# Postprint: Environmental Exposure and Health Hazard Mechanisms of Typical Pollutants

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**Date:** 2017-02-08T00:00:00+00:00

## Abstract

With the rapid growth of global population and material consumption levels, emissions of various environmental pollutants continue to increase, making environmental pollution one of the most critical factors affecting human health. The World Health Organization (WHO) reports that approximately 24% of global diseases and 23% of all deaths may be attributable to environmental factors. More alarmingly, the long-term effects of environmental pollution can endanger the health of multiple generations, impacting humanity' s long-term development. The multifaceted nature of environmental pollution presents new challenges for environmental health research, requiring interdisciplinary collaboration across environmental, biological, and medical sciences. Although the health hazards caused by pollution have been widely recognized, the molecular mechanisms through which environmental pollution induces related diseases remain an international scientific challenge, and the underlying mechanisms of organismal damage have yet to be elucidated. WHO estimates that preventing environmental risks such as unsafe water and air pollution could save the lives of approximately 4 million children under five years old annually. Concurrently, environmental improvements could prevent 13 million deaths from various diseases worldwide each year. However, due to the overall weak research foundation in this field, health protection through environmental technological interventions remains unachievable at present.

## Full Text

## Preamble

Strategic Priority Research Program (Category B) of the Chinese Academy of Sciences
ChinaXiv Partner Journal: Environmental Exposure and Health Hazard Mechanisms of Typical Pollutants

## 1. Project Background and Significance

With the rapid growth of global population and material consumption, emissions of various environmental pollutants continue to increase, making environmental pollution one of the most significant factors affecting human health. The World Health Organization (WHO) reports that approximately 24% of global diseases and 23% of deaths may be attributable to environmental factors. More critically, the long-term effects of environmental pollution can endanger the health of multiple generations, impacting humanity' s long-term development. The diversity of environmental pollution poses new challenges for environmental health research. Understanding pollution-induced health hazards requires interdisciplinary collaboration across environmental science, biology, and medicine. While consensus exists that pollution causes health damage, the molecular mechanisms by which environmental pollution triggers related diseases remain an international scientific challenge, and the mechanisms of organismal injury have yet to be elucidated. WHO estimates that preventing environmental risks such as unsafe water and air pollution could save the lives of approximately 4 million children under five annually. Simultaneously, environmental improvements could prevent 13 million deaths from various diseases worldwide each year. However, due to weak foundational research in this field, health protection through environmental technological intervention remains unachievable.

China is currently in the mid-to-late stage of industrialization and accelerated urbanization, with environmental issues emerging prominently. The risk of comprehensive population exposure to severe compound pollution is increasing. According to World Bank statistics, economic losses from environmental degradation in China account for approximately 10% of GDP, while the health costs to residents are incalculable. Diseases closely related to environmental pollution have risen significantly in China, with "cancer villages" appearing in multiple regions directly linked to environmental contamination. WHO indicates that 21% of the medical burden of disease for Chinese residents stems from environmental pollution factors. Currently, China' s overall research foundation in this field is weak, making it difficult to support the formulation of relevant prevention policies and regulations, let alone achieve health protection under environmental technological intervention. On the other hand, due to rapid economic development, health issues from different pollution stages that developed countries experienced over a century are emerging concurrently in China within a short period. These unique environmental pollution characteristics determine the distinctiveness of China' s health problems, making it impossible to simply copy foreign research models and findings to parse the causal relationships between pollution and related diseases. China' s environmental health research requires theoretical and methodological innovation. Conducting research on environmental pollution and health hazards has become a major demand for improving people' s livelihoods, building a beautiful China, and achieving sustainable national development.

In 2014, the Chinese Academy of Sciences launched the Strategic Priority Research Program (Category B) titled "Environmental Exposure and Health Hazard Mechanisms of Typical Pollutants." Through interdisciplinary collaborative research, the program aims to reveal population exposure mechanisms to regional environmental pollution and achieve breakthroughs in the molecular mechanisms of pollution-induced health hazards, including exposure and effect biomarkers, toxicity pathway interference, and epigenetics. The program's main research content encompasses four aspects: pollutant exposomics in typical regions and disease-high-incidence populations, environmental processes and bioavailability of pollutants, interaction mechanisms between pollutants and biomolecules, and toxicity and health hazard mechanisms of typical pollutants (Figure 1 [Figure 1: see original paper]).

## 2. Major Research Progress

Over the past two years, the program has produced a series of original achievements in pollutant exposomics of typical regional populations, pollutant-biomolecule interactions, and pollutant toxicity and health hazard mechanisms. During this two-year period, researchers published 345 SCI papers, including 125 with impact factors greater than 5, comprising 2 papers in *Cell*, and one each in *Nat. Nanotech.*, *Cell Stem Cell*, and *Nat. Commun.*, plus 36 papers in *ES&T*.

**(1) Important progress in basic research.** Focusing on representative halogenated organic compounds such as halogenated phenols, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and perfluoroalkyl carboxylic acids, researchers systematically investigated the molecular mechanisms of carcinogenicity and developmental toxicity across multiple levels—molecular, cellular, in vivo, and theoretical calculations. In studies of DNA oxidative damage mechanisms, definitive evidence of quinone carbon radical adducts was obtained for the first time, providing a novel molecular toxicological mechanism for the carcinogenicity of halogenated phenols. This mechanism was also found applicable to many other halogenated organic pollutants that can be metabolically or chemically dehalogenated into halogenated quinones, representing a universal new carcinogenic mechanism that has attracted significant international attention.

**(2) Breakthroughs in key technologies and applications.** For pollutants newly added to and of high concern under the Stockholm Convention—such as short-chain chlorinated paraffins (SCCPs), polychlorinated naphthalenes (PCNs), Dechlorane Plus (DCRP), hexachlorobutadiene (HCBD), toxaphene, tetrabromobisphenol A (TBBPA) and its derivatives, and methylsiloxanes—the program established sensitive and reliable analytical methods and sample pretreatment techniques for multiple environmental media, filling gaps in analytical methods for these pollutants. The program pioneered a method system in China for simultaneous determination of dioxins, PCBs, and PBDEs according to international standards, systematically investigating new principles, technologies, and methods from environmental sample pretreatment, separation, and purification to detection, providing strong support for advances in environmental monitoring technology. Additionally, a method based on surface-enhanced Raman spectroscopy was established for rapid in-situ determination of arsenic concentration and valence state. Using a portable spectrometer, the method achieves testing precision meeting drinking water standards with a detection time of only 5 seconds. This method is applicable not only to groundwater matrices but also to soil, fruit juice, and red wine, greatly improving the efficiency and accuracy of field studies.

**(3) Novel nanomaterials for arsenic removal.** The program designed and synthesized novel nanomaterials with high adsorption capacity, chemical stability, and recyclability for treating and recovering high-arsenic acidic wastewater and arsenic-contaminated groundwater. The active nano-TiO synthesized by the program (Figure 2 [Figure 2: see original paper]) achieves arsenic removal efficiency (>95%) far exceeding that of commercially available domestic and US-produced TiO adsorbents (<50%). The arsenic-adsorbed active nano-TiO can be regenerated through alkaline washing and reused. Furthermore, the regeneration solution can be heated and crystallized to generate sodium arsenite, which can be used as industrial raw material, achieving arsenic recovery. This technology has been applied in typical arsenic-contaminated regions in China. Filter cartridges for small household water purifiers designed by program researchers can reduce arsenic concentrations in local raw water from 600 µg/L to less than 10 µg/L, meeting drinking water standards. Drinking water test results showed that arsenic concentrations in local residents' urine samples decreased significantly, demonstrating that arsenic intake and toxicity were effectively controlled after using the TiO small-scale processors.

## 3. Originality and Innovation

**(1) Discovery of novel toxic pollutants through effect-directed analysis.** The program transitioned from individual compound discovery to effect-directed high-throughput screening, shifting from accidental individual findings to systematic, regular pattern discovery (Figure 3 [Figure 3: see original paper]). For example, the program discovered two previously unreported chlorinated polyfluoroalkyl ether sulfonate (Cl-PFAES) compounds and, for the first time internationally, obtained high-purity standard samples of two typical Cl-PFAES. This research has attracted significant international attention. In July 2015, Chief Scientist Academician Jiang Guibin was invited as an organizing committee member of Fluoros 2015 in the United States, chairing the risk assessment discussion session. Program researchers reached agreements with the US National Institute of Standards and Technology and the Japanese National Institute for Environmental Studies on sharing and cooperation regarding Cl-PFAES standard samples. Wellington Laboratories Inc., a renowned producer of environmental standard samples, will produce commercial natural and isotope-labeled Cl-PFAES standard samples based on technical information provided by the program.

**(2) Discovery of a new mercury methylation mechanism in the environment (Figure 4 [Figure 4: see original paper]).** The program discovered that divalent mercury in natural water bodies, as well as lower-valence monovalent and zero-valent mercury, can be methylated by methyl iodide, a reaction dependent on sunlight irradiation. In deionized water, only lower-valence monovalent and zero-valent mercury can be methylated by methyl iodide. Based on these findings, a two-step photochemical methylation mechanism of inorganic mercury by methyl iodide was proposed: (1) divalent mercury undergoes photoreduction to generate monovalent and zero-valent mercury; (2) methyl iodide photolyzes to generate methyl radicals and methyl cations, which combine with monovalent and zero-valent mercury to form highly toxic methylmercury. With the extensive use of methyl iodide as a new fumigant pesticide, methylmercury concentrations in natural water bodies will increase significantly, thereby affecting organismal health. After publication in *Nat. Commun.*, the *Nature* website highlighted this work with the title "Common fumigant found to methylate mercury."

**(3) Original breakthroughs in epigenetics research.** The program provided the first demonstration of 6mA (N6-methyladenine) modification in the *Drosophila* genome and proved that this modification is precisely regulated by the demethylase DMAD (the *Drosophila* Tet homolog) during early embryonic development. Simultaneously, the program demonstrated that DMAD catalyzes 6mA demethylation in the *Drosophila* genome *in vivo*. *In vitro* experiments also showed that DMAD possesses direct catalytic activity for 6mA demethylation. Furthermore, through MeDIP high-throughput sequencing of genomic DNA from DMAD mutants and wild-type *Drosophila* ovaries, the program discovered that 6mA modification in the *Drosophila* ovarian genome frequently occurs in transposon regions, with modifications in transposon regions significantly increased in DMAD mutants. This suggests that DMAD may regulate transposon expression by reducing 6mA modification in transposon regions. This research reveals a new DNA modification form in eukaryotes, with related results published in *Cell* (Figure 5 [Figure 5: see original paper]).

## 4. Program' s Role in Disciplinary Development and Talent Cultivation

The program' s implementation will form a dominant research cluster in China' s environmental health field, cultivate internationally influential academic teams, propose a roadmap for environmental health research in China, and guide and promote the development of environmental health as a discipline. Addressing important environmental health issues, the program organized multiple high-level workshops, including the 111th Shuangqing Forum of the National Natural Science Foundation of China on "Methodologies in Toxicological and Health Research of Environmental Pollution" and the 515th Xiangshan Science Conference on "Environmental Exposure and Health Effects of Persistent Toxic Pollutants." These meetings strongly promoted investment and development in related domestic research.

Driven by the program' s early efforts, the major NSFC research plan "Toxicological Evaluation and Health Effects of Atmospheric Fine Particles and Related Pollutants," proposed by the State Key Laboratory of Environmental Chemistry and Ecotoxicology, was approved and launched in early 2015. This plan will integrate teams with backgrounds in environmental chemistry, environmental toxicology, life sciences, medicine, and geoscience to conduct in-depth research on toxicological mechanisms of air pollution, exposure assessment methods, and epigenetic health hazards, promoting leapfrog development in environmental pollution and health research in China.

Environmental health represents both a typical interdisciplinary research field and an urgent need for translation from basic laboratory research to actual disease prevention and risk mitigation. To promote program implementation, the host and participating units organized a superior research team covering three major disciplines: environmental science, toxicology, and medicine. The core team currently comprises over 170 research staff, including 1 academician and 10 NSFC Distinguished Young Scholars. During project implementation, the talent team has continuously adjusted and expanded. Between 2014-2015, the program recruited 1 "Thousand Talents Plan" member and 2 "Young Thousand Talents Plan" members. Simultaneously, the program strengthened cultivation of young talent, with 5 team members receiving "Distinguished Young Scholar" awards, 8 receiving "Excellent Young Scholar" awards, and 1 selected for the "Ten Thousand Talents Program" of the Organization Department between 2014-2015.

Francesco Faiola, a foreign researcher recruited by the program, has long been engaged in research on molecular mechanisms of embryonic stem cell pluripotency and somatic cell reprogramming, publishing a series of articles in prestigious international journals such as *Nature* and *PNAS*. As a project leader, Francesco Faiola combined stem cell biology with environmental toxicology, proposing a new research direction in stem cell toxicology and leading the establishment of the world' s first toxicology laboratory dedicated to studying pollutant effects on stem cells.

## 5. Future Prospects

As described above, due to rapid economic development, health problems from different pollution stages that developed countries experienced over a century are emerging concurrently in China within a short period. Because of the unique characteristics of China' s environmental pollution, exposure doses and resulting health hazards differ significantly from those in developed countries, making it impossible to simply copy foreign research models and conclusions. The establishment of the "Environmental Exposure and Health Hazard Mechanisms of Typical Pollutants" Strategic Priority Research Program will lay the foundation for disciplinary development and talent team building in environmental health research in China, providing theoretical and methodological support for solving health problems caused by environmental pollution in China.

Future program efforts will target health hazard problems caused by environmental pollution, integrating teams with backgrounds in environmental science, toxicology, medicine, epidemiology, and life sciences. Following the research approach of "concentrated 攻关 by teams with diverse knowledge structures," the program will collaboratively investigate molecular mechanisms of pollution-induced health hazards, risk forecasting and early warning, intervention and elimination, and development of new technologies and instruments. This will enhance theoretical and technical levels of environmental health research and guide the field' s transformation from passive source tracing to active defense. (Host institution: Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences)

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Health hazards caused by environmental pollution have attracted widespread global attention, but the molecular mechanisms by which pollutants trigger related diseases remain an international scientific challenge. China is currently in a period of rapid economic development, and the environmental pollution and health problems brought by economic growth represent a major social issue that China faces now and in the future. The Strategic Priority Research Program "Environmental Exposure and Health Hazard Mechanisms of Typical Pollutants" established by the Chinese Academy of Sciences will pioneer new research fields in environmental health in China, lay the foundation for disciplinary development and talent team building, and provide theoretical and methodological support for solving health problems caused by environmental pollution in China.

This project features four distinct characteristics: (1) Clear research focus and well-defined approach, effectively "bridging" environmental exposomics with regional health problems through molecular mechanism studies of pollutant toxic effects. (2) Outstanding basic research achievements, with important progress in molecular mechanisms of pollutant-induced DNA damage and epigenetic changes published in high-impact journals such as *Cell*, *Cell Stem Cell*, and *PNAS*. (3) Full-chain design, covering exposomics, molecular interactions, health mechanisms, and extending to risk forecasting, early warning, and hazard intervention. (4) Diverse knowledge structure of the research team, including experts and researchers from environmental science, chemistry, toxicology, life sciences, medicine, and epidemiology, fully reflecting interdisciplinary integration.

Due to the high complexity of environmental health issues, research in this field requires stable teams and long-term support to cultivate internationally competitive academic teams and guide and promote the development of environmental health as a discipline in China.

**X. Chris Le**, Fellow of the Royal Society of Canada, recipient of the E.W.R.

Steacie Memorial Fellowship from the Natural Sciences and Engineering Research Council of Canada, Distinguished University Professor at the University of Alberta, Director of the Analytical and Environmental Toxicology Research Division, and Canada Research Chair in Bioanalytical Technology and Environmental Health. He has published over 200 research papers in high-impact journals such as *Science* and *PNAS*, and serves as Editor-in-Chief or Associate Editor for *Journal of Environmental Sciences*, *Environmental Health Perspectives*, and *Analytical Chemistry*.

Due to the unique characteristics of China' s environmental pollution, exposure doses and resulting health hazards differ significantly from those in developed countries, making it impossible to simply copy foreign research models and conclusions. Innovative research in theory and methodology is needed. The Strategic Priority Research Program "Environmental Exposure and Health Hazard Mechanisms of Typical Pollutants" has assembled high-level experts in environmental chemistry, toxicology, and epidemiology. Focusing on the core scientific issue of environmental exposure and health hazard mechanisms of typical pollutants characteristic of domestic environmental pollution, the program has achieved a series of original research results in identification of novel pollutants, pollutant exposomics, pollutant-biomolecule interactions, and pollutant toxicity and health hazard mechanisms. For example, through effect-directed analysis, novel toxic pollutants were discovered in the environment, transitioning from individual compound identification to effect-directed high-throughput screening, and from accidental individual findings to systematic pattern derivation and validation. The program provided the first demonstration of 6mA modification in the *Drosophila* genome and its precise regulation by demethylase DMAD during early embryonic development, representing an important breakthrough in epigenetics research. Project completion will guide and promote the development of environmental health as a discipline in China and provide strong scientific support for identifying environmental causes of regionally high disease incidence and developing health protection technologies.

**Li Xiangdong**, Chair Professor in the Department of Civil and Environmental Engineering at the Hong Kong Polytechnic University, Associate Dean (Research) of the Faculty of Construction and Environment at PolyU, recipient of the NSFC Distinguished Young Scholar Award (Overseas Category B), CAS Overseas Review Expert, and Associate Editor of the internationally renowned journal *Environmental Science & Technology*. He has published over 160 SCI papers with more than 9,000 citations, with five papers ranking in the top 1% most cited in environmental and geoscience fields. His main research areas include regional pollution of toxic pollutants, urban environmental geochemistry, and phytoremediation of contaminated soils.

*Note: Figure translations are in progress. See original paper for figures.*