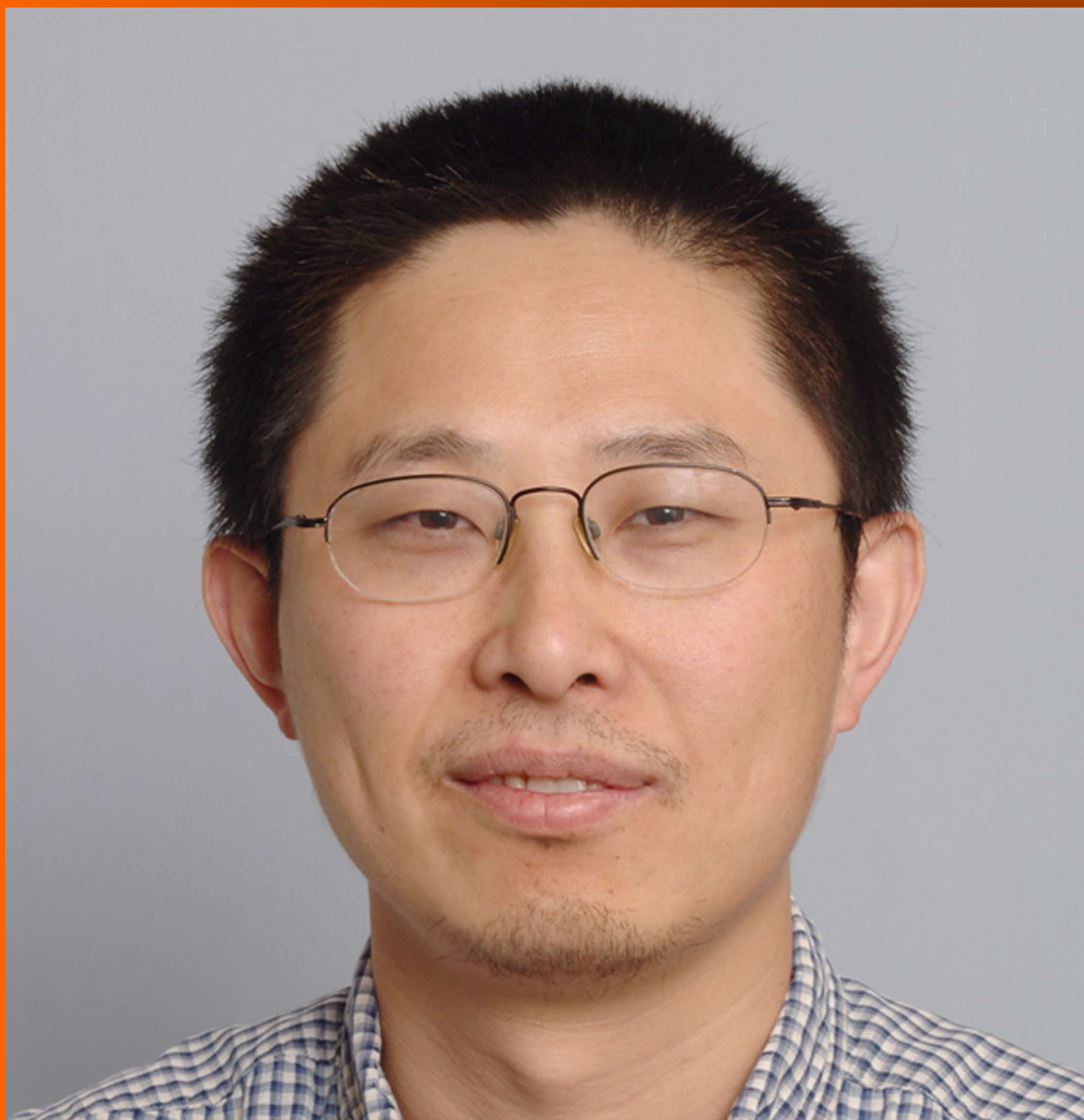


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Endocrine disrupting chemicals in mixture and obesity, diabetes and related metabolic disorders

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Abstract

Obesity and associated metabolic disorders represent a major societal challenge in health and quality of life with large psychological consequences in addition to physical disabilities. They are also one of the leading causes of morbidity and mortality. Although, different etiologic factors including excessive food intake and reduced physical activity have been well identified, they cannot explain the kinetics of epidemic evolution of obesity and diabetes with prevalence rates reaching pandemic proportions. Interestingly, convincing data have shown that environmental pollutants, specifically those endowed with endocrine disrupting activities, could contribute to the etiology of these multifactorial metabolic disorders. Within this review, we will recapitulate characteristics of endocrine disruption. We will demonstrate that metabolic disorders could originate from endocrine disruption with a particular focus on convincing data from the literature. Eventually, we will present how handling an original mouse model of chronic exposition to a mixture of pollutants allowed demonstrating that a mixture of pollutants each at doses beyond their active dose could induce substantial deleterious effects on several metabolic end-points. This proof-of-concept study, as well as other studies on mixtures of pollutants, stresses the needs for revisiting the current threshold model used in risk assessment which does not take into account potential effects of mixtures containing pollutants at environmental doses, *e.g.*, the real life exposure. Certainly, more studies are necessary to better determine the nature of the chemicals to which humans are exposed and at which level, and their health impact. As well, research studies on substitute products are essential to identify harmless molecules.

Key words: Endocrine disrupting chemicals; Persistent organic pollutants; Phthalates; Bisphenol A; Metabolic

disorders; Insulin resistance

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Core tip: Evidences are accumulating showing that some pollutants endowed with endocrine disrupting activities, the so-called endocrine disrupting chemicals, may contribute to the pandemic evolution of obesity and related metabolic disorders including diabetes. Within this review, we present the concept of endocrine and metabolic disruption and give an overview of the current knowledge of the field, including data from our laboratory and others, specifically focusing on the cocktail effect of pollutants which is one of the biggest concern caused by pollutants nowadays.

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INTRODUCTION

Obesity is a major public health problem because it is a risk factor for the development of metabolic disorders such as type 2 diabetes, cardiovascular diseases and some cancers whose evolution is pandemic. These diseases represent a major societal challenge in health and quality of life with large psychological consequences in addition to physical disabilities linked to overweight and diabetes. Metabolic disorders are also one of the leading causes of morbidity and mortality. By 2030, it is predicted that the number of overweight people will reach 3.3 billion while diabetes will affect more than 400 million people worldwide. In 2010, 10% of overweight children were between the ages of 5 and 17^[1]. Furthermore, a conservative estimate of the cost of pollutants on health impact, in the field of obesity and diabetes, exceeds the annual 18 billion in Europe^[2]. Several causative factors have been identified, especially excessive food intake and decreased physical activity. Yet, neither these well-recognized risk factors nor the genetic predispositions and the observed reductions in sleep length can explain the kinetics of the epidemic. Thus, it has been put forward that pollutants, which exponential manufacturing coincides with obesity trends and prevalence of diabetes^[3,4], may well constitute new actors of these multifactorial diseases, specifically chemicals endowed with endocrine disrupting activities, *i.e.*, the endocrine disrupting chemicals. Herein, we summarized the current knowledge about endocrine and metabolic disruptions, to illustrate that these pollutants are indeed causative factors in the obesity and diabetes pandemic. Some studies analyzing the cocktail effects were also described, as we are exposed to thousands of chemicals.

THE CONCEPT AND HYSTORY OF THE ENDOCRINE DISRUPTION

If industrialization fostered societal progress improving life expectancy, it also led to the presence, in the different compartments of the environment, of thousands of anthropic molecules sometimes transported over very long distances globalizing pollution. Some of these chemicals (an estimate of 900 molecules classified after their characteristics including their half-lives, Table 1) can affect the hormonal system, thereby interfering with the development of the organism and representing the endocrine disrupting chemicals (EDCs). Historically, the first warnings came from researchers and physicians invested in reproductive biology. They outlined the detrimental effects of some pesticides in the environment particularly on the birds^[5] or alerting on the diethylstilbestrol (DES) tragedy with DES given to millions of women between 1941 and 1971 to prevent miscarriages. An estimated 2 to 5 million children were exposed *in utero*, a large number developed genital malformations and cancers^[6-8].

At the Wingspread conference of 1991, the concept of endocrine disruptor was proposed to account for new scientific discoveries on chemicals such as pesticides, plasticizers or persistent organic pollutants (POP) capable of mimicking a hormonal action or, conversely, able to antagonize the hormone action, or to interfere with the mechanisms of hormonal production, transport or metabolism. Today, the concept of endocrine disruption is still debated, but there is a consensus on the definition given by the World Health Organization (WHO) stating that "an endocrine disruptor is an exogenous substance or mixture that alter(s) function of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations"^[9].

Thus, endocrine disruption is characterized by a modification of the endocrine system which may result in a toxic effect when the homeostatic regulations are disrupted. Specifically, the endocrine system is constituted by a set of so-called endocrine glands which secrete chemical messengers or hormones, carried by the bloodstream to target distant organs expressing the corresponding high-affinity receptors. The endocrine system includes well defined glands such as the pituitaries, gonads, adrenals or thyroid glands but also organs such as liver, pancreas, gut and adipose tissues. This system is highly sensitive, able to react to very low doses (pM) of hormones in a non-linear relationship between hormone levels and receptor occupation, with opposite effects observed when hormone levels exceed the physiological range (*e.g.*, hyper and hypothyroidism lead to opposite metabolic defects with regards to body weight and energy expenditure). Importantly, hormonal effects varied with the stage of development and the targeted organ. In adults, they are characterized by negative regulatory feedback loops with loss of biological effects at the highest hormonal doses to maintain physiological homeostasis. Besides, fetal and neonatal

Table 1 Chemicals, sources and routes of exposure, examples, and some demonstrated metabolic effects

Chemicals	Sources	Examples	Some demonstrated metabolic effects
Alkylphenols	Lubricating oil additives; detergents; emulsifiers, pesticides; NP plastics Exposure occurs <i>via</i> water drinking and food consumption ^[67]		Estrogenic activities ^[68]
Dioxins	Byproducts of industries from incomplete combustion; release during natural events such as wood burning and volcanic eruption Diet is the main route of exposure ^[69]	TCDD	Hepatic steatosis ^[70] and fibrosis ^[71] ; increased adipocyte differentiation (<i>in vitro</i>) ^[72]
Flame retardants	Used in electronic equipment, furniture, plastics...and then, present in dust, air and soil Dermal exposure is a significant route of exposure ^[73]	Penta-BDE	Decrease in glucose oxidation ^[74]
Organotin compound	Used as biocide in anti-fouling paint, heat stabilizer in Poly Vinyl Chloride Exposure mainly by consumption of seafood ^[75]	TBT	Induction of adipocyte differentiation ^[76] , increase of body weight and hepatic steatosis ^[77] , transgenerational effects on fat depots and hepatic steatosis ^[39]
Phenolic derivatives	Plastic components, cosmetics, disinfectants, thermal paper receipts Food and water drinking are the major routes of exposure ^[78]	BPA, BPS	Estrogenic activities ^[79] ; alteration of pancreatic β cell functions and hepatic insulin signaling (BPA) ^[47] ; induction of lipid accumulation and differentiation (<i>in vitro</i> , BPS) ^[80]
Pesticides	Due to their persistence, accumulation in soils and sediments; bioaccumulation throughout the food chain	DDT and its metabolite	Alteration of systemic glucose homeostasis and hepatic lipid metabolism ^[83] ; Glucose intolerance, hyperinsulinemia, dyslipidemia and altered bile acid metabolism ^[84]
Phthalates	Processing of agriculture products (banned in Europe); Dietary sources ^[81] as well as inhalation and dermal routes of exposure ^[82] Plastic components, cosmetics, medical equipment; Exposure mainly derives from dietary sources for high molecular weight phthalates (<i>e.g.</i> , DEHP) and non-dietary sources for low molecular weight phthalates (<i>e.g.</i> , DBP) ^[86]	Atrazine (C ₈ H ₁₄ ClN ₅) DBP, DEHP	Increased body weight, intra-abdominal fat and insulin resistance ^[85] Anti-androgenic effects ^[87] ; Transgenerational inheritance of obesity ^[88] ; Increased adipocyte differentiation ^[89]
PCBs	Synthetic compounds now banned but previously used, in particular, in electrical capacitors; still release in environment due to their persistence Food consumption contributes over 90% of total exposure ^[90]	PCB153 (C ₁₂ H ₅ Cl ₆), PCB170 (C ₁₂ H ₅ Cl ₇), PCB187 (C ₁₂ H ₅ Cl ₇) (non dioxin-like); PCB126 (C ₁₂ H ₅ Cl ₃), PCB77 (C ₁₂ H ₆ Cl ₄) (dioxin-like)	Increased adipocyte differentiation (<i>in vitro</i>); increased body weight, adipocyte hypertrophy ^[72] , increased hepatic steatosis and visceral adiposity in the context of a lipid-enriched diet ^[91]
PAH	Byproducts of incomplete combustion of organic compounds (cigarette smoke, wood burning, overcooked meat...) Contamination primarily through inhalation and consumption of certain foods ^[92]	B[a]P	Carcinogenic Alteration of estrogen metabolism in human mammary carcinoma-derived cell lines ^[93] Inhibition of lipolysis, increased fat accumulation and weight gain ^[94]
PFAA	Water and oil repellent; used for treatments of clothing, insulation and fire-fighting foams Oral and dermal exposure ^[95]	PFOA	Elevated serum leptin and insulin; overweight after <i>in utero</i> exposure ^[96]

PAH: Polycyclic aromatic hydrocarbon; PFAA: Perfluoroalkyl acids; PCBs: Polychlorobiphenyls; Np: Nonylphenols, C₁₅H₂₄O; DBP: Dibutyl phthalates, C₁₆H₂₂O; BPA: Bisphenol A, C₁₅H₁₆O₂; BPS: Bisphenol S, C₁₂H₁₀O₄S; TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin, C₁₂H₄Cl₄O₂; Penta-BDE: Pentabrominated diphenyl ethers, C₁₂H₅Br₅O; TBT: Tributyltin, (C₄H₉)₃Sn; DDT: Dichlorodiphenyltrichloroethane, C₁₄H₉Cl₅; DDE: p,p'-dichlorodiphenyldichloroethylene, C₁₄H₈Cl₄; DEHP: Diethyl hexyl phthalate, C₂₄H₃₈O₄; B[a]P: Benzo[a]pyrene, C₂₀H₁₂; PFOA: Perfluorooctanoic acid, C₈HF₁₅O₂.

development are periods of high sensitivity to hormonal signals, with hormones shaping sexual differentiation and behavior (testosterone, estradiol), cognitive development (thyroid hormone) but also feeding behavior (testosterone, estradiol, glucocorticoids, leptin).

While endocrine disruption is localized at the interface between endocrinology and toxicology, risk assessment relies on toxicology principles and the linearity of the harmful effects of chemicals beyond a threshold value. This is the Paracelse's statement that "all substances are poisons: There is none which is not a poison. The right dose differentiates a poison from a remedy". Hence,

health risks assessment by international agencies such as the United States Environmental Protection Agency (EPA) or the European Food Safety Agency (EFSA) relies on the setting of toxicological reference values, *e.g.*, the tolerable daily intake (TDI) doses. The TDI is an estimate of the amount of a given chemical in food or drinking water that can be ingested daily over a lifetime without a significant health risk. Its calculation is empiric in that it assumes a dose-linear response curve from the no- or the lowest-observed-adverse-effect-levels (NOAELs or LOAELs, respectively) in animal studies performed in the most sensitive species and examining the most

sensitive endpoint; the value determined is then divided by an uncertainty factor (from 100 to 1000) to take into account interspecies as well as inter-individuals variation^[10].

While such calculations result in reference doses which may appear sufficiently protective from a toxicological point of view, the discovery of adverse effects in rodents at doses lower than the TDI outlines the necessity of integrating the principles of Endocrinology for higher protection. Specifically, care should be taken at the non-monotonicity dose-response curves^[11] challenging the Paracelse' paradigm. The developmental origin of human health diseases should as well be considered. It integrates that EDCs may exert their adverse effects long after the individuals have been exposed (for instance during fetal and neonatal development)^[12,13]. It is also important to consider that humans are exposed to a plethora of chemicals, not a single chemical, some being highly persistent in the environment (e.g., the persistent organic pollutants, POPs) which outlines the necessity in risk assessment to consider the possible additive, antagonistic or synergistic activities of the resulting mixture to which humans are exposed. This is recognized as the "cocktail effect" that will be more detailed in the last part of this review.

ENERGY METABOLISM AND METABOLIC DISRUPTION

Regulation of energy metabolism relies on the integrated action of a large number of hormones operating centrally to control food behavior and peripherally to maintain glycaemia at a physiological range whilst covering energy demands. It both involves insulin secretion from pancreas and responsiveness to insulin by the metabolically active tissues (liver, muscle and adipose tissues) in response to food intake that elevates blood glucose. In addition to insulin, hormones (and their corresponding high-affinity receptors) are involved in energy metabolism. They include, but are not limited to, glucocorticoids, thyroid hormone, leptin and adiponectin, gut hormones (such as ghrelin and Glucagon-like peptide 1 or GLP1), the growth hormone and the sexual hormones estrogen/androgen, energy metabolism being highly sexually marked with sex-dimorphic insulin sensitivity, eating behavior, distribution of fat, etc. The protective role of estrogens against metabolic disturbances has been well demonstrated conferring positive metabolic adaptations to women^[14].

Obesity results in energy imbalance between energy intakes determined by food consumption and energy expenditure comprising basal metabolism, thermoregulation and physical exercise in obese patients. Along with energy supplies exceeding energy requirement, glycaemia will remain at values exceeding physiological range between meals whilst pancreas will secrete higher insulin levels in an attempt to lower glycaemia. First signs of insulin resistance will arise in the metabolic tissues

liver, muscle and adipose tissues. Hepatic production of glucose namely gluconeogenesis will be no longer well controlled by insulin resulting in higher levels of glucose in blood. Glucose uptake will be less effective in muscles and lipolysis will be enhanced leading to elevated levels of free fatty acids in circulation (lipotoxicity). Eventually, type 2 diabetes develops with persistent and progressive deterioration of glucose tolerance. Gradually, the body's ineffective use of insulin evolves as a tryptic of hyperglycemia, hyperinsulinemia and hypertriglyceridemia, in a vicious circle where hyperglycemia aggravates hyperinsulinemia and hyperinsulinemia aggravates hyperglycemia and hypertriglyceridemia^[15,16].

Importantly, lipid and glucose metabolisms are under a tight regulation not only by the hormones mentioned above and their associated hormone receptors but also by several nuclear receptors such as peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXR) and farnesoid X receptor (FXR) as well as the xenosensors Pregnane X receptor (PXR), Constitutive androstane receptor (CAR) and aryl hydrocarbon receptor (AhR). These transcription factors integrate the changes in environmental or hormonal signals through direct gene regulation or through cross-talk with other transcriptional regulators to maintain the vital function of nutrient homeostasis between the fed and the fasting states^[17]. Interestingly, PXR, CAR and AhR were first identified as controlling xenobiotic and drug metabolism and promoting their clearance^[18,19]. However, analysis of the phenotypes of mice deficient in one particular nuclear receptor or in which a xenosensor has been activated by a strong agonist showed their important roles in the metabolism of fatty acids, lipids and glucose^[20,21] and on obesity and/or insulin resistance (Table 2). Besides, like the receptors for estrogens, androgens, glucocorticoids or thyroid hormones, the PPARs, LXR, and FXR can also be targeted by specific environmental chemicals identified as endocrine disruptors (Table 3). Therefore, whilst homeostasis of the energy metabolism highly depends on the integrated and beneficial contribution of nuclear receptor activation, these receptors can as well be the sites of endocrine disruption. This underlines the concept that insulin resistance, resulting from the inappropriate activation of one of the nuclear receptor mentioned above, well constitutes an endocrine disruption. This concept does not exclude that pollutants may exert toxic effects by mechanisms distinct from endocrine disruption including oxidative stress and mitochondrial alteration^[22] as well as inflammation^[23,24].

It has been well illustrated with the studies on anti-diabetic medications that obesity does not necessary lead to insulin resistance. Indeed, the insulin sensitizer properties of the thiazolidinedione class of drugs were based on their abilities to activate PPAR γ which is a master transcription factor involved in adipogenesis^[25]. However, while enhancing insulin sensitivity, PPAR γ activation also leads to enhanced body weight. Thanks to molecular biology research, the dissection of estrogen receptor beta (ER β)-deficient mouse phenotype led to the

Table 2 Metabolic characteristics of mice deficient in some nuclear receptors¹

Insulin status	Obesity	No body weight change
Insulin resistance	ER α (-/-) in both males and females ^[38]	
No difference in insulin sensitivity	AR (-/-) in males only ^[97]	
Improved insulin sensitivity	ER β (-/-) (study on males only) ^[26]	CAR activation (study on males only in HFD context, activation by TOBOBOP) ^[99]
	ERR β (deletion in neurons; study on males only) ^[98]	AhR (-/-) (studies on males only) ^[100]
		AhR (-/-) (studies on males only, in HFD context) ^[101]
		PPAR α (-/-) (studies on males only, in HFD context) ^[102]
		PXR (-/-) (studies on males only, in HFD context) ^[103]

¹Mice were fed standard diet or high-fat diet when mentioned. HFD: High-fat diet; AhR: Aryl hydrocarbon receptor; CAR: Constitutive androstane receptor; PPAR α : Peroxisome proliferator-activated receptor α ; PXR: Pregnane X receptor.

Table 3 Interactions of some nuclear receptors with endocrine disruptors

Nuclear receptors	Interactions with chemicals
Steroid receptors	
ER	BPA (Er α ^[38] , GPR30 ^[104])
AR	BPA ^[105]
GR	BPA; phthalates ^[106]
PR	BPA ^[107]
TR	BPA ^[108] ; brominated flame retardants, BFR ^[109]
RXR heterodimers	
PPAR α	Phthalates ^[110] ; polyfluoroalkyl compounds ^[111] ; pyrethrins ^[112]
PPAR γ	Phthalates ^[110,113] ; organotin ^[76] , BPA ^[114]
FXR	Pyrethroids ^[115]
CAR	Phthalates ^[116,117]
LXR α	Phthalates; BPA ^[118]
PXR	Phthalates; BPA ^[119,120]
Other receptors	
AhR	Dioxines; PCB dioxin-like ^[72,121,122]

BPA: Bisphenol A; PCB: Polychlorobiphenyl; ER: Estrogen receptor; AR: Androgen receptor; GR: Glucocorticoid receptor; PR: Progesterone receptor; TR: Thyroid hormone receptor; PPAR: Peroxisome proliferator-activated receptor; FXR: Farnesoid X receptor; CAR: Constitutive androstane receptor; LXR: Liver X receptor; PXR: Pregnane X receptor; AhR: Aryl hydrocarbon receptor.

discovery that the metabolic actions of ER β are mediated by a negative cross-talk with PPAR γ acting as an insulin sensitizer^[26]. Several other cross-talks were evidenced and reviewed recently^[27]; for example, between the estrogens acting through estrogen receptors and the AhR allowing under some circumstances regulation of estrogen target genes by dioxins^[28]. Other examples of cross-talk include CAR-target genes regulating the metabolism of estrogens^[29]; the control of bile acid homeostasis by xenobiotics as a result of cross-talk between FXR, CAR and PXR^[27] and more recently, the evidence that liver ER α regulates female hepatic metabolism through interaction with LXR α ^[30].

Thus, the threat represented by xenobiotics is challenging an already complex and multilayer physiological mechanism that tightly regulates insulin secretion and sensitivity whilst living organisms oscillate between fed and fasting states to meet energy demands. On top of this, several EDCs can activate or interact with multiple transcription factors or hormone receptors as described above in a context of exposure to numerous pollutants

and possibly interacting with a high-fat nutritional context undermining appropriate adaptive responses. Diet is a primary route of exposure to pollutants, linking the amount of food ingested and the levels of exposure to pollutants. Other routes of exposure include dermal, inhalation as well as subcutaneous and intravenous infusions *via* medical equipment (Table 1)^[31,32].

EPIDEMIOLOGICAL AND EXPERIMENTAL EVIDENCES SUPPORTING INVOLVEMENT OF EDCs IN THE OBESITY AND DIABETES EPIDEMICS

First evidences were brought from occupational exposure to a class of toxic molecules or accidental setting as for dioxins. For example, veterans exposed to Agent Orange have an increased relative risk of developing diabetes^[33]. After the Seveso industrial explosion in Italy, the risk of developing diabetes increased in women who have been

exposed^[34]. Associations between polychlorobiphenyls (PCBs) and diabetes have also been evidenced in humans and obesity has been suggested as an aggravating factor^[35]. Recently, it has been shown that plasma POP profile could discriminate patients who are metabolically healthy or insulin resistant^[36]. In that study, menopausal women were obese based on their body mass index (BMI) and they were subdivided in 2 groups depending on their insulin sensitivity index. Interestingly, their metabolic health status was inversely correlated with plasma POP profile^[36]. Mechanisms of action have not been explored but it could be hypothesized that resistance to insulin was in part linked to the known pro-inflammatory effects of POPs.

Experimental studies mostly done in rodents with strong evidences of endocrine disrupting mechanisms and subsequent metabolic disorders advanced the understanding of the mechanisms involved in these effects. Historical examples have shown that neonatal administration of diethylstilbestrol (DES) to mice causes obesity in adult age. This effect involves at least the estrogen receptors as DES binds with very high affinity to these receptors^[37]. Strikingly enough, estrogens are protective against metabolic diseases, and male and female estrogen receptors ER α deficient mice are obese and insulin resistant^[38], illustrating the pleiotropic effects of this hormone. It could result from the various cross-talks of ERs with other receptors or transcription factors as mentioned above. Another historical chemical inducing metabolic disorders upon exposure is tributyltin (TBT). It belongs to organotin compounds and was widely used as an antifouling painting for ships (now banned). TBT provided a very clear example of endocrine disruption not only in the reproductive field area as for DES but also in metabolism. Indeed, TBT is the obesogen molecule *per se* in that it induces adipocyte differentiation targeting PPAR γ . Due to its strong and consistent effect on adipocytes, TBT has been used for multigenerational studies in mice (3 successive generations called F1, F2, F3)^[39]. In that study, mice were not tested for insulin sensitivity or tolerance to glucose. However, it was shown that early-life exposure to TBT causes hepatic accumulation of triglycerides (steatosis) and reprogramming of the adipocyte stem cells to favor the adipocyte lineage in the F1 and F2 exposed mice as well as in the non-exposed F3 generation. These experiments are an illustration of the DOHaD hypothesis. This hypothesis states that threat during the highly vulnerable period that constitutes the maternal period (e.g., food restriction or excess; adverse environmental milieu because of the presence of pollutants) will provoke diseases later in life including metabolic diseases (obesity, diabetes, cardiovascular diseases) and some cancers^[13]. Occurrence of adverse effects distant from the exposure period as well as in non-exposed generation, questioned the possible involvement of epigenetic mechanisms (e.g., acetylation or methylation of histones, DNA methylation) leading to alteration in the chromatin organization and alteration of transcriptional patterns that could explain the phenotypes described with TBT in early-life exposed TBT

mice^[39]. In addition, the TBT experiments have opened the way for addressing the question as to whether *in vitro* standardized model systems using the 3T3-L1 fibroblast cell line could be used to monitor the obesogenic properties of chemicals^[40,41]. It remains that PPAR γ is also known as an insulin sensitizer and these *in vitro* experiments will not answer to the question as to whether insulin sensitivity is altered upon exposure to the tested chemicals.

Solid evidences of insulin resistance triggered by exposure to POPs were originally reported using adult rats fed a high fat diet containing either crude salmon oil identified as a source of lipophilic compounds or refined oil (deprived of POPs) for 28 d. The authors^[42] demonstrated that rats fed the contaminated oil gained weight and developed abdominal obesity, insulin resistance and hepatic steatosis. Molecular analysis revealed an alteration of insulin signaling, indicative of an endocrine disruption. In another study, rats were exposed to ozone^[43], and the authors indicated that oxidative stress was the first hit causing later on impaired insulin signaling in muscle and whole-body insulin resistance.

An archetypal chemical of the endocrine disrupting field is Bisphenol A (BPA). BPA is widely used in the production of polycarbonates, epoxy resins and polyester resins and its global production exceeded 5 million tons in 2015. Although it does not bioaccumulate in the body, its exposure is universal and it is estimated that more than 95% of the general population is contaminated with diet as a primary route of exposure^[44]. BPA has been shown to act through several receptors including at least the estrogen receptors ER α , ER β and membrane receptor GPR30, the estrogen receptor-related ERR γ and possibly the PPAR γ ^[11,45,46] probably explaining the pleiotropic effect of this chemical and the difficulties at precisely defining its mechanism of action with effects and amplitude varying with age, sex, nutritional context, period of exposition and dosage. A selected list of publications will be presented to illustrate the large range of the reported BPA metabolic effects at doses in the range of the reference dose thus a thousand times lower than the supposed NOAEL dose of 5 mg/kg per day. To explore how exposure to environmental chemicals may affect metabolic health later in life, *i.e.*, the DOHaD hypothesis, a large number of experiments have been based on maternal exposure with a survey of metabolic traits in offspring at adulthood. Hence, maternal exposure to BPA led to the dysfunction of beta pancreatic cells and altered hepatic insulin signaling, resulting in impaired glucose tolerance and insulin sensitivity at adulthood, a phenotype that is exacerbated in offspring fed a high-fat diet^[47]. Mechanisms may involve changes in pancreatic cell mass through enhanced proliferation and diminished apoptosis of the beta-cells, partly acting *via* ER β activation which will result in excess insulin signaling during early life followed by a tendency to reduced pancreatic mass later in adulthood possibly contributing to the observed glucose intolerance^[48]. Interestingly, BPA exposure during gestation reproduced part of the effects of a high-fat diet with hyperinsulinemia and

impaired glucose tolerance in the adult male offspring^[49]. Worthy of note, BPA has been found not only to target insulin secretion through its action on pancreas but to target insulin-sensitive tissues as well with evidences of impaired insulin signaling in both muscles and liver^[50,51]. Others demonstrated that alterations in glucose tolerance and in serum levels of leptin, insulin and adiponectin with some of the effects mimicked by DES, thus indicative of an estrogen dependency^[52]. In addition to maternal effects, BPA also impacts the metabolic health of adults exposed during their adulthood. For example, exposure to low doses of BPA resulted in altered hepatic expression of genes involved in lipid synthesis and in accumulation of cholesteryl esters and triglycerides contributing to hepatic steatosis. Importantly, Marmugi *et al.*^[53] used a large range of doses and they could demonstrate non-monotonic dose-response curves for the expression of several genes related to lipid synthesis. In addition, analysis of the hepatic transcriptome of rats exposed to either TDI or NOAEL doses of BPA showed distinct sets of responsive genes depending on dosage indicating that different doses lead to different responses^[53]. The adipose tissue is also targeted by BPA and Hugo *et al.*^[54] demonstrated, using human adipose explants and adipocytes, that BPA at environmentally relevant doses could inhibit adiponectin release, a marker of insulin sensitivity. A down-regulation of adiponectin release was also demonstrated by Menale *et al.*^[55] using adipocytes from subcutaneous explants recovered from children undergoing orchidopexy surgery. In this study, the authors evidenced a strong and inverse association between BPA and adiponectin within a population of 141 obese children. A reduced glucose utilization coupled to alterations in insulin signaling was also demonstrated in human subcutaneous adipocytes^[56]. Questions remain on the possible activation of PPAR γ by BPA^[41,46], potentially explaining part of its obesogenic effect. Collectively, several *in vitro* and *in vivo* data evoke the possibility for BPA to be a metabolic disruptor with many of its adverse effects linked to endocrine disruption. Notwithstanding, some discrepancies remain in epidemiological studies due to limitations at defining causality between exposures to BPA and the risk to develop diseases. However, these limitations may be linked to difficulties at estimating the usual dietary BPA intake in a context of multiexposure^[44,51,57].

EVIDENCES OF A COCKTAIL EFFECT

In the laboratory, we aim to approach the question of the multi-exposure to environmental pollutants through setting an original mouse model of chronic and lifelong exposure starting in the prepubertal period of the dams-to-be until the adulthood of the offspring, dissecting the metabolic traits in both males and females. Intending to approach a realistic scenario, the mixture of pollutants is made of both persistent and short-lived low-dose chemicals in the range of the TDI for each chemical, all of great concern for human health and specifically

metabolic health^[18,35,58]. The mixture comprises 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), PCB153, di-[2-ethylhexyl]phthalate [DEHP] and BPA. These chemicals have been categorized as endocrine disruptors with either estrogeno-mimetic activities or anti-androgen activities. Moreover, these chemicals activate a broad range of signaling pathways as recapitulated in Table 3. In addition, to mimic the environmental main route of exposure, the mixture of pollutants was incorporated into the diet. Initially, we used a high-fat high-sucrose diet to explore the hypothesis that obese individuals may be more sensitive to exposure to pollutants because they are at risk of developing metabolic disorders. Data yielded brought solid evidences for a cocktail effect linked to endocrine disruption and resulting in metabolic disorders. Indeed, in a preliminary study, we used the NOAEL dose that is the no-observed-adverse-effect level dose in animal studies or 10 times the NOAEL doses for each pollutant of the mixture. It resulted in maternal toxicity with decreased pup survival. At the TDI dose range, there was no maternal toxicity which was compulsory for studying the metabolic health of the offspring but we evidenced sex- and age-dependent metabolic effects in the absence of weight modification^[59]. Specifically, in male offspring, although pollutants did not aggravate glucose intolerance, insulin resistance, plasma levels of triglycerides or cholesterol resulting from the high-fat high-sucrose consumption, we observed changes in cholesterol metabolism with a decrease in hepatic cholesterol levels and an increase in the expression of genes encoding proteins related to cholesterol biosynthesis. A different phenotype was observed in females which exhibited an aggravation of glucose intolerance. Although no change in insulin sensitivity was observed, we interestingly measured decreased levels of the major hepatic estrogen receptor (ER α) together with enhanced expression of the estrogen sulfotransferase (EST/SULT1E1) which metabolizes estrogens. To reconcile these data, we put forward the hypothesis that enhanced estrogen metabolism in the liver of pollutant-exposed females lowered the physiological protection of estrogens against metabolic disorders which could explain the worsening of their glucose intolerance^[59]. Furthermore females with lower plasma estrogens (*i.e.*, young adults) responded differently when exposed to the same mixture of pollutants. Specifically, females (not males) exhibited an alleviated-glucose intolerance with no change in gluconeogenesis and hepatic steatosis, an enhanced lean/fat mass ratio, an enhanced insulin sensitivity in skeletal muscle and a reduced expression of genes encoding inflammatory markers in the adipose tissue^[60]. We suggested that these opposite effects according to the age of the females may result from the hormonal environment. The pollutant mixture could exert an additional and positive estrogenic effect on metabolic traits in the young females but a negative effect in adult females when estrogens are high, with the induction of EST/SULT1E1 as a means to lower estrogen effects within physiological dose range^[32,59,60].

More experiments are underway to better characterize the effects of the mixture and to define whether they represent adverse or adaptive events, and what the contribution of the nutritional context is. For example, using a pollutant-mixed standard diet instead of a high-fat high-sucrose diet, we observed the activation of common metabolic pathways in the liver of challenged females with partial overlapping between the set of dysregulated genes induced by exposure to the mixture of pollutants in a standard diet and by a high-fat high-sucrose diet not containing the pollutant mixture. This study is highly relevant for understanding the synergistic effects between pollutants and the obesogenic diet (Labaronne *et al.*, Submitted). Collectively, these studies constitute a proof-of-concept that low doses of pollutants at supposedly ineffective doses for humans, are not harmless when in mixture.

Importantly, several laboratories have also developed studies to help answering to the today's context of exposure characterized by contamination with a plethora of chemicals at rather low levels. Combined effects of estrogens or anti-androgens chemicals have first been used to demonstrate the "something from nothing" phenomenon with mixtures of endocrine disrupters^[61]. For example, a mixture of 8 estrogenic chemicals produced strong estrogenic effects at doses too low to mediate any measurable effect when tested alone^[62]. Another study reported the same additivity when using mixtures of up to 30 anti-androgen chemicals^[63]. The toxic equivalence factor (TEF) was also formulated for dioxins, PCBs and polyaromatic hydrocarbons resulting in the summation of the doses of each chemical of the mixture multiplied by its respective TEF^[64]. Worthy of note, it was shown recently that the synergistic effect of the mixture containing a pharmaceutical estrogen and a persistent pesticide was due to their cooperative binding to the PXR receptor leading to its synergistic activation, when each chemical alone exhibited low efficacy^[65]. It illustrates how much pollutant interactions in a context of multi-exposure represent a *bona fide* challenge for policy makers^[66].

CONCLUSION

The pandemic evolution of obesity and its associated metabolic disorders that are considered as one of the major health burdens worldwide stress the need for extensive research towards the identification of new etiologic factors with the hope to prevent further augmentation and even more to reduce the kinetics of expansion. These past 20 years, evidences that endocrine disrupting compounds constitute etiologic factors have largely progressed. Certainly, more studies are to be undertaken to better determine the nature of the chemicals to which humans are exposed and at which level. In parallel, substitution research should be encouraged for identifying harmless molecules. Eventually, scientists may think on interventional strategies based on the use of benefit compounds with the aim at counteracting the deleterious metabolic effects of

pollutants. However, it should as well be considered that evidences are more than convincing and that regulatory decision makers should take into account the accumulated and solid scientific results and enjoin to considerably limit the use and spread of chemicals to better protect human health, as recently achieved for BPA in baby bottles.

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