ANNUAL REVIEWS

Annual Review of Pharmacology and Toxicology

Understanding the Chemical Exposome During Fetal Development and Early Childhood: A Review

Magdaléna Krausová,[1] Dominik Braun,[1] Tina Buerki-Thurnherr,[2] Claudia Gundacker,[3,4] Eva Schernhammer,[4,5,6] Lukas Wisgrill,[4,7] and Benedikt Warth[1,4]

[1]Department of Food Chemistry and Toxicology, Faculty of Chemistry, University of Vienna, Vienna, Austria; email: magdalena.krausova@univie.ac.at, dominik.braun@univie.ac.at, benedikt.warth@univie.ac.at

[2]Swiss Federal Laboratories for Materials Science and Technology, Laboratory for Particles Biology Interactions, St. Gallen, Switzerland; email: tina.buerki@empa.ch

[3]Center for Pathobiochemistry and Genetics, Institute of Medical Genetics, Medical University of Vienna, Vienna, Austria; email: claudia.gundacker@meduniwien.ac.at

[4]Exposome Austria, Research Infrastructure and National EIRENE Hub, Austria

[5]Center for Public Health, Department of Epidemiology, Medical University of Vienna, Vienna, Austria; email: eva.schernhammer@meduniwien.ac.at

[6]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts, USA

[7]Division of Neonatology, Pediatric Intensive Care and Neuropediatrics, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna, Austria; email: lukas.wisgrill@meduniwien.ac.at

Annu. Rev. Pharmacol. Toxicol. 2023. 63:517–40

First published as a Review in Advance on October 6, 2022

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

https://doi.org/10.1146/annurev-pharmtox-051922-113350

Keywords

chemical exposome, human biomonitoring, xenobiotics, natural contaminants, prenatal exposure, placenta

Abstract

Early human life is considered a critical window of susceptibility to external exposures. Infants are exposed to a multitude of environmental factors, collectively referred to as the exposome. The chemical exposome can be summarized as the sum of all xenobiotics that humans are exposed to throughout a lifetime. We review different exposure classes and routes that impact fetal and infant metabolism and the potential toxicological role of mixture effects. We also discuss the progress in human biomonitoring and present possible

models for studying maternal–fetal transfer. Data gaps on prenatal and infant exposure to xenobiotic mixtures are identified and include natural biotoxins, in addition to commonly reported synthetic toxicants, to obtain a more holistic assessment of the chemical exposome. We highlight the lack of large-scale studies covering a broad range of xenobiotics. Several recommendations to advance our understanding of the early-life chemical exposome and the subsequent impact on health outcomes are proposed.

INTRODUCTION

On a daily basis, humans are exposed to a vast number of foreign molecules, commonly referred to as xenobiotics, that originate from consumed food and the surrounding environment. Apart from the exposure to xenobiotics, there is also continuous exposure to other factors (e.g., stress, lifestyle, diet) that combined are referred to as the exposome. The potential health effects of all the chemical exposures, either positive or negative, depend on exposure timing, duration, and magnitude, but also on the interplay between these complex chemicals. A critical window of susceptibility toward the toxic effects of chemical exposure is during the development of an organism, i.e., embryo-fetal stages and early childhood until the age of two. The susceptibility to xenobiotic exposure is also affected by genetic background, which varies greatly among individuals and populations. Compared to an adult with adaptive immunity and a fully developed set of enzymes for xenobiotic biotransformation processes, the immune system and metabolism during development are more sensitive (1). Knowledge about the exposure, effect, and coexposure of many xenobiotics in this sensitive subpopulation is limited; therefore, more research incorporating a holistic perspective is necessary.

In 2005, Wild (2) introduced a framework that includes the totality of (co-)exposures throughout life from conception onward: the exposome. This emerging paradigm was described as a complement to the genome, yet it is much more dynamic and changes constantly during the course of life. Subsequently, the exposome has been characterized as encompassing all external and internal factors that impact humans either directly or indirectly. These factors can be further divided into smaller subgroups (illustrated in **Figure 1**), including (*a*) physical and chemical factors such as radiation, particulate matter, drugs, food contaminants, and pesticides; (*b*) the psychosocial factors of stress, household income, parental care, cultural traditions, and education; (*c*) lifestyle factors including sleep and work patterns, diet, exercise, smoking, and oral contraceptives; (*d*) ecosystems and climate, such as green areas and population density; and (*e*) food ingested during early life, including infant formula, breast milk, and complementary baby food. These factors frequently overlap and are heavily associated with one another, thus necessitating combined investigation. The concept of the exposome as the sum of all exposures has become popular as the importance of a more comprehensive assessment of coexposures and the combined toxicological effects thereof become increasingly evident. Investigating the exposome is crucial for progressing to more personalized prevention and medication strategies and to identify environmental and nutritional risk factors associated with specific exposures (3, 4).

Immunity and metabolism during early life are unique compared to adults, and any adverse exposure may be of concern during the critical window of development (5). The gut microbiome plays a pivotal role in immunity and in detoxifying potentially harmful chemicals. For many years, the in utero microbiome was thought to be sterile, and hence has been referred to as the "sterile womb paradigm" (6). According to this theory, the fetus and placenta are sterile, and the gut microbiome is acquired after birth. In more recent years, research has shown evidence of microbial

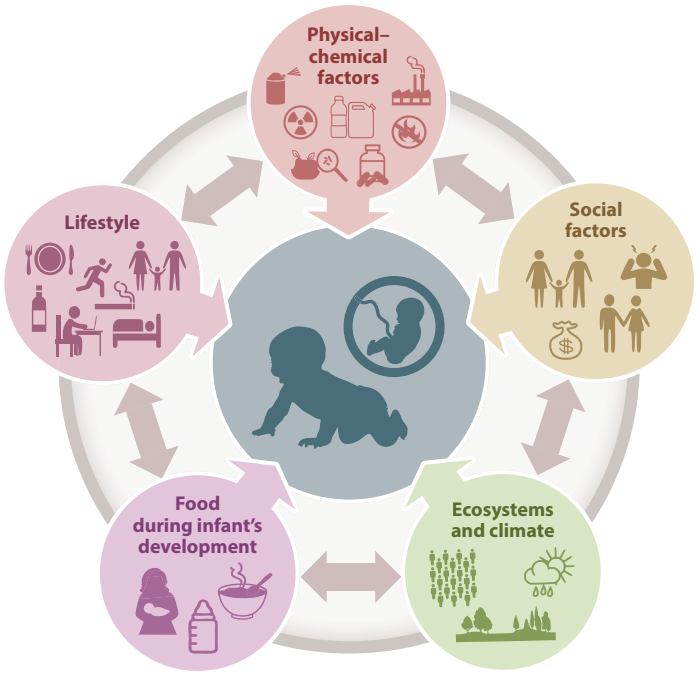

Figure 1

Early-life impact of combinatory exposures. The early-life exposome covers all exposures starting from conception and can be divided into different categories that influence each other: Lifestyle, including diet, smoking, physical activity, working habits, sleep, alcohol intake, and parental care; social factors, including stress, household income, social interactions, culture traditions, healthcare access, and parental care; ecosystems and climate, including population density, green space, residence region, and physical climate; and physical-chemical factors, including drugs, electromagnetic fields, radiation, air pollution, pesticides, molds, drinking water contaminants, plasticizers, flame retardants, food contaminants, biotoxins, and persistent organic pollutants. Another factor, specific to infants, is food during early life, including breast milk, infant food, and formula. All the exposures are interconnected and have a combined effect on the infant and fetus (directly or indirectly) that influences the exposome during gestation or after birth.

colonization during the fetal stages. This is referred to as the "in utero colonization hypothesis" (7).

We aim to review existing knowledge on toxic exposures during fetal and early-life development in a comprehensive manner, to cross traditional discipline borders, and to consider the developmental origins of health and disease hypothesis. This theory is based on the concept that exposure to environmental factors during prenatal and neonatal stages can determine the development of diseases in adulthood. We expand on different classes of toxins included in the chemical exposome and how fetuses and infants are exposed. Moreover, we focus on metabolizing capacities during early life and on potential mixture effects as a result of coexposure. Furthermore, we present several available and emerging methods to study developmental toxicity in fetuses and, in addition, analytical approaches to quantify xenobiotics in biological samples. We emphasize the shortcomings of the current state of early-life biomonitoring research and propose several recommendations for future improvements via technological advances in the field of mass spectrometry (MS).

ROUTES OF EXPOSURE DURING EARLY LIFE

The routes of exposure to external toxicants include prenatal placental transfer and postnatal oral, parenteral, inhalation, and dermal or mucocutaneous exposure. In addition, for in utero exposure, it is critical to also consider indirect developmental toxicity of contaminants even in the absence of placental crossing (8). Chemicals and particles can accumulate in the placental tissue and interfere with placental functions and the secretion of signaling mediators (e.g., vascular, inflammatory, and endocrine factors) essential to successful pregnancy and fetal health (9). Moreover, toxic metabolites could be formed and secreted to the fetal circulation.

Transfer Through the Placenta

During the prenatal stage, the placenta forms the interface between the mother and the unborn child and performs many pivotal functions, including protection against harmful compounds and pathogens. However, many xenobiotics can pass the placental barrier through separating layers (syncytiotrophoblast, cytotrophoblast, and the fetal endothelial cells) and reach the fetal circulation. For chemicals, placental transfer is directed by molecular weight, pKa, lipid solubility, and protein binding. Small lipophilic and nonionic compounds with molecular weights below 500 Da can generally pass the placenta via passive diffusion following the concentration gradient, whereas large or hydrophilic compounds require specialized carrier proteins for their transfer (9). Facilitated diffusion is not directly dependent on adenosine triphosphate (ATP) but is restricted by the abundance of carrier proteins. High-molecular-weight compounds and ionic chemicals require active transporter-mediated transfer or endocytosis pathways.

Here, the best-known transporter class is the solute carrier family (SLC) that encompasses (*a*) organic anion transporters (OATs); (*b*) organic anion transporting polypeptides; (*c*) organic cation transporters; (*d*) multidrug and toxin extruding protein 1; and (*e*) nucleoside transporters (10). OAT4 transporters are present at the apical membrane of the syncytiotrophoblast and are considered the main transporters responsible for bidirectional transport of xenobiotics and endogenous compounds (11).

Xenobiotics can be transported against a concentration gradient via ATP-hydrolyzing transporters. In humans, the main superfamily of active transporters is the ATP-binding cassette (ABC) that encompasses multiple transporters. The most important include P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). P-gp is encoded by the *ABCB1* gene and is expressed on the apical side of the syncytiotrophoblast membrane. The importance of P-gp in protecting the fetus has been reported (12). Similarly, BCRP transporter is also expressed on the apical side of the syncytiotrophoblast. Over the gestational period, P-gp and BCRP expression levels are altered. P-gp levels decrease toward the end of gestation; however, the trend is still unclear for BCRP (13, 14). The placental transfer pathways are illustrated in **Figure 2**.

Many synthetic chemicals have been reported to cross the placenta, e.g., endocrine-disrupting chemicals (EDCs) such as phthalates, polybrominated diphenyl ethers (PBDEs), pesticides, polycyclic aromatic hydrocarbons (PAHs), and perfluorinated substances (PFAS) that were measured in maternal and cord blood (15–18). In human placental perfusion models (19–21) and animal models (22), some mycotoxins have also been shown to cross the placenta; however, more data on maternal and cord blood levels from biomonitoring studies are needed. Conversely, research on phytotoxins or aquatic toxins and their potential to cross the placenta is currently lacking.

For nanoparticles, placental transport depends on their physicochemical properties (e.g., size, surface charge, chemical composition, or surface modifications) (23). Nanoparticle transfer mechanisms across the placenta are not yet exploited extensively, but there is evidence for both passive

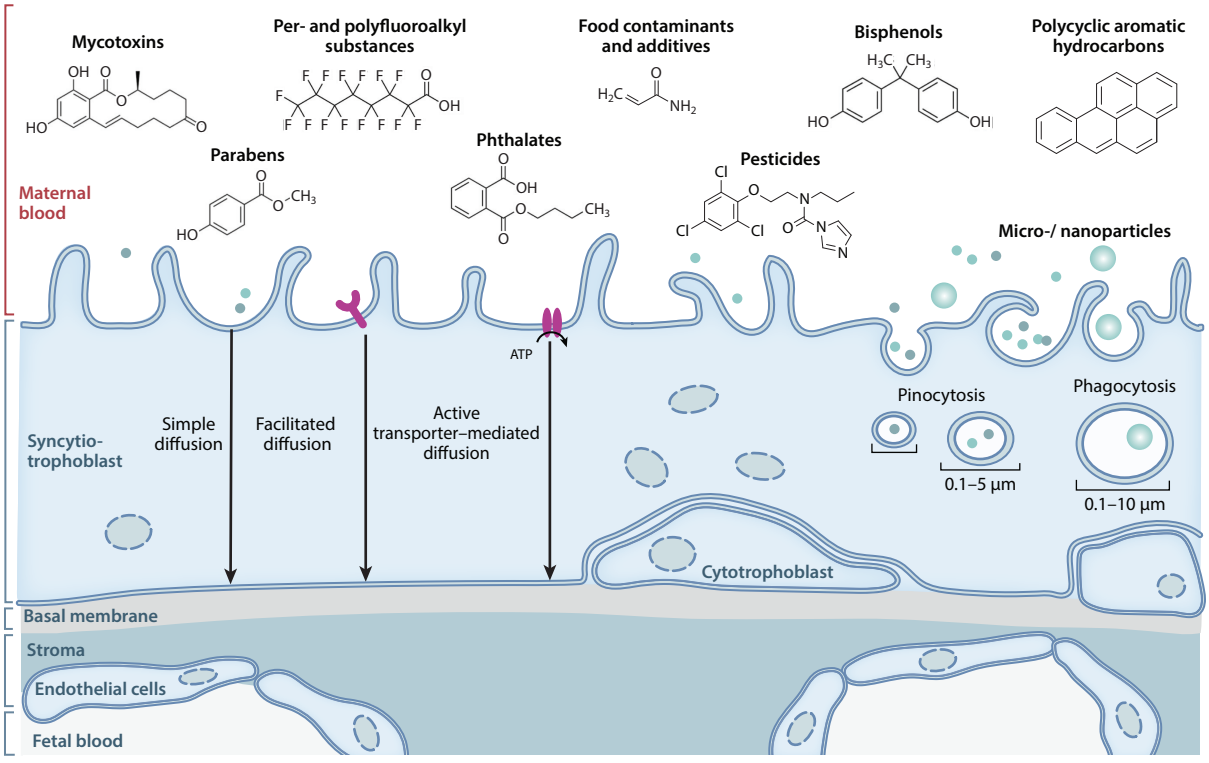

Figure 2

The fetus can be exposed to the chemical exposome comprising synthetic and natural toxicants, other xenobiotics, and micro-/nanoparticles through the placental barrier (consisting of syncytiotrophoblast, cytotrophoblast, and endothelial cells). The pathways through the placenta include simple diffusion along the concentration gradient, transporter-facilitated diffusion, active transporter–mediated diffusion, and endocytosis composed of pinocytosis for small particles (0.1–5 μm) and phagocytosis for bigger particles (0.1–10 μm). The placental tissue can biotransform some of the named molecules, but more research is needed to elucidate metabolism and exposure at the omic scale.

and active endocytic transport pathways (24). An important consideration in the context of the chemical exposome is the fact that nanoparticles can bind environmental contaminants and serve as shuttles to facilitate their transport (the Trojan horse effect), leading to coexposure and potential mixture effects via alterations in uptake, translocation, and toxicity (25, 26). This has been observed for a broad variety of combinations of nanoparticles and chemicals and most often has resulted in enhanced toxicity of the mixture compared to single-substance exposure (26).

Lactational Transfer via Breast Milk

Recent research has highlighted that ingesting breast milk provides neonates with a layer of protection against chemical exposure. Breast milk is important and beneficial for healthy development and is infants' best source of nutrients and bioactive compounds. In the case of mycotoxins, the overall exposure via breast milk is typically lower than if milk substitutes or complementary infant foods are consumed (27, 28). The transfer to breast milk depends on the chemical properties of a given xenobiotic. In general, chemicals transfer from maternal blood to breast milk via passive diffusion that corresponds to molecular lipophilicity and solubility (29). As an example, persistent organic pollutants (POPs) accumulate due to long half-lives and lipophilicity (30). Considering

infants' low body weight and size, the resultant body burden of POPs can be several times greater than the internal dose of the mother, which decreases with breastfeeding (31).

Besides chemicals, studies in pregnant rodents have shown that nanoparticles are also transported to breast milk. For instance, orally administered silver nanoparticles in lactating mice distributed to breast milk and subsequently to the brains of breastfed offspring (32).

Exposure via Infant Food, Infant Formula, and Drinking Water

Recommendations from the World Health Organization and the UN International Children's Fund are to exclusively breastfeed infants for the first six months of life, followed by the introduction of solid food and continued breastfeeding until the age of two. This is not the case for many children, and it is estimated that only 44% of infants worldwide are exclusively breastfed from birth to 6 months of age (33). Infants that are not exclusively breastfed receive infant formula and, later, infant food. Several studies have reported contamination of infant formula and food with natural toxins such as mycotoxins. This is particularly problematic in developing countries with a warm and humid climate. An example is sub-Saharan Africa where infants are frequently exposed to high levels of mycotoxins via infant food or formula (34). Mycotoxin contamination, however, is a worldwide problem, as mycotoxins are chemically stable and can withstand high temperatures. Studies have reported the presence of mycotoxins that can potentially pose a risk for infants, even when present in small quantities (35, 36).

Other environmental contaminants, including POPs, parabens, and perfluorinated compounds, have also been identified in infant food and formula. As these have long half-lives and can accumulate, the exposure can result in long-term effects (37–39).

Concerning exposure to nanoparticles, drinking water is a potential source relevant to pregnant women and infants. A recent study has shown that engineered nanoparticles are present only in small concentrations after leaving water treatment plants (40). Incidental contamination with nanoparticles or natural nanoparticles in drinking water is more concerning, particularly in economically less developed countries with a lack of clean water.

Exposure via Medical and Consumer Products

Medical devices such as feeding tubes, umbilical catheters, and endotracheal tubes are used widely in neonatal intensive care units (NICUs). Premature infants in NICUs can be exposed to contaminants from phthalates (via ingestion, inhalation, and dermal and intravenous routes) (41), in particular to diethylhexyl phthalate (DEHP), a class of plasticizer used in medical products. DEHP is metabolized to monoethylhexyl phthalate that is further metabolized to monoethylhydroxyhexyl phthalate (MEHHP) and monoethyloxohexyl phthalate. To a large extent, these are excreted via the urine (42). In a study analyzing these metabolites, Demirel et al. (43) reported high levels of phthalates during the first months of life of premature infants in NICUs, with MEHHP as the main metabolite. The level of MEHHP was even higher in extremely premature infants that were born with a body weight $<1{,}000$ g. High exposure to DEHP has been associated with increased blood pressure in infants (44).

In terms of exposure in premature infants, another important topic to consider are drugs and their interactions, so-called drug–exposome interactions (4). Premature infants often receive multiple pharmaceuticals simultaneously. To a large extent, these can sometimes include unlicensed or off-label drugs that have not been approved by the European Medicines Agency or the US Food and Drug Administration for neonatal use. It is estimated that more than 70% of infants in NICUs are exposed to drug–drug interactions (45, 46). These interactions are beyond the scope of this review but should also be addressed in the new framework of "pharmaco-exposomics" (4).

Coexposure to Chemical Mixtures

Considering the widespread presence of chemicals and contaminants in our environment and the many potential routes of uptake mentioned above, it is evident that the developing fetus and infants can be exposed to mixtures of chemicals and contaminants rather than single compounds. The chemical exposome is vast, and its definition and categorization are not straightforward. Here we intend to highlight the fact that natural and food processing contaminants, as well as anthropogenic nanoparticles, should also be incorporated in a comprehensive exposome-type evaluation, particularly of early-life (and to a lesser extent fetal) coexposure and mixture effects in addition to the priority pollutants typically covered in this context. To emphasize the need for this holistic assessment, we summarize different selected categories based on their source in **Table 1** (natural toxins contaminating food, contaminants formed during food processing, and synthetic chemicals released and accumulated in the environment that can contaminate food or

Table 1 Overview of selected natural and synthetic exposure classes from different sources[a]

Class or compound	Abbreviation(s)	Typical exposure sources	Adverse effects
Biotoxins			
Mycotoxins		Contaminated grains, nuts, dried fruit, spices	
Aflatoxins	AFs	*Aspergillus* spp.	Hepatotoxicity, carcinogenicity (Group 1, IARC) (126)
Fumonisins	FBs	*Fusarium* spp.	Carcinogenicity (Group 2B, IARC) (126), developmental toxicity
Trichothecenes	T-2, HT-2, DON, NIV	*Fusarium* spp.	Immunotoxicity, ribotoxicity (127)
Ochratoxins	OTA, OTB	*Aspergillus* spp.	Nephrotoxicity, carcinogenicity (Group 2B, IARC) (128)
Zearalenone	ZEN	*Fusarium* spp.	Estrogenicity, reprotoxicity (129)
Phytotoxins		Contaminated foods and herbal teas/medicines	
Aristolochic acids	AA	Herbal medicine (*Aristolochia* and *Asarum* genera)	Nephrotoxicity, carcinogenicity (Group 1, IARC) (130)
Pyrrolizidine alkaloids	PAs	Contaminated herbal tea, honey (Boraginaceae, Asteraceae, and Fabaceae families)	Preterm births, hepatotoxicity, pulmonary toxicity (131)
Tropane alkaloids	TAs	Nightshade (Solanaceae), coca (Erythroxylaceae genus)	Neurotoxicity (132)
Piperidine alkaloids	PAs	Hemlock (*Conium maculatum*), lupine (*Lupinus* spp.), and tobacco (*Nicotiana tabacum*)	Acute toxicosis, teratogenicity (133)
Indolizidine alkaloids	IAs	Locoweed (*Astragalus* and *Oxytropis* spp.)	Reprotoxicity (134)
Aquatic toxins		Contaminated seafood	
Microcystins	MCs	Blue-green algae	Hepatotoxicity, carcinogenicity, decreased fetal weight (135)
Ciguatoxins	CTXs	Dinoflagellates genus *Gambierdiscus* accumulated in reef fish and shellfish	Ciguatera poisoning (136)

(*Continued*)

Table 1 (*Continued*)

Class or compound	Abbreviation(s)	Typical exposure sources	Adverse effects
Food-processing contaminants			
Heterocyclic aromatic amines	HAAs	Cooking various meat and fish	Carcinogenicity (2B, IARC) (128)
Polycyclic aromatic hydrocarbons	PAHs	Smoking, drying, and grilling food	Carcinogenicity (1, 2A, 2B, 3, IARC), evidence for neurotoxicity (137)
Acrylamide	AA	Baked or fried carbohydrate-rich foods, coffee	Carcinogenicity (2A, IARC) (138), evidence for neurotoxicity (139) and developmental toxicity (140)
Furan		Thermally processed food, coffee	Carcinogenicity (2B, IARC) (141), evidence for hepatotoxicity (142)
Synthetic chemicals			
Dioxin-like polychlorinated biphenyls	dl-PCBs	Electrical insulators, insulating fluids	Endocrine disruption, developmental toxicity (143, 144)
Non-dioxin-like polychlorinated biphenyls	ndl-PCBs	Heat-transfer systems, cooling and insulating fluids	Neurotoxicity (145)
Organochlorines		Pesticides, insecticides	Neurotoxicity, carcinogenicity, developmental toxicity (146)
Organophosphates	OPs	Pesticides, insecticides	Neurotoxicity (147)
Polybrominated diphenyl ethers	PBDEs	Flame retardants	Endocrine disruption (148), neurotoxicity (149)
Per- and polyfluoroalkyl substances	PFAS	Surfactants	Endocrine disruption, developmental toxicity, diabetes, hepatotoxicity (150)
Phthalates		Plasticizers	Endocrine disruption (151), neurotoxicity (152)
Parabens		Preservatives in cosmetics	Endocrine disruption (153)
Bisphenols		Plasticizers	Endocrine disruption (154)
Persistent, mobile, and toxic substances	PMTs	Contaminated aquatic environment	
Melamine		Plastic dishware	Carcinogenicity (2B, IARC) (155)

[a]The table highlights the vast chemical space and toxicological impact of the chemical exposome: (*a*) biotoxins (mycotoxins, phytotoxins, phycotoxins); (*b*) contaminants formed during food processing; and (*c*) synthetic chemicals divided by class, their main sources, and possible adverse effects in infants and fetuses.

Abbreviation: IARC, International Agency for Research on Cancer.

can be released from consumer products). There has been extensive research on persistent and bio-accumulative chemicals (e.g., dioxins, PFAS, pesticides), grouped as synthetic chemicals, and their exposure in humans. Published background levels of several xenobiotics, including synthetic chemicals (pesticides; PFAS; PBDEs; PAHs; and persistent, mobile, and toxic substances), measured in breast milk are summarized in **Figure 3**. In addition, background levels of xenobiotics (phthalates, PAHs, PBDEs, and phenols) measured in infant urine or blood are shown in **Figure 4**. To have a representative example, the studies were selected based on cohort size (sample sizes below 50 participants were excluded) and geographical location (to include as many regions as possible). The summarized results in the figures are purely illustrative, as direct comparison of most of the studies was not possible due to differing analytical assays (different analytes studied, different quantification limits, data reporting not harmonized) and differences in the cohorts. For several xenobiotics, only a single study from one region is available, and the raw data

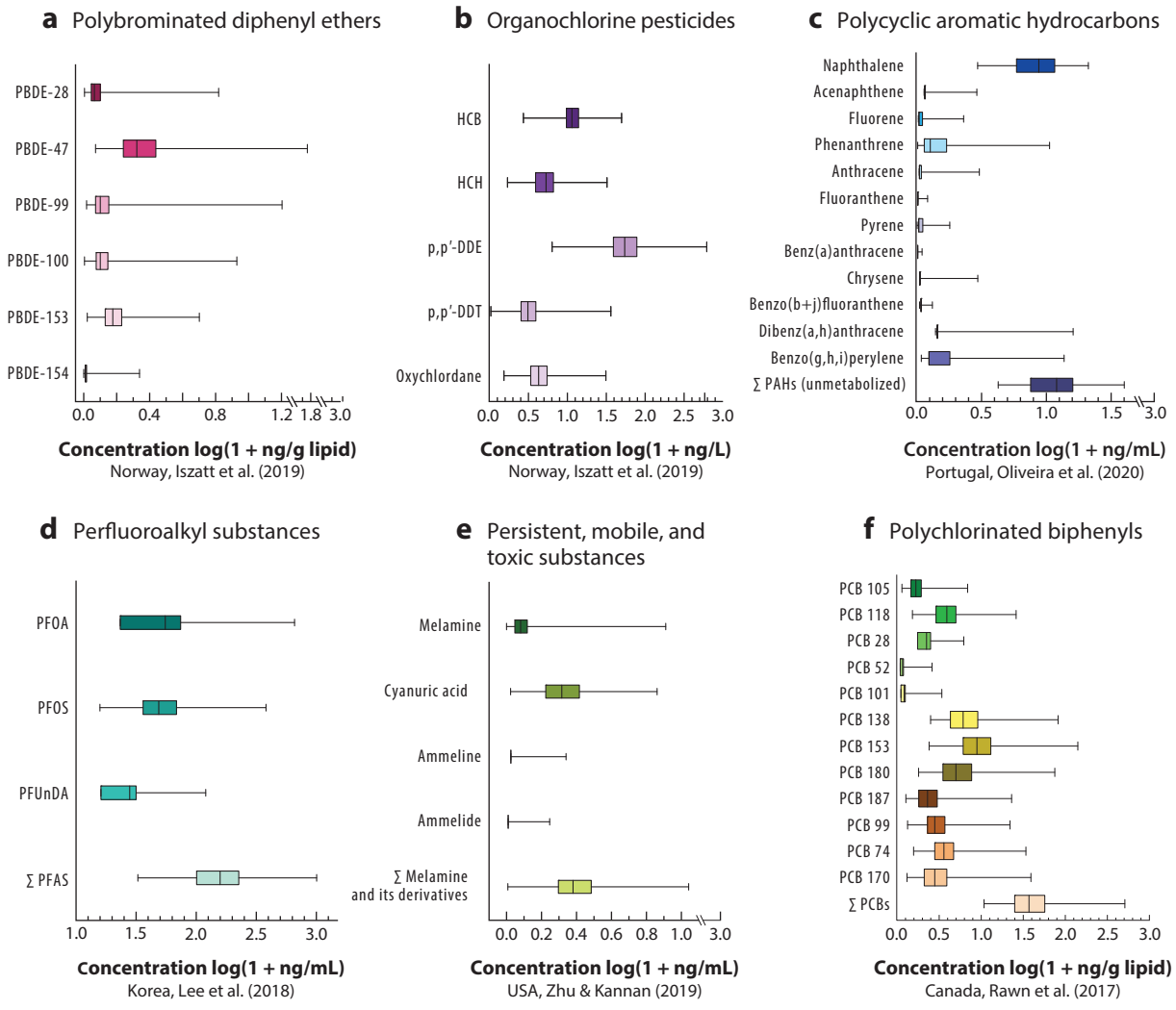

Figure 3

Concentrations of synthetic chemicals in breast milk from different countries based on selected literature reports demonstrate the diverse contamination patterns between different xenobiotic classes and countries/world regions: (*a*) polybrominated diphenyl ethers [log (1 + ng/g lipid)] from Norway ($n = 257$); (*b*) organochlorine pesticides [log (1 + ng/L)] from Norway ($n = 257$); (*c*) polycyclic aromatic hydrocarbons [log (1 + ng/mL)] from Portugal ($n = 65$); (*d*) perfluoroalkyl substances [log (1 + ng/mL)] from Korea ($n = 293$); (*e*) persistent, mobile, and toxic substances [log (1 + ng/mL)] from the United States ($n = 100$); and (*f*) polychlorinated biphenyls [log (1 + ng/g lipid)] from Canada ($n = 298$). Abbreviations: HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; p,p′-DDE, dichlorodiphenyldichloroethylene; p,p′-DDT, dichlorodiphenyltrichloroethane; PAH, polycyclic aromatic hydrocarbon; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFAS, perfluorinated substance; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonate; PFUnDA, perfluoroundecanoic acid. Data for panels *a* and *b* are from Reference 47, data for panel *c* are from Reference 48, data for panel *d* are from Reference 49, data for panel *e* are from Reference 50, and data for panel *f* are from Reference 51.

presented in published studies are often limited. Hence, **Figures 3** and **4** provide an indication of the background concentration levels in specific regions and populations. Taken together, more exposome-scale studies that would be comparable and cover different geographical regions are clearly needed.

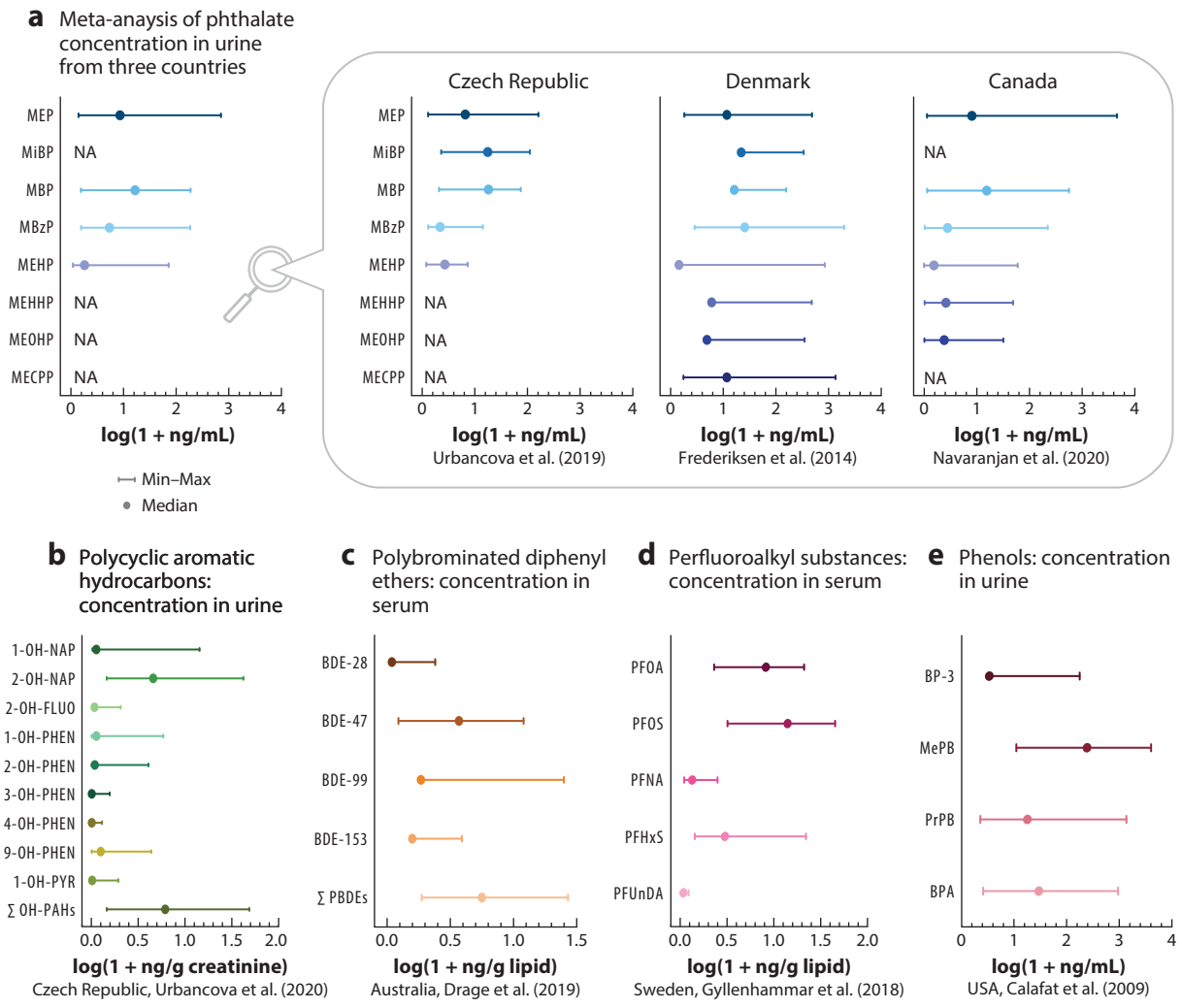

Figure 4

Concentrations of synthetic chemicals in urine or serum obtained from infants living in different countries: (*a*) average phthalate concentration in urine [log (1 + ng/mL)] of infants from different countries (Czech Republic, Canada, Denmark); (*b*) polycyclic aromatic hydrocarbons in urine [log (1 + ng/g creatinine)] from Czech Republic ($n = 330$); (*c*) polybrominated diphenyl ethers in serum [log (1 + ng/g lipid)] from Australia ($n = 800$); (*d*) perfluoroalkyl substances in serum [log (1 + ng/g lipid)] from Sweden ($n = 107$); and (*e*) phenols in urine [log (1 + ng/mL)] of premature infants from the United States ($n = 41$). Abbreviations: 1-OH-NAP, 1-hydroxynaphthalene; 1-OH-PHEN, 1-hydroxyphenanthrene; 1-OH-PYR, 1-hydroxypyrene; 2-OH-FLUO, 2-hydroxyfluorene; 2-OH-NAP, 2-hydroxynaphthalene; 2-OH-PHEN, 2-hydroxyphenanthrene; 3-OH-PHEN, 3-hydroxyphenanthrene; 4-OH-PHEN, 4-hydroxyphenanthrene; 9-OH-PHEN, 9-hydroxyphenanthrene; BDE, brominated diphenyl ether; BP-3, benzophenone-3; BPA, bisphenol A; MBP, mono-n-butyl phthalate; MBzP, monobenzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; MePB, methyl paraben; MiBP, mono-isobutyl phthalate; OH-PAH, mono-hydroxylated polycyclic aromatic hydrocarbon; PFHxS, perfluorohexanesulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS; perfluorooctanesulfonate; PFUnDA, perfluoroundecanoic acid; PrPB; propyl paraben. Data for panel *a* are from References 52–54, data for panel *b* are from Reference 55, data for panel *c* are from Reference 56, data for panel *d* are from Reference 57, and data for panel *e* are from Reference 58.

METABOLISM OF XENOBIOTICS DURING EARLY LIFE

After a certain xenobiotic enters the body, it may undergo significant human and microbial metabolism, depending on its structure. The (xenobiotic) biotransformation and the expression of enzymes in fetuses and infants are often very different in adults. Phase I metabolism involves cytochrome P450 enzymes (CYP450s), a large superfamily present primarily in the liver, that are responsible for the majority of phase I reactions. Generally, the amount of CYP450s is low in fetal tissue but increases after birth (59). CYP3A7 is the main CYP enzyme present in the fetus. After gestation, the expression decreases and CYP3A4 expression begins to dominate (60).

Metabolites of aflatoxin B_1 (AFB_1) include AFM_1 and AFQ_1, which are products of reactions by CYP enzymes. In a study of Nigerian infants, the results from analyzing urine samples showed a high incidence of AFQ_1 (68%) compared to AFM_1, which was detected in only 9% of samples (61). Previously, AFM_1 had been considered the main urinary metabolite, but in fact, infant exposure to aflatoxins could have been underestimated if the more prominent metabolite were AFQ_1 (62, 63).

Enzymes involved in phase II reactions include UDP-glucuronosyltransferases (UGTs), glutathione *S*-transferases (GSTs), and sulfotransferases (SULTs). UGTs are a superfamily of enzymes that catalyze the transfer of glucuronic acid from UDP-glucuronic acid to xenobiotics. UGTs are bound to the membrane of the endoplasmic reticulum localized in liver. The subfamilies UGT1A and UGT2B are the main UGTs involved in xenobiotic/drug metabolism (64). The abundance of UGTs increases with age, and neonates have a much lower abundance of UGT1A enzymes (<13%) compared to adults. The enzyme abundance is age dependent, indicating that the capacity to metabolize xenobiotics differs across age groups. High variability between individuals was also confirmed (65).

GSTs are a superfamily of enzymes that have a protective role against reactive oxygen species and toxic substances. These act by conjugating the xenobiotic with the reduced glutathione to produce a more hydrophilic compound that is easily excreted. GSTs are expressed mainly in the liver and are localized in several cellular compartments, including the cytosol, mitochondria, endoplasmic reticulum, nucleus, and plasma membrane, but the cytosolic GSTs are the most studied (66). The expression of GSTs is sex, species, and age dependent and, as observed in rats, increases through life (67, 68).

SULT enzymes are another superfamily of phase II enzymes responsible for transferring the sulfonate (SO_3^-) from a 3′-phosphoadenosine 5′-phosphosulfate donor to a xenobiotic, resulting in a more water-soluble product. Humans have at least 12 isoforms of SULTs, which are membrane bound or localized in the cytosol of several tissues, such as the liver, small intestine, or kidney, depending on the SULT family (69). Interestingly, in the fetus, the expression of detoxifying enzymes in general is low; however, in the case of SULTs, evidence shows that expression in the fetus is high. For several families, expression is even higher than in adults. This suggests that sulfation is the main detoxification pathway during the prenatal stages (70, 71).

In a recent study, the effect of flame-retardant PBDEs on thyroid hormone SULT activity was investigated in the BeWo placental cell line. PBDEs were shown previously to disrupt thyroid hormone levels. The results in the study revealed that the assessed PBDEs significantly reduced the basal activity of 3,3′-T2 SULT and the corresponding mRNA expression (72). PBDEs and other endocrine disruptors that cross the placenta have the potential to also disrupt other sulfation pathways for endogenous compounds such as estradiol, testosterone, and cholesterol. In sum, biotransformation and expression of enzymes in the fetus and infant are often very different to those of an adult. Enzyme levels tend to be lower during birth than later in adulthood (e.g., CYPs, UGTs), exposing the fetus and young infants to potentially higher doses of xenobiotics and toxins in general.

Endocrine-Disrupting Chemicals as an Example for Mixture Effects

In the past, toxicity assessment of xenobiotics has been done mainly on a single class or single compound and their exerted effects, as it is more straightforward and simpler than studying coexposures. Since then, however, researchers started to consider that a broad range of compound classes affect us at the same time, starting from prenatal stages (73). Compounds can interact with one another and thus may have an additive, synergistic or antagonistic effect (74). The European Food Safety Authority, for example, has proposed to use dose addition to establish cumulative risk assessment (75). Hence, it is crucial to understand the interaction between compounds, the mechanisms of action, and the resultant effect. An example for physiologically relevant mixture toxicology is endocrine disruptors that affect endocrine systems via different mechanisms. To date, EDCs are a well-studied class of chemicals that act by impairing the homeostasis of endogenous hormones and signaling chemicals of the endocrine system. Many of the chemicals mentioned in this review are known or suspected EDCs, e.g., some representatives of PFAS, phthalates, polychlorinated biphenyls (PCBs), PBDEs, mycotoxins, pesticides, and many others. Early-life exposure to EDCs is associated with obesity (76), reduced birth weight (77), preterm birth (78), neurodevelopmental defects (79), reproductive defects, and hormone-related cancers (80).

EDCs have some common underlying mechanisms of action. One of these mechanisms is the binding of estrogen and/or androgen receptors that can cause dysregulation of hormone signaling by agonism or antagonism. The estrogen receptors (ERs) are the target receptors where EDCs can bind with low affinity but still affect the transcription of downstream genes. The genomic pathway involves binding of xenoestrogen to the ER, including Erα and Erβ, which dimerizes and subsequently as a ligand/receptor complex translocates into the cell nucleus. In the nucleus, among other pathways, the complex can bind to the promoter region of the estrogen response element that results in transcription of the target genes. The nongenomic pathway begins with binding of the xenoestrogen to a membrane-bound ER that has been identified as a G protein–coupled receptor called GPER (G protein–coupled ER) or GPR30. The binding causes the rapid activation cascade of signaling messengers that results in the activation of transcription factors (81, 82). Bisphenol A is a prominent example of an EDC that has been shown to bind to ER, even at low doses, activating either pathway (83). Presumably pregnant women and infants are exposed to mixtures of EDCs (as these substances can be present in everyday products, food, or water); thus, the coexposure can potentially have additive, antagonistic or agonistic effects.

HUMAN BIOMONITORING: ANALYSIS AND INNOVATION

Human Biomonitoring

The process of determining the internal exposure to xenobiotics and their biotransformation products is called human biomonitoring (HBM). By measuring and quantifying the levels of xenobiotics from different biological matrices, the baseline of the target analytes can be evaluated (to a large extent, this was done in the studies represented in **Figures 3** and **4**). Based on their baseline levels, the most exposed groups in the population can be identified. HBM is also used to find correlations between exposure and disease outcomes and thus can aid in elucidating the mechanism of action (84). The most common biological matrices used in HBM include urine, breast milk, and blood (serum or plasma). Depending on the population and analyte of interest, other potential high-value matrices that are less-commonly used include feces, saliva, placenta, hair, nails, exhaled breath, cord blood, meconium, and teeth (85). Means to determine the exposure load in the fetus are limited, but one approach is to analyze cord blood and placental tissue collected at birth, because these are in direct contact with the fetus. For infants, it is easier to collect urine, blood, or feces to measure the exposure burden directly. Breast milk is another important bio-fluid used

to determine lactational transfer to infants. In terms of ethical approval, only a small amount of the sample is required for HBM studies. Particularly for premature infants that have very limited biofluids to sample, this is advantageous. As a consequence of the heavy use of chemicals, healthcare products, and food additives in the last century that continue to have an immense impact on humans and nature today, HBM has become increasingly important in occupational and public health over the past decades.

Analysis and Innovation

Nowadays, powerful and sensitive methods to analyze biological samples in HBM studies are based primarily on mass spectrometry (MS) and include liquid chromatography or gas chromatography coupled to MS (LC-MS and GC-MS, respectively). In the past, GC-MS was considered the gold standard, but LC-MS technology has become more common and superior in many areas because of the inherent advantages, e.g., simultaneous analysis of a wider range of analytes. GC-MS is limited primarily to analyzing volatile compounds or involves more complex sample preparation (86). Both techniques are based on chromatographic separation by using either gas or liquid as the mobile phase. The separated degradation products are then transferred to an MS ion source, where the molecules are ionized via a specific technology (e.g., electrospray ionization). The ions are converted to smaller, neutral or ionized fragments; the latter are subsequently separated based on the mass-to-charge ratio (*m/z*) by a mass analyzer. In the last step, the ions are measured by a detector to generate a mass spectrum (intensity versus *m/z*) of the analyte (87).

Two main analytical approaches are used, namely, targeted and untargeted analysis. The targeted approach focuses on analyzing predefined sets of known analytes with the possibility of using internal standards if available. Conversely, the untargeted approach aims to detect a wide range of unknown analytes. Both approaches are used in HBM to measure a broad range of compound classes. Even with a targeted method, it is possible to analyze a large number of xenobiotics, and hence obtain a more exposome-wide overview. For example, Jamnik et al. (88) recently developed a targeted LC-MS/MS method to assess 80+ xenobiotics, including phthalates, PFAS, phytoestrogens, mycotoxins, plant toxins, and others. To more accurately identify a large number of analytes, the sensitivity and accuracy of a targeted analysis can be combined with the high number of potential analytes detected in an untargeted analysis. The trend of using hybrid methods combining both approaches is slowly beginning to emerge, e.g., in the field of metabolomics (89). In the field of exposomics, targeted or untargeted MS-based approaches to measure a large number of chemicals are gradually emerging. Hu et al. (90) recently developed an untargeted GC-high-resolution MS method with a one-step sample preparation termed express liquid extraction. The method was assessed with several types of biological samples and used to detect a broad range of chemicals, showing huge potential for exposome-scale studies.

MS-based methods play an important role in omics techniques owing to their sensitivity, throughput, selectivity, and compatibility with different separation methods. Due to the possibility of quantifying a vast number of proteins, metabolites, and biological active compounds, the progress in understanding different chemical processes and cellular mechanisms has been immense. These methods can be used to identify potential biomarkers that can help determine disease diagnosis, progression, and treatment. Development of soft ionization techniques such as electrospray ionization or matrix-assisted laser desorption ionization has enabled analysis of biological macromolecules, e.g., carbohydrates, lipids, and proteins (91, 92). As an alternative to nano- and normal-flow chromatographic separations, microflow, in which the separation is done on columns with an internal diameter <1.0 mm, has become more popular at a reduced flow rate of <100 μL/min. Recent studies showed robustness and reproducibility using microflow LC-MS/MS (93–95).

MODELS TO STUDY PLACENTAL TRANSFER

To obtain human-relevant data on placental translocation and effects of xenobiotics, use of predictive models is prerequisite. Although studies in pregnant rodents can provide insights on biodistribution and bioresponses in an intact physiological organism, extrapolating the results to humans is challenging due to considerable differences in the development, physiology, and pathophysiology of the placenta between species (96). Therefore, human-based in vitro and ex vivo models are indispensable, and major technological advances in cell cultivation (e.g., microphysiological models, organoid cultures, bioprinting) and the global 3Rs strategy to reduce animal testing are pushing the development of novel advanced models for developmental toxicity assessment.

In Vitro Models

Multiple in vitro cell models have been developed to study maternal–fetal transfer of xenobiotics and drugs. The most frequently used placental transfer model is based on BeWo cells (human choriocarcinoma cell line), which are grown on a microporous membrane to a tight monolayer to model the placental villous syncytiotrophoblast barrier (97, 98). BeWo cells have morphological characteristics of human undifferentiated cytotrophoblast, including syncytial fusion (99), hormone secretions (100), and regulation of syncytin 1 and 2 proteins (101). The advantages are that the cells grow fast and form a confluent, polarized monolayer. Other, less widely used cell lines include JEG-3 and Jar, which also originate from choriocarcinoma. Importantly, BeWo cells express ABC transporters that play an important role in fetal protection, making them a good model for studying mechanisms of drug and xenobiotic transport (102). To further increase the predictive power of this model, coculture models have been developed to also include the fetal endothelium by cocultivating human placental microvascular endothelial cells (HPEC-A2) or human umbilical venous endothelial cells (HUVEC) on the opposite side of the membrane (103, 104) or by replacing the BeWo cell line with primary cytotrophoblast isolated from human term placenta (105). However, access to and cultivation of primary trophoblasts are challenging, isolated cells do not proliferate in culture, and the gene expression of ABC transporters changes rapidly in culture (102, 106).

Placental organoid cultures are another interesting model to obtain mechanistic insights on placental uptake and penetration of xenobiotics. In this regard, a 3D placental coculture microtissue consisting of BeWo trophoblasts surrounding a core of human mesenchymal fibroblasts has been developed and used to study uptake and trophoblast barrier penetration of gold nanoparticles depending on different sizes and surface modifications (107). More recently, long-term 3D trophoblast organoid cultures derived from purified first-trimester cytotrophoblast have been engineered that could be an interesting model to investigate the effects of xenobiotics on early human placental development (108, 109). However, they lack all the stromal, endothelial, and bone marrow–derived cells, and the polarity of the organoids is inside-out, with the syncytiotrophoblast layer formed within the organoid cavity.

To further recreate the highly dynamic microenvironment of the placenta, placental barrier models were integrated into microphysiological chips to recreate a maternal and/or fetal circulation. As observed by cultivating JEG-3 trophoblasts and HUVEC cells on opposite sides of a membrane under dynamic flow conditions, glucose transport rates and metabolism were in good agreement with previously reported in vivo observations (110). A similar model exploiting cocultures of BeWo and HUVEC cells further showed that at physiologic shear stress levels, the trophoblast cells expressed a higher number of microvilli and increased villous length and thickness (111). Moreover, maternal–fetal transport of glyburide, a gestational diabetes drug, was verified in this model (112). Other engineering strategies tried to better simulate the villous

structure using two-photon polymerization of a photo-cross-linkable gelatin hydrogel to replicate the 3D microstructure of placental villi (113); to integrate impedance microsensor array in the polymeric microporous membrane for online monitoring of barrier integrity (114); or to established complex cocultures of BeWo trophoblasts, together with primary placental fibroblasts within a biological membrane (simulating villous stroma) and primary human placental endothelial cells by 3D bioprinting (115).

Overall, these in vitro placenta models do not yet entirely capture the complex physiologic structure, function, and dynamics of the human placenta. Nonetheless, they are highly valuable for prescreening compounds for placental transfer and effects due to their good reproducibility, standardization, and accessibility.

Ex Vivo Models

The ex vivo dual perfusion of an isolated human placental cotyledon allows study of placental transfer of drugs and xenobiotics at near-physiological conditions in an intact tissue. In their meta-analysis, Hutson et al. (116) showed that predictions of placental drug transfer (data on 26 drugs) matched the in vivo data. The main advantage of the perfusion model is that it is the most representative model to investigate xenobiotic transfer using organized in vivo placenta tissue, but there are also a few limitations to the model, such as the short perfusion timescale (usually up to 6 h), high failure rate (mostly due to unspecific maternal–fetal leakage), and restriction to term placental tissue.

Placental explant cultures are another ex vivo model in which small fragments of villous placental tissue (approximately 3×3 mm^2) are excised from human first- or third-trimester placenta (117, 118). These cultures can be maintained for prolonged times (up to several weeks) and can be used to assess cellular uptake and tissue penetration of xenobiotics, as well as their impact on placental tissue function and signaling (118, 119). However, no maternal–fetal transfer rates can be determined with this model due to the lack of two separated circulations.

Models to Recapitulate the Maternal–Placental–Embryonic Axis in Vitro

To achieve a comprehensive understanding of the health hazards of xenobiotics and their mixtures to the developing fetus in vitro, more complex coculture systems allowing assessment of direct and indirect embryo-fetotoxicity are indispensable. Instead of performing separate studies on placental transfer and embryotoxicity (e.g., embryonic stem cell tests) that will not capture any cross-talk between these tissues (e.g., via released factors or metabolites), these models must be combined to gain systemic insight. First models have now been developed that cocultivate a placental barrier (murine trophoblast stem cells or BeWo b30 trophoblasts) together with an embryonic tissue (murine embryoid bodies) under static (120) or dynamic (121) conditions. Importantly, these studies confirmed that such models could indeed provide valuable insights into direct versus placenta-mediated toxicity mechanisms.

Observational Studies in Humans

To study the transfer of xenobiotics and drugs from the mother to the fetus, prospective observational trans-generational studies can provide important evidence. By collecting and analyzing biological samples including cord blood, we can determine exposure in mothers and to some extent in fetuses. Questionnaires can also provide important details about the lifestyle of the mother, and hence a more holistic view about the mother's exposome, and at the same time can be used to determine confounders.

IDENTIFYING KNOWLEDGE GAPS AND SUGGESTIONS

Current Knowledge Gaps and Limitations

- Biomonitoring data from infants and pregnant women that include longitudinal sampling and several types of biological matrices, particularly for natural contaminants and toxins, are lacking.
- Data on coexposure to mixtures of toxicants in general are scarce, as the main focus of the field is still directed toward a narrow range of priority substances that does not allow holistic exposure and risk assessment.
- Biomonitoring data are often limited to specific geographical regions that are not representative of the global population, as exposure pattern and intensity differ markedly based on the region chosen and the studied (sub)population.
- The metabolism of xenobiotics and the resultant biotransformation products typically are not considered adequately, which may lead to misinterpretation of the results from toxicity assessments.
- Data on drug interactions, so-called drug–exposome interactions (or pharmaco-exposomics), which are especially important for (extremely) premature infants and prenatal exposure, are lacking.
- The availability of raw and meta data is still limited, which is restricting fellow scientists attempting to reproduce or extend existing results. FAIR (findable, accessible, interoperable, and reusable) data sharing will be essential in future studies (122).
- Placental exposome and resulting indirect placenta-mediated fetotoxicity mechanisms are largely unknown.

Recommendations for Improved Assessment of Toxicant Coexposure During Early Life

- More infant biomonitoring studies including a broad range of xenobiotics are warranted and should include monitoring of natural toxins besides the typically monitored synthetic toxicants that are of high governmental and public interest.
- To encompass different exposures and generate more representative data, cohorts in HBM studies should be large (to increase the chance of determining a true effect) and from various regions and backgrounds.
- Longitudinal sampling and/or pooled sample designs to monitor background exposure dynamics are encouraged.
- A focus on nontargeted screening/analysis will result in more comprehensive exposure information and the level of biotransformation products and adducts in biological samples.
- Analytical assays should be developed and validated for low sample volumes ($<100\ \mu L$).
- Appropriate and straightforward standardized questionnaires should be used in biomonitoring studies to obtain an accurate, holistic view of exposures.
- In vitro toxicity assessments in advanced human models (e.g., organoids) should be strengthened to gain mechanistic insights on metabolism, transfer, and biological effects of the chemical exposome in early life.

CONCLUSION

Taken together, the identified gaps highlight a general lack of comprehensive data on prenatal and infant coexposure levels and their combined toxicological impact. Research is clearly shifting

toward more holistic approaches in HBM; however, several challenges remain. Firstly, approaches such as the analytical methods used for sensitive quantitation are suitable but often focus on single, or a very narrow range of, chemicals. Many more exposures should be covered simultaneously to better represent real-world scenarios. Another crucial step is to establish large cohorts focused on different age groups, various geographical regions, and numerous exposures. Within the European Union, some established projects are already gathering exposome-type data during early life, e.g., HELIX or HBM4EU (123–125). Overall, this review highlights the shortage of exposome-wide data on early-life exposure.

Secondly, most published reports focus on environmental chemicals that are released from everyday products. In addition, naturally occurring contaminants that are present in food or generated during food processing are not studied to the same degree. The same applies to xenobiotics in ambient air that can be inhaled. The data on exposure to natural contaminants are mainly outdated, are very scarce for humans, and can change rapidly, requiring frequent exposure updates in longitudinal studies. Most research in this area has been performed in animals; thus, the current relevance of the data for humans, and particularly infants, is questionable. Overall, in this article we aimed to summarize the current state of knowledge and highlight the gaps in chemical exposome research specifically in connection to infants and fetuses.

SUMMARY POINTS

1. The chemical exposome includes exposure to all synthetic chemicals, natural contaminants, and nanoparticles.
2. The critical window of susceptibility spans from the prenatal stage to the first 1,000 days of life.
3. Infants have a higher resultant body burden because of their low body weight and developing metabolism.
4. Exposure levels in pregnant women and infants are largely unknown for most contaminants.
5. Exposome-scale studies of large cohorts with a broader chemical space coverage are scarce.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors would like to thank all members of Warth Laboratory for providing valuable feedback on the figure content. This work was funded by the Austrian Science Fund stand-alone project (P33188-B), the Swiss National Science Foundation (grant 31003A_179337), and the University of Vienna and supported by the Exposome/EIRENE Austria research infrastructure.

LITERATURE CITED

1. Simon AK, Hollander GA, McMichael A. 2015. Evolution of the immune system in humans from infancy to old age. *Proc. Biol. Sci.* 282(1821):20143085

2. Wild CP. 2005. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol. Biomark. Prev.* 14(8):1847–50
3. Wild CP. 2012. The exposome: from concept to utility. *Int. J. Epidemiol.* 41(1):24–32
4. Pristner M, Warth B. 2020. Drug-exposome interactions: the next frontier in precision medicine. *Trends Pharmacol. Sci.* 41(12):994–1005
5. Rackaityte E, Halkias J. 2020. Mechanisms of fetal T cell tolerance and immune regulation. *Front. Immunol.* 11:588
6. Perez-Muñoz ME, Arrieta M-C, Ramer-Tait AE, Walter J. 2017. A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: implications for research on the pioneer infant microbiome. *Microbiome* 5:48
7. Tanaka M, Nakayama J. 2017. Development of the gut microbiota in infancy and its impact on health in later life. *Allergol. Int.* 66(4):515–22
8. Dugershaw BB, Aengenheister L, Hansen SSK, Hougaard KS, Buerki-Thurnherr T. 2020. Recent insights on indirect mechanisms in developmental toxicity of nanomaterials. *Part. Fibre Toxicol.* 17:31
9. Mathiesen L, Buerki-Thurnherr T, Pastuschek J, Aengenheister L, Knudsen LE. 2021. Fetal exposure to environmental chemicals; insights from placental perfusion studies. *Placenta* 106:58–66
10. Al-Enazy S, Ali S, Albekairi N, El-Tawil M, Rytting E. 2017. Placental control of drug delivery. *Adv. Drug Deliv. Rev.* 116:63–72
11. Roth M, Obaidat A, Hagenbuch B. 2012. OATPs, OATs and OCTs: the organic anion and cation transporters of the *SLCO* and *SLC22A* gene superfamilies. *Br. J. Pharmacol.* 165(5):1260–87
12. Daud ANA, Bergman JEH, Bakker MK, Wang H, Kerstjens-Frederikse WS, et al. 2015. P-glycoprotein-mediated drug interactions in pregnancy and changes in the risk of congenital anomalies: a case-reference study. *Drug Saf.* 38(7):651–59
13. Han LW, Gao C, Mao Q. 2018. An update on expression and function of P-gp/ABCB1 and BCRP/ABCG2 in the placenta and fetus. *Expert Opin. Drug Metab. Toxicol.* 14(8):817–29
14. Mathias AA, Hitti J, Unadkat JD. 2005. P-glycoprotein and breast cancer resistance protein expression in human placentae of various gestational ages. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* 289(4):R963–69
15. Caserta D, Pegoraro S, Mallozzi M, Di Benedetto L, Colicino E, et al. 2018. Maternal exposure to endocrine disruptors and placental transmission: a pilot study. *Gynecol. Endocrinol.* 34(11):1001–4
16. Li L-X, Chen L, Meng X-Z, Chen B-H, Chen S-Q, et al. 2013. Exposure levels of environmental endocrine disruptors in mother-newborn pairs in China and their placental transfer characteristics. *PLOS ONE* 8(5):e62526
17. Zhang X, Li X, Jing Y, Fang X, Zhang X, et al. 2017. Transplacental transfer of polycyclic aromatic hydrocarbons in paired samples of maternal serum, umbilical cord serum, and placenta in Shanghai, China. *Environ. Pollut.* 222:267–75
18. Yin S, Zhang J, Guo F, Zhao L, Poma G, et al. 2019. Transplacental transfer of organochlorine pesticides: concentration ratio and chiral properties. *Environ. Int.* 130:104939
19. Woo CSJ, Partanen H, Myllynen P, Vähäkangas K, El-Nezami H. 2012. Fate of the teratogenic and carcinogenic ochratoxin A in human perfused placenta. *Toxicol. Lett.* 208(1):92–99
20. Partanen HA, El-Nezami HS, Leppänen JM, Myllynen PK, Woodhouse HJ, Vähäkangas KH. 2010. Aflatoxin B1 transfer and metabolism in human placenta. *Toxicol. Sci.* 113(1):216–25
21. Warth B, Preindl K, Manser P, Wick P, Marko D, Buerki-Thurnherr T. 2019. Transfer and metabolism of the xenoestrogen zearalenone in human perfused placenta. *Environ. Health Perspect.* 127(10):107004
22. Sayyari A, Uhlig S, Fæste CK, Framstad T, Sivertsen T. 2018. Transfer of deoxynivalenol (DON) through placenta, colostrum and milk from sows to their offspring during late gestation and lactation. *Toxins* 10(12):E517
23. Muoth C, Aengenheister L, Kucki M, Wick P, Buerki-Thurnherr T. 2016. Nanoparticle transport across the placental barrier: pushing the field forward! *Nanomedicine* 11(8):941–57
24. Bongaerts E, Nawrot TS, Van Pee T, Ameloot M, Bové H. 2020. Translocation of (ultra)fine particles and nanoparticles across the placenta; a systematic review on the evidence of in vitro, ex vivo, and in vivo studies. *Part Fibre Toxicol.* 17:56

25. Hartmann NB, Baun A. 2010. The nano cocktail: ecotoxicological effects of engineered nanoparticles in chemical mixtures. *Integr. Environ. Assess. Manag.* 6(2):311–13
26. Naasz S, Altenburger R, Kühnel D. 2018. Environmental mixtures of nanomaterials and chemicals: the Trojan-horse phenomenon and its relevance for ecotoxicity. *Sci. Total Environ.* 635:1170–81
27. Ezekiel CN, Abia WA, Braun D, Šarkanj B, Ayeni KI, et al. 2022. Mycotoxin exposure biomonitoring in breastfed and non-exclusively breastfed Nigerian children. *Environ. Int.* 158:106996
28. Braun D, Eiser M, Puntscher H, Marko D, Warth B. 2021. Natural contaminants in infant food: the case of regulated and emerging mycotoxins. *Food Control* 123:107676
29. Anderson HA, Wolff MS. 2000. Environmental contaminants in human milk. *J. Expo. Anal. Environ. Epidemiol.* 10(6 Pt. 2):755–60
30. Haddad S, Ayotte P, Verner M-A. 2015. Derivation of exposure factors for infant lactational exposure to persistent organic pollutants (POPs). *Regul. Toxicol. Pharmacol.* 71(2):135–40
31. Lehmann GM, Verner M-A, Luukinen B, Henning C, Assimon SA, et al. 2014. Improving the risk assessment of lipophilic persistent environmental chemicals in breast milk. *Crit. Rev. Toxicol.* 44(7):600–17
32. Morishita Y, Yoshioka Y, Takimura Y, Shimizu Y, Namba Y, et al. 2016. Distribution of silver nanoparticles to breast milk and their biological effects on breast-fed offspring mice. *ACS Nano* 10(9):8180–91
33. World Health Organ. 2021. *Infant and young child feeding*. Fact Sheet, World Health Organ., Geneva. **https://www.who.int/news-room/fact-sheets/detail/infant-and-young-child-feeding**
34. Adaku Chilaka C, Mally A. 2020. Mycotoxin occurrence, exposure and health implications in infants and young children in sub-Saharan Africa: a review. *Foods* 9(11):1585
35. Juan C, Raiola A, Mañes J, Ritieni A. 2014. Presence of mycotoxin in commercial infant formulas and baby foods from Italian market. *Food Control* 39:227–36
36. Zhang K, Flannery BM, Oles CJ, Adeuya A. 2018. Mycotoxins in infant/toddler foods and breakfast cereals in the US retail market. *Food Addit. Contam. B* 11(3):183–90
37. Lehmann GM, LaKind JS, Davis MH, Hines EP, Marchitti SA, et al. 2018. Environmental chemicals in breast milk and formula: exposure and risk assessment implications. *Environ. Health Perspect.* 126(9):96001
38. Liao C, Liu F, Kannan K. 2013. Occurrence of and dietary exposure to parabens in foodstuffs from the United States. *Environ. Sci. Technol.* 47(8):3918–25
39. Fujii Y, Yan J, Harada KH, Hitomi T, Yang H, et al. 2012. Levels and profiles of long-chain perfluorinated carboxylic acids in human breast milk and infant formulas in East Asia. *Chemosphere* 86(3):315–21
40. Westerhoff P, Atkinson A, Fortner J, Wong MS, Zimmerman J, et al. 2018. Low risk posed by engineered and incidental nanoparticles in drinking water. *Nat. Nanotechnol.* 13(8):661–69
41. Stroustrup A, Bragg JB, Busgang S, Andra S, Curtin P, et al. 2020. Sources of clinically significant neonatal intensive care unit phthalate exposure. *J. Expo. Sci. Environ. Epidemiol.* 30(1):137–48
42. Frederiksen H, Skakkebaek NE, Andersson A-M. 2007. Metabolism of phthalates in humans. *Mol. Nutr. Food Res.* 51(7):899–911
43. Demirel A, Çoban A, Yıldırım Ş, Doğan C, Sancı R, İnce Z. 2016. Hidden toxicity in neonatal intensive care units: phthalate exposure in very low birth weight infants. *J. Clin. Res. Pediatr. Endocrinol.* 8(3):298–304
44. Jenkins R, Tackitt S, Gievers L, Iragorri S, Sage K, et al. 2019. Phthalate-associated hypertension in premature infants: a prospective mechanistic cohort study. *Pediatr. Nephrol.* 34(8):1413–24
45. Stark A, Smith PB, Hornik CP, Zimmerman KO, Hornik CD, et al. 2022. Medication use in the neonatal intensive care unit and changes from 2010 to 2018. *J. Pediatr.* 240:66–71.e4
46. Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, et al. 2021. Paediatric medicines in Europe: the paediatric regulation—Is it time for reform? *Front. Med.* 8:54
47. Iszatt N, Janssen S, Lenters V, Dahl C, Stigum H, et al. 2019. Environmental toxicants in breast milk of Norwegian mothers and gut bacteria composition and metabolites in their infants at 1 month. *Microbiome* 7:34

48. Oliveira M, Duarte S, Delerue-Matos C, Pena A, Morais S. 2020. Exposure of nursing mothers to polycyclic aromatic hydrocarbons: levels of un-metabolized and metabolized compounds in breast milk, major sources of exposure and infants' health risks. *Environ. Pollut.* 266:115243
49. Lee S, Kim S, Park J, Kim H-J, Choi G, et al. 2018. Perfluoroalkyl substances (PFASs) in breast milk from Korea: time-course trends, influencing factors, and infant exposure. *Sci. Total Environ.* 612:286–92
50. Zhu H, Kannan K. 2019. Occurrence of melamine and its derivatives in breast milk from the United States and its implications for exposure in infants. *Environ. Sci. Technol.* 53(13):7859–65
51. Rawn DFK, Sadler AR, Casey VA, Breton F, Sun W-F, et al. 2017. Dioxins/furans and PCBs in Canadian human milk: 2008–2011. *Sci. Total Environ.* 595:269–78
52. Urbancova K, Lankova D, Sram RJ, Hajslova J, Pulkrabova J. 2019. Urinary metabolites of phthalates and di-iso-nonyl cyclohexane-1,2-dicarboxylate (DINCH)—Czech mothers' and newborns' exposure biomarkers. *Environ. Res.* 173:342–48
53. Frederiksen H, Kuiri-Hänninen T, Main KM, Dunkel L, Sankilampi U. 2014. A longitudinal study of urinary phthalate excretion in 58 full-term and 67 preterm infants from birth through 14 months. *Environ. Health Perspect.* 122(9):998–1005
54. Navaranjan G, Takaro TK, Wheeler AJ, Diamond ML, Shu H, et al. 2020. Early life exposure to phthalates in the Canadian Healthy Infant Longitudinal Development (CHILD) study: a multi-city birth cohort. *J. Expo. Sci. Environ. Epidemiol.* 30(1):70–85
55. Urbancova K, Dvorakova D, Gramblicka T, Sram RJ, Hajslova J, Pulkrabova J. 2020. Comparison of polycyclic aromatic hydrocarbon metabolite concentrations in urine of mothers and their newborns. *Sci. Total Environ.* 723:138116
56. Drage DS, Harden FA, Jeffery T, Mueller JF, Hobson P, Toms L-ML. 2019. Human biomonitoring in Australian children: Brominated flame retardants decrease from 2006 to 2015. *Environ. Int.* 122:363–68
57. Gyllenhammar I, Benskin JP, Sandblom O, Berger U, Ahrens L, et al. 2018. Perfluoroalkyl acids (PFAAs) in serum from 2-4-month-old infants: influence of maternal serum concentration, gestational age, breast-feeding, and contaminated drinking water. *Environ. Sci. Technol.* 52(12):7101–10
58. Calafat AM, Weuve J, Ye X, Jia LT, Hu H, et al. 2009. Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. *Environ. Health Perspect.* 117(4):639–44
59. Blake MJ, Castro L, Leeder JS, Kearns GL. 2005. Ontogeny of drug metabolizing enzymes in the neonate. *Semin. Fetal Neonatal Med.* 10(2):123–38
60. Zane NR, Chen Y, Wang MZ, Thakker DR. 2018. Cytochrome P450 and flavin-containing monooxygenase families: age-dependent differences in expression and functional activity. *Pediatr. Res.* 83(2):527–35
61. Ezekiel CN, Abia WA, Braun D, Šarkanj B, Ayeni KI, et al. 2022. Mycotoxin exposure biomonitoring in breastfed and non-exclusively breastfed Nigerian children. *Environ. Int.* 158:106996
62. Sánchez EM, Diaz GJ. 2019. Frequency and levels of aflatoxin M1 in urine of children in Bogota, Colombia. *Mycotoxin Res.* 35(3):271–78
63. Chen G, Gong YY, Kimanya ME, Shirima CP, Routledge MN. 2018. Comparison of urinary aflatoxin M1 and aflatoxin albumin adducts as biomarkers for assessing aflatoxin exposure in Tanzanian children. *Biomarkers* 23(2):131–36
64. Badée J, Qiu N, Collier AC, Takahashi RH, Forrest WF, et al. 2019. Characterization of the ontogeny of hepatic UDP-glucuronosyltransferase enzymes based on glucuronidation activity measured in human liver microsomes. *J. Clin. Pharmacol.* 59(Suppl. 1):S42–55
65. Bhatt DK, Mehrotra A, Gaedigk A, Chapa R, Basit A, et al. 2019. Age- and genotype-dependent variability in the protein abundance and activity of six major uridine diphosphate-glucuronosyltransferases in human liver. *Clin. Pharmacol. Ther.* 105(1):131–41
66. Buratti FM, Darney K, Vichi S, Turco L, Di Consiglio E, et al. 2021. Human variability in glutathione-S-transferase activities, tissue distribution and major polymorphic variants: meta-analysis and implication for chemical risk assessment. *Toxicol. Lett.* 337:78–90
67. Vyskočilová E, Szotáková B, Skálová L, Bártíková H, Hlaváčová J, Boušová I. 2013. Age-related changes in hepatic activity and expression of detoxification enzymes in male rats. *Biomed. Res. Int.* 2013:408573
68. Xu S, Hou D, Liu J, Ji L. 2018. Age-associated changes in GSH S-transferase gene/proteins in livers of rats. *Redox Rep.* 23(1):213–18

69. Coughtrie MWH. 2016. Function and organization of the human cytosolic sulfotransferase (SULT) family. *Chem. Biol. Interact.* 259(Pt. A):2–7
70. Stanley EL, Hume R, Coughtrie MWH. 2005. Expression profiling of human fetal cytosolic sulfotransferases involved in steroid and thyroid hormone metabolism and in detoxification. *Mol. Cell. Endocrinol.* 240(1):32–42
71. Dubaisi S, Caruso JA, Gaedigk R, Vyhlidal CA, Smith PC, et al. 2019. Developmental expression of the cytosolic sulfotransferases in human liver. *Drug Metab. Dispos.* 47(6):592–600
72. Leonetti CP, Butt CM, Stapleton HM. 2018. Disruption of thyroid hormone sulfotransferase activity by brominated flame retardant chemicals in the human choriocarcinoma placenta cell line, BeWo. *Chemosphere* 197:81–88
73. van den Dries MA, Keil AP, Tiemeier H, Pronk A, Spaan S, et al. 2021. Prenatal exposure to non-persistent chemical mixtures and fetal growth: a population-based study. *Environ. Health Perspect.* 129(11):117008
74. Roell KR, Reif DM, Motsinger-Reif AA. 2017. An introduction to terminology and methodology of chemical synergy—perspectives from across disciplines. *Front. Pharmacol.* 8:158
75. Van Der Ven LTM, Van Ommeren P, Zwart EP, Gremmer ER, Hodemaekers HM, et al. 2022. Dose addition in the induction of craniofacial malformations in zebrafish embryos exposed to a complex mixture of food-relevant chemicals with dissimilar modes of action. *Environ. Health Perspect.* 130(4):47003
76. Heindel JJ, Newbold R, Schug TT. 2015. Endocrine disruptors and obesity. *Nat. Rev. Endocrinol.* 11(11):653–61
77. Pearce JL, Neelon B, Bloom MS, Buckley JP, Ananth CV, et al. 2021. Exploring associations between prenatal exposure to multiple endocrine disruptors and birth weight with exposure continuum mapping. *Environ. Res.* 200:111386
78. Ferguson KK, McElrath TF, Meeker JD. 2014. Environmental phthalate exposure and preterm birth. *JAMA Pediatr.* 168(1):61–67
79. Braun JM. 2017. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nat. Rev. Endocrinol.* 13(3):161–73
80. Sifakis S, Androutsopoulos VP, Tsatsakis AM, Spandidos DA. 2017. Human exposure to endocrine disrupting chemicals: effects on the male and female reproductive systems. *Environ. Toxicol. Pharmacol.* 51:56–70
81. Viñas R, Jeng Y-J, Watson CS. 2012. Non-genomic effects of xenoestrogen mixtures. *Int. J. Environ. Res. Public Health* 9(8):2694–714
82. Lee H-R, Jeung E-B, Cho M-H, Kim T-H, Leung PCK, Choi K-C. 2013. Molecular mechanism(s) of endocrine-disrupting chemicals and their potent oestrogenicity in diverse cells and tissues that express oestrogen receptors. *J. Cell. Mol. Med.* 17(1):1–11
83. Bouskine A, Nebout M, Brücker-Davis F, Benahmed M, Fenichel P. 2009. Low doses of bisphenol A promote human seminoma cell proliferation by activating PKA and PKG via a membrane G-protein-coupled estrogen receptor. *Environ. Health Perspect.* 117(7):1053–58
84. Bocato MZ, Ximenez JPB, Hoffmann C, Barbosa F. 2019. An overview of the current progress, challenges, and prospects of human biomonitoring and exposome studies. *J. Toxicol. Environ. Health B* 22(5–6):131–56
85. Yu M, Tu P, Dolios G, Dassanayake PS, Volk H, et al. 2021. Tooth biomarkers to characterize the temporal dynamics of the fetal and early-life exposome. *Environ. Int.* 157:106849
86. Gorrochategui E, Jaumot J, Lacorte S, Tauler R. 2016. Data analysis strategies for targeted and untargeted LC-MS metabolomic studies: overview and workflow. *TrAC Trends Anal. Chem.* 82:425–42
87. Vitale CM, Price EJ, Miller GW, David A, Antignac J-P, et al. 2021. Analytical strategies for chemical exposomics: exploring limits and feasibility. *Exposome* 1(1):osab003
88. Jamnik T, Flasch M, Braun D, Fareed Y, Wasinger D, et al. 2022. Next-generation biomonitoring of the early-life chemical exposome in neonatal and infant development. *Nat. Commun.* 13:2653
89. Chen L, Zhong F, Zhu J. 2020. Bridging targeted and untargeted mass spectrometry-based metabolomics via hybrid approaches. *Metabolites* 10(9):348
90. Hu X, Walker DI, Liang Y, Smith MR, Orr ML, et al. 2021. A scalable workflow to characterize the human exposome. *Nat. Commun.* 12:5575

91. Ren J-L, Zhang A-H, Kong L, Wang X-J. 2018. Advances in mass spectrometry-based metabolomics for investigation of metabolites. *RSC Adv*. 8(40):22335–50
92. Misra BB, Langefeld C, Olivier M, Cox LA. 2019. Integrated omics: tools, advances and future approaches. *J. Mol. Endocrinol.* 62(1):R21–45
93. Bian Y, Bayer FP, Chang Y-C, Meng C, Hoefer S, et al. 2021. Robust microflow LC-MS/MS for proteome analysis: 38 000 runs and counting. *Anal. Chem.* 93(8):3686–90
94. Bian Y, Zheng R, Bayer FP, Wong C, Chang Y-C, et al. 2020. Robust, reproducible and quantitative analysis of thousands of proteomes by micro-flow LC-MS/MS. *Nat. Commun.* 11:157
95. Fitz V, Berger D, Abiead YE, Koellensperger G. 2022. Systematic investigation of LC miniaturization to increase sensitivity in wide-target LC-MS-based trace bioanalysis of small molecules. *Front. Mol. Biosci.* 9:857505
96. Schmidt A, Schmidt A, Markert UR. 2021. The road (not) taken—placental transfer and interspecies differences. *Placenta* 115:70–77
97. Pattillo RA, Gey GO. 1968. The establishment of a cell line of human hormone-synthesizing trophoblastic cells *in vitro*. *Cancer Res*. 28(7):1231–36
98. Li H, van Ravenzwaay B, Rietjens IMCM, Louisse J. 2013. Assessment of an in vitro transport model using BeWo b30 cells to predict placental transfer of compounds. *Arch. Toxicol.* 87(9):1661–69
99. Gauster M, Huppertz B. 2010. The paradox of caspase 8 in human villous trophoblast fusion. *Placenta* 31(2):82–88
100. Wolfe MW. 2006. Culture and transfection of human choriocarcinoma cells. In *Placenta and Trophoblast: Methods and Protocols*, Vol. 1, ed. MJ Soares, JS Hunt, pp. 229–39. Totowa, NJ: Humana
101. Vargas A, Moreau J, Landry S, LeBellego F, Toufaily C, et al. 2009. Syncytin-2 plays an important role in the fusion of human trophoblast cells. *J. Mol. Biol.* 392(2):301–18
102. Evseenko DA, Paxton JW, Keelan JA. 2006. ABC drug transporter expression and functional activity in trophoblast-like cell lines and differentiating primary trophoblast. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 290(5):R1357–65
103. Aengenheister L, Keevend K, Muoth C, Schönenberger R, Diener L, et al. 2018. An advanced human *in vitro* co-culture model for translocation studies across the placental barrier. *Sci Rep*. 8:5388
104. Levkovitz R, Zaretsky U, Gordon Z, Jaffa AJ, Elad D. 2013. *In vitro* simulation of placental transport: part I. Biological model of the placental barrier. *Placenta* 34(8):699–707
105. Huang X, Lüthi M, Ontsouka EC, Kallol S, Baumann MU, et al. 2016. Establishment of a confluent monolayer model with human primary trophoblast cells: novel insights into placental glucose transport. *Mol. Hum. Reprod.* 22(6):442–56
106. Myllynen P, Vähäkangas K. 2013. Placental transfer and metabolism: an overview of the experimental models utilizing human placental tissue. *Toxicol. Vitro* 27(1):507–12
107. Muoth C, Wichser A, Monopoli M, Correia M, Ehrlich N, et al. 2016. A 3D co-culture microtissue model of the human placenta for nanotoxicity assessment. *Nanoscale* 8(39):17322–32
108. Turco MY, Gardner L, Kay RG, Hamilton RS, Prater M, et al. 2018. Trophoblast organoids as a model for maternal-fetal interactions during human placentation. *Nature* 564(7735):263–67
109. Haider S, Meinhardt G, Saleh L, Kunihs V, Gamperl M, et al. 2018. Self-renewing trophoblast organoids recapitulate the developmental program of the early human placenta. *Stem Cell Rep*. 11(2):537–51
110. Lee JS, Romero R, Han YM, Kim HC, Kim CJ, et al. 2016. Placenta-on-a-chip: a novel platform to study the biology of the human placenta. *J. Matern. Fetal Neonatal Med.* 29(7):1046–54
111. Blundell C, Tess ER, Schanzer ASR, Coutifaris C, Su EJ, et al. 2016. A microphysiological model of the human placental barrier. *Lab. Chip* 16(16):3065–73
112. Blundell C, Yi Y-S, Ma L, Tess ER, Farrell MJ, et al. 2018. Placental drug transport-on-a-chip: a microengineered *in vitro* model of transporter-mediated drug efflux in the human placental barrier. *Adv. Healthc. Mater.* 7(2):1700786
113. Mandt D, Gruber P, Markovic M, Tromayer M, Rothbauer M, et al. 2018. Fabrication of biomimetic placental barrier structures within a microfluidic device utilizing two-photon polymerization. *Int. J. Bioprint.* 4(2):144

114. Schuller P, Rothbauer M, Kratz SRA, Höll G, Taus P, et al. 2020. A lab-on-a-chip system with an embedded porous membrane-based impedance biosensor array for nanoparticle risk assessment on placental Bewo trophoblast cells. *Sens. Actuators B* 312:127946
115. Kreuder A-E, Bolaños-Rosales A, Palmer C, Thomas A, Geiger M-A, et al. 2020. Inspired by the human placenta: a novel 3D bioprinted membrane system to create barrier models. *Sci. Rep.* 10:15606
116. Hutson JR, Garcia-Bournissen F, Davis A, Koren G. 2011. The human placental perfusion model: a systematic review and development of a model to predict *in vivo* transfer of therapeutic drugs. *Clin. Pharmacol. Ther.* 90(1):67–76
117. Miller RK, Genbacev O, Turner MA, Aplin JD, Caniggia I, Huppertz B. 2005. Human placental explants in culture: approaches and assessments. *Placenta* 26(6):439–48
118. Valero L, Alhareth K, Gil S, Simasotchi C, Roques C, et al. 2017. Assessment of dually labelled PEGylated liposomes transplacental passage and placental penetration using a combination of two *ex-vivo* human models: the dually perfused placenta and the suspended villous explants. *Int. J. Pharm.* 532(2):729–37
119. Juch H, Nikitina L, Reimann S, Gauster M, Dohr G, et al. 2018. Dendritic polyglycerol nanoparticles show charge dependent bio-distribution in early human placental explants and reduce hCG secretion. *Nanotoxicology* 12(2):90–103
120. Lacconi V, Massimiani M, Paglione L, Messina A, Battistini B, et al. 2022. An improved *in vitro* model simulating the feto-maternal interface to study developmental effects of potentially toxic compounds: the example of titanium dioxide nanoparticles. *Toxicol. Appl. Pharmacol.* 446:116056
121. Boos JA, Misun PM, Brunoldi G, Furer LA, Aengenheister L, et al. 2021. Microfluidic co-culture platform to recapitulate the maternal-placental-embryonic axis. *Adv. Biol.* 5(8):e2100609
122. Schymanski EL, Bolton EE. 2022. FAIRifying the exposome journal: templates for chemical structures and transformations. *Exposome* 2(1):osab006
123. Tamayo-Uria I, Maitre L, Thomsen C, Nieuwenhuijsen MJ, Chatzi L, et al. 2019. The early-life exposome: description and patterns in six European countries. *Environ. Int.* 123:189–200
124. Apel P, Rousselle C, Lange R, Sissoko F, Kolossa-Gehring M, Ougier E. 2020. Human biomonitoring initiative (HBM4EU)—strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. *Int. J. Hyg. Environ. Health* 230:113622
125. Huhn S, Escher BI, Krauss M, Scholz S, Hackermüller J, Altenburger R. 2021. Unravelling the chemical exposome in cohort studies: routes explored and steps to become comprehensive. *Environ. Sci. Eur.* 33:17
126. IARC Work Group Eval. Carcinog. Risks Hum. 2002. *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*. Lyon, Fr.: IARC
127. Rocha O, Ansari K, Doohan FM. 2005. Effects of trichothecene mycotoxins on eukaryotic cells: a review. *Food Addit. Contam.* 22(4):369–78
128. IARC Work. Group Eval. Carcinog. Risks Hum. 1993. *Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins*. Lyon, Fr.: IARC
129. Rai A, Das M, Tripathi A. 2020. Occurrence and toxicity of a fusarium mycotoxin, zearalenone. *Crit. Rev. Food Sci. Nutr.* 60(16):2710–29
130. IARC Work. Group Eval. Carcinog. Risks Hum. 2012. *Plants Containing Aristolochic Acid*. Lyon, Fr.: IARC
131. Guo Y, Xiao D, Yang X, Zheng J, Hu S, et al. 2019. Prenatal exposure to pyrrolizidine alkaloids induced hepatotoxicity and pulmonary injury in fetal rats. *Reprod. Toxicol.* 85:34–41
132. Kwakye GF, Jiménez J, Jiménez JA, Aschner M. 2018. *Atropa belladonna* neurotoxicity: implications to neurological disorders. *Food Chem. Toxicol.* 116:346–53
133. Green BT, Lee ST, Panter KE, Brown DR. 2012. Piperidine alkaloids: human and food animal teratogens. *Food Chem. Toxicol.* 50(6):2049–55
134. Chenchen W, Wenlong W, Xiaoxue L, Feng M, Dandan C, et al. 2014. Pathogenesis and preventive treatment for animal disease due to locoweed poisoning. *Environ. Toxicol. Pharmacol.* 37(1):336–47
135. Lone Y, Koiri RK, Bhide M. 2015. An overview of the toxic effect of potential human carcinogen Microcystin-LR on testis. *Toxicol. Rep.* 2:289–96

136. Friedman MA, Fernandez M, Backer LC, Dickey RW, Bernstein J, et al. 2017. An updated review of ciguatera fish poisoning: clinical, epidemiological, environmental, and public health management. *Mar. Drugs* 15(3):72
137. IARC Work. Group Eval. Carcinog. Risks Hum. 2010. *Some Non-Heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures*. Lyon, Fr.: IARC
138. IARC Work. Group Eval. Carcinog. Risks Hum. 2018. *Some Industrial Chemicals*. Lyon, Fr.: IARC
139. Zong C, Hasegawa R, Urushitani M, Zhang L, Nagashima D, et al. 2019. Role of microglial activation and neuroinflammation in neurotoxicity of acrylamide in vivo and in vitro. *Arch Toxicol*. 93(7):2007–19
140. Park J-S, Samanta P, Lee S, Lee J, Cho J-W, et al. 2021. Developmental and neurotoxicity of acrylamide to zebrafish. *Int. J. Mol. Sci*. 22(7):3518
141. IARC Working Group Eval. Carcinog. Risks Hum. 1995. *Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals*. Lyon, Fr.: IARC
142. de Conti A, Kobets T, Escudero-Lourdes C, Montgomery B, Tryndyak V, et al. 2014. Dose- and time-dependent epigenetic changes in the livers of Fisher 344 rats exposed to furan. *Toxicol. Sci*. 139(2):371–80
143. Liu H, Nie F-H, Lin H-Y, Ma Y, Ju X-H, et al. 2016. Developmental toxicity, oxidative stress, and related gene expression induced by dioxin-like PCB 126 in zebrafish (Danio rerio). *Environ. Toxicol*. 31(3):295–303
144. Paul R, Moltó J, Ortuño N, Romero A, Bezos C, et al. 2017. Relationship between serum dioxin-like polychlorinated biphenyls and post-testicular maturation in human sperm. *Reprod. Toxicol*. 73:312–21
145. Brun NR, Panlilio JM, Zhang K, Zhao Y, Ivashkin E, et al. 2021. Developmental exposure to non-dioxin-like polychlorinated biphenyls promotes sensory deficits and disrupts dopaminergic and GABAergic signaling in zebrafish. *Commun. Biol*. 4(1):1129
146. IARC Work. Group Eval. Carcinog. Risks Hum. 2018. *DDT, Lindane, and 2,4-D*. Lyon, Fr.: IARC
147. Naughton SX, Terry AV. 2018. Neurotoxicity in acute and repeated organophosphate exposure. *Toxicology* 408:101–12
148. Yu L, Lam JCW, Guo Y, Wu RSS, Lam PKS, Zhou B. 2011. Parental transfer of polybrominated diphenyl ethers (PBDEs) and thyroid endocrine disruption in zebrafish. *Environ. Sci. Technol*. 45(24):10652–59
149. Zhang H, Yang X, Li X, Cheng Y, Zhang H, et al. 2020. Oxidative and nitrosative stress in the neurotoxicity of polybrominated diphenyl ether-153: possible mechanism and potential targeted intervention. *Chemosphere* 238:124602
150. Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, et al. 2021. Per- and polyfluoroalkyl substance toxicity and human health review: current state of knowledge and strategies for informing future research. *Environ. Toxicol. Chem*. 40(3):606–30
151. Qian Y, Shao H, Ying X, Huang W, Hua Y. 2020. The endocrine disruption of prenatal phthalate exposure in mother and offspring. *Front. Public Health* 8:366
152. Qian X, Li J, Xu S, Wan Y, Li Y, et al. 2019. Prenatal exposure to phthalates and neurocognitive development in children at two years of age. *Environ. Int*. 131:105023
153. Vo TTB, Yoo Y-M, Choi K-C, Jeung E-B. 2010. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. *Reprod. Toxicol*. 29(3):306–16
154. Rubin BS. 2011. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J. Steroid Biochem. Mol. Biol*. 127(1–2):27–34
155. IARC Work. Group Eval. Carcinog. Risks Hum. 2019. *Some Chemicals That Cause Tumours of the Urinary Tract in Rodents*. Lyon, Fr.: IARC