Exposome analysis in toxicology: A comprehensive review

Utsav Anand Mani[1,*], Husain Abbas[2], Mukesh Kumar[1], Haider Abbasz[1], Sharique Alam[1], Devansh Goyal[1]

[1] Department of Emergency Medicine, King George's Medical University, Lucknow, Uttar Pradesh 226003, India

[2] Department of Medicine, Jawaharlal Nehru Medical College, AMU, Aligarh, Uttar Pradesh 202002, India

*** Corresponding author:** Utsav Anand Mani, utsavanandmani@gmail.com

ARTICLE INFO

Received: 18 September 2023
Accepted: 17 November 2023
Available online: 2 December 2023

doi: 10.59400/jts.v1i1.267

ABSTRACT: Toxicology has extensively evolved with the study of how external agents impact living organisms. This manuscript examines the exposome, a paradigm representing all environmental exposures a human encounters from conception onward, introducing a holistic approach to understanding these effects on health. First coined by Dr. Christopher Wild in 2005, recent interpretations by Miller and Jones emphasize not only the environmental factors but also behavioral influences, internal biochemical processes, and the implications of the human microbiome. These augmentations underscore the body's dynamic responses and continuous adjustments to external challenges. Traditional toxicology, which primarily focused on singular compounds, often overlooked intricate interplays between multifaceted exposures; the exposome aims to bridge this gap. To analyze the vast spectrum of lifetime exposures, various state-of-the-art techniques are in use, such as untargeted high-resolution mass spectrometry, biobanking, biomonitoring, and diverse omics approaches (metabolomics, adductomics, proteomics, and transcriptomics). These methods empower scientists to uncover unknown environmental risks, offering insights into the complex nexus between external exposures and health outcomes.

KEYWORDS: exposome; metabolomics; environmental monitoring; geospatial analysis; toxicology

1. Introduction

Toxicology is the scientific study of how various chemical, physical, and biological agents interact with living organisms and impact their health. Over the years, toxicologists have made significant strides in understanding the risks posed by toxic substances, thanks to advances in analytical techniques, risk assessment methodologies, and a broader perspective on exposure. The exposome is a term coined by Dr. Christopher Wild in 2005 and encompasses the totality of human environmental (non-genetic) exposures from conception onwards, representing a promising paradigm in studying the complex interplay between environmental factors and health outcomes[1]. Within the realm of toxicology, exposome analysis offers an innovative approach to understanding the cumulative impact of diverse environmental exposures on human health. It shifts the focus from individual chemical exposures to a more comprehensive view of environmental factors. This article delves into the significance, techniques, challenges, and potential of exposome analysis in toxicology.

2. The rationale for exposome analysis

Miller and Jones have redefined exposome as "the cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, diet, behavior, and endogenous processes"[2]. There are three primary distinctions between Miller's and Jones' interpretation and that of Dr. Wild. The initial difference revolves around the idea of cumulative biological reactions. This notion encompasses the body's continuous adjustments, both beneficial and detrimental, in response to external stimuli and chemicals. This new definition symbolizes how the body copes with these external challenges.

The next distinction in Miller's and Jones' interpretation is the emphasis on behavior. Behavior is understood in an expansive context, encompassing not only individual intentional actions but also those influenced by familial, communal, and societal structures. This new definition extends beyond mere lifestyle habits. It delves deeper into how individuals dynamically engage with their environment, emphasizing the significance of interpersonal relationships, various interactions, and both physical and emotional stress factors.

Lastly, Miller's and Jones' interpretation integrates the concept of internal processes. The human body is a sophisticated network of biochemical interactions, with myriad processes taking place simultaneously. Processes like glycolysis, oxidative respiration, and the activity of microsomal p450 enzymes, among others, continually produce new molecular entities while decomposing others. Additionally, our internal microbial ecosystem, the microbiome, plays a pivotal role and is included in these "internal processes". Although external exposures remain central to this new definition, it's worth noting that the subsequent damage—be it mutations in DNA, changes in epigenetic patterns, or alterations in proteins—is as vital as the external chemicals causing them. These changes not only indicate the actual impact but might also be more accessible for study, even years after exposure. With the realization that genetic factors alone cannot explain the etiology of many diseases, attention has shifted towards environmental exposures. These exposures range from dietary components, pollutants, drugs, and infectious agents to lifestyle factors[3]. Traditional toxicology has focused on studying single compounds or a group of related compounds, but this approach may miss the complex interactions between multiple exposures. The exposome promises to fill this gap, offering a holistic perspective.

3. Techniques in exposome analysis

To capture the vast array of exposures over a lifetime, several advanced analytical techniques are employed:

Untargeted high-resolution mass spectrometry (HRMS): This allows for the identification and quantification of thousands of chemicals in biological samples without prior knowledge of their presence[4].

Biobanking and biomonitoring:

Collections of biological samples (e.g., blood, urine, tissues) stored for future analyses can be crucial for exposome studies. Over time, these samples can be tested for new or previously unmeasurable exposures[5].

Omics techniques:

Metabolomics: Analyses the suite of small molecules (metabolites) in body fluids to infer exposures.

Techniques like NMR spectroscopy and chromatography-mass spectrometry are used to measure metabolite signals, capturing over 10,000 endogenous and exogenous metabolites. By examining metabolites, one can get a sense of the chemicals and processes occurring within the body due to external exposures.

Adductomics: Focuses on identifying adducts, which are products of the reactions of toxicants with DNA or proteins. Identifying adducts can indicate exposure to specific toxins.

Proteomics and transcriptomics: Study of proteins and RNA transcripts to understand changes in cellular processes and pathways upon exposure. High-resolution metabolomics and other untargeted analytical techniques used in exposome studies can identify novel toxicants or biomarkers of exposure without prior hypotheses. This unbiased approach can lead to the discovery of previously unrecognized environmental risks. Proteomics focuses on the study of post-translational modifications to proteins at the cellular level. This approach leverages techniques such as soft ionization mass spectrometry and antibody microarrays. While it offers a breadth of coverage, capturing unknown proteins and protein complexes, its throughput ranges from low to medium. Transcriptomics offers nucleotide-level resolution of RNA expression, a pivotal aspect in understanding gene expression patterns. Hybridization-based technologies, notably RNA-seq, are the cornerstones of this approach. The capacity to identify any sequences that are part of the chosen method or technique makes its coverage expansive. Hybridization-based technologies, in particular, offer high throughput.

In the realm of epigenomics, the focus lies on DNA methylation patterns. Researchers commonly use tools such as the Illumina Methylation EPIC Bead Chip and the 850 K DNA methylation array. The coverage of this approach primarily targets promoters, CpG islands, shores, and open seas. These areas have historically shown variability across different tissues or in various disease states. The throughput for epigenomics stands at a medium to high range. Lastly, high-throughput screening is an innovative approach that measures the activities of a myriad of receptors, including but not limited to estrogen, androgen, and G-protein signaling. Techniques like chemically activated Luciferase gene expression (CALUX) and high-content analysis are at the forefront of this approach. While CALUX can target selected receptors across a vast media range, high-content analysis provides a medium throughput[6].

Environmental monitoring and sensors:

Wearable environmental sensors can track individual exposure to specific environmental factors in real-time, such as UV radiation or air pollution[7,8].

Stationary environmental sensors can provide data on pollutant levels in specific locales, like water quality sensors or air quality monitors[9].

Data Integration and Bioinformatics: Advanced computational tools are crucial for the management, integration, and interpretation of the massive datasets generated in exposure studies[10]. Machine learning and statistical models can be employed to discern patterns, correlations, and potential causations between exposures and health outcomes. The concept of the exposome wheel has been proposed as a way to visualize and organize exposome data[11]. The exposome wheel considers the temporal and spatial dimensions of exposures and their interactions, helping researchers explore the complex web of environmental factors that contribute to an individual's exposome.

Geospatial analysis:

Using tools like Geographic Information Systems (GIS), researchers can map environmental exposures and correlate them with health outcomes in specific regions or populations. Taking a comprehensive approach to assessing environmental exposure, the EXPOsOMICS project focuses on the "external exposome", or the totality of environmental exposures encountered from birth onwards. Using advanced technologies and large-scale European cohorts, EXPOsOMICS aims to capture a vast array of data on environmental factors, including air and water pollutants, physical activity, and more. By understanding these exposures and their fluctuations, the project hopes to shed light on how the environment shapes health across lifespans[12].

Longitudinal cohort studies:

Following a group of individuals over time can help establish a timeline of exposures and correlate them with health outcomes. These studies are crucial for establishing potential cause-and-effect relationships in the context of the exposome. One such study is PHENOTYPE. The PHENOTYPE (Positive Health Effects of the Natural Outdoor Environment in Typical Populations in Different Regions in Europe) project delves into the potential health benefits of natural outdoor environments, from urban parks to rural green areas. Given the increasing trend of urbanization, understanding the health implications of natural versus urban settings becomes vital. PHENOTYPE assesses how exposure to green spaces affects health, mental well-being, and vital physiological markers. It also considers how personal and socioeconomic factors can mediate these relationships[13].

Questionnaires and diaries:

Personal logs and surveys can provide valuable information on lifestyle, diet, occupational exposures, and other environmental factors.

Cellular and animal models:

Used to test the effects of specific exposures in controlled settings. These can help infer potential mechanisms of toxicity and guide further human studies.

4. Challenges in exposome analysis

The vastness and dynamism of the exposure pose several challenges. While the exposome offers a holistic framework for understanding the environmental determinants of health, its vastness and dynamism pose significant challenges in its analysis. Overcoming these challenges necessitates multidisciplinary collaboration, innovative methodological advancements, and substantial investment in research infrastructure.

Temporal variation: Exposures change over time and capturing these variations is complex[14].

Complexity and diversity of exposures:

The exposome encompasses a myriad of exposures, ranging from chemical agents, biological agents, radiation, and psychosocial factors, to name a few. Given this vastness, capturing every single exposure is a herculean task. Each exposure can have numerous sources, pathways, and health outcomes associated with it. This creates a challenge in exposure assessment and in disentangling the combined effects of various exposures on health outcomes[3].

Chemical unknowns: Many compounds detected, especially through untargeted approaches, are unidentified[15].

Dynamic nature of exposures:

The exposome is not static; it evolves throughout an individual's lifespan, influenced by factors such as lifestyle changes, relocation, dietary shifts, and more[16]. This temporal variation requires high-frequency longitudinal data collection to capture the nuances of exposure dynamics, which is resource-intensive.

Data volume: The sheer volume of data requires advanced storage, processing, and analytical strategies[17]. The assessment of the exposome generates vast amounts of data. Managing, storing, and analyzing such vast datasets, especially in a manner that ensures data integrity, security, and privacy, is a significant hurdle[18]. Advanced computational tools and infrastructures are required, often necessitating interdisciplinary collaboration between epidemiologists, bioinformaticians, and data scientists.

Lack of standardized measurement tools:

There's an inherent challenge in the absence of universally accepted tools or protocols for measuring all components of the exposome. While advancements like high-resolution metabolomics provide opportunities for untargeted exposure assessment[19], there's a need for standardization to allow comparison and meta-analysis across studies.

Causality: Linking exposures to health outcomes is challenging due to the multifactorial nature of diseases[20].

Interpretability and validation:

Identifying potential biomarkers or molecular signatures from exposome data is only one step. Validating these findings and interpreting them in the context of health outcomes requires rigorous methodological approaches and often experimental validation in model systems.

Integration with genomics:

The ultimate goal is to understand how the exposome interacts with the genome in influence health outcomes. Integrative analyses that consider both genetic and environmental factors are computationally complex and require sophisticated statistical methodologies[21]. By integrating exposome with genomics, researchers can uncover how genetic susceptibilities modulate the body's response to environmental toxicants. Such interactions can explain the variability in toxic responses among individuals[10].

5. Applications in toxicology

Several studies have employed exposome analysis to understand disease mechanisms and identify toxic agents. Examples include investigating the role of combined air pollutants in respiratory diseases, unraveling the interplay between pesticides and dietary components in neurodegenerative diseases, and identifying previously unknown environmental risk factors for rare cancers[22]. The future of exposome analysis in toxicology is bright. The evolving technologies and increasing interest in the exposome promise a transformative impact on toxicology through regulatory decisions. As our understanding grows, regulatory bodies might begin to account for combined exposures when setting safety limits. Personal exposure profiles might be used to provide individualized risk assessments for diseases related to environmental exposures[23]. There is a place for therapeutic interventions. Identifying key toxic exposures can lead to personalized intervention strategies to reduce disease risk. With a comprehensive understanding of environmental exposures and their health effects, public health policies can be better tailored. Identification of high-risk exposure combinations or vulnerable subpopulations can guide targeted interventions.

Exposome data, combined with advanced in vitro and in vivo toxicological studies, can shed light on the mechanistic pathways by which exposures lead to adverse health outcomes. This deepens the understanding of pathophysiology and can inform therapeutic strategies[24]. The dynamic nature of the exposome, evolving with age and life events, allows toxicologists to study the effects of exposures at various life stages, from in-utero to old age. This can reveal critical windows of susceptibility and the long-term health consequences of early-life exposures[25]. Exposome analysis provides a more comprehensive picture of an individual's or population's exposure history, improving the precision of risk assessments. By capturing both peak and cumulative exposures, it can better inform dose-response relationships and vulnerability assessments[26].

6. Discussion

By embracing the exposome, toxicology can evolve from a discipline of singular interactions to a more integrated science that considers the full tapestry of life's exposures. This paradigm shift has the potential to transform not just toxicology but also the broader realm of public health, environmental regulation, and personal medicine. Toxicology, at its core, is the study of how external agents affect living organisms. The exposome enriches this understanding by considering the entire spectrum of exposures throughout an individual's life. The biological mechanisms that mediate the effects of these exposures present an orchestra of metabolic and microbiome activities that translate environmental cues into biological outcomes. This approach is akin to looking behind the scenes of a performance, understanding not just the music but also the musicians and instruments at play.

Toxicological research and policy need to integrate the exposure-biology-disease nexus more explicitly. By doing so, we can better predict and mitigate the health impacts of environmental exposures. A more nuanced understanding of this nexus also opens the door to personalized interventions and more targeted public health strategies. Ultimately, the goal is to not only map the exposome but also to harness its insights for more effective prevention and treatment of diseases linked to environmental factors. The nexus between exposure and disease is a complex journey from an external event to an internal biological response, culminating in health outcomes. The exposome offers a lens to view this journey in its entirety, identifying not only the toxic agents but also the biological mediations that lead to disease. It is in this biological mediation that the potential for intervention lies—targeting not just the exposures but also enhancing biological resilience.

The complexity of the exposome cannot be unraveled by toxicology alone. It requires the concerted efforts of epidemiologists, geneticists, biostatisticians, and many others. In this collaborative future, the insights gleaned from exposome research can inform public policy, leading to more effective strategies for disease prevention and environmental health.

7. Conclusion

In conclusion, the concept of the exposome represents a significant shift in the field of toxicology, offering a more comprehensive and holistic view of environmental exposures and their impact on health. Exposome analysis, with its multi-omics approaches and integration of diverse data sources, has the potential to revolutionize risk assessment and regulatory decision-making. As our understanding of the exposome continues to evolve, it is essential for researchers, policymakers, and public health professionals to collaborate in order to address the complex challenges and uncertainties associated with exposome-based toxicology. While challenges remain, the potential benefits for public health are enormous, pushing the boundaries of traditional toxicology into a new era.

Conflict of interest

The authors declare no conflict of interest.

References

1. Wild CP. Complementing the genome with an "exposome": The outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiology, Biomarkers & Prevention* 2005; 14(8): 1847–1850. doi: 10.1158/1055-9965.EPI-05-0456
2. Miller GW, Jones DP. The nature of nurture: Refining the definition of the exposome. *Toxicological Sciences* 2014; 137(1): 1–2. doi: 10.1093/toxsci/kft251
3. Rappaport SM, Smith MT. Environment and disease risks. *Science* 2010; 330(6003): 460–461. doi: 10.1126/science.1192603
4. Vlaanderen J, Moore LE, Smith MT, et al. Application of OMICS technologies in occupational and environmental health research; current status and projections. *Occupational & Environmental Medicine* 2010; 67(2): 136–143. doi: 10.1136/oem.2008.042788
5. Calafat AM. The U.S. National Health and Nutrition Examination Survey and human exposure to environmental chemicals. *International Journal of Hygiene and Environmental Health* 2012; 215(2): 99–101. doi: 10.1016/j.ijheh.2011.08.014
6. Dennis KK, Auerbach SS, Balshaw DM, et al. The importance of the biological impact of exposure to the concept of the exposome. *Environmental Health Perspectives* 2016; 124(10): 1504–1510. doi: 10.1289/EHP140
7. Snyder EG, Watkins TH, Solomon PA, et al. The changing paradigm of air pollution monitoring. *Environmental Science & Technology* 2013; 47(20): 11369–11377. doi: 10.1021/es4022602
8. Nieuwenhuijsen MJ, Donaire-Gonzalez D, Foraster M, et al. Using personal sensors to assess the exposome and acute health effects. *International Journal of Environmental Research and Public Health* 2014; 11(8): 7805–7819. doi: 10.3390/ijerph110807805
9. Wieringa FP, Broers NJH, Kooman JP, et al. Wearable sensors: Can they benefit patients with chronic kidney disease? *Expert Review of Medical Devices* 2017; 14(7): 505–519. doi: 10.1080/17434440.2017.1342533
10. Patel CJ, Ioannidis JPA. Studying the elusive environment in large scale. *Journal of the American Medical Association* 2014; 311(21): 2173. doi: 10.1001/jama.2014.4129
11. Gudi-Mindermann H, White M, Roczen J, et al. Integrating the social environment with an equity perspective into the exposome paradigm: A new conceptual framework of the Social Exposome. *Environmental Research* 2023; 233: 116485. doi: 10.1016/j.envres.2023.116485
12. Vineis P, Chadeau-Hyam M, Gmuender H, et al. The exposome in practice: Design of the EXPOsOMICS project. *International Journal of Hygiene and Environmental Health* 2017; 220(2): 142–151. doi: 10.1016/j.ijheh.2016.08.001
13. Nieuwenhuijsen MJ, Kruize H, Gidlow C, et al. Positive health effects of the natural outdoor environment in typical populations in different regions in Europe (PHENOTYPE): A study programme protocol. *British Medical Journal* 2014; 4(4): e004951. doi: 10.1136/bmjopen-2014-004951
14. Dennis KK, Marder E, Balshaw DM, et al. Biomonitoring in the era of the exposome. *Environmental Health Perspectives* 2017; 125(4): 502–510. doi: 10.1289/EHP474
15. Schymanski EL, Singer HP, Longrée P, et al. Strategies to characterize polar organic contamination in wastewater: Exploring the capability of high resolution mass spectrometry. *Environmental Science & Technology* 2014; 48(3): 1811–1818. doi: 10.1021/es4044374
16. Vineis P, Husgafvel-Pursiainen K. Air pollution and cancer: Biomarker studies in human populations. *Carcinogenesis* 2005; 26(11): 1846–1855. doi: 10.1093/carcin/bgi216
17. Escher BI, Hackermüller J, Polte T, et al. From the exposome to mechanistic understanding of chemical-induced adverse effects. *Environment International* 2017; 99: 97–106. doi: 10.1016/j.envint.2016.11.029
18. Dennis KK, Auerbach SS, Balshaw DM, et al. The importance of the biological impact of exposure to the concept of the exposome. *Environmental Health Perspectives* 2016; 124(10): 1504–1510. doi: 10.1289/EHP140
19. Go YM, Walker DI, Liang Y, et al. Reference standardization for mass spectrometry and high-resolution metabolomics applications to exposome research. *Toxicological Sciences* 2015; 148(2): 531–543. doi: 10.1093/toxsci/kfv198
20. Vrijheid M, Slama R, Robinson O, et al. The human early-life exposome (HELIX): Project rationale and design. *Environmental Health Perspectives* 2014; 122(6): 535–544. doi: 10.1289/ehp.1307204
21. Patel CJ, Ioannidis JPA. Placing epidemiological results in the context of multiplicity and typical correlations of exposures. *Journal of Epidemiology & Community Health* 2014; 68(11): 1096–1100. doi: 10.1136/jech-2014-204195

22. Tanner CM, Kamel F, Ross GW, et al. Rotenone, paraquat, and Parkinson's disease. *Environmental Health Perspectives* 2011; 119(6): 866–872. doi: 10.1289/ehp.1002839
23. Shonkoff SB, Morello-Frosch R, Pastor M, Sadd J. The climate gap: Environmental health and equity implications of climate change and mitigation policies in California—A review of the literature. *Climatic Change* 2011; 109(S1): 485–503. doi: 10.1007/s10584-011-0310-7
24. Turner MC, Nieuwenhuijsen M, Anderson K, et al. Assessing the exposome with external measures: Commentary on the state of the science and research recommendations. *Annual Review of Public Health* 2017; 38(1): 215–239. doi: 10.1146/annurev-publhealth-082516-012802
25. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. *Annual Review of Public Health* 2005; 26(1): 1–35. doi: 10.1146/annurev.publhealth.26.021304.144505
26. Morello-Frosch R, Shenassa ED. The environmental "riskscape" and social inequality: Implications for explaining maternal and child health disparities. *Environmental Health Perspectives* 2006; 114(8): 1150–1153. doi: 10.1289/ehp.8930