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EDITORIAL

Analytical Challenges and Toxicological Implications of the Exposome: Open Issues Towards a New Frontier for Medical Sciences

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Although the genome has been a cornerstone of medical research, it alone cannot describe the complex etiology of the majority of chronic diseases. The prime role of environmental exposures and lifestyle has hence introduced the concept of the exposome. The term exposome, coined by Christopher Wild, represents the totality of environmental exposures from conception onward and is considered a complement to the genome.[1,2] Advancing exposome research offers the extraordinary opportunity for integration of exposure science, analytical chemistry, biomedicine, and toxicology within translational healthcare.

Wild's definition posited three overlapping domains: the general external environment, which includes elements such as urban/rural surroundings and climate; the specific external environment, which includes elements such as pollutants, diet, and occupation; and the internal environment, which includes metabolism, oxidative stress, and the microbiome.[3,4] This has been further elaborated to include the behavioral factors and endogenous responses, placing environmental exposures as equivalent to genomics in determining health.[5,6] Examples of these include air pollution and cardiovascular disease,[7] maternal smoking and neonatal epigenetic changes,[8] and the gut microbiome in intervening on diet and immune function.[9] Characterization of the exposome is both a major challenge and a tall opportunity for public health.

Characterization of the exposome necessitates a structured approach conceptualized into three phases: (1) analytical identification and measurement, (2) computational data processing, and (3) integrative understanding of exposure-effect interplay. Thousands of agents are present across biological matrices in the exposome with significant temporal variability.[10] Longitudinal cohort studies, such as EXPOsOMICS,[3] HELIX,[11] and CHEAR,[12] are pioneering systematic approaches to capture such data.

1. Analytical methods

Traditional targeted analytical methods are well-suited for quantifying specific known compounds, such as pesticides or drug metabolites. However, they are blind to the unknown. The exposome requires a paradigm shift towards untargeted analysis. High-resolution mass spectrometry (HRMS) is a leading technology, and integrated analytical platforms, such as liquid chromatography-HRMS, gas chromatography-HRMS, capillary electrophoresis-MS, and ion mobility spectrometry, have been developed to cover diverse chemical spaces.[13,14] Untargeted analysis using sensitive metabolomic and proteomic profiling identified biomarkers in exhaled breath condensate for asthma and chronic obstructive pulmonary disease.[15] Detecting low-abundance xenobiotics remains a challenge, and projects

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such as NECTAR identified unmonitored pesticides.[16] However, untargeted HRMS generates large amounts of "molecular dark matter" and expanded spectral libraries, necessitating harmonization strategies.[17] Analytical method validation is an essential step for identifying environmental chemicals in biological fluids, since incomplete validation can lead to unreliable results. Therefore, there is a need for adherence to the guidelines given by the International Council for Harmonisation (ICH), the United States Food and Drug Administration (FDA), and the European Medicines Agency (EMA).[18]

2. Computational processes

Computational analysis includes the pre-processing of raw data by distinguishing signals from noise, feature alignment, and peak quantification. Compound identification remains one of the most significant bottlenecks in this field; accurate mass databases, MS/MS spectra, and predictive software are required, while confirmation necessitates the use of analytical standards. Machine learning, together with Bayesian models, is increasingly applied in these high-dimensional data analyses, for instance, to predict chronic disease outcomes from multi-pollutant exposures.[19,20] Data integration combines exposome data with other omics layers, namely metabolomics, proteomics, and epigenomics, to form a multidimensional biological picture.[21]

3. Integration with toxicology

The ultimate aim is to understand how exposures translate into adverse health outcomes through the integration of epidemiology and toxicology.[22] Key approaches include: (1) exposome-wide association studies to scan for exposure-disease associations,[23] (2) mechanistic toxicology to explore biological plausibility instances, oxidative stress, and endocrine disruption mixture effects,[24] and (3) temporal/source apportionment to identify susceptibility windows and exposure sources.[25] Toxicology provides a framework for understanding biologically effective doses using in vitro models and omics technologies. Examples include animal models showing that phthalates and bisphenol A exacerbate insulin resistance[26] and urinary metabolomic signatures that detect nephrotoxicants.[27] Bridging HRMS data with toxicological assays is key to achieving mechanistic depth and elucidating causal pathways. The exposure-response relationship is modeled in computational toxicology. Research on phosphine-induced cardiotoxicity demonstrates mitochondrial dysfunction and oxidative stress, which are quantifiable via biomarkers, consistent with the exposome focus on mechanism and validation.[28] Research on chlorpyrifos-induced lung injury reveals disrupted antioxidant defenses, underscoring the roles of oxidative stress and potential protective interventions.[29] Occupational studies, such as those on anesthetic gases, have correlated external exposure with internal biomarkers, thereby reinforcing the exposome paradigm.[30] Collaborative frameworks, such as Tox21, merge high-throughput screening with exposomics toward the elucidation of toxicity mechanisms.[31]

Although the exposome has rapidly expanded our view of how environments shape health, the field is still in an early, energetic stage of discovery. Progress in high-resolution analytical tools, more sophisticated computational workflows, and deeper mechanistic toxicology is steadily transforming scattered exposure signals into clinically meaningful information. New possibilities, such as using artificial intelligence to interpret large datasets, building shared biobanks, and integrating exposome measurements into long-term clinical studies, hint at a future in which we can track environmental influences on health with greater clarity. As these pieces come together, exposome research is likely to move beyond describing exposures and toward predicting risk and guiding prevention, offering a valuable counterpart to what the genome can tell us about disease.

Despite its momentum, exposome science still faces several practical and conceptual hurdles that limit its full translational reach. Harmonizing data across studies remains difficult, as differences in analytical platforms, metadata standards, and sampling protocols can obscure genuine biological signals. Longitudinal cohorts, the backbone of exposome research, are expensive to maintain, slow to establish, and often constrained by limited geographic or demographic diversity. Even when rich datasets are available, inferring causality is challenging because exposures cluster, change over time, and interact in non-linear ways. These limitations do not diminish the promise of the exposome, but they underline the need for coordinated efforts in standardization, cost-efficient study design, and more robust analytical frameworks capable of teasing apart complex exposure–effect relationships.

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