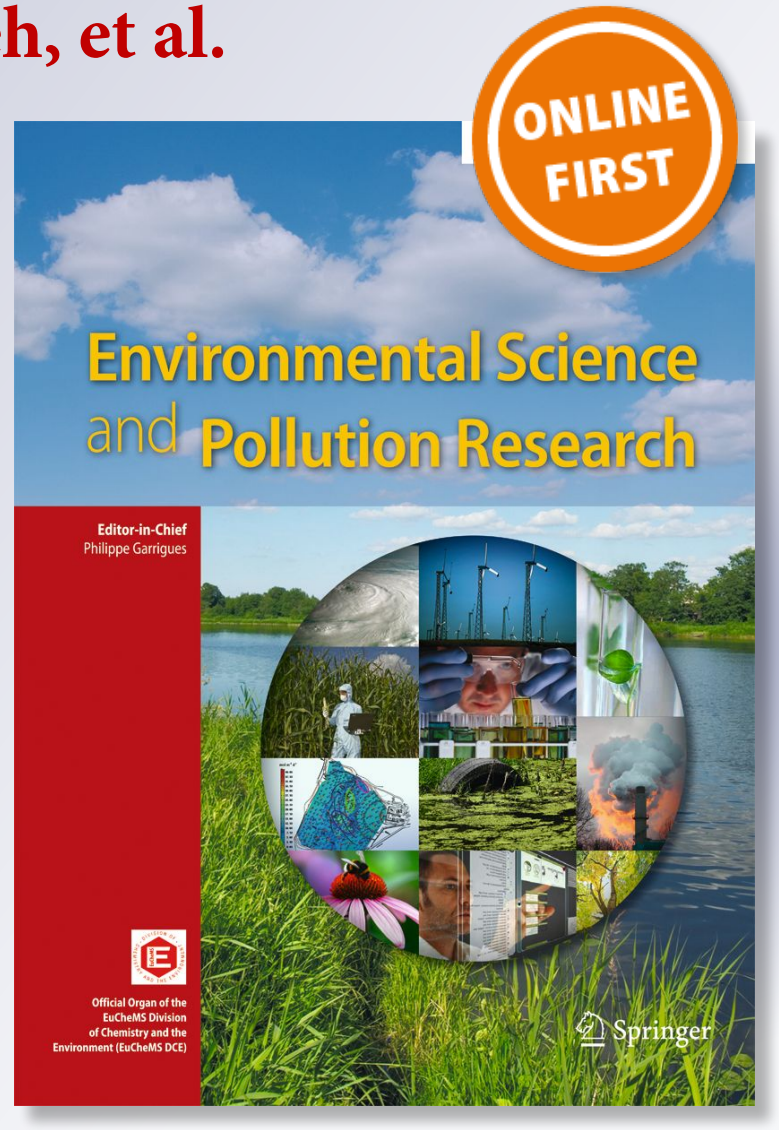
Response to "Letter to the editor re: Cheng YH, Chou WC, Yang YF, et al. Environ Sci Pollut Res *(2018). https://doi.org/10.107/s11356-017-0875-4"*

Yi-Hsien Cheng, Wei-Chun Chou, Ying-Fei Yang, Chi-Wei Huang, Chun Ming How, Szu-Chieh Chen, Wei-Yu Chen, Nan-Hung Hsieh, et al.

Environmental Science and Pollution Research

ISSN 0944-1344

Environ Sci Pollut Res
DOI 10.1007/s11356-018-3178-5



Springer

Environmental Science and Pollution Research
https://doi.org/10.1007/s11356-018-3178-5

LETTER TO THE EDITOR

Response to "Letter to the editor re: Cheng YH, Chou WC, Yang YF, et al. *Environ Sci Pollut Res* (2018). https://doi.org/10.107/s11356-017-0875-4"

Yi-Hsien Cheng[1] · Wei-Chun Chou[1] · Ying-Fei Yang[2] · Chi-Wei Huang[2] · Chun Ming How[2] · Szu-Chieh Chen[3,4] · Wei-Yu Chen[5,6] · Nan-Hung Hsieh[7] · Yi-Jun Lin[8] · Shu-Han You[9] · Chung-Min Liao[2]

Received: 28 August 2018 / Accepted: 6 September 2018

We thank Drs Travis, Clewell III, Campbell Jr., and Hinderliter for providing insightful comments on our paper entitled "PBPK/PD assessment for Parkinson's disease risk posed by airborne pesticide paraquat exposure" (Cheng et al. 2018). Here, we would like to provide some explanations and clarifications based on the section titles: Hazard assessment, Exposure assessment, and Risk assessment.

Hazard assessment

Dr Travis and co-workers argued that paraquat (PQ) as a risk factor of inducing Parkinson's disease (PD) is a hypothesis and "nothing" in the paper proved it. However, it should be cautiously noted that the risk assessment framework in this study was constructed by following the procedure in an eminent textbook describing principles of risk assessment. We have evaluated potential PD risks based on a probabilistic risk assessment approach by linking internal PQ dosimetry using a physiologically-based pharmacokinetic (PBPK) modeling framework with well-established dose-response relationships based upon in vitro assay and epidemiological causal study investigating the proportion of PQ-induced PD. The overall risk assessment framework was based on the rigorous risk assessment guidelines.

Although the dose-response data was derived from in vitro analysis, our aim was to construct a dose-response relationship between PQ exposure concentrations and neurotoxic effects. Due to the lack of in vivo dose-response data investigating dopaminergic effects resulted from PQ inhalation, we agree that the limited data source is the limitation of this study. We also mentioned this limitation in the section of discussion by describing that the constructed dose-response relationship could be improved by assessing in vivo chronic effects when more comprehensive dose-response data are investigated and available.

Exposure assessment

Among pesticides used in Taiwan, PQ ranks the second and third in sales volume and amount in non-selective

Responsible editor: Philippe Garrigues

✉ Chung-Min Liao
cmliao@ntu.edu.tw

[1] Institute of Computational Comparative Medicine, Department of Anatomy and Physiology, Kansas State University, Manhattan, KS 66506, USA

[2] Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei 10617, Taiwan, Republic of China

[3] Department of Public Health, Chung Shan Medical University, Taichung 40201, Taiwan, Republic of China

[4] Department of Family and Community Medicine, Chung Shan Medical University Hospital, Taichung 40201, Taiwan, Republic of China

[5] Department of Biomedical Science and Environmental Biology, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, Republic of China

[6] Research Center for Environmental Medicine, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, Republic of China

[7] Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77845, USA

[8] Institute of Food Safety and Health Risk Assessment, National Yang-Ming University, Taipei 11221, Taiwan, Republic of China

[9] Institute of Food Safety and Risk Management, National Taiwan Ocean University, Keelung 20224, Taiwan, Republic of China

Published online: 13 September 2018

herbicides, respectively, of 1.82×10^6 kg and ~5 million US dollars, in 2013 (Fang 2014). In addition, 2500 tons of PQ are used on farmland annually, and the herbicide is applied at least once per year on about 800,000 ha of land. In Taiwan, the application of PQ is allowed to be used with mist blower repeatedly on the same land after a fallow period and is often extensively used by farmers who grow rice, oranges, tangerines, and sugar cane. PQ is also widely used in Malaysian plantation and field crops by a mist blower mounted on a tractor or carried by workers (Morshed et al. 2010; Wibawa et al. 2009).

The agricultural community lives close by the farmland; thus, farmers and other people live nearby have higher probability to be exposed to PQ without wearing personal protective equipment when farmers apply the PQ. Travis et al. argued that according to this study, the entire population in Taiwan is assumed to be exposed with PQ. In fact, this study only considered people living in the agricultural land area where are highly likely to be posed by PQ toxicity. The agricultural land region was 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).

Several studies in developing countries have reported evidence of PQ exposures. A study related to banana plantations in Costa Rica (Van Wendel de Joode et al. 1996) measured exposure of diluted PQ (0.1–0.2%) to11 spray applicators. Results showed that urinary levels (detected in 2 of 28 samples) ranged from 0.03–0.24 mg L^{-1}. Respiratory exposure was 0–0.043 mg/L. They found that hazardous exposure presents continually due to poor working conditions. Seiber et al. (1983) reported that PQ residues in cotton plants for 4 weeks after application gave rise to PQ concentrations in air ranging from 0.47–1.2 pg m^{-3}. It was also observed that the maximum exposure by inhalation was 16.3 pg day^{-1} (based on an average breathing rate of 1.7 m^3 h^{-1} for light work and an 8-h working day) (Seiber et al. 1983). The upper level of airborne PQ concentrations was corresponding to 43.5% of the acceptable operator exposure level (AOEL), for a worker weighing 75 kg with 70% of the airborne PQ in dust had respirable size (Seiber et al. 1983).

Airborne PQ was measured in PQ users (knapsack) and non-users working in coffee, banana, and oil palm plantations in Costa Rica (Lee et al. 2009). The measured inhalable dust was 218.86 ± 253.50 μg m^{-3} (mean ± SD), whereas the airborne PQ exposure was 6.07 ± 4.77 μg m^{-3}. Based on these results we described above, we assumed a worst case scenario based on very conservative assumption to address the possible risk of PD induced by PQ exposure.

Dr Travis and co-workers mentioned that the equation of converting PQ application rate to the resulting airborne concentration of PQ droplets is unclear. We derived a simple liner equation in our work based on Morshed et al. (2010). Dr Travis and co-workers also were concerned about the inaccuracy of applied equations used in the PBPK model. The equations to determine body weight, tidal volume, and respiration frequency as a function of age were adopted from ICRP (ICRP 2002) and Altman and Dittmer (1962). The equations were also cited from the European projects 2FUN (FP6) to develop a life-stage PBPK model (Beaudouin et al. 2010). We have double-checked and confirmed the accuracy of equations applied in the PBPK model. However, some equations used to estimate physiological parameters for PQ-human PBPK modeling in our work are needed to be revised in order to reach unit consistency. Dr Travis and co-workers mentioned that the fecal excretion rate is ten times faster than the urinary excretion rate. Due to the lack of experimental data describing the partition coefficient of PQ, we used the parameters derived from near-lethal dose in animal (Murray and Gibson 1974) and a fetal human poisoning case (Arys et al. 2000). We agree that the clearance rate used in the PBPK model is low; however, this is due to the estimation based upon limited experimental data. These are the model limitation and uncertainty in the PQ-PBPK model as well.

Dr Travis and co-workers addressed that the estimated human brain concentration of PQ was extremely higher than that of the study from Dr Travis' group (Breckenridge et al. 2013, 2016). Breckenridge et al. (2013) systematically evaluated the neurotoxicity of PQ for sporadic Parkinson's disease in one widely used genotype of mice (C57BL/6J). However, there are several key differences between results of Breckenridge et al. (2013) and our assumptions. Firstly, we noticed that the groups tested were type of inbred mouse strain at 2 months-of-age (equal to the mid-teens in humans), whereas our evaluation was focused on different age groups, especially for the elderly group. Several animal models have reported a significantly higher PQ-related neurotoxicity in older animals as well (Li et al. 2005; Jiao et al. 2012; Yin et al. 2011). Secondly, Dr Travis' group estimates the maximum brain PQ concentration of 2.2 μM in animal model based on acute exposure (1 week) with intraperitoneal injection of PQ in the mouse model.

However, the results obtained from acute exposure should be carefully compared to the results of chronic exposure study. Previous study has shown that PQ could cumulate in a linear fashion depending on the dose treatment and had a prolonged retention in brain (Prasad et al. 2007). It has been suggested that subtle, chronic exposure to PQ might be associated with specific injury to SNpc (Dinis-Oliveira et al. 2006). Based upon these concerns about the possible long-term cumulative dose of PQ, we assumed the worst case scenario to estimate the cumulative PQ concentrations in human brain using the PBPK model. Due to the limited related data, the current study was not able to validate our simulated results but provided reasonable prediction of PD risks under the worst case scenario. Overall, we entirely agree with the points and concerns

addressed by Dr Travis and co-workers; however, future study is needed to address the possible association between chronic low-dose exposures to PQ and parkinsonian syndromes, and differences between acute and chronic neurotoxicity of PQ.

Risk assessment

Dr Travis and co-workers argued that this study equated effects of PQ on dopaminergic cells to the causing of PD. Although this study only applied an in vitro experiment to perform a dose-response modeling due to limitations in finding a more appropriate literature describing the dose-response relationship, results derived from the risk assessment framework in this study could still give implications for the potential neurotoxic risks of PQ. There is also a vision set by the Committee on Toxicity Testing and Assessment of Environmental Agents of the National Research Council for toxicity testing moving from testing in whole organism toward in vitro assays performed in human cells (Crump et al. 2010; NRC (National Research Council) 2007). The possibility of employing in vitro analyses to investigate dose-response of key biomarkers should be considered as a potential tool in the current study and the future risk assessment framework.

Dr Travis and co-workers mentioned that they had a problem finding which data were based on Liou et al. (1997). We adopted the data of odds ratio (OR) and proportion of PD cases given PQ exposure (θ) from Liou et al. (1997) and applied the data to estimate relative risk (RR) based on a well-defined equation for converting OR into RR. Deduction of the PAF-based population dose-response model was described in detail in the "Materials and methods" section of our work. Overall, our study provides reasonable prediction of PQ exposure-induced PD risks under the worst case scenario based on a well-developed probabilistic risk assessment framework by linking the PQ-PBPK model with the well-established dose-response relationships of in vitro assays and epidemiology causal study.

Compliance with ethical standards

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.

References

Altman PL, Dittmer DS (1962) Growth, including reproduction and morphological development. Federation of American Societies for Experimental Biology, Washington, DC

Arys K, Van Bocxlaer J, Clauwaert K, Lambert W, Piette M, Van Peteghem C et al (2000) Quantitative determination of paraquat in a fatal intoxication by HPLC-DAD following chemical reduction with sodium borohydride. J Anal Toxicol 24:116–121

Beaudouin R, Micallef S, Brochot C (2010) A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan. Regul Toxicol Pharmacol 57(1):103–116

Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck M, Mathews JM, Tisdel MO, Minnema D, Travis KZ, Cook AR, Botham PA, Smith LL (2013) Pharmacokinetic, neurochemical, stereological and neuropathological studies on the potential effects of paraquat in the substantia nigra pars compacta and striatum of male C57BL/6J mice. Neurotoxicology 37:1–14

Breckenridge CB, Berry C, Chang ET, Sielken RL, Mandel JS (2016) Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis. PLoS One 11:e0151841

Cheng YH, Chou WC, Yang YF, Huang CW, How CM, Chen SC, Chen WY, Hsieh NH, Lin YJ, You SH, Liao CM (2018) PBPK/PD assessment for Parkinson's disease risk posed by airborne pesticide paraquat exposure. Environ Sci Pollut Res 25:5359–5368

Council of Agriculture (2014) Annual Agricultural Statistics. Executive Yuan, Taiwan http://agrstat.coa.gov.tw/sdweb/public/official/officialInformation.aspx

Crump KS, Chen C, Louis TA (2010) The future use of in vitro data in risk assessment to set human exposure standards: challenging problems and familiar solutions. Environ Health Perspect 118:1350–1354

Dinis-Oliveira RJ, Remiao F, Carmo H, Duarte JA, Sanchez Navarro A, Bastos ML (2006) Paraquat exposure as an etiological factor of Parkinson's disease. Neurotoxicology 27:1110–1122

Fang LP (2014) Deep development of non-selective insecticides in a halfcentury in Taiwan, investigation of the forbiddenness of the insecticide paraquat. Annual Meeting of Weed Society of Taiwan. (in Chinese)

ICRP (2002) Basic anatomical and physiological data for use in radiological protection: reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. ICRP Publication 89. Ann ICRP 32:5–265

Jiao Y, Lu L, Williams RW, Smeyne RJ (2012) Genetic dissection of strain dependent paraquat induced neurodegeneration in the substantia nigra pars compacta. PLoS One 7:e29447

Lee K, Park EK, Stoecklin-Marois M, Koivunen ME, Gee SJ, Hammock BD, Beckett LA, Schenker MB (2009) Occupational paraquat exposure of agricultural workers in large Costa Rican farms. Int Arch Occup Environ Health 82:455–462

Li X, Yin J, Cheng CM, Sun JL, Li Z, Wu YL (2005) Paraquat induces selective dopaminergic nigrostriatal degeneration in aging C57BL/6 mice. Chin Med J 118:1357–1361

Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC (1997) Environmental risk factors and Parkinson's disease: a case control study in Taiwan. Neurology 48:1583–1588

Morshed MM, Omar D, Mohamad R, Wahed S, Rahman MA (2010) Airborne paraquat measurement and its exposure to spray operators in treated field environment. Int J Agric Biol 12:679–684

Murray RE, Gibson JE (1974) Paraquat disposition in rats, guinea-pigs and monkeys. Toxicol Appl Pharmacol 27:283–291

NRC (National Research Council) (2007) Toxicity testing in the 21st century: a vision and a strategy. National Academies Press, Washington, DC

Prasad K, Winnik B, Thiruchelvam MJ, Buckley B, Mirochnitchenko O, Richfield EK (2007) Prolonged toxicokinetics and toxicodynamics of paraquat in mouse brain. Environ Health Perspect 115:1448–1453

Seiber JN, Woodrow JE, Hermann BW, Sanders P (1983) Final report: determination of airborne residues from four harvest aid chemicals (DEF, Folex, cacodylates, and paraquat) at treated San Joaquin cotton field sites, as a measure of potential human exposure. CDFA Worker Health & Safety Report #HS-1326

Van Wendel de Joode BN, De Graaf IAM, Wesseling C, Kromhout H (1996) Paraquat exposure of knapsack appli-cators on banana plantations in Costa Rica. Int J Occup Environ Health 2:294–304

Wibawa W, Mohamad R, Juraimi AS, Omar D, Mohayidin MG, Begum M (2009) Weed control efficiency and short term weed dynamic impact of three non-selective herbicides in immature oil palm plantation. Int J Agric Biol 11:145–150

Yin L, Lu L, Prasad K, Richfield EK, Unger EL, Xu J, Jones BC (2011) Genetic-based, differential susceptibility to paraquat neurotoxicity in mice. Neurotoxicol Teratol 33:415–421