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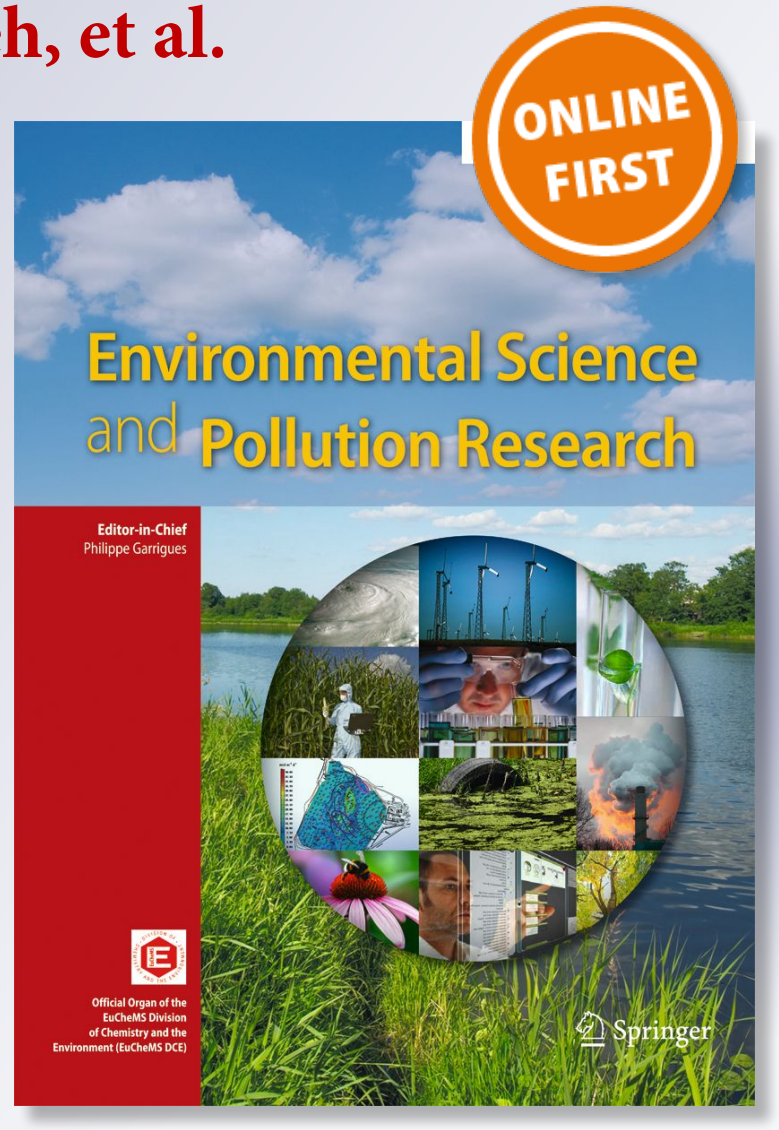

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RESEARCH ARTICLE

PBPK/PD assessment for Parkinson's disease risk posed by airborne pesticide paraquat exposure

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Abstract

Exposure to several specific pesticides has led to an increase of Parkinson's disease (PD) risk. However, it is difficult to quantify the PD population risk related to certain pesticides in regions where environmental exposure data are scarce. Furthermore, the time trend of the prevalence and incidence of PD embedded in the background relationship between PD risk and pesticide exposures has not been well characterized. It has been convincingly identified that a key pesticide associated significantly with an increased risk trend of PD is paraquat (PQ). Here, we present a novel, probabilistic population-based exposure-response approach to quantify the contribution from PQ exposure to prevalence risk of PD. We found that the largest PQ exposure contributions occurred in its positive trend during 2004–2011, with the PQ contributing nearly 21 and 24%, respectively, to the PD prevalence rates among the age groups of 70–79 and ≥ 80 years in Taiwan. We also employed the present population risk model to predict the PQ-induced PD prevalence based on the projected rates of increase in PQ exposure associated with age-specific population. The predicted outcome can be used as an early warning signal for public health authorities. We suggest that a mechanistic understanding of the contribution of a specific pesticide exposure to PD risk trends is crucial to enhance our insights into the perspective on the impacts of environmental exposure on the neurodegenerative diseases.

Keywords Parkinson's disease · Paraquat · Pesticide · Population exposure-response function · PBPK/PD · Probabilistic risk assessment

Yi-Hsien Cheng, Wei-Chun Chou, and Ying-Fei Yang contributed equally to this work that was initiated in the Fall 2015 Class "Special Topics on Bioenvironmental Systems Simulation (I)."

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Introduction

Pesticide exposure is significantly associated with incidence and prevalence of Parkinson's disease (PD). As the second most common neurodegenerative disease, there are more than 10 million people worldwide living with PD (Schultz 2007; http://www.pdf.org/en/parkinson_statistics). The onset of PD is resulted from dysfunction of dopaminergic systems, leading to movement disorders including loss of muscle control, trembling, and lack of coordination (Chen et al. 2010).

Notable effects of pesticide exposures on PD have been evidenced in laboratory experiments, epidemiological studies, and field observations (Berry et al. 2010; Betarbet et al. 2000; Fong et al. 2007; Kamel 2013; Lee et al. 2012; Liou et al. 1997; Menegon et al. 1998; Moisan et al. 2015; Pezzoli and Cereda 2013; Polito et al. 2016; Tanner et al. 2011; Wan and Lin 2016; Yang and Tiffany-Castiglioni 2008). In addition, specific gene-pesticide interactions were also found to be significant adverse factors for PD risks (Cannon and Greenamyre 2013; De Palma et al. 1998; Lin et al. 2011).

Several studies have indicated that PD risk is closely associated with agricultural pesticide exposures, suggesting that a risk assessment framework for pesticide associated PD onsets is in urgent need (Kamel 2013; Moisan et al. 2015). Paraquat (PQ), as one of the most widely used herbicides in the world, has been applied to kill weeds and desiccate foliage before harvesting crops. PQ could be exposed to field workers, gardeners, and transported via residues of food (Kamel 2013; Morshed et al. 2010). The PQ-associated PD risks were demonstrated to be approximately two times higher than other classes of pesticides (Berry et al. 2010; Liou et al. 1997; Pezzoli and Cereda 2013; Tanner et al. 2011).

The combined effects of genetic variants and environmental exposure risks on PD risk in Taiwanese population were found to be evident, implying that gene-environment interactions are closely related to PD risks (Lin et al. 2011). Tanner et al. (2011) indicated that PD-associated oxidative stress was resulted from PQ exposures with an odds ratio (OR) of 2.5 (95% CI 1.4–4.7). Pesticide exposure on southwestern Taiwan is associated with increased PD risks as well (Fong et al. 2007). Liou et al. (1997) indicated that exposure to PQ played a critical role in PD development regions of Taiwan, where occupational PQ exposure increased PD risk with an OR of 3.22 (95% CI 2.14–4.31). On the other hand, Wang et al. (1996) reported that the prevalence of PD was 119 (95% CI 80–169) per 100,000 population in Kinmen, Taiwan, substantially higher than that in mainland China (14 per 100,000 population).

In this study, we focused on how to quantify, if not impossible, the contribution of airborne PQ exposure to PD risk. We tried to develop metrics and methodologies to assess the long-term impact of airborne PQ exposure on PD burden. A physiologically based pharmacokinetic (PBPK) model was developed to estimate PD dose in the brain after inhalation/deposition of aerosolized PD droplets. We further developed a population dose-response-based probabilistic risk model to assess the contribution of PQ exposure to the age-specific prevalence of PD. A sensitivity analysis was also performed to assess the contributions of model parameters.

Materials and methods

Study data and population

To assess PD risk based on an integrated probabilistic approach, this study initiated with problem formulation constituted of PQ use, exposure, and associated individual- and population-based adverse health effects followed by exposure analysis, dose-response analysis, and risk characterization in specific age groups. The PD risk assessment framework includes data reanalysis and computational algorithms based on airborne PQ exposure (Supplementary Fig. S1).

Agricultural land area in Taiwan is approximately 22% of the total land area ranging from 8.1 to 8.3×10^3 km^2 in the period from 2005 to 2011 (Council of Agriculture 2014). PQ (24% *w*/*w*) ranks the second and third in sales volume (25%) and amounts (17%) in non-selective herbicides, respectively, of 1.82×10^6 kg and ~5 million US dollars, in 2013 (Fang 2014).

Taking into account PD-related medical claims included in the Taiwan National Health Insurance (NHI) database diagnosed based on the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) code 332.0, the age-sex-standardized incidence and prevalence rates ranged from 28.8 to 36.6 per 100,000 person-years and 84.8 to 299.3 per 100,000 population, respectively, in the period 2002–2011 (Liu et al. 2016). Collectively, in Taiwan, the average age-standardized prevalence of PD was 85 per 100,000 population in 2004 and 148 per 100,000 population in 2011, with a ~8% yearly increase, whereas the average age-standardized incidence of PD decreased steadily from 35 per 100,000 population in 2005 to 29 per 100,000 population in 2011 (Liu et al. 2016).

PQ exposure could pose substantial threats to individual as well as to population for development of neurodegenerative PD. We therefore focused on assessing PD risks probabilistically in five age groups for individual and population of <50, 50–59, 60–69, 70–79, and ≥80 years.

Exposure model: PQ-human PBPK modeling

A PBPK model allows us to quantitatively describe the bioaccumulations in tissue/organs of concern in particular human bodies. There are seven compartments of interest in the PBPK model including the blood, lung, brain, gastrointestinal

(GI) tract, liver, kidney, and rest of the body (Supplementary Fig. S2). Physiological and physicochemical parameters including blood and tissue/organ volume (V), body weight (BW), density of tissue/organs, (D) blood-tissue/organ exchange rate (Q), uptake/elimination rate constant (k), and tissue/organ partition coefficient (P) were defined as a body burden ratio by estimating the whole PQ burden in blood partitioning at specific tissue/organs based on published human and animal experimental studies. Given intake of airborne PQ, absorption, distribution, metabolism, as well as excretion of each tissue/organ in human body of specific age can be expressed mathematically and dynamically with first-order ordinary differential equations (Supplementary Table S1).

Briefly, air-sprayed PQ that suspends to become airborne PQ poses substantial threats to spray operators and residents through exposure routes of inhalation and skin contact (negligible). Based on an experimental study, air-sprayed PQ with specific use amount (A, kg km^{-2}) can be properly transformed into corresponding airborne PQ concentration (C, μg m^{-3}) by a linear equation of $C = 0.14A + 0.04$ (Morshed et al. 2010). Since PQ is a known potential factor for PD development, we thus merely estimated PQ burden in brain of certain age groups by implementing the PBPK model and treated it probabilistically with the Monte Carlo (MC) simulation methodology for further dose-response analysis.

Hill-based individual dose-response model

The in vitro bioassays in dopaminergic SH-SY5Y cell viability were applied as a biomarker to construct the individual-based dose-response profile (Yang and Tiffany-Castiglioni 2008). The SH-SY5Y cells were treated with 0.05–1 mM PQ for 48 h, and cell viability was determined by intracellular protease activity of amino-fluorocoumarin (AFC) fluorescence released from the glycyl-phenylalanyl-amino-fluorocoumarin (GF-AFC) (Yang and Tiffany-Castiglioni 2008).

The relationship of PQ concentration-dependent inhibition of dopaminergic cell viability can be constructed mechanistically by a Hill model and expressed mathematically as a conditional probability function as,

$$P(I|D) = I_{\min} + \frac{1-I_{\min}}{1+\left(\frac{ID_{50}}{D}\right)^{n}}, \quad (1)$$

where $P(I|D)$ is the conditional probability revealing inhibition effects on dopaminergic cell viability (I) given certain dose of PQ exposure (D, mM), ID_{50} is the causal PQ dose demonstrating half maximum inhibition effects on dopaminergic cell viability (mM), $I_{\min}$ is minimum inhibition of cell viability (incremental ratio compared to untreated control), and n stands for the Hill coefficient in which $n > 1$ indicates a positive cooperativity and ultrasensitive to exposed toxicant.

PAF-based population dose-response model

To estimate PQ exposure-associated population attributable fraction (PAF) for PD, we first estimated two key elements relative risk (RR) and proportion of PD cases given PQ exposure (θ) based on an epidemiological case-control study (Liou et al. 1997). Briefly, Liou et al. (1997) recruited 120 patients with PD and 240 hospital control subjects matched with age and sex of PD patients from the National Taiwan University Hospital. Among recruits of PD and controlled group, there were 31 and 22 people being exposed to PQ, respectively.

This study thus estimated RR, θ, as well as corresponding PAF and PQ use amount probabilistically through a MC simulation as,

$$\Phi(PAF|A) = \Phi(PAF = (RR-1)\theta/RR) \times \Phi(A), \quad (2)$$

where $\Phi(PAF|A)$ is conditional probability in a cumulative distribution function (CDF) by jointing CDFs of population attributable PD fraction ($\Phi(PAF)$) with certain amount of PQ in use ($\Phi(A)$). A three-parameter Hill model can then be appropriately applied to fit with extracted percentiles (2.5th, 5th, 25th, 50th, 75th, 95th, and 97.5th) of $\Phi(PAF)$ and $\Phi(A)$ as,

$$P(PAF|A) = \frac{PAF_{\max}}{1+\left(\frac{FA_{50}}{A}\right)^{n_F}}, \quad (3)$$

in that $PAF_{\max}$ stands for maximum PAF, FA_{50} characterizes half maximum PAF posed by particular air-sprayed PQ use amount A (kg km^{-2}), and n_F is the Hill coefficient revealing the slope of A-PAF dose-response relationship.

Predictive risk threshold model

To protect spray operators or residents from potentially adverse effects posed by airborne PQ exposure, this study implemented Weibull cumulative model to estimate threshold burden in brain. Specifically, given constructed Hill-based dose-response relationship of PQ exposure and inhibition effect on dopaminergic cell viability, PQ burden in brain causing 10% inhibition effect (ID_{10}) can be estimated and treated probabilistically to obtain its CDF as $\Phi(ID_{10})$.

This study then implemented a three-parameter Weibull model fitting to percentile values (2.5th, 25th, 50th, 75th, and 97.5th) extracted from $\Phi(ID_{10})$ to estimate threshold of PQ burden in brain not causing >10% inhibition effect as,

$$\Phi(ID_{10}) = \left\{1-\exp\left[-\left(\frac{D-\gamma}{\alpha}\right)^{\beta}\right],\ D > \gamma > 0,\ \alpha > 0,\ \beta > 0\right\}, \quad (4)$$

where γ is the location parameter representing the threshold value that must be smaller than D, α represents scale parameter that has effect of distribution as change on the abscissa scale, and β stands for slope

parameter that determines the shape of cumulative distribution curve.

Risk models

Based on the Bayesian inference, the PQ-induced PD risk models can be obtained through jointing prior probabilities of PQ burden in brain and PQ use amount (denoted as $P(D)$ and $P(A)$) predicted by MC simulations with conditional probabilities $P(I|D)$ and $P(PAF|A)$ (i.e., likelihoods), resulting in a joint probability (i.e., posterior probabilities) that can be mathematically expressed as,

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

$$R(PAF) = P(PAF|A) \times P(A), \quad (6)$$

where $R(I)$ indicates PQ exposure-induced inhibition of dopaminergic cell viability and $R(PAF)$ characterizes population attributable PD given certain amount of PQ use.

Additionally, PAF of PD could be transformed into population attributable risk (PAR) of PD to assess population exceedance risk by multiplying PAF with annual PD prevalence rates given by Liu et al. (2016). Notably, $P(D)$ in Eq. (5) could be predicted through a series of jointing processes as $P(D) = P(D|C) \times P(C|A) \times P(A)$ and the PBPK model in that $P(D|C)$ and $P(C|A)$ represent PQ dose in brain given certain inhaled PQ level and inhaled PQ level given specific air-sprayed PQ use amount, respectively.

Uncertainty and sensitivity analyses

We used the TableCurve 2D (Version 5.01, AISN Software Inc., Mapleton, OR, USA) optimal fit to the published in vitro experimental, epidemiological, and investigated data to determine the governing dose-response relationships. We employed MATLAB® (Version 8.1.0.604, The MathWorks, Inc., Natick, MA, USA) to perform PBPK simulations for tissue/organs of interest. We used the Crystal Ball software (Version 2000.2, Decisioneering, Inc., Denver, CO, USA) to perform MC simulation in that 10,000 iterations were exercised to ensure the stability of estimations.

A MC simulation technique was implemented to generate 2.5th, 5th, 25th, 50th, 75th, 95th, and 97.5th percentiles for quantifying the uncertainty of parameters associated with computational models including the PBPK model, the dose-response relationships, and the probabilistic PD risk models. We used Kolmogorov-Smirnov goodness-of-fit statistics to detect the optimal distributions of fitted parameters. Moreover, this study employed a one-way sensitivity analysis to assess the contribution of 10% change in each critical parameter used in the PBPK model including uptake/elimination rate constants and tissue/organs partition coefficients at one time to the simulation outcomes.

Results

Quantitative analysis of PQ exposure concentration

Based on available data for PQ sales volume and agricultural land area in Taiwan region, annual PQ use amounts were estimated ranging from 153 to 305 kg km^{-2} in the period from 2005 to 2011. The PQ use estimate can be well described by a lognormal (LN) distribution with a geometric mean (gm) of 252 kg km^{-2} and a geometric standard deviation (gsd) of 1.23, denoted as LN(252 kg km^{-2}, 1.23) (Table 1, Fig. 1b). On the other hand, linearly transformed airborne PQ concentration based on specific PQ use amount can be appropriately described as well with a LN distribution as LN(35.47 μg m^{-3}, 1.21) (Fig. 1a).

Exposure analysis: age-specific PQ dose in brain

Figure 2a displays a simplified PBPK model demonstrating PQ circulation and distribution in the human body. The physiological parameters as well as uptake/elimination rate constants and partition coefficients associated with PBPK simulation were shown in Supplementary Tables S2 and S3.

Considering a lifetime PQ exposure scenario, our results showed that PQ burden in brain accumulated gradually with increments in age; however, PQ burden increased asymptotically as age approached 50 years (Fig. 2b). Comparing lifetime exposure years of 80 with 50, PQ accumulation in people aged 80 years was 10% higher than those aged 50 years with estimates ranging approximately from 282 to 742 and 257 to 675 μM, respectively (Fig. 2b).

Furthermore, people ≥50 years including 50–59, 60–69, 70–79, and ≥80 years had significantly higher PQ exposure risks with PQ burden estimates of 424.79 (95% CI 260.13–684.71), 441.17 (274.56–708.63), 446.42 (274.50–730.66), and 455.20 (283.02–745.95), respectively, compared to younger people <50 years with estimates of 231.19 (79.98–674.02) μM (Fig. 2c).

Individual dose-response analysis/risk threshold estimate

With baseline inhibition effect of dopaminergic cell viability taken into account, three-parameter Hill model was found adequately elucidating the PQ exposure-induced dose-response profile. In particular, baseline inhibition effect I_{min} was estimated to be 0.06 ± 0.05 (mean ± SE), and ID_{50} and Hill coefficient n estimates were 0.48 ± 0.25 mM and 1.68 ± 0.89, respectively ($r^2 = 0.89$; $p < 0.001$) (Fig. 3a). Figure 3a also indicates that given 1 mM PQ exposure in brain would give rise to 79% (95% CI 66–92) inhibition effect on dopaminergic cell viability.

Table 1 PQ-related observations based on agricultural pesticide application practices and epidemiological data used to estimate PQ use and probability attributable risk (PAR) of PD induced by PQ use

Year	PQ amount (ton)[a]	Agricultural land area (ha)[b]	PQ use (kg km^{-2})	PD prevalence rate (per 100,000 population)[c]			
				50–59 years	60–69 years	70–79 years	≥ 80 years
2004	2685	–	–	63.0	303.3	814.6	857.8
2005	2203	833,176	264	73.8	360.5	1007.5	1145.4
2006	1908	829,527	230	79.5	392.8	1142.1	1342.1
2007	2440	825,947	295	86.5	417.9	1235.1	1562.4
2008	2508	822,364	305	90.7	426.6	1300.8	1690.4
2009	2105	815,462	258	93.5	432.3	1347.3	1809.8
2010	1245	813,126	153	94.8	429.5	1379.5	1953.6
2011	2403	808,294	297	96.8	410.4	1406.0	2076.6
Mean (SD)	2187 (453)	821,128 (9141)	258 (53)	84.8 (11.8)	396.7 (44.6)	1204.1 (205.8)	1554.8 (416.4)

[a] Adopted from Fang (2014)

[b] Adopted from the Council of Agriculture (2014)

[c] Adopted from Liu et al. (2016)

On the other hand, based on the established dose-response relationship between PQ and its induced inhibition effect (Fig. 3a), ID_{10} can be estimated as 0.075 (95% CI 0.030–0.182) mM (Fig. 3b). Our results indicated that the Weibull threshold model could best define the CDF of ID_{10} with PQ threshold in brain (γ) estimated to be 0.024 ± 0.004 mM along with associated parameters α and β of 0.063 ± 0.004 and 1.670 ± 0.162, respectively ($r^2 = 0.99$; $p < 0.001$) (Fig. 3c).

Population excess risk analysis

Based on the case-control study, proportion (θ) for PQ-induced PD was nearly 26% and the corresponding *RR* can be well depicted by a LN distribution (LN(3.22, 1.16)) with an estimate of 3.22 (95% CI 2.42–4.31) (Fig. 4a). On the other hand, PAF for PQ-exposed PD can therefore be estimated properly by a LN distribution as well with gm of 0.18, gsd of 1.06, and 95% CI estimates of 0.15–0.20, respectively (Fig. 4b).

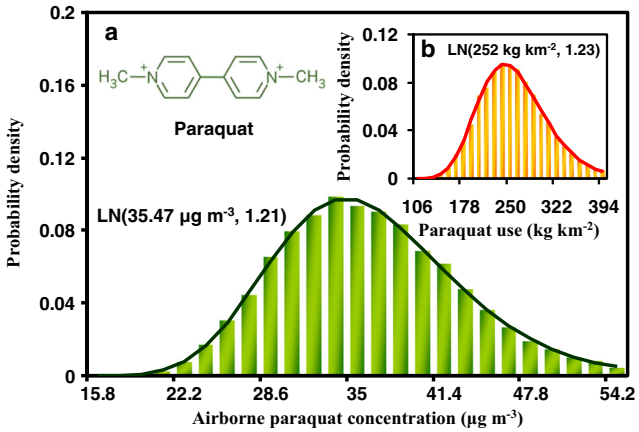

Fig. 1 The probability distributions of airborne PQ concentration (**a**) and PQ use (**b**) in Taiwan from 2005 to 2011

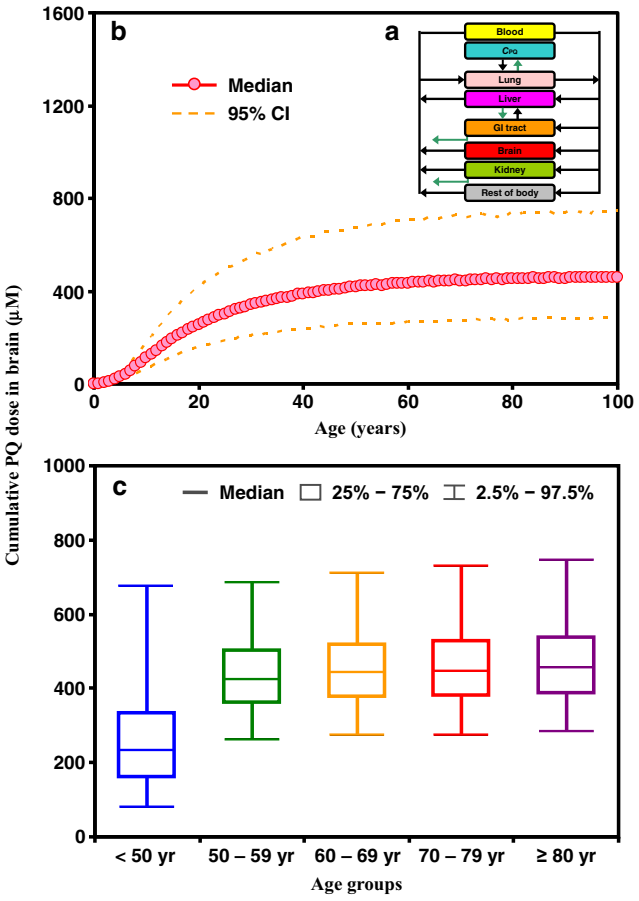

Fig. 2 A simplified PBPK model of PQ circulation and distribution in human body (**a**). Age-dependent PQ burden in brain in a lifetime PQ exposure scenario (**b**), and box and whisker plots representing PQ burden in brain of different age groups (**c**)

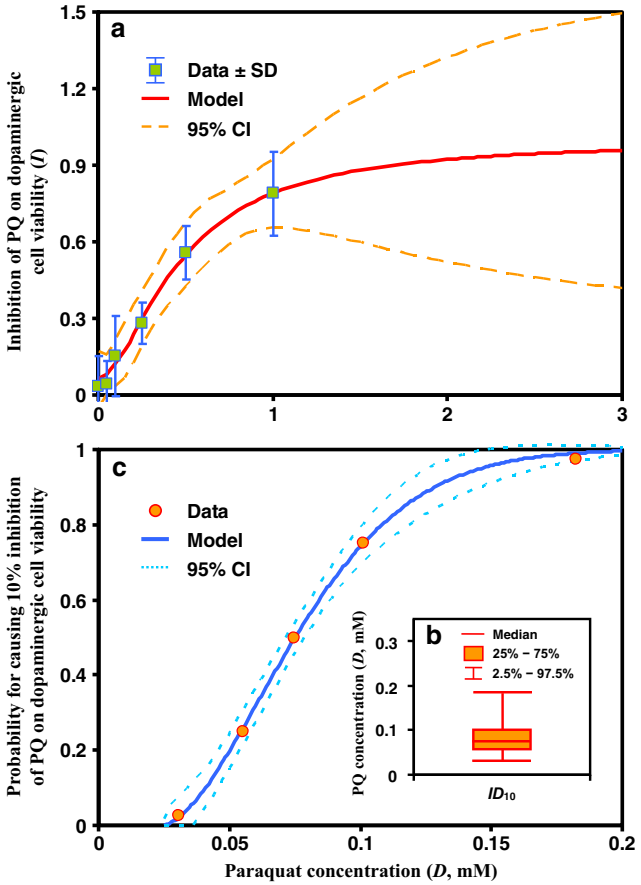

Fig. 3 Constructed PQ concentration-inhibition of dopaminergic cell viability (*I*) (**a**). Box and whisker plots of PQ concentrations corresponding to percentiles of data points extracted from 10% inhibition effect (ID_{10})-derived cumulative distribution function (CDF) (**b**) and best fit of the Weibull threshold model to the CDF of ID_{10} (**c**)

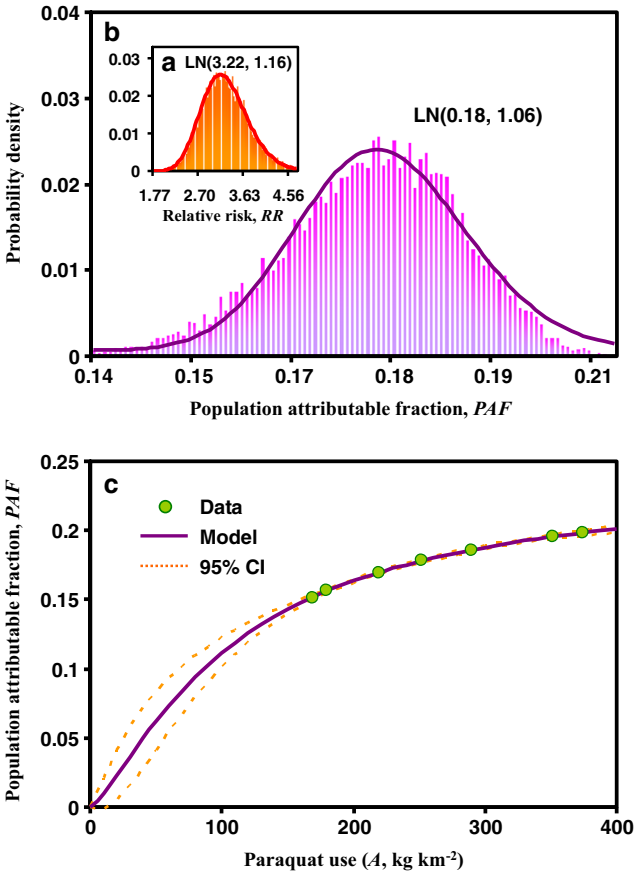

Fig. 4 The probabilities of relative risk (*RR*) (**a**) and population attributable fraction (*PAF*) (**b**) for PQ-exposed PD and the reconstructed *PAF*-PQ use amount dose-response function (**c**)

Through MC simulations, this study estimated both CDFs of PQ use amount and PAF ($\Phi(A)$ and $\Phi(PAF)$) with minimum–maximum estimates ranging from 57 to 434 kg km^{-2} and 0.13–0.21, respectively. Furthermore, a three-parameter Hill model was found best demonstrating the relationships between $\Phi(A)$ and $\Phi(PAF)$ with a maximum PAF (PAF_{max}) estimate of 0.238 ± 0.004, PQ use amount contributing to half maximum PAF (FA_{50}) of 109.695 ± 1.278 kg km^{-2}, and a Hill coefficient (n_F) of 1.321 ± 0.059 ($r^2 = 0.99$; $p < 0.001$) (Fig. 4c). Figure 4c also reveals that under the worst case scenario, PQ exposure would induce approximately 23% PD cases.

Risk characterization

Figure 5a demonstrates an estimated exceedance risk curve of inhibition effect on dopaminergic cell viability for age group-specific individuals exposed to PQ. Aforementioned simulated results indicate that with increases in exposure age, the accumulated PQ doses in brain increase as well, which in turn induce more significant neurodegenerative responses (i.e., reduced dopaminergic cell viability). As a result, people aged ≥80 years have severer neurodegenerative response than people younger than 50 years. It is likely (i.e., 50% risk probability) for people aged <50, 50–59, 60–69, 70–79, and ≥80 years to have inhibition effects on dopaminergic cell viability of 27.4% (95% CI 16.4–38.4), 48.4 (36.7–60.2), 49.7 (37.8–61.6), 50.4 (38.4–62.5), and 51.0 (38.9–63.1), respectively (Fig. 5a).

In quantifying PQ exposure-induced PD risks for different aged populations (i.e., PAR), we multiplied the probability distribution of PQ use (Fig. 1b) with its related established dose-response relationship between PQ use and PAF (Fig. 4c) as well as adopted annual prevalence rates of PD (Table 1), we can obtain PQ exposure-associated PARs in the period from 2004 to 2011 for people aged 50–59, 60–69, 70–79, and ≥80 years (Fig. 5b). In general, annual PARs display a positive trend for all age groups. Similar to individual neurodegenerative risk, people aged ≥80 years were found possessing the highest PARs in 2011 of 369 (95% CI 314–412) followed by 70–79, 60–69, and 50–59 years with PARs, respectively, estimated to be 250 (213–279), 73 (62–81), and 17 (15–19) per 100,000 population (Fig. 5b).

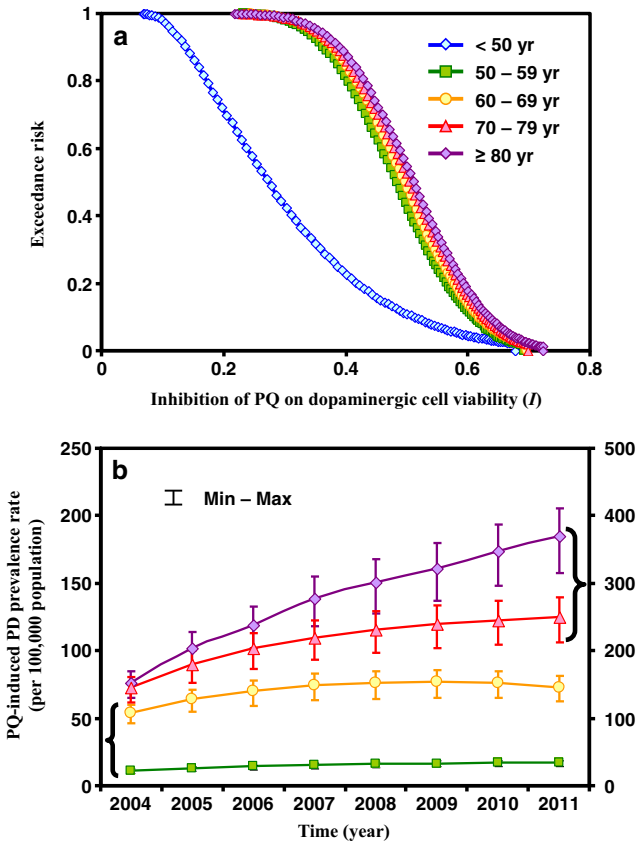

Fig. 5 Estimated exceedance risk (ER) curves for inhibition of dopaminergic cell viability (I) (**a**) and PQ-induced PD prevalence rate (per 100,000 population) (**b**) from 2004 to 2011

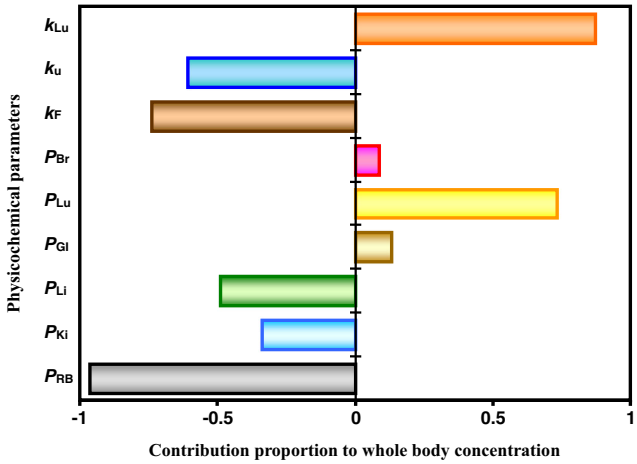

Fig. 6 Sensitivity analysis of parameters including uptake/elimination rate constants (k_{Lu}, k_u, and k_F) and partition coefficients (P_{Br}, P_{Lu}, P_{GI}, P_{Li}, P_{Ki}, and P_{RB}) in the PQ-PBPK model

Sensitivity analysis for critical PBPK parameters

This study considered key PBPK parameters including uptake/elimination rate constants and partition coefficients to assess its individual contribution to overall PQ-PBPK model (Fig. 6). In uptake phases, uptake rate and partition coefficient for lungs (k_{Lu} and P_{Lu}) contributed positively and most significantly to whole body concentration from the PBPK model with contribution proportions of 0.87 and 0.73, respectively. Partition coefficient for rest of the body (P_{RB}) contributed negatively yet most significantly to whole body concentration with a proportion of −0.96. On the other hand, in elimination phases, feces and urine (k_F and k_U) contributed negatively with proportions of −0.74 and −0.61, respectively. The partition coefficient for brain (P_{Br}) did not influence much on the PBPK model with contribution less than 10%, yet, it is detrimental to the human health (Fig. 6).

Discussion

In this paper, we estimated the PD prevalence rate attributable to airborne PQ exposure in Taiwan in the period from 2004 to 2011. We integrated advanced probabilistic risk models with an improved exposure-response function of PAF (NRC 2009) appraised with country-level population and health data. Our risk model is capable of characterizing airborne PQ exposure and PD risk with pesticide applications among different age groups on a regional scale. Our estimates of PD prevalence associated with exposure of PQ use in agricultural pesticide pollution provide some valuable results for protecting public health on a regional scale.

We estimate that airborne PQ from agricultural pesticide application practices contributes significantly to increase in PD risks. We found that the largest PQ exposure contributions occurred in its positive trend during 2004–2011, with the PQ contributing nearly 21 and 24%, respectively, to the PD prevalence rates among the age groups of 70–79 and ≥ 80 years in Taiwan. We also indicated that PQ exposure contributes nearly 17% to PD prevalence for the transition of PD prevalence rate from positive to negative during 2009–2011 for age group 70–79 years. This finding implicates that the importance of life stage and time frame for exposure ranges from 70 to 79 years. Our finding indicates that the increase rate of PQ application in rural regions is highly likely to pose PD risk for elderly ages >70 years in the near future. Our risk model enables to predict PQ-induced PD prevalence based on the projected rates of increase in PQ exposure associated with age-specific population. This prediction may be used as an early warning signal for public health agencies.

Except from PQ exposure, environmental factors such as pesticides (e.g., rotenone and maneb), insecticides (MPTP/MPP$^+$ and MCP) (Braungart et al. 2004; Jadiya and Nazir 2012; Pu and Le 2008), and heavy metals (e.g., Mn^{2+}, Al^{3+}, Hg^{2+}) may also contribute to the prevalence of PD (Negga et al. 2012; Settivari et al. 2009; Tanner et al. 2011; VanDuyn et al. 2010, 2013; Wang et al. 2011; Weisskopf et al. 2010). Moreover, genetic and environmental sources are two main factors that are ascribed to contribute to the loss of

dopaminergic neurons and the onset of PD (Dutheil et al. 2010; Thomas and Beal 2011). While approximately 10–20% of the PD cases are documented as genetic causes, the majority of the PD cases are idiopathic PD (Dawson et al. 2010; Lees et al. 2009). Therefore, an intensive and thorough examination of potential factors for onsets of PD is essentially requested.

Our analysis has several limitations. There were larger uncertainties in the PAF for PQ occurring in the exposure range of nearly 20–100 kg km^{-2}. This is due in part to limited available information of PD prevalence regarding agricultural PQ use. Moreover, there were also rare studies related to PQ-induced PD risk. The poorly characterized uncertainties about the relative toxicity of various agricultural pesticide ingredients and pesticide mixtures limit clarification of the exposure sources (Dexter and Jenner 2013; Minnema et al. 2014; Mostafalou and Abdollahi 2013). Furthermore, our model is not able to identify the importance between duration and intensity of PQ exposure (Morshed et al. 2010). Thus, more mechanistic studies are needed to identify essential aspects of the effects of environmental exposures on the neurodegenerative diseases.

Our neurotoxicity risk assessment was based on PQ-induced apoptosis in human SH-SY5Y cells (Yang and Tiffany-Castiglioni 2008). The SH-SY5Y cell line, as one of the representative in vitro models for PD research, represents dopaminergic-specific neuro-degeneration and possesses many characteristics of dopaminergic neurons such as the dopamine transporter, tyrosine hydroxylase, and dopamine-beta-hydroxylase (Xie et al. 2010). Though SH-SY5Y cell has various advantages such as the efficiency in drug screening, limitations including its dependence upon the culture conditions that could influence the toxicant-induced cytotoxicity should be taken into consideration (Falkenburger and Schulz 2006). Thus, an improved in vitro dose-response relationship is needed. In addition to the endpoint selected in this study, other chronic effects induced by PQ in vivo systems such as the impairment in mobility and degeneration of dopaminergic neurons could be taken into consideration and compared with the in vitro dose-response profiles (Allen et al. 2014; Bortolotto et al. 2014; Cicchetti et al. 2005; Shukla et al. 2016).

Despite the limitations, this study has some merits. We have pointed out that time trends in the prevalence and incidence of PD are embedded in the background relationship between PD risk and pesticide exposures. A key pesticide, PQ, was quantitatively evaluated to be significantly associated with an increased risk trend for PD. We used a novel, probabilistic PAF-based exposure-response approach to quantify the contribution from PQ exposure to prevalence risk of PD. Our population risk model can help predict PQ-induced PD prevalence on the basis of projected available data. This prediction may be used as an early warning signal for public health agencies. Thus, understanding and quantifying the contribution of a specific pesticide exposure to PD risk trends are necessary to improve our insights into the perspective on the influence of environmental exposures on neurodegenerative diseases (Tshala-Katumbay et al. 2015).

Conclusion

Our findings provide insight into the time trends in the prevalence of PD. Our results should inform how we respond to pesticide-associated environmental exposures and can guide how we understand the consequence of future relationships between the prevalence of PD and pesticide exposure. Although pesticide-associated exposure is clearly not the only factor that affects PD risk trends, our quantitative approach reveals that it is a major factor. More broadly, we suggest that a mechanistic approach to explore the pesticide exposure-associated PD risk trends is an urgent need that enhances our insights into the perspective on the impacts of pesticide exposure on the neurodegenerative diseases.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no competing interests.

Research involving human participants and animal rights The article does not contain any studies with human participants or animals performed by any of the authors.

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