The Paradox of Progress: Environmental Disruption of Metabolism and the Diabetes Epidemic

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As the tide of chemicals born of the Industrial Age has arisen to engulf our environment, a drastic change has come about in the nature of the most serious public health problems.

Rachel Carson, *Silent Spring*, 1962

Worldwide rates of diabetes and other metabolic diseases have exploded over the last several decades. Globally, more than 170 million individuals currently suffer from diabetes, and this number is projected to reach a staggering 366 million by 2030 (1). This scourge results in significant individual morbidity and mortality while contributing to the economic fragility of healthcare systems across the globe. In the U.S. alone, annual costs associated with diabetes are estimated to be $174 billion (2). As such, every effort must be made to understand the factors underlying this emerging metabolic disaster in order to mitigate its deleterious impact on the individual and society. Recently, an expanding body of scientific evidence has begun to link exposure to synthetic chemicals with a wide variety of diseases, including reproductive tract disorders and neurobehavioral diseases. The present work discusses epidemiological links between chemical exposure and disorders of glucose homeostasis, experimental data demonstrating chemical-induced changes in insulin action, and challenges facing the field of metabolic disruption as well as approaches for addressing those challenges.

Originally articulated in the early 1990s, the environmental endocrine disruptor theory proposes that some exogenous chemicals interfere with endogenous hormonal axes (3). The recognition of this potential mechanism of action was a paradigm shift in toxicology that had previously focused on a chemical's capacity to induce acute toxicity or to cause cancer via mutagenesis. The Environmental Protection Agency (EPA) defines an endocrine disrupting chemical (EDC) as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis, reproduction, development, and/or behavior" (4). Putative EDCs include structurally diverse chemicals including organic pollutants, heavy metals, pharmaceuticals, and phytochemicals, with humans exposed through agricultural

goods and consumer products, as well as water and air contaminated with industrial waste (Fig. 1). Early studies of EDCs focused on identifying chemicals with the capacity to modulate sex steroid and thyroid hormone signaling; however, recent work suggests that some chemicals may disturb signaling pathways critical for energy homeostasis (5). Despite the potential importance of EDCs in the pathogenesis of metabolic diseases, the contribution of synthetic chemical exposure to the diabetes epidemic remains largely unrecognized and underappreciated even though U.S. diabetes rates have increased in concordance with the national production of synthetic organic chemicals (Fig. 2). While such correlations are crude, emerging data supports a biologically plausible causative link between diabetes and chemical exposure. Here, we present data suggesting a role for some synthetic chemicals in the pathogenesis of diabetes that merits comprehensive efforts to address the contribution of environmental pollutants to this burgeoning metabolic catastrophe.

Environmental obesogen hypothesis. An unequivocal contributor to the diabetes epidemic is the metabolic stress induced by rising rates of obesity. Increased adiposity is closely linked to the development of insulin resistance, an important predisposing factor in the development of type 2 diabetes. Over the last several decades, obesity rates have exploded, with more than a third of the adult U.S. population now obese (6). The society-wide accumulation of body fat is undoubtedly a consequence of a widening gap between caloric intake and caloric expenditure resulting from myriad social forces; however, the magnitude and rapidity with which obesity rates have increased raise concerns about other pathogenic factors. In 2002, Baillie-Hamilton (7) proposed a link between the post–World War II increase in synthetic chemical production and the obesity epidemic. This correlation, coupled with experimental evidence demonstrating that certain environmental pollutants induce adipogenesis and weight gain in experimental models, led to the environmental obesogen hypothesis that posits a causative role for synthetic chemicals in the pathogenesis of obesity (rev. in 8).

While environmental obesogens have rightfully received much discussion, it is important to recognize that obesity per se may not lead to abnormalities in glucose homeostasis. An important distinction in obesity research is the differentiation between metabolically deleterious obesity and the "fit fat" (9). Thus, while increased fat mass may contribute to the development of diabetes, obesity is not a necessary or sufficient condition. Insulin resistance can arise independent of obesity, and the onset of frank diabetes necessitates a deficit in β-cell insulin production, as either the primary defect or the failure to compensate for diminished insulin sensitivity. Therefore, the search for pollution-induced diabetes should include a specific focus on compounds with the capacity to induce insulin resistance and/or impair β-cell function.
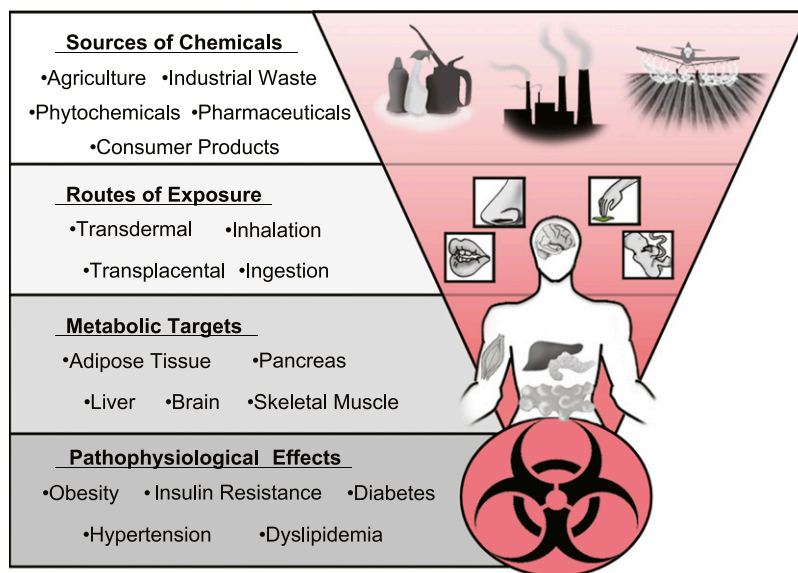
FIG. 1. Sources and targets of metabolic disruptors.

Epidemiological evidence of diabetogenic pollutants.

Data linking diabetes to environmental pollutants have come from a number of epidemiological studies performed in a variety of experimental contexts (Table 1). Environmental disasters such as the chemical plant explosion in Seveso, Italy, have suggested a link between dioxin exposure and diabetes (10), while rice oil contamination in Yucheng, China, has implicated polychlorinated biphenyl ethers (PCBs) and furans (11). Exposure of military personnel to dioxins during the Vietnam War has been associated with a higher prevalence of diabetes and a reduced latency to disease development (12). Several studies of occupational exposure have suggested links between diabetes and organochlorine pesticides (13) or dioxins (14). Recreational contact via consumption of sport fish from the Great Lakes in the U.S. tied diabetes incidence with

p,p'-diphenyldichloroethene (DDE), the principle metabolite of the insecticide p,p'-dichlorodiphenyltrichloroethane (DDT) (15). A variety of international studies demonstrated diabetogenic links to organochlorine pollutants (16) and heavy metals (17), with some studies suggesting a specific defect in insulin secretion but not in overall glucose tolerance (18). In addition to diabetes, epidemiological studies have associated various pollutants with other measures of disturbed glucose homeostasis, including prediabetes (impaired fasting glucose and/or impaired glucose tolerance) (16), the metabolic syndrome (19), and insulin resistance (20).

Many of the above studies focused on specific populations (i.e., those exposed occupationally, recreationally, or through specific industrial accidents) that may not reflect the risk posed to the general population; however, a series of recent investigations have examined the connection between various pollutants and measures of glucose homeostasis using data from the National Health and Nutrition Examination Survey (NHANES), which provides a representative sampling of the U.S. population (21). NHANES-based studies have shown associations between phthalates and various persistent organic pollutants (POPs) with insulin resistance, the metabolic syndrome, and diabetes (20,22). In addition, urinary levels of the ubiquitous plasticizer, bisphenol-A (BPA), have been detected in >95% of the NHANES cohort (23) and positively correlate with diabetes prevalence and other metabolic derangements (24). Thus, there is intriguing evidence suggesting possible connections between pollutants and the development of diabetes.

There are, however, caveats that must be considered in interpreting these studies. One significant challenge is the common use of cross-sectional design to correlate disease prevalence with current EDC levels. Such analyses are particularly problematic for chemicals that metabolize more rapidly and exhibit fewer propensities to bioaccumulate (e.g., BPA and phthalates) because their current levels may differ from concentrations during disease development. Additionally, issues related to coexposures to confounding compounds, selection of control populations, and variability in statistical analyses complicate data interpretation and
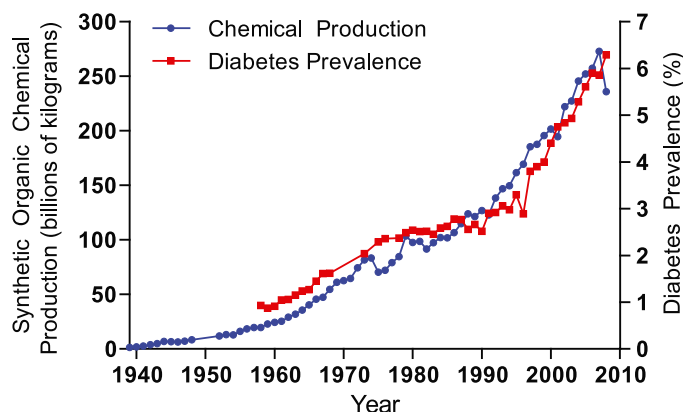
FIG. 2. U.S. synthetic chemical production and diabetes prevalence. Synthetic chemical production in the U.S. from 1939 to 1994 was obtained from the U.S. Tariff Commission reports (72). Production from 1995 to 2008 was extrapolated using the annual index of chemical production published by Chemical & Engineering News from 1989 to 2008 (73,74), with kilograms calculated from linear regression analysis of overlapping data from 1989 to 1994 (r^2 = 0.948). Diabetes prevalence was obtained from the Centers for Disease Control and Prevention (75).

TABLE 1
Epidemiological data linking EDC exposure to diabetes

Reference	EDC	Population	Association with diabetes	Notes
Morgan et al., Arch Environ Contam Toxicol 1980;9:349–382	Pesticides	2,620 pesticide exposed workers from 1971–1977	Cause-of-death questionnaires addressed to survivors indicated possible association between DDT exposure and diabetes	
Lai et al., Am J Epidemiol 1994;139:484–492	Arsenic	891 Taiwanese residents exposed to arsenic in 1988	Abnormal OGTT, medical histories of diagnosed diabetes, and use of diabetes treatments significantly associated with arsenic exposure	Dose-response relationship between arsenic exposure and diabetes prevalence
Henriksen et al., Epidemiology 1997;8:252–258	TCDD	989 Air Force veterans of Operation Ranch Hand exposed to TCDD	Glucose abnormalities, diabetes diagnosis, and use of diabetic medications associated with TCDD exposure	Significant hyperinsulinemia in exposed nondiabetic subjects
Pesatori et al., Occup Environ Med 1998;55:126–131	TCDD	Large Italian cohort (>230,000) localized in the exposure zones of the 1976 Seveso accident	Mortality study using Poisson regression to assess relative risk determined substantial TCDD exposure correlated to increased diabetes mortality in women	
Vena et al., Environ Health Perspect 1998;106:645–653	TCDD, HCD	International study of 36 cohorts from 12 countries (1939–1992) (>25,000)	Job record data and company questionnaires with biological and environmental measurements suggested possible correlation of TCDD exposure with diabetes	Strongest association found when first exposure was 10–19 years previous to assessment and with duration of exposure of 10–19 years
Calvert et al., Occup Environ Med 1999;56:270–276	TCDD	281 former workers at two U.S. chemical plants	Cross-sectional study significantly associated individuals with the highest serum lipid–adjusted TCDD concentrations with higher serum glucose levels	
Cramner et al., Toxicol Sci 2000;56:431–436	TCDD	69 individuals in Jacksonville, AR, living within 25 miles of the Vertac waste site	Higher fasting plasma insulin levels associated with individuals in the top 10% of TCDD concentrations (>15 ppt)	No associations with TCDD and glucose levels, obesity, or total lipids
Bertazzi et al., Am J Epidemiol 2001;153:1031–1044	TCDD	15-year follow-up to the 1976 Seveso accident	Mortality study associated an increase in reported diabetes with TCDD exposure in women	
Beard et al., Environ Health Perspect 2001;111:724–730	Pesticides	1999 Australian pesticide sprayers employed from 1935–1996	Mortality study and surviving morbidity questionnaire determined increased mortality due to diabetes associated with pesticide exposure	Diabetes more commonly self-reported with occupational herbicide use
Fierens et al., Biomarkers 2003;8:529–534	17 PCDD/Fs, dioxins, 4 PCBs, 12 PCB markers	257 environmentally exposed Belgians	Quantification of serum fat from a population-based study determined significantly increased levels of dioxins, PCBs, and PCB markers in diabetic patients	Diabetes risk significantly increased for individuals in the top decile of dioxin concentrations
Glynn et al., Environ Health Perspect 2003;111:349–355	7 PCBs, 5 OC pesticides	205 Swedish women	Association study of lifestyle/medical factors and serum PCB levels indicated increased prevalence of diabetes with higher serum PCB concentrations	Serum PCB concentrations also associated with age, body, BMI, diet, and location of residence

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Reference	EDC	Population	Association with diabetes	Notes
Rylander et al., Environ Health 2005;4:28	PCB-153, DDE	380 male and female Swedish fishers with a Baltic Sea marine diet	Cross-sectional study significantly associated serum PCB-153 and DDE levels with an increased prevalence of diabetes	Association stronger with PCB-153 for men and with DDE for women
Lee et al., Diabetes Care 2006;29:1638–1644	6 POPs detected in >80% of population	2,016 adults from the 1999–2002 NHANES	Prevalence of diabetes associated with increased lipid-adjusted serum concentrations of dioxins, PCBs, and organochlorines	Stronger correlations with younger age, obesity, or Mexican American heritage
Vasiliu et al., Epidemiology 2006;17:352–359	PCBs, PBBs	1,384 individuals from the Michigan PBB cohort	Enrollment questionnaires and serum samples associated serum PCB levels with an increased prevalence of diabetes in women	Exposed overweight and obese men and women had an increased prevalence of diabetes
Codru et al., Environ Health Perspect 2007;115: 1442–1447	101 PCBs, DDE, HCB	352 adult Native Americans (Mohawk)	Standardized questionnaire and fasting serum samples positively associated the highest tertile of serum HCB levels with diabetes	Nonsignificant associations with PCBs and DDE with diabetes; mirex levels inversely associated with diabetes
Cox et al., Environ Health Perspect 2007;115: 1747–1752	OC pesticides	1,303 adult Mexican Americans from the 1982–1984 HHANES	Self-reported diabetes significantly associated with lipid-adjusted serum DDT levels and serum glucose levels were elevated in individuals exposed to *trans*-nonachlor and HCH	
Everett et al., Environ Res 2007;103:413–418	HxCDD, PCB, DDT	1,830 adults from the 1999–2002 NHANES	Diabetes significantly associated with serum PCB 126, DDT, and HxCDD levels. PCB 126 and DDT levels significantly associated with undiagnosed diabetes (HbA$_{1c}$ >6.1%)	
Stahlhut et al., Environ Health Perspect 2007;115:876–882	Phthalates	U.S. men from the 1999–2002 NHANES	Insulin resistance measured by HOMA-IR was associated with three phthalates (MBP, MBzP, MEP)	Four phthalates (MBzP, MEHHP, MEOHP, MEP) associated with increased waist circumference
Lee et al., Diabetologia 2007;50:1841–1851	OC pesticides, PCBs	721 nondiabetic participants from the 1999–2002 NHANES	Fasting glucose levels and metabolic syndrome significantly associated with increased levels of OC pesticides	PCBs were significantly associated with waist circumference. OC pesticides significantly associated with elevated triacylglycerides
Lee et al., Diabetes Care 2007;30:1596–1598	PCDD/Fs, PCBs, OC pesticides	1,721 individuals from the 1999–2002 NHANES	Prevalence of diabetes strongly associated with serum concentrations of PCBs and OC pesticides	PCDDs and PCDFs weakly associated with diabetes
Lang et al., JAMA 2008;300:1303–1310	BPA	1,455 U.S. adults from the 2003–2004 NHANES	Urinary BPA concentrations associated with diabetes prevalence in a dose-dependent manner	
Lim et al., Diabetes Care 2008;31:1802–1807	5 PDBEs, PBB	637 adults from the 2003–2004 NHANES	Serum concentrations of various brominated flame retardants correlated with increased prevalence of diabetes with varying dose dependency	PBDE-153 showed an inverted U-shaped association with metabolic syndrome
Jørgensen et al., Diabetologia 2008;51:1416–1422	General POPs	692 Greenland Inuits sampled from 1999–2002 living on a marine diet	Significant inverse association between POPs and stimulated insulin concentrations and HOMA-B	No association between POP concentration and glucose intolerance or insulin resistance

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Reference	EDC	Population	Association with diabetes	Notes
Wang et al., Diabetes Care 2008;31:1574–1579	PCBs, PCDFs	1,054 Taiwanese poisoned with PCB-laced rice-bran oil during late 1970s	Blind morbidity follow-up interviews and chloracne diagnoses significantly associated PCB exposure with an increased prevalence of diabetes in women	
Turyk et al., Environ Health Perspect 2009;117:1076–1082	PCBs, DDE	Population of sport fish consumers in the Great Lakes region from 1990s–2005	Serum concentrations of DDE positively associated with increased diabetes prevalence	No association with total PCB levels
Park et al., J Prev Med Public Health 2010;43:1–8	OC pesticides	50 South Korean nondiabetic subjects with metabolic syndrome	Community-based health surveys and HOMA-IR measurements associated OC pesticide exposure with metabolic syndrome	Strong dose dependence between heptachlor epoxide and HOMA-IR
Ukropec et al., Diabetologia 2010;53:899–906	PCBs, HCB, DDE, DDT, HCH	1,220 PCBRISK survey participants from Eastern Slovakia	Abnormal OGTTs and fasting glucose levels associated with serum levels of POPs suggesting dose-dependent increased risk of diabetes and prediabetes	No association between HCB and HCH levels and diabetes

HCB, hexachlorobenzene; HCD, higher chlorinated dioxins; HCH, hexachlorocyclohexane; HHANES, Hispanic Health and Nutrition Examination Survey; HOMA-B, homeostasis model assessment of β-cell function; HxCDD, hexachlorodibenzo-*p*-dioxin; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate, NHANES, National Health and Nutrition Examination Survey; OC, organochlorine; OGTT, oral glucose tolerance test; PBB, polybrominated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PDBE, polybrominated diphenyl ethers.

extrapolation to the general population. Furthermore, there is heterogeneity in the definition of diabetes and insulin resistance used in these studies. Collectively, these challenges underscore the need for expanded longitudinal studies that can follow chemical exposures throughout disease development in order to better relate specific chemicals to the pathogenesis of diabetes.

Evidence of environmental diabetogenic pollutants in animal models. The shortcomings of epidemiological investigations can be overcome by studying suspected diabetogenic chemicals using animal models. A number of chemicals have been shown to elicit biological effects that alter glucose homeostasis (Table 2). For instance, acute exposure of male mice to BPA was found to reduce the rise in plasma glucose during an intraperitoneal glucose tolerance test; however, sustained exposure (more similar to human exposure) resulted in hyperinsulinemia, a worsening of glucose tolerance, and a concomitant reduction in insulin sensitivity (25). Interestingly, the impairment in insulin action occurred despite a demonstrated increase in β-cell insulin content after both in vivo and in vitro BPA exposure (26). One explanation for these findings is that BPA operates through multiple mechanisms that independently increase insulin synthesis/secretion while simultaneously inducing peripheral insulin resistance. Alternatively, higher insulin levels induced by BPA may result in a compensatory insulin resistance to limit hypoglycemia. Regardless of the process, the overall effects of chronic BPA exposure on glucose homeostasis suggest that it may be a diabetogenic factor (27).

Other pollutants also disrupt glucose homeostasis in experimental models. Exposure of rats to the flame retardant polybrominated diphenyl ether significantly increased lipolysis while reducing insulin-stimulated glucose uptake (28). Diethylhexyl phthalate, a common plasticizer, reduced insulin levels and raised serum glucose levels in exposed rats (29), while mice treated with tributyl tin (TBT), a fungicide and antifouling agent, demonstrated hepatic steatosis and hyperinsulinemia (30). Recently, rats fed fish oil naturally contaminated with a variety of POPs demonstrated impaired glucose homeostasis, with several chemicals in the contaminated fish oil found to suppress insulin-stimulated glucose uptake in 3T3-L1 adipocytes (31).

These results are similar to findings that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) treatment of primary murine adipose tissue impaired insulin-stimulated glucose uptake, likely by reducing glucose transporter 4 transcript levels (32). In a separate model, mice exposed to TCDD had reduced glucokinase gene expression (33), predicting a rise in blood glucose levels analogous to that seen in maturity-onset diabetes of the young type 2. Others have suggested that the diabetogenic effects of TCDD are mediated through an antagonism of peroxisome proliferator–activated receptor-γ (PPARγ) action (34) or through upregulation of the inflammatory adipokine tumor necrosis factor-α (TNF-α) in adipocytes (35). While these data are consistent with epidemiological observations linking TCDD exposure to diabetes, other studies have shown that TCDD has hypoglycemic effects. In a rat model of diabetes incorporating high-fat diet coupled with streptozotocin treatment, TCDD treatment reduced plasma glucose levels (36). However, this study may reflect an alternative metabolic disruption of quasi-starvation mediated through TCDD suppression of gluconeogenesis via inhibition of PEPCK (37). Furthermore, the hypoglycemic effects of

TABLE 2
Animal studies demonstrating EDC-induced changes in glucose homeostasis

Author	EDC	Model system	Disruption of glucose homeostasis
Weber et al., Toxicology 1991;66:133–144	TCDD	Wild-type male Sprague Dawley rats	Injection of 25 μg/kg TCDD resulted in decreased activity of PEPCK and G-6-Pase after 2 and 8 days of treatment, respectively.
Liu et al., Mol Pharmacol 1995;47:65–73	TCDD	Wild-type male C57BL/6 and DBA/2J mice	A single dose of 116 μg/kg i.p. TCDD resulted in the significant decrease in glucose transport in adipose tissue and brain after 24 h that was sustained for at least 30 days. The effect was AhR mediated.
Gayathri et al., Indian J Med Res 2004;119:139–144	DEHP	Wild-type female Wistar Kyoto rats	Administration of 75 μg/kg DEHP every other day for 14 days resulted in a decrease in serum insulin and cortisol as well as liver glycogen; blood glucose was increased. The effects were reversible upon stopping treatment.
Alonso-Magdalena et al., Environ Health Perspect 2006;114:106–112	BPA	Wild-type male Swiss albino OF1 mice	Administration of a single 10 μg/kg dose of BPA produced a rapid rise in plasma insulin and a corresponding decrease in plasma glucose; however, 4-day treatment with 100 μg/kg/day of BPA impaired glucose tolerance on an intraperitoneal glucose tolerance test and reduced the hypoglycemic effect of insulin in an insulin tolerance test.
Hoppe and Carey, Obesity 2007;15:2942–2950	Penta-BDE	Wild-type male Sprague Dawley rats	Daily gavage of 14 mg/kg penta-BDE for 4 weeks resulted in a 30% increase in isoproterenol-stimulated lipolysis and a 59% decrease in insulin-stimulated glucose oxidation in adipocytes.
Alonso-Magdalena et al., PLoS One 2008;3:e2069	BPA	Wild-type male Swiss albino OF1 mice and ERα and ERβ KO mice	Administration of 100 μg/kg BPA twice per day for 4 days resulted in a significant increase in β-cell insulin content that was ERα dependent. Isolated islets treated with 1 nmol/L BPA had an increase in insulin content.
Sato et al., Toxicol Appl Pharmacol 2008;229:1019	TCDD	Wild-type male C57BL/6 and AhR KO mouse	Oral administration of 500 ng/kg TCDD once a day for 18 days resulted in significantly increased CYP1A1 expression in the liver and changes in energy metabolism gene expression that was AhR-mediated.
Ruzzin et al., Environ Health Perspect 2010;118:465–471	General POPs	Wild-type male Sprague Dawley rats	Administration of a crude fish oil diet for 28 days resulted in systemic insulin resistance, visceral fat accumulation, and hepatosteatosis. Several genes regulating hepatic lipid metabolism were altered. Isolated POP classes impaired insulin-stimulated glucose uptake in 3T3-L1 adipocytes.
Fried et al., Drug Chem Toxicol 2010;33:261–268	TCDD	Wild-type male Sprague Dawley rats	Diabetic rats (high-fat diet/streptozotocin treatment) dosed with 12.8 μg/kg TCDD had significantly reduced serum glucose levels by day 8 of treatment.
Zuo et al., Environ Toxicol 2011;26:79–85	TBT	Wild-type male KM mice	Oral administration once every 3 days for 45 days of 0.5–50 μg/kg TBT resulted in body weight gain, hepatic steatosis, hyperinsulinemia, hyperleptinemia, and a reduction in hepatic adiponectin levels in a dose-dependent fashion.

BDE, bromodiphenyl ether; DEHP, di(2-ethylhexyl)-phthalate; G-6-Pase, glucose-6-phosphatase.

TCDD occurred at concentrations within an order of magnitude of the known lethal dose for rat. The apparent incongruence between hypoglycemic and hyperglycemic observations likely reflects dose-dependent effects. Such findings underscore the need for mechanistic studies over wide concentration ranges that reflect both variability in human exposure and the potential for different mechanisms to predominate at different concentrations.

Putative diabetogenic mechanisms

Traditional endocrine disruption. Historically, EDC research has focused on the ability of exogenous chemicals to modulate the activity of classic nuclear hormone receptors, including those for estrogens, androgens, and thyroid hormone. Several of these pathways appear to be critically important for energy regulation in general and glucose homeostasis in particular. For example, knockout models of aromatase and the estrogen receptor-α demonstrate the capacity of estrogens to augment glucose tolerance and insulin sensitivity (38,39). However, the effects of estrogen on insulin action may be context-dependent, as conditions associated with estrogen levels that are both high (e.g., pregnancy) and low (e.g., menopause) correlate with insulin resistance. BPA is known to have estrogenic properties, and as mentioned, prolonged treatment of male mice with this EDC induces changes consistent with a diabetic phenotype (25). Furthermore, the augmentation in β-cell insulin content after BPA exposure appears to be a direct result of its estrogenic properties, as the effect was not observed in estrogen receptor-α–knockout animals (26). Because estrogens can have divergent effects on

insulin action, estrogenic EDCs may modulate insulin action differently depending on the background hormonal milieu. Thus, the experimental effects may differ between males and females as well as among females at various stages of their reproductive lives (i.e., prepubertal, postmenopausal, or reproductive age).

Androgens also appear to modulate insulin sensitivity. For example, emerging data suggests that low androgen levels in men correlate with insulin resistance. In the TIMES2 trial, testosterone treatment of hypogonadal men with diabetes or the metabolic syndrome improved insulin sensitivity as assessed by homeostasis model assessment of insulin resistance (HOMA-IR) (40). In contrast, exposure to androgens can also adversely affect glucose tolerance. Rhesus monkeys prenatally exposed to androgens show evidence of insulin resistance, with the females having features consistent with the polycystic ovarian syndrome (PCOS) phenotype (41). In humans, insulin resistance is an important clinical feature of PCOS. Interestingly, recent data suggests that women with PCOS have higher levels of BPA than control subjects, and among these PCOS patients, BPA levels correlated with measures of insulin resistance (42). Various synthetic chemicals have the capacity to function as both androgen agonists and antagonists (43), suggesting their capacity to disrupt glucose homeostasis. Importantly, these data also emphasize the potential importance of the timing, context, and relative balance of EDCs on the overall impact of chemical exposure on diabetes risk.

Given the central role of thyroid hormone in energy metabolism, disruption of normal thyroid hormone action may facilitate the development of a diabetic phenotype. Many chemicals can disrupt the thyroid hormone axis (44), and levels of several thyroid disruptors have been correlated with diabetes in epidemiological studies, including PCBs (45). Likewise, glucocorticoids are known modulators of energy metabolism, and recent data suggest that some EDCs may have the capacity to stimulate signaling through the glucocorticoid receptor (46) or by altering glucocorticoid synthesis or activation (47,48). EDCs with glucocorticoid-like activity would be predicted to diminish insulin sensitivity and foster a diabetic phenotype.

Other ligand-activated nuclear hormone receptors are important for energy regulation and have been implicated as EDC targets. Of particular interest are EDCs activating the PPARs. For example, TBT promotes adipogenesis by stimulating PPARγ and its obligate heterodimeric partner retinoid X receptor (RXR) in mouse models (49) and human mesenchymal stem cell cultures (50). Conversely, TCDD inhibits adipogenesis through a suppression of PPARγ (51). The proadipogenic effects of TBT and other EDCs serve as the basis for the environmental obesogen hypothesis. Nevertheless, while PPARγ promotes fat accumulation, its activation also increases insulin sensitivity; this is the rationale for using thiazolidinediones to treat diabetes. Despite this, TBT may impair insulin sensitivity (30); however, this may reflect its promiscuous activation of heterodimeric partners of RXR other than PPARγ. EDC-mediated effects on nuclear hormone signaling are emerging as important mechanisms of metabolic disruption; however, work remains to clarify whether these compounds alter signaling directly at the ligand binding site or whether indirect mechanisms such as coactivator/corepressor recruitment, ligand activation, allosteric effects, targeted receptor degradation, or others are the principle modes of action.

Cross-talk between xenobiotic signaling and metabolism. In addition to the traditional hormone receptors, the superfamily of ligand-activated nuclear hormone receptors includes several members that function primarily in the sensing and detoxification of foreign compounds, i.e., xenobiotics. These include the aryl hydrocarbon receptor (AhR), the pregnane X receptor, and the constitutive androstane receptor. In addition to their role in the induction of drug metabolizing enzymes, these receptors have modulating effects on lipid and glucose metabolism through their interaction with a wide array of other nuclear receptors (e.g., thyroid hormone receptor, glucocorticoid receptor, PPARα, PPARγ) and transcription factors (e.g., CREB, FOXO1, PGC1α) involved in energy regulation; moreover, the xenobiotic receptors appear to influence inflammatory responses (52). Interestingly, AhR was originally identified as the receptor for dioxin, one of the chemicals most frequently associated with diabetes in epidemiological studies. It is intriguing to speculate that xenobiotic receptors evolved in part to adjust metabolic pathways to environmental stressors, and that the proliferation of anthropogenic chemicals in the environment has overwhelmed these adaptive processes, thereby contributing to the onset of metabolic diseases.

Epigenetic changes. In line with the "developmental origins of adult disease" hypothesis, a recent emphasis in EDC research has been focused on the effects of in utero and early postnatal chemical exposure on the genesis of adult diseases through modulation of the epigenome. Exposure to a variety of pollutants appears to modify the epigenome (53), and concerning evidence demonstrates that chemical-induced epigenetic changes can be heritable. In a rat model, exposure of pregnant dams to the fungicide vinclozolin led to transgenerational epigenetic modifications into at least the F4 generation (54). Intriguingly, there is now data demonstrating the epigenetic regulation of various genes influencing metabolic diseases, including diabetes (55). While links between EDC exposure and epigenetic alterations of genes controlling energy metabolism have yet to be described, current evidence supports the contention that exposure to EDCs may influence the metabolic state of an individual, with the potential for these effects to be transmitted to subsequent generations.

Alternative mechanisms. EDC effects on other molecular mechanisms implicated in the development of diabetes, e.g., inflammation and oxidative stress, have only recently been considered. For example, PCB-77 has been shown to promote expression of the proinflammatory adipokines interleukin-6 (IL-6) and TNF-α, leading to impaired insulin signaling in endothelial cells (56). BPA treatment of human adipose tissue explants also augments secretion of IL-6 and TNF-α while simultaneously inhibiting the release of the insulin-sensitizing adipokine adiponectin (57). Interestingly, the detoxification of exogenous chemicals by the cytochrome P450 enzymes generates oxidative stress, which may promote hepatic insulin resistance due to the liver's dual role in energy and drug metabolism (58). Other diabetogenic mechanisms such as induction of endoplasmic reticulum stress, implicated in arsenic-induced β-cell apoptosis (59), are intriguing but remain poorly studied. With the plethora of structurally diverse compounds present in the environment, these and additional mechanisms may be relevant in the disruption of energy regulation. Characterizing the relevant mechanisms is critical for identifying potential pharmaceutical targets to treat environmentally induced diabetes.

Challenges in endocrine/metabolic disruption research.
As alluded to above, there are a number of challenges limiting our understanding of the impact of synthetic chemicals on metabolic diseases that relate to the chemicals themselves, the exposed individuals, and the experimental approach used to study EDC effects on glucose homeostasis (Table 3). The tens of thousands of unique chemicals released into the environment create an enormous analytical challenge in quantifying human exposure while the physical properties of some compounds contribute to their bioaccumulation and persistence in human tissues long after the exposure has terminated. This contributes to the near ubiquity of certain EDCs in the U.S. population (e.g., hexachlorobenzene and DDE) (23) and raises important questions about the threshold of exposure necessary to elicit a disease phenotype. The experimental challenge is further complicated by the lack of clear structure-function relationships that preclude in silico prediction of adverse health effects, thereby necessitating the use of bioassays to characterize the physiological effects of chemical exposure.

Inter-individual variation in gene-environment interactions may also modify the deleterious effects of synthetic chemicals. For example, the adverse consequences of occupational exposure to pesticides among Costa Rican banana farmers was found to be influenced by whether they inherited "favorable" or "unfavorable" metabolizing genes (60). Other predisposing factors, such as obesity or a family history of diabetes, may also accentuate the diabetogenic effects of some chemicals (61), while high-fat diets may augment exposure to lipophilic EDCs. As discussed, EDCs that modulate sex steroid action may have divergent metabolic effects depending on the background hormonal milieu leading to sexually dimorphic effects that are also influenced by changes over the life span. Finally, evidence of in utero programming and transgenerational effects suggest that an individual's disease-related exposure may have taken place before birth or even in a prior generation.

Lastly, experimental design may influence the observed biological effect or fail to accurately recapitulate real-world scenarios. Particularly vexing are mixtures of compounds that may exert additive, antagonistic, or even synergistic biological effects. Consequently, the ultimate metabolic phenotype may differ considerably from studies of single chemicals in isolation. Furthermore, nonmonotonic dose-response relationships are seen with some chemicals (e.g., BPA [62] and polybrominated diphenyl ethers [19]), thus mandating studies across wide concentration ranges that also account for effects at extremely low doses. Finally, animal models and humans may have divergent responses to EDCs (63), and the phytochemical content of animal feeds modulates EDCs effects (64). Thus, careful selection of experimental models and appropriate controls are critical for understanding the metabolic effects of synthetic chemicals.

Diabetes and environmental injustice. One of the profound tragedies of the diabetes epidemic is its disproportionate effect on minority groups and the economically disadvantaged. National survey data from 2007–2009 show that 11.8% of Hispanics and 12.6% of non-Hispanic blacks self-identified as having diabetes compared with only 7.1% of non-Hispanic whites (65). Furthermore, rates of diabetes are inversely related to household income and education level (66). This heightened risk may reflect disproportionate exposure to chemical pollutants among these groups (67). Some studies have specifically linked chemical exposure with diabetes among high-risk groups, including Mexican Americans (68) and Native Americans (69), while others have found stronger associations between POPs and diabetes among Hispanics (22). This strengthened association may reflect coordinate exposure to other diabetes-promoting chemicals, increased susceptibility to metabolic disruption (e.g., in 60), or an interaction between diabetogenic chemicals and other predisposing risk factors, e.g., diet or limited access to healthcare. The greater synthetic chemical exposure of poor and minority groups is likely a consequence of many factors; however, one important contributor is the historical construction of chemical production facilities and toxic waste sites in poor communities (70). The causality of these intertwined relationships is difficult to dissect; nevertheless, the synergy of coexisting poverty, poor education, and pollution likely contributes to the pathogenesis of metabolic diseases.

Strategies for change. Mitigation of the detrimental effects of pollution on metabolic health will require the development and implementation of comprehensive strategies, including expanded research programs, improved regulation and public policy, and education efforts (Fig. 3). The EPA has recently begun analyzing synthetic chemicals for endocrine-disrupting effects through the Endocrine

TABLE 3
Challenges in endocrine/metabolic disruption of glucose homeostasis

Challenges related to the chemicals
  Number of structurally diverse compounds to which humans
    are exposed
  Measurement of chemicals in metabolically-relevant tissues
  Lack of clear structure-function relationships
    Multiple mechanisms of action for a single chemical
    Effects mediated by a chemical's metabolites
      Chemical breakdown differing by route of exposure
    Interactions among chemicals
      Additive, antagonistic, and synergistic effects
    Interactions between chemicals and endogenous metabolites
  Persistence of chemicals
  Ubiquity of exposure to some chemicals
Challenges related to exposed individuals
  Interindividual genetic susceptibility to EDCs
    Differences in EDC target genes
    Differences in genes regulating EDC metabolism
  Coexisting diabetes risk factors
    Obesity, high-fat diet, sedentary lifestyle, family history
  Medical comorbidities
  Pharmaceutical agents/medications
  Hormonal status
    Women versus men
    Prepubertal versus reproductive age versus postmenopausal
    Eugonadal versus hypogonadal
Challenges related to experimental design and approaches
  Cross-sectional versus longitudinal epidemiological design
  Single chemical approaches versus analyses of mixtures
    Additive, antagonistic, and synergistic effects
  Nonmonotonic dose-response relationships
  Failure of cell culture or animal models to recapitulate human
    physiology
  Background hormonal milieu of experimental animals
  Effect of timing of exposure
    in utero or early postnatal versus adult exposure
  Transgenerational effects
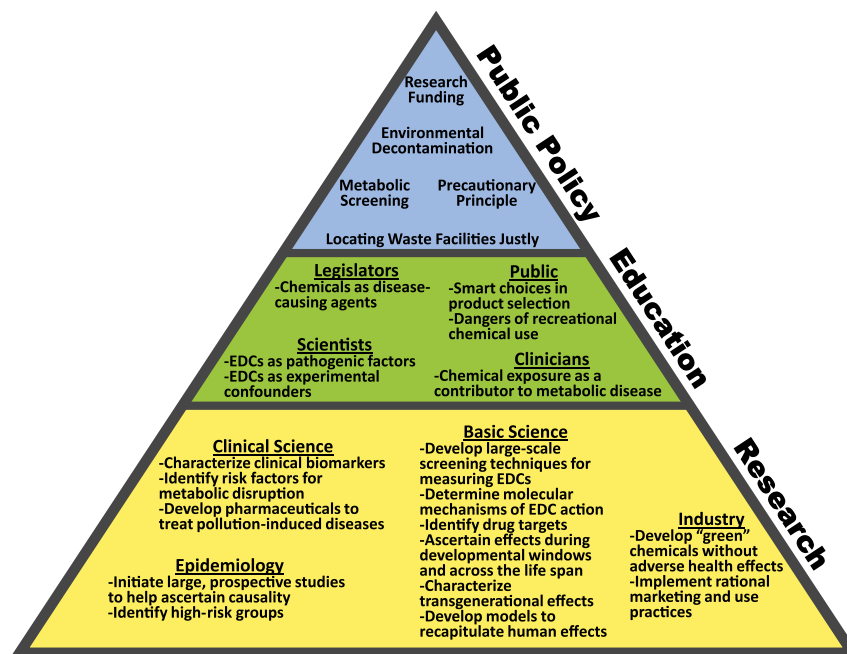 Phytochemical content of animal feed

FIG. 3. Strategies for addressing environmental disruption of metabolism.

Disruptor Screening Program. This initiative should be expanded to include analyses of metabolic disruption in order to specifically identify diabetogenic chemicals with significant emphasis placed on characterizing the molecular mechanisms in order to better identify health-threatening chemicals, to anticipate additive/synergistic effects of mixtures, and to determine potential pharmaceutical targets. Susceptibility across the life span should be assessed with special emphasis on critical developmental windows and transgenerational effects.

Risk analysis can be enhanced by identifying groups with exposures to high-risk chemicals and achieving a better understanding of factors predisposing to disruptions in energy homeostasis, including genetic polymorphisms linked to detoxification and metabolic pathways. Exposure analysis must be expanded beyond urine and serum to include lipid-rich organs that bioaccumulate POPs (e.g., brain and adipose) as well as tissues relevant to in utero and early postnatal exposure (e.g., human breast milk, cord blood, and placental tissue). Beyond direct measurement of EDCs, development of clinical biomarkers will facilitate identification of chemical-exposed individuals who can then be monitored prospectively for the development of diabetes, enhancing efforts to establish causality.

The new toxicology paradigm of endocrine and metabolic disruption mandates a transformation in regulatory policy to limit the production and use of chemicals that threaten metabolic health. Specific attention should be paid to banning chemicals with long-lasting efforts due to either their environmental persistence or ability to induce transgenerational effects. When doubts persist about a chemical's metabolic impact, the "precautionary principle" should be adopted and its use restricted. Whenever possible, decontamination of environments and individuals exposed to metabolic disruptors should be pursued to limit ongoing exposure. For individuals with exposures that cannot be cleared, drugs should be developed to modulate the specific pathways responsible for pollution-induced diabetes. Finally, scientists and clinicians must become

advocates in educating lawmakers and the public about the threat of metabolic disruptors as well as the means to limit their impact through sound government policy and smart consumer choices.

Conclusions. In 1962, Rachel Carson warned of the health threat posed by environmental pollution (71). Nearly 50 years later, evidence suggests that human exposure to synthetic chemicals may be contributing to the burgeoning diabetes epidemic. While the revolution in synthetic chemistry has facilitated vast improvements in our quality of life, these benefits increasingly appear to have come with a hidden cost. This paradox of progress now mandates a reassessment of how our consumption habits negatively impact our metabolic health in order to devise effective strategies to limit the significant individual and societal toll of diabetes.

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