REVIEW

Advances in understanding the effects of *in utero* exposure to chemicals [version 1; peer review: 2 approved]

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Abstract

The uterine environment in which a foetus develops is critical to infant, child, and adult health. Adverse intra-uterine environments have been linked to increased risk for neurobehavioral disorders and metabolic and cardiovascular disease. Rapid cell division, tissue growth, differentiation, and organization of major organs are all features rendering the developing foetus sensitive to insult from exogenous chemicals. Therefore, interest in measurement of developmental exposure to environmental chemicals during critical periods of foetal development has grown. However, determining the consequences of developmental exposure to toxic chemicals presents epidemiologists, toxicologists, and regulatory health authorities with numerous important challenges. Improvements in analytical methods have led to greater sensitivity and thus detection of chemical residues at far lower concentrations, yet the biological relevance of the documented exposure is often unknown and difficult to determine. Although the benefit of quantifying exposure during critical windows of development is well recognized, access to appropriate biological fluids at relevant periods of development continues to pose a challenge. Moreover, knowledge gaps in the toxicological data together with lack of mechanistic insight make interpretation difficult and challenge confidence in conclusions of the human health consequences. Herein, a brief overview of several important issues central to understanding the consequences of developmental exposure to environmental toxicants is considered.

Keywords

Environmental contaminants, toxicants, exposure, development, foetus

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Introduction

The demand for new products is never-ending and as a result new chemicals are constantly being discovered and introduced into commerce. Therefore, to protect human health from potential harm, all chemicals must be evaluated for potential health risk. Demand for new products must be balanced with the need for confidence in both the process of hazard identification and conclusions derived from health risk assessment. To meet this objective, regulatory health authorities rely upon constantly updated standardized and validated batteries of tests to identify and characterize hazards followed by rigorous assessment of potential risks to human health^{1,2}. A central component in the assessment of potential health consequences arising from chemical exposure is quantification of target chemicals or their metabolites in body fluids or tissues. However, there are many challenges in quantifying human chemical exposure and estimating potential risk to human health, particularly when considering exposures in pregnant women and consequences for the developing foetus.

It is estimated that between 25,000 and 85,000 chemicals are manufactured and sold commercially around the world, and the number is projected to continue to increase well into 2050³. Production of lipophilic (fat-loving) compounds that resist degradation in the environment and bioaccumulate in biological systems, biomagnify with each step in the food chain, and with documented toxic effects have been subject to regulatory decisions restricting their use or banning their production. New chemicals entering commerce in recent years tend to be readily metabolized with short half-lives (time required for half of the chemical to be metabolized and eliminated from the body). Although this has been a positive step, some of these chemicals are biologically active and capable of inducing adverse health effects in experimental animals and thus potential risks to human health are vigorously explored. Additional exposures of concern include nanomaterials and chemicals produced through the use of e-cigarettes and vaping; however, evidence of developmental exposure is sparse. In addition to commercial chemicals and their by-products, chemicals that occur naturally in the environment, such as metals (for example, lead, mercury, nickel, copper, and arsenic), poisons and toxins (for example, cyanide, aflatoxin, and bee, spider, and snake venoms), and food components (for example, plant pesticides and phytoestrogens), cannot be overlooked as exposure can be widespread or the chemicals can be toxic to biological systems (for example, neurotoxic effects of lead and mercury). Although quantification of exposure across the lifespan is important, assessing developmental exposure (exposures to the developing embryo and foetus) has increased in importance coincident with greater appreciation that *in utero* (in the womb) exposure is a particularly vulnerable period of rapid development (a period of rapid cell multiplication and tissue organization) that, if perturbed, will have lifelong consequences for health⁴⁻⁷. The concept of developmental origins of health and disease (DOHaD) postulates that developmental exposure to environmental contaminants is linked to adverse health effects, such as obesity and cardiovascular disease, in children and adults⁸.

Therefore, quantifying development exposure and understanding the health consequences of exposure are essential for health protection.

Challenges and emerging issues

Several challenges faced by toxicologists and regulatory health authorities in determining potential health consequences arising from unintended *in utero* exposure to environmental contaminants include (a) quantifying exposure, including target tissue exposure where possible; (b) determining the critical window of exposure to sample for the adverse outcome of interest; (c) accessing the most relevant tissue or body fluid; and (d) documenting evidence of adverse outcome. Though important, determining critical windows of development and accessing adverse health effects are beyond the scope of this review. Rather, attention will focus on issues related to quantifying chemical exposure.

Methods of sample collection, handling, processing, conditions of storage, sources of contamination, analytical methods employed, and selection of the appropriate analyte to measure are also important. Insight into the mode or mechanism of action, potential for interaction with other chemicals, and data interpretation (statistical analyses, temporality, and confounding from other exposures) are all important factors to consider as well. Frequently, many of the above issues are not known or the quality of the information available is weak, thus precluding confidence in the conclusions reached. Finally, evidence of exposure to a chemical cannot be considered evidence of an adverse health effect now or in the future⁹ without knowledge of the experimental findings from animal and tissue culture studies, epidemiology, and mechanistic insight. Measurement of human exposure is also important in order to monitor changes in population residue concentrations over time. Trends in residue concentrations can alert health authorities to rising exposure levels requiring intervention and to the impact of past regulatory decisions.

Chemical exposure

Chemicals enter the environment through release during the manufacturing process, unintentional consequences such as spills, leaching from finished products (for example, stain guards and plasticizers) or industrial combustion processes (for example, dioxins and polychlorinated biphenyls), and intentional application to outdoor environments for agricultural purposes (for example, pesticides). Chemicals enter the human body through direct contact with skin, ingestion of food or water, and breathing of contaminated air. Chemical residues have been widely documented in human tissues of children and adults, including pregnant women¹⁰⁻¹⁷. Although pre-conception exposure has been documented in men and women attending assisted reproductive clinics¹⁸⁻²⁰ and in pregnant women^{13,16,21,22}, less is known about exposure of the developing foetus.

Developmental exposure to chemical contaminants has frequently been documented indirectly via measurement of target chemicals in maternal blood and urine over the course of pregnancy or umbilical cord blood, placenta²³, and amniotic

fluid^{24–29}. Although these measures provide evidence of potential exposure of the developing foetus at some point during *in utero* development, the developmental stage and the concentrations reaching the foetus cannot be defined from these studies. This is critical when trying to establish the relationship between an adverse outcome whose development may occur many months ahead of the target chemical measurement. Development of body tissues and organs occurs at precisely defined times in foetal development³⁰; thus, linking exposure with an adverse effect on organ development requires evidence of exposure prior to and during to the critical window of development. The temporal association between sample collection and mechanisms regulating development of the critical endpoint in question is often not addressed or is difficult to link. Developmental stage and concentration reaching the developing foetus are critical elements central to determining the relationship between chemical exposure and adverse health outcome. For example, concentrations of persistent organic pollutants (POPs) differ across different developmental stages of foetal development, illustrating the importance of timing sample collection to critical window of development for the assessment of adverse health effects³¹. Thus, exposure measurements and adverse outcome that are temporally disconnected make it difficult to have confidence that the target chemical has a causal role in the adverse outcome under examination. This is a particular concern for chemicals that are rapidly metabolized and eliminated from the body. Maternal habits change around the time of delivery and thus exposures quantified in delivery samples may not accurately reflect developmental exposure. For example, expectant mothers may decrease or change their eating habits during pregnancy, especially around the time of delivery. For example, phthalates, used to enhance the flexibility of plastics, are found in medical devices such as intravenous tubing and bags and this may account for higher exposures in pregnant women than the general population³². Furthermore, results from residue analysis of spot blood or urine samples may not accurately reflect contaminant exposures at different developmental time points in pregnancy. Moreover, the potential that the exposure is linked to recent activities or medical interventions and not to the adverse outcome under study has led some to consider reverse causation^{33–36} to explain associations between residue levels and the health issue of concern.

To address this issue, direct exposure has been attempted by using amniotic fluid (the fluid surrounding the developing foetus) samples to measure contaminant exposure^{24–28,37–41}. Amniotic fluid is collected at between 15 and 18 weeks of development for genetic testing in pregnant women of advanced maternal age. Accessing foetal tissues and related fluids during different developmental stages is generally not practical. Therefore, understanding of tissue distribution, metabolism, and excretion from animal models is essential to inform pharmacokinetic and pharmacodynamic modeling of foetal exposure.

Human interactions with their environment, whether *in utero* or after birth, involve exposure to numerous chemicals. The vast array of chemicals to which we are exposed is now known as the exposome^{42,43}. Characterization of the exposome faces

challenges in the form of knowing what to measure and the technical capacity to measure the target chemicals in complex mixtures. Herein, advances in the methods employed to quantify exposure together with the factors that contribute to the challenges facing toxicologists, epidemiologists, and regulatory health authorities are explored.

Technological advances

Numerous technological advances in analytical chemistry have accrued over the last couple of decades, enhancing the ability to detect vanishingly small concentrations of test chemicals with greater precision. Although metals are quantified by graphite furnace atomic absorption spectrometry or inductively coupled plasma mass spectrometry (IPCMS), many commercial chemicals have been measured by gas chromatography (GC), a technique that has yielded to GC coupled MS (GC:MS) and liquid chromatography MS or liquid chromatography tandem MS (LC:MS or LC:MS-MS, respectively). Advances in methods of analysis have enabled ever lower limits of quantification (LOQs), making detection of smaller concentrations of target chemical possible^{44,45}. Although lower LOQ increases the number of subjects with quantifiable concentrations, the trend over time is toward declining levels¹⁵. Moreover, the presence of lower residue levels of POPs in recent immigrants to the US compared with the remainder of the population supports the suggestion that recent exposure to many POPs is also declining⁴⁶.

While technological advances have lowered detection limits for many chemicals, the concentrations are frequently skewed toward the limit of assay detection. It is not uncommon to find a large proportion of samples with concentrations of target chemical below the LOQ⁴⁴. A problem that arises for some chemicals is how to handle samples with values below the LOQ. In the past, values below the LOQ have been assigned the $\frac{1}{2} \times \text{LOQ}$ ^{47,48} or $\text{LOQ}/\sqrt{2}$ ^{46,49}. However, assigning a value to a large number of samples with values below the LOQ may not provide an accurate estimate of the true population mean concentration. An alternative approach that has received less attention is to use the analytical machine-generated concentration. Although this latter approach may offer a better approximation of the true mean exposure concentration for the study population, the literature is silent on its validity.

Quantifying developmental exposure

Commercial chemicals are used in a wide variety of products, including personal care products, construction materials, agricultural products, thermal paper receipts, paints, carpets, computers, food containers, and medical devices such as medication capsules and dental sealants. Consequently, commercial chemicals have the capacity to enter the environment through accidental release (polychlorinated biphenyls and dioxins), direct application to the land (for example, pesticides), volatilization (xylenes, formaldehyde, and ethylene oxide), or leaching from the finished products (for example, perfluorinated compounds, parabens, phthalates, and phenolic compounds) into different media, including food products, medical devices, building materials, consumer products, cosmetics, automobiles, computers, and dental products. Care must be taken to prevent contamination

during sample collection, handling, and processing. The procedures taken to ensure sample integrity and prevent or minimize potential contamination are essential and should be described in published reports. Ideally, the use of field and collection blanks is important. For example, lead is a ubiquitous environmental contaminant present in house dust, on the skin, and in sample collection and storage devices, including laboratory glassware. Thus, precleaned glassware, use of lead-free devices, and cleaning of the skin before sample collection are essential. Phthalates are ubiquitous chemical contaminants in the environment and are present in sampling and laboratory equipment. Therefore, to mitigate potential contamination issues, exposure is measured by quantifying their individual metabolites in blood or urine samples. Similarly, bisphenol A (BPA) has wide commercial application and thus exposure is thought to be unavoidable. Therefore, care must be taken to avoid sample contamination during collection, processing, and analysis^{50,51}.

While sample contamination, controls for collection, and lab contamination can contribute to misleading results, the sensitivity and specificity of the determination are affected by the method of analysis. For example, early studies designed to quantify developmental exposure to BPA relied upon an enzyme-linked immunosorbent assay (ELISA) method for determination of BPA residue concentrations⁵². Although ELISA uses antibodies to bind with the target chemical (BPA) and thus is sensitive, the potential for cross-reactivity of the antibody with antigenically similar or structurally related chemicals (BPA-glucuronide) affects the specificity of these assays, making them less suitable for quantification of human exposure. Thus, novel methods that maximize sensitivity and specificity for the measurement of BPA and its metabolites have been introduced^{53,54}.

Data analysis and interpretation

Responsible governance requires that chemicals be tested for potential toxicity with a goal to be thorough in our assessments. Regulatory health authorities can ill afford either to be too quick to judge a chemical to be without risk to human health or to determine a potential health risk to be present in the absence of convincing evidence. Measurement of human exposure is critical to the risk assessment process and is used together with data from hazard characterization to estimate potential risk and inform decision-making processes.

Measurement of chemical residue concentrations in human tissue samples can be concerning but, on its own, does not provide evidence of an adverse health consequence. When target chemicals are quantifiable, residue concentrations are often determined by health regulatory authorities to be too many orders of magnitude below the concentrations demonstrated through tissue culture (*in vitro*) screening methods and animal studies to pose a health risk. Regardless, reports of human exposure are often linked in the lay press with the perception of an adverse health effect. For example, residue levels may be

too low to bind with and activate receptor signaling pathways as has been suggested for BPA in adult exposures⁵⁵. Residue concentrations in human tissues during development as well as different life stages together with evidence from animal studies and *in vitro* screening experiments are critical to the risk assessment process.

In ascertaining the potential health consequences of chemical exposure, it is necessary to consider exposure, including target tissue exposure if possible, together with additional factors such as the no observable adverse effect level from experimental animal studies. In general, many chemically induced changes follow typical monotonic dose-response curves; however, chemicals that affect more than one signaling pathway or act through multiple mechanisms show non-monotonic dose-response curves that challenge interpretation and the risk assessment process^{56,57}. Also challenging is deciphering the potential for transgenerational effects arising from developmental exposures⁵⁸. Results from *in vitro* screening assays are important to consider in the context of defining the relevant animal experiments, whereas mechanistic studies are important to define the mode and mechanism of action of the chemical. Finally, where available, the results of epidemiological studies provide important insights into potential human health outcomes arising from exposure. Similarly, mechanistic studies are valuable in defining the relevance of experimental animal findings for human health. However, it is the total weight of evidence of all of the available literature, including exposure data, that is necessary to inform decisions concerning potential associations between exposure and an adverse health outcome.

Summary and conclusions

Quantification of developmental exposure to commercial chemicals is important to understand the consequences of developmental exposure to environmental toxicants. Advances in analytical chemistry have enabled the detection of ever lower concentrations of commercial chemicals; however, establishing a link between developmental exposure and adverse health effects requires careful attention to the sample collection to prevent contamination, collection during critical stages of development relevant to the outcome of interest, and insight from other disciplines such as animal toxicology and epidemiology. Moreover, moving forward, identification of critical windows of development and collection of samples from stages of development relevant to the adverse of outcome of interest will support efforts to define causal relationships between exposure and adverse health effects that may not be detectable until later in life. Finally, biomonitoring chemical exposures is important to elucidate exposure trends to inform regulatory actions, priority setting for further testing, and evaluating the impact of prior regulatory decisions.

Abbreviations

BPA, bisphenol A; ELISA, enzyme-linked immunosorbent assay; LOQ, limit of quantification; MS, mass spectroscopy; POP, persistent organic pollutant

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