



**HAL**  
open science

**ManuscriptType: REVIEW ENDOCRINE  
DISRUPTING CHEMICALS IN MIXTURE AND  
OBESITY, DIABETES AND RELATED METABOLIC  
DISORDERS Number ID: 03051109 Running Title:  
Chemicals and Metabolic Disorders**

Brigitte Le Magueresse-Battistoni, Labaronne Emmanuel, Hubert Vidal,  
Danielle Naville

► **To cite this version:**

Brigitte Le Magueresse-Battistoni, Labaronne Emmanuel, Hubert Vidal, Danielle Naville. Manuscript-Type: REVIEW ENDOCRINE DISRUPTING CHEMICALS IN MIXTURE AND OBESITY, DIABETES AND RELATED METABOLIC DISORDERS Number ID: 03051109 Running Title: Chemicals and Metabolic Disorders. World journal of biological chemistry, 2017. inserm-01848536

**HAL Id: inserm-01848536**

**<https://inserm.hal.science/inserm-01848536>**

Submitted on 24 Jul 2018

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Name of Journal:** *World Journal of Biological Chemistry*

**ManuscriptType:** REVIEW

**ENDOCRINE DISRUPTING CHEMICALS IN MIXTURE AND OBESITY,  
DIABETES AND RELATED METABOLIC DISORDERS**

Number ID: 03051109

**Running Title : Chemicals and Metabolic Disorders**

**Brigitte Le Magueresse-Battistoni, Labaronne Emmanuel, Hubert Vidal and  
Danielle Naville**

**Brigitte Le Magueresse-Battistoni**, Univ-Lyon, CarMeN laboratory, INSERM U1060, INRA U1397, Université Claude Bernard Lyon1, INSA Lyon, Charles Mérieux Medical School, F-69600 Oullins, France

**Labaronne Emmanuel**, Univ-Lyon, CarMeN laboratory, INSERM U1060, INRA U1397, Université Claude Bernard Lyon1, INSA Lyon, Charles Mérieux Medical School, F-69600 Oullins, France

**Hubert Vidal**, Univ-Lyon, CarMeN laboratory, INSERM U1060, INRA U1397, Université Claude Bernard Lyon1, INSA Lyon, Charles Mérieux Medical School, F-69600 Oullins, France

**Danielle Naville**, Univ-Lyon, CarMeN laboratory, INSERM U1060, INRA U1397, Université Claude Bernard Lyon1, INSA Lyon, Charles Mérieux Medical School, F-69600 Oullins, France

**Author contributions:** Le Magueresse-Battistoni B and Naville D generated the tables and wrote the manuscript. Labaronne E and Vidal H contributed to the writing of the manuscript.

**Supported by** INSERM to InsermU1060; Labaronne E is a recipient of “Région Rhône-Alpes”, France (ARC 2013-ARC1 SANTE-13-018955-01).

**Conflict-of-interest statement:** The authors declared no conflict of interest related to this manuscript.

**Correspondence to:** Dr. Brigitte Le Magueresse-Battistoni, PhD, CarMeN laboratory, INSERM U1060, Faculté de Médecine Lyon-Sud, Chemin du Grand Revoyet, 69600 Oullins, France. [brigitte.lemagueresse@inserm.fr](mailto:brigitte.lemagueresse@inserm.fr)

**Telephone :** + 33-42-6235919

**Fax :** + 33-42-6235916

**Acknowledgments:** The authors are very grateful to their colleagues Claudie Pinteur and Nathalie Vega from Carmen Laboratory, Lyon. The authors wish to thank Dr Alexandrine Derrien from Washington, DC for critically reading the manuscript.

## **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.

## **Keywords**

Endocrine disrupting chemicals, persistent organic pollutants, phthalates, bisphenol A, metabolic disorders (obesity, diabetes), insulin resistance,

## **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.

## **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 <sup>[1]</sup>. 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 <sup>[2]</sup>. 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 <sup>[3,4]</sup>, 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 WHO (World Health Organization) 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 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 US 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 <sup>[10]</sup>.

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 <sup>[11]</sup> 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)<sup>[12, 13]</sup>. 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 <sup>[14]</sup>.

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 triptic of hyperglycemia, hyperinsulinemia and hypertriglyceridemia, in a vicious circle where hyperglycemia aggravates hyperinsulinemia and hyperinsulinemia aggravates hyperglycemia and hypertriglyceridemia<sup>[15, 16]</sup> .

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 PXR (Pregnane X receptor), CAR (Constitutive androstane receptor) and AhR (aryl hydrocarbon receptor). 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 <sup>[17]</sup>. Interestingly, PXR, CAR and AhR were first identified as controlling xenobiotic and drug metabolism and promoting their clearance <sup>[18, 19]</sup>. 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 <sup>[20, 21]</sup> 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 $\gamma$  which is a master transcription factor involved in adipogenesis [25]. However, while enhancing insulin sensitivity, PPAR $\gamma$  activation also leads to enhanced body weight. Thanks to molecular biology research, the dissection of estrogen receptor beta (ER $\beta$ )-deficient mouse phenotype led to the discovery that the metabolic actions of ER $\beta$  are mediated by a negative cross-talk with PPAR $\gamma$  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 $\alpha$  regulates female hepatic metabolism through interaction with LXR $\alpha$  [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)<sup>[31, 32]</sup>.

## **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 $\alpha$  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 $\gamma$ . 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<sup>[39]</sup>. 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<sup>[40, 41]</sup>. It remains that PPAR $\gamma$  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 days. The authors <sup>[42]</sup> 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 <sup>[43]</sup>, 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  $\alpha$ , ER $\beta$  and membrane receptor GPR30, the estrogen receptor-related ERR $\gamma$  and possibly the PPAR $\gamma$  [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/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 $\beta$  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* 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 [53]. 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 $\gamma$  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 multi-exposure [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 $\alpha$ ) 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 disruptors [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 polycyclic aromatic 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.

| Chemicals            | Sources   | Examples   | Some demonstrated metabolic effects   |
|----------------------|---|--|---|
| Alkylphenols         | lubricating oil additives; detergents; emulsifiers, pesticides; plastics. Exposure occurs via water drinking and food consumption [67]  | nonylphenols (NP; C <sub>15</sub> H <sub>24</sub> O)   | 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]  | 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; C <sub>12</sub> H <sub>4</sub> Cl <sub>4</sub> O <sub>2</sub> )   | 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<br>Dermal exposure is a significant route of exposure [73].   | Pentabrominated diphenyl ethers (penta-BDE; C <sub>12</sub> H <sub>5</sub> Br <sub>5</sub> O)  | decrease in glucose oxidation [74]  |
| Organotin compound   | used as biocide in anti-fouling paint, heat stabilizer in PolyVinylChloride<br>Exposure mainly by consumption of seafood [75].  | Tributyltin (TBT; C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> Sn)   | 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<br>Food and water drinking are the major routes of exposure [78].  | Bisphenol A (BPA; C <sub>15</sub> H <sub>16</sub> O <sub>2</sub> ), Bisphenol S (BPS; C <sub>12</sub> H <sub>10</sub> O <sub>4</sub> S)  | estrogenic activities [79]; alteration of pancreatic βcell 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<br><br>•Processing of agriculture products (banned in Europe)<br><br>Dietary sources [81] as well as inhalation and dermal routes of exposure [82]. | dichlorodiphenyltrichloroethane (DDT; C <sub>14</sub> H <sub>9</sub> Cl <sub>5</sub> ) and its metabolite (p,p'-dichlorodiphenyldichloroethylene (DDE; C <sub>14</sub> H <sub>8</sub> Cl <sub>4</sub> )<br><br>atrazine (C <sub>8</sub> H <sub>14</sub> ClN <sub>5</sub> ) | alteration of systemic glucose homeostasis and hepatic lipid metabolism [83]; glucose intolerance, hyperinsulinemia, dyslipidemia and altered bile acid metabolism [84]<br><br>increased body weight, intra-abdominal fat and insulin resistance [85] |
| Phthalates           | Plastic components, cosmetics, medical equipment<br>Exposure mainly derives from dietary sources for high molecular weight phthalates (e.g., DEHP) and non-dietary sources for low molecular weight phthalates (e.g., DBP) [86].                              | Dibutyl phthalate (DBP; C <sub>16</sub> H <sub>22</sub> O); DiethylHexylPhthalate (DEHP; C <sub>24</sub> H <sub>38</sub> O <sub>4</sub> )  | Anti-androgenic effects [87]; transgenerational inheritance of obesity [88]; increased adipocyte differentiation [89]   |

|                                       |   |   |   |
|---------------------------------------|---|---|---|
| Polychlorobiphenyls (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 <sub>12</sub> H <sub>4</sub> Cl <sub>6</sub> ), PCB170 (C <sub>12</sub> H <sub>3</sub> Cl <sub>7</sub> ), PCB187 (C <sub>12</sub> H <sub>3</sub> Cl <sub>7</sub> ) (non dioxin-like); PCB126 (C <sub>12</sub> H <sub>5</sub> Cl <sub>5</sub> ), PCB77 (C <sub>12</sub> H <sub>6</sub> Cl <sub>4</sub> ) (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] |
| Polycyclic aromatic hydrocarbon (PAH) | Byproducts of incomplete combustion of organic compounds (cigarette smoke, wood burning, overcooked meat...). Contamination primarily through inhalation and consumption of certain foods [92].                   | Benzo[ <i>a</i> ]pyrene (B[a]P; C <sub>20</sub> H <sub>12</sub> )   | carcinogenic; alteration of estrogen metabolism in human mammary carcinoma-derived cell lines [93]; inhibition of lipolysis, increased fat accumulation and weight gain [94]                                |
| perfluoroalkyl acids (PFAA)           | Water and oil repellent; used for treatments of clothing, insulation and fire-fighting foams. Oral and dermal exposure [95].  | Perfluorooctanoic acid (PFOA; C <sub>8</sub> HF <sub>15</sub> O <sub>2</sub> )  | Elevated serum leptin and insulin; overweight after <i>in utero</i> exposure [96]   |

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

|   | <b>obesity</b>   | <b>no body weight change</b>   |
|---|--|--|
| <b>insulin resistance</b>                   | .ER $\alpha$ (-/-) in both males and females [38]  |  |
| <b>no difference in insulin sensitivity</b> | .AR (-/-) in males only [97]   |  |
| <b>improved insulin sensitivity</b>         | .ER $\beta$ (-/-) (study on males only) [26]<br>.ERR $\beta$ (deletion in neurons; study on males only) [98] | .CAR activation (study on males only in HFD context, activation by TOBOBOP) [99]<br>.AhR (-/-) (studies on males only) [100]<br>.AhR (-/-) (studies on males only, in HFD context) [101]<br>.PPAR $\alpha$ (-/-) (studies on males only, in HFD context) [102]<br>.PXR (-/-) (studies on males only, in HFD context) [103] |

**Table 2: Metabolic characteristics of mice deficient in some nuclear receptors.**

Mice were fed standard diet or High-fat diet (HFD) when mentioned.

| <b>Nuclear receptors</b>                                 | <b>Interactions with chemicals</b>  |
|--|---|
| <i>Steroid Receptors</i>                                 |   |
| Estrogen Receptor ER                                     | BPA (E $\alpha$ [38], GPR30 [104])  |
| Androgen Receptor AR                                     | BPA [105]   |
| Glucocorticoid receptor GR                               | BPA; phthalates [106]   |
| Progesterone receptor PR                                 | BPA [107]   |
| Thyroid hormone receptor TR                              | BPA [108] ; brominated flame retardants, BFR [109]                        |
| <i>RXR heterodimers</i>                                  |   |
| Peroxisome Proliferator-activated receptor PPAR $\alpha$ | Phthalates [110] ; polyfluoroalkyl compounds, PFC [111]; pyrethrins [112] |
| Peroxisome Proliferator-activated receptor PPAR $\gamma$ | Phthalates [110, 113]; organotins [76]; BPA [114]                         |
| Farnesoid X receptor FXR                                 | Pyrethroids [115]   |
| Constitutive Androstane Receptor CAR                     | Phthalates [116, 117]   |
| Liver X Receptor LXR $\alpha$                            | Phthalates ; BPA [118]  |
| Pregnane X Receptor PXR                                  | Phthalates ; BPA [119, 120]   |
| <i>Other receptors</i>                                   |   |
| Aryl Hydrocarbon Receptor AhR                            | Dioxines ; PCB dioxin-like [72, 121, 122]                                 |

**Table 3:** Interactions of some nuclear receptors with endocrine disruptors

- 1 WHO. World Health Organization, Obesity and Overweight, Fact sheet 311. <http://www.who.int/mediacentre/factsheets/fs311/en/> 2014
- 2 Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Hunt PM, Rudel R, Sathyanarayana S, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ. Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis. *Andrology* 2016; **4**(4): 565-572 [PMID: 27003928 DOI: 10.1111/andr.12178]
- 3 Neel BA, Sargis RM. The paradox of progress: environmental disruption of metabolism and the diabetes epidemic. *Diabetes* 2011; **60**(7): 1838-1848 [PMID: 21709279 PMCID: 3121438 DOI: 10.2337/db11-0153]
- 4 Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J Altern Complement Med* 2002; **8**(2): 185-192 [PMID: 12006126 DOI: 10.1089/107555302317371479]
- 5 Grier JW. Ban of DDT and subsequent recovery of reproduction in bald eagles. *Science* 1982; **218**(4578): 1232-1235 [PMID: 7146905]
- 6 Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *The New England journal of medicine* 1971; **284**(15): 878-881 [PMID: 5549830 DOI: 10.1056/NEJM197104222841604]
- 7 Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environmental health perspectives* 1993; **101**(5): 378-384 [PMID: 8080506 PMCID: 1519860]
- 8 Newbold RR, Bullock BC, Mc Lachlan JA. Exposure to diethylstilbestrol during pregnancy permanently alters the ovary and oviduct. *Biology of reproduction* 1983; **28**(3): 735-744 [PMID: 6850046]
- 9 WHO. Global assessment of the state of the science of endocrine disruptors, . *WHO-IPCS/UNEP/ILO-2002* 2002
- 10 Dorne JL. Metabolism, variability and risk assessment. *Toxicology* 2010; **268**(3): 156-164 [PMID: 19932147 DOI: 10.1016/j.tox.2009.11.004]
- 11 Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Jr., Lee DH, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, Myers JP. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocrine reviews* 2012; **33**(3): 378-455 [PMID: 22419778 PMCID: 3365860 DOI: 10.1210/er.2011-1050]
- 12 Barker DJ, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *International journal of epidemiology* 2002; **31**(6): 1235-1239 [PMID: 12540728]
- 13 Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: implications for research and public health. *Environ Health* 2012; **11**: 42 [PMID: 22715989 PMCID: 3384466 DOI: 10.1186/1476-069X-11-42]
- 14 Mauvais-Jarvis F. Sex differences in metabolic homeostasis, diabetes, and obesity. *Biology of sex differences* 2015; **6**: 14 [PMID: 26339468 PMCID: 4559072 DOI: 10.1186/s13293-015-0033-y]
- 15 Brown MS, Goldstein JL. Selective versus total insulin resistance: a pathogenic paradox. *Cell metabolism* 2008; **7**(2): 95-96 [PMID: 18249166 DOI: 10.1016/j.cmet.2007.12.009]
- 16 Guo S. Insulin signaling, resistance, and the metabolic syndrome: insights from mouse models into disease mechanisms. *The Journal of endocrinology* 2014; **220**(2): T1-T23 [PMID: 24281010 DOI: 10.1530/JOE-13-0327]
- 17 Cave MC, Clair HB, Hardesty JE, Falkner KC, Feng W, Clark BJ, Sidey J, Shi H, Aqel BA, McClain CJ, Prough RA. Nuclear receptors and nonalcoholic fatty liver disease. *Biochimica et biophysica acta* 2016; **1859**(9): 1083-1099 [PMID: 26962021 DOI: 10.1016/j.bbagr.2016.03.002]
- 18 Casals-Casas C, Desvergne B. Endocrine disruptors: from endocrine to metabolic disruption. *Annual review of physiology* 2011; **73**: 135-162 [PMID: 21054169]
- 19 Wada T, Gao J, Xie W. PXR and CAR in energy metabolism. *Trends in endocrinology and metabolism: TEM* 2009; **20**(6): 273-279 [PMID: 19595610 DOI: 10.1016/j.tem.2009.03.003]
- 20 He J, Cheng Q, Xie W. Minireview: Nuclear receptor-controlled steroid hormone synthesis and metabolism. *Molecular endocrinology (Baltimore, Md)* 2010; **24**(1): 11-21 [PMID: 19762543 PMCID: 2803680 DOI: 10.1210/me.2009-0212]

- 21 Swanson HI, Wada T, Xie W, Renga B, Zampella A, Distrutti E, Fiorucci S, Kong B, Thomas AM, Guo GL, Narayanan R, Yepuru M, Dalton JT, Chiang JY. Role of nuclear receptors in lipid dysfunction and obesity-related diseases. *Drug metabolism and disposition: the biological fate of chemicals* 2013; **41**(1): 1-11 [PMID: 23043185 PMCID: 3533426 DOI: 10.1124/dmd.112.048694]
- 22 Swedenborg E, Ruegg J, Makela S, Pongratz I. Endocrine disruptive chemicals: mechanisms of action and involvement in metabolic disorders. *Journal of molecular endocrinology* 2009; **43**(1): 1-10 [PMID: 19211731 DOI: 10.1677/JME-08-0132]
- 23 Rebourcet D, Odet F, Verot A, Combe E, Meugnier E, Pesenti S, Leduque P, Dechaud H, Magre S, Le Magueresse-Battistoni B. The effects of an in utero exposure to 2,3,7,8-tetrachloro-dibenzo-p-dioxin on male reproductive function: identification of Ccl5 as a potential marker. *International journal of andrology* 2010; **33**(2): 413-424 [PMID: 20059583 PMCID: 2871170 DOI: 10.1111/j.1365-2605.2009.01020.x]
- 24 La Merrill M, Emond C, Kim MJ, Antignac JP, Le Bizec B, Clement K, Birnbaum LS, Barouki R. Toxicological function of adipose tissue: focus on persistent organic pollutants. *Environmental health perspectives* 2013; **121**(2): 162-169 [PMID: 23221922 PMCID: 3569688 DOI: 10.1289/ehp.1205485]
- 25 Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. *Annual review of biochemistry* 2008; **77**: 289-312 [PMID: 18518822 DOI: 10.1146/annurev.biochem.77.061307.091829]
- 26 Foryst-Ludwig A, Clemenz M, Hohmann S, Hartge M, Sprang C, Frost N, Krikov M, Bhanot S, Barros R, Morani A, Gustafsson JA, Unger T, Kintscher U. Metabolic actions of estrogen receptor beta (ERbeta) are mediated by a negative cross-talk with PPARgamma. *PLoS genetics* 2008; **4**(6): e1000108 [PMID: 18584035 PMCID: 2432036 DOI: 10.1371/journal.pgen.1000108]
- 27 Pascussi JM, Gerbal-Chaloin S, Duret C, Daujat-Chavanieu M, Vilarem MJ, Maurel P. The tangle of nuclear receptors that controls xenobiotic metabolism and transport: crosstalk and consequences. *Annual review of pharmacology and toxicology* 2008; **48**: 1-32 [PMID: 17608617 DOI: 10.1146/annurev.pharmtox.47.120505.105349]
- 28 Ohtake F, Takeyama K, Matsumoto T, Kitagawa H, Yamamoto Y, Nohara K, Tohyama C, Krust A, Mimura J, Chambon P, Yanagisawa J, Fujii-Kuriyama Y, Kato S. Modulation of oestrogen receptor signalling by association with the activated dioxin receptor. *Nature* 2003; **423**(6939): 545-550 [PMID: 12774124 DOI: 10.1038/nature01606]
- 29 Kliewer SA, Lehmann JM, Willson TM. Orphan nuclear receptors: shifting endocrinology into reverse. *Science* 1999; **284**(5415): 757-760 [PMID: 10221899]
- 30 Della Torre S, Mitro N, Fontana R, Gomaraschi M, Favari E, Recordati C, Lolli F, Quagliarini F, Meda C, Ohlsson C, Crestani M, Uhlenhaut NH, Calabresi L, Maggi A. An Essential Role for Liver ERalpha in Coupling Hepatic Metabolism to the Reproductive Cycle. *Cell reports* 2016; **15**(2): 360-371 [PMID: 27050513 PMCID: 4835581 DOI: 10.1016/j.celrep.2016.03.019]
- 31 Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN, Vom Saal F. Metabolism disrupting chemicals and metabolic disorders. *Reprod Toxicol* 2016 [PMID: 27760374 DOI: 10.1016/j.reprotox.2016.10.001]
- 32 Le Magueresse-Battistoni B, Vidal H, Naville D. Lifelong consumption of low-dosed food pollutants and metabolic health. *Journal of epidemiology and community health* 2015; **69**(6): 512-515 [PMID: 25472636 DOI: 10.1136/jech-2014-203913]
- 33 Michalek JE, Pavuk M. Diabetes and cancer in veterans of Operation Ranch Hand after adjustment for calendar period, days of spraying, and time spent in Southeast Asia. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine* 2008; **50**(3): 330-340 [PMID: 18332783 DOI: 10.1097/JOM.0b013e31815f889b]
- 34 Bertazzi PA, Consonni D, Bachetti S, Rubagotti M, Baccarelli A, Zocchetti C, Pesatori AC. Health effects of dioxin exposure: a 20-year mortality study. *American journal of epidemiology* 2001; **153**(11): 1031-1044 [PMID: 11390319]
- 35 Lee DH, Porta M, Jacobs DR, Jr., Vandenberg LN. Chlorinated persistent organic pollutants, obesity, and type 2 diabetes. *Endocrine reviews* 2014; **35**(4): 557-601 [PMID: 24483949 DOI: 10.1210/er.2013-1084]

- 36 Gauthier MS, Rabasa-Lhoret R, Prud'homme D, Karelis AD, Geng D, van Bavel B, Ruzzin J. The metabolically healthy but obese phenotype is associated with lower plasma levels of persistent organic pollutants as compared to the metabolically abnormal obese phenotype. *The Journal of clinical endocrinology and metabolism* 2014; **99**(6): E1061-1066 [PMID: 24606089 DOI: 10.1210/jc.2013-3935]
- 37 Newbold RR, Padilla-Banks E, Snyder RJ, Phillips TM, Jefferson WN. Developmental exposure to endocrine disruptors and the obesity epidemic. *Reprod Toxicol* 2007; **23**(3): 290-296 [PMID: 17321108 PMCID: 1931509 DOI: 10.1016/j.reprotox.2006.12.010]
- 38 Heine PA, Taylor JA, Iwamoto GA, Lubahn DB, Cooke PS. Increased adipose tissue in male and female estrogen receptor-alpha knockout mice. *Proceedings of the National Academy of Sciences of the United States of America* 2000; **97**(23): 12729-12734 [PMID: 11070086 PMCID: 18832 DOI: 10.1073/pnas.97.23.12729]
- 39 Chamorro-Garcia R, Sahu M, Abbey RJ, Laude J, Pham N, Blumberg B. Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal exposure to the obesogen tributyltin in mice. *Environmental health perspectives* 2013; **121**(3): 359-366 [PMID: 23322813 PMCID: 3621201 DOI: 10.1289/ehp.1205701]
- 40 Janesick AS, Dimastrogiovanni G, Vanek L, Boulous C, Chamorro-Garcia R, Tang W, Blumberg B. On the Utility of ToxCast and ToxPi as Methods for Identifying New Obesogens. *Environmental health perspectives* 2016; **124**(8): 1214-1226 [PMID: 26757984 PMCID: 4977052 DOI: 10.1289/ehp.1510352]
- 41 Pereira-Fernandes A, Vanparys C, Vergauwen L, Knapen D, Jorens PG, Blust R. Toxicogenomics in the 3T3-L1 cell line, a new approach for screening of obesogenic compounds. *Toxicological sciences : an official journal of the Society of Toxicology* 2014; **140**(2): 352-363 [PMID: 24848799 DOI: 10.1093/toxsci/kfu092]
- 42 Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock EJ, Lillefosse H, Ma T, Pesenti S, Sonne SB, Marstrand TT, Malde MK, Du ZY, Chavey C, Fajas L, Lundebye AK, Brand CL, Vidal H, Kristiansen K, Froyland L. Persistent organic pollutant exposure leads to insulin resistance syndrome. *Environmental health perspectives* 2010; **118**(4): 465-471 [PMID: 20064776 PMCID: 2854721 DOI: 10.1289/ehp.0901321]
- 43 Vella RE, Pillon NJ, Zarrouki B, Croze ML, Koppe L, Guichardant M, Pesenti S, Chauvin MA, Rieusset J, Geloën A, Soulage CO. Ozone exposure triggers insulin resistance through muscle c-Jun N-terminal kinase activation. *Diabetes* 2015; **64**(3): 1011-1024 [PMID: 25277399 DOI: 10.2337/db13-1181]
- 44 Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine reviews* 2015; **36**(6): E1-E150 [PMID: 26544531 PMCID: 4702494 DOI: 10.1210/er.2015-1010]
- 45 Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, Vandenberg JG, Walser-Kuntz DR, vom Saal FS. In vivo effects of bisphenol A in laboratory rodent studies. *Reprod Toxicol* 2007; **24**(2): 199-224 [PMID: 17683900 PMCID: 2151845 DOI: 10.1016/j.reprotox.2007.06.004]
- 46 Pereira-Fernandes A, Demaegdt H, Vandermeiren K, Hectors TL, Jorens PG, Blust R, Vanparys C. Evaluation of a screening system for obesogenic compounds: screening of endocrine disrupting compounds and evaluation of the PPAR dependency of the effect. *PloS one* 2013; **8**(10): e77481 [PMID: 24155963 PMCID: 3796469 DOI: 10.1371/journal.pone.0077481]
- 47 Wei J, Sun X, Chen Y, Li Y, Song L, Zhou Z, Xu B, Lin Y, Xu S. Perinatal exposure to bisphenol A exacerbates nonalcoholic steatohepatitis-like phenotype in male rat offspring fed on a high-fat diet. *The Journal of endocrinology* 2014; **222**(3): 313-325 [PMID: 25112833 DOI: 10.1530/JOE-14-0356]
- 48 Garcia-Arevalo M, Alonso-Magdalena P, Servitja JM, Boronat T, Merin B, Villar S, Medina-Gomez G, Novials A, Quesada I, Nadal A. MATERNAL EXPOSURE TO BISPENOL-A DURING PREGNANCY INCREASES PANCREATIC Beta-CELL GROWTH DURING EARLY LIFE IN MALE MICE OFFSPRING. *Endocrinology* 2016; en20161390 [PMID: 27623287 DOI: 10.1210/en.2016-1390]
- 49 Garcia-Arevalo M, Alonso-Magdalena P, Rebelo Dos Santos J, Quesada I, Carneiro EM, Nadal A. Exposure to bisphenol-A during pregnancy partially mimics the effects of a high-fat diet altering

- glucose homeostasis and gene expression in adult male mice. *PLoS one* 2014; **9**(6): e100214 [PMID: 24959901 PMCID: 4069068 DOI: 10.1371/journal.pone.0100214]
- 50 Alonso-Magdalena P, Quesada I, Nadal A. Endocrine disruptors in the etiology of type 2 diabetes mellitus. *Nature reviews Endocrinology* 2011; **7**(6): 346-353 [PMID: 21467970 DOI: 10.1038/nrendo.2011.56]
- 51 Alonso-Magdalena P, Quesada I, Nadal A. Prenatal Exposure to BPA and Offspring Outcomes: The Diabetogenic Behavior of BPA. *Dose-response : a publication of International Hormesis Society* 2015; **13**(2): 1559325815590395 [PMID: 26676280 PMCID: 4674176 DOI: 10.1177/1559325815590395]
- 52 Angle BM, Do RP, Ponzi D, Stahlhut RW, Drury BE, Nagel SC, Welshons WV, Besch-Williford CL, Palanza P, Parmigiani S, vom Saal FS, Taylor JA. Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol A (BPA): evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation. *Reprod Toxicol* 2013; **42**: 256-268 [PMID: 23892310 PMCID: 3886819 DOI: 10.1016/j.reprotox.2013.07.017]
- 53 Marmugi A, Ducheix S, Lasserre F, Polizzi A, Paris A, Priymenko N, Bertrand-Michel J, Pineau T, Guillou H, Martin PG, Mselli-Lakhal L. Low doses of bisphenol A induce gene expression related to lipid synthesis and trigger triglyceride accumulation in adult mouse liver. *Hepatology (Baltimore, Md)* 2012; **55**(2): 395-407 [PMID: 21932408]
- 54 Hugo ER, Brandebourg TD, Woo JG, Loftus J, Alexander JW, Ben-Jonathan N. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. *Environmental health perspectives* 2008; **116**(12): 1642-1647 [PMID: 19079714 PMCID: 2599757 DOI: 10.1289/ehp.11537]
- 55 Menale C, Grandone A, Nicolucci C, Cirillo G, Crispi S, Di Sessa A, Marzuillo P, Rossi S, Mita DG, Perrone L, Diano N, Miraglia Del Giudice E. Bisphenol A is associated with insulin resistance and modulates adiponectin and resistin gene expression in obese children. *Pediatric obesity* 2016 [PMID: 27187765 DOI: 10.1111/ijpo.12154]
- 56 Valentino R, D'Esposito V, Passaretti F, Liotti A, Cabaro S, Longo M, Perruolo G, Oriente F, Beguinot F, Formisano P. Bisphenol-A impairs insulin action and up-regulates inflammatory pathways in human subcutaneous adipocytes and 3T3-L1 cells. *PLoS one* 2013; **8**(12): e82099 [PMID: 24349194 PMCID: 3857211 DOI: 10.1371/journal.pone.0082099]
- 57 Chevalier N, Fenichel P. Bisphenol A: Targeting metabolic tissues. *Reviews in endocrine & metabolic disorders* 2015; **16**(4): 299-309 [PMID: 26820262 DOI: 10.1007/s11154-016-9333-8]
- 58 Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. *Environmental health perspectives* 2012; **120**(6): 779-789 [PMID: 22296744 PMCID: 3385443 DOI: 10.1289/ehp.1104597]
- 59 Naville D, Pinteur C, Vega N, Menade Y, Vigier M, Le Bourdais A, Labaronne E, Debard C, Luquain-Costaz C, Begeot M, Vidal H, Le Magueresse-Battistoni B. Low-dose food contaminants trigger sex-specific, hepatic metabolic changes in the progeny of obese mice. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 2013; **27**(9): 3860-3870 [PMID: 23756648 DOI: 10.1096/fj.13-231670]
- 60 Naville D, Labaronne E, Vega N, Pinteur C, Canet-Soulas E, Vidal H, Le Magueresse-Battistoni B. Metabolic outcome of female mice exposed to a mixture of low-dose pollutants in a diet-induced obesity model. *PLoS one* 2015; **10**(4): e0124015
- 61 Kortenkamp A. Low dose mixture effects of endocrine disrupters and their implications for regulatory thresholds in chemical risk assessment. *Current opinion in pharmacology* 2014; **19**: 105-111 [PMID: 25244397 DOI: 10.1016/j.coph.2014.08.006]
- 62 Silva E, Rajapakse N, Kortenkamp A. Something from "nothing"--eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. *Environmental science & technology* 2002; **36**(8): 1751-1756 [PMID: 11993873]
- 63 Orton F, Ermler S, Kugathas S, Rosivatz E, Scholze M, Kortenkamp A. Mixture effects at very low doses with combinations of anti-androgenic pesticides, antioxidants, industrial pollutant and

- chemicals used in personal care products. *Toxicology and applied pharmacology* 2014; **278**(3): 201-208 [PMID: 24055644 DOI: 10.1016/j.taap.2013.09.008]
- 64 (EFSA) EFSA. Cumulative risk assessment of pesticides to human health: the way forward. *EFSA Scientific Colloquium Summary Report, Parma* (<http://onlinelibrarywileycom/doi/102903/spefsa2007EN-117/pdf>) 2006: 1-160
- 65 Delfosse V, Dendele B, Huet T, Grimaldi M, Boulahtouf A, Gerbal-Chaloin S, Beucher B, Roecklin D, Muller C, Rahmani R, Cavailles V, Daujat-Chavanieu M, Vivat V, Pascussi JM, Balaguer P, Bourguet W. Synergistic activation of human pregnane X receptor by binary cocktails of pharmaceutical and environmental compounds. *Nature communications* 2015; **6**: 8089 [PMID: 26333997 PMCID: 4569708 DOI: 10.1038/ncomms9089]
- 66 Sarigiannis DA, Hansen U. Considering the cumulative risk of mixtures of chemicals - a challenge for policy makers. *Environ Health* 2012; **11 Suppl 1**: S18 [PMID: 22759500 PMCID: 3388441 DOI: 10.1186/1476-069X-11-S1-S18]
- 67 Suen JL, Hung CH, Yu HS, Huang SK. Alkylphenols--potential modulators of the allergic response. *The Kaohsiung journal of medical sciences* 2012; **28**(7 Suppl): S43-48 [PMID: 22871601 DOI: 10.1016/j.kjms.2012.05.009]
- 68 Bonfeld-Jorgensen EC, Long M, Hofmeister MV, Vinggaard AM. Endocrine-disrupting potential of bisphenol A, bisphenol A dimethacrylate, 4-n-nonylphenol, and 4-n-octylphenol in vitro: new data and a brief review. *Environmental health perspectives* 2007; **115 Suppl 1**: 69-76 [PMID: 18174953 PMCID: 2174402 DOI: 10.1289/ehp.9368]
- 69 Schafer KS, Kegley SE. Persistent toxic chemicals in the US food supply. *Journal of epidemiology and community health* 2002; **56**(11): 813-817 [PMID: 12388566 PMCID: 1732058]
- 70 Angrish MM, Mets BD, Jones AD, Zacharewski TR. Dietary fat is a lipid source in 2,3,7,8-tetrachlorodibenzo-rho-dioxin (TCDD)-elicited hepatic steatosis in C57BL/6 mice. *Toxicological sciences : an official journal of the Society of Toxicology* 2012; **128**(2): 377-386 [PMID: 22539624 PMCID: 3493189 DOI: 10.1093/toxsci/kfs155]
- 71 Duval C, Teixeira-Clerc F, Leblanc AF, Touch S, Emond C, Guerre-Millo M, Lotersztajn S, Barouki R, Aggerbeck M, Coumoul X. Chronic Exposure to Low Doses of Dioxin Promotes Liver Fibrosis Development in the C57BL6/J Diet-Induced Obesity Mouse Model. *Environmental health perspectives* 2016 [PMID: 27713108 DOI: 10.1289/EHP316]
- 72 Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. *Environmental health perspectives* 2008; **116**(6): 761-768 [PMID: 18560532 PMCID: 2430232 DOI: 10.1289/ehp.10554]
- 73 Liu X, Yu G, Cao Z, Wang B, Huang J, Deng S, Wang Y. Occurrence of organophosphorus flame retardants on skin wipes: Insight into human exposure from dermal absorption. *Environment international* 2016 [PMID: 28029386 DOI: 10.1016/j.envint.2016.10.021]
- 74 Hoppe AA, Carey GB. Polybrominated diphenyl ethers as endocrine disruptors of adipocyte metabolism. *Obesity (Silver Spring, Md)* 2007; **15**(12): 2942-2950 [PMID: 18198302 DOI: 10.1038/oby.2007.351]
- 75 Sarkar A, Ray D, Shrivastava AN, Sarker S. Molecular Biomarkers: their significance and application in marine pollution monitoring. *Ecotoxicology* 2006; **15**(4): 333-340 [PMID: 16676218 DOI: 10.1007/s10646-006-0069-1]
- 76 Kanayama T, Kobayashi N, Mamiya S, Nakanishi T, Nishikawa J. Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor gamma/retinoid X receptor pathway. *Molecular pharmacology* 2005; **67**(3): 766-774 [PMID: 15611480 DOI: 10.1124/mol.104.008409]
- 77 Zuo Z, Chen S, Wu T, Zhang J, Su Y, Chen Y, Wang C. Tributyltin causes obesity and hepatic steatosis in male mice. *Environmental toxicology* 2011; **26**(1): 79-85 [PMID: 19760618 DOI: 10.1002/tox.20531]

- 78 Volkel W, Kiranoglu M, Fromme H. Determination of free and total bisphenol A in human urine to assess daily uptake as a basis for a valid risk assessment. *Toxicology letters* 2008; **179**(3): 155-162 [PMID: 18579321 DOI: 10.1016/j.toxlet.2008.05.002]
- 79 Krishnan AV, Stathis P, Permuth SF, Tokes L, Feldman D. Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving. *Endocrinology* 1993; **132**(6): 2279-2286 [PMID: 8504731 DOI: 10.1210/endo.132.6.8504731]
- 80 Boucher JG, Ahmed S, Atlas E. Bisphenol S Induces Adipogenesis in Primary Human Preadipocytes From Female Donors. *Endocrinology* 2016; **157**(4): 1397-1407 [PMID: 27003841 DOI: 10.1210/en.2015-1872]
- 81 Brantsaeter AL, Ydersbond TA, Hoppin JA, Haugen M, Meltzer HM. Organic Food in the Diet: Exposure and Health Implications. *Annual review of public health* 2016 [PMID: 27992727 DOI: 10.1146/annurev-publhealth-031816-044437]
- 82 Ugranli T, Gungormus E, Kavcar P, Demircioglu E, Odabasi M, Sofuoglu SC, Lammel G, Sofuoglu A. POPs in a major conurbation in Turkey: ambient air concentrations, seasonal variation, inhalation and dermal exposure, and associated carcinogenic risks. *Environmental science and pollution research international* 2016; **23**(22): 22500-22512 [PMID: 27552996 DOI: 10.1007/s11356-016-7350-5]
- 83 Howell GE, 3rd, Mulligan C, Meek E, Chambers JE. Effect of chronic p,p'-dichlorodiphenyldichloroethylene (DDE) exposure on high fat diet-induced alterations in glucose and lipid metabolism in male C57BL/6H mice. *Toxicology* 2015; **328**: 112-122 [PMID: 25541407 DOI: 10.1016/j.tox.2014.12.017]
- 84 La Merrill M, Karey E, Moshier E, Lindtner C, La Frano MR, Newman JW, Buettner C. Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring. *PloS one* 2014; **9**(7): e103337 [PMID: 25076055 PMCID: 4116186 DOI: 10.1371/journal.pone.0103337]
- 85 Lim S, Ahn SY, Song IC, Chung MH, Jang HC, Park KS, Lee KU, Pak YK, Lee HK. Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance. *PloS one* 2009; **4**(4): e5186 [PMID: 19365547 PMCID: 2664469 DOI: 10.1371/journal.pone.0005186]
- 86 Koch HM, Lorber M, Christensen KL, Palmke C, Koslitz S, Bruning T. Identifying sources of phthalate exposure with human biomonitoring: results of a 48h fasting study with urine collection and personal activity patterns. *International journal of hygiene and environmental health* 2013; **216**(6): 672-681 [PMID: 23333758 DOI: 10.1016/j.ijheh.2012.12.002]
- 87 Mylchreest E, Cattley RC, Foster PM. Male reproductive tract malformations in rats following gestational and lactational exposure to Di(n-butyl) phthalate: an antiandrogenic mechanism? *Toxicological sciences : an official journal of the Society of Toxicology* 1998; **43**(1): 47-60 [PMID: 9629619 DOI: 10.1006/toxs.1998.2436]
- 88 Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. *PloS one* 2013; **8**(1): e55387 [PMID: 23359474 PMCID: 3554682 DOI: 10.1371/journal.pone.0055387]
- 89 Hao C, Cheng X, Xia H, Ma X. The endocrine disruptor mono-(2-ethylhexyl) phthalate promotes adipocyte differentiation and induces obesity in mice. *Bioscience reports* 2012; **32**(6): 619-629 [PMID: 22953781 PMCID: 3497724 DOI: 10.1042/BSR20120042]
- 90 Liem AK, Furst P, Rappe C. Exposure of populations to dioxins and related compounds. *Food additives and contaminants* 2000; **17**(4): 241-259 [PMID: 10912239 DOI: 10.1080/026520300283324]
- 91 Wahlang B, Falkner KC, Gregory B, Ansert D, Young D, Conklin DJ, Bhatnagar A, McClain CJ, Cave M. Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL6/J mice. *The Journal of nutritional biochemistry* 2013; **24**(9): 1587-1595 [PMID: 23618531 PMCID: 3743953 DOI: 10.1016/j.jnutbio.2013.01.009]
- 92 Pope CA, 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological

- evidence of general pathophysiological pathways of disease. *Circulation* 2004; **109**(1): 71-77 [PMID: 14676145 DOI: 10.1161/01.CIR.0000108927.80044.7F]
- 93 Telang NT, Katdare M, Bradlow HL, Osborne MP. Estradiol metabolism: an endocrine biomarker for modulation of human mammary carcinogenesis. *Environmental health perspectives* 1997; **105 Suppl 3**: 559-564 [PMID: 9167995 PMCID: 1469897]
- 94 Irigaray P, Ogier V, Jacquenet S, Notet V, Sibille P, Mejean L, Bihain BE, Yen FT. Benzo[a]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. *The FEBS journal* 2006; **273**(7): 1362-1372 [PMID: 16689925 DOI: 10.1111/j.1742-4658.2006.05159.x]
- 95 Banzhaf S, Filipovic M, Lewis J, Sparrenbom CJ, Barthel R. A review of contamination of surface-, ground-, and drinking water in Sweden by perfluoroalkyl and polyfluoroalkyl substances (PFASs). *Ambio* 2016 [PMID: 27844420 DOI: 10.1007/s13280-016-0848-8]
- 96 Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Molecular and cellular endocrinology* 2009; **304**(1-2): 97-105 [PMID: 19433254 DOI: 10.1016/j.mce.2009.02.021]
- 97 Fan W, Yanase T, Nomura M, Okabe T, Goto K, Sato T, Kawano H, Kato S, Nawata H. Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipolytic activity but show normal insulin sensitivity with high adiponectin secretion. *Diabetes* 2005; **54**(4): 1000-1008 [PMID: 15793238]
- 98 Byerly MS, Al Salayta M, Swanson RD, Kwon K, Peterson JM, Wei Z, Aja S, Moran TH, Blackshaw S, Wong GW. Estrogen-related receptor beta deletion modulates whole-body energy balance via estrogen-related receptor gamma and attenuates neuropeptide Y gene expression. *The European journal of neuroscience* 2013; **37**(7): 1033-1047 [PMID: 23360481 PMCID: 3618562 DOI: 10.1111/ejn.12122]
- 99 Gao J, He J, Zhai Y, Wada T, Xie W. The constitutive androstane receptor is an anti-obesity nuclear receptor that improves insulin sensitivity. *The Journal of biological chemistry* 2009; **284**(38): 25984-25992 [PMID: 19617349 PMCID: 2757999 DOI: 10.1074/jbc.M109.016808]
- 100 Wang C, Xu CX, Krager SL, Bottum KM, Liao DF, Tischkau SA. Aryl hydrocarbon receptor deficiency enhances insulin sensitivity and reduces PPAR-alpha pathway activity in mice. *Environmental health perspectives* 2011; **119**(12): 1739-1744 [PMID: 21849270 PMCID: 3261983 DOI: 10.1289/ehp.1103593]
- 101 Xu CX, Wang C, Zhang ZM, Jaeger CD, Krager SL, Bottum KM, Liu J, Liao DF, Tischkau SA. Aryl hydrocarbon receptor deficiency protects mice from diet-induced adiposity and metabolic disorders through increased energy expenditure. *Int J Obes (Lond)* 2015; **39**(8): 1300-1309 [PMID: 25907315 PMCID: 4526411 DOI: 10.1038/ijo.2015.63]
- 102 Guerre-Millo M, Rouault C, Poulain P, Andre J, Poitout V, Peters JM, Gonzalez FJ, Fruchart JC, Reach G, Staels B. PPAR-alpha-null mice are protected from high-fat diet-induced insulin resistance. *Diabetes* 2001; **50**(12): 2809-2814 [PMID: 11723064]
- 103 He J, Gao J, Xu M, Ren S, Stefanovic-Racic M, O'Doherty RM, Xie W. PXR ablation alleviates diet-induced and genetic obesity and insulin resistance in mice. *Diabetes* 2013; **62**(6): 1876-1887 [PMID: 23349477 PMCID: 3661619 DOI: 10.2337/db12-1039]
- 104 Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. *The Journal of steroid biochemistry and molecular biology* 2006; **102**(1-5): 175-179 [PMID: 17088055 DOI: 10.1016/j.jsbmb.2006.09.017]
- 105 Lee HJ, Chattopadhyay S, Gong EY, Ahn RS, Lee K. Antiandrogenic effects of bisphenol A and nonylphenol on the function of androgen receptor. *Toxicological sciences : an official journal of the Society of Toxicology* 2003; **75**(1): 40-46 [PMID: 12805653 DOI: 10.1093/toxsci/kfg150]
- 106 Sargis RM, Johnson DN, Choudhury RA, Brady MJ. Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. *Obesity*

(Silver Spring, Md 2010; **18**(7): 1283-1288 [PMID: 19927138 PMCID: 3957336 DOI: 10.1038/oby.2009.419]

107 Rehan M, Ahmad E, Sheikh IA, Abuzenadah AM, Damanhour GA, Bajouh OS, AlBasri SF, Assiri MM, Beg MA. Androgen and Progesterone Receptors Are Targets for Bisphenol A (BPA), 4-Methyl-2,4-bis-(P-Hydroxyphenyl)Pent-1-Ene--A Potent Metabolite of BPA, and 4-Tert-Octylphenol: A Computational Insight. *PloS one* 2015; **10**(9): e0138438 [PMID: 26379041 PMCID: 4574962 DOI: 10.1371/journal.pone.0138438]

108 Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, Kanamoto N, Hataya Y, Shimatsu A, Kuzuya H, Nakao K. Thyroid hormone action is disrupted by bisphenol A as an antagonist. *The Journal of clinical endocrinology and metabolism* 2002; **87**(11): 5185-5190 [PMID: 12414890 DOI: 10.1210/jc.2002-020209]

109 Darnerud PO. Brominated flame retardants as possible endocrine disrupters. *International journal of andrology* 2008; **31**(2): 152-160 [PMID: 18315715 DOI: 10.1111/j.1365-2605.2008.00869.x]

110 Hurst CH, Waxman DJ. Activation of PPARalpha and PPARgamma by environmental phthalate monoesters. *Toxicological sciences : an official journal of the Society of Toxicology* 2003; **74**(2): 297-308 [PMID: 12805656 DOI: 10.1093/toxsci/kfg145]

111 Cheng X, Klaassen CD. Perfluorocarboxylic acids induce cytochrome P450 enzymes in mouse liver through activation of PPAR-alpha and CAR transcription factors. *Toxicological sciences : an official journal of the Society of Toxicology* 2008; **106**(1): 29-36 [PMID: 18648086 PMCID: 2563145 DOI: 10.1093/toxsci/kfn147]

112 Takeuchi S, Matsuda T, Kobayashi S, Takahashi T, Kojima H. In vitro screening of 200 pesticides for agonistic activity via mouse peroxisome proliferator-activated receptor (PPAR)alpha and PPARgamma and quantitative analysis of in vivo induction pathway. *Toxicology and applied pharmacology* 2006; **217**(3): 235-244 [PMID: 17084873 DOI: 10.1016/j.taap.2006.08.011]

113 Feige JN, Gelman L, Rossi D, Zoete V, Metivier R, Tudor C, Anghel SI, Grosdidier A, Lathion C, Engelborghs Y, Michielin O, Wahli W, Desvergne B. The endocrine disruptor monoethyl-hexyl-phthalate is a selective peroxisome proliferator-activated receptor gamma modulator that promotes adipogenesis. *The Journal of biological chemistry* 2007; **282**(26): 19152-19166 [PMID: 17468099 DOI: 10.1074/jbc.M702724200]

114 Li L, Wang Q, Zhang Y, Niu Y, Yao X, Liu H. The molecular mechanism of bisphenol A (BPA) as an endocrine disruptor by interacting with nuclear receptors: insights from molecular dynamics (MD) simulations. *PloS one* 2015; **10**(3): e0120330 [PMID: 25799048 PMCID: 4370859 DOI: 10.1371/journal.pone.0120330]

115 Hsu CW, Zhao J, Huang R, Hsieh JH, Hamm J, Chang X, Houck K, Xia M. Quantitative high-throughput profiling of environmental chemicals and drugs that modulate farnesoid X receptor. *Scientific reports* 2014; **4**: 6437 [PMID: 25257666 PMCID: 4894417 DOI: 10.1038/srep06437]

116 Eveillard A, Mselli-Lakhal L, Mogha A, Lasserre F, Polizzi A, Pascussi JM, Guillou H, Martin PG, Pineau T. Di-(2-ethylhexyl)-phthalate (DEHP) activates the constitutive androstane receptor (CAR): a novel signalling pathway sensitive to phthalates. *Biochemical pharmacology* 2009; **77**(11): 1735-1746 [PMID: 19428328 DOI: 10.1016/j.bcp.2009.02.023]

117 DeKeyser JG, Laurenzana EM, Peterson EC, Chen T, Omiecinski CJ. Selective phthalate activation of naturally occurring human constitutive androstane receptor splice variants and the pregnane X receptor. *Toxicological sciences : an official journal of the Society of Toxicology* 2011; **120**(2): 381-391 [PMID: 21227907 PMCID: 3107492 DOI: 10.1093/toxsci/kfq394]

118 Mozzicafreddo M, Cuccioloni M, Bonfili L, Cecarini V, Palermo FA, Cocci P, Mosconi G, Capone A, Ricci I, Eleuteri AM, Angeletti M. Environmental pollutants directly affect the liver X receptor alpha activity: Kinetic and thermodynamic characterization of binding. *The Journal of steroid biochemistry and molecular biology* 2015; **152**: 1-7 [PMID: 25869557 DOI: 10.1016/j.jsbmb.2015.04.011]

119 Takeshita A, Koibuchi N, Oka J, Taguchi M, Shishiba Y, Ozawa Y. Bisphenol-A, an environmental estrogen, activates the human orphan nuclear receptor, steroid and xenobiotic

receptor-mediated transcription. *European journal of endocrinology / European Federation of Endocrine Societies* 2001; **145**(4): 513-517 [PMID: 11581012]

120 Milnes MR, Garcia A, Grossman E, Grun F, Shiotsugu J, Tabb MM, Kawashima Y, Katsu Y, Watanabe H, Iguchi T, Blumberg B. Activation of steroid and xenobiotic receptor (SXR, NR1I2) and its orthologs in laboratory, toxicologic, and genome model species. *Environmental health perspectives* 2008; **116**(7): 880-885 [PMID: 18629309 PMCID: 2453155 DOI: 10.1289/ehp.10853]

121 Denison MS, Heath-Pagliuso S. The Ah receptor: a regulator of the biochemical and toxicological actions of structurally diverse chemicals. *Bulletin of environmental contamination and toxicology* 1998; **61**(5): 557-568 [PMID: 9841714]

122 Sato S, Shirakawa H, Tomita S, Ohsaki Y, Haketa K, Tooi O, Santo N, Tohkin M, Furukawa Y, Gonzalez FJ, Komai M. Low-dose dioxins alter gene expression related to cholesterol biosynthesis, lipogenesis, and glucose metabolism through the aryl hydrocarbon receptor-mediated pathway in mouse liver. *Toxicology and applied pharmacology* 2008; **229**(1): 10-19 [PMID: 18295293 DOI: 10.1016/j.taap.2007.12.029]