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The History, Status, Gaps, and Future Directions of Neurotoxicology in China

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Background: Rapid economic development in China has produced serious ecological, environmental, and health problems. Neurotoxicity has been recognized as a major public health problem. The Chinese government, research institutes, and scientists conducted extensive studies concerning the source, characteristics, and mechanisms of neurotoxicants.

Objectives: This paper presents, for the first time, a comprehensive history and review of major sources of neurotoxicants, national bodies/legislation engaged, and major neurotoxicology research in China.

Methods: Peer-reviewed research and pollution studies by Chinese scientists from 1991 to 2015 were examined. PubMed, Web of Science and Chinese National Knowledge Infrastructure (CNKI) were the major search tools.

Results: The central problem is an increased exposure to neurotoxicants from air and water, food contamination, e-waste recycling, and manufacturing of household products. China formulated an institutional framework and standards system for management of major neurotoxicants. Basic and applied research was initiated, and international cooperation was achieved. The annual number of peer-reviewed neurotoxicology papers from Chinese authors increased almost 30-fold since 2001.

Conclusions: Despite extensive efforts, neurotoxicity remains a significant public health problem. This provides great challenges and opportunities. We identified 10 significant areas that require major educational, environmental, governmental, and research efforts, as well as attention to public awareness. For example, there is a need to increase efforts to utilize new *in vivo* and *in vitro* models, determine the potential neurotoxicity and mechanisms involved in newly emerging pollutants, and examine the effects and mechanisms of mixtures. In the future, we anticipate working with scientists worldwide to accomplish these goals and eliminate, prevent and treat neurotoxicity.

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Introduction

This review is based on proceedings of the International Neurotoxicology Conference held in Xi'an China June 2011. The purpose of the Conference was to review the current status of neurotoxicology, identify research gaps, and make recommendations concerning future directions for neurotoxicology in China. The use of neurotoxicants in China can be traced to 3000 BCE (Table 1). In 1975, a bronze sword from ~ 3000 BCE was found in Gansu Province. From then until the Tang Dynasty (618–907), Chinese bronze, an alloy of copper, tin, and lead, was used in cooking and food containers. Early treatises (200–600 CE) focused on mushroom-induced neurotoxicity and treatments (Table 1). In 1593, lead and tetrodotoxin neurotoxicity, and updated herbal treatments for mushroom-induced neurotoxicity were described (Table 1). In the 1980s, modern neurotoxicology research in China started when neurobehavioral tests were implemented to protect occupational workers. In 1986, the Neurobehavioral Core Test Battery (NCTB), translated into Chinese, was introduced (Chen et al. 1999). In 1988, a computer-based Chinese version of the Neurobehavioral Evaluation System (NES-C1) was established. The NES-C1 was updated in 1992 and 1998 (Chen et al. 1999). In the 1990s, laboratory-based mechanistic studies, epidemiology studies, biomarker studies, and neuroprotective studies of neurotoxicants were initiated.

This paper reviews the major sources of neurotoxicants, the history of national bodies, and regulations and legislation related to neurotoxicity, major neurotoxicology research institutes and organizations, and papers describing research on selected neurotoxicants in China.

Methods

Peer-reviewed research and pollution studies by Chinese scientists from 1991 to 2015 were examined. PubMed, Web of Science and Chinese National Knowledge Infrastructure (CNKI) were the major search tools.

Results

Major Sources of Neurotoxicants in China

China's recent economic expansion is one of the strongest in world history (Kan et al. 2012). However, accelerated urbanization and industrialization has increased the release of numerous toxicants and neurotoxicants, and produced numerous adverse ecological, environmental, and health problems (Kan et al. 2012; Ahearn 2011). Approximately 2.4 million deaths in China per year are attributed to the poor environmental quality (Zhang and Xu 2011).

Air pollution. Air pollution is a major exposure pathway of neurotoxicants. In China, fine particulate matter ($PM_{2.5}$, particles with aerodynamic diameters ≤ 2.5 μm) is the largest contributor to the air pollution (Wang et al. 2014). Particulate matter (PM) has strong potential for absorbing toxic metals, which makes heavy metals, a family of neurotoxicants, the important components of PM (Li H et al. 2013). Compared with coarse PM, $PM_{2.5}$ has a greater surface area per unit mass, allowing it to accumulate heavy metals more effectively (Li H et al. 2013). It is also more poisonous than coarser PM because of its longer residence in air and deeper penetration into lungs (Li H et al. 2013). Globally, 1.6 million premature deaths per year are associated with indoor air pollution; of these, 420,000 are in China (Mestl and Edwards 2011). Although improved, China still has the worst air pollution in the world (Kan et al. 2009). As a result of industrialization,

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A multidisciplinary group that attended the International Neurotoxicology Conference held in Xi'an China 5–10 June 2011 authored this article.

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urbanization, and increased vehicle use, air pollution occurs in major cities (Chen B et al. 2011). Coal constitutes ~ 75% of energy sources in China and outdoor air pollution predominantly consists of coal smoke (Kan et al. 2009). Decreased childhood exposure to polycyclic aromatic hydrocarbons emitted from coal-burning plants in China was associated with improved neurobehavioral development (Perera et al. 2008). Indoor air pollution is another leading environmental health risk, as ~ 70% of Chinese households burn coal or biomass for cooking and heating (Millman et al. 2008). Tobacco made in China contains high levels of heavy metals (O'Connor et al. 2010) and tobacco smoke is a large source of indoor air pollution (Salo et al. 2004). Unregulated chemicals and neurotoxicants used in the manufacturing of toys, floors, and furniture also contribute to indoor air pollution. For example, polybrominated diphenyl ethers (PBDEs), a family of brominated flame retardants (BFRs) with known developmental neurotoxicity effects (Costa et al. 2014), are widely used in numerous household products, with the domestic demand increasing at a rate of approximately 8% per year in China (Ni et al. 2013).

Water pollution. Polluted water is another ubiquitous exposure pathway to neurotoxicants. For instance, China has the greatest industrial use of mercury, a typical heavy metal, and leads to the elevated water pollution in China (Lin et al. 2012). China has ~ 20% of the world's population, but only 8% of its fresh water (Beach 2001). About 700 million Chinese drink water that does not meet the Chinese Standards for Drinking Water Quality (Beach 2001). From 2000 to 2008, 6,677 water pollution accidents occurred in China threatening the safety of water sources (Zhang XJ et al. 2011). For example, the explosion of an aniline production factory in 2005 resulted in the discharge of more than 100 tons of nitrobenzene and related compounds into the Songhua River, the fourth longest river in China, forcing Harbin, a city with four million inhabitants, to be out of water for 4 days (Li et al. 2008). For groundwater, neurotoxic pesticides and fertilizers seep underground and pollute the only available source of drinking water for millions, especially in rural areas where dependence on well water is absolute (Beach 2001). For surface water, heavy metals from mining-related industries, and the extensive use of fertilizers from farmlands are major sources of pollution (Zhang and Shan 2008; Zhang X et al. 2012). Increased shipping and industrial wastes contribute heavy metals to waterways (Ye et al. 2011).

Food contamination. Food safety problems attracted increased public attention in recent years. Improper use of agrochemicals, fertilizers, and pesticides in agriculture all threaten the primary food production (Lam et al. 2013). In China, food safety is threatened by the contamination of heavy metals and pesticides (Lu et al. 2015). In farming areas either adjacent to lead and zinc mines (Li et al. 2006) or using wastewater on soils (Xue et al. 2012), fruits and vegetables contain high levels of heavy metals. In the Pearl River Estuary, high concentrations of cadmium were found in crab, shrimp and shellfish samples and of lead in fish (Ip et al. 2005). In Nanjing, ~ 97% of breast milk samples had lead levels > 5 μg/L, the limit set by the World Health Organization (WHO) (Liu KS et al. 2013; Parr et al. 1991).

Due to the large population and relatively small arable farmland, pesticides are used extensively to increase agricultural yield (Hu et al. 2015). Approximately 10% of rice samples in China contain detectable residues of organophosphate pesticides (OPs) (Chen et al. 2009). In Xiamen, ~ 20% of cabbage, legumes, and leaf mustard had pesticide residues exceeding maximum residue limits (MRLs) allowed by Chinese regulations (Chen C et al. 2011). In Shaanxi Province, mean levels of omethoate, phorate, chlorpyrifos, methidathion, and ethoprophos residues in vegetables exceeded MRLs (Wang S et al. 2013).

E-waste recycling. Uncontrolled e-waste recycling–induced pollution is of global concern (Yang et al. 2012). Contamination exists in a number of locations in China, especially South China (Luo et al. 2011). High levels of polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs), persistent organic pollutants polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs),

Table 1. Chronicle of major neurotoxicology events in China from 3000 BCE to 2014 AD.

Date	Events
3000 BCE	Bronze use began in China (Lee et al. 2008)
200 CE	Zhongjing Zhang described the symptoms and treatment of mushroom-induced neurotoxicity in *Synopsis of Prescriptions of the Golden Chamber* (Zhang 2012)
610 CE	Yuanfang Chao further described mushroom-induced neurotoxicity in *General Treatise on the Cause and Symptoms of Diseases* (Chao 2009)
1593 CE	Shizhen Li described the toxicity of lead, use of herbal medicines against mushroom-induced toxicities, and neurotoxicity of tetrodotoxin from globefish in *Compendium of Materia Medic* (Li 2005)
1965 CE	Chelating therapy for lead intoxications was introduced into China (Wang et al. 1965)
1979 CE	Environmental Protection Law approved for trial implementation (National People's Congress 1979)
1982 CE	First edition of Ambient Air Quality Standard issued (SEPA 1982); Marine Environment Protection Law adopted (National People's Congress 1982)
1984 CE	Law on Prevention and Control of Water Pollution adopted (National People's Congress 1984)
1985 CE	First edition of Standards for Drinking Water Quality released (MOH 1985)
1986 CE	WHO Neurobehavioral Core Test Battery (NCTB) introduced into China (Chen et al. 1999)
1987 CE	First edition of Law on the Prevention and Control of Atmospheric Pollution enacted (National People's Congress 1987)
1988 CE	Computer-based Chinese Version of the Neurobehavioral Evaluation System (NES-C1) was formed (Chen et al. 1999)
1989 CE	Environmental Protection Law amended and formal one adopted (National People's Congress 1989); six cases of chronic manganese intoxication in workers at a ferromanganese factory reported (Huang et al. 1989)
1995 CE	Law on Prevention and Control of Environmental Pollution by Solid Waste adopted (National People's Congress 1995b); second edition of Law on the Prevention and Control of Atmospheric Pollution adopted (National People's Congress 1995a)
1996 CE	Second edition of Ambient Air Quality Standard released (SEPA 1996); second edition of Law on Prevention and Control of Water Pollution adopted (National People's Congress 1996)
1999 CE	Second edition of Marine Environment Protection Law adopted (National People's Congress 1999)
2000 CE	Third edition of Law on the Prevention and Control of Atmospheric Pollution adopted (National People's Congress 2000); use of leaded gasoline banned (He et al. 2009)
2002 CE	Indoor Air Quality Standard of China released (SEPA 2002)
2004 CE	Second edition of Law on Prevention and Control of Environmental Pollution by Solid Waste adopted (National People's Congress 2004)
2006 CE	Second edition of Standards for Drinking Water Quality released (MOH 2006b); the "Trial Implementation Guide to The Classification and Treatment Principles for Child-Related High Blood Lead Levels and Lead Poisoning Cases" was released (MOH 2006a)
2008 CE	China upgraded State Environmental Protection Administration (SEPA) to be Ministry of Environmental Protection (MEP) (Qiu and Li 2008); third edition of Law on Prevention and Control of Water Pollution adopted (National People's Congress 2008)
2010 CE	The Chinese Neurotoxicology Association (CNA) established (Chinese Society of Toxicology 2010)
2011 CE	Xi'an International Neurotoxicology Conference (XINC) held (Fox et al. 2012; Zheng 2012)
2012 CE	Third edition of Ambient Air Quality Standard released (MEP 2012)
2013 CE	Third edition of Law on Prevention and Control of Environmental Pollution by Solid Waste adopted (National People's Congress 2013a); third edition of Marine Environment Protection Law adopted (National People's Congress 2013b)
2014 CE	Second edition of Environmental Protection Law adopted (National People's Congress 2014)

and heavy metals from the e-waste recycling processes were detected in tissue and blood samples from children and neonates (Song and Li 2014). In areas surrounding primitive e-waste processing facilities, the soil and vegetables contain high levels of neurotoxicants (Luo et al. 2011).

Manufacturing of household products. After decades of economic expansion, China is a worldwide producer of daily household products such as toys and stationeries (Weidenhamer 2009). In 2007, most of the toys recalled in the USA for lead contamination were manufactured in China (Weidenhamer 2009). Bisphenol A (BPA), a potential neurotoxicant (Perera et al. 2012), is an important industrial chemical primarily used as an intermediate in the production of polycarbonate plastics and epoxy resins, which are widely used in digital media, electronic equipment, automobiles, construction glazing, sports safety equipment, medical devices, tableware, reusable bottles (e.g., baby bottles) and food containers (Huang et al. 2012). The demand and production capacity of BPA in China have grown rapidly (Huang et al. 2012).

National Agencies and Legislation of Major Toxicants in China

National agencies. In China, the National Health and Family Planning Commission (NHFPC) [former Ministry of Health (MOH)] and the Ministry of Environmental Protection (MEP) are the major governmental bodies responsible for environmentally related neurotoxicology issues. In March 2013, China established the NHFPC by merging MOH with NHFPC. For environmental areas, the responsibilities of NHFPC are to draft health standards and supervise their enforcement; conduct health education; develop programs on prevention and treatment of diseases; and organize comprehensive prevention and treatment of major pollution-related diseases. Upgraded from State Environmental Protection Administration (SEPA) in 2008 (Qiu and Li 2008), the MEP is a cabinet-level ministry charged with protecting China's air, water, and land from pollution and contamination and is required to implement environmental policies and enforce environmental laws and regulations. The Chinese Center for Disease Control and Prevention (CCDC) is an agency of the NHFPC. Its predecessor was the Chinese Academy of Preventive Medicine founded in 1983 and was renamed trans-CCDC in 2002. CCDC focuses national attention on developing and applying disease prevention and control, environmental health, occupational safety and health, health promotion, and prevention and education activities.

Legislation and regulation of major toxicants. The Environmental Protection Law was approved for trial implementation in 1979 (National People's Congress 1979) and was amended in 1989 (National People's Congress 1989) and 2014 (National People's Congress 2014). In 1987, the Law on the Prevention and Control of Atmospheric Pollution was enacted (National People's Congress 1987): amended in 1995 (National People's Congress 1995a) and 2000 (National People's Congress 2000). Several other environmental laws such as the Law on Prevention and Control of Environmental Pollution by Solid Waste [adopted in 1995 (National People's Congress 1995b); amended in 2004 (National People's Congress 2004) and 2013 (National People's Congress 2013a)], the Law on Prevention and Control of Water Pollution [adopted in 1984 (National People's Congress 1984); amended in 1996 (National People's Congress 1996) and 2008 (National People's Congress 2008)], and the Marine Environment Protection Law [adopted in 1982 (National People's Congress 1982); revised in 1999 (National People's Congress 1999) and 2013 (National People's Congress 2013b)] were formulated. Furthermore, the Criminal Law (National People's Congress 1997) provides detailed measures for the penalty of criminals leading to environmental pollution in Article 338 and 339. Whoever causes severe environmental pollution through the discharging of pollutants, or import and disposition of overseas solid pollutants, shall be sentenced to imprisonment up to 10 years with/without fines (National People's Congress 1997).

Mostly drafted by MOH and MEP, China formulated its own environmental standards system. In 1982 (SEPA 1982), the national Ambient Air Quality Standard was issued and amended in 1996 (SEPA 1996) and 2012 (MEP 2012). There are standards for 10 pollutants: sulfur dioxide, total suspended particulates, 2.5 and 10 μm inhalable particulate matter, nitrogen oxides, nitrogen dioxide, carbon monoxide, ozone, fluoride, lead and benzo[*a*]pyrene. In 2002, the Indoor Air Quality Standard was released: 19 indexes were included and carbon monoxide was the only neurotoxicant (SEPA 2002). In 1985, the first edition of Standards for Drinking Water Quality was released with 35 indexes including six heavy metals: arsenic (0.05 mg/L), cadmium (0.01 mg/L), copper (1.0 mg/L), lead (0.05 mg/L), manganese (0.1 mg/L) and mercury (0.001 mg/L) (MOH 1985). In 2006, the second edition increased the number of indexes from 35 to 106 and had two different types of standards: one for common centralized water supply projects, the other for small or non-centralized water supply projects. In the former, the limits decreased for arsenic (0.05 to 0.01 mg/L), cadmium (0.01 to 0.005 mg/L) and lead (0.05 to 0.01 mg/L), and aluminum (0.2 mg/L) was added. In the latter, the limits were 0.05 mg/L for arsenic and 0.3 mg/L for manganese, with no differences for aluminum, cadmium, copper, lead and mercury (MOH 2006b).

Codex Alimentarius Commission, created by the Food and Agriculture Organization (FAO) and WHO, established pesticides residues standards for agricultural products. The National Standards for MRLs of Pesticides in Food were issued in August 2014 by the NHFPC and Ministry of Agriculture (MOA) in China (Song et al. 2014). MRLs restrict the permitted concentration of a residue and type of commodity on which it is allowed. This new standard includes 3,650 MRLs for 387 pesticides in 284 different kinds of agricultural products and foods. MRLs are based on risk assessment using pesticide residue analysis data from market samples or appropriate supervised field trials and food consumption data. These MRLs are in compliance with internationally recognized food standards (Song et al. 2014).

Overview of Neurotoxicology Research by Chinese Authors

Using the Web of Science TM Core Collection with the Citation Indexes as Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI), we searched for peer-reviewed original papers or reviews published in international journals with co-application of the following strategies—topic was neurotoxicity, and authors' addresses were in China (at least one author was from China). From 2001 to 2014, there were 23,235 papers published on the subject of neurotoxicology worldwide and 10.8% of those papers were written by Chinese authors. The annual number of papers from Chinese authors increased from 17 in 2001 to 488 in 2014 (Figure 1A) or 1.4% and 22.7% of the total number of papers for those years, respectively (Figure 1B), indicating that Chinese scientists were actively engaged in international neurotoxicology research.

Highlights of Major Neurotoxicology Research Areas

Due to space limitations, only highlights on major neurotoxicants will be presented. These studies contributed important new information on the sites/mechanisms of and potential neuroprotection from major neurotoxicants. Research on the neurotoxicity of brominated flame retardants, polycyclic aromatic hydrocarbons, solvents, some biotoxins and electromagnetic fields will not be discussed.

Heavy Metals: Lead, Manganese, Mercury, Aluminum and Arsenic

Lead. Globally, China is one of the largest lead producers and consumers of lead (Zhang X et al. 2012). The main sources of lead pollution in China are ore and metal processing, manufacturing, and combustion of coal,

petroleum fuel, and wastes (Cheng and Hu 2010). Childhood lead poisoning is a major public health problem in China (Zhang SM et al. 2009). Although blood lead levels decreased after its use in gasoline was banned (July 2000), mean blood lead levels of Chinese children is still higher than in developed countries (He et al. 2009). Lead pollution from e-waste recycling and tinfoil processing also is a threat to children (Wang X et al. 2012).

Developmental lead exposure produces cognitive, behavioral, auditory, retinal, and visual-motor dysfunction as well as neuropsychiatric alterations (Canfield et al. 2003; Fox and Boyes 2013; Goyer 1993; Nagpal and Brodie 2009; Osman et al. 1999; Rothenberg et al. 2000, 2002; Wasserman et al. 2000). Many Chinese scientists contributed to this research and helped elucidate sites and mechanisms of lead neurotoxicity. For example, they found that lead exposure produced hearing loss (Liu S et al. 2011) and retinal ganglion cell dysfunction (Ruan et al. 1994) in rats. Wang Q et al. (2011a) reported that *in vitro* lead is transported through the blood–brain barrier by a divalent metal transporter 1 IRE-positive isoform, which can be inhibited by iron (Wang Q et al. 2011a). Others showed that blood delta-aminolevulinic acid dehydratase (ALAD) activity (Wang Q et al. 2011b) and its polymorphisms (Gao et al. 2010) were susceptibility biomarkers for lead neurotoxicity.

Synaptic plasticity plays a critical role in learning and memory and its impairment plays a critical role in lead neurotoxicity. Chinese scientists found that postnatal lead exposure produced age-dependent alterations in the induction of long-term depression and potentiation (Ruan et al. 1998; Xu et al. 1998), paired-pulse facilitation (Ruan et al. 1998), and short-term depression (Ruan et al. 2000) in rat hippocampus. Moreover, lead induced thyroid dysfunction (Wu et al. 2011); impaired calcium flux (Yan et al. 2008); altered ion channels (Gu et al. 2005); inhibited neural cell adhesion molecules (NCAMs) and sialyltransferase activity (Hu et al. 2008); and alterated neurotransmitters and metabolites (Sheng et al. 2005; Tang HW et al. 1996; Tang M et al. 2009), which likely contribute to synaptic plasticity impairments.

Chinese scientists found that lead altered activation of Ca2+/calmodulin-dependent enzymes (Zhang GS et al. 2012) and extracellular–regulated protein kinase (ERK) signaling (Zhang Y et al. 2007); altered methylation patterns of amyloid precursor (Li YY et al. 2012) and ALAD genes (Li C et al. 2011); increased tau phosphorylation and beta amyloid (Li et al. 2010); induced oxidative stress (Zhang YM et al. 2009), inflammation (Li N et al. 2009), and endoplasmic reticulum Ca2+ release (Fan et al. 2013); and decreased nitric oxide (NO) (Sun L et al. 2005).

Treatment and prevention of lead poisoning remains a major health problem worldwide (Bazrgar et al. 2015). In 1965, chelation therapy was initiated in China. In 2006, MOH issued two official documents: "Guide to the Preventive Measures Against Child-Related High Blood Lead Levels and Lead Poisoning" and "Trial Implementation Guide to the Classification and Treatment Principles for Child-Related High Blood Lead Levels and Lead Poisoning Cases" in which chelation therapies by meso-2,3-dimercaptosuccinic acid (DMSA) and calcium disodium ethylenediamine tetraacetic acid ($CaNa_2EDTA$) are major treatment measures (MOH 2006a). However, both agents have potential risks: DMSA can lead to gastrointestinal discomfort, skin reaction, mild neutropenia, and elevated liver enzymes while $CaNa_2EDTA$ can lead to renal failure, arrhythmias, tetany, hypocalcaemia, hypotension, bone marrow depression, prolonged bleeding time, convulsions, and respiratory arrest (Flora and Pachauri 2010). Chinese scientists examined alternative novel therapeutic strategies. Various drugs and herbs partially or totally rescued lead-induced neurotoxicity, such as omega-3 fish oil (Cao et al. 2010), methionine choline (Fan G et al. 2010), hippophae rhamnoides L. juice (Xu et al. 2005), selenium (Liu MC et al. 2013), puerarin (Liu CM et al. 2013), ginsenoside Rd (Wang B et al. 2013), tea catechins (Chen et al. 2003), and iron (Wang Q et al. 2007).

Manganese. Due to high industrial use and low self-protection, there are many people affected by chronic manganese toxicities in China (Wang Y et al. 2012). Clinical studies found that long-term manganese exposure to welders was associated with impaired brainstem parasympathetic and sympathetic centers receiving axon projections from cortical and diencephalic areas (He and Niu 2004), and changes in mood, behavior, and peripheral neurotransmitters (Yuan et al. 2006). Susceptibility to manganese-induced neurotoxicity is influenced by a CYP2D6L gene polymorphism (Zheng et al. 2002). Furthermore, laboratory studies have reported that manganese neurotoxicity was related to enhanced oxidative stress (Xiao et al. 2009; Zhang S et al. 2004); reduced mitochondrial enzyme activity (Zhang S et al. 2003); proteasome dysfunction (Cai et al. 2007); and nuclear localization and subsequent binding of NF-E2-related factor 2 (Nrf2) to the antioxidant-responsive element (ARE); and/or upregulation of heme oxygenase-1 protein (Li H et al. 2011). Manganese also adversely affected astrocytes (Deng et al. 2011; Fan X et al. 2010); activated microglia (Zhao et al. 2009); increased tau hyperphosphorylation

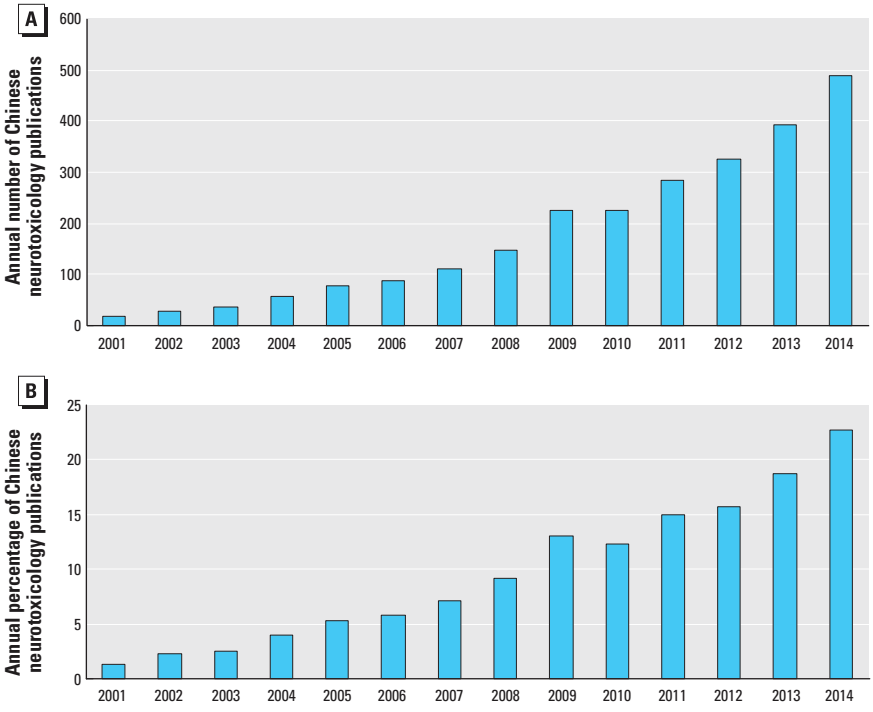

Figure 1. Peer-reviewed neurotoxicology papers published from 2001 through 2014 by Chinese authors. (*A*) Annual number of Chinese neurotoxicology publications. (*B*) Worldwide annual percentage of neurotoxicology papers published by Chinese authors. Data were obtained from Web of Science TM Core Collection with the Citation Indexes as Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI) up to 1 January 2015 with co-application of the following strategies: topic was neurotoxicity, authors' addresses were in China, and document types were peer-reviewed articles and reviews.

and α-synuclein expression (Cai et al. 2010, 2011); increased extracellular glutamate and inhibited expression of its *N*-methyl-D-aspartate (NMDA) receptor subunits in rat striatum (Xu B et al. 2010); increased [Ca2+] (Xu et al. 2009); induced p21 expression (Zhao et al. 2012b); and disrupted the Glu-Gln cycling (Deng et al. 2009). Interestingly, riluzole, taurine, dextromethorphan, para-aminosalicylic acid and increased dietary fiber antagonized manganese-induced neurotoxicity (Deng et al. 2012; Jiang et al. 2006; Shi et al. 2012; Xu Z et al. 2010).

Mercury. Mercury adversely affects neurodevelopment (Llop et al. 2012). China contributes ~ 28% of global mercury emissions (> 600,000 kg per year) (Pacyna et al. 2006), which increased 164% from 1992 to 2007 (Liang et al. 2013). Consumption of methylmercury contaminated rice is the main source of mercury exposure (Zhang J et al. 2010). In Songyuan City (Jilin Province), 17% of the residents' hair contains mercury > 1 mg/kg (reference dosage value set by U.S. EPA) (U.S. EPA 1997) even after the closure (20 years ago) of the acetic acid plant responsible for local mercury pollution (Zhang and Wong 2007). Gestational exposure to low doses of inorganic mercury ($HgCl_2$) selectively increased hippocampal and cerebellar mercury levels (Feng et al. 2004). Mercury-induced neurotoxicity was associated with oxidative stress-dependent c-fos and c-jun expression (Cheng et al. 2005, 2006) (in rats fed by rice cropped in mercury-polluted farmlands) and tau protein aggregation (*in vitro*) (Yang et al. 2010). In fish, mercuric chloride impaired the development of the hypothalamic serotonergic system (Tsai et al. 1995).

Aluminum. High brain levels of aluminum are neurotoxic and cause learning and memory deficits in laboratory animals (Cui et al. 2012; Struys-Ponsar et al. 1997). Chinese aluminum electrolytic workers have altered motor coordination, mood and parasympathetic nervous function (He et al. 2003). Experimental results suggest that aluminum-induced deficits in learning and memory result from altered synaptic configuration (Jing et al. 2004), activation/inactivation of ion currents of hippocampal CA1 neurons (Zhang B et al. 2004), enhanced function of nACh receptors (Hu et al. 2007), altered mitochondrial structure/function (Niu et al. 2005), decreased activities of kinases involved in LTP induction and formation (Wang et al. 2010), disturbed trace metal homeostasis (Yang et al. 1998), oxidative stress (Ding and Yang 2010) and/or apoptosis of cortical neurons and primary astrocytes (Fu et al. 2003; Guo and Liang 2001).

Neuroprotection studies found that vasopressin (Wang et al. 2001), naloxone (Sun SL et al. 2005), ginkgo biloba extract (Gong et al. 2005), meloxicam (Yang et al. 2006), caffeic acid (Yang et al. 2008), zinc (Song et al. 2008), tetrahydroxy stilbene glucoside (Luo et al. 2009), and ginsenoside Rb1 (Zhao et al. 2013) differentially prevented aluminum-induced neurotoxicity. Dipsacus asper (Zhang ZJ et al. 2003), gastrodia elata (He et al. 2008), and icariin (Luo et al. 2007) improved learning and memory in aluminum-intoxicated rats. Biochemical/genetic inactivation of Bcl-2 antagonist/killer (BAK) and caspase-3 delayed the onset of apoptosis in aluminum-treated cells (Zhang QL et al. 2009, 2010) suggesting the therapeutic potential of RNAi-based methods against aluminum-induced neurodegeneration.

Arsenic. Arsenic is released into the atmosphere during coal processing and combustion (Kang et al. 2011). In China, approximately 520, 21 and 250 tons of arsenic are emitted annually by industries, residential buildings and coal-fired power plants, respectively (Kang et al. 2011). In Shanyin County (Shanxi province), arsenic exposure was associated with impaired children's intelligence and growth (Wang SX et al. 2007). Experimental studies showed that arsenic exposure produced hippocampal ultrastructural changes, down-regulation of NMDA receptor and postsynaptic signaling (Luo et al. 2012), and inhibited hippocampal neurogenesis (Liu et al. 2012). Arsenic also modulated DNA methylation and contributed to neural tube defects via epigenetic mechanisms (Han et al. 2011), promoted nitrative DNA lesions (Piao et al. 2011), and down-regulated mitochondrial succinate dehydrogenase subunit A (Hong et al. 2009) and Camk4 (Wang et al. 2009). Neuroglobin (Ngb) had a protective role in the cerebellum against arsenite-induced oxidative stress (Wang J et al. 2012). Arsenic exposure resulted in lower brain nitric oxide synthase (NOS) activity and levels (Wang Y et al. 2011), and inhibited glutamate metabolism in astrocytes (Zhao et al. 2012a), which could impair synaptic formation (Wang Y et al. 2013).

Fluoride

Fluoride exposure has been associated with altered intelligence in children (Tang et al. 2008) and it is prevalent throughout China (Chen et al. 2014). Animal studies have indicated that exposure to high concentrations of fluoride can affect performance in learning and memory tasks (Gui et al. 2010; Jiang S et al. 2014). Exposure to high concentrations of fluoride was associated with inhibited brain glucose utilization (Jiang C et al. 2014). It also down-regulates NCAMs (Zhang M et al. 2007), synaptic membrane fluidity (Zhu et al. 2011), and postsynaptic density protein-95 (Zhu et al. 2011) in hippocampus. On the other hand, fluoride exposure led to upregulated vesicle-associated membrane protein-2 (VAMP-2) (Han et al. 2014) in hippocampus and dysregulated intercellular Ca^{2+} *in vitro* (Xu Z et al. 2013; Zhang J et al. 2011). Other potential mechanisms include increased ERK1/2 (Liu et al. 2010), JNK (Liu YJ et al. 2011), and NF-κB (Zhang J et al. 2011) expression, microglia activation (Yan et al. 2013), abnormal mitochondrial dynamics (Lou et al. 2013), hippocampus glutamate alterations (Niu et al. 2009), and altered acetylcholine receptors and cholinesterase (Liu et al. 2010; Zhao and Wu 1998). Ginkgo biloba extract (Zhang et al. 2013) and selenium (Qian et al. 2013) had neuroprotective effects.

Pesticides

In China, ~ 770 approved pesticides are on the market (Wu and Sun 2004). More than one million tons are used annually, ~ 60% are organophosphates (OPs) and ~ 20% are pyrethroids (Wang et al. 2008). Pesticide intoxication is a serious threat to human health as there are > 150,000 deaths per year from pesticide poisoning (Li Y et al. 2009). Pesticide poisonings account for ~ 20% of poisoning cases at emergency departments of 25 hospitals and have the highest fatality rate (5%) among all poisoning cases (Li Y et al. 2009).

OPs and Carbamates

OP-induced delayed neuropathy (OPIDN). OPIDN is the chronic neurotoxicity induced by OPs, characterized by distal axonopathy and progressive muscle weakness and flaccidity (Abou-Donia and Lapadula 1990; Glynn 2006). The underlying mechanism of OPIDN is complex and not fully understood. Suggested targets include cytoskeletal protein degradation (Chang and Wu 2006; Song et al. 2009), neuropathy target esterase (Chang and Wu 2006; Hou et al. 2009) and calcium homeostasis (Wu and Leng 1997; Wu et al. 2007). Intentional or accidental exposure to a number of OPs including mipafox, omethoate, leptophos, trichlorphon, parathion, methamidophos, fenthion and chlorpyrifos caused OPIDN in humans (Abou-Donia and Lapadula 1990; Jokanović et al. 2011). However, it is not clear whether some of these pesticides directly cause OPIDN (Lotti and Moretto 2005). Although some OPs were banned in China (methamidophos and parathion), others are still widely used such as omethoate (Ding and Tian 2014).

Typical OPs and carbamates. **Methyl parathion.** Although methyl parathion was banned in 2007, its residue persists (Chen et al. 2009). In zebrafish brain, methyl parathion-induced protein changes were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Huang and Huang 2011). Proteomics also identified changes in protein levels after joint exposure to cadmium and methyl parathion in zebrafish brain (Ling et al. 2012).

Chlorpyrifos. In brain of common carp, chlorpyrifos treatment induced nitric oxide (NO) and inducible NO synthase (iNOS) and led to oxidative stress and brain tissue damage (Wang LL et al. 2013). A novel non-cholinergic mechanism, the hyper-phosphorylation of GSK-3β, may contribute to its cellular and behavioral (depression) neurotoxicity (Chen et al. 2012). Mancozeb is an organometallic dithiocarbamate fungicide. Potentiation of voltage-gated KCNQ2 potassium channels was found to be a possible neurotoxic mechanism for mancozeb (Li P et al. 2013).

Pyrethroids. Besides being axonal excitotoxicants that block sodium channels, newer modes of action for pyrethroids have been determined by a number of Chinese research groups. For example, deltamethrin increased the activities of NOS and poly(ADP-ribose) polymerase (Wu and Liu 1999), and induced apoptotic cell death in rat brains (Wu and Liu 2000). Deltamethrin inhibited tyrosine hydroxylase activity and dopamine synthesis in the nigrostriatal pathway in SD rats (Liu et al. 2006). In PC12 cells, NF-E2 related factor 2 activation protected cells from deltamethrin-induced oxidative stress (Li et al. 2007). In zebrafish embryos, Cypermethrin induced oxidative stress and apoptosis via caspase activation (Shi et al. 2011), whereas fenvalerate produced brain morphological abnormalities and apoptosis (Gu et al. 2010).

Other pesticides/herbicides. **Paraquat.** Microglia activation, astrocyte edema, and neuronal cells apoptosis were found to be typical neurotoxic signs of paraquat acute exposure in rat brain (Wu et al. 2013). Cyperquat (1-methyl-4-phenylpyridinium, MPP+), structurally similar to paraquat, was used to study the mechanisms and possible therapies for Parkinson's diseases (Ruan et al. 2011; Xu X et al. 2013; Zhai et al. 2013; Zhou et al. 2013). Simvastatin (Xu X et al. 2013), catechins (Ruan et al. 2011), secalonic acid (Zhai et al. 2013), and 3-O-demethylswertipunicoside (Zhou et al. 2013) were found to be able to protect neuronal cells from MPP+-induced apoptosis in cultured cells.

Rotenone. A broad-spectrum pesticide, rotenone inhibits mitochondrial electron transport, induces oxidative damage and produces apoptosis of dopaminergic neurons in mesencephalic neuron/glia cultures (Wang XJ et al. 2011). The flavone Baicalein exerted *in vivo* and *in vitro* neuroprotective effects on rotenone-induced neurotoxicity (Li XX et al. 2012).

Avermectins. Avermectins are widely used parasiticides in human/veterinary medicine and as pesticides in agriculture/horticulture (Lasota and Dybas 1991). Chinese scientists found that subcytotoxic levels of two avermectin derivatives were neurotoxic in differentiating neuronal cells, which may result from the down-regulation of P-glycoprotein 1 pump and cytoskeletal proteins (Sun et al. 2010).

Conclusions, Gaps and Future Directions

In recent years, Chinese neurotoxicology researchers significantly contributed to laboratory studies of major environmental and industrial neurotoxicants. This produced an increased number of peer-reviewed publications by Chinese scientists, especially those employing cellular/molecular, bioinformatic, electrophysiological, morphological, neurobehavioral, neurochemical, and neuroimaging methodologies. Major problems and research areas still need attention. For example, there are only a few epidemiological studies compared to laboratory experiments. To date, no nationwide investigation on the breadth and extent of pediatric or adult human lead or pesticide neurotoxicity exists. Although laboratory experiments explored protective measures against lead neurotoxicity, no clinical studies have been conducted. For laboratory studies, more attention was focused on high-dose or high-concentration related models, and less on the adverse effects of low-level exposures. Moreover, the current neurotoxicology studies lack the necessary connection between field studies and laboratory research.

Following our comprehensive analysis, we propose that the following additional efforts are needed:

- Although environmental standards and laws were formulated, they need strengthening in accordance with international standards.
- Increase implementation of the laws across all of China. This is especially important in regions where more attention is directed to economic development than environmental protection.
- Increase efforts to utilize new *in vivo* and *in vitro* models. In China, rodents are the major experimental animals employed for neurotoxicity studies. Studies on alternative species such as zebrafish and c. elegans for screening neurological impairments and developmental neurotoxicology should be enhanced. As of January 2015, only 46 and 21 neurotoxicology studies from Chinese authors used zebrafish or C. elegans, respectively.
- Determine the potential neurotoxicity and mechanisms involved in newly emerging pollutants, especially those with potential gestational/neonatal and childhood exposure. In 2008, melamine-contaminated infant formula caused urinary tract stone in 290,000 children in China (Chen 2009). Then animal studies found that melamine could induce cognitive impairment in rats (An et al. 2012).
- Examine the additive and/or synergistic effects and mechanisms of mixtures or combination of neurotoxicants. For example, lead has synergistic neurotoxicity with arsenic (Rai et al. 2010), cadmium (Kim Y et al. 2013), ethanol (Flora et al. 2012), manganese (Kim et al. 2009) and benzo[*a*]pyrene (Qi et al. 2013).
- Determine the cellular interactions between progenitor cells and differentiated neurons and glia. Reciprocal interactions between glia and neurons are essential for many critical functions in brain health and disease (Carnevale et al. 2007). Deciphering the reciprocal interactions provides novel insights in understanding molecular mechanisms in both physiological and pathological conditions (Eyo and Wu 2013; Kim KH et al. 2013).
- Enhance research devoted to solving practical matters, such as determining the subclinical features of neurotoxicities, finding new biomarkers, determining the translational links between laboratory work and improving human health, and evaluating effective neuroprotective measures. To promote applied research in combination with laboratory studies, the National Natural Science Foundation of China and Ministry of Science and Technology should emphasize and increase funding for combined neurotoxicology field and laboratory studies as well as for preventative measures and biomarker systems. In 2012, the first such large new project entitled "The mechanisms of environmental lead exposure-induced brain development impairment in children" was granted to Professor Jingyuan Chen, supported by Major State Basic Research Development Program of China (973 Program) from the Ministry of Science and Technology.
- Enhance international collaborations. Environmental pollution is a global problem that needs to be solved cooperatively. With the world's largest population (~ 1.5 billion) and its heavy environmental pollution, China has various endemic disease-affected areas, such as endemic arseniasis (Li S et al. 2012). A recent Science report suggested that 19.6 million people are at risk of being affected by the consumption of arsenic-contaminated groundwater in China (Rodríguez-Lado et al. 2013).
- Investigate neurotoxicity in the aged population. China has an increasing aged population that will develop neurodegenerative diseases. However, little work has examined the epidemiology, preventive measures, and susceptibility of neurotoxicity in the aged.
- Increase health awareness and education of the public. Although Chinese scientists and institutions have published more papers recently (Figure 1) than 10 years before, little attention and effort were made to disperse this knowledge.

In conclusion, this paper reviews the major sources of neurotoxicants, history of national agencies and regulations/legislation related to neurotoxicity, major neurotoxicology research institutes and organizations, and papers describing research on selected neurotoxicants in China. Furthermore, non-Chinese neurotoxicologists significantly contributed, educated and inspired Chinese investigators and authorities, especially during the early stages of Chinese neurotoxicology research. These collaborative efforts between Chinese and foreign scholars are ongoing. Collectively, Chinese neurotoxicologists face great challenges and opportunities. We believe the prevention of human neurotoxicity is not only a scientific, but also a social obligation and problem. We will continue to work with the scientists worldwide to eliminate, prevent, and treat neurotoxicity.

References

Abou-Donia MB, Lapadula DM. 1990. Mechanisms of organophosphorus ester-induced delayed neurotoxicity: type I and type II. Annu Rev Pharmacol Toxicol 30:405–440.

Ahearn A. 2011. Air pollution in China, with Junfeng (Jim) Zhang [Podcast]. Environ Health Perspect (8 June 2011), doi:10.1289/ehp trp060811.

An L, Li Z, Yang Z, Zhang T. 2012. Melamine induced cognitive impairment associated with oxidative damage in rat's hippocampus. Pharmacol Biochem Behav 102:196–202.

Bazrgar M, Goudarzi I, Lashkarbolouki T, Elahdadi Salmani M. 2015. Melatonin ameliorates oxidative damage induced by maternal lead exposure in rat pups. Physiol Behav 151:178–188.

Beach M. 2001. Water, pollution, and public health in China. Lancet 358:735.

Cai T, Che H, Yao T, Chen Y, Huang C, Zhang W, et al. 2011. Manganese induces tau hyperphosphorylation through the activation of ERK MAPK pathway in PC12 cells. Toxicol Sci 119:169–177.

Cai T, Yao T, Li Y, Chen Y, Du K, Chen J, et al. 2007. Proteasome inhibition is associated with manganese-induced oxidative injury in PC12 cells. Brain Res 1185:359–365.

Cai T, Yao T, Zheng G, Chen Y, Du K, Cao Y, et al. 2010. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1359:201–207.

Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. 2003. Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N Engl J Med 348:1517–1526.

Cao XJ, Cao JJ, Chen TT, Chen WH, Ruan DY. 2010. Protective effects of omega-3 fish oil on lead-induced impairment of long-term potentiation in rat dentate gyrus *in vivo*. Sheng Li Xue Bao 62:225–230.

Carnevale D, De Simone R, Minghetti L. 2007. Microglia-neuron interaction in inflammatory and degenerative diseases: role of cholinergic and noradrenergic systems. CNS Neurol Disord Drug Targets 6:388–397.

Chang PA, Wu YJ. 2006. Effect of tri-*o*-cresyl phosphate on cytoskeleton in human neuroblastoma SK-N-SH cell. Mol Cell Biochem 290:145–151.

Chao YF. 2009. General Treatise on the Cause and Symptoms of Diseases [in Chinese]. Beijing:People's Medical Publishing House.

Chen B, Kan H, Chen R, Jiang S, Hong C. 2011. Air pollution and health studies in China—policy implications. J Air Waste Manag Assoc 61:1292–1299.

Chen C, Li Y, Chen M, Chen Z, Qian Y. 2009. Organophosphorus pesticide residues in milled rice (*Oryza sativa*) on the Chinese market and dietary risk assessment. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 26:340–347.

Chen C, Qian Y, Chen Q, Tao C, Li C, Li Y. 2011. Evaluation of pesticide residues in fruits and vegetables from Xiamen, China. Food Control 22:1114–1120.

Chen J, Liu G, Kang Y, Wu B, Sun R, Zhou C, et al. 2014. Coal utilization in China: environmental impacts and human health. Environ Geochem Health 36:735–753.

Chen JS. 2009. A worldwide food safety concern in 2008—melamine-contaminated infant formula in China caused urinary tract stone in 290,000 children in China. Chin Med J (Engl) 122:243–244.

Chen L, Yang X, Jiao H, Zhao B. 2003. Tea catechins protect against lead-induced ROS formation, mitochondrial dysfunction, and calcium dysregulation in PC12 cells. Chem Res Toxicol 16:1155–1161.

Chen WQ, Ma H, Bian JM, Zhang YZ, Li J. 2012. Hyperphosphorylation of GSK-3β: possible roles in chlorpyrifos-induced behavioral alterations in animal model of depression. Neurosci Lett 528:148–152.

Chen Z, Wang G, Liang S. 1999. A profile of study on neurobehavioral toxicology in China. J Health Toxicology 13:234–238.

Cheng H, Hu Y. 2010. Lead (Pb) isotopic fingerprinting and its applications in lead pollution studies in China: a review. Environ Pollut 158:1134–1146.

Cheng JP, Hu WX, Liu XJ, Zheng M, Shi W, Wang WH. 2006. Expression of c-fos and oxidative stress on brain of rats reared on food from mercury-selenium coexisting mining area. J Environ Sci (China) 18:788–792.

Cheng JP, Wang WH, Qu LY, Jia JP, Zheng M, Ji XL, et al. 2005. Rice from mercury contaminated areas in Guizhou Province induces c-jun expression in rat brain. Biomed Environ Sci 18:96–102.

Chinese Society of Toxicology. 2010. The Inaugural Meeting and First Congress of Chinese Neurotoxicology Association Were Held in Dandong, Liaoling Province [in Chinese]. Available: http://www.chntox.org/news-js.asp?id=221 [accessed 12 January 2015].

Costa LG, de Laat R, Tagliaferri S, Pellacani C. 2014. A mechanistic view of polybrominated diphenyl ether (PBDE) developmental neurotoxicity. Toxicol Lett 230:282–294.

Cui X, Wang B, Zong Z, Liu S, Xing W. 2012. The effects of chronic aluminum exposure on learning and memory of rats by observing the changes of Ras/Raf/ERK signal transduction pathway. Food Chem Toxicol 50:315–319.

Deng Y, Xu D, Xu B, Xu Z, Tian Y, Feng W, et al. 2011. G0/G1 phase arrest and apoptosis induced by manganese chloride on cultured rat astrocytes and protective effects of riluzole. Biol Trace Elem Res 144:832–842.

Deng Y, Xu Z, Xu B, Tian Y, Xin X, Deng X, et al. 2009. The protective effect of riluzole on manganese caused disruption of glutamate–glutamine cycle in rats. Brain Res 1289:106–117.

Deng Y, Xu Z, Xu B, Xu D, Tian Y, Feng W. 2012. The protective effects of riluzole on manganese-induced disruption of glutamate transporters and glutamine synthetase in the cultured astrocytes. Biol Trace Elem Res 148:242–249.

Ding G, Tian Y. 2014. Organophosphate pesticide exposure and child health in China. Environ Sci Pollut Res Int 21:759–761.

Ding R, Yang Y. 2010. Aluminum chloride induced oxidative damage on cells derived from hippocampus and cortex of ICR mice. Brain Res 1324:96–102.

Eyo UB, Wu LJ. 2013. Bidirectional microglia-neuron communication in the healthy brain. Neural Plast 2013:456857, doi:10.1155/2013/456857.

Fan G, Feng C, Wu F, Ye W, Lin F, Wang C, et al. 2010. Methionine choline reverses lead-induced cognitive and N-methyl-D-aspartate receptor subunit 1 deficits. Toxicology 272:23–31.

Fan G, Zhou F, Feng C, Wu F, Ye W, Wang C, et al. 2013. Lead-induced ER calcium release and inhibitory effects of methionine choline in cultured rat hippocampal neurons. Toxicol In Vitro 27:387–395.

Fan X, Luo G, Yang D, Ming M, Liu H, Pu P, et al. 2010. Critical role of lysosome and its associated protein cathepsin D in manganese-induced toxicity in cultured midbrain astrocyte. Neurochem Int 56:291–300.

Feng W, Wang M, Li B, Liu J, Chai Z, Zhao J, et al. 2004. Mercury and trace element distribution in organic tissues and regional brain of fetal rat after in utero and weaning exposure to low dose of inorganic mercury. Toxicol Lett 152:223–234.

Flora SJ, Gautam P, Kushwaha P. 2012. Lead and ethanol co-exposure lead to blood oxidative stress and subsequent neuronal apoptosis in rats. Alcohol Alcohol 47:92–101.

Flora SJ, Pachauri V. 2010. Chelation in metal intoxication. Int J Environ Res Public Health 7:2745–2788.

Fox DA, Boyes WK. 2013. Toxic responses of the ocular and visual system. In: Casarett & Doull's Toxicology: The Basic Science of Poisons (Klaassen CD, ed). 8th ed. New York:McGraw-Hill, 767–798.

Fox DA, Lucchini R, Aschner M, Chen J, Anger WK, Kim EA, et al. 2012. Local effects and global impact in neurotoxicity and neurodegeneration: the Xi'an International Neurotoxicology Conference. Neurotoxicology 33:629–630.

Fu HJ, Hu QS, Lin ZN, Ren TL, Song H, Cai CK, et al. 2003. Aluminum-induced apoptosis in cultured cortical neurons and its effect on SAPK/JNK signal transduction pathway. Brain Res 980:11–23.

Gao A, Lu XT, Li QY, Tian L. 2010. Effect of the delta-aminolevulinic acid dehydratase gene polymorphism on renal and neurobehavioral function in workers exposed to lead in China. Sci Total Environ 408:4052–4055.

Glynn P. 2006. A mechanism for organophosphate-induced delayed neuropathy. Toxicol Lett 162:94–97.

Gong QH, Wu Q, Huang XN, Sun AS, Shi JS. 2005. Protective effects of *Ginkgo biloba* leaf extract on aluminum-induced brain dysfunction in rats. Life Sci 77:140–148.

Goyer RA. 1993. Lead toxicity: current concerns. Environ Health Perspect 100:177–187.

Gu A, Shi X, Yuan C, Ji G, Zhou Y, Long Y, et al. 2010. Exposure to fenvalerate causes brain impairment during zebrafish development. Toxicol Lett 197:188–192.

Gu Y, Wang L, Xiao C, Guo F, Ruan DY. 2005. Effects of lead on voltage-gated sodium channels in rat hippocampal CA1 neurons. Neuroscience 133:679–690.

Gui CZ, Ran LY, Li JP, Guan ZZ. 2010. Changes of learning and memory ability and brain nicotinic receptors of rat offspring with coal burning fluorosis. Neurotoxicol Teratol 32:536–541.

Guo GW, Liang YX. 2001. Aluminum-induced apoptosis in cultured astrocytes and its effect on calcium homeostasis. Brain Res 888:221–226.

Han H, Du W, Zhou B, Zhang W, Xu G, Niu R, et al. 2014. Effects of chronic fluoride exposure on object recognition memory and mRNA expression of SNARE complex in hippocampus of male mice. Biol Trace Elem Res 158:58–64.

Han ZJ, Song G, Cui Y, Xia HF, Ma X. 2011. Oxidative stress is implicated in arsenic-induced neural

tube defects in chick embryos. Int J Dev Neurosci 29:673–680.
He K, Wang S, Zhang J. 2009. Blood lead levels of children and its trend in China. Sci Total Environ 407:3986–3993.
He S, Niu Q, Niu P, He M, Sun X, Shao F, et al. 2008. Protective effects of gastrodia elata on aluminium-chloride-induced learning impairments and alterations of amino acid neurotransmitter release in adult rats. Restor Neurol Neurosci 26:467–473.
He SC, Niu Q. 2004. Subclinical neurophysiological effects of manganese in welding workers. Int J Immunopathol Pharmacol 17(2 suppl):11–16.
He SC, Qiao N, Sheng W. 2003. Neurobehavioral, autonomic nervous function and lymphocyte subsets among aluminum electrolytic workers. Int J Immunopathol Pharmacol 16:139–144.
Hong Y, Piao F, Zhao Y, Li S, Wang Y, Liu P. 2009. Subchronic exposure to arsenic decreased Sdha expression in the brain of mice. Neurotoxicology 30:538–543.
Hou WY, Long DX, Wu YJ. 2009. The homeostasis of phosphatidylcholine and lysophosphatidylcholine in nervous tissues of mice was not disrupted after administration of tri-*o*-cresyl phosphate. Toxicol Sci 109:276–285.
Hu Q, Fu H, Ren T, Wang S, Zhou W, Song H, et al. 2008. Maternal low-level lead exposure reduces the expression of PSA-NCAM and the activity of sialyltransferase in the hippocampi of neonatal rat pups. Neurotoxicology 29:675–681.
Hu R, Huang X, Huang J, Li Y, Zhang C, Yin Y, et al. 2015. Long- and short-term health effects of pesticide exposure: a cohort study from China. PLoS One 10:e0128766, doi:10.1371/journal.pone.0128766.
Hu WP, Li XM, Chen JG, Li ZW. 2007. Potentiation of the nicotinic acetylcholine receptor by aluminum in mammalian neurons. Neuroscience 149:1–6.
Huang CC, Chu NS, Lu CS, Wang JD, Tsai JL, Tzeng JL, et al. 1989. Chronic manganese intoxication. Arch Neurol 46:1104–1106.
Huang QY, Huang HQ. 2011. Differential expression profile of membrane proteins in zebrafish (*Danio rerio*) brain exposed to methyl parathion. Proteomics 11:3743–3756.
Huang YQ, Wong CK, Zheng JS, Bouwman H, Barra R, Wahlström B, et al. 2012. Bisphenol A (BPA) in China: a review of sources, environmental levels, and potential human health impacts. Environ Int 42:91–99.
Ip CC, Li XD, Zhang G, Wong CS, Zhang WL. 2005. Heavy metal and Pb isotopic compositions of aquatic organisms in the Pearl River Estuary, South China. Environ Pollut 138:494–504.
Jiang C, Zhang S, Liu H, Guan Z, Zeng Q, Zhang C, et al. 2014. Low glucose utilization and neurodegenerative changes caused by sodium fluoride exposure in rat's developmental brain. Neuromolecular Med 16:94–105.
Jiang S, Su J, Yao S, Zhang Y, Cao F, Wang F, et al. 2014. Fluoride and arsenic exposure impairs learning and memory and decreases mGluR5 expression in the hippocampus and cortex in rats. PLoS One 9:e96041, doi:10.1371/journal.pone.0096041.
Jiang YM, Mo XA, Du FQ, Fu X, Zhu XY, Gao HY, et al. 2006. Effective treatment of manganese-induced occupational Parkinsonism with *p*-aminosalicylic acid: a case of 17-year follow-up study. J Occup Environ Med 48:644–649.
Jing Y, Wang Z, Song Y. 2004. Quantitative study of aluminum-induced changes in synaptic ultrastructure in rats. Synapse 52:292–298.
Jokanović M1, Kosanović M, Brkić D, Vukomanović P. 2011. Organophosphate induced delayed polyneuropathy in man: an overview. Clin Neurol Neurosurg 113:7–10.
Kan H, Chen B, Hong C. 2009. Health impact of outdoor air pollution in China: current knowledge and future research needs [Editorial]. Environ Health Perspect 117:A187, doi:10.1289/ehp.12737.
Kan H, Chen R, Tong S. 2012. Ambient air pollution, climate change, and population health in China. Environ Int 42:10–19.
Kang Y, Liu G, Chou CL, Wong MH, Zheng L, Ding R. 2011. Arsenic in Chinese coals: distribution, modes of occurrence, and environmental effects. Sci Total Environ 412–413:1–13.
Kim KH, Son SM, Mook-Jung I. 2013. Contributions of microglia to structural synaptic plasticity. J Exp Neurosci 7:85–91.
Kim Y, Ha EH, Park H, Ha M, Kim Y, Hong YC, et al. 2013. Prenatal lead and cadmium co-exposure and infant neurodevelopment at 6 months of age: the Mothers and Children's Environmental Health (MOCEH) study. Neurotoxicology 35:15–22.
Kim Y, Kim BN, Hong YC, Shin MS, Yoo HJ, Kim JW, et al. 2009. Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. Neurotoxicology 30:564–571.
Lam HM, Remais J, Fung MC, Xu L, Sun SS. 2013. Food supply and food safety issues in China. Lancet 381:2044–2053.
Lasota JA, Dybas RA. 1991. Avermectins, a novel class of compounds: implications for use in arthropod pest control. Annu Rev Entomol 36:91–117.
Lee CS, Qi SH, Zhang G, Luo CL, Zhao LY, Li XD. 2008. Seven thousand years of records on the mining and utilization of metals from lake sediments in central China. Environ Sci Technol 42:4732–4738.
Li C, Xu M, Wang S, Yang X, Zhou S, Zhang J, et al. 2011. Lead exposure suppressed ALAD transcription by increasing methylation level of the promoter CpG islands. Toxicol Lett 203:48–53.
Li H, Qian X, Wang Q. 2013. Heavy metals in atmospheric particulate matter: a comprehensive understanding is needed for monitoring and risk mitigation. Environ Sci Technol 47:13210–13211.
Li H, Wu S, Shi N, Lian S, Lin W. 2011. Nrf2/HO-1 pathway activation by manganese is associated with reactive oxygen species and ubiquitin–proteasome pathway, not MAPKs signaling. J Appl Toxicol 31:690–697.
Li HY, Zhong YF, Wu SY, Shi N. 2007. NF-E2 related factor 2 activation and heme oxygenase-1 induction by *tert*-butylhydroquinone protect against deltamethrin-mediated oxidative stress in PC12 cells. Chem Res Toxicol 20:1242–1251.
Li J, Xie ZM, Xu JM, Sun YF. 2006. Risk assessment for safety of soils and vegetables around a lead/zinc mine. Environ Geochem Health 28:37–44.
Li N, Yu ZL, Wang L, Zheng YT, Jia JX, Wang Q, et al. 2009. Early-life lead exposure affects the activity of TNF-α and expression of SNARE complex in hippocampus of mouse pups. Biol Trace Elem Res 132:227–238.
Li N, Yu ZL, Wang L, Zheng YT, Jia JX, Wang Q, et al. 2010. Increased tau phosphorylation and beta amyloid in the hipocampus of mouse pups by early life lead exposure. Acta Biol Hung 61:123–134.
Li P, Zhu J, Kong Q, Jiang B, Wan X, Yue J, et al. 2013. The ethylene bis-dithiocarbamate fungicide Mancozeb activates voltage-gated KCNQ2 potassium channel. Toxicol Lett 219:211–217.
Li S, Xiao T, Zheng B. 2012. Medical geology of arsenic, selenium and thallium in China. Sci Total Environ 421–422:31–40.
Li SZ. 2005. Compendium of materia medica [in Chinese]. Beijing:People's Medical Publishing House.
Li XX, He GR, Mu X, Xu B, Tian S, Yu X, et al. 2012. Protective effects of baicalein against rotenone-induced neurotoxicity in PC12 cells and isolated rat brain mitochondria. Eur J Pharmacol 674:227–233.
Li Y, Sun C, Qiu Z, Ma S, Yu X, Wang Z, et al. 2009. Clinical toxicology in China: current situation and future development. Clin Toxicol (Phila) 47:263–269.
Li YY, Chen T, Wan Y, Xu SQ. 2012. Lead exposure in pheochromocytoma cells induces persistent changes in amyloid precursor protein gene methylation patterns. Environ Toxicol 27:495–502.
Li Z, Yang M, Li D, Qi R, Liu H, Sun J, et al. 2008. Nitrobenzene biodegradation ability of microbial communities in water and sediments along the Songhua River after a nitrobenzene pollution event. J Environ Sci (China) 20:778–786.
Liang S, Xu M, Liu Z, Suh S, Zhang T. 2013. Socioeconomic drivers of mercury emissions in China from 1992 to 2007. Environ Sci Technol 47:3234–3240.
Lin Y, Vogt R, Larssen T. 2012. Environmental mercury in China: a review. Environ Toxicol Chem 31:2431–2444.
Ling XP, Lu YH, Huang HQ. 2012. Differential protein profile in zebrafish (*Danio rerio*) brain under the joint exposure of methyl parathion and cadmium. Environ Sci Pollut Res Int 19:3925–3941.
Liu CM, Zheng GH, Ming QL, Sun JM, Cheng C. 2013. Protective effect of puerarin on lead-induced mouse cognitive impairment via altering activities of acetyl cholinesterase, monoamine oxidase and nitric oxide synthase. Environ Toxicol Pharmacol 35:502–510.
Liu GP, Ma Q, Shi N. 2006. Tyrosine hydroxylase as a target for deltamethrin in the nigrostriatal dopaminergic pathway. Biomed Environ Sci 19:27–34.
Liu KS, Hao JH, Xu YQ, Gu XQ, Shi J, Dai CF, et al. 2013. Breast milk lead and cadmium levels in suburban areas of Nanjing, China. Chin Med Sci J 28:7–15.
Liu MC, Xu Y, Chen YM, Li J, Zhao F, Zheng G, et al. 2013. The effect of sodium selenite on lead induced cognitive dysfunction. Neurotoxicology 36:82–88.
Liu S, Piao F, Sun X, Bai L, Peng Y, Zhong Y, et al. 2012. Arsenic-induced inhibition of hippocampal neurogenesis and its reversibility. Neurotoxicology 33:1033–1039.
Liu S, Zhang K, Wu S, Ji X, Li N, Liu R, et al. 2011. Lead-induced hearing loss in rats and the protective effect of copper. Biol Trace Elem Res 144:1112–1119.
Liu YJ, Gao Q, Wu CX, Guan ZZ. 2010. Alterations of nAChRs and ERK1/2 in the brains of rats with chronic fluorosis and their connections with the decreased capacity of learning and memory. Toxicol Lett 192:324–329.
Liu YJ, Guan ZZ, Gao Q, Pei JJ. 2011. Increased level of apoptosis in rat brains and SH-SY5Y cells exposed to excessive fluoride—a mechanism connected with activating JNK phosphorylation. Toxicol Lett 204:183–189.
Llop S, Guxens M, Murcia M, Lertxundi A, Ramon R, Riaño I, et al. 2012. Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in Spain: study of potential modifiers. Am J Epidemiol 175:451–465.
Lotti M, Moretto A. 2005. Organophosphate-induced delayed polyneuropathy. Toxicol Rev 24:37–49.
Lou DD, Guan ZZ, Liu YJ, Liu YF, Zhang KL, Pan JG, et al. 2013. The influence of chronic fluorosis on mitochondrial dynamics morphology and distribution in cortical neurons of the rat brain. Arch Toxicol 87:449–457.
Lu Y, Song S, Wang R, Liu Z, Meng J, Sweetman AJ, et al. 2015. Impacts of soil and water pollution on food safety and health risks in China. Environ Int 77:5–15.
Luo C, Liu C, Wang Y, Liu X, Li F, Zhang G, et al. 2011.

Heavy metal contamination in soils and vegetables near an e-waste processing site, South China. J Hazard Mater 186:481–490.
Luo HB, Yang JS, Shi XQ, Fu XF, Yang QD. 2009. Tetrahydroxy stilbene glucoside reduces the cognitive impairment and overexpression of amyloid precursor protein induced by aluminum exposure. Neurosci Bull 25:391–396.
Luo JH, Qiu ZQ, Zhang L, Shu WQ. 2012. Arsenite exposure altered the expression of NMDA receptor and postsynaptic signaling proteins in rat hippocampus. Toxicol Lett 211:39–44.
Luo Y, Nie J, Gong QH, Lu YF, Wu Q, Shi JS. 2007. Protective effects of icariin against learning and memory deficits induced by aluminium in rats. Clin Exp Pharmacol Physiol 34:792–795.
MEP (Ministry of Environmental Protection). 2012. Ambient Air Quality Standards [in Chinese]. Available: http://kjs.mep.gov.cn/hjbhbz/bzwb/dqhjbh/dqhjzlbz/201203/W020120410330232398521.pdf [accessed 1 August 2015].
Mestl HE, Edwards R. 2011. Global burden of disease as a result of indoor air pollution in Shaanxi, Hubei and Zhejiang, China. Sci Total Environ 409:1391–1398.
Millman A, Tang D, Perera FP. 2008. Air pollution threatens the health of children in China. Pediatrics 122:620–628.
MOH (Ministry of Health). 1985. Standards for Drinking Water Quality [in Chinese]. Available: http://www.hmsd.com.cn/law/law3_45.htm [accessed 22 April 2016].
MOH. 2006a. Notice of Ministry of Health: The Issue of Guide to the Preventive Measures against Child-Related High Blood Lead Levels and Lead Poisoning, and Trial Implementation Guide to the Classification and Treatment Principles for Child-Related High Blood Lead Levels and Lead Poisoning Cases [in Chinese]. Available: http://www.moh.gov.cn/fys/s3585/200804/f8742aef6c654935866fa7cbf4e78d94.shtml [accessed 1 August 2015].
MOH. 2006b. Standards for Drinking Water Quality [in Chinese]. Available: http://www.moh.gov.cn/cmsresources/zwgkzt/wsbz/new/20070628143525.pdf [accessed 1 August 2015].
Nagpal AG, Brodie SE. 2009. Supranormal electroretinogram in a 10-year-old girl with lead toxicity. Doc Ophthalmol 118:163–166.
National People's Congress. 1979. Environmental Protection Law of the People's Republic of China (for Trial Implementation). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=12845&CGid= [accessed 1 August 2015].
National People's Congress. 1982. Marine Environment Protection Law of the People's Republic of China. Available: http://www.lawinfochina.com/display.aspx?lib=law&id=20&CGid= [accessed 1 August 2015].
National People's Congress. 1984. Water Pollution Prevention and Control Law of the People's Republic of China. Available: http://www.lawinfochina.com/display.aspx?id=39&lib=law&SearchKeyword=&SearchCKeyword= [accessed 1 August 2015].
National People's Congress. 1987. Law of the People's Republic of China on the Prevention and Control of Atmospheric Pollution. Available: http://www.lawinfochina.com/display.aspx?id=1178&lib=law&SearchKeyword=&SearchCKeyword= [accessed 1 August 2015].
National People's Congress. 1989. Environmental Protection Law of the People's Republic of China. Available: http://www.lawinfochina.com/display.aspx?lib=law&id=1208&CGid= [accessed 1 August 2015].
National People's Congress. 1995a. Law of the People's Republic of China on the Prevention and Control of Atmospheric Pollution (95 Amendment). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=114&CGid= [accessed 1 August 2015].
National People's Congress. 1995b. Law of the People's Republic of China on the Prevention and Control of Environmental Pollution by Solid Waste. Available: http://www.lawinfochina.com/display.aspx?lib=law&id=119&CGid= [accessed 1 August 2015].
National People's Congress. 1996. Water Pollution Prevention and Control Law of the People's Republic of China (1996 Amendment). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=349&CGid= [accessed 1 August 2015].
National People's Congress. 1997. Criminal Law of the People's Republic of China (97 Revision). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=354 [accessed 1 August 2015].
National People's Congress. 1999. Marine Environment Protection Law of the People's Republic of China (1999 revision). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=6216&CGid= [accessed 1 August 2015].
National People's Congress. 2000. Law of the People's Republic of China on the Prevention and Control of Atmospheric Pollution (2000 revision). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=1661&CGid= [accessed 1 August 2015].
National People's Congress. 2004. Law of the People's Republic of China on the Prevention and Control of Environmental Pollution by Solid Wastes (2004 Revision). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=3874&CGid= [accessed 1 August 2015].
National People's Congress. 2008. Water Pollution Prevention and Control Law of the People's Republic of China (2008 Revision). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=6722&CGid= [accessed 1 August 2015].
National People's Congress. 2013a. Law of the People's Republic of China on the Prevention and Control of Environmental Pollution by Solid Wastes (2013 Amendment). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=14873&CGid= [accessed 1 August 2015].
National People's Congress. 2013b. Marine Environment Protection Law of the People's Republic of China (2013 Amendment). Available: http://www.lawinfochina.com/display.aspx?id=16756&lib=law [accessed 1 August 2015].
National People's Congress. 2014. Environmental Protection Law of the People's Republic of China (2014 Revision). Available: http://www.lawinfochina.com/Display.aspx?lib=law&Cgid=223979 [accessed 1 August 2015].
Ni K, Lu Y, Wang T, Kannan K, Gosens J, Xu L, et al. 2013. A review of human exposure to polybrominated diphenyl ethers (PBDEs) in China. Int J Hyg Environ Health 216:607–623.
Niu PY, Niu Q, Zhang QL, Wang LP, He SE, Wu TC, et al. 2005. Aluminum impairs rat neural cell mitochondria in vitro. Int J Immunopathol Pharmacol 18:683–689.
Niu R, Sun Z, Cheng Z, Li Z, Wang J. 2009. Decreased learning ability and low hippocampus glutamate in offspring rats exposed to fluoride and lead. Environ Toxicol Pharmacol 28:254–258.
O'Connor RJ, Li Q, Stephens WE, Hammond D, Elton-Marshall T, Cummings KM, et al. 2010. Cigarettes sold in China: design, emissions and metals. Tob Control 19(suppl 2):i47–i53.
Osman K, Pawlas K, Schütz A, Gazdzik M, Sokal JA, Vahter M. 1999. Lead exposure and hearing effects in children in Katowice, Poland. Environ Res 80:1–8.
Pacyna EG, Pacyna JM, Steenhuisen F, Wilson S. 2006. Global anthropogenic mercury emission inventory for 2000. Atmos Environ 40:4048–4063.
Parr RM, DeMaeyer EM, Iyengar VG, Byrne AR, Kirkbright GF, Schöch G, et al. 1991. Minor and trace elements in human milk from Guatemala, Hungary, Nigeria, Philippines, Sweden, and Zaire. Results from a WHO/IAEA joint project. Biol Trace Elem Res 29:51–75.
Perera F, Li TY, Zhou ZJ, Yuan T, Chen YH, Qu L, et al. 2008. Benefits of reducing prenatal exposure to coal-burning pollutants to children's neurodevelopment in China. Environ Health Perspect 116:1396–1400, doi:10.1289/ehp.11480.
Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, Rauh V, et al. 2012. Prenatal bisphenol A exposure and child behavior in an inner-city cohort. Environ Health Perspect 120:1190–1194, doi:10.1289/ehp.1104492.
Piao F, Li S, Li Q, Ye J, Liu S. 2011. Abnormal expression of 8-nitroguanine in the brain of mice exposed to arsenic subchronically. Ind Health 49:151–157.
Qi Y, Chen C, Tang Y, Jiang X, Qiu C, Peng B, et al. 2013. The synergistic effect of benzo[a]pyrene and lead on learning and memory of mice. Toxicol Ind Health 29:387–395.
Qian W, Miao K, Li T, Zhang Z. 2013. Effect of selenium on fluoride-induced changes in synaptic plasticity in rat hippocampus. Biol Trace Elem Res 155:253–260.
Qiu M, Li H. 2008. China's Environmental Super Ministry Reform: Background, Challenges and the Future. Available: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1273230 [accessed 12 January 2016].
Rai A, Maurya SK, Khare P, Srivastava A, Bandyopadhyay S. 2010. Characterization of developmental neurotoxicity of As, Cd, and Pb mixture: synergistic action of metal mixture in glial and neuronal functions. Toxicol Sci 118:586–601.
Rodríguez-Lado L, Sun G, Berg M, Zhang Q, Xue H, Zheng Q, et al. 2013. Groundwater arsenic contamination throughout China. Science 341:866–868.
Rothenberg SJ, Poblano A, Schnaas L. 2000. Brainstem auditory evoked response at five years and prenatal and postnatal blood lead. Neurotoxicol Teratol 22:503–510.
Rothenberg SJ, Schnaas L, Salgado-Valladares M, Casanueva E, Geller AM, Hudnell HK, et al. 2002. Increased ERG a- and b-wave amplitudes in 7- to 10-year-old children resulting from prenatal lead exposure. Invest Ophthalmol Vis Sci 43:2036–2044.
Ruan DY, Chen JT, Zhao C, Xu YZ, Wang M, Zhao WF. 1998. Impairment of long-term potentiation and paired-pulse facilitation in rat hippocampal dentate gyrus following developmental lead exposure in vivo. Brain Res 806:196–201.
Ruan DY, Tang LX, Zhao C, Guo YJ. 1994. Effects of low-level lead on retinal ganglion sustained and transient cells in developing rats. Neurotoxicol Teratol 16:47–53.
Ruan DY, Yan KF, Ge SY, Xu YZ, Chen JT, Wang M. 2000. Effects of chronic lead exposure on short-term and long-term depression in area CA1 of the rat hippocampus in vivo. Chemosphere 41:165–171.
Ruan HL, Yang Y, Zhu XN, Wang XL, Chen RZ. 2011. Similar potency of catechin and its enantiomers in alleviating 1-methyl-4-phenylpyridinium ion cytotoxicity in SH-SY5Y cells. J Pharm Pharmacol 63:1169–1174.
Salo PM, Xia J, Johnson CA, Li Y, Kissling GE, Avol EL,

et al. 2004. Respiratory symptoms in relation to residential coal burning and environmental tobacco smoke among early adolescents in Wuhan, China: a cross-sectional study. Environ Health 3:14, doi:10.1186/1476-069X-3-14.

SEPA (State Environmental Protection Administration). 1982. Ambient Air Quality Standard [in Chinese]. Available: http://www.tsinfo.js.cn/inquiry/gbtdetails.aspx?A100=GB%203095-1982 [accessed 1 August 2015].

SEPA. 1996. Ambient Air Quality Standard [in Chinese]. Available: http://www.mep.gov.cn/image20010518/5298.pdf [accessed 1 August 2015].

SEPA. 2002. Indoor Air Quality Standard [in Chinese]. Available: http://www.mep.gov.cn/image20010518/5295.pdf [accessed 1 August 2015].

Sheng W, Hang HW, Ruan DY. 2005. In vivo microdialysis study of the relationship between lead-induced impairment of learning and neurotransmitter changes in the hippocampus. Environ Toxicol Pharmacol 20:233–240.

Shi X, Gu A, Ji G, Li Y, Di J, Jin J, et al. 2011. Developmental toxicity of cypermethrin in embryo-larval stages of zebrafish. Chemosphere 85:1010–1016.

Shi XQ, Yan W, Wang KY, Fan QY, Zou Y. 2012. Protective effects of dietary fibre against manganese-induced neurobehavioral aberrations in rats. Arh Hig Rada Toksikol 63:263–270.

Song F, Yan Y, Zhao X, Zhang C, Xie K. 2009. Neurofilaments degradation as an early molecular event in tri-ortho-cresyl phosphate (TOCP) induced delayed neuropathy. Toxicology 258:94–100.

Song Q, Li J. 2014. A systematic review of the human body burden of e-waste exposure in China. Environ Int 68:82–93.

Song WC, Bai XN, Duan LF, Ke CJ, Institute for the Control of Agrochemicals (Ministry of Agriculture). 2014. Present situation and development ideas for construction of China's pesticide residue standards system [in Chinese]. J Food Safety Quality 5:335–338.

Song Y, Xue Y, Liu X, Wang P, Liu L. 2008. Effects of acute exposure to aluminum on blood-brain barrier and the protection of zinc. Neurosci Lett 445:42–46.

Struys-Ponsar C, Kerkhofs A, Gauthier A, Soffié M, van den Bosch de Aguilar P. 1997. Effects of aluminum exposure on behavioral parameters in the rat. Pharmacol Biochem Behav 56:643–648.

Sun L, Zhao ZY, Hu J, Zhou XL. 2005. Potential association of lead exposure during early development of mice with alteration of hippocampus nitric oxide levels and learning memory. Biomed Environ Sci 18:375–378.

Sun SL, Ma GY, Li HB, Zhu YB, Dong HM, Xu XH. 2005. Effect of naloxone on aluminum-induced learning and memory impairment in rats. Neurol India 53:79–82.

Sun YJ, Long DX, Li W, Hou WY, Wu YJ, Shen JZ. 2010. Effects of avermectins on neurite outgrowth in differentiating mouse neuroblastoma N2a cells. Toxicol Lett 192:206–211.

Tang HW, Hu XH, Liang YX. 1996. Alterations of striatal monoamine metabolites in young rats following pre- and postnatal lead exposure. Environ Toxicol Pharmacol 1:147–153.

Tang M, Luo L, Zhu D, Wang M, Luo Y, Wang H, et al. 2009. Muscarinic cholinergic modulation of synaptic transmission and plasticity in rat hippocampus following chronic lead exposure. Naunyn Schmiedebergs Arch Pharmacol 379:37–45.

Tang QQ, Du J, Ma HH, Jiang SJ, Zhou XJ. 2008. Fluoride and children's intelligence: a meta-analysis. Biol Trace Elem Res 126:115–120.

Tsai CL, Jang TH, Wang LH. 1995. Effects of mercury on serotonin concentration in the brain of tilapia, *Oreochromis mossambicus*. Neurosci Lett 184:208–211.

U.S. EPA (U.S. Environmental Protection Agency). 1997. Mercury Study Report to Congress, Volume 1: Executive Summary. EPA-452/R-97-003. Available: http://www.epa.gov/ttn/oarpg/t3/reports/volume1.pdf [accessed 1 August 2015].

Wang B, Feng G, Tang C, Wang L, Cheng H, Zhang Y, et al. 2013. Ginsenoside Rd maintains adult neural stem cell proliferation during lead-impaired neurogenesis. Neurol Sci 34:1181–1188.

Wang B, Xing W, Zhao Y, Deng X. 2010. Effects of chronic aluminum exposure on memory through multiple signal transduction pathways. Environ Toxicol Pharmacol 29:308–313.

Wang J, Zhang W, Sun D, Song L, Li Y, Xu C. 2012. Analysis of neuroglobin mRNA expression in rat brain due to arsenite-induced oxidative stress. Environ Toxicol 27:503–509.

Wang LL, Liu T, Wang C, Zhao FQ, Zhang ZW, Yao HD, et al. 2013. Effects of atrazine and chlorpyrifos on the production of nitric oxide and expression of inducible nitric oxide synthase in the brain of common carp (*Cyprinus carpio* L.). Ecotoxicol Environ Saf 93:7–12.

Wang M, Chen JT, Ruan DY, Xu YZ. 2001. Vasopressin reverses aluminum-induced impairment of synaptic plasticity in the rat dentate gyrus *in vivo*. Brain Res 899:193–200.

Wang Q, Luo W, Zhang W, Dai Z, Chen Y, Chen J. 2007. Iron supplementation protects against lead-induced apoptosis through MAPK pathway in weanling rat cortex. Neurotoxicology 28:850–859.

Wang Q, Luo W, Zhang W, Liu M, Song H, Chen J. 2011a. Involvement of DMT1 +IRE in the transport of lead in an *in vitro* BBB model. Toxicol In Vitro 25:991–998.

Wang Q, Ye LX, Zhao HH, Chen JW, Zhou YK. 2011b. Benchmark dose approach for low-level lead induced haematogenesis inhibition and associations of childhood intelligences with ALAD activity and ALA levels. Sci Total Environ 409:1806–1810.

Wang S, Wang Z, Zhang Y, Wang J, Guo R. 2013. Pesticide residues in market foods in Shaanxi province of China in 2010. Food Chem 138:2016–2025.

Wang SC, Ting KS, Wu CC. 1965. Chelating therapy with Na-DMS in occupational lead and mercury intoxications. Chin Med J 84:437–439.

Wang SX, Wang ZH, Cheng XT, Li J, Sang ZP, Zhang XD, et al. 2007. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province, China. Environ Health Perspect 115:643–647, doi:10.1289/ehp.9270.

Wang SY, Li YH, Chi GB, Xiao SY, Ozanne-Smith J, Stevenson M, et al. 2008. Injury-related fatalities in China: an under-recognised public health problem. Lancet 372:1765–1773.

Wang X, Miller G, Ding G, Lou X, Cai D, Chen Z, et al. 2012. Health risk assessment of lead for children in tinfoil manufacturing and e-waste recycling areas of Zhejiang Province, China. Sci Total Environ 426:106–112.

Wang XJ, Zhang S, Yan ZQ, Zhao YX, Zhou HY, Wang Y, et al. 2011. Impaired CD200–CD200R-mediated microglia silencing enhances midbrain dopaminergic neurodegeneration: roles of aging, superoxide, NADPH oxidase, and p38 MAPK. Free Radic Biol Med 50:1094–1106.

Wang Y, Li S, Piao F, Hong Y, Liu P, Zhao Y. 2009. Arsenic down-regulates the expression of Camk4, an important gene related to cerebellar LTD in mice. Neurotoxicol Teratol 31:318–322.

Wang Y, Xue J, Cheng S, Ding Y, He J, Liu X, et al. 2012. The relationship between manganism and the workplace environment in China. Int J Occup Med Environ Health 25:501–505.

Wang Y, Ying Q, Hu J, Zhang H. 2014. Spatial and temporal variations of six criteria air pollutants in 31 provincial capital cities in China during 2013–2014. Environ Int 73:413–422.

Wang Y, Zhao F, Jin Y, Zhong Y, Yu X, Li G, et al. 2011. Effects of exogenous glutathione on arsenic burden and NO metabolism in brain of mice exposed to arsenite through drinking water. Arch Toxicol 85:177–184.

Wang Y, Zhao F, Liao Y, Jin Y, Sun G. 2013. Effects of arsenite in astrocytes on neuronal signaling transduction. Toxicology 303:43–53.

Wasserman GA, Musabegovic A, Liu X, Kline J, Factor-Litvak P, Graziano JH. 2000. Lead exposure and motor functioning in 4½-year-old children: the Yugoslavia prospective study. J Pediatr 137:555–561.

Weidenhamer JD. 2009. Lead contamination of inexpensive seasonal and holiday products. Sci Total Environ 407:2447–2450.

Wu A, Liu Y. 1999. Effects of deltamethrin on nitric oxide synthase and poly(ADP-ribose) polymerase in rat brain. Brain Res 850:249–252.

Wu A, Liu Y. 2000. Apoptotic cell death in rat brain following deltamethrin treatment. Neurosci Lett 279:85–88.

Wu B, Song B, Yang H, Huang B, Chi B, Guo Y, et al. 2013. Central nervous system damage due to acute paraquat poisoning: an experimental study with rat model. Neurotoxicology 35:62–70.

Wu CY, Liu B, Wang HL, Ruan DY. 2011. Levothyroxine rescues the lead-induced hypothyroidism and impairment of long-term potentiation in hippocampal CA1 region of the developmental rats. Toxicol Appl Pharmacol 256:191–197.

Wu YJ, Leng XF. 1997. Comparison of effects of verapamil and quercetin on delayed polyneuropathy induced by tri-o-cresyl phosphate in hens. Bull Environ Contam Toxicol 58:611–618.

Wu YJ, Li M, Li YX, Li W, Dai JY, Leng XF. 2007. Verapamil abolished the enhancement of protein phosphorylation of brainstem mitochondria and synaptosomes from the hens dosed with tri-*o*-cresyl phosphate. Environ Toxicol Pharmacol 24:67–71.

Wu YQ, Sun CY. 2004. Poison control services in China. Toxicology 198:279–284.

Xiao J, Rui Q, Guo Y, Chang X, Wang D. 2009. Prolonged manganese exposure induces severe deficits in lifespan, development and reproduction possibly by altering oxidative stress response in *Caenorhabditis elegans*. J Environ Sci (China) 21:842–848.

Xu B, Xu ZF, Deng Y. 2009. Effect of manganese exposure on intracellular Ca^{2+} homeostasis and expression of NMDA receptor subunits in primary cultured neurons. Neurotoxicology 30:941–949.

Xu B, Xu ZF, Deng Y. 2010. Manganese exposure alters the expression of *N*-methyl-D-aspartate receptor subunit mRNAs and proteins in rat striatum. J Biochem Mol Toxicol 24:1–9.

Xu X, Gao W, Dou S, Cheng B. 2013. Simvastatin inhibited the apoptosis of PC12 cells induced by 1-methyl-4-phenylpyridinium ion via inhibiting reactive oxygen species production. Cell Mol Neurobiol 33:69–73.

Xu Y, Li G, Han C, Sun L, Zhao R, Cui S. 2005. Protective effects of *Hippophae rhamnoides* L. juice on lead-induced neurotoxicity in mice. Biol Pharm Bull 28:490–494.

Xu YZ, Ruan DY, Wu Y, Jiang YB, Chen SY, Chen J, et al. 1998. Nitric oxide affects LTP in area CA1 and CA3 of hippocampus in low-level lead-exposed rat. Neurotoxicol Teratol 20:69–73.

Xu Z, Jia K, Xu B, He A, Li J, Deng Y, et al. 2010. Effects of MK-801, taurine and dextromethorphan

on neurotoxicity caused by manganese in rats. Toxicol Ind Health 26:55–60.

Xu Z, Xu B, Xia T, He W, Gao P, Guo L, et al. 2013. Relationship between intracellular Ca^{2+} and ROS during fluoride-induced injury in SH-SY5Y cells. Environ Toxicol 28:307–312.

Xue ZJ, Liu SQ, Liu YL, Yan YL. 2012. Health risk assessment of heavy metals for edible parts of vegetables grown in sewage-irrigated soils in suburbs of Baoding City, China. Environ Monit Assess 184:3503–3513.

Yan D, Xiao C, Ma FL, Wang L, Luo YY, Liu J, et al. 2008. Excitatory effects of low-level lead exposure on action potential firing of pyramidal neurons in CA1 region of rat hippocampal slices. J Neurosci Res 86:3665–3673.

Yan L, Liu S, Wang C, Wang F, Song Y, Yan N, et al. 2013. JNK and NADPH oxidase involved in fluoride-induced oxidative stress in BV-2 microglia cells. Mediators Inflamm 2013:895975, doi:10.1155/2013/895975.

Yang DJ, Shi S, Zheng LF, Yao TM, Ji LN. 2010. Mercury(II) promotes the in vitro aggregation of tau fragment corresponding to the second repeat of microtubule-binding domain: coordination and conformational transition. Biopolymers 93:1100–1107.

Yang J, Liu B, He B, Zhou Q. 2006. Protective effects of meloxicam on aluminum overload-induced cerebral damage in mice. Eur J Pharmacol 547:52–58.

Yang JQ, Zhou QX, Liu BZ, He BC. 2008. Protection of mouse brain from aluminum-induced damage by caffeic acid. CNS Neurosci Ther 14:10–16.

Yang MS, Wong HF, Yung KL. 1998. Determination of endogenous trace metal contents in various mouse brain regions after prolonged oral administration of aluminum chloride. J Toxicol Environ Health A 55:445–453.

Yang R, Luo C, Zhang G, Li X, Shen Z. 2012. Extraction of heavy metals from e-waste contaminated soils using EDDs. J Environ Sci (China) 24:1985–1994.

Ye C, Li S, Zhang Y, Zhang Q. 2011. Assessing soil heavy metal pollution in the water-level-fluctuation zone of the Three Gorges Reservoir, China. J Hazard Mater 191:366–372.

Yuan H, He S, He M, Niu Q, Wang L, Wang S. 2006. A comprehensive study on neurobehavior, neurotransmitters and lymphocyte subsets alteration of Chinese manganese welding workers. Life Sci 78:1324–1328.

Zhai A, Zhu X, Wang X, Chen R, Wang H. 2013. Secalonic acid A protects dopaminergic neurons from 1-methyl-4-phenylpyridinium (MPP^+)-induced cell death via the mitochondrial apoptotic pathway. Eur J Pharmacol 713:58–67.

Zhang B, Nie A, Bai W, Meng Z. 2004. Effects of aluminum chloride on sodium current, transient outward potassium current and delayed rectifier potassium current in acutely isolated rat hippocampal CA1 neurons. Food Chem Toxicol 42:1453–1462.

Zhang C, Ren C, Chen H, Geng R, Fan H, Zhao H, et al. 2013. The analog of *Ginkgo biloba* extract 761 is a protective factor of cognitive impairment induced by chronic fluorosis. Biol Trace Elem Res 153:229–236.

Zhang GS, Ye WF, Tao RR, Lu YM, Shen GF, Fukunaga K, et al. 2012. Expression profiling of Ca^{2+}/calmodulin-dependent signaling molecules in the rat dorsal and ventral hippocampus after acute lead exposure. Exp Toxicol Pathol 64:619–624.

Zhang H, Shan B. 2008. Historical records of heavy metal accumulation in sediments and the relationship with agricultural intensification in the Yangtze-Huaihe region, China. Sci Total Environ 399:113–120.

Zhang J, Mauzerall DL, Zhu T, Liang S, Ezzati M, Remais JV. 2010. Environmental health in China: progress towards clean air and safe water. Lancet 375:1110–1119.

Zhang J, Zhu WJ, Xu XH, Zhang ZG. 2011. Effect of fluoride on calcium ion concentration and expression of nuclear transcription factor kappa-B p65 in rat hippocampus. Exp Toxicol Pathol 63:407–411.

Zhang L, Wong MH. 2007. Environmental mercury contamination in China: sources and impacts. Environ Int 33:108–121.

Zhang M, Wang A, He W, He P, Xu B, Xia T, et al. 2007. Effects of fluoride on the expression of NCAM, oxidative stress, and apoptosis in primary cultured hippocampal neurons. Toxicology 236:208–216.

Zhang M, Xu J. 2011. Nonpoint source pollution, environmental quality, and ecosystem health in China: introduction to the special section. J Environ Qual 40:1685–1694.

Zhang QL, Niu Q, Niu PY, Ji XL, Zhang C, Wang L. 2010. Novel interventions targeting on apoptosis and necrosis induced by aluminum chloride in neuroblastoma cells. J Biol Regul Homeost Agents 24:137–148.

Zhang QL, Niu Q, Shi YT, Niu PY, Liu CY, Zhang L, et al. 2009. Therapeutic potential of *BAK* gene silencing in aluminum induced neural cell degeneration. J Inorg Biochem 103:1514–1520.

Zhang S, Fu J, Zhou Z. 2004. *In vitro* effect of manganese chloride exposure on reactive oxygen species generation and respiratory chain complexes activities of mitochondria isolated from rat brain. Toxicol In Vitro 18:71–77.

Zhang S, Zhou Z, Fu J. 2003. Effect of manganese chloride exposure on liver and brain mitochondria function in rats. Environ Res 93:149–157.

Zhang SM, Dai YH, Xie XH, Fan ZY, Tan ZW, Zhang YF. 2009. Surveillance of childhood blood lead levels in 14 cities of China in 2004–2006. Biomed Environ Sci 22:288–296.

Zhang X, Yang L, Li Y, Li H, Wang W, Ye B. 2012. Impacts of lead/zinc mining and smelting on the environment and human health in China. Environ Monit Assess 184:2261–2273.

Zhang XJ, Chen C, Lin PF, Hou AX, Niu ZB, Wang J. 2011. Emergency drinking water treatment during source water pollution accidents in China: origin analysis, framework and technologies. Environ Sci Technol 45:161–167.

Zhang Y, Ye LP, Wang B, Cao SC, Sun LG. 2007. Effect of lead on ERK activity and the protective function of bFGF in rat primary culture astroglia. J Zhejiang Univ Sci B 8:422–427.

Zhang YM, Liu XZ, Lu H, Mei L, Liu ZP. 2009. Lipid peroxidation and ultrastructural modifications in brain after perinatal exposure to lead and/or cadmium in rat pups. Biomed Environ Sci 22:423–429.

Zhang ZJ. 2012. Synopsis of Prescriptions of the Golden Chamber [in Chinese]. Beijing:People's Medical Publishing House.

Zhang ZJ, Qian YH, Hu HT, Yang J, Yang GD. 2003. The herbal medicine *Dipsacus asper* Wall extract reduces the cognitive deficits and overexpression of β-amyloid protein induced by aluminum exposure. Life Sci 73:2443–2454.

Zhao F, Cai T, Liu M, Zheng G, Luo W, Chen J. 2009. Manganese induces dopaminergic neurodegeneration via microglial activation in a rat model of manganism. Toxicol Sci 107:156–164.

Zhao F, Liao Y, Jin Y, Li G, Lv X, Sun G. 2012a. Effects of arsenite on glutamate metabolism in primary cultured astrocytes. Toxicol In Vitro 26:24–31.

Zhao F, Zhang JB, Cai TJ, Liu XQ, Liu MC, Ke T, et al. 2012b. Manganese induces p21 expression in PC12 cells at the transcriptional level. Neuroscience 215:184–195.

Zhao HH, Di J, Liu WS, Liu HL, Lai H, Lü YL. 2013. Involvement of GSK3 and PP2A in ginsenoside Rb1's attenuation of aluminum-induced tau hyperphosphorylation. Behav Brain Res 241:228-234.

Zhao XL, Wu JH. 1998. Actions of sodium fluoride on acetylcholinesterase activities in rats. Biomed Environ Sci 11:1–6.

Zheng W. 2012. Editorial: the Xi'an International Neurotoxicology Conference. Neurotoxicology 33:627–628.

Zheng YX, Chan P, Pan ZF, Shi NN, Wang ZX, Pan J, et al. 2002. Polymorphism of metabolic genes and susceptibility to occupational chronic manganism. Biomarkers 7:337–346.

Zhou J, Sun Y, Zhao X, Deng Z, Pu X. 2013. 3-*O*-demethylswertipunicoside inhibits MPP^+-induced oxidative stress and apoptosis in PC12 cells. Brain Res 1508:53–62.

Zhu W, Zhang J, Zhang Z. 2011. Effects of fluoride on synaptic membrane fluidity and PSD-95 expression level in rat hippocampus. Biol Trace Elem Res 139:197–203.