



News & Views

Human exposome and biomarker database for soil pollutants at typical sites of industrial contamination

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Rapid economic development and industrialization have left many risk sites around the world with significant or potential soil contamination due to industrial production or the shutdown or relocation of industrial facilities. Soil pollutants pose significant threats to human health, especially at sites used by the chemical, mining, and metalworking industries, among others [1]. Petrochemical processing, coking, and nonferrous metal smelting are all important industries in China. Unfortunately, processes used in these industries generate a wide range of toxic pollutants including heavy metals and volatile organic compounds/semivolatile organic compounds [2,3]. As a result, 34.9% of these sites are contaminated by heavy metals including Pb, Cr, and As, as well as organic pollutants such as polycyclic aromatic hydrocarbons, at levels exceeding the upper limits stipulated in applicable regulations [4]. These contaminants pose a risk to the health and well-being of people living nearby as well as to the nation's food security. At present, there are over 500,000 contaminated sites in China, affecting tens of millions of people [5]. During the last decade there have been several serious public safety incidents due to contaminants at such sites.

Most published studies on soil contamination and their influence on human health have estimated health risks based simply on external exposure to the contaminated soil. Few have considered the effect of bioavailability, although some risk assessments have included estimates of bioaccessibility generated using *in vitro* methods. Internal exposure analyses focus on the effective dose and structure of pollutants in the human body rather than simple external exposure, and thus provide more reliable data for assessing health risks and early warning of human body for possible diseases. When exogenous substances enter the human body, they may be metabolized into small molecules or form macromolecular adducts [6]. Exposure group biomonitoring mainly relies

on non-targeted metabolomic approaches using high-resolution, high-throughput mass spectrometric trace component analyses to detect the greatest possible number of pollutants and their metabolites in human samples to comprehensively characterize internal exposure to various pollutants [7,8]. Most studies reported to date have only analyzed the exposure characteristics of selected heavy metals or groups of organic pollutants that behave similarly in the human body. Unfortunately, such approaches are inefficient in that they cannot provide a comprehensive picture of the human exposure characteristics of multiple pollutants and do not generate datasets that can support further analysis of the complex relationships among exposure biomarkers.

Researchers around the world have made significant progress in assessing exposure risks at contaminated sites, human exposome characterization, and development of exposure biomarkers [9,10]. The term “exposomics” was first put forward and defined in 2005. Exposomics research can clarify human exposure to environmental chemicals at different stages of life, as well as the contribution of exposure processes to the occurrence and development of diseases [11]. The United States and European Union have taken the lead in using exposomic data to study the health effects of environmental hazards in children and during the early stages of human life, as well as the mechanisms underlying these effects [12]. In 2013, Li and his team [13] established the Evidence-Based Metabolome Library (<http://www.mycompoundid.org>) in Canada to facilitate the identification of compounds of interest based on their molecular properties such as their accurate masses and mass spectrometric fragment ion spectral patterns. The International Agency for Research on Cancer subsequently established the first biomarker database (Exposome-Explorer: <http://exposome-explorer.iarc.fr>) for environmental exposure. However, no published works have used exposome analysis to evaluate the pollution at contaminated industrial sites in China, although many studies have investigated the contamination profiles at such sites.

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To ensure human health and safety, there is thus a clear need for reliable methods for source identification of pollutants in contaminated soils, a comprehensive understanding of the transformations such pollutants undergo and their adverse effects on human health, and models describing their association with disease. Simply monitoring and reducing the mass concentration of pollutants is not enough to ensure public health because human health risk does not generally vary linearly with the concentrations of soil pollutants. To reduce or eliminate the health risks posed by soil pollution at industrial sites in China, it will be necessary to move beyond existing risk evaluation models and develop new technologies that are acceptable to the public, operable by the government, recognized by industrial groups, and straightforward to use.

In January 2020, the National Key Research and Development Project “Human Exposome and Biomarker of Soil Pollutants in Typical Industries Contaminated Sites” was supported to address these significant issues. Its main aims are to develop a system for health risk assessment of soil pollutants at typical contaminated industrial sites, to clarify the relationships between contaminants and human health, and to generate the first human exposure database for contaminated industrial sites in China. As shown in Fig. 1, the project is focused on four distinct topics: (1) source identification of soil pollutants presenting human exposure risks at typical contaminated industrial sites; (2) development of new technologies for analyzing human exposomes and biomarker screening; (3) characterizing the human exposomes of soil pollutants at typical industrial sites and constructing the first exposome database in China; (4) developing models of the relationships between biomarkers and health risks based on four typical contaminated industrial sites.

The main objective within the first topic is to develop source identification technologies for assessing the multi-path/pathway exposure risks of soil pollutants originating from various major industries. To this end, stable isotope technology, a good source tracing technique, has been combined with multi-medium migration models to reveal potential exposure routes of various pollutants at contaminated sites. In future, pollutant exposure parameters from previous studies will be also updated using

bioavailability/bioaccessibility measurements based on field-optimized population exposure parameters. This will enable the development of a source identification method for accurately assessing exposure risks of soil pollutants at typical contaminated sites. This new method will be more comprehensive than existing alternatives with significantly improved applicability and accuracy. As such, it will provide a sound platform to support follow-up research and the development of a model associating exposure biomarkers with health risk assessments, ensuring the success of the project as a whole.

The main goal within the second topic is to overcome the challenges of analyzing human samples, which stem from the complexity of human exposure to pollutants at contaminated industrial sites and the unknown processes by which pollutants are metabolized and transformed in the human body. This will be done by developing and validating a method for the simultaneous extraction and qualitative and quantitative analysis of multiple target contaminants in human samples with low individual sample volume. Data acquired using this method will then be analyzed to identify biomarkers of exposure to common pollutants at contaminated industrial sites in China. The resulting biomarkers will be verified by conducting *in vivo* exposure experiments using animal model. This will involve cutting-edge research on exposome biomonitoring to evaluate the characteristics of complex soil pollutants and explore diverse exposure scenarios for individuals living or working in or near to the contaminated industrial sites. Mass spectrometric techniques such as GC/LC-QTOF-MS and GC/LC-MS/MS will be used with targeted-, nontargeted-, and suspect screening to comprehensively analyze all possible exposed pollutants and their possible metabolites in human samples, as well as endogenous low molecular products. State-of-the-art bioinformatics technologies including natural language processing will then be used to enable efficient automated screening and identification of mass spectrometry fragments; pattern recognition will be combined with statistical analysis to characterize exposome and metabolome profiles in the human body following exposure to industrial soil pollutants and to identify biomarkers of such exposure.

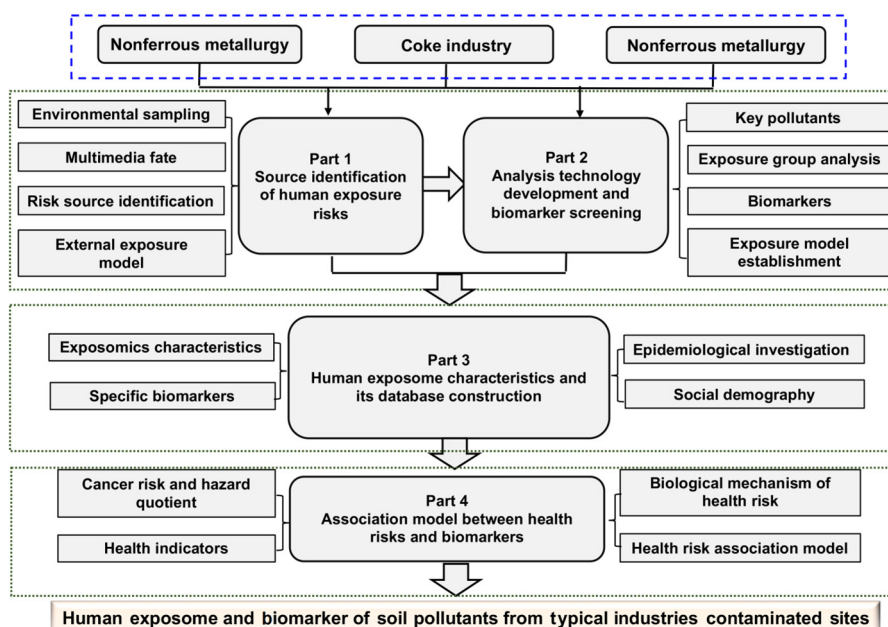


Fig. 1. (Color online) Relationships of four topics of the project.

The third topic aims to clarify the human exposomic characteristics of soil pollutants in typical industrial sites, and to identify specific biomarkers of the pollutants at four sites from three types of key industries with different contamination characteristics. In addition, a population exposomics database of soil pollutants will be established for three types of industrial sites, namely sites associated with the petrochemical, coking, and non-ferrous metals industries. Work within this topic will focus on estimating human exposure to various soil pollutants, understanding the associated exposure pathways and common exposure scenarios at typical sites, and revealing the relationships between them. This will be done by applying techniques from the frontiers in exposomics and methods drawn from metabonomics, bioinformatics, and systems biology together with spatial–temporal statistical models. Furthermore, the population exposome characteristics of soil pollutants at typical industrial sites will be clarified, and specific biomarkers will be screened. Finally, an exposome database covering the three types of contaminated industrial sites mentioned above will be created by integrating epidemiological data, field survey results, specific biomarkers, and key population compound exposure parameters.

The fourth topic tries to reveal the relationships between specific biomarkers of the combined exposure to multiple soil pollutants and human health risks at three types of contaminated industrial sites, and establish regression models to describe such dose–effect relationships. An additional goal is to elucidate the mechanisms responsible for the health effects of multiple pollutant exposure in humans by performing cell culture experiments and studies using animal models under different exposure scenarios, and to explore the adverse health outcomes caused by exposure to multiple soil pollutants. Understanding these relationships and the underlying mechanisms will facilitate the development of improved health risk assessments and new methods for evaluating risks of exposure to various pollutants at typical contaminated sites.

So far, the project has been running as planned and a large amount of basic data has been obtained from four major contaminated industrial sites, including two oil refining sites located in Shandong and Guangdong Province, a coal carbonization site in Shanxi Province, and a non-ferrous metal metallurgy site in Hubei Province. On the basis of field investigations and an analysis of industry characteristics, validated self-administered questionnaires were used to assess the exposure and physical condition of subjects including employees and nearby residents at these four contaminated industrial sites. At the same time, human biomatrix samples including blood, urine, hair, fingernail, and skin wipe samples were collected. At present, over 2000 environmental samples (soil, air, fine particles, drinking water, and food) and over 2300 biomatrix samples representing over 600 subjects have been obtained from the four industrial sites. Additionally, a new online technology was developed to determine levels of hydroxylated polycyclic aromatic hydrocarbons in urine. This new method offers greater detection accuracy than previously available alternatives and will provide important data to support analysis of exposure characteristics and molecular biomarkers. Furthermore, preliminary investigations have highlighted several common soil pollutants posing high health risks including short-chain chlorinated paraffins, tetrabromobisphenol A, and lead.

There is an urgent need for new methods for evaluating human health risks due to multiple soil pollutants and clarifying the pathways of human exposure to various pollutants at typical sites with complex contamination profiles. This project seeks to address these needs and to thereby deliver important social, economic, and ecological benefits. Specifically, the results obtained in the project will facilitate the formulation of improved industrial pollution control policies and the development of better pollution control

technologies, help clarify industrial social responsibilities, and promote transparency in pollution control and public health. The human exposome analysis technology developed during the project will enable accurate assessment of risks to human health due to soil pollutant exposure at diverse contaminated industrial sites. Additionally, the data on pollutant characteristics obtained through exposome analysis will provide theoretical support for the development of guidelines for preventing and controlling soil pollution at typical industrial sites. Importantly, the health risk models developed in this work will be extendable, allowing them to be used when performing health risk assessments at other contaminated sites. The successful implementation of this project will thus reduce the need to duplicate research efforts and will thereby support economic development while also reducing pollution control and environmental protection costs.

The project presented herein has been ongoing for a year, during which field investigations have been conducted at contaminated industrial sites and a number of human blood and urine samples have been collected. While some important advances have been made as a result, many challenges and difficulties remain to be overcome given the richness and breadth of the planned research. The first such challenge relates to the selection of suitable contaminated industrial sites when assessing the health risks facing nearby populations: sites should be chosen based on the extent to which they are representative of common contaminated sites as well as the availability of human and financial resources to the research team. The second challenge concerns the collection of human samples, which requires careful consideration of ethical issues, public awareness, and the support of local government. This is particularly important because the project relies heavily on measuring internal exposure using a large set of human samples. A third major challenge is that the health risks posed by various pollutants in contaminated soils are directly linked to their points of emission, which can vary widely within a broad exposure parameter space. To construct reliable and meaningful exposure–biomarker–disease networks, it will be necessary to find ways of developing effective co-exposure assessment technologies that can be used to identify representative characteristic exposure biomarkers and co-exposure patterns at different contaminated sites. A fourth challenge to overcome is that while human samples are important in current health risk assessments, there have been few comparative evaluations of methods for biological sample analysis due to the limited volume of most samples and the extremely low concentrations of the target pollutants within those samples. Therefore, the characterization of various pollutants in human samples and their target and nontarget analyses should be performed using optimized methods for sample extraction, purification, and quantitative MS analysis that account for the analytes' physicochemical properties. Finally, although the analysis of pollutants in human samples is expected to uncover several biomarkers and signaling pathways potentially associated with pollutant exposure, there is a lack of methods for establishing relationships between the external and internal exposure levels of various pollutants and changes in the associated biomarkers and/or clinical epidemiological indicators. Developing methods for this purpose and identifying such relationships are a major goal of this project, and will represent an important breakthrough.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Key Research and Development Project of China (2019YFC1804500).

Appendix A. Supplementary materials

Supplementary materials to this article can be found online at <https://doi.org/10.1016/j.scib.2021.04.039>.

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