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Early exposure to endocrine disruptors and the metabolic syndrome: a review of animal studies.

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ABSTRACT

Title. Early exposure to endocrine disruptors and the metabolic syndrome. A review of animal studies.

Background. The prevalence of non communicable diseases, such as cardiovascular (hypertension) and metabolic (obesity, type 2 diabetes, dyslipidemia) diseases, often clustered under the definition of metabolic syndrome, is remarkably increasing worldwide and is among causes of premature mortality. Numerous studies have shown that part of their origins can be found during development, schematically from peri-conceptional period to the end of the second year of the child's life. This period represents a vulnerability window during which alterations of fetus', newborn's or young child's environment can imprint durable epigenetics marks, designing life trajectories which may be at risk for chronic diseases during their course. It has been hypothesized that an early exposure to substances altering hormonal homeostasis, namely endocrine disruptors, play a role in the metabolic syndrome manifesting later in life.

Objectives.
- To identify in scientific literature studies on cardio-metabolic alterations induced by early exposure to endocrine disruptors.
- To characterize at best scientific evidence from animal studies, linking early exposure to endocrine disruptors with the metabolic syndrome at adulthood, and its limitations.
- To determine the endocrine disruptors shown to be responsible for such alterations, exposition doses and the most sensitive period to their effects.
- To describe the main pathogenic mechanisms for every biological system concerned, at cellular and molecular levels, with particular attention to epigenetic alterations (CpG islands promoters methylation of some genes, histones modifications, non coding RNA).
- To identify possible preventative interventions aiming to decrease endocrine disruptors influence during the sensitive period and identify early metabolic syndrome biomarkers.

Method. This is a narrative and critical review of scientific literature. Bibliographic research of scientific literature was principally realized in PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Embase (https://www.elsevier.com/solutions/embase-biomedical-research) databases, completed by Google Schoolar (https://scholar.google.ch/). Two librarians from the medicine university library helped us with search strategies. Animal model studies were included.

Results. Animals exposed to endocrine disruptors early in their life displayed phenotypes associated with metabolic syndrome features at adulthood. An exposure occurring between the peri-conceptional period and the weaning, mainly to bisphenol A, but also to other plasticizers and industry related compounds such as phthalates, dioxins and flame retardants, has been associated with: body weight increase with adipose tissue accumulation, insulin resistance and glucose intolerance, dyslipidemia and hypertension (these last two conditions have been less but still observed). Concerning underlying mechanisms proposed, lipid metabolism-related pathways such as Peroxisome Proliferator-Activated Receptor-alpha and -gamma, Fatty acid synthase and Carnitine palmitoyltransferase among others have been associated with obesity. In T2DM ones, Glucokinase and Glucose Transporter gene appeared possible involved pathways, while implication of Lipoprotein lipase and RAAS-related genes have been observed in dyslipidemia and HT studies respectively. Also, epigenetic mechanisms such as CpG hypermethylation of key genes promoters have been reported as potential "programming" mechanisms involved in obesity and T2DM.

Key words. Metabolic syndrome, developmental programming, endocrine disruptors, epigenetics, non communicable chronic diseases

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BACKGROUND

Metabolic Syndrome

The metabolic syndrome is defined as a cluster of cardio-metabolic conditions including abdominal obesity (assessed by waist circumference, ≥ 94 cm and ≥ 80 cm for Caucasian men and women respectively), hypertriglyceridemia (≥ 150 mg/dL or an established drug therapy for elevated triglycerides), decreased serum HDL-cholesterol (< 40 mg/dL for men and < 50 mg/dL for women or drug therapy for low HDL-cholesterol), elevated blood pressure (systolic ≥ 130 mmHg and/or diastolic ≥ 80 mmHg or antihypertensive drug therapy) and fasting hyperglycemia (≥ 100 mg/dL or drug therapy for elevated glucose): if ≥ 3 of these criteria are present the diagnosis of metabolic syndrome can be made (1). These non communicable chronic conditions manifesting together significantly raise the risk of developing cardiovascular diseases at adulthood (2). Worldwide epidemiological analysis on metabolic syndrome showed a constantly increasing prevalence situated around 25% in the past decade. Variability depends on region assessed and population characteristics such as sex, ethnicity and age, with over 60 years-old man from Pacific or Middle East countries representing the most typical individual displaying metabolic syndrome features (https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome). Comprehension of chronic diseases pathogeny manifesting late in life should help to reduce their morbidity and mortality.

Developmental Origins of Health and Diseases (DOHaD)

Genome and life style at adulthood contribute to the development of metabolic syndrome, but according to scientific opinion they are not sufficient to explain the increasing disease burden observed in the last decades (3). Interest of researchers has therefore been focusing on early developmental environment. Epidemiological studies correlating intrauterine and early life conditions to late cardio-metabolic outcomes exist since 1980s, when Professor David Barker and colleagues published their first works on the subject. The “Developmental programming of health and diseases” (DOHaD) hypothesis has then taken shape acquiring relevance among possible explanations of late non communicable chronic diseases pathogeny. According to DOHaD hypothesis, the period extending from conception throughout pregnancy to early infancy (the first 1000 days of life) show particular sensitiveness to environmental conditions, and potential insults occurring during this timespan may program tissue/organ structure and function in a process known as developmental plasticity, which is adapted to short term prevailing environment but possibly not to the further life course. This process could have remarkable consequences on health later in life, regardless of individual behavior and environment characterizing following lifetime (4). Epigenetic modifications occurring in early development such as DNA methylation/demethylation, histones modification and non-coding RNAs have been recognized as possible DOHaD mechanisms at the basis of developmental programming (5). Concerning potential insults that may lead to metabolic syndrome, endocrine disruptors have been proposed.

Endocrine disruptors

Existing literature relates endocrine disruptors to metabolic syndrome outcomes when exposition occurs at adulthood. Endocrine disruptors are defined by the European Union as "[…] exogenous substances or mixture that alter the function of the endocrine system, causing adverse effects on the health of an organism, or its progeny, or (sub)population" (*European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife, Weybridge, UK, 2–4/12/1996*). Endocrine disrupting chemicals may be classified based on their source, on their own chemical composition, on their molecular action as well as on their metabolic or reproductive effects on human beings and animals. In addition to an exposure at adulthood, a link between early exposure to these substances and the metabolic syndrome has been reported mainly in experimental, but also in epidemiological studies (6). Following described molecules are those we found in studies selected for this review.

Bisphenol A (BPA) is a phenolic monomer widely used in chemical industry, especially in plastics production, conferring robustness to food and beverages containers as well as to dental composites among others (7). To the same family belongs nonylphenol (NP), an alkylphenol acting as a surfactant in detergents and solubilizers (8). Other plasticizers compounds are phthalates, such as diethylhexyl phthalate (DEHP), its metabolite mono-(2-ethylhexyl) phthalate (MEHP) and dibutyl phthalate (DBP), usually exploited as softeners giving flexibility and elasticity to plastic polymers, or polyfluoroalkyl compounds, such as perfluorooctanoic acid (PFOA), a repellent for both water and oil used for example in food packing papers (9), and perfluorooctane sulfonate (PFOS), a degradation product of ployfluorolakyl chemicals with commercial use (10). 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polychlorinated biphenyl 153 (PCB153) are dioxins found in environment notably as a consequence of chlorine-containing substances incineration (6). Among fire retardants we found Firemaster® 550, composed by triphenyl phosphate (TPhP) with a mixture of isopropylated triphenylphosphate isomers (ITPs), 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) and bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate (TBPH).

Other substances related with endocrine disruption are ethanol, the tobacco-derived compounds nicotine and benzo[a]pyrene (BaP), the corticosteroid dexamethasone (Dex), the soy-derived phytoestrogen genistein, the banned-insecticide Dichlorodiphenyltrichloroethane (DDT) and the pesticide chlorpyrifos.

METHOD

This work consists of a narrative review of scientific literature. Bibliographic research of scientific literature was principally realized in following databases: PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Embase (https://www.elsevier.com/solutions/embase-biomedical-research). It was completed by Google Schoolar (https://scholar.google.ch/) and manual researches. Publication dates of considered papers was comprised between January the 1st of 1980 and July the 31st, 2017. Animal model studies were included, both in longitudinal and transverse researches. Publication languages considered were english and french. Two librarians from the medicine university library helped us to define search strategies. Researches were realized using database thesaurus terms in association with free terms. Boolean operator "OR" was used for 3 large research fields, namely "endocrine disruption", "developmental programming" and "cardio-metabolic regulations", and results were crossed using operator "AND" in order to select relevant papers, first by title and abstract screening, then by full text analysis (see Prisma flow chart in the ANNEXES section). Research strategies for each database are exposed below. Papers were included if they reported studies conducted on animal models showing potential developmental programming of cardio-metabolic regulations figuring in the metabolic syndrome definition and caused by endocrine disruptors compounds.

Research strategies

Embase

('endocrine disruptor'/exp OR 'persistent organic pollutant'/exp OR 'environmental stress'/exp OR 'plasticizer'/exp OR 'phenol derivative'/de OR '4,4 isopropylidenediphenol'/exp OR 'phytoestrogen'/exp OR 'flame retardant'/exp OR 'pesticide'/de OR 'benzhydryl derivative'/exp OR ('endocrine disrupt*' OR 'hormon*disruptor*' OR 'environmental pollutant*' OR 'Persistent organic pollutant*' OR 'phthalate plasticizer*' OR 'Phenol*' OR 'Bisphenol A' OR 'synthetic hormone*' OR 'phytoestrogen*' OR 'pesticide*' OR 'flame retardant*' OR 'benzhydryl compound*'):ab,ti) **AND** ('prenatal exposure'/exp OR 'prenatal development'/exp OR 'pregnancy'/de OR 'maternal nutrition'/de OR 'prenatal drug exposure'/exp OR 'weaning'/exp OR 'gene expression regulation'/exp OR 'epigenetics'/exp OR ('developmental programming' OR 'Fetal programming' OR 'Gestational programming' OR 'early exposure' OR 'Pregnancy' OR 'Early development' OR 'maternal exposure' OR 'Weaning' OR 'Epigenetics' OR 'epigenomics' OR 'developmental gene expression regulation'):ab,ti) **AND** ('non communicable disease'/exp OR 'late onset disorder'/exp OR 'metabolic syndrome X'/exp OR 'dyslipidemia'/exp OR 'abnormal blood pressure'/exp OR 'disorders od carbohydrate metabolism'/de OR ('non communicable disease*' OR 'adult onset disease' OR 'Metabolic disease*' OR 'metabolic syndrome' OR 'obesity' OR 'abdominal obesity' OR 'dyslipidemia' OR 'Hypertriglyceridemia' OR 'Hypolipoproteinemia*' OR 'hypertension' OR 'glucose intolerance' OR 'insuline resistance' OR 'type 2 diabetes'):ab,ti)

Equation issued from Embase thesaurus (Emtree) relevant terms combined with a free terms selection.

PubMed

("Endocrine disruptors"[Mesh] OR "Endocrine disruptors"[Pharmacological Action] OR "Plasticizers"[Mesh] OR “Environmental pollutants”[Mesh] OR “Environmental pollutants”[Pharmacological Action] OR "Plasticizers"[Pharmacological Action] OR "Phenols"[Mesh:noexp] OR "Bisphenol A"[Supplementary Concept] OR “benzhydryl compounds”[Mesh] OR “phytoestrogens”[Mesh] OR “phytoestrogens”[Pharmacological Action] OR “flame retardants”[Mesh] OR “flame retardants”[Pharmacological Action] OR “pesticides”[Mesh:noexp] OR “pesticides”[Pharmacological Action] OR Endocrine disrupt*[tiab] OR Hormone* disrupt*[tiab] OR Persistent organic pollutant*[tiab] OR Environmental pollutants[tiab] OR plastic*[tiab] OR Phthalate*[tiab] OR Phenol*[tiab] OR Bisphenol A[tiab] OR Pesticide*[tiab]) **AND** ("Prenatal exposure delayed effects"[Mesh] OR “Fetus/drug effects”[Mesh:NoExp] OR “Pregnancy”[Mesh:NoExp] OR “Maternal exposure”[Mesh] OR “weaning”[Mesh] OR "Epigenesis, genetic"[Mesh] OR "Epigenomics"[Mesh] OR "Gene expression regulation, developmental"[Mesh] OR Developmental programming[tiab] OR Fetal programming[tiab] OR Gestational programming[tiab] OR Early exposure[tiab] OR Pregnancy[tiab] OR Early development[tiab] OR Weaning[tiab] OR Epigenetics[tiab] OR Epigenomics[tiab] OR Developmental gene expression regulation[tiab]) **AND** ("Late onset disorders"[Mesh] OR "Metabolic syndrome X"[Mesh] OR “Obesity"[Mesh] OR "Obesity, abdominal"[Mesh] OR "Abdominal obesity metabolic syndrome"[Supplementary Concept] OR "Glucose intolerance"[Mesh] OR "Insulin resistance"[Mesh] OR "Diabetes mellitus, type 2"[Mesh] OR Non communicable disease*[tiab] OR Adult onset disease*[tiab] OR Late onset disease*[tiab] OR Metabolic disease*[tiab] OR Metabolic syndrome[tiab] OR Obesity[tiab] OR Abdominal obesity[tiab] OR Dyslipidemia*[tiab] OR Hypertriglyceridemia[tiab] OR Hypolipoproteinemia*[tiab] OR Hypertension[tiab] OR Glucose intolerance[tiab] OR Insulin resistance[tiab] OR Type 2 diabetes[tiab])

Equation issued from PubMed thesaurus (Mesh) relevant terms combined with a free terms selection.

RESULTS

Obesity

(Details about different studies can be found in the ANNEXES section, “OBESITY” table)

BPA is the most studied endocrine disrupting compound in the “cardio-metabolic programming” research field. Recent literature proposes a rising number of papers assessing obesity related outcomes following an early exposition to this molecule. Rodents and sheep animal models are treated during their gestational and/or lactational periods with doses mostly ranging between the order of μg/kg of body weight per day and mg/kg of body weight per day, considered in this review as “low” and “high” dose respectively (exceptionally, smaller doses are also observed). Concerning rodent experiments, exposition windows have a timespan extending from 2 weeks before mating in certain studies (11-15) to the postnatal day 30 in some of them (13, 16), even if in most of papers the exposition window reported is reduced to smaller time-lapse, and for many of them the upper limit is fixed on postnatal day 21 (usually corresponding to weaning) (11, 12, 14, 15, 17-25). Different exposition windows are comprehensibly found in sheep research: in the study selected for this review treatment period has been set between gestational days 30 and 90 (26). An exposure of pregnant or nursing mothers to BPA has led in young or adult offsprings to the following obesity related phenotypes: body weight increase (14, 16, 17, 19, 20, 22-25, 27), adipose tissue accumulation (14, 16, 17, 21, 25, 27, 28) characterized by adipocytes hypertrophy (26, 28) and hyperplasia (28), hepatic steatosis (22, 24, 27), serum leptin increase (16, 19, 28) and adiponectin decrease (23, 25, 28). Body weight gain has been described either as a consequence of adipose tissue accumulation (14, 16, 17, 25, 27) or as a result of subcutaneous adipocytes hypertrophy (23). When fat pads weight increase has not been reported, hepatic steatosis has been however observed (22, 24). Sites of adipose tissue accumulation such as perigonadal (17, 21, 25, 27, 28), intrascapular (21), peritoneal (25), retroperitoneal (21), subcutaneous (21) and renal (28) have been specified in some papers, but adipocytes morphology description has been proposed only by a few authors: cellular hypertrophy has been observed in rodents (23, 28) and sheep (26), while hyperplasia has been reported one time in mice perigonadal fat pad (28). Importantly to point up is that some of the above mentioned studies refer to phenotypes resulting in individuals not yet having reached adulthood (16, 17, 25) or in animals fed with an high-fat diet following the endocrine disruptor exposition (16).

Metabolic pathways potentially involved in “obesity programming” following an early BPA exposure concern: adipogenesis, lipogenesis and lipids turnover in white adipose tissue (17, 25, 27) and in liver (17, 20, 24, 25, 27, 29), reactive oxygen species (ROS) generation in liver (22) as well as in serum (23), hepatic apoptosis and mitochondrial activity (22) or adipose tissue inflammation (26), the melanocortin-related pathways in the central nervous system (21) and hepatic DNA-methylation (20). Also, POMC fibers density decrease in the paraventricular nucleus and estrogen receptor-alpha expressing cells in the posterior arcuate nucleus of hypothalamus (21), as well as hepatocytes organelles dysfunction (22) and specific proteins abundance such as DNA methyl-transferase 3B (hepatocytes DNA methylation) and adipose TG lipase (20, 25) have been proposed among cellular mechanisms. At the molecular level, mRNA expression of some lipid metabolism key genes such as adiponectin gene (23, 25), *Atgl* (25), *Ppar-alpha* (24, 27) and *Ppar-gamma* (17, 27, 30), *Pomc* (21), *Srebp* (17, 24, 27), *Cpt* (24, 27), *Fas* (17, 24) and several others was impaired, leading to the obesity related phenotypes previously described.

However, in contrast with the hypothesis according to which BPA could have an “obesogen” effect in rodents (mice and rats) offsprings following an early life exposure, some studies gave no significant results (13, 18) or even partially opposite outcomes (11, 12, 15).

Equally interesting to mention are two studies where transgenerational effects of early BPA exposition have been assessed. Manikkam *et al.* reported obesity related outcomes such as body weight gain following abdominal adipose tissue accumulation in F3 generation indirectly caused by a plastic mixture containing BPA (together with DEHP and DBP) to which previously exposed F1 generation individuals did not show any sign of obesity phenotype; F3 sperm analysis revealed significantly alterations in DNA methylation regions of obesity associated genes (31). Body fat percentage increase was instead described in F2 generation mice whose parents were formerly exposed to BPA from 2 weeks before gestation to weaning (14).

Other endocrine disrupting chemicals than BPA are also linked to cardio-metabolic programming, and obesity related phenotypes have been reported in rodent laboratory models. Low and/or high doses administered during gestation and/or lactation induced body weight increase following TPhP (32), MEHP (33), Chlorpyrifos (34), DEHP (35), NP (36) and BaP (37) exposition. Adipose tissue accumulation has been reported as a body fat percentage increase (38, 39) or observed in visceral (37, 40), mesenteric (32), gonadal (32, 33, 41), inguinal (32) and perirenal (33) fat pads. Hepatic steatosis has been described consequently to a PFOS (41) and a BaP (37) exposition. Concerning histology description, adipocytes hypertrophy has been found in DEHP (35, 39) and PFOA (42) exposed mice. Finally, obesity hormones have been analyzed in some studies, with serum leptin increase reported in adult rats following low dose exposition to TPhP from gestational day 8 to weaning (32) and subjected to high dose exposition to PFOS during gestation and lactation; these last individuals also showed serum adiponectin decrease (41). However, some studies in which rodents were early exposed to potentially endocrine disrupting compounds did not show any obesity related late effects: Genistein induced normal or decreased body weight in mice (43), while TCDD (44) and PFOA (42) exposition did not give any metabolic relevant phenotype.

A well known early exposure toxic substance is ethanol, even if its role as a metabolic programming agent has not been thoroughly investigated. Dobson *et al.* reported that pregnant guinea pigs exposition induced increase in body weight, visceral and subcutaneous adipose tissue in adult female offsprings (40).

Regarding metabolic pathways with associated cellular and molecular underlying mechanisms, main outcomes concern adipose tissue and hepatic key genes altered expression. Hepatic pathways include genes such as *Srebp-1c* (Sterol regulatory element-binding transcription factor 1) in PFOS exposed rats (41), *Ppar-gamma* (Peroxisome proliferator-activated receptor-gamma) and *Fasn* (Fatty acids synthase) in BaP exposed mice (37), while adipose tissue pathways also comprehend *Pparg-amma* and *Fasn*, and *Fabp4* (Fatty acids binding protein 4) in DEHP exposed rats (39) and adiponectin gene in nicotine exposed rats (45) among others.

Type 2 Diabetes Mellitus (T2DM)

(Details about different studies can be found in the ANNEXES section, “T2DM” table)

An exposure to BPA in the period between conception and weaning has been associated in rodents to T2DM related phenotypes such as insulin sensitivity decrease (46) and insulin resistance (14, 20, 23, 24, 28, 47), glucose intolerance (14, 19, 21, 27, 28, 46, 47), fasting hyperglycemia (23), serum adiponectin decrease (12, 15, 23, 28), serum free fatty acids (24, 27) and leptin (19, 28) increase. In sheep the only relevant outcome reported is insulin resistance in young females offsprings (26).
Transgenerational effects have also been described in some papers. Authors observed both insulin resistance and glucose intolerance in 23 weeks old (48) and in 21 weeks old (49) F2 generation rats, while glucose intolerance only was detected in F2 generation mice aged around 4 months (14).
Concerning other endocrine disruptors and their potential role in T2DM programming, relations have been highlighted between insulin resistance together with glucose intolerance and ethanol in gestational exposed guinea pigs (40), TPhP in rats (32), DDT in mice only if fed with an high-fat diet after the endocrine disruptor exposure (50), PFOS in young adult rats (41) and DEHP in pubertal stage rats (38). Peripheral insulin resistance alone has been reported in nicotine exposed rats (45), while isolated glucose intolerance has been described by Patisaul *et al.*, who assessed rats exposure to a flame retardant containing mixture of potential endocrine disruptors named Firemaster 550 (51). Other T2DM related outcomes found are fasting hyperinsulinemia in DEHP exposed rats (52), fasting hyperglycemia following a PCB53 exposure (44) and serum adiponectin decrease induced by PFOS (41). PCB53 as well as TPhP exposure have also been associated with an increase in serum FFA (44)(32).
Some authors tried to link these metabolic features with possible underlying cellular and molecular mechanisms, which allowed them to describe interesting outcomes, mostly in pancreas and liver tissues. Beta-cells impaired turnover (47) and decreased proliferation (46), as well as signs of cellular dysfunction such as swollen organelles and reduction in insulin-filled granules associated to key transcription factors and genes such as *Glut2* and *Gck* mRNA expression diminution have been observed (19). Altered intracellular signaling mediated by Ca2+ has also been reported (27, 46). About mechanisms underlying transgenerational effects of BPA early exposure, Mao *et al.* described smaller beta-cells islets with swollen mitochondria in F2 generation tissues, associated to hypermethylation of CpG islands in the *Igf2* promoter in pancreatic beta cells of F2 generation and F1 generation sperm cells (49). Concerning liver, glucose and lipid metabolism related genes altered expression (27, 29), and specifically down-regulation of insulin-stimulated phosphorylated proteins have been reported (24). GCK pathway has also been investigated, showing decrease in gene expression and subsequent protein activity with CpG in promoter region hypermethylation (20), also in F2 generation (48). Down-regulated expression of adiponectin in subcutaneous adipose tissue (23) and *Igf2* mRNA over-expression, as well as specific CpG site methylation increase in F2 generation embryos at GD10 (14) have also been observed.
Other chemicals have been assessed for their possible cellular or molecular early disruption. Ethanol and nicotine induced pancreatic beta-cells number decrease (40, 45), while ethanol only influenced insulin signaling in central nervous system (53). Impaired expression of glucose metabolism-related genes has also been linked nicotine (45) and DEHP, also causing pancreatic beta-cells swollen mitochondria and insulin secretion decrease (52). Rajesh *et al.* studied DEHP effects and found interesting involvement of skeletal muscle related mechanisms, such as decreased insulin binding with consequent reduction of glucose uptake and oxidation. Many glucose processing related genes in skeletal muscle such as *Insr* and *Glut4* showed impaired expression with subsequent associated proteins dysfunctional activity (38).

Hypertension (HT)

(Details about different studies can be found in the ANNEXES section, “HT” table)

BPA seems to play a role in hypertension pathogeny, even if only one paper has been included in this review. Mean and systolic blood pressure increase has been measured in 21 months old female sheep exposed to BPA for 60 days during gestation only manifest in individuals fed with an high fat diet after weaning (54). Two other endocrine disruptors were associated with hypertensive-related issues: DEHP exposition from 1 month before mating until weaning rose blood pressure in young mice (35), whereas NP has been related to elevated plasma aldosterone in adult rats (36). Sheep also showed sensitiveness to early dexamethasone exposure, that induced remarkable elevation in mean blood pressure after Angiotensin II stimulation (55). The same corticosteroid compound has been associated with similar outcomes in rats, where an increase in basal plasma aldosterone levels has also been described (56). As already mentioned starting this section, physiological basis of hypertension is quite complex. Nevertheless, some possible cellular and molecular mechanisms have been proposed. Increased expression and activity of enzymes involved in aldosterone synthesis pathway (36), as well as AT1 receptors expression augmented in brainstem (55) and in periphery (35) figure among RAAS-related mechanisms. Other possible underlying causes of “programmed” hypertension have been reported by MohanKumar *et al.* (54) and by Koneva *et al.* (57), both describing impaired ventricular expression of natriuretic peptides.

Dyslipidemia

(Details about different studies can be found in the ANNEXES section, “DYSLIPIDEMIA” table)

BPA has been investigated as potential early insult involved in the “programming” of metabolic syndrome-related dyslipidemia. Following gestational and lactational exposure, offsprings rats showed significant TG and total cholesterol elevation associated to a decrease in serum HDL and adiponectin levels; authors described important down-regulation of a lipid turnover related-gene in hepatic tissue, consistent with hyperlipidemia and cholesterol accumulation in hepatocytes (25). Increase in total cholesterol has been reported in a study where two doses of BPA were used, with an elevation of TG only in males exposed to the lower dose (16). Diminished serum free fatty acids, TG, leptin and adiponectin in female mice have been reported following exposure to 7 different doses of BPA from 2 weeks before mating until the end of lactation (12). High TG and low HDL levels have been observed this time in male adult offsprings (19). Concerning other endocrine disrupting chemicals, DEHP early exposure impaired hepatic cholesterol turnover with down-regulation of some genes involved in key lipid metabolic pathways governed by proteins (such as LDLR, SR-BI, CYP7A1, ABCG5 and ABCG8) (35). Mice exposed to DDT showed dyslipidemia features only in female individuals fed with high-fat diet. Hepatic molecular analysis of these animals resulted in altered mRNA expression of lipogenic related genes, such as *lpl*, *pnpla* and *cpt2* (50). Finally, MEHP early exposure induced an increase in serum total cholesterol and in TAG in young male mice (33).

DISCUSSION

We reviewed here animal studies assessing the potential role of early exposure to the endocrine disruptors and the development of metabolic syndrome later in life. We found 35 papers describing cardio-metabolic phenotypes compatible with obesity, T2DM, dyslipidemia and hypertension, with obesity and T2DM being largely more represented than dyslipidemia and hypertension. In 19 of them authors reported results related with two of these four metabolic syndrome conditions, but only in 2 papers obesity and dyslipidemia appeared together with T2DM in one (19) and with hypertension the other (35). These observations arouse two early considerations. First, since this a narrative review, the lack of statistical analysis prevents a quantitative estimation of endocrine disruptors potential effect on metabolic syndrome programming. The literature we found on the argument suggests however that these compounds play an important role in the pathogeny of late cardio-metabolic chronic diseases. Second, if we take in account the exact definition of metabolic syndrome as presented in our introduction, only two papers meet the criteria (19, 35). Nevertheless, we decided to include studies treating even just one of these criteria, suggesting that a background for metabolic syndrome development could still be present.

BPA seems to be the most effective endocrine disruptor in cardio-metabolic programming, appearing in more than half of the papers describing obesity and T2DM outcomes. It is also associated with hypertension in sheep (54) and with rodents dyslipidemia (16, 19, 25). Concerning obesity, an early exposure to BPA has been mostly related to body weight increase following adipose tissue accumulation, but only few papers reported other outcomes such as adipocytes hypertrophy or hyperplasia, hepatic steatosis, adiponectin decrease and leptin increase. Similarly, insulin resistance and glucose intolerance appeared in most of T2DM studies where BPA was used, while adiponectin decrease, FFA and serum leptin increase have been less described. As much for obesity as for T2DM this outcomes incompleteness may be put on the account of the kind of analysis the authors made on animal models, on animal models themselves, as well as on variables chosen for their intervention such as dose and window of exposure. Doses range from the order of the picogram per kilogram of body weight to milligram per kilogram of body weight, and differ among studies. Authors often refer their choice to previous studies where similar doses induced relevant outcomes or to reference thresholds causing directly observables effects (11, 46). Variability of doses does not allow to propose programming-active reference values, even if we can however suggest that relatively low doses (not causing direct toxic effects) administered in early development are sufficient to provoke significant cardio-metabolic related phenotypes later in life. This last consideration turns the discussion on the sensitive exposition window. Only few papers provided precise reasons about their exposition temporality choice. Angle *et al*. exposed pregnant mice between gestational days 8 and 19 justifying this period with correspondence to preadipocytes differentiation: they could observe adipocytes hypertrophy and hyperplasia associated to other obesity and T2DM outcomes in young adult offsprings (28). Liu *et al.* proposed several exposure periods and reported glucose intolerance and insulin resistance in adult offsprings mice born from mothers exposed to BPA between day 6 of gestation and delivery, indicating this period as potentially more sensitive to disrupting action of the molecule compared to early gestation (GD0 to GD6) or lactation (PND0 to PND21) (47). Larger windows used in other studies do not consent to suggest more precisely disruption-susceptible periods, even if peri-conceptional to weaning window clearly relates with significant metabolic syndrome programming outcomes. Considerations about doses and exposition windows can be applied also for the other endocrine disrupting chemicals.

Among review objectives figures description of potential biological pathways involved in metabolic syndrome pathogeny by developmental programming, with underlying cellular and molecular mechanisms. Our research highlights variability and incompleteness among results, meaning that the same endocrine disruptor is associated with different cellular and molecular outcomes, and that epigenetic mechanisms are explicitly reported only in few papers.

In BPA studies some pathways appeared more than once. Among those related to obesity, *Srebp* mRNA expression was increased in rats white adipose tissue (17) and liver (17, 24) following a gestational and lactational low dose exposure. SREBP is a transcription factor known to control lipid biosynthesis as well as lipogenic enzymes expression (58), what is in accordance with liver steatosis and white adipose tissue fad pads increase observed. Similarly, *Ppar-gamma* mRNA expression increased in liver (20, 27) and white adipose tissue (17) meet the obesity related outcomes reported in these papers, knowing that PPAR-gamma plays a role in lipid metabolism involved genes regulation (59). Another Peroxisome proliferator-activated receptor, *Ppar-alpha* showed mRNA expression decrease in white adipose tissue (27). This nuclear receptor senses lipids from diet and promotes fatty acid beta-oxidation exerting an hypolipidemic action (60). Its reduction may thus result in adipose tissue stores increase. *Cpt, a* mitochondrial enzyme involved in FA metabolism (24, 27), *Fas* (17, 24) and many other genes involved in lipid metabolism pathways showed mRNA expression impairment following early BPA treatment, suggesting possible programming targets of this plastic derived molecule, even if epigenetic mechanism are not specified. Concerning T2DM, hepatic GCK figures among metabolic pathways potentially influenced by early BPA exposition. Decreased activity of this protein in the liver has already been associated with T2DM (61). We found a paper describing *Gck* mRNA expression down-regulation in hepatocytes of rats showing insulin resistance. CpG islands hypermethylation in the promoter region of *Gck* gene has been reported as well, and has previously been related to decreased gene expression (62). In this case *Dnmt* mRNA expression was increased, producing a CpG methylation enhancement (20). Another study described decreased expression of *Igf2* mRNA in pancreatic beta-cells in association with gene promoter CpG hypetmethylation. Dysregulation of *Igf2* is known to play a role in impaired beta-cells development and in T2DM (63). Indeed, histologic assessment showed smaller islets and signs of cellular dysfunction. Interesting, this cellular and molecular outcomes appeared in F2 generation, which was never directly exposed to BPA. Analysis of F1 generation sperm displayed *Igf2* CpG hypermethylation, suggesting possible transgenerational effects of endocrine disruptor early exposure mediated by epigenetic mechanisms (49). Other metabolic pathways appearing in T2DM studies concern subcutaneous adiponectin (23), hepatic *Cd36* (27), *Glut4* in skeletal muscle in relation to DEHP exposition (38) and several others.

Endocrine disruptors possibly exerting programming effects other than BPA also exist in literature and display interesting significative results, not only in obesity and T2DM studies, but also in those reporting dyslipidemia and hypertension.

DEHP may induce hypertension in mice by altering eNOS phosphorylation in aorta and increasing AT1 receptor expression, knowing that endothelial nitric oxide synthase produces NO, an endothelial relaxant factor regulating vascular tone (35), while dexamethasone exposure along 2 days during gestation could as well promote hypertension in sheep by increasing AT1 receptors in the brainstem (55). However, in these studies, potential epigenetic mechanisms have not been proposed. Likewise dyslipidemia has been described as a possible consequence of BPA, MEHP, DEHP, DDT and PFOA early exposure, without any potential underlying mechanism elucidated.

Contrasting literature also exists. We found indeed 7 papers where endocrine disruptor chemicals seem to be ineffective or even prevent the development of metabolic syndrome related phenotypes. It is however necessary to specify that one of them focused on genistein, a phytoestrogen compound known to prevent obesity: associated CpG hypermethylation in the promoter region of AvyIAP locus, compatible with reduction of obesity risk, supports this hypothesis (43). The six remaining papers deal instead with BPA (11-13, 15, 18) and with PFOA (42), two compounds rather supposed to have “obesogenic” effects. Only one of them proposed possible underlying mechanism following BPA exposure from peri-conception to weaning, putting in front *ucp1* mRNA expression increase in brown adipose tissue, as an indicator of energy expenditure increase through thermoregulation and subsequent decrease of obesity risk (12). Doses and exposition windows of contrasting literature do not differ substantially from those proposed by studies in which endocrine disruptors have metabolic syndrome-related effects, so that potentially causes of divergent results must be searched elsewhere.

Among objectives of this review appeared the identification of biomarkers possibly enabling to early discover a biological ground for adulthood metabolic syndrome development and therefore allowing to propose possible preventive interventions. We did not find any study explicitly describing such biomarkers, even if some parameters such as serum adiponectin were quite often proposed among early outcomes. Best characterization is however needed to improve scientific evidence and then to eventually elaborate some guidelines. Neither possible preventive interventions were proposed among studies. Genistein supplementation showed metabolic phenotypes opposed to those of metabolic syndrome, but further investigation about potential use of this compound are also necessary. Human approach should be further developed, as actual literature lacks of enough temporal distance since the start of follow-up. Try to avoid endocrine disruptors during the period between conception and weaning seems to be the most natural preventive action suggested by findings in this review.

Improving scientific evidence is crucial. Selected studies are all interventional randomized trials ensuring high evidence under this aspect. Nevertheless variability in methodology, uncertain study quality and consistency do not let us express about evidence of outcomes observed and reported in this review.

In conclusion, most of the studies included in this review show that an early exposure to endocrine disruptor may have consistent influence in the pathogeny of metabolic syndrome features manifesting at adulthood. The hypothesis of “metabolic syndrome programming by endocrine disruptors” is supported by animal studies showing that a dose under the toxic threshold of an endocrine disruptor provided in a timespan ranging from peri-conceptional period to weaning induces in young and adult offsprings particular phenotypes related to metabolic syndrome features. Other kind of studies are needed to best characterize the role of endocrine disruptors in the metabolic syndrome pathogeny by developmental programming and increase the evidence level, implementing animal research and keeping improving epidemiological studies on human.

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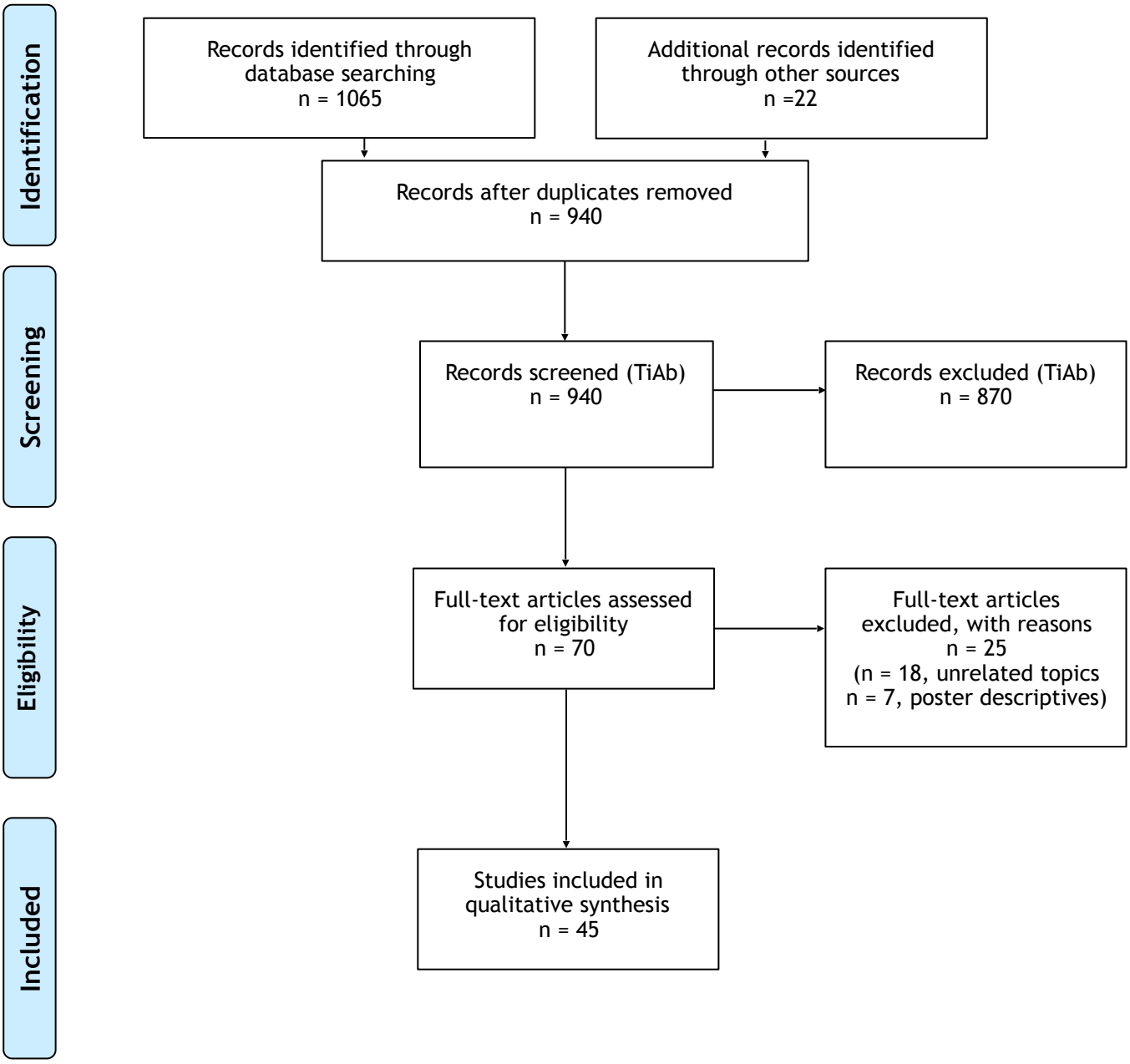
ANNEXES

Flow chart

PRISMA 2009 Flow Diagram

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

www.prisma-statement.org.



Summary tables

OBESITY

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Anderson et al., 2013	Wild type mouse (genotype: *a/a* for *Agouti* gene)	BPA	Diet (*ad libitum*)	50 ng/kg diet 50 µg/kg diet 50 mg/kg diet	From 2 weeks before mating to PND 21	Fat mass decrease Serum adiponectin increase (females)	50 ng/kg diet	6 months 10 months		
Angle et al., 2013	CD-1 mouse	BPA	Dosage by micropipetter	5 µg/ kg bw 50 µg/ kg bw 500 µg/ kg bw 5000 µg/ kg bw 50000 µg/ kg bw (daily)	From GD9 to GD18 (preadipocytes differentiation period)	Gonadal and renal fat pads weight increase Gonadal and renal adipocytes hyperplasia Renal adipocytes hypertrophy Serum leptin increase Serum adiponectin decrease (males)	500 µg/kg bw 5 and 500 µg/ kg bw 5000 µg/kg bw 500 µg/kg bw 5, 50 and 5000 µg/kg bw	18-19 weeks		
Gao et al., 2016	Sprague-Dawley rat	BPA	Drinking solution	1 µg/mL 10 µg/mL	From GD6 to PND21	Body weight increase Peritoneal adipose tissue increase Serum adiponectin decrease (males) Body weight increase Perigonadal fat pad weight increase Serum adiponectin decrease (females)	1 µg/mL 10 µg/mL	PND 50 (pubertal stage)		Visceral adipose tissue adiponectin mRNA expression decrease Liver *Atgl* mRNA expression decrease
García-Arevalo et al., 2014	OF-1 mouse	BPA	Subcutaneous injection	10 µg/kg bw (daily)	From GD 9 to GD 16	Body weight increase Perigonadal fat pad increase Hepatic TG increase (males)	10 µg/kg bw	28 weeks		Perigonadal fat pad mRNA expression decrease of *Srebp1c* *Pparalpha* *Cpt1beta* Liver mRNA expression increase of *Ppargamma* *Acacbeta* *Prkaa* and *Cd36* decrease (at 17 weeks)

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Ilagan et al., 2017	CD-1 mouse	BPA	Intraperitoneal infusion via Alzet osmotic minipumps	5 mg/kg bw (daily)	From GD 9 to GD18		5 mg/kg	8 weeks (pubertal stage)		Hepatic mRNA expression of lipid and glucose metabolism related genes increase *Cox1* *G6pc* *Cyp17a1* *Pnpla3* *Rgs16* *Scd1* *Cyp21a1* and decrease *Nucb2* *Tff3* *Fkbp11* *Saa3* *Gstt3*
Jiang et al., 2014	Wistar rat	BPA	Oral	40 *µ*g/kg diet (daily)	From GD0 to PND21	Body weight Hepatic steatosis Hepatic TG increase Serum ALT increase (males)	40 *µ*g/kg bw	15 and 26 weeks	Liver: ROS generation increase Apoptotic markers increase(cytosolic CytC, Caspase-3 and Bax increase, Bcl-2 decrease) MRC (mitochondrial respiratory complex) activity decrease	Hepatic mRNA expression of lipid metabolism related genes increase *Fdps* *Hmgcr* *Apof* *Apoc1* *Apoc4* *Slc27a1* mRNA expression of mitochondrial function related genes decrease *Uqcrc2* *Uqcrfs1* *Etfa* *Atp51* *Slc25a23*
Johnson et al., 2015	California mouse	BPA	Diet (*ad libitum*)	50 mg/kg diet	From 2 weeks before mating to PND30	No body weight, fat pads, leptin, adiponectin differences compared to control group	50 mg/kg diet	90 days		
Ma et al., 2013	Wistar rat	BPA	Oral gavage	50 *µ*g/kg bw (daily)	From GD0 to PND21	Body weight increase (males)	50 *µ*g/kg	21 weeks	Liver: DNMT3B protein activity increase	Hepatic mRNA expression increase of *Dnmt3b* *Ppargamma*
MacKay et al., 2013	CD-1 mouse	BPA	Diet *(ad libitum)*	0.275 *µ*g/kg bw 5.345 *µ*g/kg bw	From GD0 to PND21	Retroperitoneal and intrascapular brown adipose fat pads weight increase (males) Perigonadal, retroperitoneal, brown adipose tissue, and subcutaneous fat pad weight increase (females)	5.345 *µ*g/kg bw	PND 90	POMC fiber density decrease in the paraventricular nucleus (PVN) (males) ERalpha positive cells increase in posterior arcuate nucleus (ARC) (females)	Neuropeptide Y and Agouti-related peptide mRNA expression increase in the arcuate nucleus **(only if challenged with high-fat diet)** (males) ERalpha mRNA expression increase in the hypothalamus and reduced proopiomelanocortin mRNA expression in the arcuate nucleus **(only if challenged with high-fat diet)** (females)

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Manikkam et al., 2013	Sprague-Dawley rat	Plastic mixture with: BPA DEHP DBP	Intraperitoneal injection	"Plastics": 50 mg/kg bw (BPA) + 750 mg/kg bw (DEHP) + 66 mg/kg bw (DBP) "lower dose plastics": 25 mg/kg bw (BPA) + 375 mg/kg bw (DEHP) + 33 mg/kg bw (DBP) (daily)	From GD8 to GD14 (gonadal sex determination period)	F3 generation Body weight increase Abdominal adipose tissue accumulation ("lower dose plastics" in males) ("plastics" in females)	"Plastics" and "lower dose plastics"	1 year old		F3 generation Altered DNA methylation of obesity related genes in sperm *Tnfrsf12a* *Esrra* *Fgf19* *Wnt10b* *Gdnf*
Miyawaki et al., 2007	ICR mouse	BPA (**high-fat diet after BPA exposure**)	Drinking solution	0.26 (**LD**) mg/kg bw 2.72 (**HD**) mg/kg bw (daily)	From GD10 to PND30	Males: body weight (**HD**) and adipose tissue weight (**HD**) increase Females: body weight (**LD** and **HD**), adipose tissue weight (**LD**) and serum leptin (**LD**) increase	0.26 and 2.72 mg/kg bw (daily)	PND31 (pubertal stage)		
Ryan et al., 2010	CD-1 mouse	BPA	Diet *(ad libitum)*	0.25 µg/kg bw (daily)	From GD0 to PND21	Normal body weight and fat percentage	0.25 µg/kg bw	8-9 weeks (pubertal stage)		
Somm et al., 2009	Sprague Dawley rat	BPA	Drinking solution	70 µg/kg bw (daily)	From GD6 to PND21	Body weight increase Perigonadal fat pad increase (females) Body weight increase (**only if fed with HFD**) (males)	70 µg/kg bw	PND21 (weaning) 14 weeks (young adult stage)		Perigonadal adipose tissue mRNA expression of the proadipogenic transcription factors increase *c/ebp-alpha* *Ppargamma* *srebp-1c* *lpl* *fas* *scd-1* Liver mRNA expression increase of *srebp-1c* *acc* *fas*
Song et al., 2014	Sprague-Dawley rat	BPA	Drinking solution	80 µg/kg bw 758 µg/kg bw (daily)	From GD6 to PND21	Body weight increase Adipocytes hypertrophy in subcutaneous adipose tissue Serum adiponectin decrease Serum MDA levels increase (males)	80 and 758 µg/kg bw	PND 100		Subcutaneous adipose tissue mRNA expression of adiponectin decrease Serum SOD activity decrease
Susiarjo et al., 2015	C57BL/6 mouse	BPA	Diet (*ad libitum*)	10 µg/kg bw 10 mg/kg bw (daily)	From 2 weeks before mating to PND21	F1 generation Body weight increase Fat percentage increase F2 generation Body fat percentage increase (males)	10 µg/kg bw and 10 mg/kg bw	PND98-117		
Veiga-Lopez et al., 2016	Sheep	BPA	Subcutaneous injection	0.05 mg/kg 0.5 mg/kg 5 mg/kg (daily)	From GD30 to GD90	Visceral adipose tissue adipocytes hypertrophy	0.5 mg/kg	**13-21 months (adulthood?)**		Subcutaneous adipose tissue mRNA expression increase of inflammation marker CD68

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
van Esterik et al., 2014	C57BL/6J x FVB mouse	BPA	Diet (ad libitum)	3 µg/kg bw 10 µg/kg bw 30 µg/kg bw 100 µg/kg bw 300 µg/kg bw 1000 µg/kg bw 3000 µg/kg bw (daily)	From 2 weeks before mating to PND21	Fat pads, leptin and adiponectin dose-dependent decrease (females)	3, 10, 30, 100, 300, 1000 and 3000 µg/kg bw	18-23 weeks		Brown adipose tissue mRNA expression of *ucp1* dose-dependent increase
van Esterik et al., 2015	C57BL/6J x FVB mouse	BPA	Diet (ad libitum)	3 µg/kg bw 10 µg/kg bw 30 µg/kg bw 100 µg/kg bw 300 µg/kg bw 1000 µg/kg bw 3000 µg/kg bw (dialy)	From 2 weeks before mating to PND21	Fat pads, leptin and adiponectin dose-dependent decrease (females)	3, 10, 30, 100, 300 and 3000 µg/kg bw	18-23 weeks		
Wei et al., 2011	Wistar rat	BPA	Oral gavage	50 µg/kg 250 µg/kg 1250 µg/kg (daily)	From GD0 to PND21	Body weight increase Serum leptin increase	50 µg/kg	15-27 weeks		
Wei et al., 2014	Wistar rat	BPA	Oral gavage	50 µg/kg (daily)	From GD0 to PND21	Body weight Liver TG and FFA increase Serum ALT increase (males)	50 µg/kg	27 weeks	Disordered cell cords and increased lipid droplets in liver	Hepatic mRNA expression increase of *Srebf1* *Fas* *Pparalpha* *Cpt1a* GSH:GSSG ratio decrease
Dolinoy et al., 2006	Avy mouse (genotype: Avy/a for Agouti gene)	Genistein	Diet (ad libitum)	250 mg/kg diet	From 2 weeks before mating to PND 21	Normal or decreased body weight	250 mg/kg diet	60 weeks		CpG methylation increase in the promoter region of AvyIAP locus
Chang et al., 2012	Sprague-Dawley rat	NP	Drinking solution	2 µg/mL	From GD0 to PND21	Body weight increase (males)	2 µg/mL	13-14 weeks		
Dobson et al., 2012	Dunkin-Hartley guinea pigs	Ethanol	Drinking solution	4 g/kg bw (daily)	From GD0 to GD68	Visceral adiposity increase	4 g/kg bw	PND 100-200		
Green et al., 2016	UCD-T2DM rat#	TPhP	Oral	170 µg (daily)	From GD8 to PND21	Body weight increase (males and females) Mesenteric fat pad weight increase (females) Inguinal, gonadal and mesenteric fat pad weight increase Plasma leptin increase (males)	170 µg	3.5 months up to 6 months		
Hao et al., 2012	C57BL/6J mouse	MEHP	Oral gavage	0.05 mg/kg bw 0.25 mg/kg bw 0.5 mg/kg bw (daily)	From GD12 to PND7	Body weight increase Epididymal and perirenal fat pad weight increase (males)	0.05 mg/kg bw	8 weeks		White adipose tissue mRNA expression increase of *Ppargamma* Liver mRNA expression increase of *Pparalpha*
Lassiter et al., 2008	Long-Evans rat	Chlorpyrifos	Oral gavage	1 mg/kg 2.5 mg/kg 4 mg/kg (daily)	From GD7 to PND21	Body weight increase (males)	2.5 mg/kg	PND95-101		

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Lee et al., 2016	C57BL/6 mouse	DEHP	Oral	30 mg/kg bw (daily)	From 4 week before mating to PND28 (weaning)	Body weight increase White and brown adipose tissue increase White adipose tissue adipocytes hypertrophy Brown adipose tissue adipocytes hyperplasia	30 mg/kg bw	8 weeks		
Lv et al., 2013	Wistar rat	PFOS	Oral (daily)	0.5 mg/kg bw 1.5 mg/kg bw	From GD0 to PND21	Serum leptin increase Serum adiponectin decrease Hepatic steatosis Gonadal fat pad weight increase	0.5 and 1.5 mg/kg bw	13, 18, 21 and 22 weeks		Hepatic mRNA expression increase of *Srebp-1c*
Ortiz et al., 2014	C57BL/6J mouse: *Gclm+/+* and *Gclm-/-* genotypes (expressing GSH or not respectively)	BaP	Oral gavage	2 mg/kg 10 mg/kg (daily)	From GD7 to GD16	Body weight increase Visceral adipose tissue weight increase Hepatic steatosis (*Gclm+/+* females)	2 and 10 mg/kg	7.5-8 months	Hepatic lobular, periportal and central vein inflammatory infiltrates (*Gclm+/+* individuals)	Liver mRNA expression of lipid metabolism involved genes increase *Ucp2* *Ppargamma* (*Gclm+/+* individuals) Lipogenesis involved genes mRNA expression decrease *Srebf1* *Fasn* *Fabp4* (*Gclm-/-* individuals)
Rajesh et al., 2014	Wistar rat	DEHP	Oral gavage	1 mg/kg bw 10 mg/kg bw 100 mg/kg bw (daily)	From GD9 to GD21 From GD9 to PND0	Body fat weight increase (both exposition windows) (males and females)	10 and 100 mg/kg bw	PND 60 (pubertal stage)		
Somm et al., 2008	Sprague-Dawley rat	Nicotine	Subcutaneous infusion via Alzet osmotic minipumps	3 mg/kg (daily)	From GD4 to GD17	Epididymal white adipose tissue weight increase	3 mg/kg	20 and 26 weeks		White adipose tissue adiponectin mRNA expression increase
Strakovsky et al., 2015	Sprague-Dawley rat	DEHP	Oral gavage	300 mg/kg bw (daily)	From GD6 to PND21	Body fat percentage increase (males)	300 mg/kg bw	PND 90-110	Gonadal white adipose tissue adipocytes hypertrophy	Gonadal white adipose tissue mRNA expression increase of *Ppargamma1* *Cebpa* *Fasn* *Igf1* *Adipoq* *Ppardelta* *Fabp4* and decreased expression of *Lep* *Bmp2* *Bmp4* *Stat1* *Stat5a*
van Esterik et al., 2015	C57BL/6J x FVB mouse	TCDD	Diet (ad libitum)	10-10000 pg/kg bw (daily)	From 2 weeks before mating to PND14	Perigonadal and perirenal fat pads increase (females)	TCDD: 10-10000 pg/kg bw	53-55 weeks		

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
van Esterik et al., 2016	C57BL/6J x FVB mouse	PFOA	Diet (ad libitum)	3 µg/kg bw 10 µg/kg bw 30 µg/kg bw 100 µg/kg bw 300 µg/kg bw 1000 µg/kg bw 3000 µg/kg bw (daily)	From 2 weeks before mating to PND21	Body weight decrease (males) Body weight decrease Perigonadal and perirenal fat pads decrease (females)	3, 10, 30, 100, 300, 1000 and 3000 µg/kg bw	19-28 weeks	Perirenal adipose tissue adipocytes hypotrophy (females)	

T2DM

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Alonso-Magdalena et al., 2010	OF-1 mouse	BPA	Subcutaneous injection (*daily*)	10 *µ*g/kg bw 100*µ*g/kg bw	From GD 9 to GD 16	Insulin sensitivity decrease Glucose intolerance (males)	10 *µ*g/kg	6 months	Enhanced glucose-stimulated insulin secretion associated to increase in global intracellular Ca2+ entry Reduced pancreatic beta-cells proliferation	
Angle et al., 2013	CD-1 mouse	BPA	Daily dose by micropipetter	5 *µ*g/ kg bw 50 *µ*g/ kg bw 500 *µ*g/ kg bw 5000 *µ*g/ kg bw 50000 *µ*g/ kg bw	From GD9 to GD18 (preadipocytes differentiation period)	Serum leptin increase Serum adiponectin decrease Glucose intolerance Insulin resistance (males)	5, 50, 500, 5000 *µ*g/kg bw	18-19 weeks		
García-Arevalo et al., 2014	OF-1 mouse	BPA	Subcutaneous injection (daily)	10 *µ*g/kg bw	From GD 9 to GD 16	Glucose intolerance Serum NEFA increase (males)	10 *µ*g/kg bw	28 weeks	Glucose-stimulated intracellular Ca2+ signaling increase	Hepatic mRNA expression of *Cd36* decrease
Ilagan et al., 2017	CD-1 mouse	BPA	Intraperitoneal infusion via Alzet osmotic minipumps	5 mg/kg (daily)	From GD 9 to GD18		5 mg/kg	8 weeks (pubertal stage)		Hepatic mRNA expression of lipid and glucose metabolism related genes increase *Cox1* *G6pc* *Cyp17a1* *Pnpla3* *Rgs16* *Scd1* *Cyp21a1* and decrease *Nucb2* *Tff3* *Fkbp11* *Saa3* *Gstt3*
Johnson et al., 2015	California mouse	BPA	Diet	50 mg/kg diet	From 2 weeks before mating to PND30	No glucose, insulin, adiponectin differences compared to control group	50 mg/kg diet	90 days		
Li et al., 2014	Sprague-Dawley rat	BPA	Oral gavage	40 *µ*g/kg bw (daily)	From GD0 to PND21	F2 generation Glucose intolerance Insulin resistance	40 *µ*g/kg bw	23 weeks	F2 generation Hepatic GCK protein activity decrease	F1 generation *Gck* gene promoter CpG hypermethylation and global DNA hypomethylation in sperm F2 generation Hepatic *Gck* mRNA expression decrease associated to *Gck* gene promoter CpG hypermethylation and global hepatic DNA hypomethylation

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Liu et al., 2013	C57BL/6 mouse	BPA	Subcutaneous injection	100 µg/kg bw (daily)	From GD1 to GD 6 = **A** from GD6 to PND0 = **B** from PND0 to PND21 = **C** from GD6 to PND21 = **D**	Glucose intolerance Insulin resistance (males of group **B**)	100 µg/kg bw	3, 6 and 8 months	Impaired pancreatic beta-cells turnover with cleaved caspase-3 and cyclin D1 decrease (females of group **B**; males of groups **C** and **D**)	
Ma et al., 2013	Wistar rat	BPA	Oral gavage	50 µg/kg (daily)	From GD0 to PND21	Insulin resistance (males)	50 µg/kg	21 weeks	Hepatic glycogen stores decrease, Hepatic DNMT3B protein activity increase Hepatic GCK protein activity decrease	Hepatic global DNA hypomethylation with *Gck* gene promoter CpG hypermethylation and subsequent mRNA expression decrease Hepatic *Dnmt3b* mRNA expression increase
MacKay et al., 2013	CD-1 mouse	BPA	Diet	0.275 5.345 µg/kg bw (daily)	From GD0 to PND21	Glucose intolerance (males)	5.345 µg/kg bw	PND 90		
Mao et al., 2015	Sprague-Dawley rat	BPA	Oral	40 µg/kg (daily)	From GD0 to PND21	F2 generation Glucose intolerance Insulin resistance (males and females)	40 µg/kg	21 weeks	F2 generation Smaller pancreatic beta-cells islets (male and females) Swollen beta-cells endoplasmic reticulum (males)	F1 generation *Igf2* gene promoter CpG hypermethylation in sperm F2 generation Pancreatic beta-cells *Igf2* and *h19* mRNA expression decrease with *Igf2* gene promoter CpG hypermethylation (males)
Ryan et al., 2010	CD-1 mouse	BPA	Diet	0.25 µg/kg bw (daily)	From GD0 to PND21	Normal glucose tolerance	0.25 µg/kg bw	8-9 weeks (pubertal stage)		
Song et al., 2014	Sprague-Dawley rat	BPA	Drinking solution	80 µg/kg bw 758 µg/kg bw (daily)	From GD6 to PND21	Serum adiponectin decrease Hyperglycemia Insuline resistance	80 and 758 µg/kg bw	PND 100		Subcutaneous adipose tissue mRNA expression of adiponectin decrease
Susiarjo et al., 2015	C57BL/6 mouse	BPA	Diet	10 µg/kg bw 10 mg/kg bw (daily)	From 2 weeks before mating to PND21	F1 generation Glucose intolerance Insulin resistance F2 generation: Glucose intolerance (males)	10 µg/kg bw and 10 mg/kg bw	PND98-117		F2 generation *Igf2* mRNA expression increase with specific CpG site methylation increase **in embryos at GD10**
Veiga-Lopez et al., 2016	Sheep	BPA	Subcutaneous injection	0.05 mg/kg 0.5 mg/kg 5 mg/kg (daily)	From GD30 to GD90	Insulin resistance (females)	0.5 mg/kg	13-21 months		
van Esterik et al., 2014	C57BL/6J x FVB mouse	BPA	Diet (*ad libitum*)	3 µg/kg bw 10 µg/kg bw 30 µg/kg bw 100 µg/kg bw 300 µg/kg bw 1000 µg/kg bw 3000 µg/kg bw (daily)	From 2 weeks before mating to PND21	Serum FFA decrease Serum leptin decrease Serum adiponectin decrease (females)	3, 10, 30, 100, 300, 1000 and 3000 µg/kg bw	18-23 weeks		

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
van Esterik et al., 2015	C57BL/6J x FVB mouse	BPA	Diet (*ad libitum*)	3 *µ*g/kg bw 10 *µ*g/kg bw 30 *µ*g/kg bw 100 *µ*g/kg bw 300 *µ*g/kg bw 1000 *µ*g/kg bw 3000 *µ*g/kg bw (daily)	From 2 weeks before mating to PND21	Serum FFA decrease Serum leptin decrease Serum adiponectin decrease (females)	3, 10, 30, 100, 300 and 3000 *µ*g/kg bw	18-23 weeks		
Wei et al., 2011	Wistar rat	BPA	Oral gavage	50 *µ*g/kg 250 *µ*g/kg 1250 *µ*g/kg (daily)	From GD0 to PND21	Glucose intolerance Serum leptin increase	50 *µ*g/kg	15-27 weeks	Pancreatic beta-cells swollen mitochondria and rough endoplasmic reticulum Reduction in insulin-filled granules (males)	Pancreatic beta-cells mRNA expression decrease of *Pdx-1* *Nkx6.1* *Glut2* *Gck* and increase of *Ucp2*
Wei et al., 2014	Wistar rat	BPA	Oral gavage	50 *µ*g/kg (daily)	From GD0 to PND21	Serum FFA increase Insulin resistance (males)	50 *µ*g/kg	27 weeks		Hepatic mRNA expression and protein activity decrease of insulin-stimulated p-INSR p-AKT1 p-GSK3B
Dobson et al., 2012	Dunkin-Hartley guinea pigs	Ethanol	Drinking solution	4 g/kg bw (daily)	From GD0 to GD68	Glucose intolerance Insulin resistance	4 g/kg bw	PND 100-200	Pancreatic beta-cells number decrease	
Dobson et al., 2014	Dunkin-Hartley guinea pigs	Ethanol		4 g/kg bw (daily)	From GD2 to the end of gestation		4 g/kg bw	PND 150-200		Liver and prefrontal cortex insulin signaling involved genes mRNA expression alteration
Green et al., 2016	UCD-T2DM rat#	TPhP	Oral	170 *µ*g (daily)	From GD8 to PND21	Insulin resistance Serum NEFA increase Serum leptin increase T2DM onset acceleration (males)	170 *µ*g	3.5 months up to 6 months		
LaMerrill et al., 2014	C57BL/6J mouse	DDT	Oral administration	1.7 mg/kg bw	From GD11 to PND5 (liver and white- and brown- adipose tissue ontogenesis and programming])	Glucose intolerance Insulin resistance **(only if fed with HFD)** (females)	1.7 mg/kg bw	9 months		Brown adipose tissue mRNA expression decrease of *Glut4* *Cpt2*
Lin et al., 2011	Wistar rat	DEHP	Oral gavage	1.25 mg/kg bw 6.25 mg/kg bw (daily)	From GD0 to PND21	Hyperinsulinemia (males) Hyperinsulinemia Glucose intolerance (females)	1.25, 6.25 mg/kg bw	15 and 27 weeks	Pacreatic beta-cells swollen mitochondria and reduced insulin secretion (females)	Pancreatic beta-cells mRNA expression decrease of *Pdx-1* and increase of *Atf4* *Atf6* *Bip* *Ucp2*
Lv et al., 2013	Wistar rat	PFOS	Oral	0.5 mg/kg bw 1.5 mg/kg bw (daily)	From GD0 to PND21	Glucose intolerence Insulin resistance Serum adiponectin decrease	0.5 and 1.5 mg/kg bw	13, 18, 21 and 22 weeks		

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Patisaul et al., 2013	Wistar rat	Firemaster® 550 (= triphenyl phosphate (TPP) + a mixture of isopropylated triph-enylphosphate isomers (ITPs) + 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) + bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate (TBPH))	Diet	100 *µg* 1000 *µg* (daily)	From GD8 to PND21	Glucose intolerance (males and females)	1000 *µg*	PND 220		
Rajesh et al., 2014	Wistar rat	DEHP	Oral gavage	1 mg/kg bw 10 mg/kg bw 100 mg/kg bw (daily)	From GD9 to GD21 (= **A**) From GD9 to PND0 (= **B**)	Glucose intolerance Insulin resistance (all doses and exposition windows)	10 and 100 mg/kg bw	PND 60 (pubertal stage)	Skeletal muscle decreased insulin binding (**A**) with reduction in glucose uptake and oxidation Nuclear concentration of MYOD, SREBP1c decrease and HDAC2 increase	Skeletal muscle mRNA expression decrease of *Insr* *Akt1* *Glut4* and increase of *Dnmt1* *Dnmt3a* and *3b* MYOD-binding site methylation in *Glut4* gene increase
Somm et al., 2008	Sprague-Dawley rat	Nicotine	Subcutaneous infusion via Alzet osmotic minipumps	3 mg/kg (daily)	From GD4 to GD17	Peripheral tissue insulin resistance	3 mg/kg	20 and 26 weeks	Beta-cells islets size and number decrease	Pancreatic beta-cells mRNA expression decrease of *Pdx-1* *Pax-6,* *Nkx6.1* *Kir6.2* *Glut2* *Gck* *Survivin* White adipose tissue adiponectin mRNA expression increase
van Esterik et al., 2015	C57BL/6J x FVB mouse	PCB153	Diet (*ad libitum*)	0.09 *µg*/ kg bw 0.45 *µg*/ kg bw 2.25 *µg*/ kg bw 11.3 *µg*/ kg bw 56 *µg*/ kg bw 281 *µg*/ kg bw 1406 *µg*/ kg bw (daily)	From 2 weeks before mating to PND21	Hyperglycemia FFA increase	0.09, 0.45, 2.25, 11.3, 56, 281, 1406 *µg*/ kg bw	53-55 weeks		

HT

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Chang et al., 2012	Sprague-Dawley rat	NP	Drinking solution	2 μg/mL	From GD0 to PND21	Serum ACTH increase Serum corticosterone increase Serum aldosterone increase (males) Serum corticosterone increase Serum aldosterone increase Adipose tissue corticosterone increase (females)	2 μg/mL	13-14 weeks	Adipose tissue and hepatic increased activity of 11beta-HSD1 (males and females) Adrenal increased activity of 11beta hydroxylase (males) Adrenal increased activity of aldosterone synthase (males and females)	Hepatic mRNA expression of *11beta-hsd1* increase (males) Adrenal mRNA expression of *StAR* increase (males)
Dodic et al., 2006	Sheep	Dex	Continuous IV infusion during 48h	23.04 mg (0.48 mg/h)	From GD26 to GD28	Elevated mean arterial pressure following angiotensin II stimulation (males)	23.04 mg	50-52 months	Increased in brainstem AT1 receptors (Dodic et al., 2002)	Increase in brainstem AT1 receptor gene expression (Dodic et al., 2002)
Hadoke et al., 2006	Wistar rat	Dex	Subcutaneous injection	100 μg/kg bw (daily)	Throughout pregnancy	Elevated arterial blood pressure Elevated basal plasma aldosterone (females)	100 μg/kg bw	12 and 16 weeks		
Lee et al., 2016	C57BL/6 mouse	DEHP	Oral	30 mg/kg bw (daily)	From 4 week prior mating to PND28 (weaning)	Blood pressure increase	30 mg/kg bw	8 weeks		Aorta altered eNOS phosporylation and mRNA expression of AT1 receptor increase
MohanKumar et al., 2017	Sheep	BPA	Subcutaneous injection	0.5 mg/kg (daily)	From GD 30 to GD 90	SBP and MBP increase **only in high fat diet fed individuals** (females)	0.5 mg/kg	21 months		ANP (atrial natriuretic peptide) expression increase in left ventricle (normal diet) NPR3 (Natriuretic Peptide Receptor 3) expression decrease in left ventricle (normal diet) **(Koneva et al., 2017)**

DYSLIPIDEMIA

Reference	Animal model	Endocrine disruptor	Administration way	Exposition: dose	Exposition: window	Cardio-metabolic alteration: main outcomes (according to sex)	Cardio-metabolic alteration: endocrine disruptor effective dose	Cardio-metabolic alteration: individuals age	Metabolic pathways and underlying mechanisms: cellular	Metabolic pathways and underlying mechanisms: molecular
Gao et al., 2016	Sprague-Dawley rat	BPA	Drinking solution	1 µg/mL 10 µg/mL	From GD6 to PND21	Serum total cholesterol increase (males) Serum TG and total cholesterol increase Serum HDL decrease (females)	1 µg/mL 10 µg/mL	PND 50 (pubertal stage)		
Hao et al., 2012	C57BL/6J mouse	MEHP	Oral gavage	0.05 mg/kg bw 0.25 mg/kg bw 0.5 mg/kg bw (daily)	From GD12 to PND7	Serum total cholesterol and TAG increase (males)	0.05 mg/kg bw	8 weeks		White adipose tissue mRNA expression of *Ppargamma* increase Liver mRNA expression of *Pparalpha* increase
LaMerrill et al., 2014	C57BL/6J mouse	DDT	Oral administration	1.7 mg/kg bw	From GD11 to PND5	Females: fasting cholesterol increase **ONLY if challenged with HFD**	1.7 mg/kg bw	9 months		Brown adipose tissue mRNA expression of *Lpl* *Pnpla* *Cpt2* decrease Liver mRNA expression of *Ldlr* decrease and *Cyp7a1* increase
Lee et al., 2016	C57BL/6 mouse	DEHP	Oral	30 mg/kg bw (daily)	From 4 week prior mating to PND28 (weaning)	Blood cholesterol increase Hepatic cholesterol accumulation	30 mg/kg bw	8 weeks		
Miyawaki et al., 2007	ICR mouse	BPA (**high-fat diet feeding**)	Drinking solution	0.26 (**LD**) mg/kg bw 2.72 (**HD**) mg/kg bw (daily)	From GD10 to PND30	Serum TG and NEFA (**LD**) increase (males) Serum cholesterol (**LD** and **HD**) increase (females)	0.26 and 2.72 mg/kg bw	PND31 (pubertal stage)		
van Esterik et al., 2016	C57BL/6J x FVB mouse	PFOA	Diet (ad libitum)	3 µg/kg bw 10 µg/kg bw 30 µg/kg bw 100 µg/kg bw 300 µg/kg bw 1000 µg/kg bw 3000 µg/kg bw (daily)	From 2 weeks prior mating to PND21	Serum TG and cholesterol decrease (females)	3, 10, 30, 100, 300, 1000 and 3000 µg/kg bw	19-28 weeks		
Wei et al., 2011	Wistar rat	BPA	Oral gavage	50 µg/kg 250 µg/kg 1250 µg/kg (daily)	From GD0 to PND21	Serum TG increase Serum HDL decrease	50 µg/kg	15-27 weeks		

Abbreviations

11beta-HSD = 11β-hydroxysteroid dehydrogenase
Abcg =ATP-binding cassette sub-family G gene
Acacbeta = acetyl-coenzymeA carboxylase beta gene
Acc = acetyl-coenzymeA carboxylase gene
ALT = alanine aminotransferase
Apoc = apolipoprotein C gene
Apof = apolipoprotein F gene
Adipoq = adiponectin gene
ANP = atrial natriuretic peptide
Akt = RAC-alpha serine/threonine-protein kinase
Atf = basic-region leucine zipper transcription factor gene
ARC = arcuate nucleus
ATGL = adipose triglyceride lipase
AT1 = angiotensin II receptor 1
Avy IAP = viable yellow agouti gene intracisternal A particle
BaP = benzo[a]pyrene
Bax = Bcl-2 associated X protein
Bcl-2 = anti-apoptotic protein
Bip = binding immunoglobulin protein gene
Bmp = bone morphogenic protein gene
BPA = bisphenol A
bw = body weight
Cpt = carnitine palmitoyltransferase gene
Cd36 = cluster of differentiation 36 gene
CD68 = cluster of differentiation 86 protein
Cebpa = CCAAT/enhancer-binding protein alpha
Cox = cyclooxygenase gene
CytC = cytochrome C
Cyp = cytochrome P450 gene
DBP = dibutyl phthalate
DDT = dichlorodiphenyltrichloroethane
DEHP = diethylhexyl phthalate
Dex = dexamethasone
DiBP = diisobutyl phthalate
DNMT = DNA methyltransferase
eNOS = endothelial nitric oxyde synthase
ERalpha = estrogen receptor alpha
Essra = estrogen related receptor alpha
Etfa = electron-transfer-flavoprotein
Firemaster® 550 contains: triphenyl phosphate, isopropylated triphenylphosphate isomers, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate, bis(2-ethylhexyl)-2,3,4,5-tetrabromophtalate
Fabp = fatty-acid-binding protein gene
Fas = fatty acids synthase gene
Fdps = farnesyl diphosphate synthase
FFA = free fatty acids
Fgf = fibroblast growth factor gene
Fkbp = FK506 binding protein gene
G6pc = glucose-6-phosphatase gene
Gclm +/+ = homozygosity for glutamate-cysteine ligase gene
Gck = glucokinase gene
GD = gestational day
Gdnf = glial derived neurotrophic factor gene
Glut2 = glucose transporter type 2 gene
GLUT4 = glucose transporter type 4
GSH:GSSG = glutathione
h19 = gene of non-coding RNA
HD = high dose
HDL = high-density lipoprotein
HFD = high-fat diet
Hmgcr = 3-hydroxy-3-methylglutaryl-Coenzyme A reductase
Igf = insulin-like growth factor gene
Insr = insulin receptor gene
Kir 6.2 = major subunit of the ATP-sensitive K channel
LD = low dose
Lep = leptin gene
Lpl = lipoprotein lipase gene
MBP = mean blood pressure
MDA = melanoma differentiation-associated protein
MEHP = mono-(2-ethylhexyl) phthalate
MRC = mitochondrial respiratory complex
NEFA = non esterified fatty acids
Nkx = negative regulator of *Wnt* gene
NP = nonylphenol
Nucb = deoxyribonuclease gene
p-AKT = phosphorylated kinase protein
PCB153 = polychlorinated biphenyl 153
Pdx = insulin promoter factor gene
PFOA = perfluorooctanoate
PFOS = perfluorooctane sulfonate
p-GSK = phosphorylated glycogen synthase kinase
PND = post natal day
Pnpla = patatin-like phospholipase domain-containing protein
POMC = proopiomelanocortin
PPAR = peroxisome proliferator-activated receptor
ppm = part per million
Prkaa = protein kinase AMP-activated catalytic subunit alpha
PVN = paraventricular nucleus
RAAS = renin-angiotensin-aldosterone system
Rgs = regulator of G-protein signaling gene
ROS = reactive oxygen species
Saa = serum amyloid A
SBP = systolic blood pressure
Scd = stearoyl Coenzyme A desaturase gene
Scl = transcription factor gene
SOD = superoxide dismutase
Srebf = sterol regulatory element binding factor
Srebp = sterol regulatory element binding protein
StAR = steroidogenic acute regulatory protein
Stat = signal transducer and activator of transcription gene
T2DM = type 2 diabetes mellitus
TAG = triacylglycerol
TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin
Tff = trefoil factor gene
TG = triglycerides
Tnfrsf = tumor necrosis factor receptor superfamily
TPhP = triphenyl phosphate
Ucp1 = uncoupling protein 1 gene, also known as thermogenin gene
Uqcrc = ubiquinol-cytochrome C reductase core protein gene
Uqcrfs = ubiquinol-cytochrome c reductase gene
Wnt = proto-oncogene signalling protein gene

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