**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 recommendations concerning future directions for neurotoxicology in China.

**Aim:** To review the current status of neurotoxicology in China and make recommendations concerning future directions for neurotoxicology in China.

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urbanization, and increased vehicle use, air pollution occurs in major cities (Chen 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 (Liu 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 land, 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 polychlorinated biphenyls (PCBs), polychlorinated diphenyl ethers (PBDEs), persistent organic pollutants polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs),...
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 stationery (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 bioptoxins 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,
Treatment and prevention of lead poisoning remains a major health problem worldwide (Bazargar 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 (CaNa₂EDTA) 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 CaNa₂EDTA can lead to renal failure, arrhythmias, tetany, hypocalcaemia, hypertension, 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 (Gao et al. 2010), methionine choline (Fan G et al. 2010), hippocae rhamnoides L. juice (Xu et al. 2005), selenium (Li 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 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. 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 (HgCl₂) 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 containing > 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). Consumption of methylmercury contaminated rice is the main source of mercury exposure (Zhang J et al. 2005), ginkgo biloba extract (Gong et al. 2006), methylmercury contaminated rice is the main source of mercury exposure (Zhang and M et al. 2007), synaptic membrane fluidity (Wang et al. 2004). Biochemical/genetic inactivation of Bel-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, dynamin-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 (Gu 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 (Zheng 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 vesicular-associated membrane protein-2 (VAMP-2) (Han et al. 2014) in hippocampus and dysregulated intercellular Ca²⁺ 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 Y et al. 2011), and NF-KB (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) have 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; Jokanovic 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).
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Fenvalerate produced brain morphological caspase activation (Shi et al. 2011), whereas factor 2 activation protected cells from et al. 2006). In PC12 cells, NF-E2 related in the nigrostriatal pathway in SD rats (Liu 2000). Deltamethrin inhibited tyrosine apoptotic cell death in rat brains (Wu and Wu 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 cell 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), scelalonic 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, biochemical, 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 epideiology, 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 119:1165–1167.

An L, Li Z, Yang Z, Zhang T. 2012. Melamine induced impairment of long-term potentiation in rat brain. Brain Res 152:239–244.

Ahearn A, et al. 2012. Manganese induces tau hyperphosphorylation through the activation of ERK MAPK pathway in PC12 cells. Toxicol Sci 131:189–197.

Antonelli A, et al. 2011. Melatonin ameliorates oxidative damage induced by maternal lead exposure in rat pups. Physiol Behav 108:85–90.

Beach M. 2001. Water, pollution, and public health in China: a review. Environ Sci (China) 18:788–792.

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

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Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

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

Cai T, Yao T, Zhan Y, Chen Q, Tao C, Li C, et al. 2011. Manganese induces the overexpression of α-synuclein in PC12 cells via ERK activation. Brain Res 1539:201–207.

Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Justo TA, Landheer BP. 2003. Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N Engl J Med 348:1517–1526.
tube defects in chick embryos. Int J Dev Neurosci 29:1483–1491.

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 gastrolia elata on aluminum-chloride-induced learning impairments and alterations of amino acid neurotransmitter release in adult rats. Restor Neurol Neurosci 26:467–473.

He SC, Ni 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 Sdhα expression in the brain of mice. Neurotoxicology 30:538–543.

Hou WY, Long X, Wu YJ. 2009. The homeostasis of phosphatidylincholine and lysophosphatidylincholine in nervous tissues of mice was not disrupted after administration of tri-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 MTA/NRAMP3 and the activity of sialyltransferase in the hippocampus of neonatal rat pups. Neurotoxicology 29:673–681.

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, Chen MY, Chen JG, Li ZW. 2007. Potentiation of learning and memory and decreases mGluR5 transcription by increasing methylation level of the promoter CpG islands. Toxicol Lett 177:204–205.

Larosta JA, Dvir DA. 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. Ten 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 X, Zhou S, Zhang J, et al. 2011. Lead exposure suppressed ALAD transcription by increasing methylation level of the promoter CpG islands. Toxicol Lett 203:44–53.

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 47:12310–12311.

Liu H, Wu S, Shi N, Lin S, Lin W. 2011. Nrf2/HO-1 protective effect of copper. Biol Trace Elem Res 144:1112–1119.

Liu KS, Hao JH, Xu YQ, Gu XG, Shi J, Dai CF, et al. 2013. Breast milk lead and manganese levels in suburban adults of Nanjing, China. Chin Med Sci J 28:7–15.

Liu MC, Yu X, Chen YM, Li J, Zhao F, Zheng G, et al. 2013. The effect of selenium on selenite led induced cognitive dysfunction. Neurotoxicology 36:82–88.

Luo C, Liu C, Wang Y, Liu X, Li F, Zhang G, et al. 2011. Nrf2/HO-1 gene silencing by siRNA and its reversibility. Neurotoxicology 32:1033–1039.

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-SYSY cells exposed to excessive fluoride—a mechanism connected with activating JNK phosphorylation. Toxicol Lett 204:183–189.

Llop S, Guexens 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 175:461–465.

Lotti M, Moretto A. 2005. Organophosphate-induced delayed polyneuropathy. Toxicol Rev 24:37–49.

Luo 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.

Li 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 77:75–86.

Luo C, Liu G, 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 201:681–690.

Luo HB, Yang Y, Zhu XN, Wang XL, Chen RZ. 2011. Abnormal expression of NMDA receptor and postsynaptic signaling proteins in rat hippocampus. Toxicol Lett 211:39–44.

Luo Y, Nie J, Gong GH, Lu YF, Wu Q, Shi JS. 2007. Protective effects of icsar in against learning and memory deficits induced by aluminum in rats. Clin Exp Pharmacol Physiol 34:792–795.

MEP (Ministry of Environmental Protection). 2012. Ambient Air Quality Standards [in Chinese]. Available: http://www.mep.gov.cn/hjsb/bzwb/dqhjhzjzl/201203/DQHJH2012030322398521.pdf [accessed 1 August 2015].

Mest HE, Edwards R. 2011. Global burden of disease as a result of air pollution in Shanxi, 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/law64.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 of Lead Poisoning in Children. Available: http://www.moh.gov.cn/fys/s3558/200804/f8742aef654935866afa7cbf476d94.shtml [accessed 1 August 2015].

MOH. 2006b. Standards for Drinking Water Quality [in Chinese]. Available: http://www.moh.gov.cn/cmsresources/czkgzt/wzbz/new/20070626143525.pdf [accessed 1 August 2015].

Nagpal AG, Brodie SE. 2009. Supranormal electrophysiology of the retina in alleviating 1-methyl-4-phenylpyridinium ion toxicity in SH-SY5Y cells. J Pharm Pharmacol 61:387–395.

National People’s Congress. 2015a. Law of the People’s Republic of China on the Prevention and Control of Atmospheric Pollution (2015 Amendment). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=1148&CGid=[accessed 1 August 2015].

National People’s Congress. 2015b. 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=3498&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=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=16618&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 (2013 Amendment). Available: http://www.lawinfochina.com/display.aspx?lib=law&id=3874&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=14793&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?lib=law&id=6722&CGid=[accessed 1 August 2015].

National People’s Congress. 2013c. Law of the People’s Republic of China on the Prevention and Control of Environmental Pollution by Solid Wastes. Available: http://www.lawinfochina.com/display.aspx?lib=law&id=232979[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&id=223979[accessed 1 August 2015].

Ni K, Lu Y, Wang T, Kannon 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 Q, Niu Q, Zhang QL, Wang LP, He SE, Wu TC, et al. 2005. Aluminum impairs rat neural cell mitogenesis in vitro. J Immunopharmacol Pharmacol 28:693–699.

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-Morgan MR, Hughes S, et al. 2010. Cigarettes sold in China: design, emissions and toxins. Tob Control 19(suppl 2):47–53.

Osmar K, Kazura K, Schlafer N, Gazdzik M, Sokal JA, Vaher M. 1999. Lead exposure and hearing effects in children in Katowice, Poland. Environ Res 80:1–8.

Pacyna EG, Pacyna JM, Steenhusen F, Wilson S. 2006. Global anthropogenic mercury emission inventory for 2000. Atmos Environ 40:4048–4063.

Parr RM, DeMaeyer EM, Iyengar VR, Byrne AR, Kirkbright GF, Schön 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. Bioc 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, Herbstein 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 159:253–260.

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=1273320 [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 341:886–888.

Rothenberg SJ, Poblano A, Schnaas L. 2000. Brainstem auditory evoked response at five years and prenatal and postnatal lead blood. Neurotoxicol Teratol 22:503–510.

Rothenberg SJ, Schnaas L, Salgado-Valladares M, Casanueva E, Gerlier 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 808:196–201.

Ruan DY, Tang LX, Zhao C, Guo YJ. 1994. Effects of low-level lead on retinal sympathetic and transient cells in developing rats. Neurotoxicol Teratol 16:47–53.

Ruan DY, Yan FK, 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. Chromosome Inf Sci 43:2036–2044.

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 63:1191–1174.

Salmo PM, Xia J, Johnson CA, Li Y, Kissingel GE, Avol EL,
et al. 2004. Respiratory symptoms in relation to residential coal burning and environmental tobacco smoke among young 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.mep.gov.cn/image20010516/5298.pdf [accessed 1 August 2015].

SEPA. 1996. Ambient Air Quality Standard [in Chinese]. Available: http://www.mep.gov.cn/image20010516/5295.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.

Song LL, Liu T, Wang C, Zhao FQ, Zhang ZW, Yao HD, et al. 2013. Effects of atrazine and chlorpyrifos on the induction of nitric oxide and expression of inducible nitric oxide synthase in the brain of common carp (Cyprinus carpio L.). Ecotoxicol Environ Saf 93:67–12.

Song M, Chen JT, Ruan DY, Yu YZ. 2002. Vasopressin reverses aluminum-induced impairment of synaptic plasticity in the rat dentate gyrus in vivo. Brain Res Bull 56:251–258.

Song Q, Li J. 2014. A systematic review of the human body burden of e-waste exposure in China. Environ Health Perspect 124:41–47.

Song Q, Li J. 2014. A systematic review of the human body burden of e-waste exposure in China. Environ Health Perspect 124:41–47.

Struys-Ponsar C, Kerkhofs A, Gauthier A, Soffié M, van den Bosch de Aguilar P. 1997. Effects of aluminum and the protection of zinc. Neurosci Lett 445:42–46.

Wang LL, Liu T, Wang C, Zhao FQ, Zhang ZW, Yao HD, et al. 2013. Effects of atrazine and chlorpyrifos on the induction of nitric oxide and expression of inducible nitric oxide synthase in the brain of common carp (Cyprinus carpio L.). Ecotoxicol Environ Saf 93:67–12.

Song Q, Li J. 2014. A systematic review of the human body burden of e-waste exposure in China. Environ Health Perspect 124:41–47.
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 Ca²⁺ and ROS during fluoride-induced injury in SH-SYSY 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 Y, 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 85:3665–3673.
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 to the second region 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. Selenocalcic 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 fluoride. Biol Trace Elem Res 153:229–236.
Zheng GS, Ye WP, Tao RR, Lu YM, Shen GF, Fukunaga K, et al. 2012. Expression profiling of Ca²⁺/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 389:113–120.
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 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 NCAAM, oxidative stress, and apoptosis in primary cultured hippocampal neurons. Toxicology 238:208–216.
Zhang M, Xu J. 2011. Nonpoint source pollution, environmental quality, and ecosystem health in China: introduction to the special section. J Environ Qual 40:1685–1688.
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 24:119–123.
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. 2007. Surveillance of childhood blood lead levels in 14 cities of China in 2004–2006. Biomed Environ Sci 20:298–306.
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 184:2291–2273.
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 meloxicam on aluminum overload-induced cerebral damage in mice. Eur J Pharmacol 547:52–58.
Zhang YM, Liu XZ, Li H, Mei L, Liu ZP. 2008. 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 215:198–205.
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-demethylswertumipuricoside inhibits MPP⁺-induced oxidative stress and apoptosis in PC12 cells. Brain Res 1508:421–427.
Zhu W, Zhang J, Zhang Z. 2011. Effects of fluoride on synaptosome membrane fluidity and PSD-95 expression level in rat hippocampus. J Trace Elem Exp Med 25:228–236.