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REVIEW

# Environmental neglect: endocrine disruptors as underappreciated but potentially modifiable diabetes risk factors

Robert M. Sargis[1,2] · Rebecca A. Simmons[3,4,5]

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## Abstract

Type 2 diabetes prevalence is increasing dramatically across the globe, imposing a tremendous toll on individuals and healthcare systems. Reversing these trends requires comprehensive approaches to address both classical and emerging diabetes risk factors. Recently, environmental toxicants acting as endocrine-disrupting chemicals (EDCs) have emerged as novel metabolic disease risk factors. EDCs implicated in diabetes pathogenesis include various inorganic and organic molecules of both natural and synthetic origin, including arsenic, bisphenol A, phthalates, polychlorinated biphenyls and organochlorine pesticides. Indeed, evidence implicates EDC exposures across the lifespan in metabolic dysfunction; moreover, specific developmental windows exhibit enhanced sensitivity to EDC-induced metabolic disruption, with potential impacts across generations. Importantly, differential exposures to diabetogenic EDCs likely also contribute to racial/ethnic and economic disparities. Despite these emerging links, clinical practice guidelines fail to address this underappreciated diabetes risk factor. Comprehensive approaches to stem the tide of diabetes must include efforts to address its environmental drivers.

**Keywords** Beta cell · Bisphenol A · Diabetes · Endocrine disruptor · Endocrine-disrupting chemical · Environmental justice · Glucose · Insulin · Life course development · Review

**Abbreviations**

| | |
|---|---|
| BPA | Bisphenol A |
| DMR1 | Differentially methylated region 1 |
| EDC | Endocrine-disrupting chemical |
| GDM | Gestational diabetes |
| GSIS | Glucose-stimulated insulin secretion |
| PCBs | Polychlorinated biphenyls |
| PPARγ | Peroxisome proliferator-activated receptor γ |
| RXR | Retinoid X receptor |
| TBT | Tributyltin |

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✉ Robert M. Sargis
rsargis@uic.edu

[1] Division of Endocrinology, Diabetes, and Metabolism Department of Medicine, University of Illinois at Chicago, 835 S. Wolcott, Suite E625; M/C 640, Chicago, IL 60612, USA

[2] ChicAgo Center for Health and EnvironmenT (CACHET), University of Illinois at Chicago, Chicago, IL, USA

[3] Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

[4] Center for Research on Reproduction and Women's Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[5] Center of Excellence in Environmental Toxicology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

## Introduction

The global burden of diabetes is projected to reach a staggering 629 million individuals by 2045 [1], and the WHO envisages metabolic disorders will be a major cause of death by 2030, placing substantial economic stresses on healthcare systems worldwide [2]. Indeed, 12% of global health expenditures are already estimated to be spent on diabetes [1] and, in the USA alone, annual diabetes-associated economic costs are calculated to be $327 billion [3]. Most of the diabetes health burden arises from type 2 diabetes, which accounts for 90–95% of all diabetes cases. As both disease prevalence and treatment costs continue to rise dramatically [4], comprehensive approaches to reverse these trends are desperately needed. Essential to this effort are strategies that simultaneously

address the myriad risk factors contributing to diabetes pathogenesis. While this certainly includes efforts to tackle the contributions of excess food intake and sedentary lifestyles, it is also essential to identify other modifiable risk factors that promote diabetes development.

One emerging but underappreciated realm of risk is our ubiquitous exposure to environmental chemicals through food and water, skin contact and the air we breathe. Indeed, exposures to endocrine-disrupting chemicals (EDCs) are associated with an increased risk of various endocrine-related disorders in both human and animal studies [5]. The Endocrine Society classifies exogenous chemicals as EDCs based upon their ability to disrupt any aspect of hormone secretion or action [6]. Over the last two decades, exposure to many EDCs from multiple sources has been associated with increased risk of diabetes, obesity and other metabolic disorders (Fig. 1). These metabolism-disrupting EDCs include a variety of inorganic and organic molecules of natural or synthetic origin, including many to which humans are frequently exposed, including arsenic, bisphenol A (BPA) and phthalates, as well as legacy compounds, which have profound chemical and biological stability and persist in the environment despite regulatory action to eliminate or curtail their use, such as polychlorinated biphenyls (PCBs) and organochlorine pesticides. With increasing evidence linking exposure to various EDCs with diabetes in human populations, as well as diabetes-associated pathophysiological defects in cell-based and animal studies [7–10] (Fig. 2), the time has come to incorporate environmental interventions into comprehensive strategies to reduce the individual and societal burden of this devastating disease.

## Exposures during sensitive developmental windows

While EDC exposures occur across the lifespan, specific developmental windows are recognised as periods of unique vulnerability (Fig. 3). The period from conception to birth is a time of cellular replication and differentiation, functional organ system maturation and rapid growth. These processes are exquisitely sensitive to perturbations in the intrauterine metabolic milieu that exert long-lasting effects on offspring. Animal and epidemiology data demonstrate that several critical periods during development influence the later-life onset of type 2 diabetes, including preconception and gestation, early infancy, the adiposity rebound period between 5 and 7 years of age, and puberty. Until recently, most studies examining

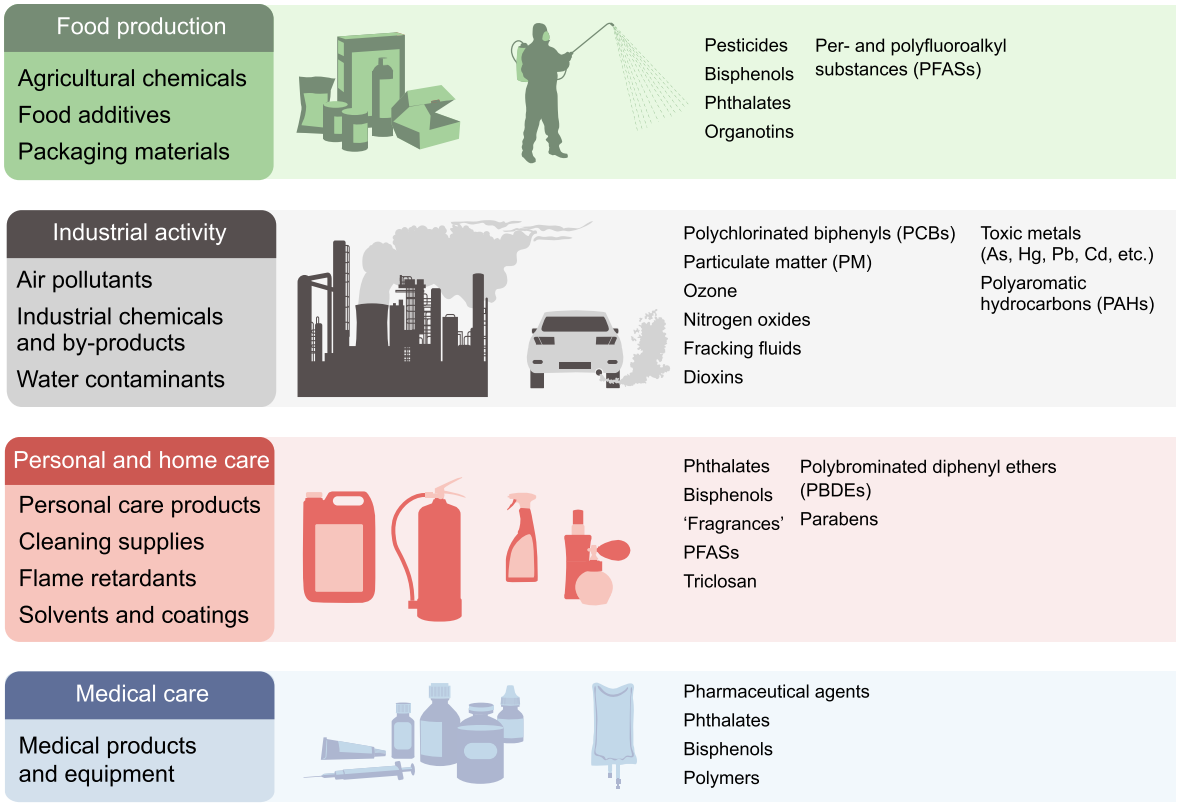


**Fig. 1** Sources of EDCs. A diverse array of chemicals from various sources have been linked to metabolic dysfunction in cell-based, animal and epidemiological studies. These metabolism-disrupting EDCs include both inorganic and organic compounds of both natural and synthetic origin. Humans are exposed through the use, production and environmental dissemination of these chemicals in food production, industrial activity, and home and personal care, as well as through medical care. This figure is available as part of a downloadable slideset

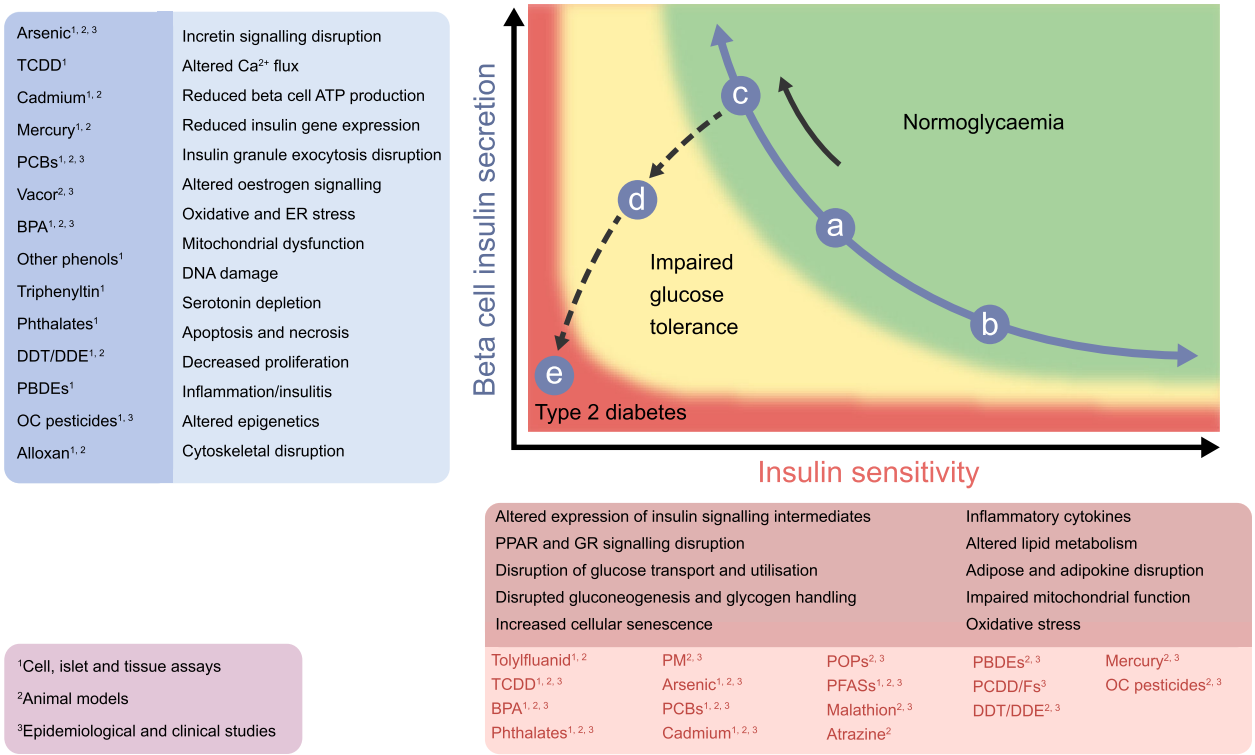


**Fig. 2** EDCs associated with type 2 diabetes pathogenesis and their proposed mechanisms of action. Type 2 diabetes arises from a combination of reduced insulin sensitivity (solid black arrow) and progressive beta cell failure (dashed black arrow). The blue circles, labelled a to e, represent individual states. Starting at state 'a', (in the middle of the normoglycaemia curve, green shading), if a person with these levels of insulin sensitivity and insulin secretion were to exercise, lose weight and get better sleep, they would slide down the curve to 'b'. Unfortunately, our society is instead less active, consuming excess food and sleeping less, driving individuals from state 'a' to state 'c'. This situation is, however, untenable in the long run. As one's beta cells begin to fail, they fall off the curve (dashed line) to 'd' (impaired glucose tolerance, yellow shading); this condition then further deteriorates to 'e' (type 2 diabetes, red). Several EDCs have been linked to altered insulin sensitivity (darker red text box), beta cell disruptions (darker blue text box), or both. Multiple mechanisms have been ascribed to EDC-induced beta cell dysfunction and altered functioning of insulin-responsive tissues (lighter blue and lighter red text boxes). Data supporting EDC-mediated diabetes pathogenesis are derived from: cell-, islet- and tissue-based studies; animal models; and epidemiological and clinical studies (indicated by the superscript numbers; purple text box). BPA, bisphenol A; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; GR, glucocorticoid receptor; OC, organochlorine; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PFASs, per- and polyfluoroalkyl substances; PCDD/Fs, polychlorinated dibenzo-*p*-dioxins and furans; PM, particulate matter; POPs, persistent organic pollutants; PPARs, peroxisome proliferator-activated receptors; TCDD, 2,3,7,8-tetrachlorodibenzodioxin. Data compiled from [7–10]. Figure adapted by permission from Springer Nature [129], ©2006 Nature Publishing Group. This figure is available as part of a downloadable slideset

developmental programming were focused on inadequate nutrition or uteroplacental insufficiency; however, it is now apparent that developmental exposure to EDCs may also increase the incidence of type 2 diabetes [7, 11].

Perhaps the prototypical EDC is BPA, a common contaminant used widely in polycarbonate and other plastics, epoxy resins lining cans and the thermal paper of cash register receipts. BPA binds both oestrogen receptor α (ERα) and β (ERβ), although with less affinity than 17β-oestradiol (E2). Humans are ubiquitously exposed to BPA, with low levels detectable in the blood and urine of virtually all individuals across multiple populations [12–14]. Importantly, human fetuses and children are likely to be at heightened risk of endocrine disruption from BPA, since BPA clearance enzymes are not fully functional at these life stages [15]. Consequently, blood and urine levels of BPA are higher in fetuses than in their pregnant mothers [13], and in infants and children compared with adults [12]. Importantly, while exact human exposures are difficult to estimate, animal studies demonstrate that levels below those considered safe for human health are sufficient to induce metabolic dysfunction [16].

Multiple animal studies have explored the impact of developmental BPA exposure on metabolic programming; however, controversy persists regarding the effects of maternal BPA exposure on offspring. Differences across studies, include species and strain, developmental stage during exposure, ages at metabolic interrogation, levels of exposure, housing, diet, control conditions and exposure routes have all contributed to a lack of consensus on the gestational effects of BPA. Particularly robust debate has focused upon the importance of the route of exposure (oral vs subcutaneous) as well as evidence of non-monotonic dose–response relationships

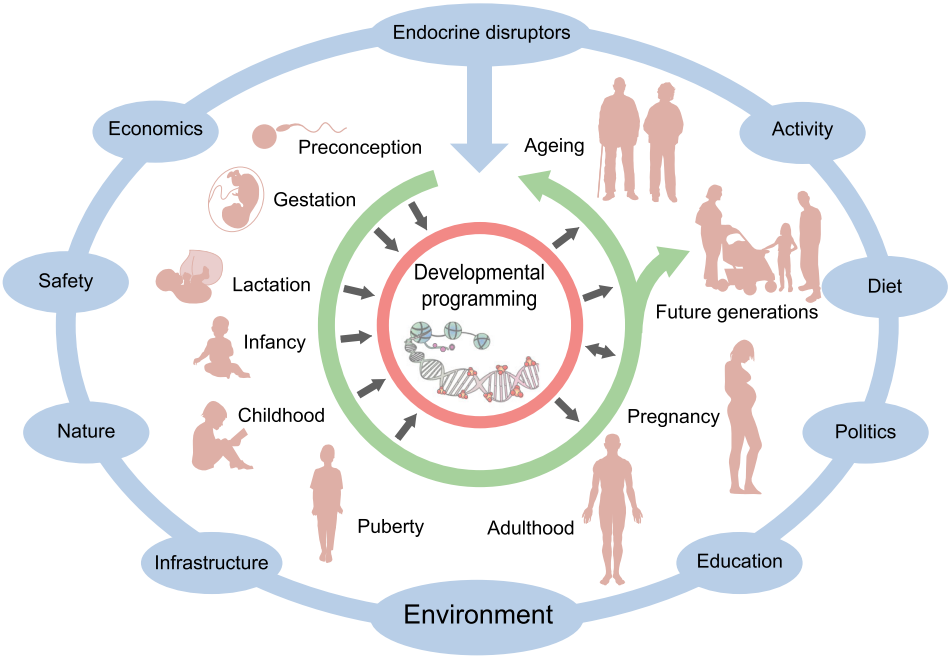


**Fig. 3** Influence of EDCs across the lifespan. EDCs and other environmental toxicants are an important component of the overall environmental milieu (blue) that interacts with genetic susceptibility to influence diabetes pathogenesis across the lifespan (green arrow). Importantly, exposures during sensitive windows can disrupt developmental programming and result in long-term metabolic dysfunction in both the exposed individual as well as future generations (black arrows). This figure is available as part of a downloadable slideset

demonstrating that BPA exposures at or below the current US Environmental Protection Agency's reference dose often yield metabolic disruptions that are either not observed or different at higher doses [17–19]. Acknowledging these challenges, when experimental conditions are strictly maintained, reproducible and stable metabolic disruptions are consistently observed in the offspring of BPA-exposed dams [20].

Some of the first evidence that developmental EDC exposure alters metabolic health came from studies exposing pregnant rats to BPA. Exposure resulted in dose- and sex-specific increases in offspring body weights that persisted into adulthood [21]. Since then, multiple studies have examined links between perinatal EDC exposure and the later-life development of metabolic dysfunction, including obesity. Fewer studies have examined the effects of EDCs on beta cell development and function. Importantly, all three oestrogen receptors (ERα, ERβ and the G-protein coupled ER [GPER]) are present in rodent and human beta cells, where they play essential roles in islet survival and function [22]; thus, beta cells are primed for disruption by ER-active EDCs like BPA. Indeed, fetal offspring of C57BL/6 dams fed a BPA-containing diet from embryonic day 7.5 (E7.5) to E18.5 exhibited altered endocrine pancreas development, with disruptions in the number and relative cellular composition of islets [23]. Using similar exposures, male offspring of pregnant mice exposed subcutaneously to BPA exhibited enhanced insulin secretion at 17 weeks of age, suggesting BPA-induced insulin resistance; moreover, by 28 weeks, the mice exhibited hyperglycaemia without alterations in glucose-stimulated insulin secretion (GSIS) [24]. Of note, follow-up studies using a similar exposure window and a higher BPA dose demonstrated that the lower BPA dose, but not the higher dose, decreased GSIS at postnatal day 30, despite increased beta cell mass, which was attributed to increased expression of pro-proliferative genes and decreased expression of genes regulating beta cell death [25]. Intriguingly, beta cell mass was actually decreased in BPA-treated animals by postnatal day 120. The discrepancies in the two studies are likely to be related to the different postnatal ages examined; however, it remains unclear why GSIS was impaired in young animals but was normal at later ages.

To better mimic exposures during human development, we examined the impact of dietary exposure of mice to environmentally relevant BPA doses from 2 weeks prior to pregnancy to the end of lactation using a low phytoestrogen control diet and BPA-free cages; serum BPA levels approximated those in humans [17]. Male offspring of exposed dams, but not females, developed abnormal glucose tolerance associated with insulin secretory defects, including increased basal rates of insulin release at the higher BPA dose that was suggestive of insulin resistance. Interestingly, differences in insulin release using a glucose gradient were not observed between control males and those that received a higher dose of BPA, nor was KCl-induced insulin release in islets altered by the higher BPA dose, suggesting an intact insulin secretory apparatus. In contrast, male offspring exposed to the lower BPA dose exhibited similar basal rates of insulin release; however, maximal GSIS was impaired [17]. These data suggest that the metabolic consequences of developmental BPA exposure exhibit complex dose–response relationships.

An area of intense interest in the developmental programming of metabolism is the multigenerational heritability of metabolic traits after ancestral EDC exposure. To determine whether BPA-induced metabolic disruptions persisted into F2 offspring, BPA-exposed F1 females were mated to unexposed

males [17]. Like F1 offspring, F2 males of dams exposed to a higher dose of BPA were glucose intolerant with preserved GSIS, while F2 males of dams exposed to a lower dose of BPA exhibited blunted GSIS. In addition, lower dose BPA exposure significantly reduced beta cell mass and increased beta cell death in F1 males, which persisted into the F2 generation; transcriptomic analyses indicated significant dose-specific changes in genes regulating inflammation and mitochondrial function [18]. Collectively, these results demonstrate multigenerational dose- and sex-specific metabolic effects of developmental BPA exposure.

These data fit within a broadening context of multigenerational and transgenerational effects of multiple EDC classes on various endocrine and metabolic tissues [7, 26–29]. Recently, studies have demonstrated that changes in the expression and methylation of imprinted genes in the brain persist across three generations after BPA exposure in mice [30]. In examining the transgenerational (F3) effects of BPA on metabolic health, we found that F3 adult males exposed ancestrally to either the lower or higher BPA dose had increased body weight with preserved glucose tolerance [19]. F3 male offspring of dams exposed to the lower BPA dose had reduced beta cell mass and smaller islets that exhibited enhanced GSIS. There was no effect of BPA in F3 females. These studies show that maternal BPA exposure resulted in fewer metabolic defects in F3 than F1 and F2 offspring, and these were sex- and dose-specific. Interestingly, while these data suggest a decay in EDC effects over generations, the relationships may be more complex for other exposures. For example, the fungicide and booster biocide tributyltin (TBT) has been shown to exert transgenerational effects on adipose tissue, with some phenotypes that amplify over successive generations [31].

## Mechanisms of EDC action

There are a number of possible mechanisms by which EDCs can influence health outcomes. These include interference with the activity of nuclear receptors, noncanonical steroid hormone receptors and orphan receptors, as well as disruptions in the enzymatic pathways regulating steroid biosynthesis and/or metabolism. For example, BPA can bind multiple oestrogen receptor subtypes. Moreover, several studies indicate that BPA also promotes signalling via extranuclear signal transduction pathways, including extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and Akt [32], and BPA also exerts oestradiol-like effects by binding to ERα and thereby activating extranuclear pathways [33]. Thus, it is increasingly clear that the diverse effects of BPA are likely to arise from interactions across multiple signal transduction pathways [34]. Adding complexity is the fact that epidemiological data have linked BPA to disruptions in androgen-dependent developmental outcomes [35], despite few mechanistic data demonstrating that BPA alters androgen receptor activity or interferes with androgen-dependent extranuclear receptors. Finally, there is some evidence that BPA may also disrupt glucocorticoid receptor signalling [36–38]. Because endocrine signalling adapts to tonic activation through feedback circuits and because metabolic phenotypes arise from the integrated crosstalk of multiple signalling cascades that act additively, antagonistically or synergistically, the diversity of BPA actions illustrates how this and other EDCs may exhibit non-monotonic dose–response relationships in which phenotypic changes at low doses are not necessarily observed with higher exposures.

While significant literature linking developmental EDC exposures to metabolic disorders focuses on oestrogen receptor actions, robust data also indicate that perinatal exposures to some EDCs alter the expression or activity of the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) and its heterodimeric partner retinoid X receptor (RXR), which play essential roles in adipocyte development and function. Interestingly, BPA has been shown to increase PPARγ expression [39]. While no studies have shown that BPA directly binds to PPARγ, brominated BPA analogues, also found in high quantities in the environment, bind to the receptor at low concentrations [40]. The prototypical obesogen TBT binds and activates both PPARγ and RXR at very low concentrations, augmenting adipocyte differentiation, promoting adipocyte dysfunction and resulting in transgenerational disruptions in metabolic homeostasis [26, 31, 41–43].

Our recent studies suggest that mitochondrial dysfunction could be an early event in the BPA-induced impairment of beta cells [18, 19]. Low-dose exposure of pregnant dams impairs beta cell mitochondria function, blunts GSIS, and reduces beta cell mass in male offspring [18]. These effects persisted into the second, but not the third, generation [19]. In another study, perinatal BPA exposure decreased activity of Complexes I and III of the electron transport chain in the livers of suckling rats, with later-life development of microvesicular liver steatosis and enhanced lipogenic gene expression [44]. Beyond BPA, other common EDCs have also been shown to disrupt mitochondrial function after developmental exposure, including arsenic [45].

Collectively, these data underscore the complexity of endocrine disruption with regard to metabolic outcomes. Unlike pharmaceutical agents that are designed to hit specific molecular targets, EDCs often interfere with multiple pathways, with specific effects likely dependent on both the dose and timing of exposure as well as the target and the background hormonal milieu. However, to date, while multiple studies have demonstrated that EDCs exhibit multiple modes of action, very few studies have definitively ascribed specific mechanisms to particular phenotypes. This greatly complicates our understanding of the molecular

mechanisms of these agents and argues for comprehensive unbiased approaches for uncovering the network of metabolic toxicities induced by these agents.

## Epigenetic mechanisms

With studies demonstrating transgenerational effects of EDCs on metabolic health, attention has turned to how EDCs directly influence the epigenome. Multiple studies report associations between developmental exposures to EDCs and epigenetic changes in key metabolic tissues, including beta cells, liver, adipose and muscle [7]. One of the earliest studies examining this phenomenon demonstrated that developmental BPA exposure shifts the coat colour of Agouti mice through stable epigenetic changes [46]. In general, imprinted genes are particularly vulnerable to de novo epigenetic modifications. Dams exposed to BPA from 2 weeks prior to mating to the end of gestation yielded offspring with loss of imprinting and biparental expression of *Igf2*, increased embryonic *Igf2* gene expression and enhanced methylation of the *Igf2* differentially methylated region 1 (DMR1) [17]. Extension of these studies demonstrated that *Igf2* DMR1 hypermethylation persisted in islets of F1 and F2 offspring of BPA-exposed dams with an associated increased expression of *Igf2* [18]. While *Igf2* has multiple functions, it is a key regulator of beta cell development, and aberrant early-life *Igf2* imprinting could potentially disrupt beta cell development.

Epigenetic alterations have also been described for several other metabolically active EDCs [7]. Phthalates are a family of phthalic acid diesters that are commonly found in consumer products, resulting in ubiquitous exposure in the USA. Limited but growing evidence in human studies indicate that phthalate exposure is associated with DNA methylation changes of imprinted genes in cord blood and placenta [47]. Animal studies demonstrate associations between phthalates and global and site-specific methylation [48]; however, studies were performed in mixed cell populations, and changes in DNA methylation were usually modest.

In addition to BPA and phthalates, other EDCs linked to epigenetic modifications include the metabolism-disrupting chemicals arsenic [49] and TBT [26]. Importantly, epigenetic modifications are cell- and tissue-specific, and findings from one tissue or cell type may not serve as a proxy for another. Moreover, even single cell types are often heterogeneous, and this lack of uniformity is likely to reflect differences in cell state or cell-specific functions. For example, not all beta cells function similarly in an islet, and this may be reflected in epigenetic differences. Demonstrating that epigenetic modifications induce changes in gene expression that, in turn, cause abnormal phenotypes is experimentally challenging; however, it is imperative to link exposure-associated changes to metabolic dysregulation.

## Beyond offspring: impact of gestational exposures on mothers

While environmental exposures during gestation and lactation can clearly impact the long-term metabolic trajectory of offspring, the consequences of exposures during this window on mothers is less appreciated. Gestational diabetes (GDM) imposes unique pregnancy-associated risks, including gestational hypertension, preeclampsia, future diabetes and obstetric complications. Assessments of EDC effects on GDM in humans remain in their infancy; however, emerging data suggest potential associations. Commonly found in cosmetics, pharmaceuticals and food, parabens were associated with glucose levels during pregnancy in a cohort of women at high risk of GDM [50], while the widely used antibacterial triclosan was nearly significantly associated with GDM in another cohort [51]. In the Infant Development and Environment Study, monoethyl phthalate levels were associated with increased GDM risk [52]. Among the inorganic EDCs, arsenic has been associated with GDM in a host of studies. In the Maternal-Infant Research on Environmental Chemicals Study, the risk of GDM was nearly fourfold greater in the highest vs lowest tertile of dimethylarsinic acid levels [53]. Overall, arsenic has been associated with GDM in many [54–57] but not all studies [58]. In addition to disruptions during gestation, the dynamic changes that happen in the pancreatic islet under the influence of pregnancy hormones suggest that environmental insults that occur during this window may permanently reprogram beta cells and thereby alter their long-term function. Indeed, gestational BPA exposure was shown to not only induce metabolic dysfunction in adult offspring [59], but exposed dams also exhibited glucose intolerance later in life [60]. While more studies that employ comprehensive exposure assessments throughout pregnancy are needed, these data highlight pregnancy as a unique window of susceptibility to EDC-induced metabolic dysfunction.

## Exposures in later life and metabolic dysfunction

Robust evidence now links exposure to a variety of EDCs with diabetes risk (reviewed extensively in refs. [7–10]). The majority of cross-sectional and prospective epidemiological analyses have been conducted in adult populations, while most animal studies have employed exposure paradigms using adult mice. Across these studies, there is great diversity in the spectrum of environmental toxicants linked to diabetes, with multiple potential mechanisms of metabolic toxicity (Fig. 2). EDCs linked to diabetes and/or alterations in insulin–glucose dynamics in human studies include arsenic, BPA, dioxins, organochlorine pesticides, PCBs and phthalates, among others [61–72]. In animal studies, disruptions in glucose homeostasis

have been linked to arsenic, atrazine, BPA, cadmium, dioxins, malathion, particulate matter air pollution, PCBs, phthalates, persistent organic pollutants, tolylfluanid, and TBT [73–93]. Importantly, the diversity of EDCs now linked with metabolic dysfunction, coupled with the frequency with which human populations are exposed, now raise important questions with regard to how these diabetogenic agents interact with each other, as well as with traditional diabetes risk factors, to augment disease risk [94].

Indeed, diabetogenic EDC exposures do not exist within a vacuum; rather, exposures occur concurrently with other metabolic stressors. Recent animal models demonstrate that excess energy intake induced by provision of a high-fat or high-fat/high-sucrose diet augments the metabolic dysfunction induced by BPA [90, 95, 96], dichlorodiphenyltrichloroethane (DDT) [97], perfluoroalkyl substances [98], tolylfluanid [79] and phthalates [99]. Intriguingly, some studies suggest an EDC–diet potentiation that evolves over time as with dichlorodiphenyldichloroethylene (DDE) [100]. In contrast, other data suggest that changes in diet may precipitate adverse EDC effects; this has been suggested for PCBs, which may specifically impair glucose tolerance after diet-induced weight loss [91, 101]. Importantly, since many EDCs are lipophilic, high-fat diets are likely to augment exposure, whereas reductions in adipose mass with weight loss release EDCs into the circulation [102–105]. Whether this mobilisation from adipose tissue antagonises subsequent weight loss remains under debate.

## Environmental diabetogens and health justice

It has long been recognised that diabetes disproportionately afflicts racial and ethnic minorities, as well as those with lower incomes. Despite this knowledge, these disparities have been amplified over time [106]. In addition to higher rates of disease, African-Americans and Latinx/Hispanics are more likely to suffer microvascular complications, including nephropathy [107], neuropathy/amputations [108] and retinopathy [109]. Furthermore, diabetes-related mortality is also higher in these communities [110]. While various social factors are posited to contribute to diabetes disparities, less appreciated is the additional contribution of environmental injustice to this heightened risk. In our recent analysis, five classes of EDCs associated with diabetic phenotypes in cell-based and animal studies (PCBs, organochlorine pesticides, chemical constituents of air pollution, BPA and phthalates) were shown to be linked with incident diabetes in prospective epidemiological studies [111]. Importantly, for each of these EDC classes, data indicated that racial and ethnic minorities, as well as those with lower incomes, are more highly exposed [111]. In addition, studies suggest that racial and ethnic minorities may be at heightened risk for EDC-induced metabolic dysfunction. In a meta-analysis, exposure to higher vs lower levels of both PCBs and organochlorine pesticides was associated with greater diabetes risk in non-white compared with white populations [65]. In a study of phthalates and metabolic control, phthalate-associated insulin resistance was observed in Mexican Americans and African-Americans but not in non-Hispanic whites [112]. In another study, phthalates were associated with worse glucose control and more severe insulin resistance in African-Americans and Mexican Americans compared with non-Hispanic whites [113]. A recent analysis examining the links between phthalates and GDM suggested potentially higher phthalate-associated risk among Asians [52]. Finally, in a study of overall mortality, the hazard ratio for death per unit increase in particulate matter air pollution was higher in Hispanics and much greater in blacks than in whites [114]. Whether the enhanced diabetes- and mortality-associated risks of environmental toxicants in communities with heightened diabetes risk arises from higher baseline exposures, gene–environment interactions or environment-amplified social risk factors remains to be clarified; however, regardless of the origin of this enhanced risk, addressing environmental potentiators of diabetes is essential for reducing disease disparities and improving health equity.

## From abdication to engagement

With mounting evidence that EDCs contribute to diabetes pathogenesis, it is incumbent upon the diabetes care community to address the environmental drivers of the disease; however, current clinical practice guidelines wholly neglect environmental toxicants as diabetes risk factors [115]. While data are required to definitively demonstrate that exposure reduction improves outcomes, emerging evidence provides a framework for action [116]. Importantly, paradigms for environmental risk reduction are available in other fields, such as chronic obstructive lung disease [117] and asthma [118], which acknowledge the health threat posed by air pollution, an exposure also linked to diabetes [119, 120]. In addition, leadership from the American College of Obstetricians and Gynecologists, International Federation of Gynecology and Obstetrics, and the Endocrine Society provide further guidance on areas for risk reduction [5, 121, 122]. The urgency for such action is underscored by data from the European Union estimating that five EDCs alone add €18–29 billion annually to obesity- and diabetes-associated healthcare costs [123]. Conversely, data from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study indicate that 25% reductions in only four target compounds (PCB 153, monoethylphthalate, DDE and perfluorononanoic acid) would reduce diabetes prevalence by 13% in Europe (over 150,000 cases), with associated cost savings of €4.51 billion annually [124]. Given the narrow focus of these analyses

relative to the total burden of human chemical exposure, reducing contact with diabetogenic chemicals has potential to substantially lower the individual and societal toll of diabetes and its complications. Capitalising on this, however, requires both improved clinical guidance, as well as transformations in public policy to incorporate diabetes and its associated costs into the development of environmental policies [125].

## Challenges and controversies

Despite consensus statements regarding EDC risks from the Organisation for Economic Co-operation and Development in the European Union and the Endocrine Society, some controversies persist. These include robust discussion regarding methodologies used in biomonitoring studies, including the validity of ELISA for measuring BPA concentrations in bodily tissues. Importantly, more recent studies have employed more sensitive and reliable techniques to measure very low levels of EDCs. It has also been suggested that low levels of unconjugated BPA in bodily tissues and fluids arise from contamination of collection materials and/or deconjugation of BPA metabolites during storage. To address this concern, multiple human and animal studies have detected BPA in a variety of biological specimens using alternative methods, and storage vials are now BPA-free. Furthermore, high-quality animal studies are now designed to limit background EDC exposure from diet, caging, bedding and water bottles. The route of exposure used in animal studies also remains hotly debated. While differences in exposure routes can affect circulating BPA levels, several studies have shown that there are fewer differences in route-dependent BPA metabolism and excretion than previously thought [126]. Collectively, these issues mandate rigorously designed epidemiological and animal studies. Importantly, recent clinical studies have demonstrated that administering BPA to humans alters glucose–insulin homeostasis [127, 128]. While these data validate the robust cell-based, animal and epidemiological evidence linking BPA to metabolic disruptions, they also raise an important ethical question: Will such direct evidence of harm be required for each of the thousands of chemicals to which humans are exposed before action is taken to protect public health?

## Conclusions

Burgeoning evidence now implicates exposure to a variety of environmental toxicants in the pathogenesis of diabetes. These exposures occur across the lifespan; however, certain developmental periods are uniquely sensitive windows during which metabolism can be permanently disrupted in both the exposed individual and subsequent generations. Importantly, several communities at heightened diabetes risk are also exposed to higher levels of chemicals linked to the disease. Despite this evidence, clinical practice remains blind to EDCs as diabetes drivers. While more work is required to address knowledge gaps regarding environmental exposures and diabetes risk, the weight of the evidence now mandates action to empower individuals and governments to address environmental contributors to diabetes risk.

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