Environmental Pollution 159 (2011) 1017–1022

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Short communication

Low-level maternal methylmercury exposure through rice ingestion and potential implications for offspring health

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Studies concerning maternal methylmercury exposure and cognitive outcomes for offspring should include populations where rice ingestion is the primary methylmercury exposure pathway.

ARTICLE INFO

Article history:
Received 2 June 2010
Received in revised form
3 September 2010
Accepted 21 December 2010

Keywords:
Methylmercury
Rice
Confounding
Neurodevelopment
Micronutrients

ABSTRACT

Fish consumption is considered the primary pathway for MeHg (MeHg) exposure; however, MeHg exposure also occurs through rice ingestion. Rice is grown in an aquatic environment and although documented MeHg concentrations in rice are lower compared to fish tissue, human exposures exceed international guidelines in some regions where rice is a staple food and rice MeHg levels are elevated. Studies concerning human health exposure to MeHg should also include populations where maternal MeHg exposure occurs through ingestion of rice. Rice does not contain long-chain polyunsaturated fatty acids, which are associated with confounding developmental outcomes in offspring. Rice is also a staple food for more than half the world's population; therefore, it is critical to investigate the potential health risks of maternal ingestion of rice to the developing fetus, the most susceptible population to the deleterious effects of MeHg. Data concerning MeHg in rice are reviewed and micronutrients in rice are discussed.

1. Introduction

Mercury (Hg) is a global pollutant and known neurotoxin. MeHg (MeHg) is one of the most toxic forms of Hg due to its ability to cross the blood brain and placental barriers (Clarkson and Magos, 2006). Intake of fish is considered the primary exposure pathway because Hg is highly concentrated in the aquatic food web and the Hg dose from seafood is greater than 95% MeHg in predatory fish (USEPA, 2001a). Historical MeHg poisonings in Japan (Swedish Expert Group, 1971) and Iraq (Bakir et al., 1973) confirmed human health impacts from MeHg exposure were most severe in the developing fetus due to irreversible neural damage. Exposure to MeHg occurred through ingestion of fish tissue (Japan) and ingestion of grain treated with MeHg fungicide (Iraq). Aside from one study in Sweden concerning a population exposed to MeHg through poultry and swine that were fed fish meal (Lindberg et al., 2004), the possible importance of other food sources was not previously investigated, as biomagnification of MeHg in the terrestrial food web was considered negligible.

2. Hg cycling in rice paddies

Hg exists in the atmosphere as elemental Hg (Hg^o), or oxidized Hg (Hg(II)), or may be bound to particulates (Hg_p) (Schroeder and Munthe, 1998). After deposition to the earth's surface, less toxic inorganic Hg(II) may be converted to MeHg by anaerobic microbes in aquatic environments (Benoit et al., 2003). MeHg yields tend to be higher in wetlands and recently flooded reservoirs due to anoxic conditions that promote anaerobic microbial activity (Bodaly et al., 1997; Hurley et al., 1995; Kelly et al., 1997; Marvin-DiPasquale et al., 2003; St. Louis et al., 1994). In lowland rice paddies water is stored in the field during most of the rice growing season, and like other wetlands, are considered important Hg methylation sites (Qiu et al., 2008). Average MeHg bioaccumulation factors (BAFs) for predatory fish are 10^6 due to biomagnification of MeHg through the aquatic food web (USEPA, 2001a), while MeHg BAFs between brown rice grains and root soil from contaminated and control sites in southwestern China ranged from 0.71 to 50 (Zhang et al., 2010a). Although terrestrial bioconcentration of MeHg is lower, in some mining villages in Guizhou province, China, where rice is a staple food and Hg contamination is elevated, rice may be more important than fish for MeHg exposure (Feng et al., 2008; Zhang et al., 2010b).

3. Rice MeHg

Several studies reported MeHg concentrations in unmilled brown rice from Guizhou province, China (Horvat et al., 2003; Cheng et al., 2009a; Meng et al., 2010; Qiu et al., 2006, 2008; Zhang et al., 2010a, 2010b), but polished white rice is more

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doi:10.1016/j.envpol.2010.12.024

commonly consumed in Asia. Since the polishing process may reduce the concentrations of trace elements (Heinemann et al., 2005; Villareal et al., 1991), this discussion is limited to white rice. To the best of our knowledge, the results in Table 1 were the only studies that reported MeHg concentrations in white rice.

All studies were completed in China, including Zhoushan Island (Cheng et al., 2009b), Guizhou province (Feng et al., 2008; Li et al., 2008a, 2009), and Hubei province (Rothenberg et al., in press). For one study, rice was purchased in a Shanghai market (Cheng et al., 2009a) and for another study, rice samples were compared from markets in 15 provinces throughout China (Shi et al., 2005). Methods for MeHg determination differed slightly between labs. Cheng et al. (2009a, 2009b) utilized toluene extraction, then analysis of MeHg by gas chromatography (GC) with an electron capture detector (NIMD, 2001). Shi et al. (2005) extracted MeHg using potassium bromide-copper sulfate and dichloromethane (CH_2Cl_2) (Alli et al., 1994; Cai et al., 1997), then separation and measurement of Hg species by capillary gas chromatography (GC) coupled with atomic fluorescence spectrometry (AFS). Feng et al. (2008), Li et al. (2008a, 2009) and Rothenberg et al. (in press) leached samples with KOH and dichloromethane, then quantified MeHg by GC-CVAFS (cold vapor atomic fluorescence spectrometry) (Liang et al., 1996; USEPA, 2001b). The method detection levels were 0.005 ng, 0.003 ng/g, and 0.075 ng/g for Shi et al. (2005), Feng et al. (2008), and Rothenberg et al. (in press), respectively, and average or range of recoveries were 86% and 95% (both from Shi et al., 2005), 85–120% (Feng et al., 2008), 80–111% (Li et al., 2008a), 110% (Li et al., 2009), and 99% (Rothenberg et al., in press).

In China, the 2008 average daily rice consumption was 270 g/d, which was calculated from the 2008 annual consumption of rice for China (130 778 × 10^3 t, from IRRI, 2009) and the population of China (1 324 655 × 10^3, from World Bank, 2010). The average daily consumption was slightly higher in 2004 (280 g/day), but did not change the number of exceedances in Table 1. In some mining villages in Guizhou province, rice consumption was higher (620 g/d, Qiu et al., 2008). Guizhou province is the poorest province in China, where higher rice ingestion in some rural villages is partially due to a lack of roads connecting villages to larger towns, which limits access to alternative food sources. In Table 1, daily MeHg exposure was quantified using low and high ingestion rates, i.e., 270 g/d and 620 g/d.

Based on maximum MeHg levels in white rice and assuming 620 g rice/day consumption rate, at least one international health-based standard was exceeded in the mining villages in Guizhou province (Feng et al., 2008; Li et al., 2008a, 2009) and in local markets in Guanxi and Anhui provinces (Shi et al., 2005). Using the mean MeHg value in rice and the higher rice ingestion rate, the EPA acceptable daily intake level (0.1 μg kg^{-1} d^{-1}, from USEPA, 2001a) was exceeded in the mining villages (Feng et al., 2008). Utilizing the lower daily rice ingestion rate (270 g rice/day) and the maximum rice MeHg concentrations, exceedances were observed in one mining village in Guizhou province (Feng et al., 2008), but no standards were exceeded using the mean MeHg levels. International health-based standards using both ingestion rates were not exceeded for rice consumed in Zhoushan Island (Cheng et al., 2009b), in samples collected from a Shanghai market (Cheng et al., 2009a), and in rice samples collected from markets in 13 out of 15 provinces including Guizhou province (Shi et al., 2005). These results suggested in some areas of China, daily intake of MeHg through rice ingestion exceeded safe exposure levels, when assuming a higher than average rice ingestion rate (620 g rice/d). However, this is a small data set and more widespread sampling is needed to verify the extent of these results. Future research should include other regions where rice is a staple food (e.g., India, Indonesia, Bangladesh, Vietnam and the Philippines) (IRRI, 2009), especially where Hg contamination is already well documented (e.g., artisanal gold mining in the Philippines) (Appleton et al., 2006).

4. Hair MeHg

Table 2 summarizes hair Hg and MeHg concentrations for studies in China. Highest hair Hg levels were observed in mining villages in Guizhou province, where atmospheric Hg levels are elevated due to ongoing Hg artisanal smelting activities (Li et al., 2008a, 2008b). Higher Hg hair levels may reflect proximity to smelters and exogenous contamination from atmospheric Hg, which may not be completely removed by standard IAEA hair washing procedures (Li et al., 2008). Hair MeHg levels were highest

Table 1
Exceedances of international health-based standards calculated from the maximum methylmercury (MeHg) level in polished white rice and assuming an ingestion rate of 270 g rice/d or 620 g rice/d, and average body weight of 60 kg.

Citation	Region in China	City or village	MeHg in rice: Mean (Range) (μg/kg)	Maximum daily MeHg intake (μg kg^{-1} d^{-1}) 270 g rice/d	Maximum daily MeHg intake (μg kg^{-1} d^{-1}) 620 g rice/d	Exceeds daily intake levels[a]	
						270 g rice/d	620 g rice/d
Cheng et al. (2009a)	Shanghai	Shanghai market, control site	6.0	0.027	0.062	No exceedances	No exceedances
Cheng et al. (2009b)	Zhoushan Island	Fishing village	4	0.03	0.04	No exceedances	No exceedances
Feng et al. (2008)	Guizhou province	3 mining villages near Wanshan	14.5, 5.7, 4.0 (1.9–27.6)	0.18	0.29	EPA	EPA, JECFA, FSC
		Changshun, control site	2.5 (0.80–4.3)	0.029	0.044	No exceedances	No exceedances
Li et al. (2008a)	Guizhou province	6 sites in a mining village near Wuchuan	7.8 (3.1–13.4)	0.089	0.14	No exceedances	EPA
Li et al. (2009)	Guizhou province	2 mining villages near Wanshan	8.96 (2.51–20.9)	0.14	0.22	No exceedances	EPA
		Wanshan market, Control site	6.85 (3.91–8.71)	0.039	0.090	No exceedances	No exceedances
		Guiyang market, Control site	1.31 (0.62–1.99)	0.013	0.021	No exceedances	No exceedances
Rothenberg et al. (in press)	Hubei province	3 sites in Zhanghe Irrigation District, Hubei province	1.6, 0.71, 1.7 (0.60–3.1)	0.021	0.032	No exceedances	No exceedances
Shi et al. (2005)	15 provinces	NA	1.9–10.5[b]	0.013–0.070	0.020–0.11	No exceedances	EPA

[a] Acceptable daily intake levels (μg kg^{-1} d^{-1}): EPA: 0.1 (USEPA, 2001a), JECFA: 0.23 (JECFA, 2003); FSC: 0.29 (FSC, 2005) ATSDR: 0.3 (ATSDR, 1999).
[b] Values represented 1–2 samples from each province. Exceedances occurred in rice samples from Guanxi and Anhui provinces, but not in samples from Jiangsu, Fujian, Liaoning, Hubei, Heilongjiang, Neimenggu, Henan, Sichuan, Ninxia, Shandong, Guizhou, Tianjin, and Hebei provinces.

Table 2
Hair mercury (Hg) and methylmercury (MeHg) concentrations and fish ingestion rate in China, including the mean and/or range (in parentheses) or not available (NA).

Reference	Region in China	City or village	Hair Hg Mean (range) (ppm)	Hair MeHg Mean (range) (ppm)	Fish ingestion Mean (range) (g/wk)
Cheng et al., 2009b	Zhoushan Island	Fishing village, Male	5.7 (1.3–29.9)	3.8 (0.9–9.5)	1700 (350-3500)
		Fishing village, Female	2.3 (0.8–6.4)	1.8 (0.3–4.1)	680 (350–2100)
Gao et al., 2007	Zhoushan Island	Zhoushan city, Female	1.247 (0.927–1.67)[a]	NA	NA
Feng et al., 2008	Guizhou Province	3 mining villages near Wanshan	1.9, 2.3, 7.3 (0.6–58.5)	0.7, 0.7, 1.4 (0.2–5.6)	(4.2–6.0)
		Changshun, control site	0.75 (0.32–1.72)	0.62 (0.26–1.1)	NA
Li et al., 2008a	Guizhou Province	6 sites in a mining village near Wuchuan	2.71–33.9[b] (0.49–93.1)	0.78–2.25 [b] (0.45–4.21)	5.6
Li et al., 2008b	Guizhou Province	Mining areas near Wuchuan	69.3 (9.91–143)	2.32 (0.83–5.89)	NA
		Changshun, control site	0.78 (0.32–1.72)	0.65 (0.26–1.38)	NA
Li et al., 2009	Guizhou Province	2 mining villages near Wanshan	4.6 (1.5–16)	1.7 (0.70–4.4)	NA
Li et al., 2006	Jilin Province	Changchun	0.448 (0.092–10.463)	NA	140
Liu et al., 2008	East coast	Shanghai, Ningbo, Dalian, Xiamen, Zhoushan	0.83 (0.03–8.70)	NA	NA

[a] Interquartile range.
[b] Represents the range of mean values for 6 sites in the mining area.

in the fishing village on Zhoushan Island, where weekly fish ingested was 1700 g/wk (Cheng et al., 2009b). In the mining villages in Guizhou province, hair MeHg levels were lower but weekly fish ingestion rate was only 4.2–6.0 g/wk (Feng et al., 2008). The authors reported 81–99% of MeHg exposure was through rice ingestion, which was estimated by measuring MeHg in white rice, meat, vegetables and drinking water from each mining village, and calculating the relative contribution of each based on food consumption data provided by each family (Feng et al., 2008). Fish ingestion was low in these mining villages, and the main pathway for MeHg exposure was through ingestion of white rice (Feng et al., 2008). In populations where rice is the primary MeHg exposure pathway, it is important to investigate the risk to the developing fetus.

5. Earlier studies on MeHg exposure

Following the tragedies in Japan and Iraq, researchers investigated the effect of low-level maternal MeHg exposure on cognitive development in offspring. Results differed between the three most comprehensive studies, which were conducted in New Zealand (Kjellstrom et al., 1986, 1989), the Faroe Islands (Grandjean et al., 1997, 2001; Debes et al., 2006), and the Republic of Seychelles (Davidson et al., 1998; Myers et al., 2003). In New Zealand, residents regularly consumed shark meat containing Hg concentrations up to 4 ppm Hg (Kjellstrom et al., 1986; data reviewed by Clarkson and Magos, 2006). Using a matched-pairs design, the New Zealand study reported offspring born to mothers, whose maternal hair Hg levels were greater than 6 ppm, had lower scores on psychological and scholastic tests compared to offspring born to mothers, whose hair Hg was less than 6 ppm (Kjellstrom et al., 1989). In the Faroe Islands, where residents periodically consumed whale blubber and meat high in Hg (mean: 1.6 ppm Hg), elevated Hg levels in cord blood were associated with lower scores on neuropsychological tests (Debes et al., 2006; Grandjean et al., 1997). In Seychelles, residents consumed a wide variety of ocean fish daily that were considered low in Hg (<0.3 ppm Hg), and no significant associations were observed between maternal Hg levels and the offspring's scores on neurodevelopmental tests, and in fact, some associations were positive (Davidson et al., 1998; Myers et al., 2003).

Differences between these studies may be due to confounding from micronutrients (e.g., long-chain polyunsaturated fatty acids, LCPUFA), which are present in fish and benefit neural development (Clarkson and Strain, 2003). The LCPUFA, docosahexaenoic acid ([22:6(n-3)], DHA) is the most abundant n-3 LCPUFA in the brain (Innis, 2007); depletion of DHA results in reduced visual function and decreased cognitive abilities (Innis, 2003). The LCPUFA, arachidonic acid ([20:4(n-6)], AA), is found in membranes throughout the body and is a precursor for signaling molecules that control immunity and the central nervous system (Georgieff and Innis, 2005). Other confounding factors included the choice of biomarker (maternal hair versus cord blood, Cernichiari et al., 2007), exposure to other pollutants such as PCBs (Grandjean et al., 2001), and the potential mitigating effect of selenium (Choi et al., 2008a).

Confounding is a common statistical problem, which occurs when a parameter contributes important information but is not measured. A regression equation with two predictors may be written as follows:

$$y = B_0 + B_1 x + B_2 z + \varepsilon \quad (1)$$

where y represents the dependent variable, B_0 represents the intercept, B_1 and B_2 are values for the slope for predictors x and z, respectively, and ε represents the errors, which satisfy assumptions (i.e., normally distributed, mean = 0, constant variance). The slope for x (i.e., B_1) may be calculated as follows:

$$B_1 = \frac{r_{yx} - r_{xz} r_{yz}}{(1 - r_{xz}^2)} \times \frac{\mathrm{SD}(y)}{\mathrm{SD}(x)} \quad (2)$$

where $r(.)$ is the Pearson correlation coefficient and SD(.) is the standard deviation. From equation (2), B_1 depends partially on the other predictor, z. If z is not measured the slope for x may be biased high or low, depending on the product of r_{xz} and r_{yz}. Therefore, leaving out an important predictor may bias results for B_1.

Budtz-Jørgensen et al. (2007) re-analyzed Faroe Islands data from the original birth cohort assembled from 1986 to 1987 and included information on the number of maternal fish meals. Fish intake (z) was positively associated with higher scores on neurobehavioral tests (y) (i.e., $r_{yz} > 0$), while maternal blood Hg levels (x) were negatively associated with most outcomes on neurobehavioral tests (i.e., $r_{yx} < 0$). Since $r_{xz} > 0$ (i.e., more Hg, more micronutrients), the adverse effects from MeHg exposure on neurobehavioral test scores were more negative when controlling for fish exposure (Table 1, from Budtz-Jørgensen et al., 2007).

Using another Seychelles cohort, Davidson et al. (2008) and a companion paper from Strain et al. (2008) measured LCPUFA and other nutritional parameters (e.g., iodine, iron, and choline) and tested the hypothesis that maternal consumption of fish obscures the effect of MeHg on offspring neurodevelopment. Sixteen neurodevelopmental endpoints were measured at 9 and 30 months, including the Bayley's Scale of Infant Development-II, which yielded a Mental Developmental Index [MDI] and a Psychomotor Developmental Index [PDI]. The strength of the relationship between LCPUFA and the PDI at 30 months was stronger when maternal Hg levels were included in the regression models (Davidson et al., 2008). For example, without controlling for DHA, the estimate of the slope for maternal hair Hg levels was −0.44, which decreased to −0.55 when DHA was included in the model (Table 3, from Davidson et al., 2008). Since DHA (i.e., z) promoted brain development, DHA was positively correlated with neurological outcomes (y) (i.e., $r_{yz} > 0$) and positively correlated with maternal Hg levels (x) (i.e., $r_{xz} > 0$), while $r_{yx} < 0$. To interpret the new model: when controlling for DHA, the effect of maternal Hg levels on infant development was more adverse.

Follow-up studies in the Faroe Islands (Budtz-Jørgensen et al., 2007) and Seychelles (Davidson et al., 2008; Strain et al., 2008) indicated micronutrients were important when assessing the effect of maternal MeHg intake through fish ingestion. There is more evidence that maternal intake of fish high in beneficial nutrients but low in MeHg may increase infant cognition, while fish tissue with higher Hg levels may impair child cognition (Daniels et al., 2004; Mahaffey et al., 2008; Mozaffarian and Rimm, 2006; Oken et al., 2005). However, there remains a knowledge gap concerning safe maternal MeHg levels in the absence of beneficial micronutrients.

6. Micronutrients in white rice

Unlike fish, rice is a poor source of micronutrients and vitamins. When rice is harvested, the outer inedible husk is removed exposing brown rice, which is comprised of pericarp (about 2%), seed coat and aleurone layers (about 5%), the germ (3–4%) and endosperm (89–92%) (Cai and Corke, 2006). During the milling process, the germ, pericarp and aleurone are removed, leaving polished white rice (Cai and Corke, 2006). Brown rice contains higher concentrations of some micronutrients, including 35% more zinc (Zn) and iron (Fe) (Villareal et al., 1991), since these nutrients are concentrated in the pericarp, aleurone and germ (Lombi et al., 2009). Rice also contains phytate, an anti-nutrient that binds cations and limits the absorption of some micronutrients (Brinch-Pedersen et al., 2007). In the developing world, where a high percentage of caloric intake is from polished white rice, Fe and Zn deficiencies are endemic (WHO, 2006). Micronutrients in rice, including Fe, Zn and selenium (Se), may affect cognitive outcomes or interact with Hg. Unlike fish tissue, rice is not a source of LCPUFA or iodine (nutrients in fish tissue reviewed by Choi et al., 2008b).

Iron (*Fe*). Most Fe in the body is present in the erythrocytes as hemoglobin, where its main function is to transport oxygen from the lungs to the tissues. Fe deficiency potentially affects developmental brain processes, which are dependent on Fe-containing proteins and Fe-sulfur compounds (Georgieff and Innis, 2005). The maternal daily requirement for Fe increases during the second half of pregnancy due to the expansion of red blood cell mass and transfer of Fe to the developing fetus and placenta (Bothwell, 2000). It is estimated 50% of pregnant women, and infants and children 1–2 years old are anemic, mostly in developing nations, and many more are Fe deficient (WHO, 2006). Maternal Fe deficiency may cause premature delivery (Scholl and Reilly, 2000), resulting in decreased Fe delivery to the fetus (Georgieff and Innis, 2005). Fe deficiency in infants and children affects cognitive function and psychomotor development (Lozoff et al., 2000; Pollitt, 1993).

Zinc (*Zn*). Zn is an essential component in a large number of enzymatic reactions, which may reflect its flexible coordination geometry and lack of redox sensitivity (Hambridge, 2000). Maternal Zn deficiency decreased fetal neurobehavioral development, which was assessed through fetal movement and heart monitoring (Merialdi et al., 1998), while maternal Zn supplements were associated with a 0.4 cm increase in head circumference, a possible indicator of increased neurodevelopment (Goldenberg et al., 1995).

Selenium (*Se*). Rice and fish tissue contain trace levels of Se (for fish tissue nutrients, see Choi et al., 2008b), and Se concentrations are not decreased when rice is milled (Villareal et al., 1991). Se is an essential micronutrient and forms selenoproteins, which function as antioxidants and catalysts for the production of active thyroid hormone (Rayman, 2000). Se may reduce the toxicity of Hg by forming inert metal selenide complexes; also, antioxidant properties associated with selenoproteins help eliminate reactive oxygen species induced by Hg exposure (Chen et al., 2006). However, evidence for reduction in MeHg toxicity in humans is not consistent. In two birth cohorts recruited in the Faroe Islands, Choi et al. (2008a) did not find total Se levels in cord blood were protective in terms of neurotoxic outcomes. It is possible binding between Se and Hg may limit the benefits from Se (Rayman, 2000).

7. Interaction between micronutrients in rice and MeHg

To determine the effect of low-level maternal MeHg exposure on offspring neurodevelopment, it is important to include populations where beneficial micronutrients from fish ingestion will not confound results. However, other confounding is likely to occur and the importance of these interactions should be considered a priori. For example, phytate naturally occurs in rice and binds micronutrients, and is indigestible by monogastric animals (Brinch-Pedersen et al., 2007). Bioavailability of micronutrients in rice may be increased when anti-phytates are consumed simultaneously (e.g., ascorbic acid increases absorption of Fe, from Hallberg et al., 1989). In a population where MeHg exposure is primarily through rice, the following may occur:

$r_{xy} > 0$, when anti-phytates are ingested regularly with each meal that includes rice

$r_{xy} < 0$, when anti-phytates are not consumed regularly with each meal that includes rice

$r_{xy} = 0$, when anti-phytates are sometimes consumed

Although this analysis may be premature, and the relationship between nutrients and toxicants is likely more complex, it is important to consider these potential confounders when investigating MeHg in a population where rice is the primary exposure pathway.

8. Conclusions

Half the world's population depends on rice as a staple food, and despite the challenges, studies concerning maternal-offspring low-level MeHg exposure should also include populations where polished white rice is the primary exposure pathway. Unlike a cohort that consumes fish tissue regularly, populations depending on polished white rice as a staple food may be underexposed to micronutrients, which may confound results. However, the interaction between MeHg and micronutrients in rice is unknown and should be investigated to determine the risk of low-level maternal MeHg exposure to the developing fetus.

Acknowledgements

S. Rothenberg was supported by the U.S. National Science Foundation International Research Development Program (grant #0802014), X. Feng was funded by the Natural Science Foundation of China (grant #40721002), and all authors were supported by the State Key Laboratory of Environmental Geochemistry, Institute of Geochemistry, Chinese Academy of Sciences, in Guiyang, China. The authors wish to thank the anonymous reviewers for their helpful suggestions.

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