significant higher than those in control groups of rats. We had not ever find the transform factor of 8-OHdG level from animal to human. Yet, our estimates at least showed the same trend between 8-OHdG level and cancer incidence.

Peluso et al. (2005) evidenced that the DNA adducts were associated with the subsequent lung cancer risk, especially for never-smokers. Kodell et al. (2006) also provided a concept to link pre-cancer biomarkers and cancer incidence with hierarchical methods. In fact, the USEPA recommended the legislation of standard of DEP exposure for occupational settings based on the DNA damage toxicity mechanisms or mode of action of DEP (Ris, 2007).

We used these two outcomes, 8-OHdG production and cancer incidence, as the responses to the DEP exposures in our study. Although we tried to find the robust relationship between the pre-cancer DNA damage biomarker and incidence, yet we only found that they were similar with positive correction. The evidence did not support that these two outcomes had significant relationships here. Therefore, we concluded "positive yet insignificant association" on our risk estimates.

4.3. Risk quantification and cancer epidemiological evidence

We found that the tumor incidence risk in Kaohsiung populations ranged between 22 and 26 per 10^5 populations at most severe scenario. Ko et al. (1997) showed that there were three major positive risk factors affecting lung cancer occurrence: (i) living adjacent to industrial district for greater than 20 years (odd ratio (OR): 2.8, 1.2–6.5), (ii) tuberculosis (OR: 4.7, 1.5–14.7), (iii) use of fume extractor (OR: 6.4, 2.9–14.1); in that one factor of daily consumption of vegetables had negative effect to lung cancer (OR: 0.4, 0.2–0.8).

Yang and Hsieh (1998) showed that lung cancer outcome for the cohorts with population density indicator in the period 1982–1991 depended on the urbanization factor. Yang et al. (1999, 2000) revealed two findings: (i) the age-adjusted incidence rate (AAR) was 15.3 and 34.9 per 10^5 populations for female and male, respectively, and (ii) the petrochemical air-pollution exposure index and lived near petroleum refinery plant were the influence factors in female lung cancer incidence.

Chen et al. (2002) showed that the AARs of lung cancer incidences were 13.1 and 28.7 per 10^5 populations for female and male in the period 1988–1992, respectively. Ko et al. (2005) indicated that AARs of lung cancer incidences for a medical center in south Taiwan were 0.44–0.54 and 1.06–0.91 per 10^5 populations for female and male in the period 1997–2002, respectively. Liaw et al. (2005) showed that age-adjusted mortality rate (AMR) for lung cancer ranged from 16.03 to 26.43 per 10^5 populations for female and ranged from 32.08 to 58.44 per 10^5 populations for male in the periods 1971–1975 and 1991–1995, respectively, indicating that two risk factors, smoking prevalence and fat consumption, might be the influence factors.

Chiu et al. (2006) indicated that AARs for lung cancer mortality were 19.49 and 30.63 per 10^5 populations for female and male in the period 1994–2003, respectively, in that risk factors were confirmed as high air-pollution exposure index and urbanization level of residence. By comparing with the previous cancer epidemiological studies shown in Table S1 (see Supplementary material), our estimates fell within the range values. Our estimates, however, did not take into account the gender-specific subgroups.

4.4. Limitations and implications

There are limitations in this study. First, we only counted the DEP with $PM_{2.5}$ due to nearly 80–95% DEP categorized in this size range (Ris, 2007; Wichmann, 2007). The other sources including fugitive, industrial, and biomass burning emissions did not take into account the risk estimation (Tsai and Chen, 2006a,b). Our sampling program was at least 2 consequence sampling days per month in each site, except for August, and the sample size for each site was 22. We had performed the monthly dynamic trends of $PM_{2.5}$ mass concentrations and associated vehicle contributions in five selected sites in Fig. 1. In order to obtain the exposure dose of site-specific DEP, we used the probabilistic framework to describe the most likely with their uncertainties of DEP exposures. It was believed that the most likely of site-specific DEP doses was convergent.

Second, the selected health effects from animal studies might affect the risk estimates due to the small sizes of experimental animals and inter-/intra-species differences (Ichinose et al., 1997; Iwai et al., 2000). Meanwhile, the Hill model is properly to describe the relationships between dose (DEP exposure) and responses (pre-cancer biomarker and tumor incidence) based on the biological plausibility, particularly used in non-linear conditions. Here we used 4-parameters Hill equations to well fit the dose–response data ($r^2 = 0.88–0.94$) with background values of 2.645 (SD 0.319) 8-OHdG production per 10^5 dG and 11.994 (SD 3.031) per 10^5 populations of tumor incidence, respectively.

Third, variability and uncertainty of data sources used for exposure and dose–response profiles could influence the DEP risk estimates. In addition, the genetic susceptibility might be the other factor in DEP-induced biomarker response and cancer risk estimates (Norppa, 2003). Although the exposure duration was 1 year for different scenarios, we found the associated uncertainties were different. Here we intended to emphasize the uncertainties in different data types, including annual, seasonal, monthly bases. They might cause different confident intervals of estimated risks for different data types. Indeed, our risk estimates did not take into account the gender-specific subgroup. In our exposure model shown in Table 1, female subgroup might have lower air breathed rate (BR) than male. In addition, if the air breathed rate had changed then the deposition fraction (d_F) might shift. In our dose–response models, however, we did not have gender-specific data on 8-OHdG production and tumor incidence effects. Even though, our predictions had taken into account many parameters as distribution forms to estimate a probabilistic risk with 95% confident interval. Therefore, the gender effect should not affect the final outcomes here. However, our results could not point out the gender differences of the risk estimates.

However, this study provides several useful messages to environmental experts, risk assessors, and governmental authorities. Our study proposed an integrated framework to study cancer risk assessment comparing with the investigation of cancer epidemiology. Although our study only focused on the DEP extracted from ambient PM, the health impacts from other sources could be obtained by applying our method. Yuan et al. (2002) indicated that the motor vehicle exhaust was the first large source for $PM_{2.5}$, followed by crustal materials (soil dust and paved road dust) and secondary aerosols (ammonium sulfate and nitrate). Moreover, the estimates in cancer incidence in south Taiwan residents agreed well with the epidemiological investigations. Recently, the research experts and environmental protect authority have incorporated risk-based human health outcomes into air quality standard establishment for $PM_{2.5}$ in Taiwan (Cheng et al., 2009).

Recently, Taiwan Environmental Protection Administration (TWEPA) had recommended that the daily and annual standards of $PM_{2.5}$ are 35 and 15 μg m^{-3}, respectively (http://ivy5.epa.gov.tw/epalaw/index.aspx). By comparing with other countries, the $PM_{2.5}$ daily standard is the same as that in USEPA (http://www.epa.gov/air/criteria.html) and higher than the WHO guideline (25 μg m^{-3}) (http://www.euro.who.int/Document/E87950.pdf). In addition, the

annual $PM_{2.5}$ standard is higher than USEPA (12 μg m^{-3}) and WHO (10 μg m^{-3}) but lower than EU guideline (25 μg m^{-3}) (http://ec.europa.eu/environment/air/quality/standards.htm).

There were many strategies to mitigate the $PM_{2.5}$ exposure. The mask use was the easy way on mitigation of $PM_{2.5}$ exposure from vehicle emission now. In Taiwan, the government also provides the real-time air quality information to guide the residents avoiding to the outdoors for protection reason during the episodes such as unhealth dispersion conditions, biomass burning, and dust storm periods, particularly for the susceptible subgroups. For major Taiwan metropolitans, the mass rapid transit (MRT) systems had been established or ongoing now. It was believed that the vehicle emissions should be reduced based on the on-road vehicle flows. At the same time, the gasoline and diesel fuels were improved or replaced by bio-fuels with novel technology (ITRI, http://www.itri.org.tw/index.jsp). Finally, the lower emission standards for different vehicles for protecting the residents' health were recommended.

5. Conclusions

There were three major findings could be drawn from this study: (i) DEP dose estimates and cancer risk quantification experienced heterogeneously spatiotemporal difference in south Taiwan, (ii) the pre-cancer DNA damage biomarker and cancer incidence estimates had a positive association yet insignificant, and (iii) all the estimates of cancer incidence for populations in south Taiwan were consistent with the previous cancer epidemiological investigations. Moreover, our work implicates the importance of incorporating both environmental and health risk impacts into models of air pollution exposure to guide adaptive mitigation strategies.

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Appendix A. Supplementary material

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atmosenv.2013.11.072.

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