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REVIEW

Combinatorial pathway disruption is a powerful approach to delineate metabolic impacts of endocrine disruptors

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The prevalence of metabolic diseases, such as obesity, diabetes, metabolic syndrome and chronic liver diseases among others, has been rising for several years. Epidemiology and mechanistic (*in vivo*, *in vitro* and *in silico*) toxicology have recently provided compelling evidence implicating the chemical environment in the pathogenesis of these diseases. In this review, we will describe the biological processes that contribute to the development of metabolic diseases targeted by metabolic disruptors, and will propose an integrated pathophysiological vision of their effects on several organs. With regard to these pathomechanisms, we will discuss the needs, and the stakes of evolving the testing and assessment of endocrine disruptors to improve the prevention and management of metabolic diseases that have become a global epidemic since the end of last century.

Keywords: appetite; bisphenol; dioxin; inflammation; insulin resistance; microbiota; perfluorinated compounds; phthalate; TBT

Abbreviations
BPA, bisphenol A; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; EDs or EDCs, endocrine disrupting compounds; HCB, hexachlorobenzene; MDCs, metabolism disrupting chemicals; PBDE, polybrominated diphenyl ether; PCBs, polychlorinated biphenyls; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; TBT, tributyl tin.

Introduction to the history of obesogenic endocrine disrupting chemicals

Since the middle of the twentieth century, the prevalence of obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) has dramatically increased in developed countries. Now the rise is even faster in the low- and medium-income countries. In 2016, about 2 billion adults aged 18 or older and 340 million children and adolescents were overweight or obese. In parallel, the number of people with diabetes quadrupled from 1980 to 2014. NAFLD, which concerns around 25% of adults, is worsened by obesity, insulin resistance and type 2 diabetes [1]. Thus, these pathologies are related to each other and have common primary causative factors such as unbalanced diets, malnutrition, and lack of physical exercise or sedentary lifestyle. Besides psychosocial and physical factors, the environment, in particular the chemical environment, is suspected of contributing to the spread of this worldwide epidemic.

In 2006, Grun and Blumberg were the first to propose that endocrine disruptors (EDs), which are chemicals affecting endocrine systems and provoke deleterious effects, could induce or increase weight gain. They coined the name obesogens to describe these substances [2]. Obesogens have multiple modes of action: they can lead to an excessive development of the adipose tissue, increased inflammation that leads to abnormal adipocytes (e.g. resistant to insulin), increase in the production of pro-inflammatory cytokines, triacylglycerols storage, a decrease in fat consumption that leads to dysfunction of other organs, such as the liver and the pancreas, and of the inter-organ' communication. These EDs have also been termed 'metabolism disrupting chemicals' (MDCs) [3] and there is converging evidence confirming their role in the development of metabolic diseases. At this stage, obesogens and MDCs overlap considerably and either term is suitable.

Among 1000 chemicals with presumed endocrine effects, epidemiological data indicate that exposure to some chemicals classified as persistent organic pollutants (POPs) by the Stockholm Convention alters metabolic functions and increases obesity. They include polychlorinated biphenyls (PCBs), polybrominated diphenyl ether (PBDE), perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) (present in electrical appliances, paper, textiles or kitchenware), pesticides such as dichlorodiphenyltrichloroethane (DDT) (or its metabolite dichlorodiphenyldichloroethylene, DDE) and hexachlorobenzene (HCB). Forbidden or restricted, these pesticides or chemicals used for their insulating, flame retardant or anti-adhesive properties, are lipophilic and accumulate in fat mass of living organisms because of their resistance to biodegradation, except for PFAS. Alternatively, and more recently, many non-persistent pollutants present in everyday consumer products, used as plasticisers, food/cosmetic additives and preservatives (monosodium glutamate, phthalates and parabens) but also heavy metals (cadmium and arsenic) released from industrial, agricultural products and tobacco, are also suspected of favouring either increased weight mass or disturbed carbohydrate and lipid homeostasis. Thus, new and more appropriate terms, MDCs or obesogens, are now used to name the EDs that induce metabolic disorders and promote the development of obesity, type 2 diabetes and fatty liver diseases. In this review, we will describe the mechanisms targeted by the substances in key organs, that is, adipose tissue, liver, pancreas, gut and brain, which can alter inter-organ communication and lead to the development of metabolic diseases.

Epidemiological evidence for the metabolic effects of MDCs

The occurrence of metabolic diseases at the population level is influenced by exposure to several families of toxicants as shown by several epidemiological studies: evidence for inorganic compounds such as metals (arsenic, mercury and cadmium) remains limited [4,5] despite some trends of association (arsenic, mercury and dyslipidaemias [6-8]), while evidence of presumed risk for organic compounds is more conclusive. For persistent molecules such as organochlorine pesticides [beta-hexachlorocyclohexane (β-HCH) and heptachlor epoxide], associations are suggested with type 2 diabetes and metabolic syndrome [9-12].

There is growing evidence for a causal link to metabolic disorders concerning perfluorinated compounds (e.g. used to produce Teflon) such as PFOA and PFOS, which are highly persistent molecules (ecosystems and organisms): in young children exposed *in utero*, an increased risk of obesity, dyslipidaemia and hypertension is observed [13-15]. Exposure of adolescents or adults is associated with an increased risk of obesity, dyslipidaemia and type 2 diabetes in adults [16-18]. Alternatives to these perfluorinated compounds (GenX, Gi-PFESA) do not appear to be safer either, according to recent studies [19].

A large number of observations have also been carried out on compounds that are not persistent by nature but to which we are regularly exposed through our lifestyles: thus, among bisphenols (used in the plastics and packaging industries), a major focus on bisphenol

A (BPA) over the past several years has suggested that exposure to BPA, both during the perinatal period and in adulthood, increases the risk of metabolic syndrome, in particular, obesity and insulin resistance (one of the components of type 2 diabetes) [20-23]. Recent experimental studies suggest that BPA substituents (notably bisphenol S and F) are not safe alternatives [24].

For phthalates, which are also produced by the plastics industry, obesity appears to be one of the most common pathologies due to exposure during early life (*in utero*, childhood) or during adulthood [20,25,26]. In adults, disorders of glucose metabolism and hypertension are also identified with yet unexplained dimorphic effects [27].

Exposure to polycyclic aromatic hydrocarbons (PAHs, compounds resulting from combustion and cooking processes that are important air pollutants and food contaminants) is also associated with an increased risk of obesity in children and adults [28]. In adults, an increased risk of diabetes and hypertension is observed in association with environmental PAH exposure [29,30].

Experimental evidence for metabolic effects of MDCs

Numerous studies have been conducted on organs involved in the development of metabolic diseases including adipose tissue, liver, intestine, pancreas and specific systems or processes such as the microbiome, the central nervous system (regarding the control of appetite) or epigenetic mechanisms. We will now describe the most recent effects of EDs on these specific systems below.

Alteration of adipocyte functions: adipogenesis, adipokine secretion, insulin response

White adipose tissue (WAT) has a central role in metabolic homeostasis and its enlargement *via* hyperplasia and hypertrophy of adipocytes, is an essential adaptive response to caloric excess. This tissue is well studied in toxicology for several reasons: it is a target organ of EDs that can affect its development and functions; it is also a storage organ of POPs that can be released during lipolysis or on a long-term basis [31]. Formation of adipocytes or adipogenesis includes commitment of stem cells into the adipocyte lineage, proliferation of preadipocytes (the precursor adipocytic cells) and their differentiation into adipocytes [32]. Adipogenesis requires a sequential cooperation of transcription factors among which CCAAT-enhancer-binding protein-alpha (C/EBPα) and peroxisome proliferator-activated receptor-gamma (PPARγ) play a crucial role. They activate target genes such as lipoprotein lipase (LPL), performing the lipolysis of circulating triacylglycerol-rich lipoproteins, CD36, a fatty acid (FA) cell-membrane transporter, fatty acid-binding protein 4 (FABP4), which binds and translocates intracellular FA, and perilipins that stabilise oil globules, all of them contributing to the formation of the lipid droplet of functional adipocytes that also secrete adipokines like leptin [33]. When the storage capacity of WAT is exceeded, this process is altered and leads to ectopic fat depots (in visceral WAT, liver and muscles) characterised by hypertrophic, inflammatory and insulin-resistant adipocytes [34].

Among the *in vitro* models used to assess the mechanisms of action of MDCs, 3T3-L1 and OP9 cell lines and C3H10-T1/2 mesenchymal stem cells (MSCs) are the most common murine models. The use of human models such as the Simpson–Golabi–Behmel syndrome (SGBS) preadipocytes and human adipose-derived stem cells is less common because of their more limited availability and their high cost. Rodents and zebrafish are essential *in vivo* models to highlight obesogenic and metabolic effects resulting from direct or *in utero* exposure to MDCs.

Organotin compounds such as tributyltin (TBT) represent an example of an environmental obesogen linked to abnormal adipocyte functions as shown by *in vivo* (rodents and zebrafish) and *in vitro* experiments. In different models, pre- or post-natal exposure to TBT increases body weight, fat mass, number of inflammatory cells in WAT, glycaemia and insulinaemia, while it decreases muscle mass [35-37]. Some of these effects persisted into adulthood and the next generations.

Similarly, BPA or its structural analogues (bisphenols AF, B, E, F and S) and halogenated derivatives [tetrabromobisphenol A (TBBPA) and tetrachlorobisphenol-A], phthalates [e.g. diethylhexyl phthalate (DEHP)], parabens, PFOS, PFOA and organochlorine pesticides such as DDT/DDE and HCB are associated with an increased adipogenesis and subsequently to an increased body weight and other disorders such as inflammation, hyperglycaemia, dyslipidaemia, glucose intolerance and insulin resistance [38-43]. For some chemicals such as tetrachlorodibenzo-*p*-dioxin (TCDD), PCB153, a second hit (e.g. an exposure to a high-fat diet) is necessary to observe an obesogenic effect, hyperglycaemia, or glucose and insulin intolerance [44-46].

At the molecular level, several receptors have been involved in the effects of most MDCs: three xenobiotic receptors mediate such signalling including constitutive androstane receptor (CAR) and pregnane X receptor (PXR) whose activation by mono(2-thylhexyl)

phthalate (MEHP) and monoisononyl phthalate [47] can explain the ability of these phthalates to regulate the expression of genes involved in glyceroneogenesis and triacylglycerol metabolism [48]. *In vitro* data concerning TCDD and dioxin-like PCBs that activate the aryl hydrocarbon receptor (AhR) (a bHLH/PAS transcription factor), argue in favour of their anti-adipogenic and pro-inflammatory effects [46,49,50,51] (see above the necessity to have a second type of hit to observe an obesogenic effect).

Interestingly, receptors which were not traditional xenobiotic receptors are also involved in MDC effects: for example, BPA and its substitutes (AF, F and S), parabens (ethyl-, propyl-, butyl- and benzyl-parabens), PFOS and PFOA, act *via* the binding or upregulation of PPARγ and C/EBPα, which increases expression of adipogenic genes such as FABP4, LPL, leptin and perilipin [42,52,53,54]. Some pollutants display multiple targets: obesogenic effects of TBT are related to its ability to activate several nuclear receptors (NRs) such as retinoid X receptor-alpha (RXRα) and PPARγ [55], which increase the adipogenic commitment of MSCs, stimulate adipocyte proliferation and differentiation, and induce lipid uptake by adipocytes [3]. Similarly, phthalates and their metabolites can interact with different PPARs as agonists, and the androgen receptor (AR) as antagonists, and elicit endocrine-disrupting effects possibly contributing to obesity [56,57]. Several environmental compounds may activate the PPARγ of different vertebrate species similarly [57]. In addition, oestrogen receptor-alpha (ERα) activation and/or AR inhibition by bisphenols, DDT/DDE and parabens [58,59] and glucocorticoid receptor (GR) activation by parabens [53] are also observed. Thus, MDCs by promoting the formation of hypertrophic and inflammatory adipocytes and counteracting the effects of endogenous ligands of several nuclear receptors (NRs), impair WAT functions. However, several signalling mechanisms appear to contribute to these effects.

Alteration of the hepatic functions: glucido-lipidic metabolism, secretion of hepatokines, response to insulin

During the last decades, the impact of EDs and/or MDCs on the liver and their consequences on metabolic disease outcomes have been largely supported. Most of them lead to NAFLD which are further linked to obesity, metabolic syndrome, insulin resistance (IR) and diabetes [1,60]. Thereafter, some examples of the effects of MDCs on mechanisms involved in the development of liver diseases from steatosis (lipid accumulation as droplets in hepatocytes) to non-alcoholic steatohepatitis (NASH, characterised by liver cell death and inflammation) are presented through four non-exhaustive parts: (a) disruption of lipid homeostasis, (b) disruption of carbohydrate metabolism, (c) alteration of insulin responses and (d) inflammation and secretion of hepatokines.

With regard to the (a) disruption of lipid homeostasis, the first step of NAFLD is the accumulation of FA in the hepatocytes, mainly stored in the form of triglycerides; this can be driven by multiple processes: increased FA uptake, increased *de novo* lipogenesis (DNL), decreased mitochondrial FA oxidation (mFAO) and decreased FA export. These processes are highly regulated by nuclear receptors and other xenoreceptors, including PPARs, liver X receptors (LXRs), CAR, PXR, AhR and/or by other transcription factors, such as sterol regulatory element binding protein 1c (SREBP1c). Each of them has been shown to be altered by EDs [1,61]. A good example of such perturbations leading to liver steatosis could be the effect of an exposure to PCB156 which activates the AhR in mice while decreasing the expression of PPARβ/δ, a nuclear receptor which promotes FA oxidation [62]. Both PCB156 effects may then contribute to: an increased expression of CD36 (a plasma membrane transporter involved in FA uptake), and of SREBP1c (a transcription factor which regulates the expression of DNL-associated and cholesterol metabolism genes), a decreased expression of carnitine palmitoyl-transferase 1B (CPT1B) (a regulatory enzyme involved in mitochondrial FA entrance) and of apolipoprotein C2 (APOC2) (the co-factor activator of LPL), and ATP-binding cassette subfamily A member 1, ABCA1, involved in cellular cholesterol efflux [63]. Accumulation of lipids and disruption of expression of genes involved in the control of lipid metabolism can be similarly observed in liver cells exposed to perfluorinated compounds, such as PFOS [64] or in mice exposed to low doses of BPA (5 and 50 $\mu g \cdot kg^{-1} \cdot day^{-1}$) increases the liver expression of lipogenic enzymes (Acc, Fasn, Scd1) and transcription factors which regulate lipogenesis (LXR, SREBP1c, ChREBP or carbohydrate responsive element binding protein). This effect is not observed at high doses (5000 $\mu g \cdot kg^{-1} \cdot day^{-1}$) [65].

Regarding the (b) disruption of carbohydrate metabolism, it has been shown that several EDs bind CAR in hepatocytes. CAR is a nuclear receptor which binds xenobiotics and endobiotics, including retinoic acids and steroids, and it forms dimers with its partner, RXRα. In addition to xenobiotic metabolism and transport regulation, CAR regulates several liver functions, including, carbohydrate and lipid metabolism,

through a transcriptional activation associated with histone acetylation and a transcriptional repression when competing on enhancers with other regulatory factors such as HNF4α, PPARα or FXR [66]. CAR has been described as a repressor of gluconeogenesis: it binds to the transcriptional regulator FoxO1 and thus induces transactivation of several gluconeogenic genes including cytoplasmic phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase) []. Phtalates and perfluorinated compounds have been described as CAR agonists [DEHP, Dibutyl phthalate (DBP) or PFOS] or antagonists (PFOA) [67-69]. Bisphenols have been described as either agonists (BPA) or antagonists (TBBPA). BPA acts on CAR as an inverse agonist, that is, its binding to the receptor exerts an opposite effect compared with an agonist [70]. In that case, BPA might favour gluconeogenesis and increase glycaemia. Moreover, BPA and its analogues can decrease glucokinase expression leading to an impairment of glucose sensing and glucose intolerance [71]. Glucose metabolism is also highly linked to insulin regulation and response, and EDs are also well-known to interfere with this pathway, as discussed in the next section.

Concerning the (c) alteration of insulin responses, the secretion of insulin, the main blood glucose-regulating hormone, is induced by increased blood glucose, upon the body shifting from a fasted to a fed state, and promotes liver glycogenesis and lipogenesis, while inhibiting liver gluconeogenesis and glucose secretion [72,73]. EDs are known to interfere with insulin response in the liver and other peripheral organs (muscles and AT) [74,75]. An example of direct effects of EDs on the liver is the disruption of insulin signalling by BPA, which reduces the level of insulin receptor and glycogenesis in the liver of rats [76]. It should be noted that reduction of insulin response by EDs in muscles or adipose tissues, leading respectively to hyperglycaemia or hyperlipidaemia, also promote both NAFLD and other metabolic diseases [74,75].

Finally, about (d) inflammation and secretion of hepatokines, it is worth noting that cytokines and pro-inflammatory proteins produced by the liver are crucial players in NAFLD progression to non-alcoholic steatohepatitis (NASH). NASH is a pathophysiological state in which liver steatosis is combined with inflammation and sometimes fibrosis; it can eventually lead to cirrhosis or hepatocellular carcinoma. Cytokine expression and secretion are regulated by EDs [1] such as PFOA in mice [77] or BPA that increases IL-8 and TNF-alpha secretion in HepG2 cells [78]. EDs such as BPA, PFOS and TCDD mediate liver inflammatory responses not only through pro-inflammatory cytokines secretion but also by the activation and the polarisation of Kupffer cells (KCs) into pro-inflammatory M1-phenotype [79], the infiltration of immune cells in the liver and the activation of quiescent hepatic stellate cells (HSCs) into myofibroblast-like cells [80]. Furthermore, it has been shown in mice that polychlorinated biphenyls (PCBs) could increase the expression of several secreted proteins, known as hepatokines (Fgf21, Igf1 and betatrophin), thus promoting NAFLD progression and pancreatic alteration favouring diabetes [81].

Impaired pancreatic functions

Pancreatic β-cell dysfunction is known to be the hallmark of type 2 diabetes but also a major contributing factor in the aetiology of other metabolic diseases like obesity or metabolic syndrome. Experimental evidence has revealed that certain EDs may display direct effects on pancreatic β-cells leading to several adverse outcomes including oxidative stress, mitochondrial damage, cell apoptosis, altered electrical activity, impaired Ca^{2+} signalling and insulin secretory defects. Here we give a brief overview of the currently known EDs affecting β-cells and of the mechanisms of action of POPs and non-POPs.

Current experimental evidence supports that BPA can disrupt glucose metabolism by affecting pancreatic β-cell physiology. Acute low doses of BPA have been reported to alter the expression and activity of the main ion channels implicated in the coupling of glucose metabolism to insulin secretion. In particular, BPA was found to promote the closure of the K_{ATP} channel, increase the frequency of $[Ca^{2+}]_i$ oscillations, as well as to reduce Na^+ and K^+ currents in mouse and human pancreatic β-cells. Furthermore, BPA significantly disturbed the expression of genes encoding important Na^+ and K^+ subunits. These changes ultimately led to increased glucose-stimulated insulin secretion (GSIS) through the activation of the extranuclear oestrogen receptor beta (ERβ) [82,83]. Longer exposures to BPA upregulated insulin content in an oestrogen receptor alpha (ERα)-mediated manner [84]. BPA-treated animals also manifested an excessive insulin secretory response leading to hyperinsulinaemia and insulin resistance [85,86].

A number of studies have also examined the impact of a direct DEHP exposure on pancreatic β-cells and, although limited to immortalised β-cell lines, they all indicate that DEHP can promote increased apoptosis [87-90]; various mechanisms have been proposed to explain this effect including oxidative stress [87-90], DNA damage [90], decline of antioxidant protection

[89], activation of ER (endoplasmic reticulum) stress responses [89] or interaction between oxidative stress and autophagy [88]. DEHP exposure has also been shown to suppress GSIS [87,89], which could be partially explained by the DEHP-induced β-cell loss.

Among POPs, studies performed in the mouse pancreatic β-cell line β-TC6 have revealed that PFOS may differently impact pancreatic β-cell function depending on time of exposure. Thus, acute PFOS treatment for 1 h resulted in augmented intracellular $[Ca^{2+}]_i$ and, consequently, insulin release, in a mechanism depending on G protein coupled receptor (GPR40) activation [91,92]. This was confirmed *in vivo* [91]. In contrast, longer exposure to PFOS (48 h) promoted decreased mitochondrial membrane potential, ATP production, Ca^{2+} influx, as well as insulin secretion, *via* downregulation of SIRT1-UCP2 pathway [93]. Decreased ATP levels and GSIS were also reported in *ex vivo* treated mouse islets together with a significant reduction on Pdk1-AktmTOR pathway expression levels [94].

As it was the case for PFOS, TBT effects on pancreatic β-cells was largely dependent on the length of treatment. Acute exposure (4 h) significantly increased $[Ca^{2+}]_i$ and insulin secretion. These effects were attenuated in the presence of the oestrogen receptor antagonist ICI 182780, the antioxidant *N*-acetylcysteine, and the specific PKC inhibitor Ro32-0432, suggesting that both oestrogen-related and ROS/PKC signalling pathways were involved. This was confirmed in the β-cell line Rin-m5F but also in mouse and human islets treated *ex vivo* [95]. TBT exposure for 24 h led to oxidative stress and consequent activation of JNK pathway resulting in increased apoptosis and decreased GSIS in RIN-m5F b-cells and mouse isolated islets [96].

Among dioxins, TCDD is the best known to be harmful for pancreatic β-cells. Studies in mouse and human islets have demonstrated that TCDD may impair insulin release through an AhR-dependent pathway, as CYP1A1 expression and activity were found to be elevated [97]. In addition, TCDD has been reported to promote increased apoptosis through ERK1/2 and JNK signalling pathways [98]. Both increased apoptosis and decreased GSIS were related to ultrastructural alterations such as increased mitophagy and mitochondrial swelling in mouse and human islets [99].

Impaired intestinal and microbiota functions

While the impact of EDs on the liver: adipose axis has been well studied through their roles on metabolic diseases like NAFLD, diabetes or obesity [100-102], their effect on the intestine still needs to be investigated. Notwithstanding, the gastrointestinal tract constitutes a prime target of many pharmaceuticals and xenobiotics that can affect human health and disease [103].

The gut microbiota is an organ, capable of producing a large number of biologically active molecules that influence the physiological functions of the host whose secretions in turn influence the composition and function of the microbiota.

Indeed, there is mounting evidence that the gut microbiome, through crosstalk with the gut–liver and gut–brain axis, could mediate the outcome of ED chemical exposure. This could lead to reproductive and mental disorders as well as to metabolic diseases by altering hormone regulation of food intake, appetite and satiety [104]. Even if the mechanisms behind this dysbiosis are still not clarified, the impact of EDs on intestinal microbiota may be responsible for obesity even in young children [105]. EDs influence the gut-microbiome dialogue and can lead to dysbiosis. The microbiota can also be responsible for the metabolism of food contaminants (dechlorination of DDT to DDD). Finally, a sexual dimorphism in the composition of microbiota could play a role in sexual predisposition to diseases [106], including metabolic syndrome (NAFLD) [107].

Some studies have identified putative mechanisms leading to metabolic pathologies: indeed, in different animal models (mice, zebrafish and dogs), BPA is able to induce changes in the microbiota, both in terms of its composition and its function: BPA (a) favours Proteobacteria populations (as in case of exposure to a high-fat diet) or CKC4 [108,109] and disfavours the phylum Bacteroides, Flexispiraphyla, Oscillospira and Ruminococcaceae [110,111], (b) changes the blood metabolome (increased plasma bicarbonate concentrations in relation to Bacteroides disruptions), [110], (c) feminises the microbiota [112]. Other EDCs have been studied such as phthalates, diethylphthalate (DEP), methylparaben (MP) and triclosan (as well as their mixture) but they had significantly different population effects with a relative increase in Bacteroides and decrease in Firmicutes in female rats [113]. In contrast, MEHP causes a relative increase of Firmicutes and a reduction in Verrucomicrobia in mice, whereas DEP causes a decrease in Firmicutes [114]. The importance of pattern and chemical nature of molecules is confirmed with pesticides: carbemazine, a reprotoxic fungicide, and DDE and β-HCH, insecticidal organochlorines, reduce microbiota diversity by decreasing bacteroids, and favouring firmicutes [115,116] while pentachlorophenol (PCP), a herbicide and insecticide, favours bacteroids at the expense of firmicutes [117]. These studies raise the question of

antagonistic and potentiating effects of mixtures of molecules especially since some persistent molecules (such as 2,3,7,8-tetrachlorodibenzofuran, PCB126, TCDD and DDE) are also responsible for these imbalances, for some in relation to metabolic diseases [116,118,119]. In particular, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine and triacylglycerols have been identified as key metabolites affected by DDE treatment, the levels of which are strongly correlated with altered microbiota composition [119]. At this stage it is not completely clear whether the effects on microbiota account for the MDC metabolic effects or whether the impacts on metabolism can account for the observed imbalance in microbial species.

Several studies attempted to address these mechanisms. Male mice treated with BPA showed, in addition to the bacterial composition alterations seen above, an accumulation of hepatic lipids. The suspected mechanism is that the decrease in the diversity of the gut microbiota leads to increased permeability related to elevated levels of endotoxins, and an increase in liver inflammation (IL-1β and 6, TNF-alpha) that promotes steatosis [120]. In BPA-treated rats, intestinal imbalance (decrease in faecal bifidobacterial elements) is associated with impaired glucose tolerance that subsequently leads to the development of obesity, type 2 diabetes (through insulin resistance and inflammation of peripheral tissues such as adipose tissue) [121].

TCDD, a ubiquitous POP, could alter the composition of the microbiota in male rats and thus disrupt the enterohepatic cycle leading to a significant decrease in faecal bile acids, and thus an increase in intestinal transit time and intestinal permeability [122]. One of the modes of action of dioxins is through their binding to the AhR; however, this receptor also binds tryptophan metabolites that can be produced by the microbiota, and an alteration of this metabolic capacity is associated with the metabolic syndrome, in mice and humans. Dioxins such as TCDD could hijack 'Trp metabolites – AhR' signalling; indeed, restoration of AhR signalling through the use of natural agonists, attenuates both intestinal permeability and metabolic syndrome in mice [122-124].

Finally, the microbiota produces short-chain FA (SCFAs) such as propionate, an anti-inflammatory molecule that may reduce the development of hepatic steatosis by reducing the transcription of several *de novo* lipogenesis enzymes [125]. Butyrate potentiates the secretion of pituitary GH and its stimulatory factor, ghrelin [126] which increases food intake. Yet it has been shown that chronic exposure to chlorpyrifos (an organophosphate insecticide) can reduce the production of SCFA and lactate.

The intestine itself plays a central role in fat homeostasis by regulating intestinal lipid transport. Furthermore, several relevant molecular actors are expressed in the intestine. For instance, PXR is a ligand-dependent transcription factor that is activated by numerous endogenous hormones, dietary steroids, pharmaceutical agents, and xenobiotics and regulates the expression of genes required for xenobiotic metabolism in the liver and intestine, including Phase I–III proteins [127]. Whereas the role of PXR in xenobiotic metabolism has been well established, its role in mediating the pathophysiological effects of ED chemicals in humans and animals has been less investigated although recent studies reported the role of PXR in dyslipidaemia and atherosclerosis. The principal role of PXR in the intestine is to maintain barrier function and reduce inflammation, as well as to regulate intestinal transcription of metabolic enzymes [100]. The dietary xenobiotics resulting from PXR-regulated intestinal absorption could impact the physiological function of the liver and adipose tissue and promote steatosis and obesity (among others) [100]. Recently, Kim et al. [128] showed the role of PXR in physiopathology of NAFLD, obesity and inflammation linked to gut microbiome dysbiosis using PXR-knockout mice. The activation of intestinal PXR is responsible for transcriptional activity of key metabolic enzymes such as the CYP3A4 which is the major expressed P450 in intestinal enterocytes, with levels uncorrelated to those of liver. It is involved in the metabolism of endogenous compounds like cholesterol [129] and contributes to the first-pass metabolism of drugs [130]. PXR may link hypercholesterolaemia and exposure to ED chemicals as it is involved in both cholesterol and xenobiotics metabolism [131]. Thus, the disruption of intestinal PXR and/or CYP3A4 expression could lead to serious metabolic diseases through the deregulation of signalling pathways implicated in intestinal barrier function, inflammation, xenobiotics detoxification and endogenous metabolism.

Alteration of appetite and thermogenesis

Endocrine disruptors can influence food intake and thermogenesis at multiple levels and thus contribute to an increased risk of obesity [132,133].

Obesogenic molecules are likely to influence the function of the hypothalamus, an area of the brain responsible for controlling eating behaviour. Similarly, at the peripheral level, they influence the secretion and production of adipokines by the adipose tissue.

Specifically, perinatal exposure to BPA in rats influences pre- and post-synaptic connections at the hypothalamic level, increasing food consumption by stimulating compulsive eating behaviours, which ultimately leads to obesity [134]. A recent study shows that exposure to BPA and a brominated derivative, TBBPA at concentrations commonly found in the environment (between 20 and 500 $\mu g \cdot L^{-1}$) alters the behaviour of adult male zebrafish. The latter consumes a greater amount of food, which leads to obesity and hepatic steatosis. BPA and its derivative bind the cannabinoid receptor type 1 (CB1), a G protein-coupled receptor expressed in the peripheral and central nervous system. Selective antagonists of this CB1 receptor are used for weight reduction. Binding of BPA or TBBPA may promote food intake and contribute to the development of metabolic diseases [135].

Obesogens also control the levels of adipokine production and secretion that influence food intake; for example, in humans, serum BPA levels are associated with increased body weight and serum leptin and ghrelin levels [136]. In mice, at the level of adipocytes, BPA promotes the production of leptin transcripts (using the 3T3-L1 cell line), which leads to the hypothesis of an increased production of this hormone, which could therefore influence food intake [137]. This is also observed *in vivo* in mice treated with methyl-paraben and DEHP which increase serum leptin levels; the latter (DEHP) also decreases adiponectin levels [138,139].

Regarding thermogenesis, recent studies deciphered the mechanisms of communication between organs which govern the metabolic switches and potentially, how pollutants may affect this communication [140]. Indeed, cold-induced thermogenesis leads to the release of free fatty acids from white adipose tissue, which are taken up by the liver, which in turn produces a large amount of acylcarnitines in an HNF4α-dependent process. These molecules reach the brown adipose tissue (BAT) but neither the liver nor the white adipose tissue, for which the capture is blocked [141]. A recent study showed that chlorpyrifos impairs mitochondrial respiration in BAT in mice at very low concentrations (1 pM). Rearing temperature is a key element of this experiment since at thermoneutrality, subjected to a high-fat diet, mice treated with chlorpyrifos develop obesity, NAFLD and insulin resistance. Thus chlorpyrifos, seems to inhibit diet-induced thermogenesis and activation of BAT [142].

Epigenetic effects of EDs

Several EDs are associated with epigenetic modifications (modifications of DNA methylation, post-translational histones modifications and microRNA expression), possibly transgenerational: diethylstilbestrol (DES) represents a classical example: DES, a nonsteroidal oestrogen commonly prescribed during pregnancy between 1947 and 1971, is a potent ED whose prenatal exposure in animals causes developmental defects of the reproductive system; several epidemiological and animal studies suggest that prenatal exposure to this EDC is linked to obesity. More recently, it was shown that exposure to three EDs that are constituents of certain plastics, BPA, DEHP and DBP, to female rats (F0) during gestation induced in the F3 generation (which has never been in contact with these EDCs), changes in DNA methylation at genes associated with obesity, with increased susceptibility to this pathology in both males and females [143].

This is also true for POPs such as methoxychlor [144], DDT [145,146] or TBT, an organotin antifouling agent, historically used to control the appearance of organisms on the hulls of ships. TBT is indeed a prominent example of obesogens as it has been documented to have obesogenic effects in animals [2,37,147]. TBT is a potent environmental ligand of RXR and promote adipogenesis and alter lipid homeostasis *via* RXR-dependent pathways [148]. TBT promotes, in different generations (F1 and F3), an increase in perigonadal fat deposits but without any change in body weight [149]. However, a susceptibility to weight gain is observed specifically in males of the next generation (F4) [150]. Changes in DNA methylation are also observed for example in the leptin gene [151]. For DDT, a 2019 study suggests by isolating adipocytes, that this insecticide has a sexual dimorphic effect in terms of DNA methylation modification [152].

Inorganic pollutants exerting endocrine disrupting effects such as cadmium (in a mixture associated with mercury), are also incriminated by studies conducted in rats exposed over several generations, to metabolic alterations (glucose intolerance and increased abdominal fat deposition) up to the F4 generation [153].

Multi-organ alterations contributing to the development of metabolic diseases: an integrative view

Several types of pollutants have been epidemiologically associated with the development of metabolic diseases in young children, adolescents or adults (sometimes due to perinatal exposure) and several inter-organ mechanisms of action can be identified for these molecules.

The most common mechanism of action is the stimulation of inflammatory processes that can impact, for example, the function of adipose tissue (particularly in terms of insulin resistance) or that of the liver; inflammation being an essential component of NASH. Metabolic processes can also be directly affected: for example, the membrane FA transporter CD36 is regulated by several transcriptional factors in certain tissues (such as C/EBPα for AT), some of which are also nuclear receptors (PPARγ) or xenobiotic receptors (AhR). CD36 allows the import of FA into cells, particularly at the adipocyte and hepatic levels, contributing respectively to adipogenesis and NAFLD formation. Another example is SREBP1c, a transcription factor that is synthesised as a precursor anchored to the nuclear membrane and the endoplasmic reticulum. Its expression is increased by insulin, which induces, after cleavage of the precursor, translocation of the mature protein to the nucleus leading to the regulation of genes involved in lipogenesis and glucose metabolism. Several pollutants increase the expression of CD36 or SREBP1c such as TCDD [154,155], PCB156 [62], PFOS [64], BPA [156] or atmospheric particles [157].

Some pollutants such as BPA have the capacity to target several key organs in metabolic regulation; their mode of action can thus be understood at the scale of the organism and of the inter-organ communication. Indeed, BPA displays a variety of effects in different organs that concur in leading to metabolic disruption. (a) BPA acts as an endocrine disruptor by impacting the production and secretion of insulin by the pancreas in an ER-dependent manner. While BPA augments insulin content through an ERα/ERK pathway, ERβ modulates the expression and activity of ion channels in pancreatic β-cells leading to an increase in glucose-stimulated insulin release. Overall, this excessive secretory response may be a contributing factor in the long-term development of insulin resistance [82-86]. (b) At the hepatic level, there are multiple targets of BPA: it behaves as a reverse agonist of CAR [70], a receptor suppressing gluconeogenesis; as a consequence, BPA potentially contributes to hyperglycaemia but it also reduces the level of insulin receptor contributing to insulin resistance [76], which could be enhanced by inflammatory cytokine production [78] and polarisation of KCs to a pro-inflammatory phenotype. (c) BPA promotes in AT, increased adipogenesis associated with increased body weight but also inflammation that contributes to insulin resistance and hyperglycaemia [38-40]. BPA and its substitutes (AF, F and S), act by modulating the activity of PPARγ; it should be noted that, in this tissue, the effects of the BPA substitute, BPS, are even more powerful and include a robust induction of adipogenic genes such as FABP4, LPL, leptin and perilipin [52].

Beyond the liver–pancreas–adipose tissue network, other tissues are impacted by BPA, such as the intestine, in particular the microbiota. The diversity of the gut microbiota appears to be reduced in favour of endotoxin-producing bacteria leading to increased permeability of the gut barrier, increased inflammation of the liver, and consequently insulin resistance and steatosis [120]. BPA would also act at the central level (hypothalamus) by increasing compulsive eating behaviours [134] and peripheral (AT) by increasing leptin secretion [137]. In addition to all the direct effects mentioned, this would result in a dietary energy imbalance (Fig. 1).

Conclusion and future perspectives

A major step forward in toxicology has been an increasing attention to combinations of exposure pathways, of stressors and of mechanisms of action. In this review, we did not discuss either aggregated exposure pathways or mixture effects, which are highly relevant but have been covered elsewhere [158,159].

The importance of taking into account multi-organs interaction needs to be addressed and we thus have highlighted that combining the disrupting effects that a given environmental chemical has on different organs is key to providing a better understanding of toxicity at the organism level. The combinatorial approach whereby organ-level pathway disruption is integrated into a global organism-level toxicity is particularly well suited for metabolic disruption. Indeed, it is well known that bodily metabolism is influenced by endocrine and signalling pathways at play in multiple organs and that exhibit considerable crosstalk: the gut–liver–pancreas–adipose–muscle–brain network governs organism metabolism and therefore it is particularly important to assess the effects of chemicals on these organs and to attempt to integrate them. This is what we have tried to do here for BPA.

The Adverse Outcome Pathway Network (AOPN) provides a particularly suitable framework to address combinatorial pathway disruption effects. By integrating different mechanisms of action at the molecular, cellular, organ and organism levels, it allows researchers to describe how combinations of multiple organ- or cellular-level pathways disruptions contribute to adverse outcomes. AOPN makes it possible to better determine the critical events leading to metabolic outcomes and possibly to identify effect markers for epidemiological or toxicological studies. Such markers

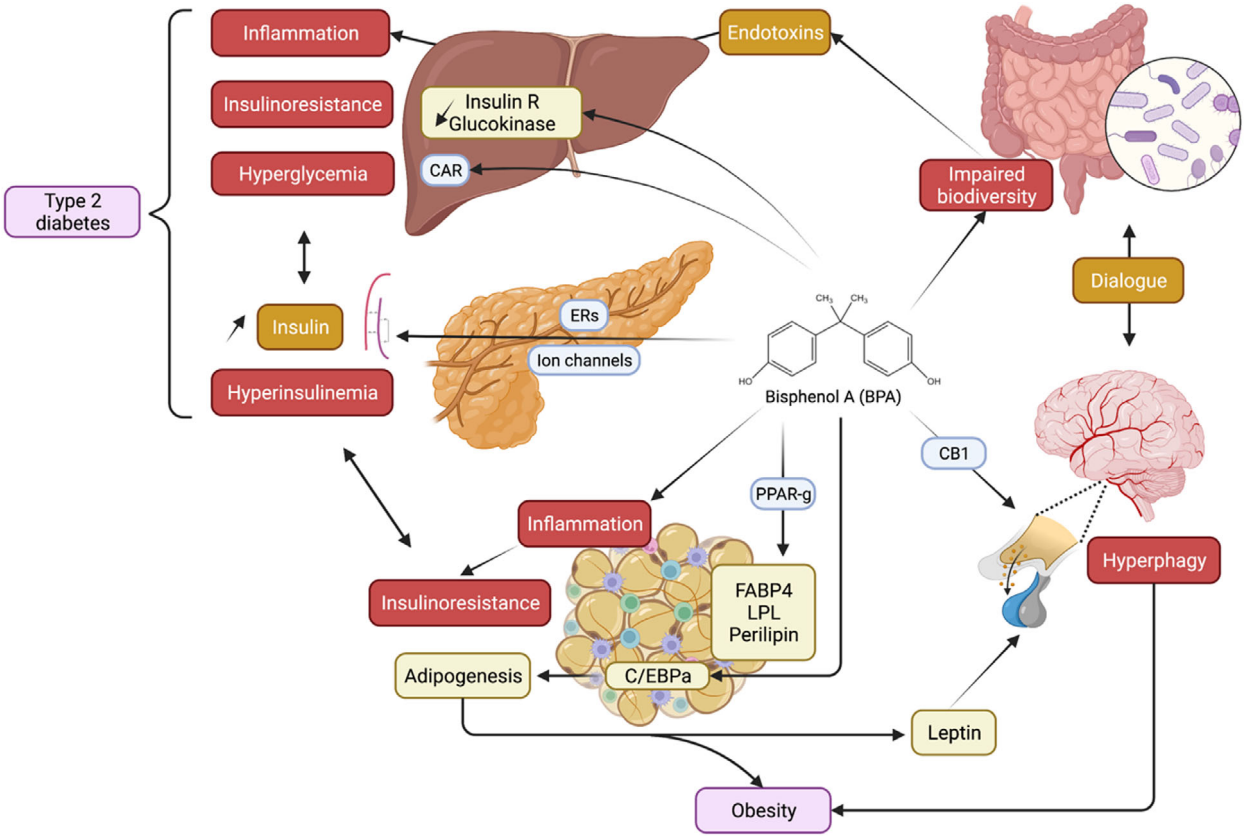

Fig. 1. An integrated view of the modes of action of bisphenol A (BPA) on metabolic parameters. In blue, the molecular targets of BPA; in yellow, indirect targets of BPA. In red, impaired physiological functions. In purple, the adverse outcomes (created with BioRender.com).

could also be useful to rapidly verify the safety of chemical substituents and contribute to a safe by design approach to the development of new chemicals.

While integrated multi-organ toxicity can obviously be tested *in vivo*, it is also possible to address these integrated multi-organ mechanisms by combining several *in vitro* and *in silico* assays. This requires a mechanistic understanding of ED effects at the organ level. While significant advances in our understanding of the modes of action and effects of EDs on the metabolic physiopathology of organisms have been made in recent years, there is still a need to pursue this research to enhance such knowledge at the molecular, cellular and tissue levels, particularly in order to develop mechanism-based assays, which could be implemented at the regulatory level and thereby fill existing gaps in hazard and risk assessment of chemicals. In this perspective, it is important to design these assays so that they could be used to efficiently establish causal and possibly quantitative links between mechanisms and adverse effects by taking advantage of the Adverse Outcome Pathways. The development of species-specific *in silico*, *in vitro* and *in vivo* models and their integration into an efficient strategy to monitor human health must precede their regulatory recognition and use.

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