The Exposome: Pursuing the Totality of Exposure

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Abstract

Environmental determinants of health need to be measured and analyzed using system approaches that account for interactions between different agents that can elicit a biological response. The exposome offers a useful framework to examine the totality of exposures and their contribution to health and disease. Advances in exposure science, analytical chemistry, molecular biology, and toxicology have primed us to investigate the health effects of exposure to mixtures and concomitant exposures.

1 Introduction

The role of the environment in disease etiology has received increased attention over the past several years. The genome and genetic variations account for far less of the disease burden in the population than was previously thought and the variation in population burden of disease is now largely attributed to nongenetic factors. A meta-analysis of 2,748 twin studies reported that the environmental contribution to thousands of complex human phenotypes was nearly equal to that of genetics (Polderman et al. 2015). A study in monozygotic twins found that the average genetic risk attributed to 28 chronic diseases was just 19% (range: 3–49%) (Rappaport 2016).

The environment encompasses a broad range of factors in the physical world. It includes but is not limited to dietary factors, exposure to infectious and synergistic organisms, toxicant exposures through various media and routes, the built environment, and neighborhood-level characteristics such as access to healthy food and parks. Furthermore, it includes structural policies that control access to healthcare and influence other health-related behaviours and choices. Given how diverse the environmental health umbrella is, it is not surprising that there are several definitions of what the environment constitutes. For the purpose of this chapter, we define the environment as all nongenetic factors that can be measured in the human body which may contribute to variability in disease risk and burden in an individual and the population.

2 Historical Perspective

The effect of the environment on human health has been suggested for millennia. In 400 BC, Hippocrates penned "On Airs, Waters, and Places" discussing the possible role of air and water quality, and climate on human health (Hippocrates 1881). The ancient Romans were aware of the adverse effects from exposure to lead from pipes that conducted water. Vitruvius, a Roman architect and civil engineer, noted that using earthen pipes to transport water would be safer for health than using pipes that contained lead (Hodge 1981). In the nineteenth century, public health efforts were focused on preventing exposure to infectious agents in the environment. Using epidemiological approaches, John Snow discovered a point of water contamination as the cause of a cholera epidemic in London in 1854 (Ruths 2009). These findings and others led to changes in water distribution systems, sewage treatment, and food handling in London. Water and sanitation remain important environmental determinants of health in many developing countries.

Most modern environmental epidemiology studies begin with observations of regional differences in disease rates. Adverse health effects associated with exposure to air pollution were discovered through atmospheric inversion phenomena that led to greater exposure for an extended period over specific geographic regions like Donora in the USA

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G. B. Jiang and X. D. Li (eds.), *A New Paradigm for Environmental Chemistry and Toxicology*, https://doi.org/10.1007/978-981-13-9447-8_1

(1948), London in the UK (1952), and the Meuse Valley in Belgium (1930) (Nemery et al. 2001; Bell et al. 2004; Jacobs et al. 2018). Several other ecological studies were seminal in establishing relationships between air pollution exposure and adverse health outcomes (Dockery 1753). In the 1960s–70s, research focus shifted toward chemical and physical agents in the environment that can affect human health. Several researchers and public health agencies studied the effect of exposure to volatile organic compounds, metals, particulate matter, pesticides, and radiation on health. Books like *Silent Spring* (1962) and *Our Stolen Future* (1996) were critical in raising public awareness in the US on the societal cost of exposure to persistent organic pollutants and endocrine-disrupting chemicals. Recently, the effects of natural disasters, the built environment and global climate change on health have also been investigated.

Increased research efforts in precision medicine have also benefited environmental health research. Advances in molecular techniques have made it possible to study gene x environment interactions that can alter disease risk. The human genome project provided tools to make environmental determinants of health personalized, offering the opportunity to discern how certain genotypes may be more susceptible to effects of an environmental exposure (Collins et al. 2003). Apart from the geographical and genotypic context, the life stage during exposure can also alter disease risk and susceptibility to exposure. The developmental origins of health and disease (DoHAD) hypothesis has led to the discovery of epigenetic transfer of information from parent to offspring and unveiled the vulnerability of the fetus to environmental toxicants and their effect on development and health in later life (Barker 2007).

Advances in environmental chemistry and toxicology have been critical in understanding environmental contributors of human disease. Environmental epidemiology uses both to assign exposure and to determine the biological plausibility of observed association between exposure and outcome.

3 The Exposome

In order to understand the mechanisms by which environmental exposures can affect human health, researchers and regulators have studied exposures in great detail and described the effect of exposure in isolation to a number of chemicals on various health outcomes. However, real-world exposures do not occur in isolation and are accompanied with other exposures and context-specific factors. Besides, human interaction with the environment is lifelong, constant, and spatiotemporally dynamic. Most epidemiological and toxicological studies do not account for this chronic, low-dose exposure to environmental chemicals. To account for this reality, Christopher Wild formally introduced the concept of the exposome in 2005. He defined it as the "life-course environmental exposures (including lifestyle factors), from the prenatal period onwards" (Wild 2005). The formal definition has undergone several revisions but most versions agree that the exposome comprises the entire set of lifelong environmental exposures and the biological response associated with these exposures (Wild 2012; Rappaport 2011; Miller and Jones 2014; Miller 2014). Investigating the biological response to an exposure accounts for toxicity mechanisms and interindividual variability in response. It also allows for the measurement of transient exposures that would be invisible through traditional approaches of exposure assessment. Since the environment is dynamic across the life course, assessing all exposures appears a daunting task. However, recent advances in methods bring optimism and avenues for creativity in the field.

3.1 Tools to Monitor the Exogenous Exposures at the Population Level

Remote sensing is the science of gaining information on objects from a distance and has been used to identify exposures related to the urban environment. Specifically, they can be used to estimate population-level exposure to air pollution, changes in temperature, amount of green space assessed using a normalized difference vegetation index, and provide information on outdoor light-at-night exposure (Larkin and Hystad 2018; Markevych et al. 2017; Turner et al. 2017; Kloog et al. 2008; Rybnikova et al. 2016). Further, remote sensing data from a number of satellites has been integrated to determine global fine particulate matter concentrations (van Donkelaar et al. 2010).

Mobile and stationary sensing monitors are usually used to make exposure measurements in specific locations. They can be a part of national networks of measurement or be related to study-specific measurement campaigns. National networks tend to have limited coverage but can be used as part of a distributed sensor network, which uses low-cost sensors to fill in spatial gaps that national networks are unable to meet. These have been implemented in West Oakland, California (West Oakland Air Quality Study), and in Eindhoven, The Netherlands (AERIAS Project). However, low-cost sensors still require rigorous validation, limiting their widespread application (Curto et al. 2018). Mobile measurement campaigns have been implemented more recently in a few places, like Karlsruhe, Germany, and Zurich, Switzerland (Hagemann et al. 2014; Hasenfratz et al. 2015).

Modeling approaches find utility in distilling GIS and satellite data or spatial resolution. Models such as land use regression, kriging, and maximum entropy models have

been considered by researchers and will need to be elaborated (Jerrett et al. 2010). Data generated from population-level exposure assessments provides opportunity to create ecological studies that can provide links between exposure and population health. Most of these data sources, however, are ineffective at determining individual exposure levels. They will need to be integrated with individual-level measures for validation.

3.2 Tools to Monitor the Exogenous Exposures at the Individual Level

External sensors can be used to track a myriad of personal information. Personal location data obtained through GPS devices enable integration of exposure maps with individual location markers to get personal exposure estimates (Asimina et al. 2018). Accelerometers and other activity tracking personal devices like Jawbone, FitBit, Apple Watch, and Polar (Loh 2017) can be used to ascertain both external exposures and certain lifestyle factors related to exercise and diet. Personal sensing technologies can also be used to assess air pollution exposure, changes in ambient temperature, and presence of green space (Nieuwenhuijsen et al. 2014). Passive dosimeters like silicone wristbands can also be used for personal exposure assessment and provide valuable semi-quantitative information on several chemicals (O'Connell et al. 2014).

Smartphone-based sensors and assessments can integrate data from personal sensors like accelerometers, GPS, barometers, thermometers, and ambient light sensors to record personal exposures. Their high penetrance worldwide provides a unique opportunity to obtain large amounts of personal data from diverse individuals (Murphy and King 2016; van Wel et al. 2017).

Personal sensors to monitor heart rate, glucose levels, blood pressure, muscle activity, body temperature, and sweat production are being developed and will require validation before their implementation in large population studies. Compared to measurements of external exposure, individual-level data is more actionable, can be used for personalized advice, and can be related to internal dose and associated biological responses.

3.3 Tools to Measure Endogenous Response and the Exposome

Techniques in molecular biology have shown exponential advancement in the past three decades. These advances have increased the resolution at which biological response to perturbations from environmental exposures is measured. Exposures to environmental factors can induce local and global changes in gene expression, enzyme activity, metabolite pathway alterations, and protein synthesis/folding. Deep molecular phenotyping can provide information on acute biological responses and also provide measures of long-term changes in physiology which can be viewed as markers of exposure memory (Go and Jones 2016; Weinhold 2006; Jeanneret et al. 2014).

Metabolomics. The metabolome is comprised of small molecules in a biological matrix that is <2000 Daltons in molecular mass. It is thought of as the functional output of genes and proteins, and their interaction with the environment. Recent advances in mass spectrometric techniques have made it possible to capture previously undetected small molecules, with estimates suggesting the metabolome may comprise of more than 1 million chemical features (Uppal et al. 2016). Chemical signals derived from a biological sample can arise from an endogenous metabolism, environmental chemical exposures, diet, the microbiome, personal care products, and drugs (Petrick et al. 2017; Liu et al. 2016; Jones 2016; Walker et al. 2019; Walker et al. 2016). Using an untargeted approach, metabolomics can expand surveillance of environmental chemicals, detect new xenobiotic chemicals, and identify unknown pollutants (Bonvallot et al. 2013; Roca et al. 2014; Jamin et al. 2014). Historically, metabolomics has not focused on those exogenous chemicals, but recent efforts are increasing the identity of environmental chemicals through these untargeted approaches. By simultaneously measuring exposure and biological response, metabolomics offers the opportunity to link exposure to molecules associated with exposure. While the identity of most chemical features that are measured using untargeted high-resolution metabolomics remain unknown, the technique offers a powerful opportunity for hypothesis generation and identification of unknown chemicals of interest related to a health outcome.

Transcriptomics. Gene expression is the process by which genetic data encoded by DNA is transcribed to RNA, which then initiates and directs protein synthesis in a cell. Cellular function regulation involves a complex series of steps that control the amount of RNA, and in turn, protein that is synthesized. Thus, exposures that alter functional regulation in the cell can be detected using transcriptomic and metabolomic analyses. Chemical exposures have been linked with distinct gene expression profiles that have been seen in humans and model organisms (Hamadeh et al. 2002). Transcriptomic analyses in human samples involve DNA microarray hybridization, which uses 40,000–50,000 molecular probes to seek RNA transcripts (McHale et al. 2009; Spira et al. 2004; Fry et al. 2007). Next-generation sequencing has made it possible to measure the effect of exposures on different types of RNA in a sample, including mRNA, microRNA, small interfering RNA, and long non-coding RNA. Databases that curate gene expression

profiles across different exposures and model organisms provide opportunities to compare experimental data with previously generated gene expression profiles (Grondin et al. 2018).

Proteomics. Protein measurement can elucidate signaling, inflammation, oxidative stress, and tissue damage in a biological sample. Levels of proteins and their posttranslational modifications are closer to function than gene expression data. Measuring proteins can be targeted using enzyme-linked immunosorbent assays (ELISA), or newer multiplexed bead-based assays that are capable of measuring more than 50 proteins in a small amount of biological material (Elshal and McCoy 2006; Tighe et al. 2015). While the use of high-resolution mass spectrometers in untargeted proteomics is insightful, it is also challenging due to difficulties in detecting low-abundance proteins. Chemical exposure to reactive electrophiles has been achieved through protein adductomics platforms, which can measure more than 100 human serum albumin adducts at the Cys34 site. Protein adductomics has been used to assess exposure to lifestyle factors, indoor air pollution, and ambient air pollution (Rappaport et al. 2012; Grigoryan et al. 2016; Liu et al. 2018).

Epigenomics. Epigenetic changes on DNA can alter gene expression. These changes can occur through the addition or removal of methyl groups on CpG dinucleotides, or through histone modifications. These modifications can be long term and have the potential to be transferred to the next generation if they occur in germ cells. Different stressors including chemical exposures can lead to specific epigenetic signatures that persist even after the stressor has been removed (Fernandez et al. 2012). Thus, epigenetic profiles can be used to monitor exposure history and to assess acute or chronic stress (Go and Jones 2016; Go and Jones 2014). High-throughput assays based on parallel sequencing of DNA with bisulfite conversions can measure up to 850,000 CpG sites within the human genome. Epigenome-wide association studies have revealed distinct methylation patterns associated with chemical exposures, providing insight into the mechanisms underlying the biological responses (Bollati et al. 2007; Seow et al. 2014; Hou et al. 2012).

Multi-omics assessment of the exposome. Information from different layers of the biochemical dogma can be integrated to paint a holistic picture of biological response to an environmental perturbation (Fig. 1). Using approaches from systems biology, we can gain a deeper understanding of environmental influences on human health by integrating across epigenomic, transcriptomic, proteomic, and metabolomic changes associated with exposures. The integration of high-dimensional data has benefited from the development of statistical approaches that identify interactions among biological response networks (Uppal et al. 2018; Kalia et al. 2019). The continued use of deep molecular phenotyping of cohort studies will generate data needed to spur new discoveries and methods (Vineis 2017; Vrijheid 2014; Li et al. 2017; Barouki et al. 2018; Carvaillo et al. 2019).

3.4 Considerations in Measuring Exposure and Biological Response

We have learned several lessons from environmental epidemiology about associations between exposure and disease. Investigators have recognized the importance of accuracy and precision while measuring exposure. Accurate exposure assessment is essential to detect and quantify a dose–response relationship. Inaccuracy can lead to mis-measurement of a continuous exposure measure or can lead to misclassification of a dichotomous exposure status, which can severely bias results toward the null. Using biomarkers of exposure has several advantages: 1. Detection of the biomarker proves absorption of the compound, 2. It accounts for bioavailability of the compound, and 3. It integrates measures over all routes of exposure. However, it remains hard to tell where in the environment the compound came from, positing the need to compare internal dose data with data collected from external monitors and measurements. Further, since biomarker collection is expensive and relies on access to biological matrix availability, we can also validate other less expensive measurement methods by validation against biomarkers measured in a subset of the population. Epidemiological studies that provide causal interpretation of observations have good study designs. These study designs account for all variables that can confound relationships between exposure and response, and provide the means to uncover temporal relationships.

4 An International Perspective

Chris Wild's article (Wild 2005) describing the exposome concept raised a huge interest in the scientific community, which did not translate immediately into identified projects in Europe until the European commission launched research calls on the exposome within the seventh framework (FP7). In 2012 and 2013, three projects were launched, HELIX, Exposomics, and then HEALS. The concept was not to develop facilities, but rather to form integrated projects that would encompass the complexity of the exposome. Each project had its own perspective. HELIX, for example, focused on the pregnancy exposome by studying several EU birth cohorts (Maitre et al. 2018), Exposomics focused on the short and long-term effects of exposure to water and air pollutants (Turner et al. 2018), and HEAL focused on modeling and multidisciplinarity to develop a new "exposome" cohort (Steckling et al. 2018). More recently, the

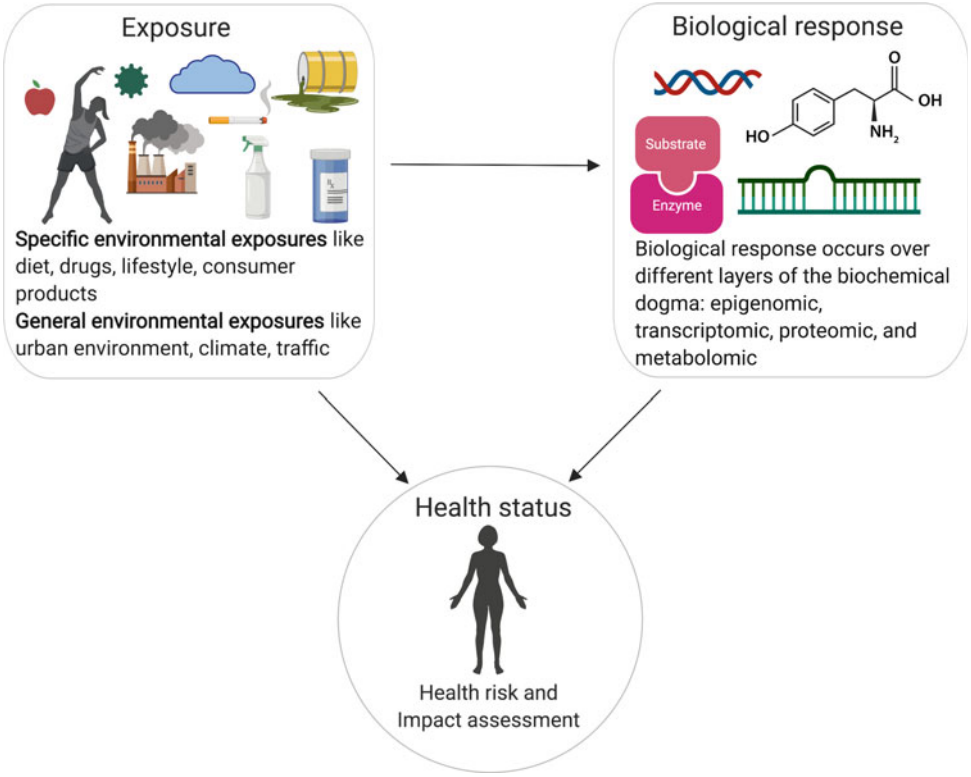

Fig. 1 The exposome concept Environmental exposures can derive from individual factors (like diet) and from general sources (like air pollution). Exposures that affect health leave a biological fingerprint that can be measured through changes in biological response in different biochemical layers. Integrating measures of external exposure and internal biological response create the exposomic framework to assess health status through risk and impact assessment. (Created with BioRender)

European Commission launched a new call within the H2020 framework, which will support 4–5 projects with a clear focus on the development of an exposome toolbox that should be coordinated by a cluster gathering of those projects. It is fair to say that several other projects within the EU are inspired by or address one of the exposures that constitute the exposome (Karjalainen et al. 2017). As an example, the EU biomonitoring program, HBM4EU, focuses on chemical exposures, while the project Lifepath addresses primarily socioeconomic aspects. There are other projects addressing urban exposures or the eco-exposome. While all these projects do not focus per se on technology developments, they do allow significant technological progress, most notably in analytical methodologies, sensor technology, biostatistics, and bioinformatics. Clearly, the upcoming exposome toolbox cluster will highlight and further develop these methodologies with the aim to support public health and regulatory decisions as well as informed individual prevention.

5 Environmental Chemistry and the Exposome

Chemicals released into the environment usually undergo transformations under different environmental conditions to produce intermediate chemicals. Several tools have been developed (Ruttkies 2016; Djoumbou-Feunang et al. 2019) which can help predict and identify unknown chemical signals measured in human and environmental samples. Efforts are underway to use high-resolution mass spectrometers to characterize all chemicals present in an environmental sample. Methods have been developed to identify "known unknown" chemicals using spectral fragmentation patterns that can help deduce chemical structure and identity (Schymanski et al. 2015; Gago-Ferrero et al. 2015).

In an epidemiological setting, Liang and colleagues used high-resolution metabolomics to characterize plasma and saliva samples from participants of a traffic-related air pollution exposure study. They measured a number of traffic-related air pollutants using external monitors and measured the association between exposure and metabolic profiles of the participants. Chemical features of interest that were significantly associated with exposure belonged to metabolic pathways related to inflammation and oxidative stress, including leukotriene and vitamin E metabolism (Liang et al. 2018).

6 The Exposome and Toxicology

More than 85,000 chemicals are registered with the EPA for manufacture, import, and use in commercial products. Approximately, 112,000 chemicals and compounds are registered with the US Food and Drug Administration as drugs or food additives (Niedzwiecki et al. 2019).

A majority of these chemicals have little information on their health effects at low concentrations and their influence as complex mixtures seen in real-world scenarios. This poses a significant challenge that requires expertise across several disciplines. Toxicologists have been systematically working through this list of chemicals that contribute to the chemical exposome. High-throughput screening assays have gained popularity for their efficiency and the high resolution of data they produce. They both conserve time and provide valuable insight for researchers toward the affected organ system or pathway that may be perturbed due to an exposure. The National Toxicology Program in the US has been leading a shift in current toxicological research, moving away from in vivo testing and incorporating high-throughput in vitro assays, model organisms, and computational models to study the adverse effects of exposure to chemical mixtures (Council 2007). Some of these methods are discussed below.

Structure–activity relationship (SAR). This method uses physical and chemical characteristics to predict toxicity based on the similar-property principle, i.e., similar structure = similar biological activity (Tong et al. 2003). These methods can be quantitative (mathematical modeling) or qualitative (recognize substructures that afford toxic properties). They have found utility in predicting toxicokinetics, half-lives, and the ability of chemicals to cross the blood brain barrier.

In vitro testing. Human cell lines and animal cell lines transfected to express human genes can be used to create assays to measure molecular changes due to different exposures. Modifying assay parameters and changing culture conditions can alter the context of exposures to answer specific biological questions. As an example, in vitro cell lines have been used to study the effect of exposure to mixtures on receptor ligand binding and activation. A group of researchers found that at low concentrations, a combination of two known pregnane X receptor (PXR) ligands resulted in a synergistic effect on activation of the receptor, which was not observed with each chemical alone. The researchers suggested that the two ligands together form a "supermolecular ligand" within the ligand-binding pocket of the nuclear receptor (Delfosse 2015). Findings such as these support the exposome concept in toxicological studies.

Cell-based in vitro assays can be used for high-throughput screens, which offer an economical way to screen a large number of chemicals in a short period. These screens are widely accepted in the pharmaceutical industry to predict therapeutic action, pharmacokinetics, interactions with enzymes, biotransformation, metabolic products, and have been used to rapidly detect interactions of drugs with genetic polymorphisms. Further, all methods described to measure biological response (Sect. 3.3.) can be applied on a cellular level to ascertain changes in gene expression, protein expression, metabolism, and epigenetic modifications due to an exposure.

Model organisms. While cell-based assays serve as excellent screening tools, single cells don't represent complex tissue interactions of a whole organism. To this end, model organisms like *Caenorhabditis elegans* (worms) and *Danio rerio* (zebrafish) have been gaining popularity as toxicological models. The short generation times of *C. elegans* make them excellent models to study aging and life course specific changes in response to exposure. Several molecular pathways have been conserved across evolution-making discoveries and observations in these models relevant for the human context. In a metabolomic study, Jones and colleagues described changes in metabolism in *C. elegans* as a result of exposure to a mixture of the heavy metal nickel and the pesticide chlorpyrifos. The authors noted changes in metabolism of the branched-chain amino acids and tricarboxylic acid cycle intermediates. They also found changes in reproduction (brood size) due to exposure to this mixture of toxicants (Jones et al. 2012).

7 Conclusion and Future Directions

Understanding the relationship between the totality of environmental exposures and health poses many challenges. Many exposures are largely involuntary and dynamic, and not all environmental exposures have been fully characterized. Studying the exposome thus relies on cutting-edge technologies that can detect and identify chemicals we are exposed to, moving beyond a targeted list of known chemicals of interest. Analysis and interpretation of this data requires various data analytical techniques: dimension reduction techniques, data integration, network analysis, and longitudinal analysis to name a few. Apart from novel data analytical applications, the field will also need to think about confounders and effect modifiers when measuring associations between exposure and disease. For example, how should social class or socioeconomic status be treated in a model—as a confounder, effect modifier, or a determinant of exposure? Uncovering the exposome will need input from scientists working in the fields of environmental chemistry, toxicology, exposure science, epidemiology, molecular biology, analytic chemistry, bioinformatics, and engineering. Thus, a multifaceted problem will be best tackled with multidisciplinary research teams.

Acknowledgements National Institutes of Health ES023839 and ES030163, Inserm, and University of Paris Descartes-USPC.

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