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Viewpoint

Enhancing the Utilization of Nontarget Screening to Holistically Identify Chemical Exposure Fingerprints in Human Blood Biomonitoring and Epidemiological Study

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Humans are exposed daily to diverse synthetic chemicals through a variety of routes, including diet, inhalation, skin contact, and even through the umbilical cord to the fetus. Numerous chemicals (e.g., per- and polyfluoroalkyl substances, polycyclic aromatic hydrocarbons, triazine pesticides, benzotriazole UV stabilizers, synthetic phenolic antioxidants) have been definitively documented as developmental neurotoxicants, endocrine disruptors, and carcinogens. Chemical exposure is an important cause of many noncommunicable diseases such as cancer, miscarriage, birth defects, obesity, asthma, pneumonia, diabetes mellitus, and depression.[1−3] Despite progress in exploring associations between certain chemicals and diseases, some significant scientific issues still remain unresolved, including identifying chemicals currently used in commerce that are capable of jeopardizing human health, and accurately estimating the contribution of chemical pollution to disease or death.[1] Therefore, comprehensive identification of toxic chemicals in the human body is of particular concern worldwide, exacerbated by the rapidly increasing trends in the number and production of chemicals.

Target analysis is the basic means of identifying chemicals over the past decades. This approach relies critically on authentic standards and covers a limited chemical space of compounds,[4] i.e., limited pollutants in a single analysis. The number of synthetic chemicals exceeds 219 million as of December 17, 2024, of which approximately 5000 chemicals are classified as high production volume chemicals by the Organization for Economic Co-operation and Development.[5] It is supported that at least thousands of synthetic chemicals have been dispersed extensively in the environment,[1] and may cause mixture effects in the case of near-universal human exposure. The complexity of coexposure to diverse synthetic chemicals in the real-world scenarios emphasizes the limitations of current target analysis in human biomonitoring.

High-resolution mass spectrometry (HRMS) provides a solution for the identification of tens of thousands of chemicals from complex sample matrices in a single injection. Based on HRMS, nontarget screening (NTS) analysis, as an advanced analytical strategy that refers to identification of known and unknown pollutants without the assistance of authentic standards and a priori knowledge of component constituents, is a chemical monitoring approach with the broadest chemical space currently.[4] Blood is the preferred matrix for human biomonitoring since it is more readily available than tissues and more representative for organ exposure than urine.[6] Moreover, blood biomonitoring can effectively model the associations between chemical exposures and human health, accounting for environmental factors of diseases and health risks of chemicals.[7] However, NTS is rarely utilized in human blood biomonitoring and epidemiological studies, with only 1.4% and 0.5% of applications from 2010 to 2024, respectively (Figure 1A). There is an urgent need to enhance the application of NTS in future human blood biomonitoring and epidemiological studies to holistically identify chemical cocktails.

A standardized and robust workflow of NTS for large-scale samples is fundamental to conduct routine human blood biomonitoring and epidemiological studies. The common NTS methodology involves multiple procedures, including sampling, extraction, instrumental detection, data analysis, and (semi)-quantitative reporting.[5] As an evolving analytical method, the reproducibility of NTS results and their comparability across studies has been criticized,[8] especially for data analysis and (semi)quantitative reporting. To address this, analyte coverage, recovery, feature prioritization and annotation, linear range of detection, and (semi)quantitative reliability, need to be documented in detail in the harmonized analytical workflow to provide comparable and validated NTS data.

In recent years, the utilization of NTS in environmental science has grown in size, and the number of peer-reviewed publications is increasing rapidly (Figure 1B). In comparison to other environmental applications of NTS (e.g., air, water, and soil monitoring), the utilization of NTS in human blood biomonitoring and epidemiological studies requires additional three points of attention. First, identification of transformation products (TPs) should be included in the standardized data analysis, and the roles of TPs in the health impacts of parent pollutants should be considered critically. From the blood exposome perspective, even toxicants of natural products (e.g., pyrrolizidine alkaloids, aristolochic acids) and pharmaceuticals posing potential toxicity issues should also be monitored by

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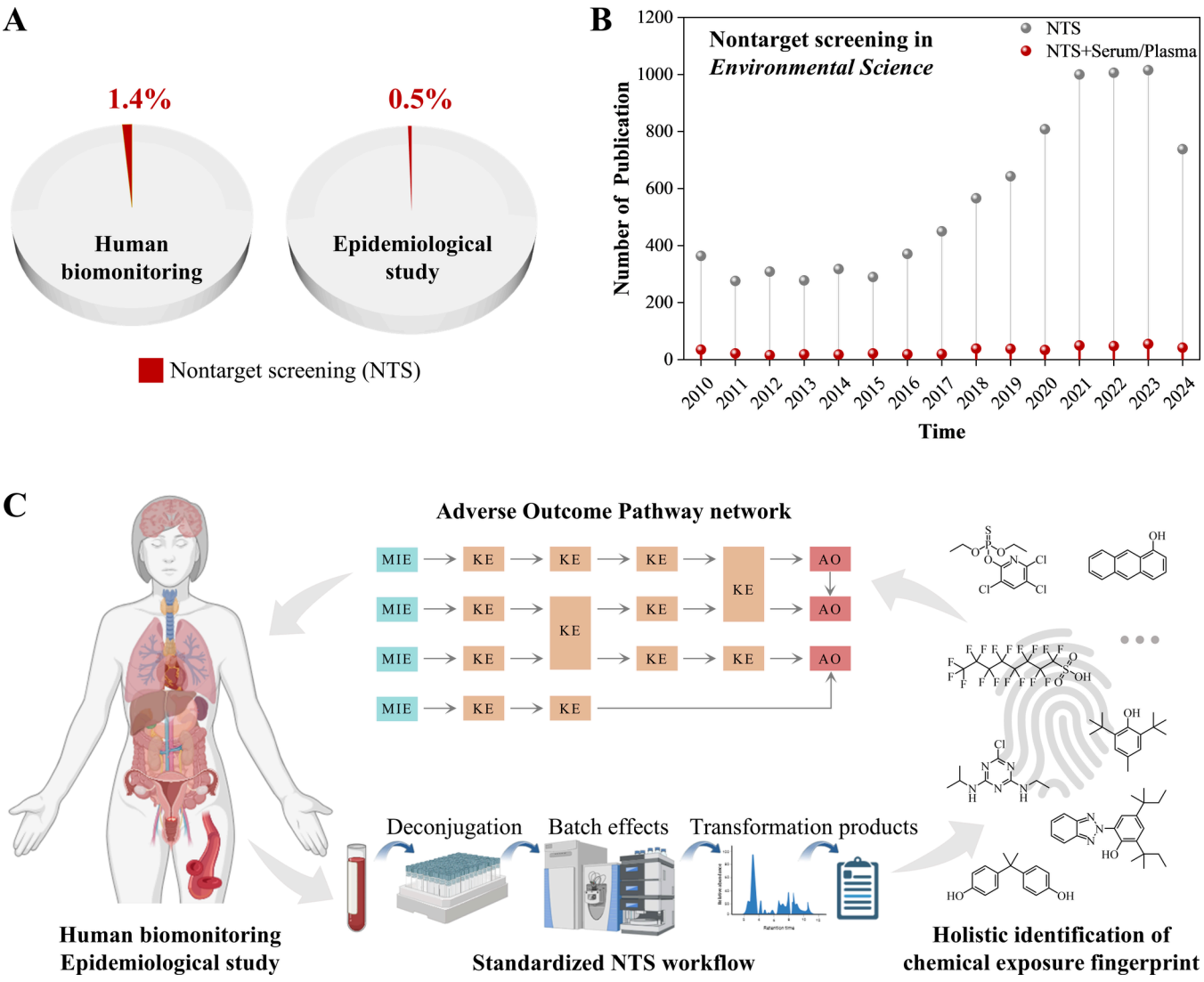

Figure 1. Enhancing the utilization of nontarget screening (NTS) to holistically identify chemical mixtures in human blood biomonitoring and epidemiological study. (A) Proportions of human blood biomonitoring and epidemiological studies using NTS in the period of 2010−11/29/2024. There were 2502 and 36 peer-reviewed publications in Web of Science by searching "human biomonitoring + serum/plasma" and "human biomonitoring + serum/plasma + nontarget screening/non-targeted analysis/suspect screening", respectively, on November 29th, 2024. For epidemiological studies, 26054 and 122 peer-reviewed papers were obtained by searching "epidemiological study + serum/plasma" and "epidemiological study + serum/plasma + nontarget screening/non-targeted analysis/suspect screening", respectively. (B) Trend of peer-reviewed studies using NTS in environmental science. Data was retrieved on November 29th, 2024 in Web of Science using the keyword "nontarget screening/non-targeted analysis/suspect screening" with the restrictions of research area "environmental science ecology" and document type "article." The red balls and lines indicate the number of peer-reviewed literature with the additional restriction of the keyword "serum/plasma". (C) New research paradigm integrating standardized NTS workflow and Adverse Outcome Pathway network facilitates the holistic identification of chemical exposure fingerprints and supports cumulative risk assessment in future human biomonitoring and epidemiological studies. MIE, molecular initiating event; KE, key event; AO, adverse outcome.

NTS, as these substances may also be drivers of health risks.[6] Second, deconjugation is a critical step in the standardized extraction procedure. Deconjugation experiments destroy the chemical structures of TPs (mainly phase II metabolites) in samples theoretically, and thus extraction with and without deconjugation is simultaneously recommended. Furthermore, batch effects should be scrutinized with respect to the large-scale instrumental detection lasting days, months or even (intermittently) years, as sample sizes for human biomonitoring and epidemiologic studies are often in the hundreds or thousands.[7] The correction of batch effects is required once they are apparent.

A high-profile issue existing in human biomonitoring and epidemiological studies is the associations between chemical exposures and disease outcomes. The associations between a single chemical and health effects have been the focus of current studies, whereas the mixture effects of chemical cocktails have been neglected largely.[7] Based on the standardized NTS methodology, complex association modeling between chemical cocktails and health outcomes can be constructed, and underlying "cocktail effects" can be revealed to a certain extent. NTS provides opportunities to holistically recognize human exposure information on chemical cocktails, and informative exposure variables are able to be introduced for association analysis with diseases in epidemiological

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studies. Through the construction of multidimensional networks of associations between diversified pollutants and various diseases, the characteristic pollutants leading to a specific disease can be captured, known as "chemical exposure fingerprints" (Figure 1C). Undoubtedly, the diagnostic "chemical exposure fingerprints" are basic information and essential references for the future focus of the advanced human biomonitoring and epidemiological studies.

Traditional concepts of cumulative risk assessment (i.e., concentration or dose addition and independent action) fail in calculating combined effects in certain cases because of the diversity of chemical mixtures on chemical structure and mode of action (e.g., enzyme inhibition, neurotoxicity, photosynthesis inhibition). By linking to toxicological database such as ToxCast program supported by the U.S. Environmental Protection Agency, molecular initiating event, key event, and adverse outcome for certain "chemical exposure fingerprints" can be obtained or predicted, allowing the introduction of an Adverse Outcome Pathway (AOP) concept to characterize health impacts of chemical mixtures. An AOP connects the toxicity pathway at the cellular level to the organ-level response, followed by the organism-level response. The interactions of multiple AOPs with shared key events (i.e., AOP network) can provide rational solutions to the multiplicity of information from NTS and toxicity data to predict and interpret the combined effects in a cumulative risk assessment.[9] Moreover, the incorporation of omics and systems biology approaches into the AOP network enables further exploration on the molecular mechanisms of adverse outcomes induced by chemical mixtures.

Overall, the research paradigm integrating a standardized NTS workflow and AOP network will facilitate the holistic identification of "chemical exposure fingerprints" and support cumulative risk assessment in future human biomonitoring and epidemiological studies (Figure 1C). This operational framework holds the promise of accurately identifying combined exposure to organic pollutants in humans and the burden of disease or death associated with them.

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Notes

The authors declare no competing financial interest.

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